UNIVERSITY OF
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Asymmetric Organocatalytic Allylation of Acetals

by

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ABSTRACT

The addition of allylmetals to aldehydes, particularly in an asymmetric fashion, is of prime importance in the synthetic chemist's arsenal of C–C bond-forming methodologies, as the secondary homoallylic alcohol products are primed for further transformations. So far, reagent-controlled approaches with chiral metal-based Lewis acids have been the most effective means for controlling the enantioselectivity of this reaction. However, this approach cannot be used when acetals are employed as the latent electrophiles. Since Brønsted acids also mediate the Hosomi-Sakurai reaction of acetals, we hypothesised that a chiral Brønsted acid HY* has the potential to introduce stereoselectivity into this bond-forming process *via* the formation of a chiral contact ion pair in which the chiral conjugate base controls the nucleophilic addition to the achiral oxacarbenium ion with which it will be associated. For the investigation, three types of Brønsted acids with different acidity, all based on a binaphthyl core, have been synthesised. 3,3'-Substituted phosphoric acids and phosphoramides were employed in a brief study of the reaction of acyclic dialkyl acetals with allyltrimethylsilane. However, since the rate of reaction was very slow, we turned our attention to more reactive acetal substrates. A more detailed study was carried out with racemic cyclic acetals: 1-alkoxyisochromans were reacted with allyltrimethylsilane in the presence of different phosphoramide catalysts. Non-polar solvents gave the best e.r. values. The optimisation procedure also revealed the new 10-Br-9-anthracenyl phosphoramide (*R*)-**45g** as the catalyst of choice for this particular acetal substrate. An interesting leaving group effect on the

enantioselectivity of the 1-allylisochroman product was also observed. A range of 1-ethoxyisochromans were synthesised to probe the scope and the limitations of the method. The products were obtained in moderate to good yields and moderate to very good enantioselectivities. The synthetic utility of the developed method was also demonstrated by two applications, one of these being a drug synthesis. To shed light on the origins of the enantioselectivity, several experiments were carried out. These confirmed that the process is a dynamic kinetic resolution. Finally, all results and observations were used to formulate a transition state which rationalises the observed stereochemical outcome. In summary, the first enantioselective asymmetric organocatalytic allylation of acetals is presented.

Dedicated to my PARENTS

For their endless love, support and encouragement

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ABBREVIATIONS

ACDC	asymmetric counteranion-directed catalysis
AO	atomic orbital
Ar	aryl
BINOL	1,1’-bi(2-naphthol)
BINSA	1,1’-binaphthalene disulfonic acid
Cp	cyclopentadienyl
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DEAD	diethyl azodicarboxylate
DIBALH	diisobutylaluminium hydride
DIPEA	*N*,*N*-diisopropylethylamine
DFT	density functional theory
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
e.r.	enantiomeric ratio
EI	electron impact/ionisation
FDMA	formaldehyde dimethyl acetal
FGI	functional group interconversion

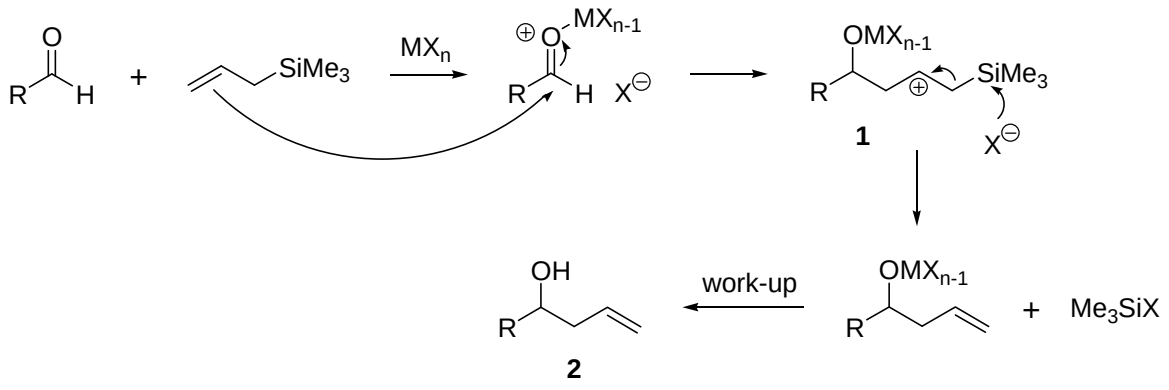
GC	gas chromatography
H_8-BINOL	2,2'-dihydroxy-5,6,7,8,5',6',7',8'-octahydro-[1,1']-binaphthalenyl
HMDS	hexamethyldisilazane
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
IR	infra-red
MS	mass spectrometry
MsCl	methanesulfonyl chloride
MTBE	methyl *t*-butyl ether
NMR	nuclear magnetic resonance spectroscopy
NTf_2	triflimidate
OTf	triflate
*p*TSA	*p*-toluenesulfonic acid
R_f	relative front
R.T.	room temperature
STRIP	6,6'-bis(2,4,6-triisopropylphenyl)-1,1'-spirobiindan-7,7'-diyl hydrogen phosphate
TADDOL	2,2-dimethyl-$\alpha,\alpha,\alpha',\alpha'$-tetraaryl-1,3-dioxolane-4,5-dimethanol
TBAF	tetra-*n*-butylammonium fluoride
TBS	*t*-butyldimethylsilyl
TEBAC	triethylbenzylammonium chloride
Tf	triflyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethylethylenediamine

TMS	trimethylsilyl
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TOF-ES	time of flight-electron spray

1 Introduction

1.1 The Hosomi-Sakurai reaction – an important allylation process

The Hosomi-Sakurai reaction of a carbon electrophile (such as aldehydes, ketones, Michael acceptors, imines, acetals, epoxides and acid chlorides) with an allylsilane is a particularly widely used method for forming C–C bonds.[1-3] Allylsilanes are very popular reagents because they are thermally stable and relatively inert to water and oxygen. In contrast to other allylating reagents, they are therefore isolable and storable without having to take special precautions. Allyl metals have been classified by Denmark[4] into three types according to the way in which they react with aldehydes. Allyltrialkylsilanes are so-called Type II allylating agents. This type of allyl nucleophile reacts with aldehydes through an open acyclic transition state in which there is no interaction between the silicon group in the nucleophile and the carbonyl oxygen (Scheme 1).



Scheme 1. Mechanism of the allylation of aldehydes by a Type II allylating agent.

Allylsilanes are not particularly nucleophilic so an external activator (e.g. Lewis acid) is generally required to effect reaction. The allylation reaction is a stepwise process, and proceeds *via* a cationic intermediate **1** in which the positive charge is stabilised by the *β*-effect of silicon. In this stabilising interaction, the unfilled pAO on the carbocationic carbon is in hyperconjugation with the filled σ(C–Si) bond. Maximum hyperconjugation, and therefore stabilisation, is obtained when the σ(C–Si) bond is aligned parallel to the adjacent p orbital (Figure 1).[5] In the second step, cleavage of the silyl group then provides the homoallylic alcohol product **2**. This type of allylation reaction is not a stereospecific process, however, it can be highly stereoselective.

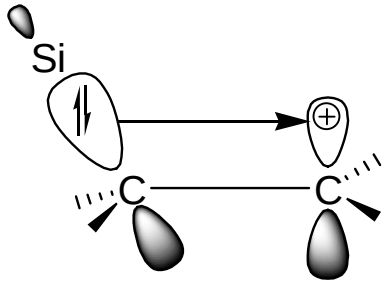


Figure 1. Stabilisation of a positive charge by the *β*-effect of silicon.

1.2 Asymmetric allylation

1.2.1 Stereoselective synthesis

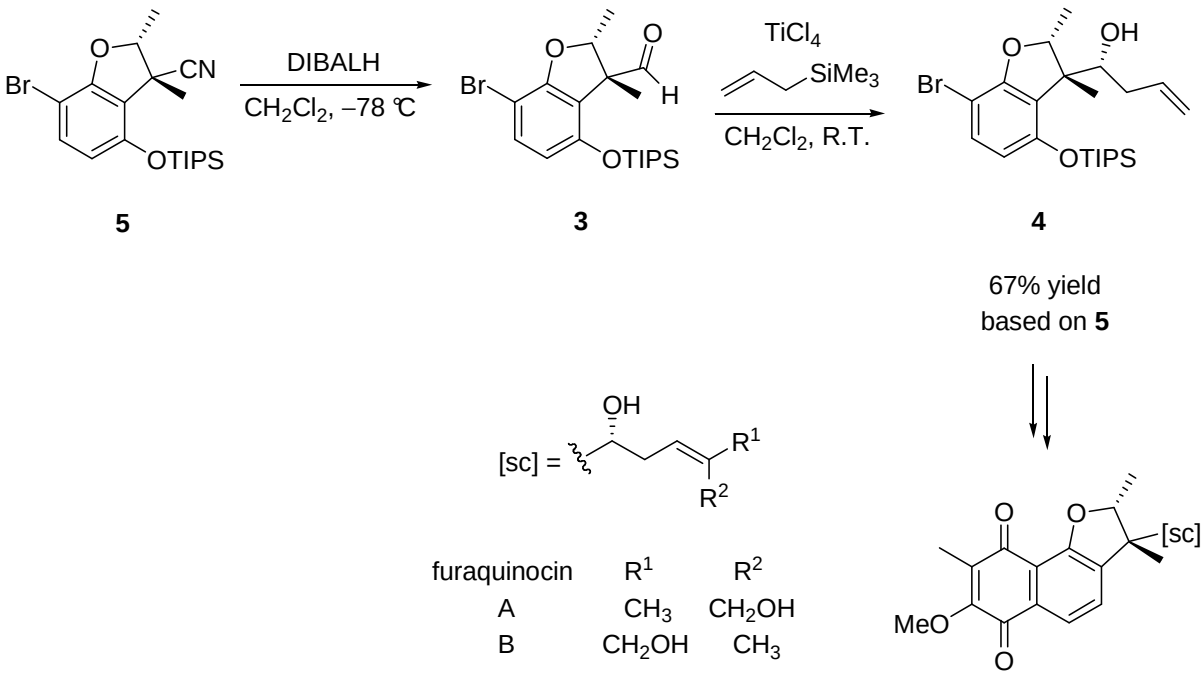
Controlling the stereochemical outcome of a reaction is one of the most challenging aspects of synthetic organic chemistry. Traditionally, substrate-controlled approaches have been employed, and indeed, are still widely used, particularly in the synthesis of complex molecular architectures.[as an example: 6] When chiral information is not present in the substrate, however, it needs to be introduced. Modifying the substrate through covalent attachment of a chiral auxiliary has proven to be an immensely useful strategy; however in recent decades,

attention has increasingly focused on developing reagent-controlled processes, which offer a more general and atom-economical approach to asymmetric synthesis.

1.2.2 Asymmetric allylation of aldehydes

The reaction of allylsilanes with aldehydes is of prime importance in the synthetic chemist's arsenal of C–C bond-forming methodologies, as the secondary homoallylic alcohol product is particularly suitable for further transformations. Controlling the stereochemical outcome of this type of allylation reaction, in both an absolute (enantioselectivity) and relative (diastereoselectivity) sense, is integral for maximising its synthetic utility.

An example of a substrate-controlled allylation is that used by Trost *et al.* in the total syntheses of furaquinocin A and B (Scheme 2).[6] The side-chain core was introduced by reaction of allyltrimethylsilane with aldehyde **3** mediated by $TiCl_4$ and proceeded with high diastereoselectivity (d.r. 9:1). The desired homoallylic alcohol **4** could be obtained in pure form after purification by column chromatography (67% from **5**).



Scheme 2. Substrate-controlled allylation in the total syntheses of furaquinocin A and B.

The observed diastereoselectivity can be explained by the polar model proposed by Evans (Figure 2).[7,8] The Newman projection depicts the conformation that minimises the dipole moment in the molecule. The bottom face of the aldehyde is blocked toward the attack of the nucleophile by the *β*-methyl substituent.

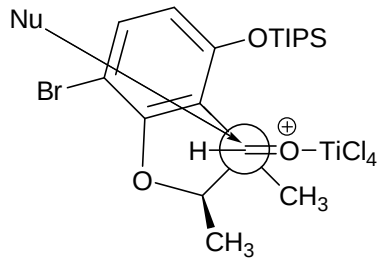
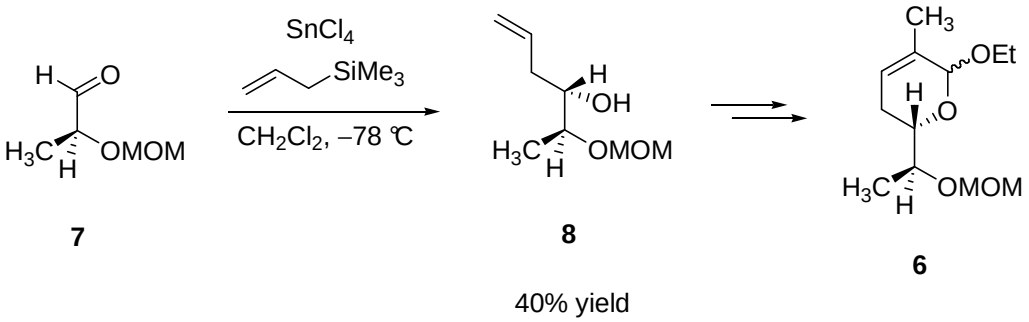


Figure 2. Evans' polar model explains the observed diastereoselectivity.

Williams used a chelation-controlled allylation in the synthesis of one of the building blocks **6** required for the total synthesis of (+)-4,5-deoxyneodolabelline (Scheme 3).[9] Aldehyde **7** was

reacted with allyltrimethylsilane in the presence of $SnCl_4$ to afford a single diastereoisomer **8** in 40% yield.



Scheme 3. Chelation-controlled allylation in the total synthesis of (+)-4,5-deoxyneodolabelline.

The chelation model explains the observed diastereoselectivity in this reaction (Figure 3). In the favoured conformation, chelation to tin holds the oxygen from the carbonyl group and the oxygen on the α-position close in space and the nucleophile attacks from the less hindered side.

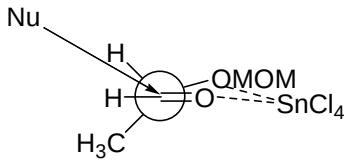
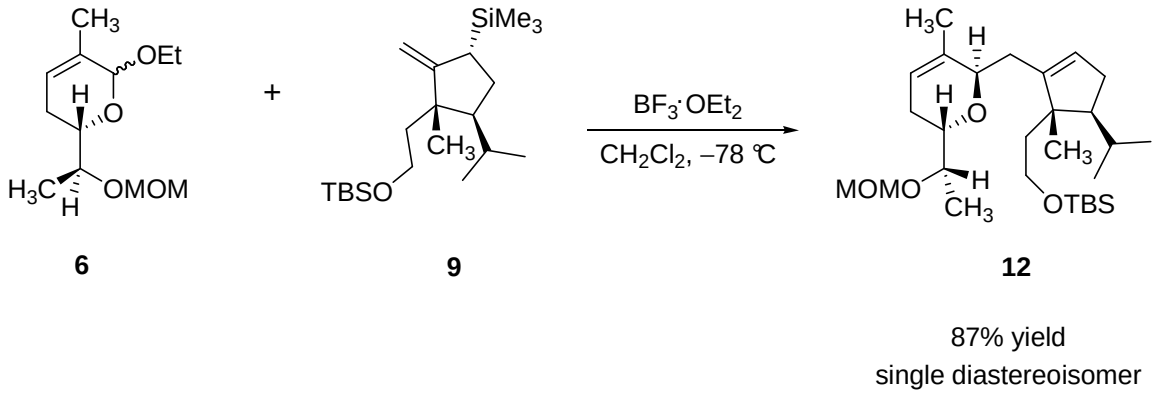


Figure 3. The chelation model explains the observed diastereoselectivity.

Another substrate-controlled allylation was utilised in the same publication when coupling the two building blocks **6** and **9** (Scheme 4). The reaction, activated this time by $BF_3{\cdot}OEt_2$, proceeded with complete diastereoselectivity in 87% yield.



Scheme 4. Substrate-controlled allylation in the total synthesis of (+)-4,5-deoxyneodolabelline.

An intensive study revealed that both anomers of the starting acetal were equally reaction-competent *via* a common oxacarbenium ion or rapid acetal isomerisation. Two conformers of the oxacarbenium intermediate were recognised and distinguished by the pseudoequatorial substituent in **10** and the pseudoaxial substituent in **11** (Figure 4). The stereoelectronically controlled axial attack of the allylsilane **9** on the more stable conformer **10** dominates the reaction coordinate leading to the observed product **12** *via* a developing chair-like transition state **13**.

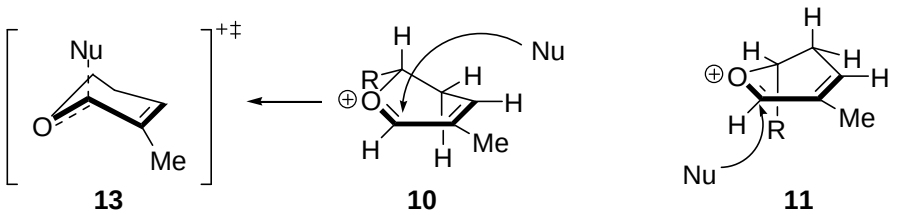
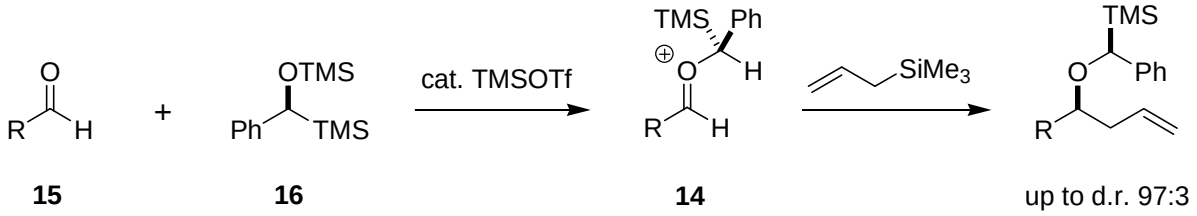


Figure 4. The two conformers of the oxacarbenium intermediate in coupling the two building blocks **6** and **9**.

Another way of controlling the stereochemistry of an allylation using allyltrialkylsilanes is to use a chiral auxiliary. Indeed this strategy was exploited in Rychnovsky's approach to the asymmetric allylation of aldehydes.[10,11] The group investigated the diastereoselective

addition of allyltrimethylsilane to oxacarbenium ion **14** which was generated *in situ* from a variety of aldehydes **15** and TMS-protected phenylsilylcarbinol **16** using Markó's protocol (cat. TMSOTf)[12] (Scheme 5).



Scheme 5. Asymmetric allylation of aldehydes using chiral auxiliary **16**.

The excellent diastereoselectivities observed in these reactions could be rationalised by Linderman's model,[13-16] which predicts (*E*)-oxacarbenium ion (*E*)-**14** as an intermediate in a well-defined conformation as the result of a stereoelectronic preference analogous to the *β*-silyl effect (Figure 5). This preferred conformation provides maximum overlap of the σ(C–Si) and π*(C=O) orbitals of the oxacarbenium ion. The nucleophile then adds to the face opposite to the bulky silyl group, resulting in the observed diastereoselectivities.

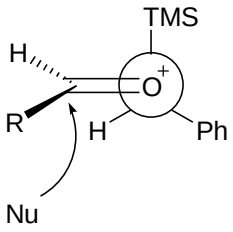
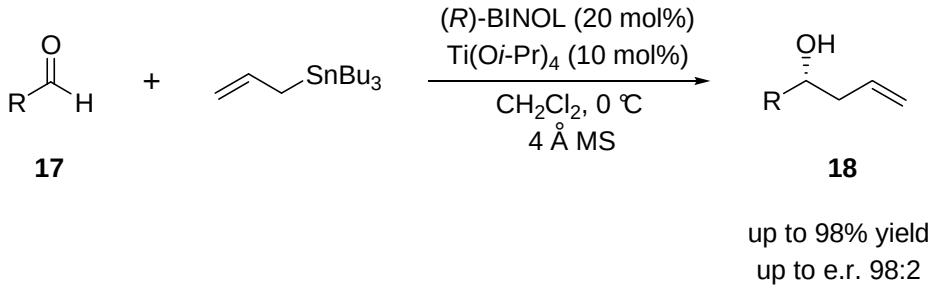


Figure 5. Linderman's model of (*E*)-oxacarbenium ion (*E*)-**14** adopting a well-defined conformation rationalises the observed diastereoselectivities.

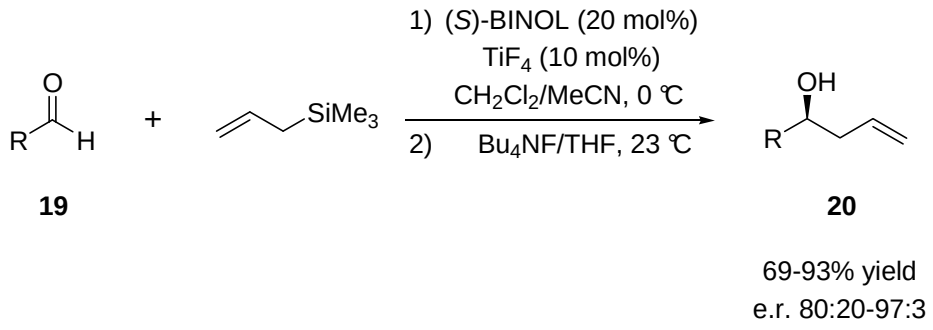
Reagent-controlled approaches provide the most powerful means for controlling the stereochemical outcome of a reaction. Since allylation reactions with allyltrimethylsilane

generally require an external source of activation, chiral metal-based Lewis acids have been the most effective way for controlling the enantioselectivity of this transformation. The metal-BINOL Lewis acids developed by Keck and Carreira provide important examples in this area. Keck developed the allylation of aldehydes **17** with allyltributylstannane using a (*R*)-BINOL/Ti(O*i*-Pr)$_4$ complex as the catalyst (Scheme 7).[17,18] The products **18** were obtained in high yields and enantioselectivities.



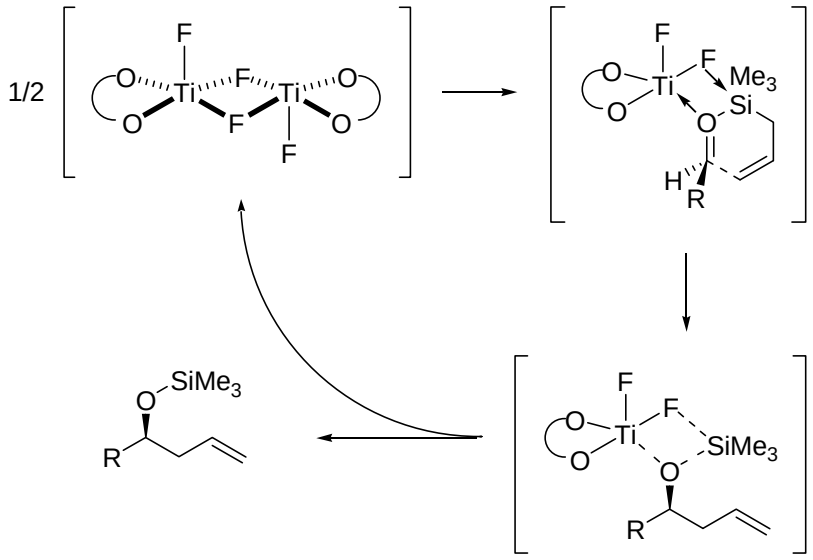
Scheme 7. Reagent-controlled asymmetric allylation of aldehydes by Keck.

Since the BINOL/Ti(IV) catalysts are relatively weak Lewis acids, they found little use for promoting reactions with the less nucleophilic (and less toxic) allylsilanes. An elegant solution to this problem was developed by Carreira, who found that enhanced reactivity could be secured by using TiF_4 instead of Ti(O^{i}Pr)$_4$ (Scheme 8).[19,20] The allylation of aldehydes **19** with allyltrimethylsilane employing (*S*)-BINOL/TiF_4 complex as the catalyst now led to products **20** in moderate to high yields with moderate to high enantioselectivities.



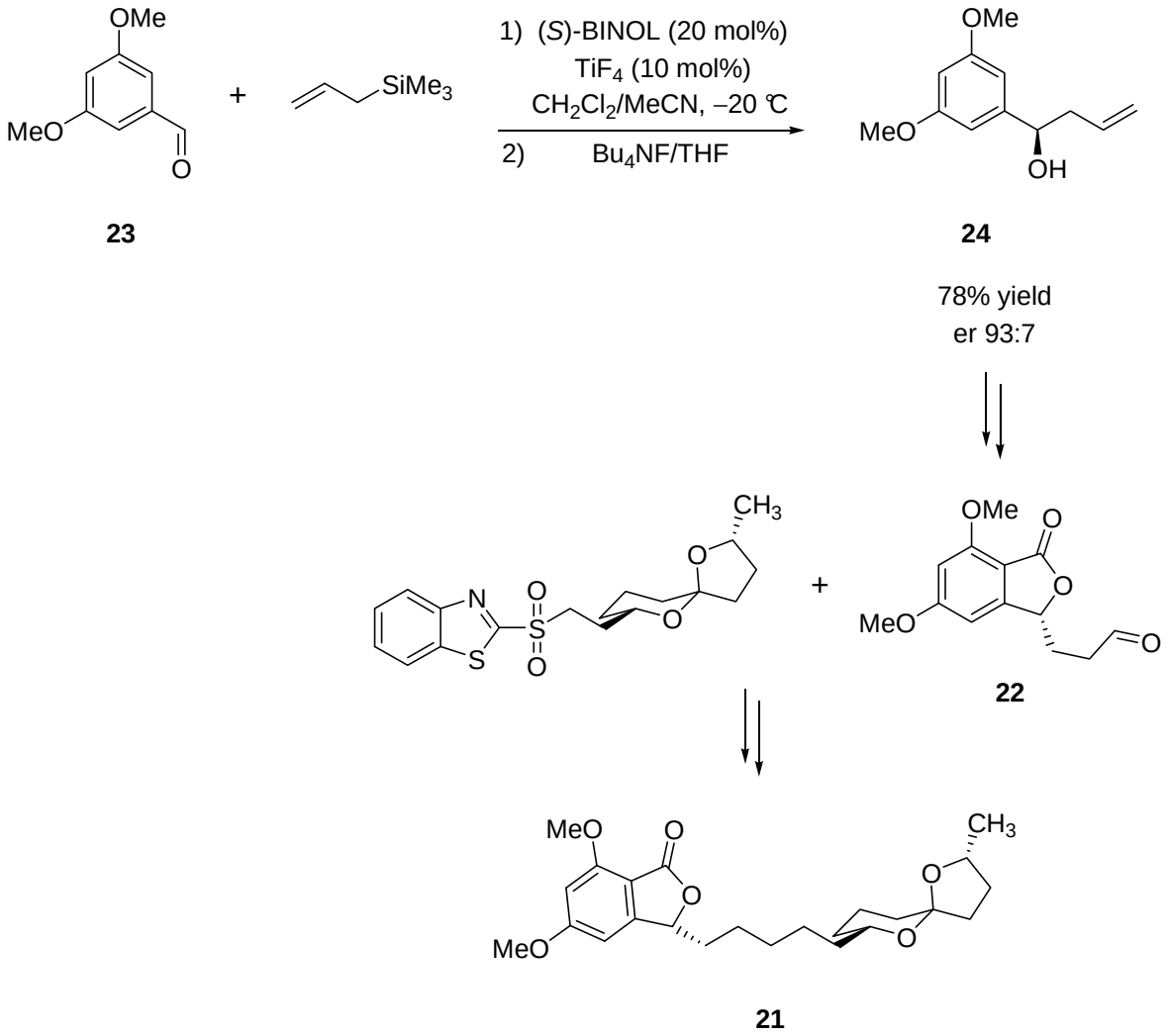
Scheme 8. Reagent-controlled asymmetric allylation of aldehydes by Carreira.

Carreira attributed the high reactivity of the catalyst to two important factors: i) the strong Lewis acidity of TiF_4-derived complexes and ii) the greater strength of the Ti–F bond compared to the Si–F bond which assists in catalyst turnover. In addition, Duthaler proposed a ternary transition structure in which the electrophilic titanium centre activates the aldehyde and a nucleophilic fluoride bridge to silicon increases the reactivity of the allylsilane (Scheme 9).[21] A reaction that proceeds through this transition structure could give the silylated adduct directly with concomitant regeneration of the catalyst.



Scheme 9. Duthaler's proposal of a ternary transition structure.

Carreira's method has found application in the total synthesis of the anti-*Helicobacter pylori* agent (+)-spirolaxine methyl ether **21** (Scheme 10).[22] The (3*R*)-stereochemistry in phthalide-aldehyde **22** was set up *via* asymmetric allylation of 3,5-dimethoxybenzaldehyde **23**, providing (*R*)-homoallylic alcohol **24** in 78% yield with 93:7 enantioselectivity.



Scheme 10. Reagent-controlled asymmetric allylation in the total synthesis of the anti-*Helicobacter pylori* agent (+)-spirolaxine methyl ether **21**.

This short overview gave examples for substrate-controlled allylations, which find particular application in the synthesis of complex molecules, as well as an example of a chiral auxiliary approach. The most common, and indeed most desirable, way for achieving an asymmetric allylation is to exploit reagent-control with chiral metal-based Lewis acids. Among the methods developed for simple allylation with Type II reagents, the addition of allyltributylstannane catalysed by the BINOL/Ti(IV) complexes has the broadest substrate scope and is therefore particularly useful in target-oriented synthesis.[23] The use of

allyltrimethylsilane is also possible if stronger Lewis acidic BINOL/Ti(IV) systems are employed.

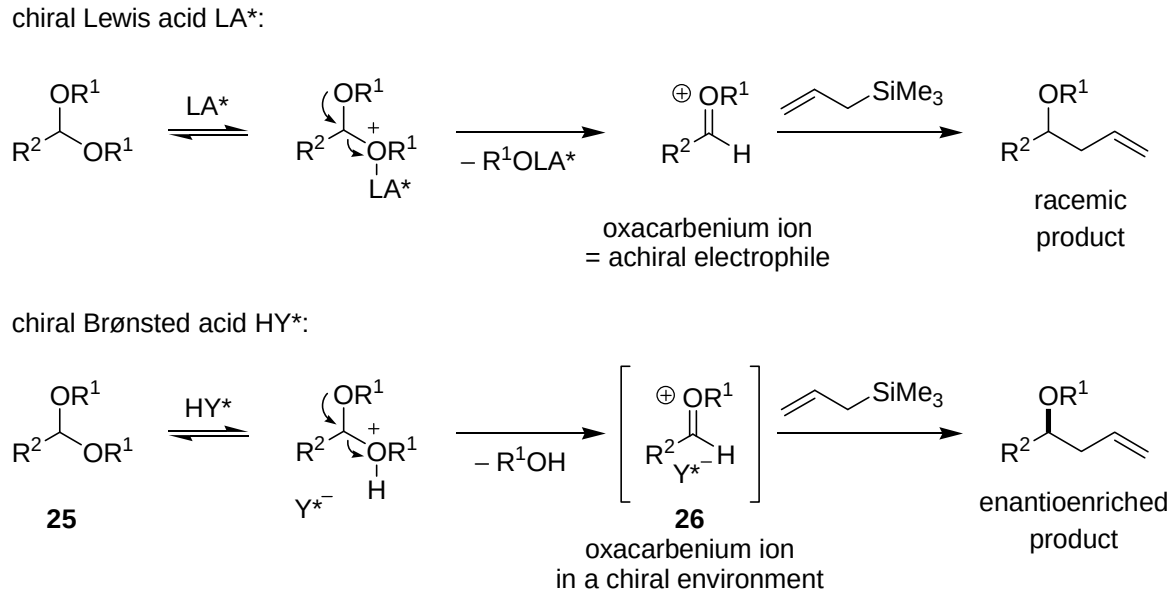
1.3 Allylation of acetals

1.3.1 Racemic allylation of acetals

Acetals are useful intermediates in organic synthesis and undergo coupling reactions with different nucleophiles *via* C–C bond formation.[24] Successfully used nucleophiles include silyl enol ethers,[25-31] allyl transfer reagents,[32] vinyl ethers,[33] as well as simple olefins[34-36] and cyanide sources.[37-44] A particularly valuable transformation is the already mentioned Hosomi–Sakurai reaction of acetals with allyltrimethylsilane,[45,46] which furnishes homoallylic ethers. Such protected homoallylic alcohols can simplify the synthetic planning in target-oriented synthesis. Catalysts, which have been employed for the racemic version of this transformation in sub-stoichiometric quantities, include Lewis acids such as $ReBr(CO)_5$,[47] $NbCl_5/AgClO_4$,[48] $AlBr_3/CuBr$,[49] $FeCl_3$,[50] TMSOTf,[51-53] $Bi(OTf)_3$,[54] $Sc(OTf)_3$,[55] $BiBr_3$,[56] $TMSNTf_2$,[57] $TMSN(SO_2F)_2$,[58] $TiCp_2(CF_3SO_3)_2$,[59] montmorillonite,[60] trityl perchlorate,[61] diphenylboryl triflate,[61] and TMSI.[62] Stoichiometric Lewis acidic activators, including $TiCl_4$,[63] $AlCl_3$,[64] $BF_3{\cdot}Et_2O$,[64-66] liquid SO_2,[67] and CuBr/microwave, have also been used.[68] Several of these methods suffer from drawbacks such as the involvement of compounds that are corrosive, difficult to handle, expensive, or toxic. Others require strictly anhydrous conditions or less practical reaction temperatures. Brønsted acids offer a useful alternative to these metal-based activators, and have great potential as easily tunable, economic, and environmentally acceptable catalysts. Surprisingly, the use of Brønsted acids in this important allylation has only been reported in a few recent publications.[69-71]

1.3.2 Hypothesis for an asymmetric allylation of acetals

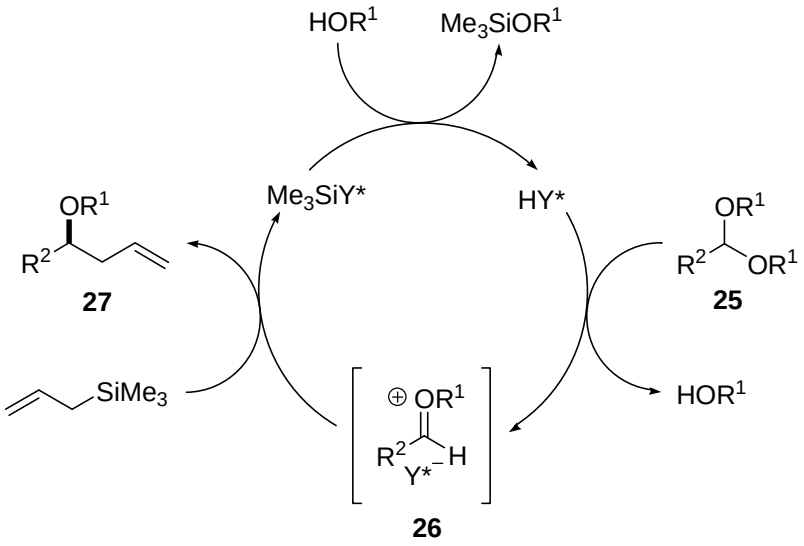
Chiral metal-based Lewis acids have to-date been the most effective means for controlling the enantioselectivity of the asymmetric allylation of carbonyl compounds. However, my supervisor and me hypothesised that they are not applicable to the asymmetric allylation of acetals, since the activator is not a component of the oxacarbenium ion, which is the active electrophile in this important variant of the allylation reaction (Scheme 11). Since Brønsted acids also mediate this type of allylation reaction, I hypothesised that a *chiral* Brønsted acid HY* has the potential to impart stereoselectivity on this bond-forming process (Scheme 11). So far, no examples exist of chiral Brønsted acids catalysing the intermolecular allylation of acetals. Analogously to Lewis acid activation, protonation of the acetal **25** and displacement of R^1OH through anchimeric assistance from the adjacent alkoxy group provides the active oxacarbenium ion electrophile **26**.[72-74] In the case of Lewis acid activation, the chiral information is carried away in the alkoxy leaving group; however, this is not necessarily the case when a chiral Brønsted acid is employed since the chirality is now embedded in the conjugate base, Y^{*-}, which will be associated with the positively charged oxacarbenium ion electrophile.



Scheme 11. Whilst chiral Lewis acids do not effect the asymmetric allylation of acetals, a chiral Brønsted acid potentially can.

Of course, the nature of this ion pair **26** will depend critically on the reaction environment. There are three different types of ion pairs.[75,76] In a contact ion pair (or tight ion pair) the two ions of opposite charge are in contact, with no solvent molecules between them. In a solvent-separated ion pair (or loose ion pair) the two ions are more separated from each other, with a small number of solvent molecules between them; however they are still held together by coulombic attraction. The ions are considered to be completely dissociated if the solvent radius is large enough so as not to allow any coulombic attraction between the two ions. A contact ion pair will maximise the opportunity for the chirality embedded in the associated anion to differentiate the enantiotopic faces of the oxacarbenium ion; non-coordinating solvents of low dielectric constant, such as CH_2Cl_2 and even better, cyclohexane and toluene, which have been used for allylation reactions, should encourage this. Indeed this has been exploited in Rychnovsky's chiral auxiliary approach to asymmetric allylation of acetals, where the highest selectivities were observed under conditions that produce tight ion pairs.[10,11]

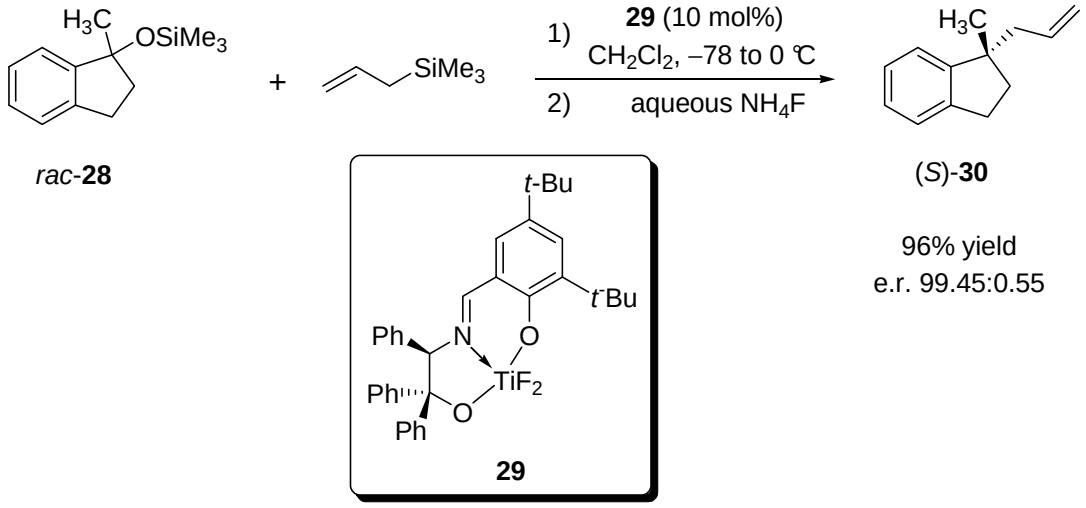
Another point which needs to be considered is catalyst turnover. My supervisor and me hypothesised that the alcohol leaving group will allow catalyst turnover and permit the use of sub-stoichiometric quantities of the catalyst (Scheme 12). Acetal **25** is protonated by the chiral Brønsted acid HY* and forms an intermediate chiral ion pair **26**, involving the oxacarbenium ion and the conjugate base, after displacement of alcohol R^1OH. Allyltrimethylsilane attacks the electrophile in the chiral environment to release the enantioenriched homoallylic ether **27**. The silylated conjugate base reacts with alcohol R^1OH to give silylether Me_3SiOR^1 and the regenerated chiral Brønsted acid HY*. A strong driving force of this reaction is the thermodynamic strength of a Si–O bond because on pK_a grounds the equilibrium lies on the side of R^1OH and Y^{*-} instead of R^1O^- and HY*. Indeed, this catalytic cycle has been described already for the use of achiral Brønsted acids by List.[69]



Scheme 12. Catalytic cycle for employing a chiral Brønsted acid in sub-stoichiometric quantities.

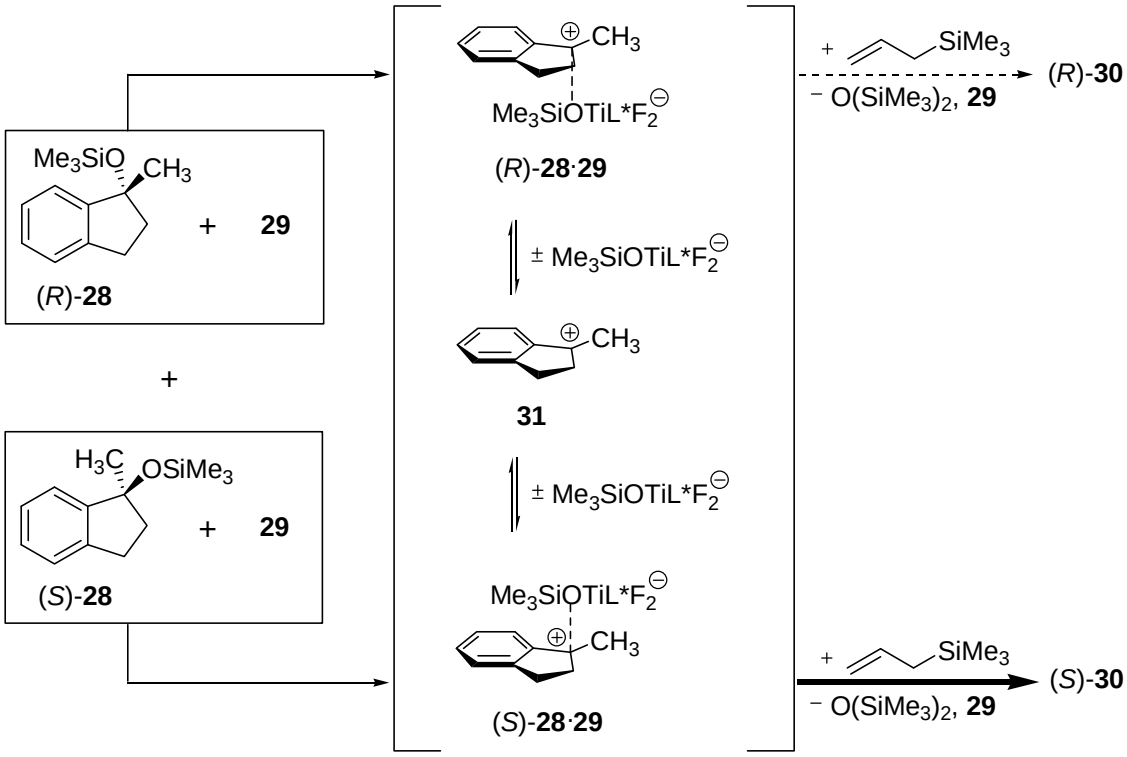
To the best of my knowledge there is no literature example of chiral Brønsted acids catalysing the enantioselective intermolecular allylation of acetals and only one example where a chiral Lewis acid catalyst has successfully controlled the enantioselectivity of an allylation with

allyltrimethylsilane involving a planar, achiral carbenium ion.[77] Braun discovered the asymmetric allylation of silyl ether *rac*-**28** catalysed by the chiral titanium complex **29** (Scheme 13). The product (*S*)-**30** was obtained in 96% yield with 99.45:0.55 enantioselectivity.



Scheme 13. The only example where a *chiral Lewis acid* controls the intermolecular allylation involving an achiral intermediate.

The essentially complete conversion of the racemic substrate *rac*-**28** into the allylation product (*S*)-**30** was rationalised as a dynamic kinetic asymmetric transformation (Scheme 14): First, it is assumed that the chiral Lewis acid **29** and both enantiomers of the silyl ether **28** form two diastereomeric contact ion pairs, (*R*)-**28**·**29** and (*S*)-**28**·**29**. They rapidly equilibrate *via* the planar, achiral carbenium ion **31**. In the subsequent reaction with allyltrimethylsilane, one of the ion pairs, (*S*)-**28**·**29**, is postulated to react faster than its diastereomer (*R*)-**28**·**29**. Presumably, the allyl residue attacks the indanyl cation from the face that is not occupied by the titanium residue.



Scheme 14. Braun's allylation is a dynamic kinetic asymmetric transformation.

1.4 Organocatalysis

1.4.1 Chiral BINOL-based Brønsted acids

The area of chiral Brønsted acids has grown strongly within organocatalysis and is now able to deliver extremely active catalysts.[78-84] Chiral Brønsted acids can be classified into three categories (Figure 6):

i) neutral Brønsted acids, such as thiourea (pK_a ~ 21)[82] and TADDOL (pK_a ~ 20)[85] derivatives. The characteristic mode of activation of this class of acid involves a single or double hydrogen bond (H-bond) to the substrate; in these cases, the proton is still bound to the catalyst.

ii) stronger Brønsted acids, which include phosphoric acids (pK_a ~ 1.4)[86] and phosphoramides (pK_a < 1.4)[87,88] derived from BINOL. The characteristic mode of activation for this class of acid likely involves a more complete transfer of a proton to the substrate potentially leading to an ion pair in the case of the more acidic phosphoramides. Depending on the reaction, phosphoric acids are able to transfer their proton completely or still form a weak O---H bond.

iii) neutral Brønsted acids, such as BINOL derivatives (pK_a ~ 10).[1] Since these acids are weakly acidic, they can be classified somewhere between H-bond catalysis and stronger Brønsted acid catalysis.

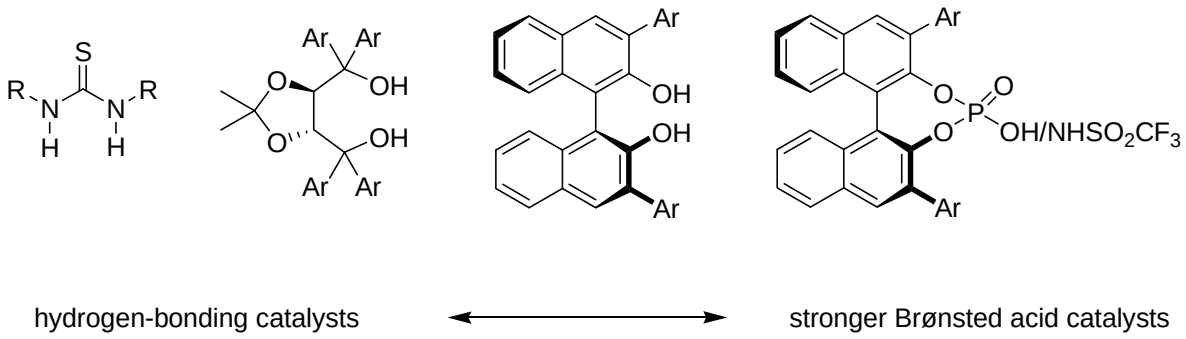
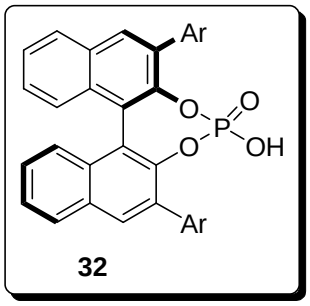


Figure 6. Chiral Brønsted acids.

[1] derived from p*Ka*(phenol)~10

In early 2004, Akiyama[89] and Terada[90] independently introduced the chiral phosphoric acids **32** (Figure 7).



32a: Ar = 4-$NO_2C_6H_4$
32b: Ar = 4-β-naphthyl-C_6H_4
32c: Ar = 2,4,6-(*i*-Pr)$_3C_6H_2$
32d: Ar = 1-naphthyl
32e: Ar = *t*-BuC_6H_4
32f: Ar = Ph

Figure 7. Chiral phosphoric acids **32**.

Only the enantiomerically pure 3,3'-unsubstituted compound **33** was known at that time. Apart from employing **33** as a chiral resolving agent,[91] Inanaga *et al.* had used its lanthanide salt as a catalyst for hetero Diels-Alder reactions.[92] Phosphoric acids **32** attracted the attention of synthetic organic chemists for several reasons (Figure 8):

i) they are bifunctional catalysts bearing both a Brønsted-acidic site (O–H) and a Lewis-basic site (P=O).

ii) the 3,3'-substituents can play a crucial role in realising high enantioselectivity and can be varied depending on the respective substrate/reaction.

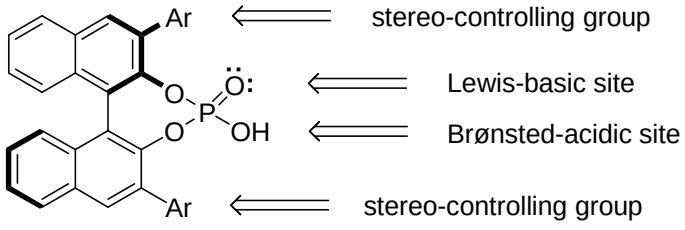
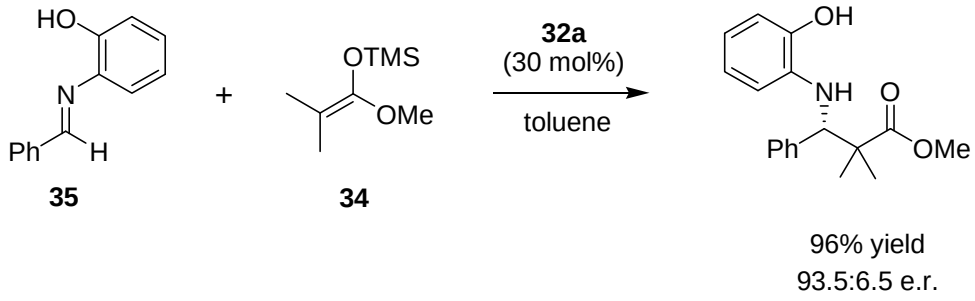


Figure 8. Functional chiral phosphoric acids.

Akiyama and co-workers presented the Mannich-Type reaction of ketene silyl acetals **34** with aldimines **35** in the presence of various chiral phosphoric acids **32** (Scheme 15).[89] While 3,3'-unsubstituted **33** gave a racemic mixture, **32a** bearing 4-nitrophenyl groups at the 3,3'-positions led to 96% yield and 93.5:6.5 e.r.



Scheme 15. Akiyama's asymmetric Mannich-Type reaction of silyl ketene acetals **34** with aldimines **35** catalysed by chiral **32a**.

On the basis of experimental results (the *o*-hydroxy group in the aldimines is essential to realise excellent enantioselectivity) and DFT calculations, the reactions proceeds *via* the nine-membered zwitterionic cyclic transition-state **36** (Figure 9).[93] There is a dicoordination between the aldimine and the phosphoric acid due to the bifunctionality of the catalyst. The nine-membered cyclic structure and the aromatic π-stacking interaction between the 4-nitrophenyl group and the *N*-aryl group fix the geometry of the aldimine in the transition state. The 3,3'-aryl substituents lead to a sterically hindered *si*-face ensuring nucleophilic attack proceeds on the *re*-face.

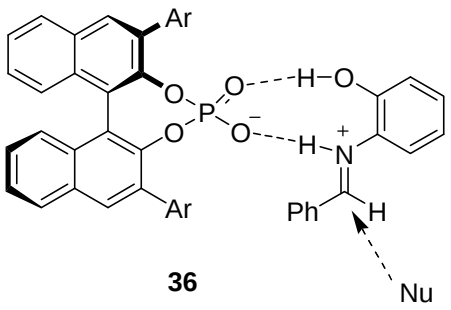
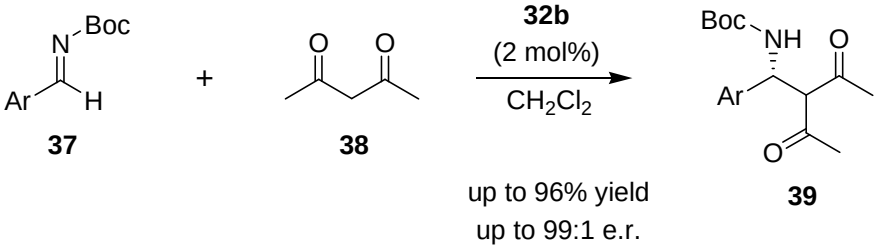


Figure 9. Proposed nine-membered zwitterionic cyclic transition-state **36** between phosphoric acid and aldimine substrate.

Terada and Uraguchi also reported a Mannich-type reaction.[90] Aldimines **37** react with 2,4-pentandione **38** in the presence of chiral catalyst **32b** providing β-aminoketones **39** in excellent yields and enantioselectivities (Scheme 16).



Scheme 16. Terada's asymmetric Mannich-Type reaction of 2,4-pentandione **38** with aldimines **37** catalysed by chiral **32b**.

They used computational and NMR analyses to rationalise the observed enantioselectivities.[94] Preliminary computational results show that the exothermic formation of associates between the chiral phosphoric acid and the imine substrate is sterically controlled by the bulky substituents of the catalyst. The activation of the substrate happens *via* a H-bond between the N-atom of the imine and the acidic H-atom of the catalyst which allows the substrate to accommodate itself in only two different ways using either of the two otherwise equivalent oxygen atoms (Figure 10).

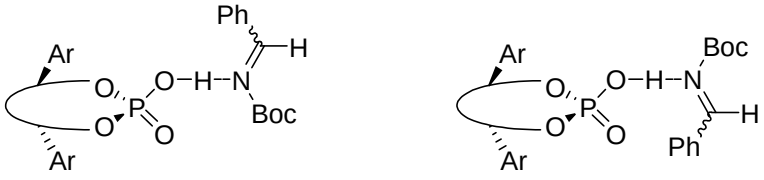


Figure 10. The H-bond between the imine and the catalyst allows two lowest conformations.

Furthermore, the isomerisation of the more stable *E*-aldimine into its *Z*-isomer (which could be the one reacting faster in the transition state as shown by Jacobsen)[95] needs to be considered. A detailed analysis of the four different conformations of the H-bond associates

revealed that only the one presented in Figure 11 makes the imine susceptible to the enantioselective nucleophilic attack.

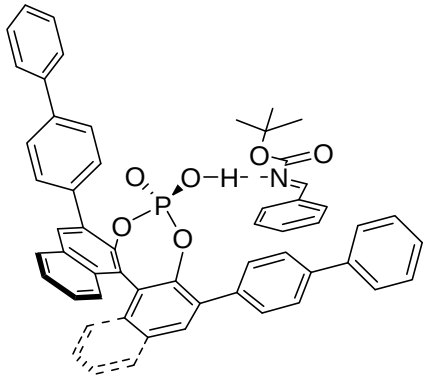


Figure 11. Conformation which makes the imine susceptible to the enantioselective nucleophilic attack.

The sterically bulky *t*-Bu group in the imine acts like an anchor preventing the free rotation around the H-bond, thus ensuring the high order of the enantioselection as shown by the drop of e.r. with smaller protecting groups.

In a very recent set of publication, Goodman has developed a model, based on DFT calculations, which predicts the correct enantioselectivity of imine reactions catalysed by BINOL-based phosphoric acids.[96] He rationalised the different factors on which the enantioselectivity depends, focusing on the *E*- or *Z*-preference of the transition structures and the orientation of the catalyst with respect to the electrophile (Type I and Type II reaction). Application of the model to the above reaction would predict a (Type I, *E*)-transition state which indeed accounts for the observed enantioselectivity as shown in Figure 12.

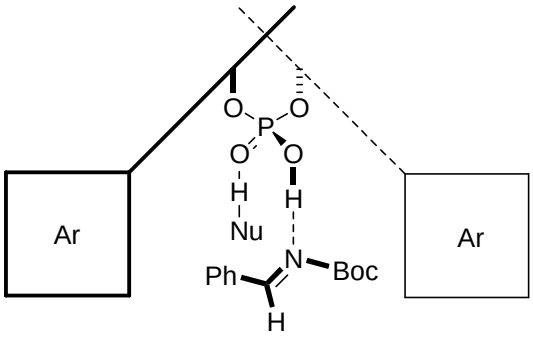


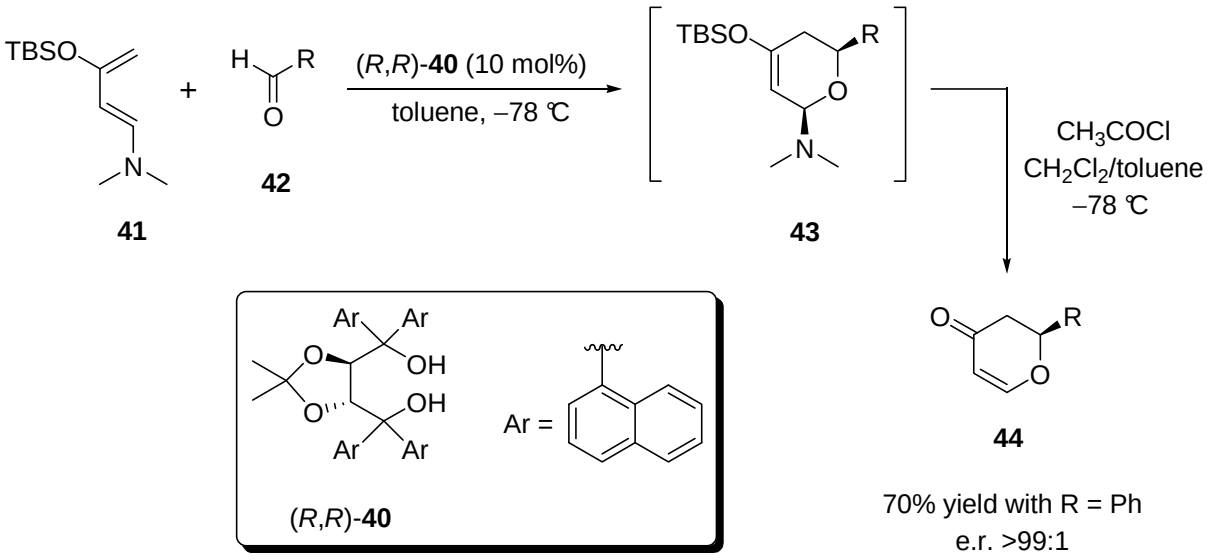
Figure 12. Goodman's model predicts the correct enantioselectivity.

A great number of publications employing various chiral phosphoric acids **32** has followed these pioneering studies.[82,97-99] In the beginning, a common feature of the reactions catalysed by these catalysts has been an imine as the substrate. More recently, synthetic organic chemists have started to investigate the activation of carbonyl compounds which will be described in the next Chapter.

1.4.2 Organocatalytic activation of carbonyl compounds

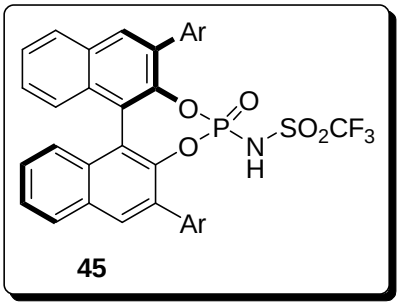
Carbonyl compounds play a central role in a diverse array of organic reactions. In particular, the activation of aldehydes for further reaction represents one of the most important strategies for employing this functional group in synthesis, and in particular enantioselective synthesis.[100] The following summary mainly contains carbonyl compounds as electrophiles which are activated by either ester- or trifluoromethyl substituents. A phosphoric acid as catalyst is acidic enough to induce reaction with these more reactive electrophiles. For non-activated carbonyl compounds more acidic Brønsted acids like phosphoramides or thiophosphoramides are usually necessary.

The activation of carbonyl compounds by using a chiral Brønsted acid was first reported by Rawal and co-workers, who performed a hetero Diels-Alder reaction in the presence of a sub-stoichiometric amount of (*R*,*R*)-1-naphthyl TADDOL (*R*,*R*)-**40** (Scheme 17).[101] 1-Amino-3-siloxy diene **41** was reacted with a range of aldehydes **42** and the resulting cycloadducts **43** were converted into dihydropyrones **44** in good overall yields and high enantioselectivities (e.r. >99:1).



Scheme 17. Rawal's hetero Diels-Alder reaction catalysed by TADDOL (*R*,*R*)-**40**.

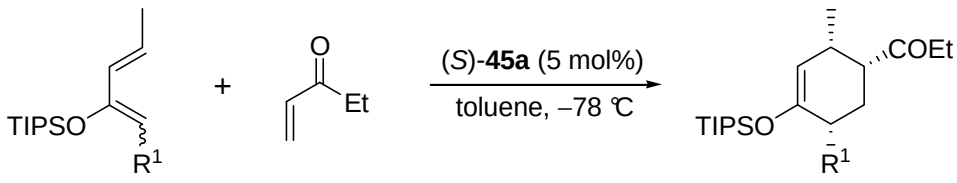
BINOL-derived phosphoric acids and phosphoramides have been scarcely explored in the activation of carbonyl compounds. In 2006, Yamamoto introduced the highly reactive and acidic chiral *N*-triflyl phosphoramide Brønsted acid catalysts **45** (Figure 13).



45a: Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$
45b: Ar = 9-phenanthryl
45c: Ar = 4-MeOC$_6$H$_4$

Figure 13. Chiral *N*-triflyl phosphoramides **45**.

He employed the 2,4,6-triisopropylbenzene-substituted derivative (*S*)-**45a** in an asymmetric Diels-Alder reaction of *α*,*β*-unsaturated ethyl vinyl ketone **46** with silyloxydienes **47** (Scheme 18).[87] In most cases, the *endo* Diels-Alder adducts **48** were obtained quantitatively with high enantioselectivities (up to 96:4 e.r.).



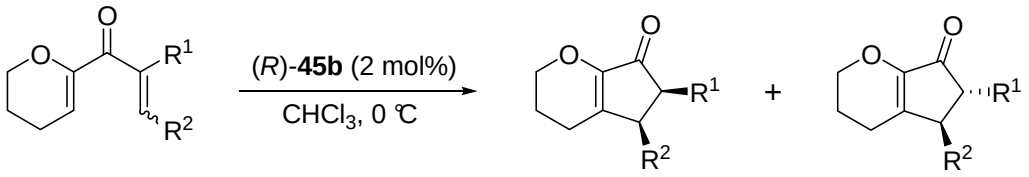
47 **46** **48**

up to >99% yield
up to 96:4 e.r.

Scheme 18. Yamamoto's Diels-Alder reaction of *α*,*β*-unsaturated ethyl vinyl ketone **46** with silyloxydienes **47** catalysed by (*S*)-**45a**.

The activation of carbonyl compounds was subsequently expanded by Rueping *et al.* who reported the asymmetric Nazarov cyclisation of dienones **49** catalysed by *N*-triflyl phosphoramide (*R*)-**45b** (Scheme 19).[102] This method provides the corresponding

cyclopentenones **50** in good yields and with excellent enantioselectivities for the *cis* as well as the *trans* product.

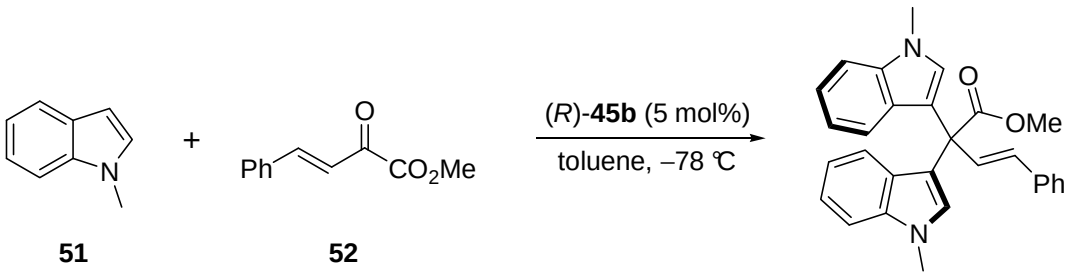


49 **50**

up to 92% yield
up to 9.3:1 *cis*:*trans*
up to 96:4 e.r.(*cis*)
up to 98:2 e.r.(*trans*)

Scheme 19. Rueping's Nazarov cyclisation of dienones **49** catalysed by (*R*)-**45b**.

One year later, the same group published an asymmetric Friedel-Crafts alkylation of indoles, also catalysed by *N*-triflyl phosphoramide (*R*)-**45b**.[103] In the reaction of *N*-methylindole **51** with *α*-keto ester **52**, a variety of *N*-triflyl phosphoramides gave mainly bisindole **53** with the highest atropisomeric ratio being 81:19 (Scheme 20). Two molecules of indole added to the *α*-keto group, the first in a 1,2-addition to the enone contained in *α*-keto ester **52**, and the second in an overall nucleophilic substitution of the resulting hydroxyl group.

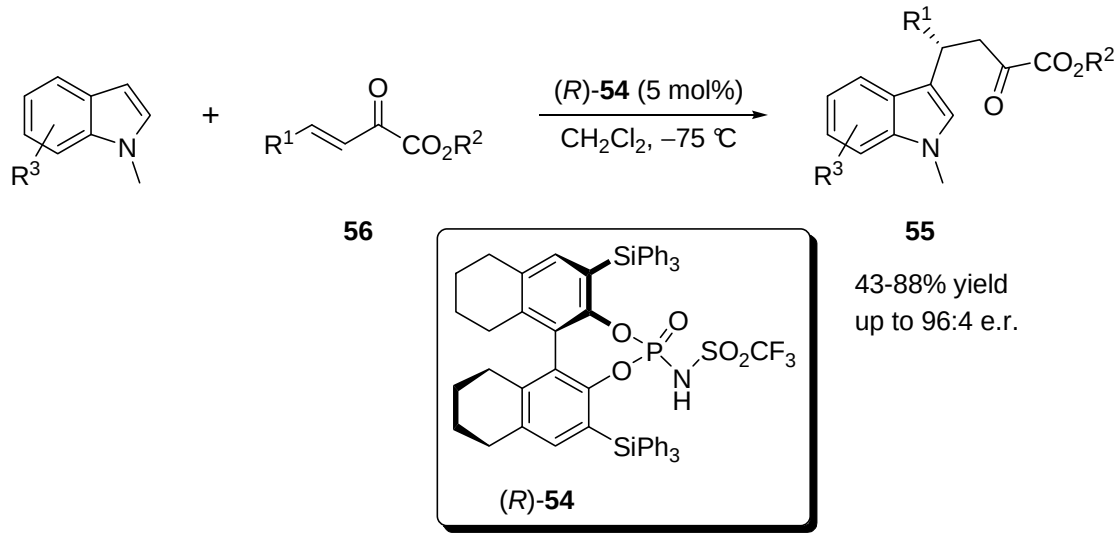


51 **52** **53**

atropisomeric ratio 81:19

Scheme 20. A variety of *N*-triflyl phosphoramides (*R*)-**45b** gave bisindole **53** in the Friedel-Crafts alkylation of *N*-methylindole **51**.

Interestingly, employing catalyst (*R*)-**54** led to the predominant formation of the 3-substituted indole product **55** resulting from a highly enantioselective 1,4-addition to **56** (Scheme 21). The authors reasoned this may be attributed to the steric properties of the catalyst. The 3,3'-C–Si bond is longer than the corresponding C–C bond in catalysts (*R*)-**45**, and the spherically arranged phenyl groups on the silicon atoms increase the steric demand at the catalytically active centre, resulting in better shielding of the carbonyl groups in the activation process, which gives rise to the regioselective 1,4-addition of indole.

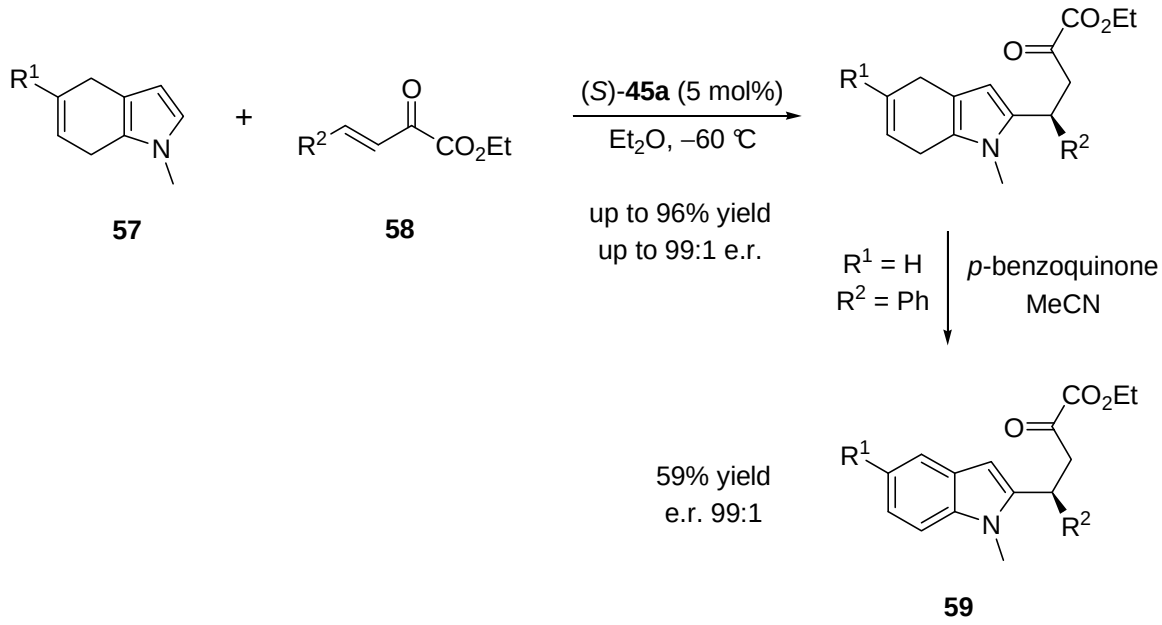


Scheme 21. (*R*)-**54** led to the 3-substituted indole product **55** resulting from a 1,4-addition to **56**.

This publication was followed by three other examples on the Friedel-Crafts reaction of indoles. Activation of carbonyl compounds by chiral Brønsted acids afforded a range of 2- and 3-substituted indoles.

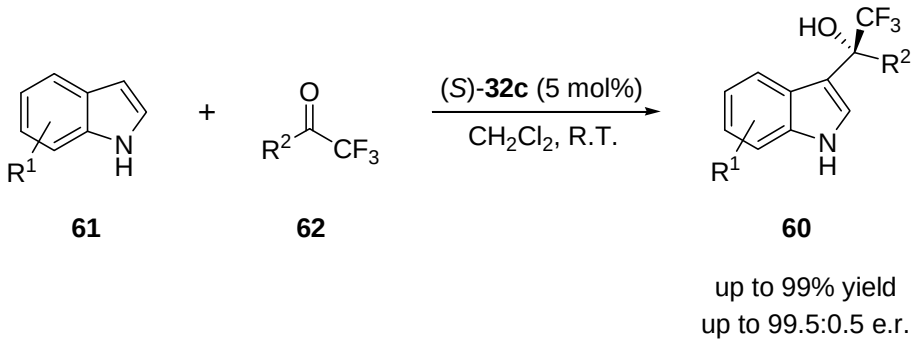
The work of You and co-workers opened the door to enantiopure 2-substituted indole derivatives, which hitherto had been difficult to access by catalytic asymmetric synthesis.[104] They developed the Friedel-Crafts alkylation of 4,7-dihydroindole **57** with β,γ-unsaturated α-keto esters **58**. The reaction was catalysed by *N*-triflyl phosphoramide (*S*)-**45a** and proceeded

in a highly enantioselective manner (up to 99:1 e.r.) (Scheme 22). Subsequent oxidation of the products with *p*-benzoquinone led to 2-alkylated indole derivatives **59** with perfect retention of the stereochemistry.



Scheme 22. You's route to enantiopure 2-substituted indole derivatives **59**.

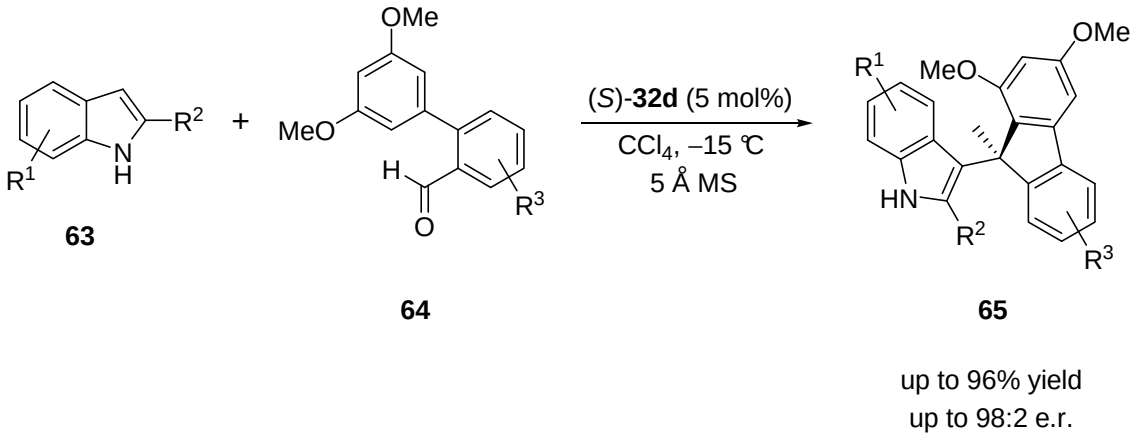
Ma *et al.* reported the asymmetric synthesis of trifluoromethyl-substituted tertiary alcohols **60** by the reaction of indole derivatives **61** with aryl trifluoromethyl ketones **62** (Scheme 23).[105] The CF_3 group, with its electron-withdrawing ability, improved the reactivity of substrates and allowed the less acidic phosphoric acid (*S*)-**32c** to be the catalyst of choice.



Scheme 23. Ma's synthesis of trifluoromethyl-substituted tertiary alcohols **60**.

In contrast to Rueping's publication[103] (see above), the reaction stops at the tertiary alcohol. A plausible explanation for this is given by DFT calculations showing that Brønsted acid-catalysed OH activation would be difficult due to an apparent shortening of the C–O bond in comparison to its non-fluorinated analogue (CF_3 = CH_3). The consequence is a suppression of further arylation of the alcohol products by another indole molecule.

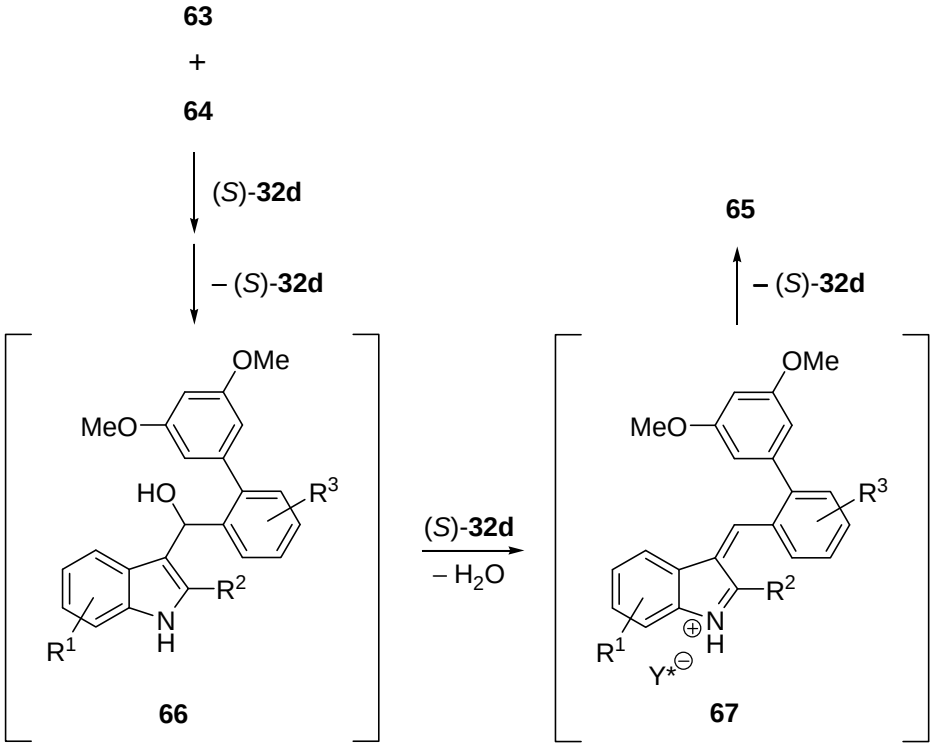
In another publication from You *et al.*, the chiral phosphoric acid (*S*)-**32d** catalysed the tandem double Friedel-Crafts reaction of indoles **63** with 2-formylbiphenyl compounds **64**, affording fluorene derivatives **65** with high enantioselectivity (up to 98:2 e.r.) (Scheme 24).[106]



Scheme 24. You published the tandem double Friedel-Crafts reaction of indoles **63** with 2-formylbiphenyl compounds **64** catalysed by (*S*)-**32d**.

The use of more reactive aldehydes allows the less acidic phosphoric acid (*S*)-**32d** to promote the first Friedel-Crafts reaction (Scheme 25). The secondary alcohol **66** is unstable under the reaction conditions and undergoes loss of H_2O to form a contact ion pair **67,** in which the chiral phosphate counteranion creates a chiral environment to differentiate the enantiotopic

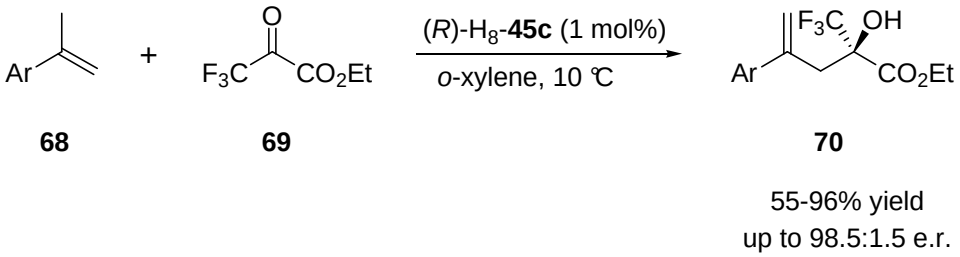
faces of the 3-benzylidene-3*H*-indolium cation in the second Friedel-Crafts reaction. Rearomatisation gives fluorene product **65** and regenerates (*S*)-**32d**.



Scheme 25. The reaction proceeds *via* contact ion pair **67**.

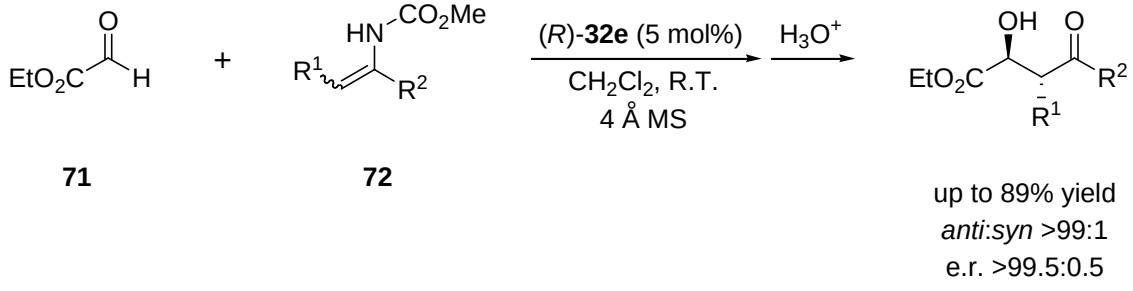
Only a few months after their work on 3-substituted indoles, Rueping *et al.* published a highly enantioselective organocatalytic carbonyl-ene reaction (Scheme 26).[107] Similar to the allylation of aldehydes, this reaction is an important C–C bond-forming process for the preparation of synthetically valuable homoallylic alcohols. A broad range of styrene derivatives **68** were reacted with trifluoropyruvate **69** to afford *α*-hydroxyesters **70** in good yields (55-96%) and with excellent enantioselectivities (up to 98.5:1.5 e.r.). Only 1 mol% of phosphoramide (*R*)-H_8-**45c** was necessary to mediate the reaction of the highly reactive carbonyl starting material **69**. The structure of the chiral Brønsted acids was also described for the first time in this publication and demonstrated that the catalyst which was put into the

reaction is the protonated *N*-triflyl phosphoramide and not the corresponding salt (a detailed discussion of the nature of the catalyst is described in Chapter 3.1).



Scheme 26. Rueping's enantioselective carbonyl-ene reaction.

The first example of the activation of carbonyl compounds by chiral *phosphoric acids* was described by Terada *et al*. in early 2008.[108] They reported the activation of glyoxylate **71** for an aza-ene-type reaction with ene-carbamates **72** which proceeded in a highly enantio- and diastereoselective manner (Scheme 27).



Scheme 27. Terada's aza-ene-type reaction of glyoxylate **71** with enecarbamates **72** catalysed by (*R*)-**32e**.

DFT computational analysis of the complexation modes demonstrated that a double hydrogen bonding interaction between the phosphoric acid and the glyoxylate is crucial in providing the high enantioselectivity (Figure 14). The hydrogen bond between the formyl hydrogen atom and the phosphoryl oxygen atom forces a coplanar orientation of the formyl group and the

phosphoric acid sub-unit, which results in one enantiotopic face of the aldehyde being effectively shielded by one of the phenyl groups. In contrast, the other face is fully accessible to attack by the enecarbamate.

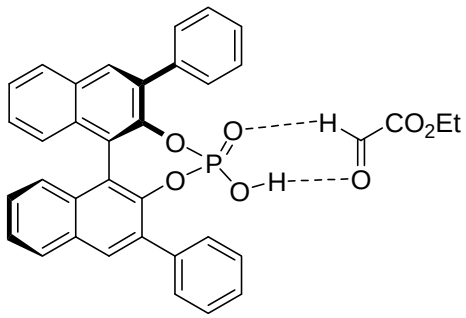
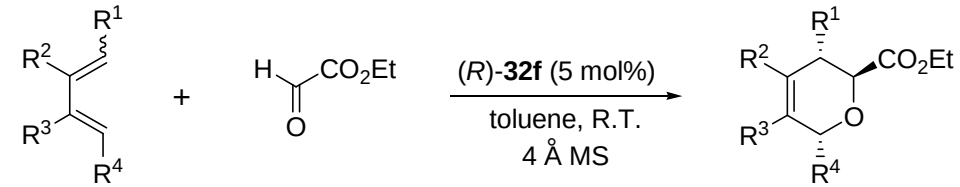


Figure 14. DFT computational analysis demonstrates the importance of double hydrogen bonding interaction between the phosphoric acid and the glyoxylate.

One year later, the same group published the highly enantio- and *anti*-selective hetero Diels-Alder reaction between glyoxylate **71** and siloxy- or methoxydienes **73** catalysed by chiral phosphoric acid (*R*)-**32f** (Scheme 28).[109] The *anti*-dihydropyran products **74** (d.r. >99:1) were obtained in good yields (51-95%) and with excellent enantioselectivity (all examples greater than 97.5:2.5 e.r.).



73

R^2 = OTBS
R^4 = OMe

71

74

51-95% yield
anti:*syn* >99:1
e.r. >97.5:2.5

Scheme 28. Terada's hetero Diels-Alder reaction between glyoxylate **71** and dienes **73** catalysed by (*R*)-**32f**.

It is noteworthy that for this type of reaction, only chiral Lewis acids (e.g. enantiomerically pure BINOL complexed with Ti(O*i*-Pr)$_4$ and tridentate Schiff base ligands complexed with Ti(O*i*-Pr)$_4$)[110] had been used previously to provide high levels of stereoselectivity, albeit with a *syn* relationship between the vicinal substituents of the dihydropyran. When $BF_3 \cdot OEt_2$ was employed in this Diels-Alder reaction, the diastereoselectivity dropped to 1:1. This result indicates that i) the secondary orbital interactions are weak in this hetero-Diels-Alder reaction and ii) the steric demand of the catalyst seems to be the dominant factor in increasing the *syn* selectivity. The last consideration was supported by the fact that incorporating bulkier groups than the phenyl substituent, such as 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$-substituents on the 3,3'-positions of the catalyst, led to a significant reduction in selectivity in favour of the *syn* diastereoisomer. Two plausible transition-state structures were reported where the *endo* orientation is not favourable because of the steric repulsion between the diene substituents and the glyoxylate (Figure 15).

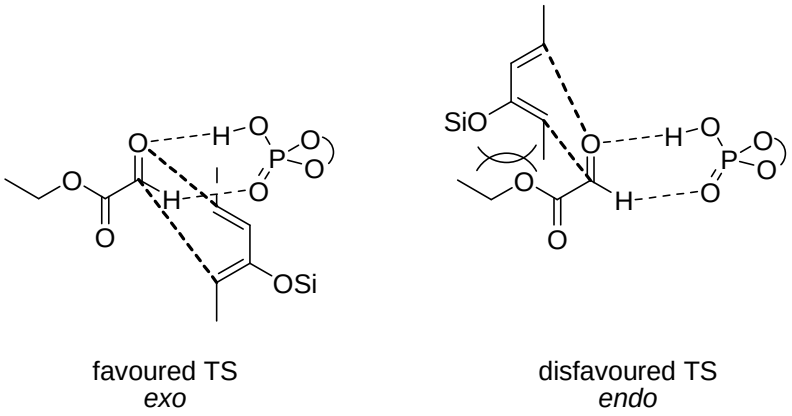
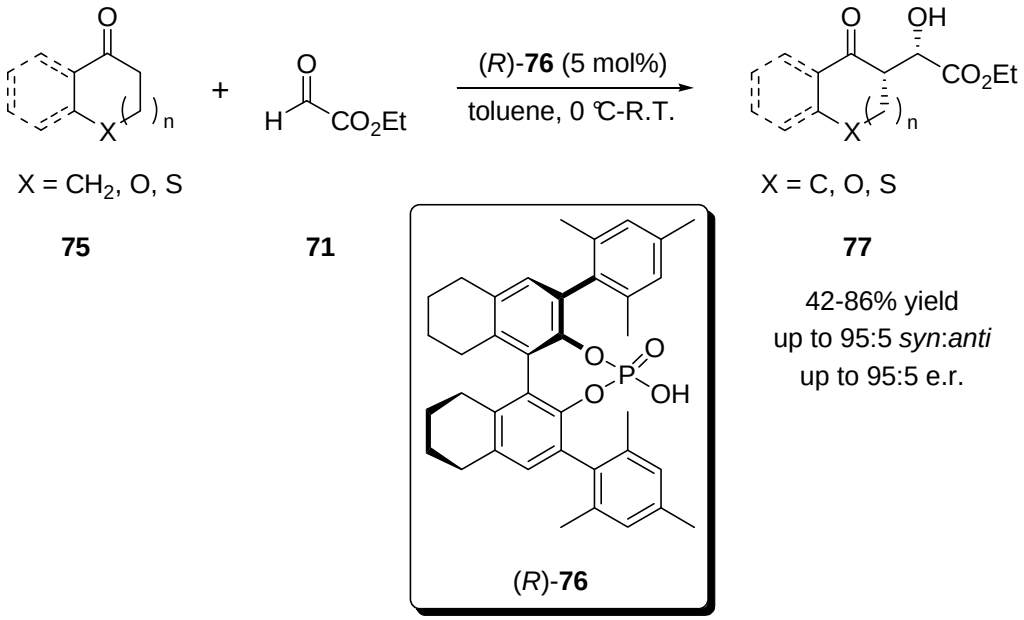


Figure 15. In the transition state the *exo* orientation is favoured over the *endo* one.

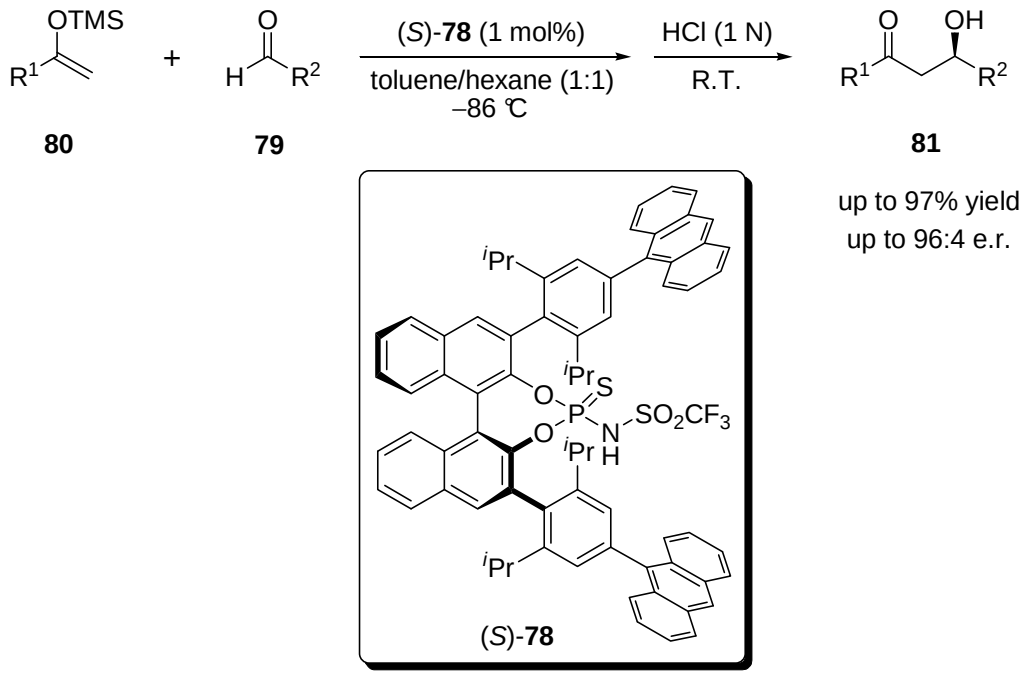
The following two examples describe the first aldol reactions where chiral phosphoric acids and *N*-triflyl phosphoramides are used to catalyse this powerful C–C bond-forming process. Blanchet and coworkers developed the direct aldol reaction between ethyl glyoxylate **71** and different ketone nucleophiles **75** in the presence of the H$_8$-BINOL-derived phosphoric acid

catalyst (*R*)-**76** (Scheme 29).[111] The *β*-hydroxy ketone products **77** were obtained in moderate to excellent diastereo- and enantioselectivities (up to 95:5 d.r. and 95:5 e.r.). Notably, this *syn*-enantioselective aldol reaction is complementary to enamine (proline) catalysis, which usually favours the *anti* diastereoisomer.



Scheme 29. Blanchet's direct aldol reaction between ethyl glyoxylate **71** and ketones **75** catalysed by (*R*)-**76**.

Yamamoto used the more acidic *N*-triflyl thiophosphoramide (*S*)-**78** to catalyse an asymmetric Mukaiyama aldol reaction between various aldehydes **79** and silyl enol ethers **80** (Scheme 30).[112] The aldol products **81** showed good to excellent enantioselectivities (up to 96:4 e.r.).



Scheme 30. Yamamoto's Mukaiyama aldol reaction between various aldehydes **79** and silyl enol ethers **80** catalysed by (*S*)-**78**.

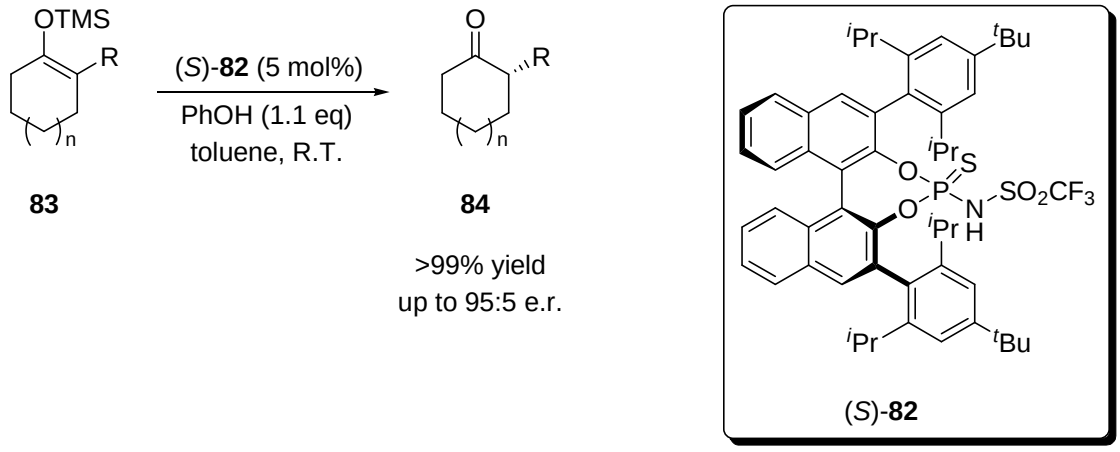
Mechanistic studies revealed that the silylated Brønsted acid may be an actual catalyst at R.T. (Lewis acid pathway), whereas at low temperature, the Brønsted acid itself may be the actual catalyst (Brønsted acid pathway).

1.4.3 Organocatalytic activation *via* reactive intermediates

Another challenge within the growing field of chiral Brønsted acid catalysis is the investigation of reactions where a positively charged reactive intermediate (carbocation, oxacarbenium ion) is associated with the negatively charged conjugate base in a contact ion pair. The intermediate might be stabilised through intermolecular π-π stacking interactions as well as electrostatic interactions and hydrogen bonding. These interactions determine the relative orientation of the cationic intermediate in the chiral environment created by the

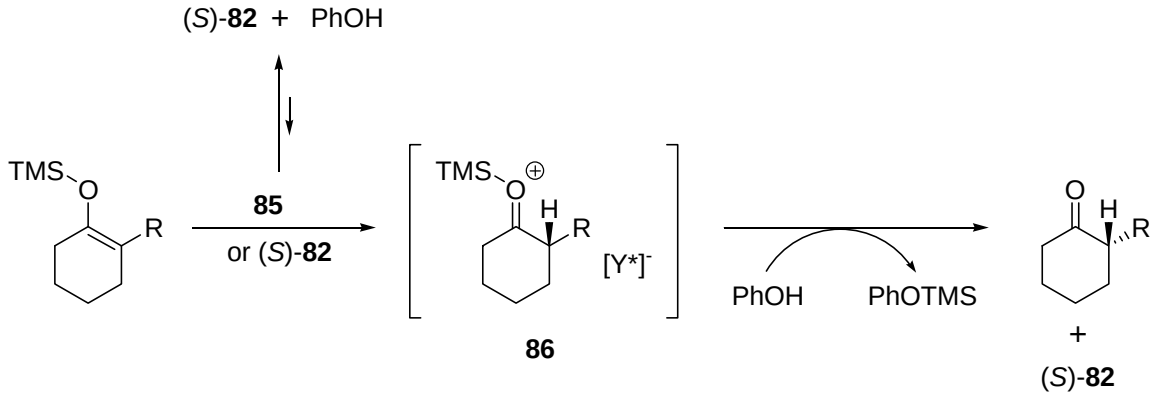
associated anion. The underlying principle, namely Asymmetric Counteranion-Directed Catalysis (ACDC), was first introduced by List[113] and forms the basis for our hypothesis on the asymmetric allylation of acetals. So far, there have been only four examples in the literature where this challenge has been tackled using organocatalysts. Noteworthy is the work of Jacobsen and co-workers who have applied the principle of H-bond donor catalysis by anion binding of urea and thiourea derivatives to the enantioselective transformation of oxacarbenium ions[114] and carbocations.[115] The above mentioned nucleophilic additions of indole to carbonyl groups (Chapter 1.4.2) also follow the concept of ACDC because in each case a mesomeric stabilised cation is formed.

Yamamoto again employed the more acidic *N*-triflyl thiophosphoramide (*S*)-**82** as a catalyst for the enantioselective protonation of prochiral enol derivatives to prepare enantiomerically enriched α-substituted carbonyl compounds.[116] This work provides the first metal-free Brønsted acid-catalysed asymmetric protonation of silyl enol ethers **83** using a chiral Brønsted acid catalyst in the presence of achiral Brønsted acid media (Scheme 31). The ketone products **84** were obtained quantitatively with excellent enantioselectivity (up to 95:5 e.r.).



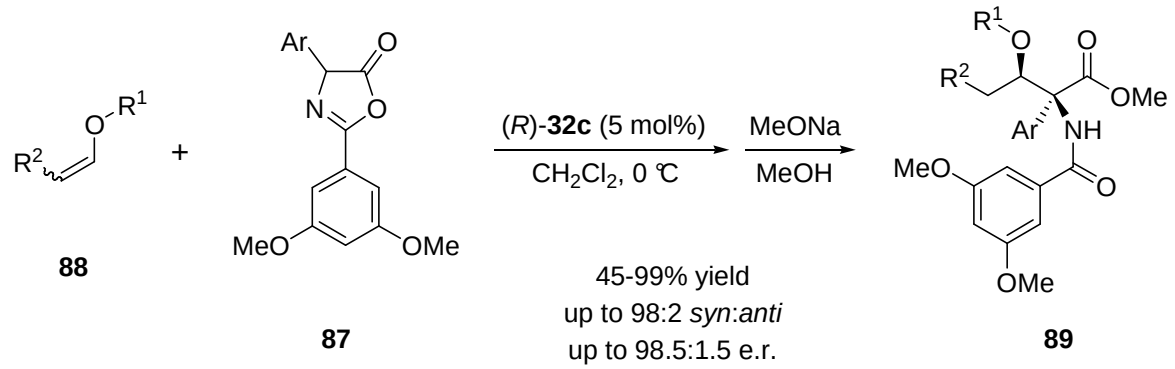
Scheme 31. Yamamoto published the enantioselective protonation of prochiral enol derivatives.

Scheme 32 outlines the proposed mechanism of this interesting reaction: Initially, the protonation of silyl enol ether **83** takes place enantioselectively from the chiral Brønsted acid HY* (*S*)-**82** or achiral oxonium ion pair $[PhOH_2]^+ \cdot [Y^*]^-$ **85**, generated by rapid proton transfer between (*S*)-**82** and the achiral proton source PhOH. An intermediate chiral ion pair $[\mathbf{83}H]^+ \cdot [Y^*]^-$ **86** of the oxacarbenium ion and the conjugate base is formed. This is followed by desilylation with PhOH to form the corresponding ketone **84**, the silylated achiral proton source PhOTMS with concomitant regeneration of HY* (*S*)-**82**.



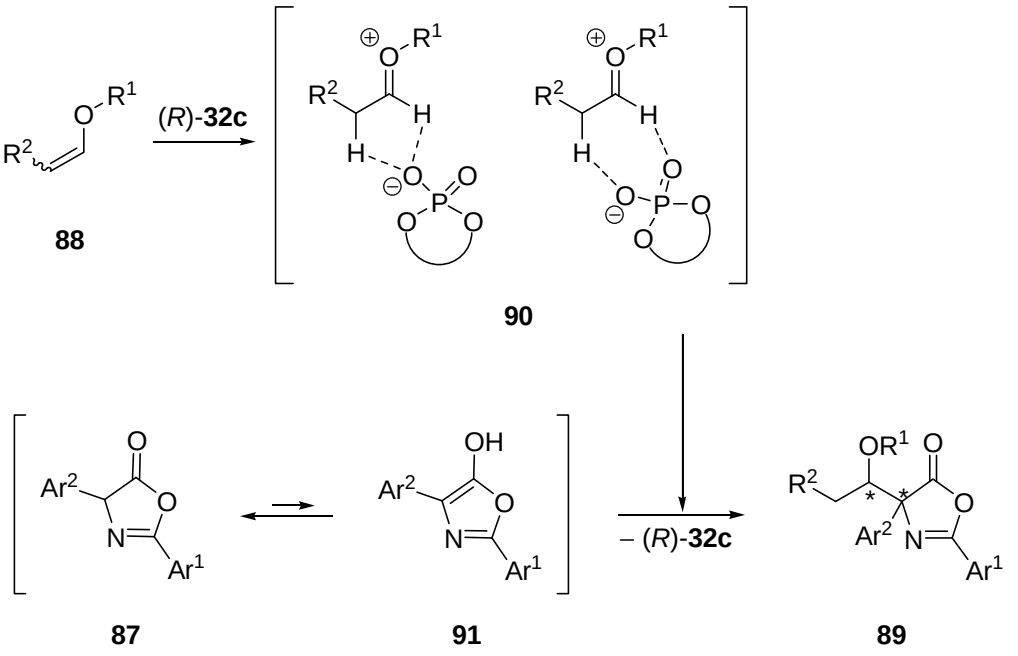
Scheme 32. Proposed mechanism for the enantioselective protonation reaction.

Terada *et al.* demonstrated the direct aldol-type reaction of azlactones **87** *via* protonation of vinyl ethers **88** by chiral Brønsted acid (*R*)-**32c** (Scheme 33).[117] The *β*-hydroxy-*α*-amino acid products **89** possessing a quaternary stereogenic centre at the *α*-carbon atom were afforded in good to excellent yields in a highly enantio- and *syn*-diastereoselective manner.



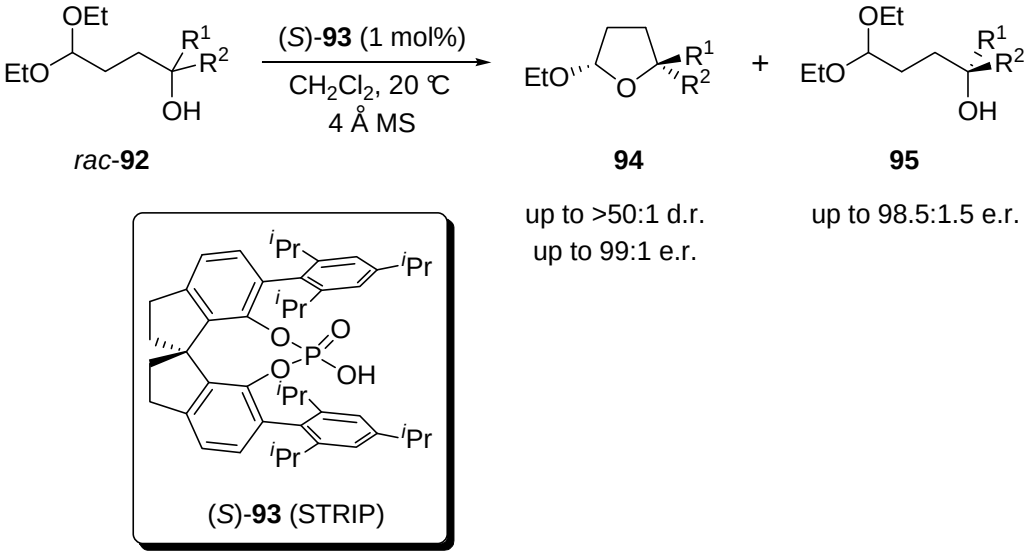
Scheme 33. Terada's direct aldol-type reaction of azlactones **87** *via* protonation of vinyl ethers **88** catalysed by (*R*)-**32c**.

The proposed mechanism suggests proton transfer from the chiral Brønsted acid (*R*)-**32c** to vinyl ether **88** to generate an oxacarbenium ion, which forms an intermediate chiral ion pair [**88**H]$^{+}$·[Y*]$^{-}$ **90** with the negatively charged conjugate base (Scheme 34). Asymmetric induction occurs *via* stereochemical communication, namely *via* hydrogen bonding, between the cationic intermediate and the chiral counteranion. This ion pair then reacts with the azlactone **87** *via* its oxazole tautomer **91** to form the corresponding product **89** and the regenerated (*R*)-**32c**.



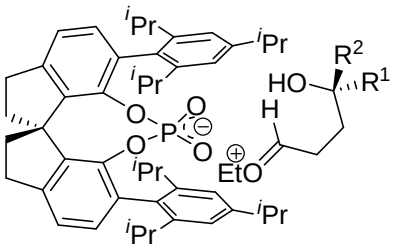
Scheme 34. The proposed mechanism suggests an oxacarbenium ion as intermediate, which forms a chiral ion pair **90** with the conjugate base.

List *et al.* described the highly enantioselective kinetic resolution of alcohols tethered to an acetal moiety *via* a transacetalisation reaction.[118] Both secondary and tertiary acetal homoaldols (*γ*-hydroxyacetals) *rac*-**92** were exposed to the newly designed spirocyclic phosphoric acid STRIP (*S*)-**93** [6,6'-bis(2,4,6-triisopropylphenyl)-1,1'-spirobiindan-7,7'-diyl hydrogen phosphate] to lead to enantioenriched (up to 99:1 e.r.) cyclic acetals **94** as *cis* diastereoisomers (up to >50:1 d.r.) and enantioenriched acetal homoaldols **95** (up to 98.5:1.5 e.r.) (Scheme 35).



Scheme 35. List's kinetic resolution of alcohols *rac*-**92** *via* a transacetalisation reaction.

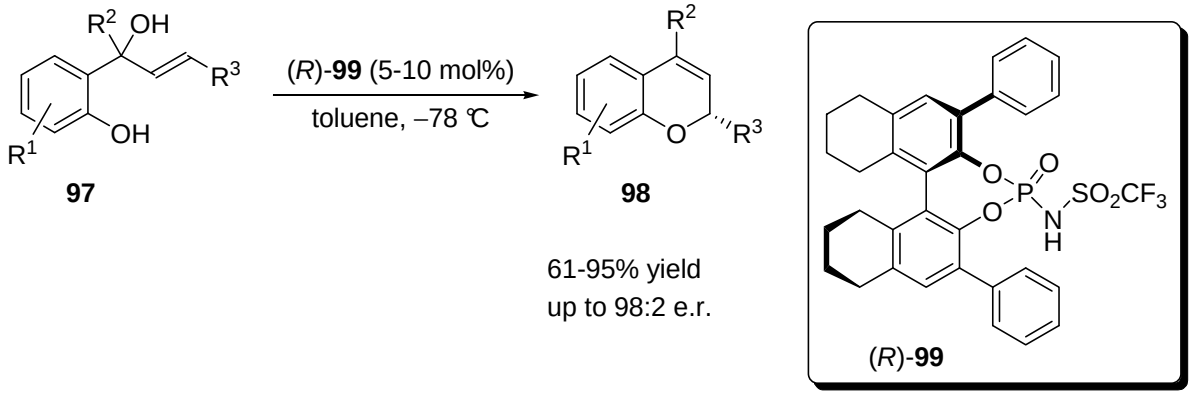
The method represents a very atom-economical kinetic resolution because it does not require any stoichiometric reagents and forms EtOH as the only by-product. Furthermore, the acetal group in cyclic acetals **94** can easily be modified, giving access to enantioenriched tetrahydrofurans and *γ*-butyrolactones. Although the authors did not comment on the actual mechanism, one possibility is that the reaction proceeds *via* contact ion pair **96** where the cationic oxacarbenium ion comes from the one homoaldol enantiomer that undergoes cyclisation (Figure 16).



96

Figure 16. A possible contact ion pair for the transacetalisation reaction.

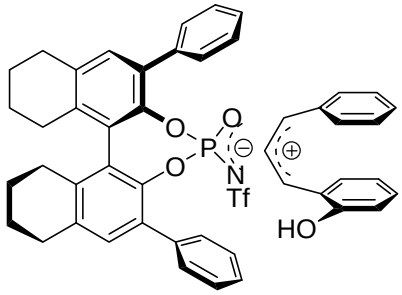
In the fourth example, Rueping and coworkers described the asymmetric intramolecular allylic substitution of allylic alcohols **97** to 2*H*-chromenes **98** (Scheme 36).[119] The reaction is catalysed by chiral *N*-triflyl phosphoramide (*R*)-**99** and proceeds with good to excellent yields (61-95%) and in a highly enantioselective manner (up to 98:2 e.r.).



Scheme 36. Rueping's intramolecular allylic substitution of allylic alcohols **97** to 2*H*-chromenes **98** catalysed by (*R*)-**99**.

On the basis of different experiments described in the article, they propose that the Brønsted acid (*R*)-**99** protonates the allylic alcohol **97**. Subsequent dehydration gives a carbocation which is associated with the phosphoramide anion in a chiral contact ion pair **100** (Figure 17). Their model favours a carbocation with an *anti,anti* configuration, which is stabilised through intramolecular π-π stacking interactions as well as an intermolecular electrostatic interaction

with the counteranion. The two ions of the ion pair orientate in such a way that the positive charge of the cation is compensated by the negative charge delocalised on the OPNTf system. The HO phenolic group is subsequently deprotonated by the catalyst, enabling intramolecular attack of the oxygen nucleophile and regeneration of the effective catalyst. Cation-π interactions between the substrate and the catalyst are most likely responsible for the excellent enantioselection observed in this reaction.

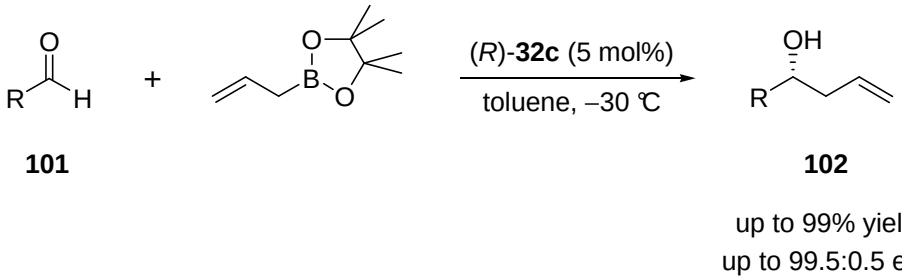


100

Figure 17. Proposed contact ion pair **100** in the allylic substitution.

1.4.4 Organocatalytic allylations

To the best of my knowledge, no allylation reaction involving one of those reactive intermediates mentioned in Chapter 1.4.3 has been reported in the literature. There are only two examples of an allylation process mediated by chiral phosphoric acids. In 2010, Antilla reported the chiral phosphoric acid-catalysed allylboration of aldehydes **101** (Scheme 37).[120] The homoallylic alcohol products **102** were obtained in high yields (up to 99%) and with high enantioselectivities (up to 99.5:0.5 e.r.).



Scheme 37. Antilla's allylboration of aldehydes **101** catalysed by (*R*)-**32c**.

They propose that activation *via* protonation of the boronate oxygen would provide a reasonable explanation for the reactivity (Figure 18). Work by Hall[121,122] and Schaus[123] support this hypothesis.

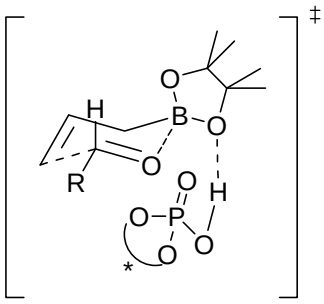
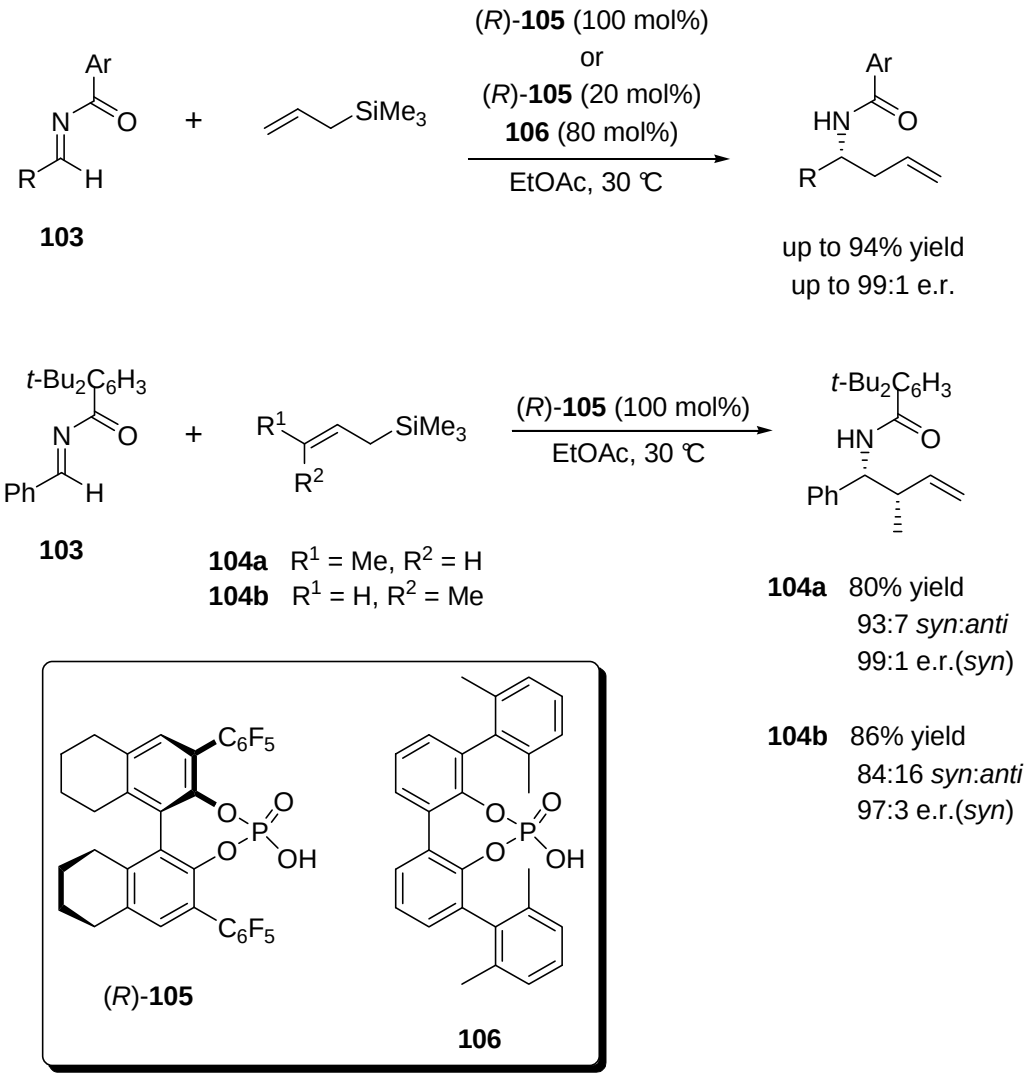


Figure 18. Antilla proposes protonation of the boronate oxygen as activation mode.

Very recently Terada developed the highly enantio- (up to 99:1 e.r.) and *syn* diastereoselective (up to 93:7 d.r.) Hosomi-Sakurai reaction of imines **103** with allyl- and crotyltrimethylsilane **104** (Scheme 38) employing 100 mol% of chiral Brønsted acid (*R*)-**105**.[124]



Scheme 38. Terada's Hosomi-Sakurai reaction of imines **103** catalysed by (*R*)-**105**.

A combined Brønsted acid system employing chiral phosphoric acid (*R*)-**105** (20 mol%) and achiral Brønsted acid **106** (80 mol%) allowed for an enantioselective catalytic process. In this system, regeneration of the chiral Brønsted acid HY* is possible by proton transfer from the additional achiral Brønsted acid HY to chiral silylated phosphoric acid SiY* (Figure 19).

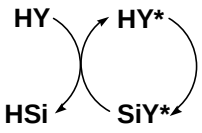


Figure 19. A combined Brønsted acid system allows an enantioselective catalytic process.

This section on organocatalysis has introduced into the concept of chiral Brønsted acids, in particular BINOL-based phosphoric acids and phosphoramides (Chapter 1.4.1). The first two examples of chiral phosphoric acid-mediated processes were described in 2004 and all involve an imine as the substrate. In the following years, the number of publications describing enantioselective additions to imines has increased rapidly, enabling Goodman to introduce his model for imine reactions catalysed by BINOL-based phosphoric acids in 2011. Turning the focus to the activation of carbonyl compounds (Chapter 1.4.2), the research community found a clear trend: Reactive carbonyl compounds (with ester- or trifluoromethyl substituents) can be activated by phosphoric acids whilst "normal" carbonyl groups require more acidic phosphoramides and thiophosphoramides. To the best of our knowledge only a few reactions have been described, which involve a positively charged reactive intermediate (carbocation, oxacarbenium ion) following the concept of ACDC (Chapter 1.4.3) and so far, no allylation reaction involving one of those reactive intermediates has been reported (Chapter 1.4.4). There are only two examples of an allylation process mediated by a chiral phosphoric acid. One involves the allylboration of aldehydes reported by Antilla in 2010, which proceeds *via* a six-membered transition state. In the second example, Terada achieved the Hosomi-Sakurai reaction using the less nucleophilic allyltrimethylsilane with imines in early 2011. An obvious next stage in the development of this field would be to investigate the Hosomi-Sakurai reaction of allyltrimethylsilane with a latent electrophile like an acetal. This is the aim of our project, which will be described in detail in the next Chapter.

2 Project Aims and Objectives

Based on the hypothesis described in Chapter 1.3.2, our group wished to investigate the use of different chiral Brønsted acids derived from BINOL in an asymmetric allylation of acetals. To this end we have the following objectives:

i) To synthesise a range of enantiomerically pure phosphoric acids based on a BINOL core, some of which have already been successfully employed in other Brønsted acid-mediated processes (Figure 20).

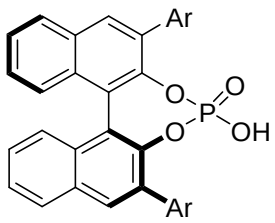


Figure 20. Chiral phosphoric acids based on a BINOL core.

ii) To synthesise a range of enantiomerically pure phosphoramides based on a BINOL core, which are more acidic than the phosphoric acids and which have also already been successfully employed in other Brønsted acid-mediated processes (Figure 21).

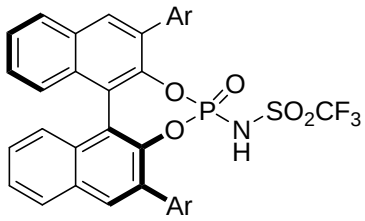


Figure 21. Chiral phosphoramides based on a BINOL core.

iii) To synthesise a range of enantiomerically pure sulfonic acids, which represent a new class of even stronger chiral Brønsted acids (Figure 22).

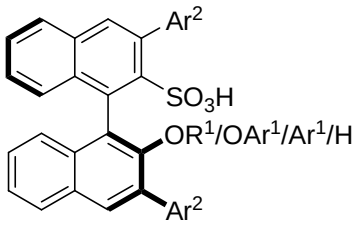
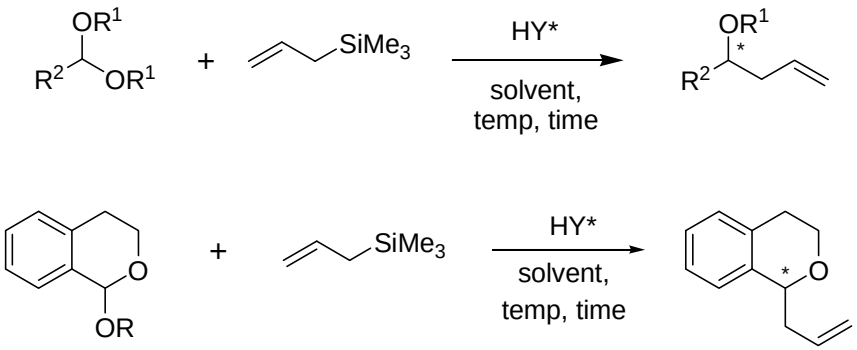


Figure 22. Chiral sulfonic acids based on a binaphthyl core.

iv) To investigate the use of these chiral Brønsted acids, which differ in their acidity, in a catalytic asymmetric allylation of acetals (Scheme 39).

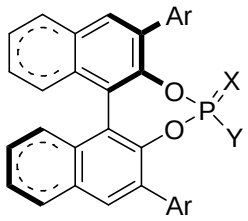


Scheme 39. Asymmetric allylation of acetals.

3 Results and Discussion

3.1 Synthesis of chiral BINOL-based phosphoric acids and phosphoramides

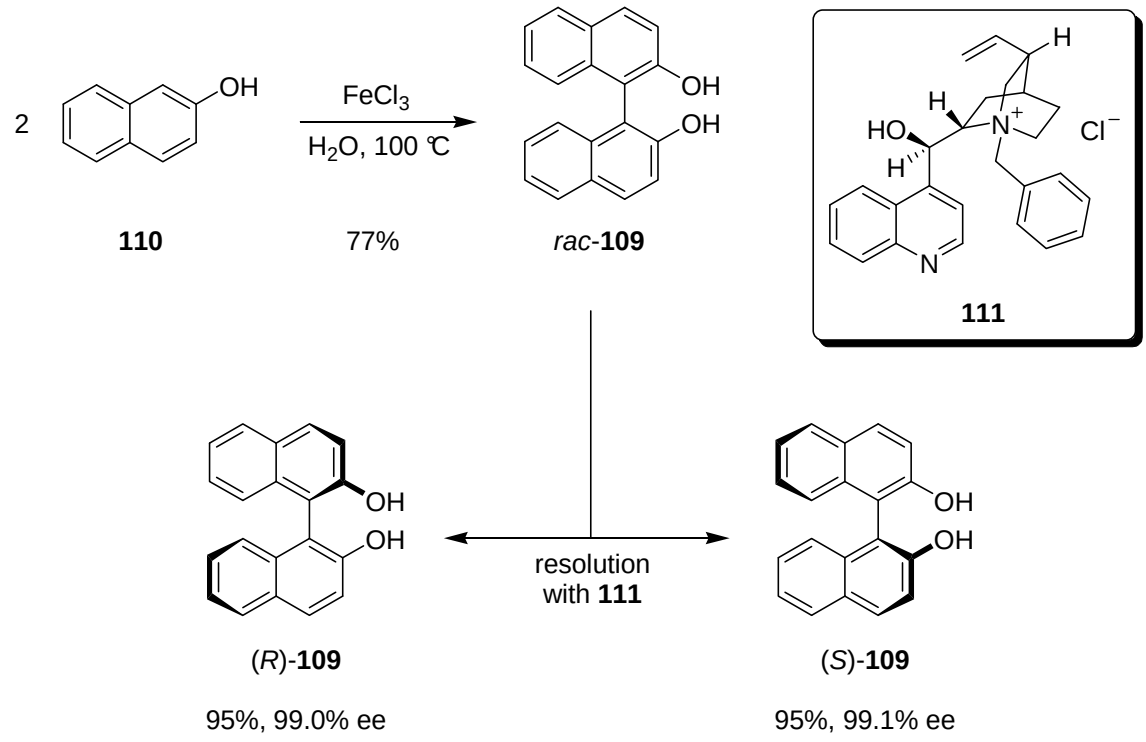
As described in Chapter 1.4.1, various 3,3'-disubstituted phosphoric acids and phosphoramides based on a BINOL core, have already proven their worth as catalysts in a range of asymmetric processes.[97-99] Models which are used to rationalise the observed stereoselectivity in these reactions commonly refer to well-defined molecular conformations associated with non-covalent π-π interactions (face-face and edge-face) between the aromatic substrate/intermediate and the aromatic 3,3'-substituents in the accompanying BINOL catalyst. There is no single 3,3'-substituent which is universally successful for all transformations. We therefore synthesised a range of BINOL-based phosphoric acids and phosphoramides bearing different substituents on the 3,3'-positions (Table 1). Our synthetic strategy is already well established in the literature.



catalyst	Ar	X	Y
(*S*)-**45d** and (*R*)-**45d**	*p*-tolyl	O	NHTf
(*S*)-**45e**	3,5-$(CF_3)_2C_6H_3$	O	NHTf
(*R*)-**45a**	2,4,6-(*i*-Pr)$_3C_6H_2$	O	NHTf
(*R*)-**45f**	9-anthracenyl	O	NHTf
(*R*)-**45g**	10-Br-9-anthracenyl	O	NHTf
(*R*)-**45h**	10-*p*-tolyl-9-anthracenyl	O	NHTf
(*R*)-**45i**	4-Br-1-naphthyl	O	NHTf
(*R*)-H_8-**45j**	10-Br-9-anthracenyl	O	NHTf
(*R*)-**107**	10-Br-9-anthracenyl	O	NHC_6F_5
(*R*)-**108**	10-Br-9-anthracenyl	S	NHTf
(*S*)-**32g**	*p*-tolyl	O	OH
(*R*)-**32h**	10-Br-9-anthracenyl	O	OH
(*R*)-**32i**	10-F-9-anthracenyl	O	OH

Table 1. Synthesised BINOL-based phosphoric acids and phosphoramides.

Preparatively useful syntheses generally begin with BINOL *rac*-**109**, which was prepared from 2-naphthol **110** and $FeCl_3$ in an oxidative radical coupling reaction in 77% yield.[125,126] Subsequent resolution of this racemic material with *N*-benzylcinchonidium chloride **111** gave (*R*)-BINOL (*R*)-**109** in 99.5:0.5 e.r., and (*S*)-BINOL (*S*)-**109** in 99.55:0.45 e.r., as determined by chiral HPLC, with 95% recovery of the starting material (Scheme 40).[127]

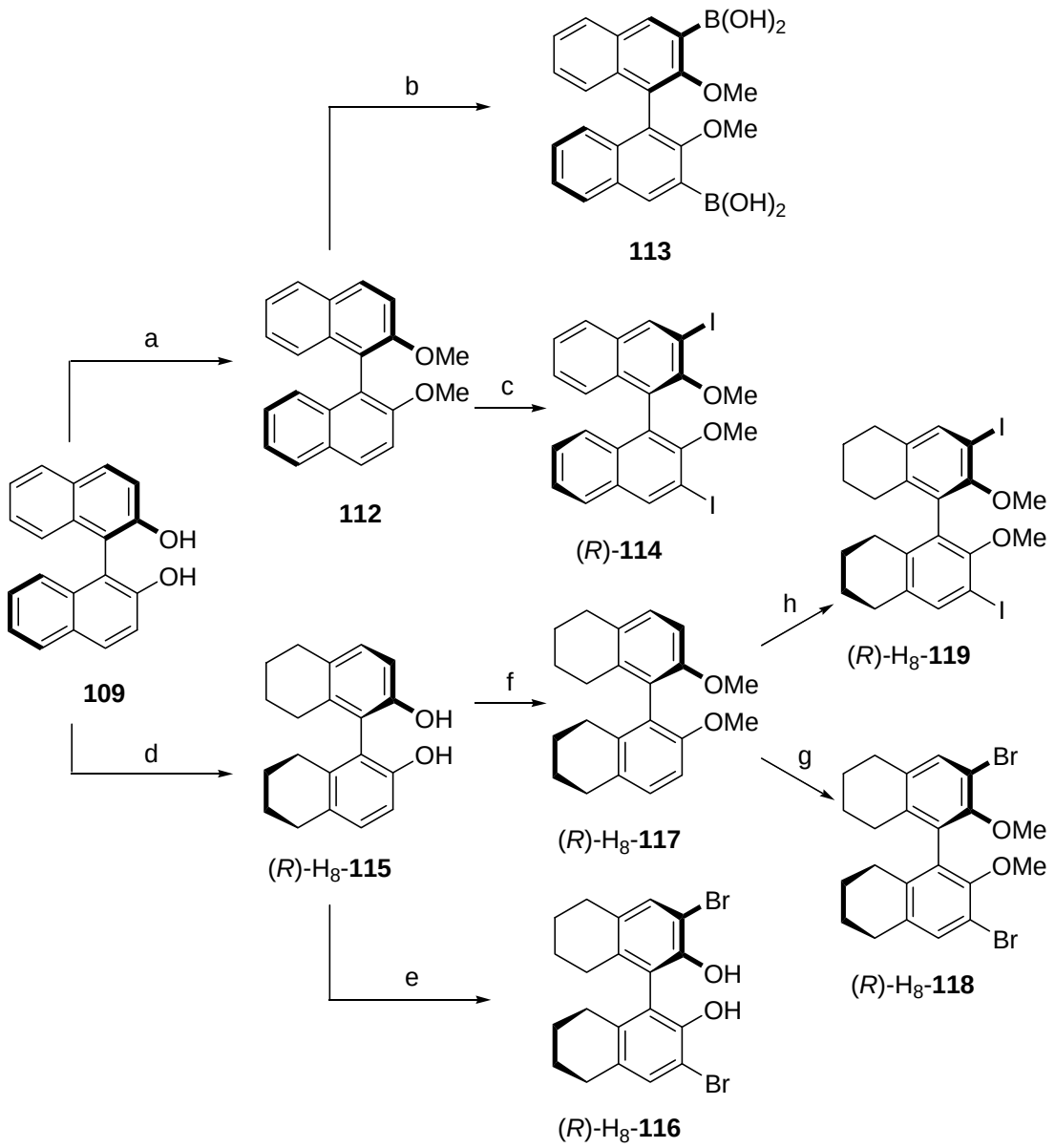


Scheme 40. Synthesis of BINOL *rac*-**109** and
its subsequent resolution with *N*-benzylcinchonidium chloride **111**.

Aryl groups on the 3,3'-positions of the BINOL scaffold are usually introduced by a cross-coupling reaction of a boronic acid with an aryl halide.[128] To obtain these precursors, the alcohol functionality in enantiomerically pure BINOL **109** was first protected by reaction with MeI in the presence of K_2CO_3 to afford dimethoxy-ether **112** in 97% yield (85% yield after recrystallisation) (Scheme 41).[128,129] In the next step, directed ortholithiation, trapping the resulting dilithio intermediate with $B(OEt)_3$, and subsequent hydrolysis, provided bis-boronic acid **113** in 55% yield after recrystallisation.[128] Bis-iodo-ether (*R*)-**114** was also synthesised by ortholithiation of (*R*)-**112** and subsequent trapping with I_2.[130] Recrystallisation of the crude product afforded the enantiomerically pure product in 67% yield.

Reduction of the BINOL core in (*R*)-**109** was achieved quantitively with Adams' catalyst under H_2 atmosphere.[131] Beller has developed an elegant synthetic sequence for the direct

Suzuki coupling of unprotected H_8-BINOLs which would allow us to avoid the use of a protecting group.[132] Following this lead, we brominated diol (*R*)-H_8-**115** at –30 °C to obtain bis-bromo-diol (*R*)-H_8-**116** in 82% yield. The other precursors for the Suzuki coupling on route to catalyst (*R*)-H_8-**45j** were obtained by protection of diol (*R*)-H_8-**115** with MeI in the presence of K_2CO_3 to afford dimethoxy-ether (*R*)-H_8-**117** in 85% yield after recrystallisation.[128,129] Subsequent bromination[131] or ortholithiation-iodination[133] gave bis-bromo-ether (*R*)-H_8-**118** quantitatively, and bis-iodo-ether (*R*)-H_8-**119** in 71% yield, respectively.

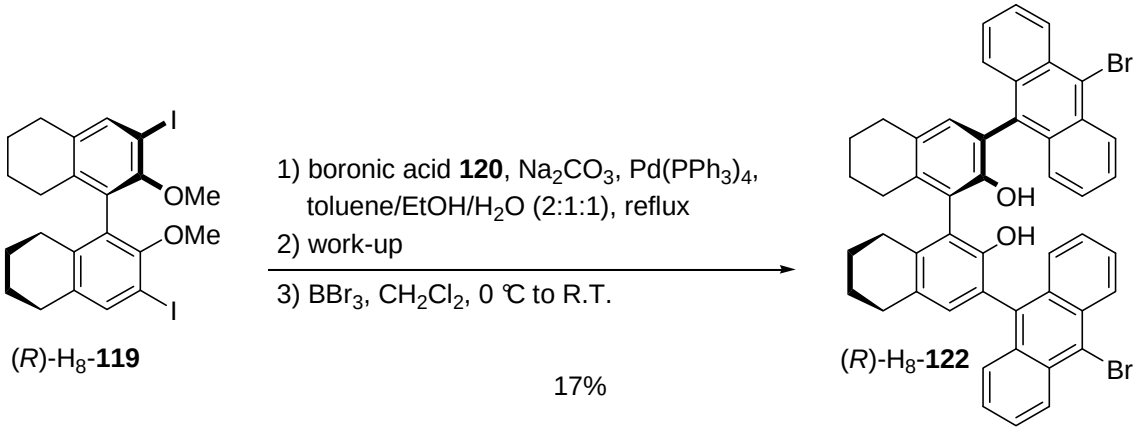


Conditions: (a) MeI, K_2CO_3, acetone, reflux, 97% (85% after recrystallisation). (b) (i) *n*-BuLi, TMEDA, Et_2O, R.T.; (ii) $B(OEt)_3$, –78 °C to R.T.; (iii) 1 M HCl, R.T., 55%. (c) (i) *n*-BuLi, TMEDA, Et_2O, R.T. (ii) I_2, –78 °C to R.T., 67%. (d) H_2, PtO_2, AcOH, quantitative. (e) Br_2, CH_2Cl_2, –30 °C, 82%.(f) MeI, K_2CO_3, acetone, reflux, 97% (85% after recrystallisation). (g) Br_2, CH_2Cl_2, –30 °C, quantitative. (h) (i) *t*-BuLi, Et_2O, –78 °C to R.T.; (ii) I_2, 0 °C to R.T., 71%.

Scheme 41. Synthesis of cross-coupling precursors.

Bis-bromo-diol (*R*)-H_8-**116** and bis-bromo-ether (*R*)-H_8-**118** were employed in a Suzuki coupling with 10-bromoanthracene-9-boronic acid **120** following a literature procedure for coupling the structurally similar 9-anthracene boronic acid **121** with 3,3'-diiodo-2,2'-dimethoxy-[1,1']-binaphthalenyl (*R*)-**114**.[134]; however both substrates were not sufficiently

reactive to give the desired bis-coupled product under the coupling conditions employed. Although I could have investigated more reactive catalysts, I instead decided to turn to the more reactive bis-iodo-ether (*R*)-H_8-**119** as the aryl halide component in the Suzuki coupling. Now the desired bis-coupled product was formed (Scheme 42). After work-up, the crude product was demethylated with BBr_3 and diol (*R*)-H_8-**122** was isolated in 17% yield after column chromatography.[128] In comparison to the high-yielding Suzuki coupling of (*R*)-bis-iodo-ether (*R*)-**114** with boronic acid **120** (*vide infra*), the low yield in this reaction can be explained by the fact that more electron-rich aryl halides are less reactive substrates in this type of coupling reaction.

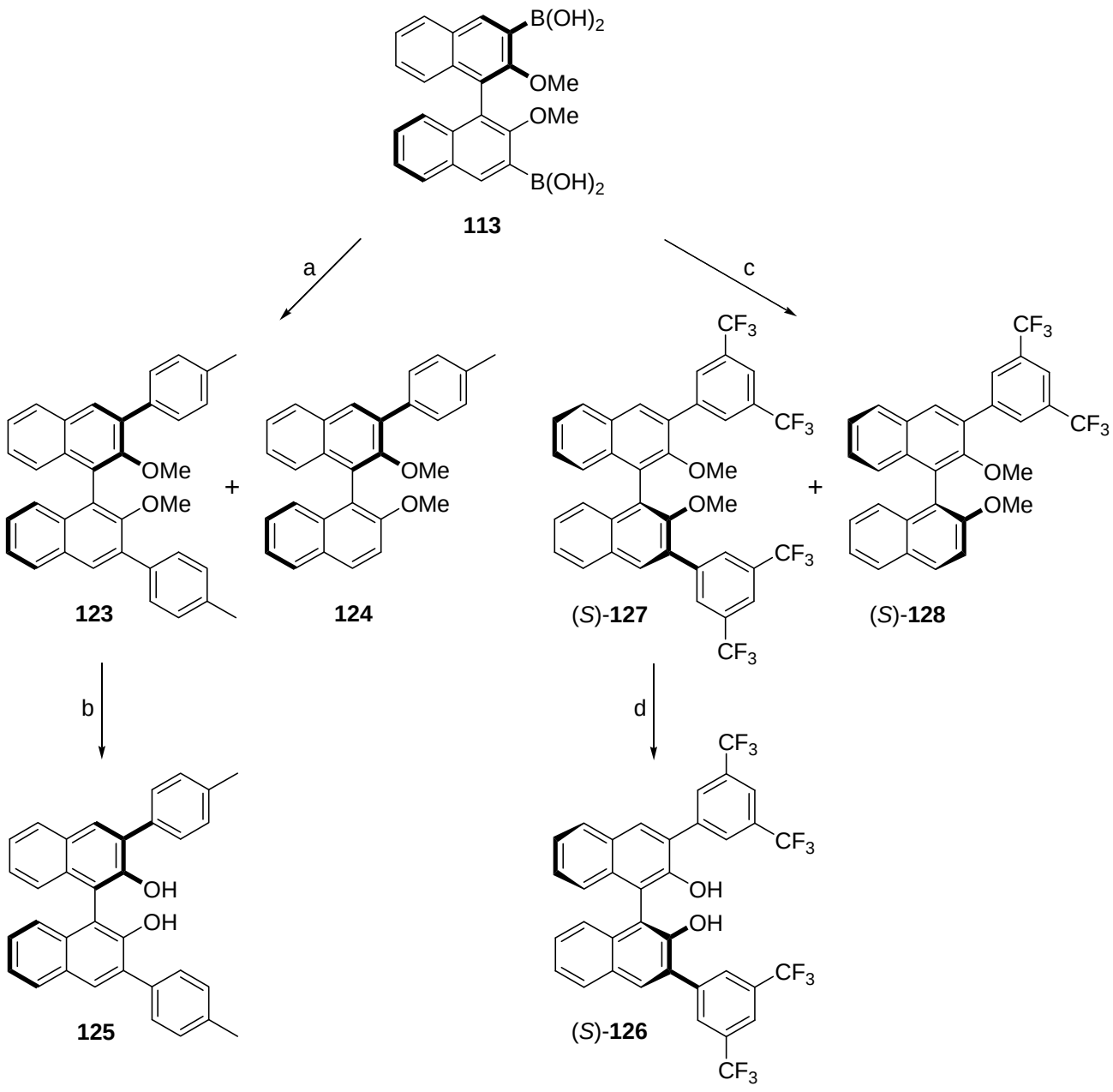


(*R*)-H_8-**119** (*R*)-H_8-**122**

Scheme 42. Suzuki coupling and demethylation to obtain diol (*R*)-H_8-**122**.

Bis-boronic acid **113** was used as a precursor *en route* to catalysts (*S*)- and (*R*)-**45d** and (*S*)-**45e** (Scheme 43). Suzuki coupling with 4-bromotoluene provided the desired bis-coupled product **123** in 61% yield, together with a small amount of the mono-coupled product **124** in 18% yield, which was readily separable from bis-tolyl **123** by flash column chromatography. Subsequent deprotection of bis-tolyl product **123** with BBr_3 gave diol **125** in 97% yield.[128] The same sequence was followed for the preparation of diol (*S*)-**126**: Suzuki coupling of bis-boronic acid (*S*)-**113** with 3,5-bis(trifluoromethyl)iodobenzene led to bis- and mono-coupled

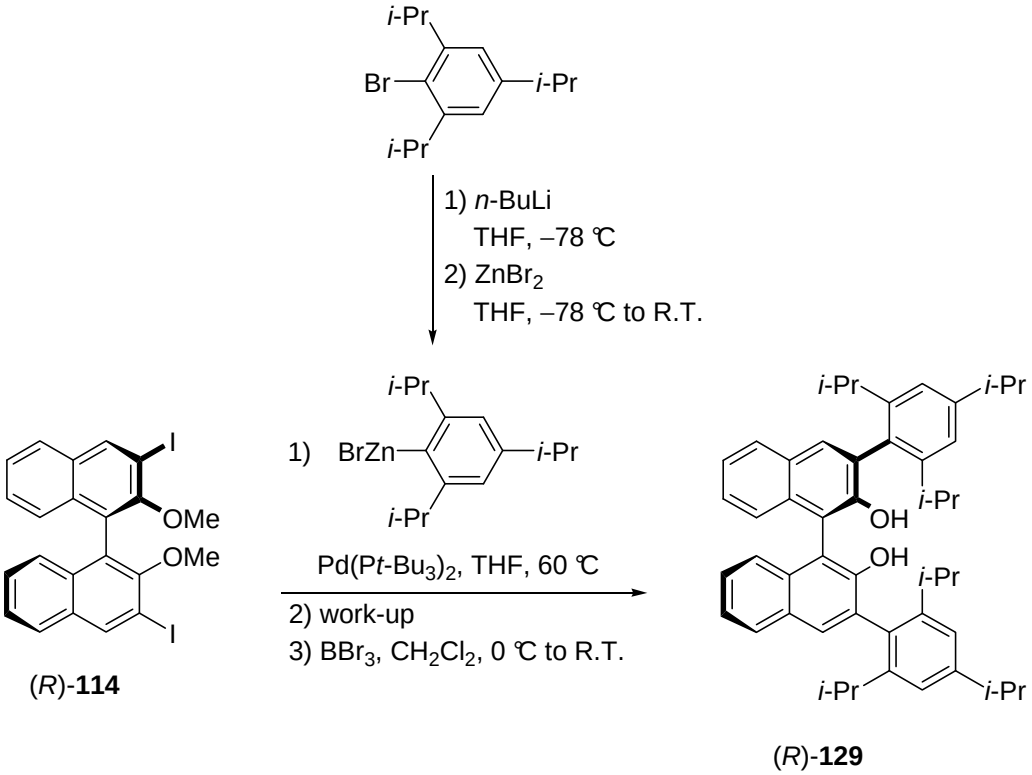
product (*S*)-**127** and (*S*)-**128** in 49% and 10% yield, respectively. Demethylation of bis-ether (*S*)-**127** afforded diol (*S*)-**126** in 97% yield.[135]



Conditions: (a) 4-bromotoluene, $Ba(OH)_2$, $Pd(PPh_3)_4$, dioxane/H_2O (3:1), reflux, bis-ether **123**: 61%, mono-ether **124**: 18%. (b) BBr_3, CH_2Cl_2, 0 ℃ to R.T., 97%. (c) 3,5-bis(trifluoromethyl)iodoenzen e, Na_2CO_3, $Pd(PPh_3)_4$, DME/EtOH/H_2O, reflux, bis-ether (*S*)-**127**: 49%, mono-ether (*S*)-**128**: 10%. (d) BBr_3, CH_2Cl_2, 0 ℃ to R.T., 97%.

Scheme 43. Suzuki coupling and demethylation to obtain diols (*R*)- and (*S*)-**125** and (*S*)-**126**.

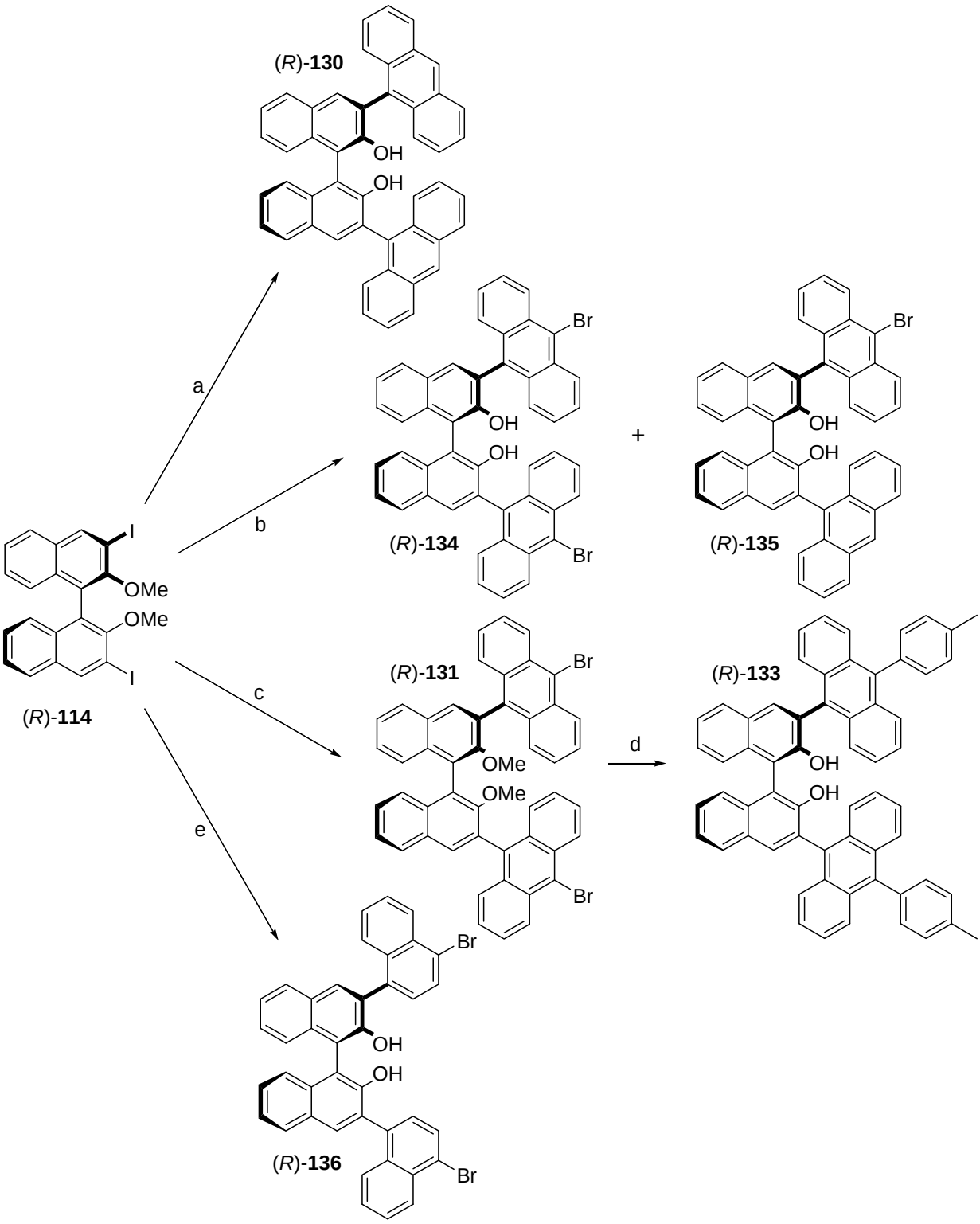
A Negishi coupling was employed in the synthesis of catalyst (*R*)-**45a** (Scheme 44). Sterically hindered 1-bromo-2,4,6-triisopropylbenzene was converted into the corresponding organozinc reagent, which was bis-coupled to bis-iodo-ether (*R*)-**114** in the presence of 1 mol% of a highly reactive bis-(tri-*tert*-butylphosphine)palladium catalyst. After work-up, the crude product was demethylated to provide diol (*R*)-**129** in 53% yield.[136]



Scheme 44. Negishi coupling and demethylation to obtain diol (*R*)-**129**.

For the synthesis of the diol-precursor (*R*)-**130**, 9-anthracene boronic acid **121** was prepared by reaction of 9-lithioanthracene (generated by the action of *n*-BuLi on 9-bromoanthracene) with $B(OMe)_3$ and subsequent hydrolysis (Scheme 45).[137] The crude product was used in a Suzuki coupling with bis-iodo-ether (*R*)-**114** to afford diol (*R*)-**130** in 93% yield after deprotection with BBr_3.[134] The same conditions were used in the Suzuki coupling of bis-iodo-ether (*R*)-**114** with commercially available 10-bromoanthracene-9-boronic acid **120** to

provide bis-ether (*R*)-**131** in 80% yield. This compound was exposed to another cross-coupling[138] with 4-tolylboronic acid **132**[139] which was prepared from 4-bromotoluene by lithiation and treatment with $B(OMe)_3$, followed by hydrolysis to the boronic acid. After demethylation with BBr_3, diol (*R*)-**133** was isolated in 96% yield.[128] When preparing diol (*R*)-**134**, bis-ether (*R*)-**131** was not isolated; instead the crude product was treated with BBr_3 to provide the diol (*R*)-**134** in 75% yield, alongside mono-bromo-diol (*R*)-**135** in 19% yield.[128] The Suzuki coupling–deprotection sequence was also applied to the synthesis of diol (*R*)-**136** in 73% overall yield.



Conditions: (a) (i) 9-anthracene boronic acid **121**, Na_2CO_3, $Pd(PPh_3)_4$, toluene/EtOH/H_2O (2:1:1), reflux; (ii) work-up; (iii) BBr_3, CH_2Cl_2, 0 ℃ to R.T., 93%. (b) (i) 10-bromoanthracene-9-boronic acid **120**, Na_2CO_3, $Pd(PPh_3)_4$, toluene/EtOH/H_2O (2:1:1), reflux; (ii) work-up; (iii) BBr_3, CH_2Cl_2, 0 ℃ to R.T., bis-diol (*R*)-**134**: 75%, mono-diol (*R*)-**135**: 19%. (c) 10-bromoanthracene-9-boronic acid **120**, Na_2CO_3, $Pd(PPh_3)_4$, toluene/EtOH/H_2O (2:1:1), reflux, 80%. (d) (i) 4-tolylboronic acid **132**, K_2CO_3, $Pd(OAc)_2$, tri(3-tolyl)-phosphine, toluene/DME/H_2O (2:2:1), reflux; (ii) work-up; (iii) BBr_3, CH_2Cl_2, 0 ℃ to R.T., 96%. (e) (i) 4-bromonaphthyl-1-boronic acid, Na_2CO_3, $Pd(PPh_3)_4$, toluene/EtOH/H_2O (2:1:1), reflux; (ii) work-up; (iii) BBr_3, CH_2Cl_2, 0 ℃ to R.T., 73%.

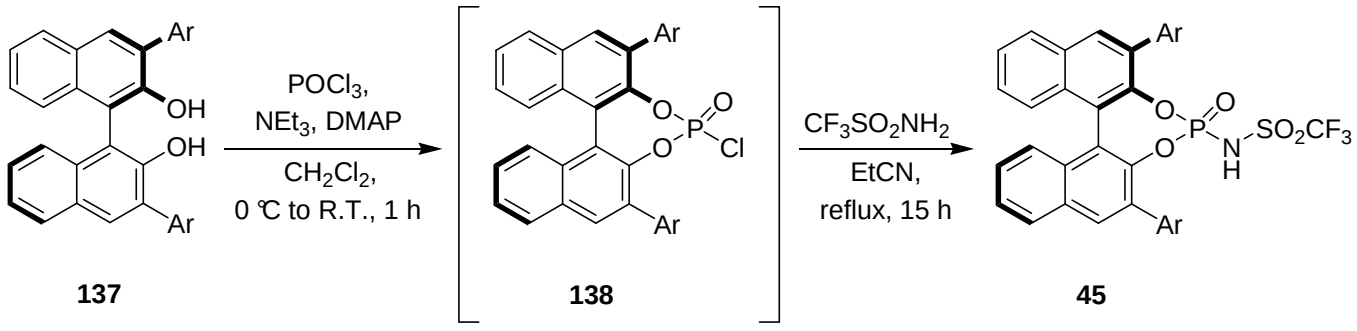
Scheme 45. Suzuki coupling–deprotection sequences to obtain diol precursors.

For the synthesis of the *N*-triflyl phosphoramide catalysts **45**, a general procedure was followed which was published by Yamamoto when he first introduced this class of chiral Brønsted acids in 2006.[87] The diol precursors **137** were first reacted with phosphorus oxychloride to generate the corresponding phosphoryl chloride intermediates **138** which were not isolated (Table 2). Instead, the reflux temperature of the reaction mixture was increased by adding EtCN and then trifluoromethanesulfonamide was added to convert the phosphoryl chlorides into the corresponding *N*-triflyl phosphoramides **45**. All catalysts were prepared uneventfully in this manner and the yields of this final step are summarised in Table 2 (entries 1-8). The *N*-pentafluorophenylsulfonyl phosphoramide **107**, which is a more acidic Brønsted acid, was synthesised by addition of pentafluorophenylsulfonamide instead of trifluoromethanesulfonamide (entry 9).

N-Triflyl thiophosphoramide **108** represents a class of more acidic chiral Brønsted acids and was obtained by the use of phosphorus thiochloride in place of phosphorus oxychloride (entry 10). Yamamoto introduced this type of catalyst in 2008.[116] In general, acidity increases on descending a group of the Periodic Table due to the larger atoms better stabilising the negatively charged conjugate base. For example, the pK_a values of PhOH, PhSH, and PhSeH in DMSO are 18.0, 10.3, and 7.1, respectively.[140] Yamamoto showed by X-ray crystallography that their synthesised *N*-triflyl thiophosphoramide has a P=S double bond rather than a P=N double bond, which implies the proton is located on the nitrogen and not the sulfur atom..

It is important to note that an acid wash with 4 M hydrochloric acid (twice) was necessary with all phosphoramides after purification of the crude product by column chromatography to convert the obtained phosphoramide salt into the acid. After removing the solvent (usually Et_2O) *in vacuo*, with each product, a change in consistency and colour in comparison to the

salt was observed. This fits with Rueping's observations.[141] He examined the X-ray crystal structure of a *N*-triflyl phosphoramide **PA** isolated after column chromatography and showed that this was not the free acid, but the corresponding calcium salt Ca(**PA**)$_2$. Since no calcium ions are present during the synthesis or work-up procedures, it is likely that the **PA** sequestered calcium cations from the silica gel used for the final column chromatography.[2] After the extraction with hydrochloric acid no calcium was detected in a sample analysed by energy-dispersive X-ray spectroscopy.



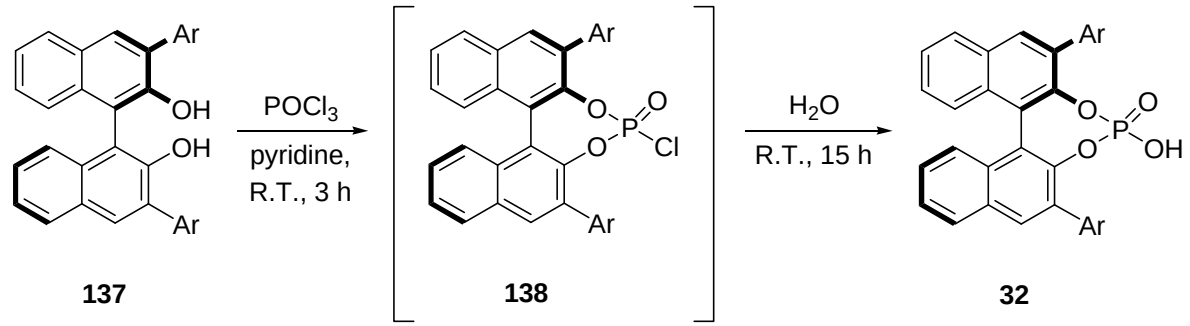
137 **138** **45**

entry	catalyst	Ar	X	Y	yield [%]
1	(*S*)-**45d** and (*R*)-**45d**	*p*-tolyl	O	NHTf	89
2	(*S*)-**45e**	3,5-$(CF_3)_2C_6H_3$	O	NHTf	91
3	(*R*)-**45a**	2,4,6-$(i\text{-Pr})_3C_6H_2$	O	NHTf	83
4	(*R*)-**45f**	9-anthracenyl	O	NHTf	75
5	(*R*)-**45g**	10-Br-9-anthracenyl	O	NHTF	70
6	(*R*)-**45h**	10-*p*-tolyl-9-anthracenyl	O	NHTf	63
7	(*R*)-**45i**	4-Br-1-naphthyl	O	NHTf	72
8	(*R*)-H_8-**45j**	10-Br-9-anthracenyl	O	NHTf	70
9	(*R*)-**107**	10-Br-9-anthracenyl	O	NHC_6F_5	78
10	(*R*)-**108**	10-Br-9-anthracenyl	S	NHTf	46
11	(*S*)-**32g**	*p*-tolyl	O	OH	87
12	(*R*)-**32h**	10-Br-9-anthracenyl	O	OH	93
13	(*R*)-**32i**	10-F-9-anthracenyl	O	OH	91

Table 2. Synthesised *N*-triflyl phosphoramide and phosphoric acid catalysts.

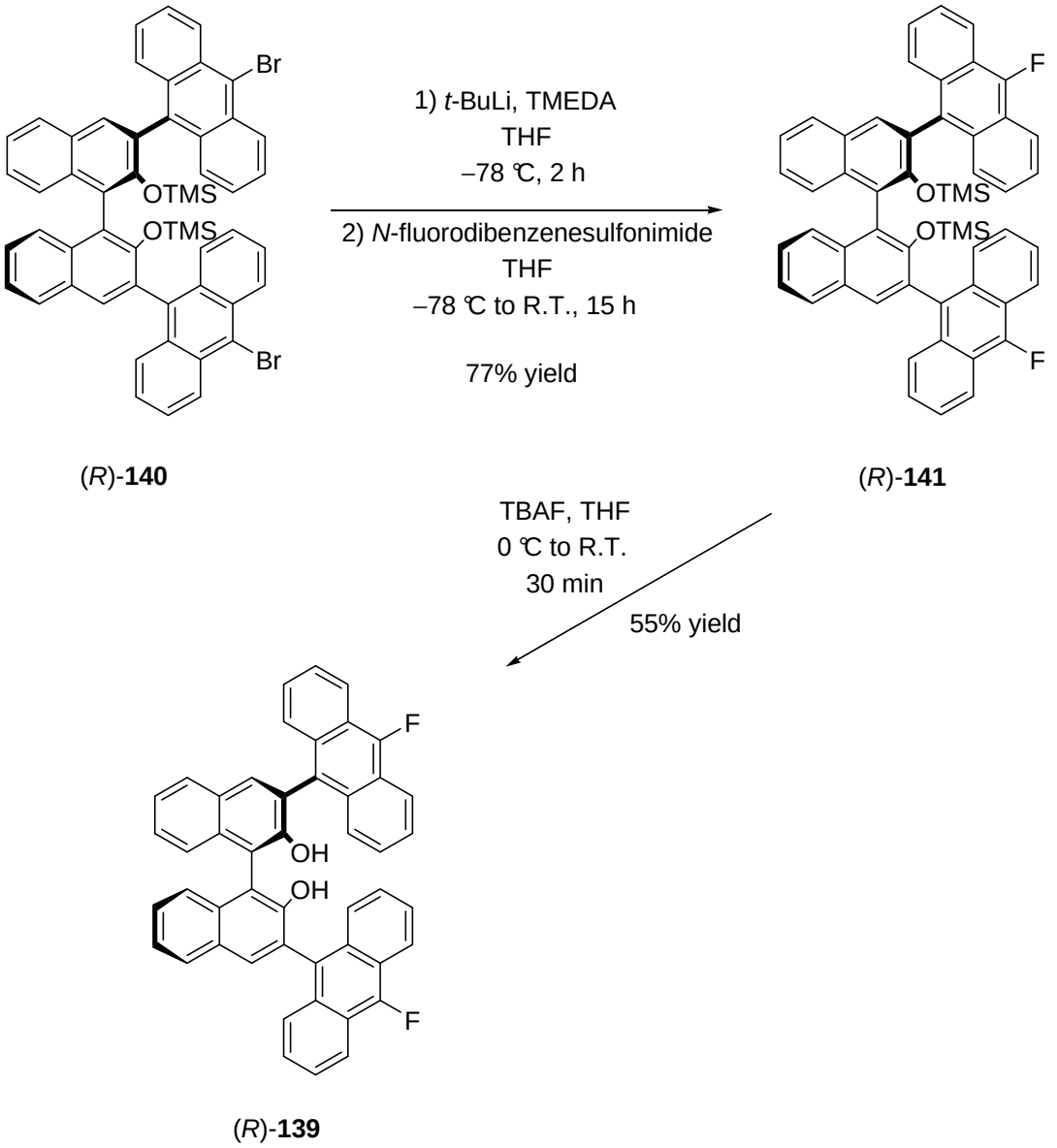
[2] commercially available silica gel contains traces of calcium

Phosphoric acids **32** were prepared following a general procedure.[90] Again, the diol precursors **137** were reacted with phosphorus oxychloride, this time in pyridine, to generate the corresponding phosphoryl chloride intermediates **138**, which were not isolated (Scheme 46), but hydrolysed directly to provide the corresponding phosphoric acids **32**. Since BINOL-derived phosphoric acids are also known to bind calcium upon purification on silica, an acid wash was carried out to release the cation and ensure the phosphoric acid was isolated.[142] Phosphoric acids **32g**-**32i** were prepared in this manner and the yields of this final step are summarised in Table 2 (entries 11-13).



Scheme 46. Synthesis of phosphoric acid catalysts.

Diol precursor (*R*)-**139** was synthesised from diol (*R*)-**134** in three additional steps (Scheme 47). The TMS-protection was achieved with HMDS and a sub-stoichiometric amount I_2 to afford TMS-protected bis-bromo-diol (*R*)-**140** in 96% yield.[143] In the next step, a metal-halogen exchange with *t*-BuLi afforded the bis-lithiated species, which was quenched by the addition of *N*-fluorodibenzenesulfonimide to provide TMS-protected bis-fluoro-diol (*R*)-**141** in 77% yield. Three long columns with the mixed fractions were needed to fully separate TMS-protected bis-fluoro-diol (*R*)-**141** from TMS-protected mono-fluoro-diol (*R*)-**142** and bis-anthracenyl-diol (*R*)-**130**. TBAF was used for the deprotection to afford diol precursor (*R*)-**139** in 55% yield.



(*R*)-**140** (*R*)-**141** (*R*)-**139**

Scheme 47. Synthesis of bis-fluoro-diol (*R*)-**139**.

Originally, it was planned to convert diol (*R*)-**139** into the corresponding *N*-triflyl phosphoramide (see Chapter 3.2.2.2). Following the general procedure,[87] the diol was readily transformed into the phosphoryl chloride intermediate; however I was surprised to discover that the subsequent phosphoramidation step failed. I had expected the bis-fluoro-phosphoryl chloride intermediate to be even more reactive than the corresponding bis-bromo-phosphoryl chloride; however for unknown reasons the reaction failed. Therefore, we hydrolysed the

phosphoryl chloride to provide phosphoric acid (*R*)-**32i** in 91% yield after column chromatography and a final acid wash (entry 13).

In summary a range of phosphoric acids and phosphoramides were synthesised and then used to investigate the asymmetric allylation of acetals as described in the next section.

3.2 Investigation of the asymmetric allylation of acetals

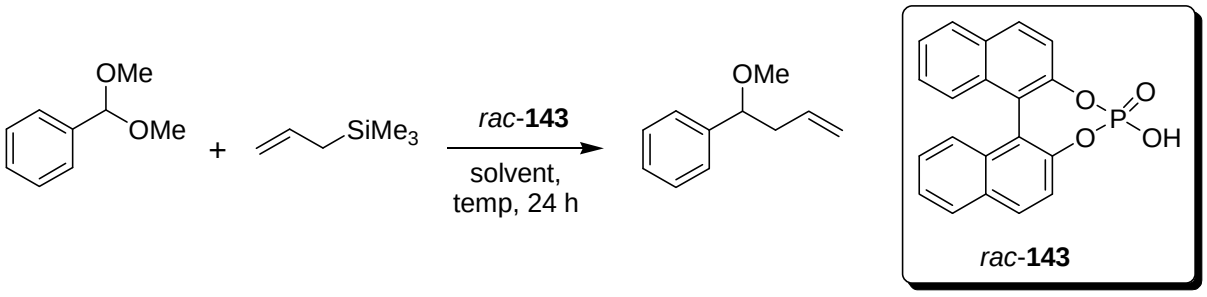
We first chose to focus on acetals derived from aryl aldehydes, since the proposed oxacarbenium ions, generated from these types of substrate, may form favourable non-covalent π-π interactions with the binaphthalene scaffold and a well defined conformation in which the enantiotopic faces of the electrophile are differentiated. All reported e.r. values were measured twice by chiral HPLC which usually led to the same value or to a maximum in error of 1%. In the later case the reported e.r. is the higher value.

3.2.1 Acyclic acetals derived from different benzaldehyde derivatives

3.2.1.1 Investigation of phosphoric acids

In order to investigate whether phosphoric acids based on a BINOL core (pK_a ~ 1.4)[86] are sufficiently acidic to activate acyclic acetals, we investigated the reaction between commercially available benzaldehyde dimethyl acetal as the latent electrophile and allyltrimethylsilane under different reaction conditions. Since the racemic phosphoric acid *rac*-**143** is commercially available we started our study with this 3,3'-unsubstituted

compound. Table 3 summarises the results from these reactions and includes information on the catalyst solubility.



entry	SiMe$_3$ [equiv]	*rac*-**143** [mol%]	solvent	temp [°C]	solubility of acid	% yield[a] of allylation product
1	1.1	100	toluene	R.T.	low	-
			CH_2Cl_2		low	-
			Et_2O		low	-
			CH_3CN		low	-
2	1.1	10	toluene		not fully	-
			CH_2Cl_2	R.T.	yes	< 5
			CH_3CN		yes	-
3	5	10	toluene	R.T.	not fully	< 1
4	1.1	10	toluene	80	yes	< 2
			CH_2Cl_2	30	yes	< 4

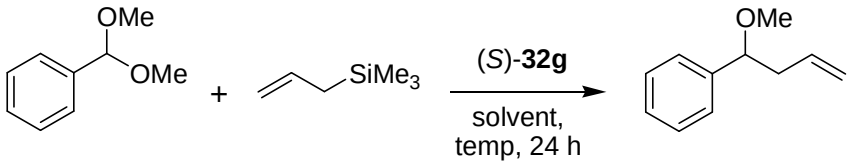
[a] determined by GC

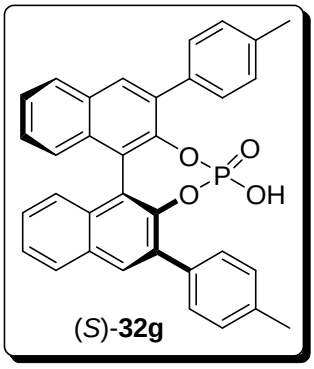
Table 3. Allylation reactions carried out using phosphoric acid *rac*-**143** as the activator.

Carrying out the reaction with 1 equivalent of phosphoric acid *rac*-**143** in different solvents (toluene, CH_2Cl_2, Et_2O and CH_3CN) failed to afford any allylation product as indicated by TLC (entry 1). A significant problem was the low solubility of the acid activator in all four solvents tested. Reducing the amount of Brønsted acid *rac*-**143** to 10 mol% (entry 2) proved to be the right choice: the catalyst was now completely soluble in CH_2Cl_2 and CH_3CN but not in our favoured solvent, toluene, which is an aromatic solvent with low dielectric constant.

The allylation product was only observed in the reaction with CH_2Cl_2 in < 5% yield. Employing 5 equivalents of allyltrimethylsilane in toluene provided only trace quantities of the allylation product (entry 3). Increasing the reaction temperature in toluene and CH_2Cl_2 also failed to improve the yield of the desired product (entry 4).

In order to overcome the solubility problems of catalyst *rac*-**143** in toluene, we decided to synthesise the 3,3'-substituted phosphoric acid (*S*)-**32g**. This acid catalyst was then used in the allylation reaction with benzaldehyde dimethyl acetal. Table 4 summarises the results from these reactions and includes information about the catalyst solubility.





entry	SiMe$_3$ [equiv]	(*S*)-**32g** [mol%]	solvent	temp. [°C]	acid soluble	product[a]
1	1.1	10	toluene		yes	-
			CH_2Cl_2	R.T.	yes	-
			$CHCl_3$		yes	-
2	1.1	10	toluene	50	yes	-
			CH_2Cl_2	30	yes	-
			$CHCl_3$	50	yes	-

[a] indicated by TLC

Table 4. Summary of allylation study using phosphoric acid (*S*)-**32g**.

Gratifyingly, the Brønsted acid catalyst (*S*)-**32g** was now soluble in toluene at R.T. but still no allylation product was observed after 24 h as evidenced by TLC, neither in toluene nor in

CH_2Cl_2 or $CHCl_3$ (entry 1). Increasing the reaction temperature failed to improve matters (entry 2).

The conclusions which could be drawn from these experiments with catalysts *rac*-**143** and (*S*)-**32g** were:

i) These phosphoric acids are not sufficiently acidic to induce the allylation reaction of benzaldehyde dimethyl acetal with allyltrimethylsilane.

ii) We would need to be aware of the potential solubility issues when moving to more acidic catalysts based on a BINOL core.

3.2.1.2 Investigation of phosphoramides

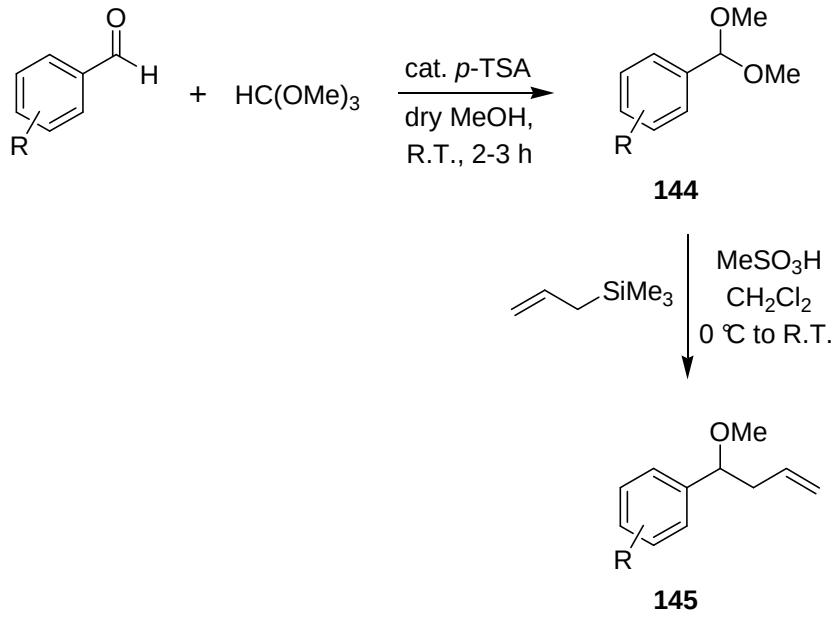
Since the Brønsted acidity of the employed phosphoric acids proved too low to activate the dimethyl acetal, we turned towards more acidic BINOL-based phosphoramides (pK_a ~ –3 to –4),[141] although in light of List's work (Chapter 1.4.3) and our own observations with the 10-F-9-anthracenyl phosphoric acid (*R*)-**32i** (*vide infra*), it may have been worthwhile investigating a wider range of phosphoric acids.

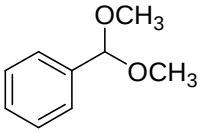
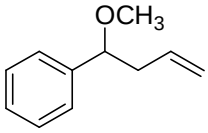
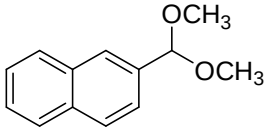
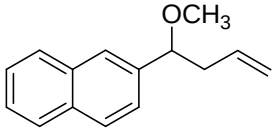
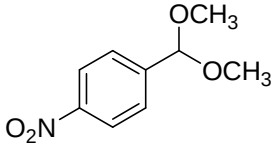
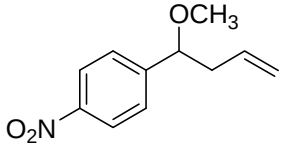
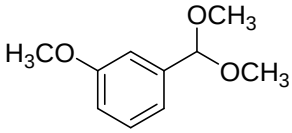
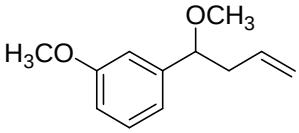
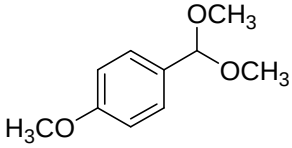
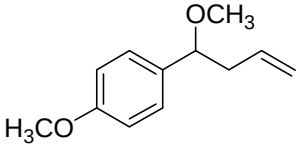
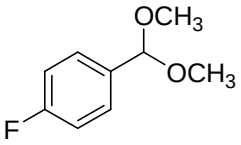
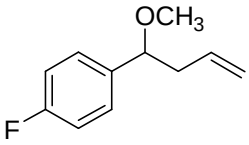
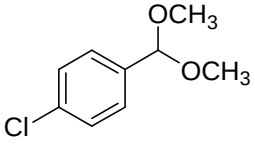
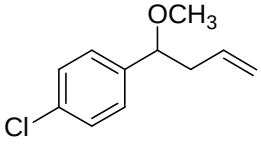
All the following reactions were conducted with 10 mol% of the phosphoramide (*S*)-**45d** in different solvents and at ambient temperature (19 to 25 ºC), unless otherwise stated. Since we did not want to waste any precious material, all reactions were carried out on a very small scale (0.300 mmol) although this led to a few problems:

i) Trace amounts of H_2O led to competing hydrolysis of the acyclic acetals to their corresponding aldehydes. We planned to overcome this issue, if it were still a problem on scale up, by using molecular sieves or other drying agents as an additive.

ii) Material is lost during work-up and purification by column chromatography and for this reason, isolated yields for these reactions are not representative of the efficiency of the reaction and therefore are not reported.

At this stage of the investigation I wanted to focus on the possible chirality transfer from the Brønsted acid activator, and I was therefore mainly interested in isolating sufficient pure material to allow determination of the enantiomeric ratio (e.r.) by HPLC. In order to be able to determine the e.r. of our allylation products, the retention times of both enantiomers were identified by first analysing racemic samples. For this purpose, all products were prepared by carrying out a reaction of the acyclic acetals with allyltrimethylsilane in the presence of the achiral acid, methanesulfonic acid.[69] The starting acyclic acetals were prepared uneventfully by reacting the corresponding aldehyde with trimethylorthoformate in MeOH in the presence of *p*TSA.[144] In all cases, the crude product was sufficiently pure to be used directly in the next allylation step. Table 5 summarises the acyclic acetals **144** and allylation products **145** which were prepared.



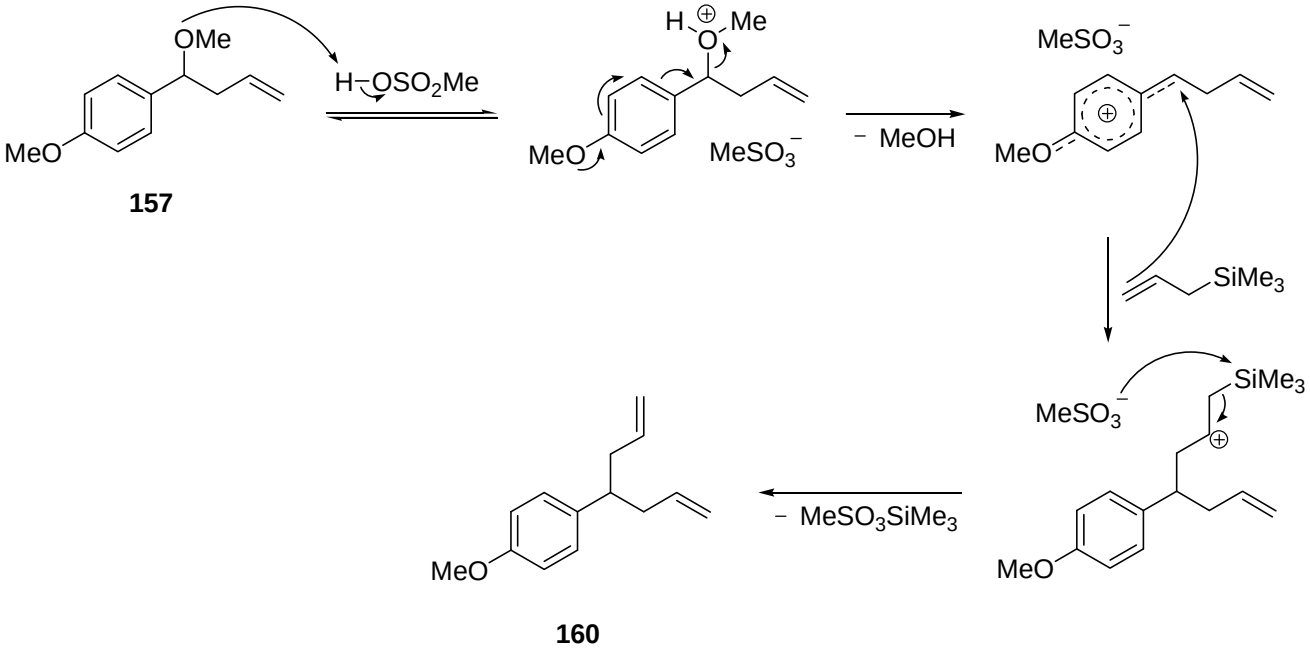
acyclic acetal	yield [%]	racemic allylation product	yield [%]
 **146**	commercially available	 **153**	47[a]
 **147**	97	 **154**	72
 **148**	98	 **155**	25
 **149**	100	 **156**	61
 **150**	100	 **157**	71
 **151**	91	 **158**	36[a]
 **152**	91	 **159**	55

[a] reduced yield owing to high volatility of the product

Table 5. Acyclic acetals and their corresponding racemic allylation products.

The isolated yields of the racemic allylation products correlate with the reactivity of the starting acetals under Brønsted acid activation as indicated by TLC. Whilst the electron-poor 4-nitro-acetal **148** was not very reactive (after 17 h stirring at R.T. only 25% allylation product was isolated) the electron-rich 4-methoxy-acetal **150** was consumed within 20 min

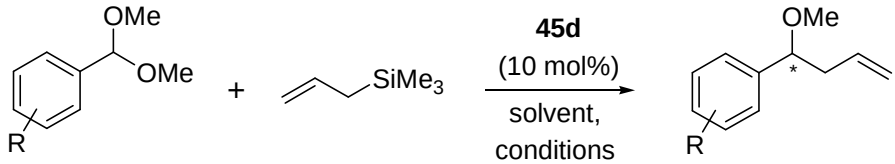
stirring at 0 °C. In this particular case, in addition to the mono-allylated product **157**, the bis-allylated product **160** was also isolated, albeit in 1% yield (Scheme 48).



157 **160**

Scheme 48. Mechanism of formation of bis-allylated product **160**.

Next, phosphoramide (*S*)-**45d** was employed in a series of asymmetric allylation reactions with acetals **144** under different reaction conditions as summarised in Table 6. Since we were unable to obtain baseline separation of the enantiomeric methyl ether products **153**, **154**, and **156** we were unable to determine accurately the enantioselectivity of these reactions and in these cases, simply state whether or not any enantioselectivity was observed.



144 **145**

entry	acetal	**45d**	solvent	conditions	e.r.
1	acetal **146**	(*S*)	CH_2Cl_2	24 h, R.T.	yes[a]
			toluene		yes[a]
2	2-naphthyl-acetal **147**	(*S*)	toluene	24 h, R.T.	yes[a]
3	4-nitro-acetal **148**	(*S*)	CH_2Cl_2	48 h, R.T.	almost no product formed
			toluene		
4	3-methoxy-acetal **149**	(*S*)	CH_2Cl_2	7 h, R.T.	yes[a]
			toluene	7 h, R.T.	yes[a]
5	4-methoxy-acetal **150**	(*S*)	toluene	7 h, 0 °C	54:46
			toluene	–78 to –25 °C, then 4 h –25 °C	54:46
6	4-fluoro-acetal **151**	(*S*)	toluene	24 h, R.T.	62:38
7	4-chloro-acetal **152**	(*S*)	CH_3CN	24 h, R.T.	50:50
			MTBE		54:46
			hexane/toluene (2 :1)		55:45
			CH_2Cl_2		55:45
			Et_2O		57:43
			m-xylene		61:39
			toluene		63:37
			$CHCl_3$		64:36
			benzene		65:35
			p-xylene		66:34
			cyclohexane		67:33
8	4-chloro-acetal **152**	(*R*)	toluene	24 h, R.T.	37:63

[a] the chromatogram does not allow the accurate determination of e.r.

Table 6. Asymmetric allylation reactions employing phosphoramide **45d**.

The reactions of acetals **146** and **147** (entries 1 and 2) supported the postulate of the catalytic cycle described in Chapter 1.3.2. In both reactions with CH_2Cl_2, the starting material was consumed completely as indicated by TLC, and despite the loss of material during work-up and column chromatography, the isolated yield of the allylation product was in both cases higher than 10% (this was the amount of Brønsted acid employed). In general, the reactions in CH_2Cl_2 or solvents with higher polarity showed better conversion than those carried out in toluene or solvents with a similarly low polarity (Table 7). This is to be expected because the rate-determining step in the allylation reaction of acetals (Scheme 11) is the formation of the oxacarbenium ion and a more polar solvent better stabilises both the charged intermediate, and the transition state leading up to it.

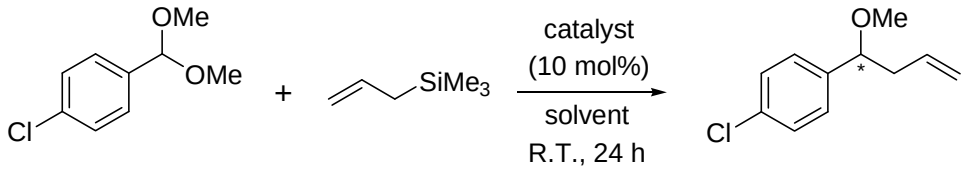
solvent	dielectric constant ε_r
CH_3CN	37.5
CH_2Cl_2	9.1
$CHCl_3$	4.8
MTBE	4.5
Et_2O	4.3
m-xylene	2.4
toluene	2.4
p-xylene	2.3
benzene	2.3
cyclohexane	2.0
hexane	1.9

Table 7. Solvents employed in the asymmetric allylation and their dielectric constant at 20 °C.[145]

The influence of the substituents on the aromatic ring can be observed nicely by comparing entries 3 and 4 in Table 6. In the case of the electron-deficient 4-nitro-acetal **148**, almost no product was formed even after 48 h. In contrast, reaction with the more electron-rich 3-

methoxy-acetal **149** was complete within 7 h. This was also the case with the 4-methoxy-acetal **150** even though the reactions were performed at lower temperatures (entry 5). Interestingly, both reactions (at 0 °C and –25 °C) gave the same e.r. Originally, I had postulated a slightly higher value might be observed in the reaction with 4-fluoro-acetal **151** in comparison to 4-chloro-acetal **152** reasoning that the more electron-withdrawing fluoro-substituent might lead to a tighter ion pair between the oxacarbenium ion and the chiral anion and therefore to a better differentiation of the enantiotopic faces. The reaction with 4-fluoro-acetal **151** was performed in toluene and surprisingly, gave a slightly lower e.r. than the reaction with 4-chloro-acetal **152** under the same conditions (entry 6 and 7). Since the reaction with 4-methoxy-acetal **150** did not give a good e.r. in toluene we chose to screen different solvents in the reaction with the less reactive 4-chloro-acetal **152** because the allylation products from this substrate showed baseline separation by chiral HPLC analysis (entry 7). The fact that cyclohexane and *p*-xylene gave the best e.r. values was in line with our expectations; both non-polar solvents (Table 7) should maintain a contact ion pair in the reactive intermediate which we postulated would be critical for effective enantiocontrol. Unfortunately, when cyclohexane was employed as the solvent, the catalyst precipitated out of solution after 1.5 h; this was not a problem using *p*-xylene as solvent. I also synthesised the (*R*)-enantiomer of the phosphoramide (*R*)-**45d** to check that this woul provide the opposite enantiomer. Indeed, employing this acid in the reaction of 4-chloro-acetal **152** in toluene pleasingly led to the same e.r. value for the product although now favouring the opposite enantiomer (entry 8).

In order to investigate the influence of different 3,3'-substituents on the e.r., we synthesised catalysts (*S*)-**45e**, (*R*)-**45a** and (*R*)-**45g** and employed these in the allylation reaction with 4-chlorobenzaldehyde dimethyl acetal **152** in different solvents. Table 8 summarises the results from these reactions.



152 **159**

entry	catalyst	solvent	e.r.
1	(*S*)-**45e**	toluene	41:59
2	(*S*)-**45e**	cyclohexane/toluene (2:1)	41:59
3	(*S*)-**45e**	$CHCl_3$	48:52
4	(*R*)-**45a**	toluene	58:42
5	(*R*)-**45a**	cyclohexane	60:40
6	(*R*)-**45a**	$CHCl_3$	50:50
7	(*R*)-**45g**	toluene	54:46
8	(*R*)-**45g**	*p*-xylene	57:43
9	(*R*)-**45g**	$CHCl_3$	52:48

Table 8. Catalyst and solvent study of the asymmetric allylation of 4-chloro-acetal **152**.

With each catalyst the highest selectivity was obtained again with non-polar solvents (entries 1, 2, 5, 8) in comparison to $CHCl_3$ (entries 3, 6, 9). Catalysts (*S*)-**45e** and (*R*)-**45g** are more acidic due to their electron-withdrawing groups and, as indicated by TLC, showed better activity than catalysts **45d** and (*R*)-**45a**. Sterically demanding *i*-Pr-(*R*)-**45a** catalyst which has proved to be the catalyst of choice in many asymmetric Brønsted acid-catalysed reactions,[81] did not show a significantly higher selectivity in our case. Unfortunately, 10-Br-9-anthracenyl-(*R*)-**45g** catalyst with a flat anthracene moiety, which maybe predisposed to forming non-covalent π-π interactions with the substrate/intermediate, gave the lowest selectivities. Overall, the tolyl-(*S*)-**45d** catalyst was the best match for the dimethyl acetal system in terms of enantioselectivity affording allylated methyl ether **159** in 67:33 e.r under the best conditions.

Finally, I looked at other dialkyl acetals and found that 4-chlorobenzaldehyde diethyl acetal gave poor results with the tolyl-(*S*)-**45d** catalyst in terms of conversion and enantioselectivity (48:52). The corresponding di-*n*-propyl and dibenzyl acetals were also investigated but we were unable to obtain baseline separation of the enantiomers to allow an accurate determination of the enantioselectivity with these substrates.

The conclusions which can be drawn from this set of experiments with different phosphoramide catalysts **45** and the different starting acetals **144** were:

i) A chiral Brønsted acid can impart enantioselectivity on the allylation of dimethyl acetals.

ii) Reactions carried out in solvents with a low polarity like toluene, *p*-xylene and cyclohexane (note: solubility issues) were more enantioselective than those carried out in more polar solvents like CH_3CN and CH_2Cl_2. This can be explained by a contact ion pair as an intermediate, which is better maintained in a less polar solvent.

iii) However, whilst a non-polar solvent is necessary to obtain noticeable e.r. values, conversion of the starting acetal is significantly reduced by carrying out the reaction in such solvents. Decreasing the reaction temperature might improve the e.r. but it will also lead to a further reduction in the rate of the reaction.

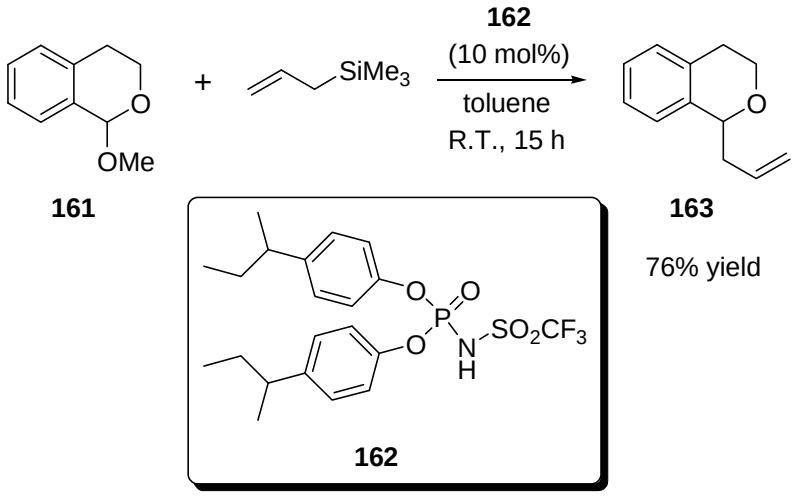
iv) Catalyst (*S*)-**45d** gave the highest enantioselectivities for the dimethyl acetal system.

3.2.2 Racemic cyclic acetals derived from an isochroman framework

The outline study had shown that a chiral Brønsted acid could be used to catalyse an enantioselective Hosomi Sakurai allylation of a simple acetal; however the very slow rate of reaction suggested that this was not going to be a particularly efficient process. Whilst I could have investigated more acidic activators (*vide infra*), we instead turned our primary attention

to a more reactive acetal substrate, namely 1-methoxyisochroman **161**, which proved more suitable for a detailed study. Acetals contained within an isochroman framework are particularly attractive substrates since this structural motif is present in a number of drugs (medicines, agrochemicals), and drug candidates, as well as in a range of natural products.[146]

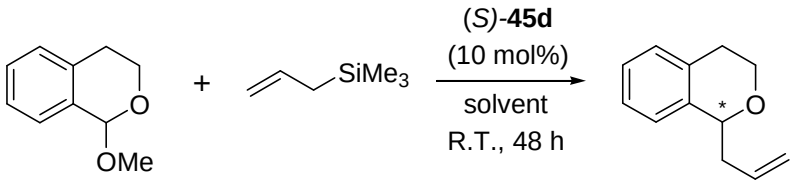
1-Methoxyisochroman **161** was prepared in one step by DDQ oxidation of isochroman in the presence of MeOH (*vide infra*). A test reaction with racemic catalyst **162** revealed that this new class of acetal reacts more readily under *N*-triflyl phosphoramide catalysis than did the dimethyl acetals we had investigated in our outline study (Scheme 49). The 1-allylisochroman product **163** was isolated in 76% yield. Racemic *N*-triflyl phosphoramide **162** was prepared from 4-*sec*-butylphenol in 48% yield according to the general procedure.[87]



Scheme 49. Allylation of 1-methoxyisochroman **161** using racemic *N*-triflyl phosphoramide **162** as catalyst.

3.2.2.1 Solvent screen

A small solvent screen, employing tolyl-(*S*)-**45d** as the catalyst, once again highlighted the importance of this variable on enantioselectivity (Table 9).



161 **163**

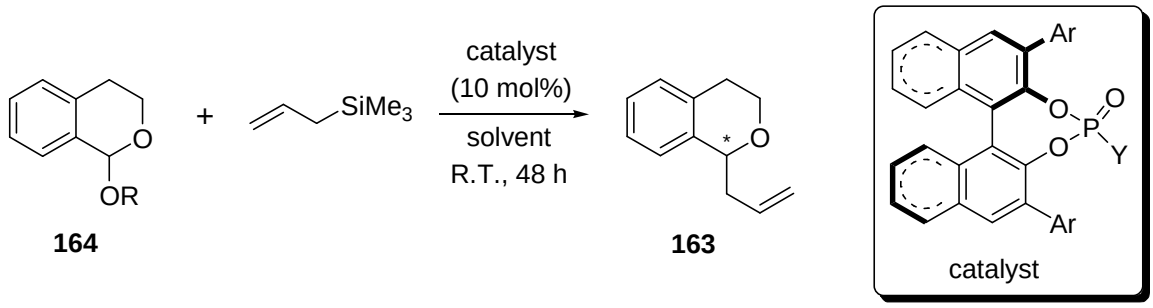
entry	solvent	e.r.
1	CH_3CN	53:47
2	CH_2Cl_2	57:43
3	toluene	60:40
4	*p*-xylene	62:38

Table 9. Solvent screen with 1-methoxyisochroman **161** employing tolyl-(*S*)-**45d** as catalyst.

CH_3CN and CH_2Cl_2 functioned as good solvents in terms of reactivity but were poor choices for enantioselectivity (entries 1 and 2). Using toluene as the solvent, a product e.r. of 60:40 was obtained (entry 3); the use of *p*-xylene led to a further small improvement (e.r. 62:38) (entry 4). Thus once again, reactions carried out in non-polar solvents led to better e.r. values.

3.2.2.2 Screening of different catalysts

In order to identify the optimal catalyst for our system, a selection of chiral Brønsted acids was screened with 1-alkoxyisochromans **164** (Table 10). Their synthesis was described in Chapter 3.1.



entry	catalyst	Ar	Y	solvent	e.r. R = Me	e.r. R = Et
1	(*S*)-**45d**	*p*-tolyl	NHTf	*p*-xylene	62:38	
2	(*S*)-**45e**	3,5-$(CF_3)_2C_6H_3$	NHTf	*p*-xylene	50:50	
3	(*R*)-**45a**	2,4,6-(*i*-Pr)$_3C_6H_2$	NHTf	*p*-xylene	50:50	
4	(*R*)-**45f**	9-anthracenyl	NHTf	*o*-xylene	73:27	84:16
5	(*R*)-**45g**	10-Br-9-anthracenyl	NHTf	*o*-xylene	82:18	90:10
6	(*R*)-**45g**	10-Br-9-anthracenyl	NHTf	*p*-xylene	82:18	
7	(*R*)-**45g**	10-Br-9-anthracenyl	NHTf	*m*-xylene	80:20	
8	(*R*)-**45h**	10-*p*-tolyl-9-anthracenyl	NHTf	*o*-xylene	63:37	67:33
9	(*R*)-**45i**	4-Br-1-naphthyl	NHTf	*o*-xylene	56:44	65:35
10	(*R*)-H_8-**45j**	10-Br-9-anthracenyl	NHTf	*o*-xylene	69:31	72:28
11	(*R*)-**107**	10-Br-9-anthracenyl	$NHSO_2C_6F_5$	*o*-xylene	50:50	50:50
12	(*R*)-**32h**	10-Br-9-anthracenyl	OH	*o*-xylene		no conversion
13	(*R*)-**32i**	10-F-9-anthracenyl	OH	*o*-xylene		50:50

Table 10. Catalyst screening of asymmetric allylation of 1-alkoxyisochromans **164** in xylenes.

Analogues possessing the commonly used 3,5-bis-trifluoromethylphenyl and 2,4,6-triisopropylphenyl substituents at the 3,3'-positions of the binaphthyl scaffold, catalysed the reaction, but afforded racemic product (entries 2 and 3). It was only when we introduced anthracenyl substituents at the 3,3'-positions that we began to observe more significant levels of enantioselectivity (entry 4). Incorporating a bromo substituent into the 10-position of the anthracene unit led to a further improvement from 73:27 to 82:12 in enantiomeric ratio (entry 5). The 10-bromoanthracene-9-boronic acid is commercially available and therefore as readily accessible as its unsubstituted analogue, and from a practical viewpoint, phosphoramide (*R*)-**45g** is a more soluble catalyst compared with unsubstituted anthracenyl derivative (*R*)-**45f**. Employing *p*- and *m*-xylene as solvents with this catalyst, gave the same level of enantioselectivity than in *o*-xylene (entries 6 and 7). In a brief structure-activity study, the significance of the anthracenyl framework was demonstrated by the poor enantioselectivity observed with the 4-bromo-naphthyl derivative (*R*)-**45i** (entry 9). Partially reducing the binapthyl core to afford an acid with a tetrahydronaphthyl core ((*R*)-H_8-**45j**) also failed to improve matters (entry 10). When we replaced the bromo substituent in (*R*)-**45g** with a larger 4-tolyl substituent ((*R*)-**45h**), this change also led to a reduction in enantioselectivity and also in reactivity (entry 8). Racemic product was obtained when the triflyl group in (*R*)-**45g** was substituted for a pentafluorophenylsulfonyl group ((*R*)-**107**), which makes the catalyst more acidic (entry 11). In order to probe the influence of the bromo substituent on the 10-anthracenyl position, I planned to synthesise the other 10-halo-9-anthracenyl phosphoramides. My first target was the 10-fluoro-9-anthracenyl phosphoramide, which turned out not to be accessable as described in Chapter 3.1. However, whilst we were unable to access the phosphoramide, we did synthesise the phosphoric acid. The fluoro substituents appeared to have a significant effect on the acidity of this phosphoric acid. While the 10-bromo-9-anthracenyl phosphoric acid (*R*)-**32h** was not acidic enough to induce allylation (entry 12), 10-fluoro-9-anthracenyl phosphoric acid (*R*)-**32i** was now able to catalyse the

allylation, although with no enantioselectivity (entry 13), which might suggest a different reaction mechanism. With this result and the synthetic problems in mind, we decided not to pursue the preparation of other 10-halo-9-anthracenyl phosphoramides.

In summary, catalyst (*R*)-**45g**, bearing a 10-Br-9-anthracenyl substituent on the 3,3'-positions of the binaphthyl scaffold provided the highest enantioselectivities. This catalyst has not been reported in the literature before and might find applications in other Brønsted acid-catalysed reactions.

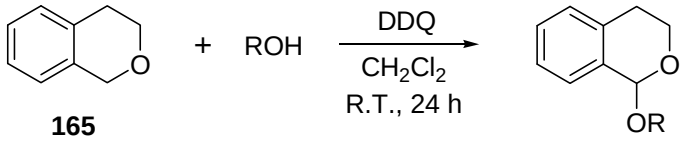
3.2.2.3 Further optimisation

With the optimal catalyst in hand, we next investigated the effect of different catalyst loadings and reaction concentrations on the enantioselectivity of the product. Employing 30 mol% of (*R*)-**45g** increased the reaction rate, as indicated by TLC, but led to the same level of enantioselectivity (e.r. 80:20) than when 10 mol% catalyst was used (e.r. 82:18). Similar observations were made by running the reaction at 0.1 M (e.r. 76:24) and 2 M (e.r. 80:20) in comparison to 0.5 M (e.r. 82:18). While the more concentrated reaction gave almost the same e.r. and an increase of the rate, more dilute reaction concentrations exhibited a slight decrease in both selectivity and rate.

We were pleased to find out that catalyst (*R*)-**45g** could be recovered and re-used without observing any decrease in enantioselectivity or activity. To achieve this, the catalyst was eluted from the column by increasing the polarity of the eluents after the allylated product had been collected. When a significant amount of the used catalyst from several reactions had been collected, the material was columned again with the usual eluents (see Experimental Section). After the HCl wash the catalyst was ready to be used again.

3.2.2.4 Effect of the leaving group

Before moving on to investigate the scope of the reaction with various substituted isochroman acetals, I chose to study one last variable in the substrate, namely the nature of the alkoxy leaving group. Whilst the generally accepted mechanism of reaction of acetals involves an S_N1-like process in which expulsion of the leaving group precedes nucleophilic addition, detailed mechanistic studies have shown that S_N2-like pathways or at least 'exploded transition states' in which the leaving group is still associated with the substrate as the new bond is being formed, can also operate.[71,147,148] We therefore investigated the allylation of different 1-alkoxyisochromans **164**, which were synthesised by DDQ oxidation of isochroman **165** in the presence of the corresponding alcohol ROH.[114] Table 11 summarises the isolated yields after column chromatography.

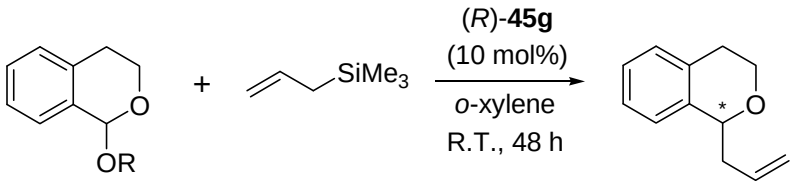


165 **164**

R	yield [%]	R	yield [%]
Me	74	*i*-Pr	52
Et	58	*t*-Bu	22
n-Pr	49	CH_2CF_3	52

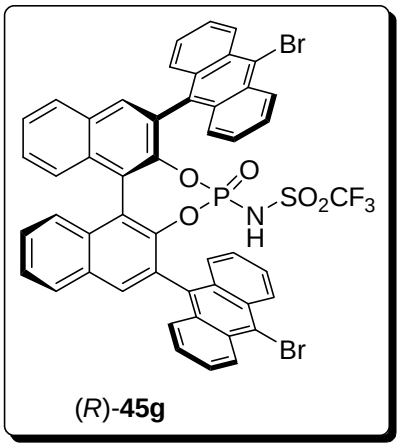
Table 11. Summary of yields of 1-alkoxyisochromans **164** prepared by DDQ oxidation of isochroman **165** in the presence of the corresponding alcohol.

These alkyl acetals were employed in the allylation using our optimal phosphoramide catalyst (*R*)-**45g**. The observed e.r. values of the 1-allylisochroman product **163** are summarised in Table 12.



164 **163**

entry	R	e.r.
1	H	59:41
2	Me	82:18
3	Et	90:10
4	*n*-Pr	76:24
5	*i*-Pr	70:30
6	*t*-Bu	50:50
7	**171**	59:41
8	Ph	53:47
9	CH_2CF_3	51:49

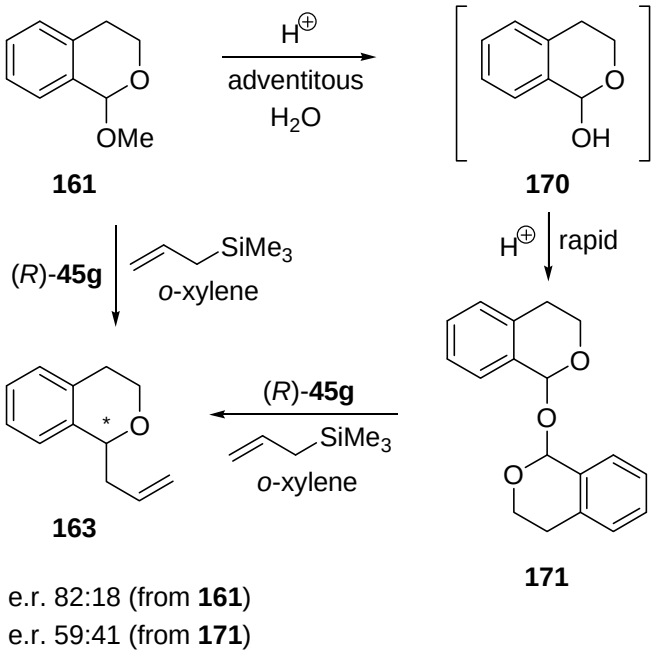


(*R*)-**45g**

Table 12. Summary of e.r. values obtained from the asymmetric allylation of different 1-alkoxyisochromans **164** employing (*R*)-**45g** as catalyst.

In the allylation of ethyl acetal **166** we observed a change, and more specifically, an increase in enantioselectivity (e.r. 90:10) (entry 3) when the reaction was performed under otherwise identical reaction conditions as with methyl acetal **161**. Increasing the size of the leaving group further, however, had a deleterious effect; thus the *n*-propoxy acetal **167** gave the allylation product in 76:24 e.r. (entry 4), and with *i*-propoxy acetal **168**, a further reduction to 70:30 e.r. was observed (entry 5). The *t*-butyl acetal **169** was not only a comparatively poor substrate in terms of reactivity, but also afforded essentially racemic product (entry 6). These results follow a trend, namely that the more sterically hindered the leaving group in the starting material, the lower is the e.r. of the allylated product. Only the methyl acetal **161** did not follow this trend, giving a lower e.r. (82:12) than might have been expected (entry 2). Analysis of the reaction mixture revealed this particular starting material reacted rapidly

(within minutes) with adventitious water, to provide the lactol **170**, which under the reaction conditions, led to the dimer **171**. We prepared this bis-acetal independently by DDQ oxidation of isochroman **165** in the presence of H_2O in 78% yield as single diastereoisomer[149] (stereochemistry was not determined), and showed that not only was this a substrate for the reaction, but it also provided the allylation product in much lower enantioselectivity (e.r. 59:41) (entry 7) (Scheme 50).



Scheme 50. Competing allylation between 1-methoxyisochroman **161** and dimer **171**.

The same result was obtained by employing lactol **170** as the starting material (entry 1), which was prepared quantitatively by DIBALH-reduction of isochroman-1-one **172**.[150] Since the methyl acetal is more susceptible to hydrolysis than ethyl acetal **166** (as indicated by TLC), this racemic background reaction serves to erode the enantioselectivity in the former reaction and goes some way to accounting for the reduced enantioselectivity observed with methyl acetal **161**. In an effort to prevent this racemic background reaction, we added 3 Å molecular sieves to the reaction mixture, hoping that these would scavenge any adventitious

H_2O from the reaction mixture. However, we now observed a significant decrease in product enantioselectivity when employing methyl acetal **161** (e.r. 63:37) as well as ethyl acetal **166** (65:35) in distilled *o*-xylene. The drop in enantioselectivity may arise from an interaction of the molecular sieves with the catalyst since no reaction was observed when stirring ethyl acetal **166** with allyltrimethylsilane in distilled *o*-xylene in the presence of molecular sieves. In synthesising phenyl acetal **173**, we hoped the flat leaving group might lead to an increase in enantioselectivity; however, this substrate afforded essentially racemic allylation product (e.r. 53:47) (entry 8). A similar result was observed in the allylation of 1-(2',2',2'-trifluoroethoxy)isochroman **174** (e.r. 51:49) (entry 9). This result was particularly disappointing considering the structural similarity to 1-ethoxyisochroman **166**.

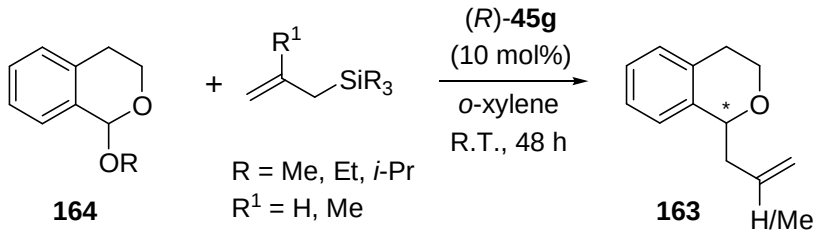
The leaving group effect described above was also observed when ethyl acetal **166** was employed in the allylation with different phosphoramide catalysts (Table 10). In each case, the product enantioselectivity was higher than when using methyl acetal **161** as the starting material. Again, the 10-Br-9-anthracenyl phosphoramide (*R*)-**45g** gave the best selectivity, and in the case of ethyl acetal **166**, a pleasing 90:10 e.r. In another attempt to improve this enantioselectivity we reduced the reaction temperature to 5 °C; however this had no effect on the enantioselectivity but, as indicated by TLC, the reaction rate was significantly lower. The e.r. value dropped to 81:19 when the reaction temperature was increased to 40 °C although as expected, the rate of the reaction was slightly higher.

In summary, I have shown that the alkoxy leaving group in the starting material plays a significant role in the product enantiomeric ratio. Generally, the smaller the alkoxy leaving group, the higher is the e.r. of the product. Methyl acetal **161** is an apparent exception to this rule, although in this particular case, reaction of the starting acetal with adventitious water provides dimer **171** which reacts in an almost racemic allylation, leading to a reduced overall enantioselectivity. Ethyl acetal **166** together with catalyst (*R*)-**45g** gave the highest product

enantioselectivity (90:10) which provides the basis for the investigation of the scope and limitations of the developed method in Chapter 3.2.2.7.

3.2.2.5 Employing different allylsilanes

In employing different allylsilanes, we investigated a last variable in the optimisation of our developed process. Table 13 gives an overview of the allylsilanes which were examined in the reaction with different isochroman acetals **164** together with the observed e.r. values of the corresponding allylated product.



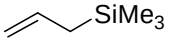
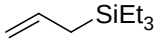
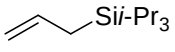
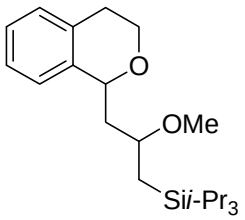
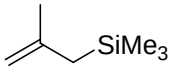
entry	allylsilane	e.r. R = Me	e.r. R = Et
1		82:12	90:10
2		67:33	75:25
3		 single diastereoisomer **175**	
4		60:40	59:41

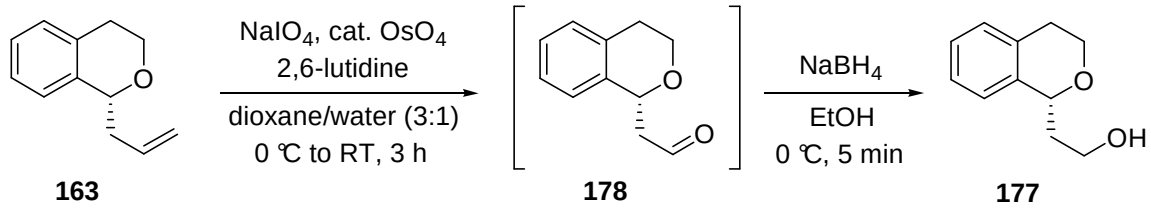
Table 13. Summary of e.r. values obtained from the asymmetric allylation of 1-alkoxyisochromans **164** employing different allylsilanes.

In comparison to allyltrimethylsilane (entry 1), the use of allyltriethylsilane (entry 2) led to a reduction in enantioselectivity with methyl acetal **161** (e.r. 67:33) as well as ethyl acetal **166** (e.r. 75:25) as starting material. Again, the latter gave the higher e.r. value. Allyltriisopropylsilane did not provide the desired allylation product (entry 3); instead, compound **175** was isolated in 26% yield as a single diastereoisomer amongst a range of unidentified by-products. The stereochemistry in **175** was not determined. 2-Methallyltrimethylsilane afforded the corresponding allylation product **176** with low enantioselectivtiy with both starting materials (e.r. 60:40 and 59:41, respectively) (entry 4).

In conclusion, allyltrimethylsilane is the allylsilane of choice and was used as the nucleophile when investigating the scope and limitations of the reaction (Chapter 3.2.2.7).

3.2.2.6 Determination of the absolute stereochemistry

The absolute stereochemistry of 1-allylisochroman **163**, which was prepared by employing phosphoramide **45g** with (*R*)-configuration, was determined by comparison of the observed $[\alpha]_D$ value with the literature $[\alpha]_D$ value of enantiomerically enriched alcohol **177**. **177** was prepared by a one-pot oxidative cleavage–reduction sequence in 77% yield (the intermediate aldehyde **178** was not isolated) (Scheme 51).[151] For a sample of **163** with 82:18 e.r. we measured an $[\alpha]_D^{20}$ = +102.2 (*c* 1.08, CH_2Cl_2) and compared it with the literature $[\alpha]_D^{20}$ = +43.5 (*c* 0.20, CH_2Cl_2) for a sample with 80:20 e.r.[152] This leads to a (*R*)-(+)-configuration which has been established in a previous publication by a crystal structure of a derivative of alcohol **177**.[153]

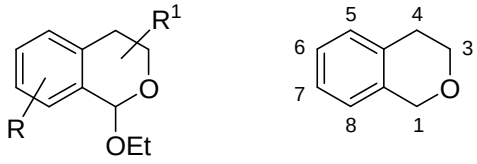


Scheme 51. One-pot oxidative cleavage–reduction sequence of 1-allylisochroman **163** to obtain alcohol **177**.

The absolute stereochemistry of other allylation products from different substrates was assigned by analogy.

3.2.2.7 Scope and Limitations

In order to probe the scope and limitations of our developed method, we next synthesised a range of differently substituted ethyl acetal substrates **179**, which were reacted with allyltrimethylsilane in the presence of phosphoramide (*R*)-**45g**. Figure 23 outlines the numbering of atoms for isochroman systems.

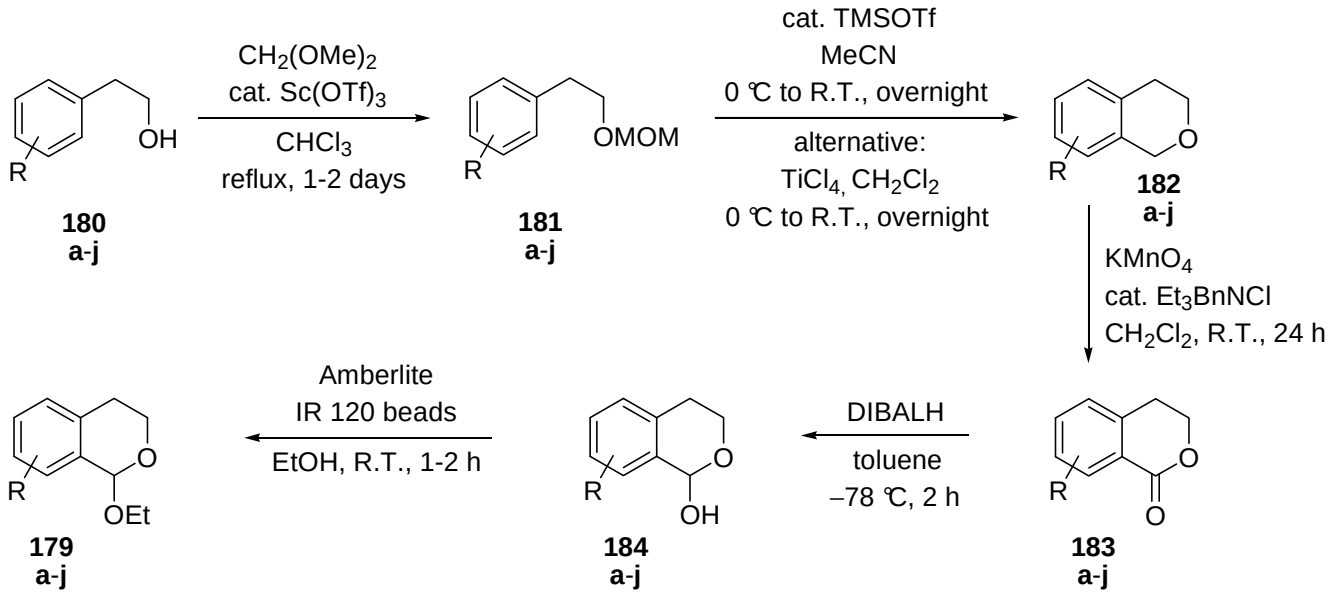


179

Figure 23. Substituted ethyl acetals **179** and numbering of the isochroman system.

3.2.2.7.1 Synthesis of substrates

The majority of substrates were prepared following the steps in the Scheme in Table 14. It summarises these substrates together with the corresponding yields for each step.

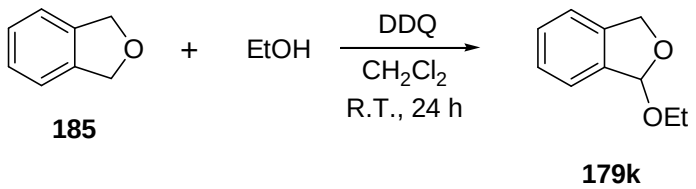


entry	substituent	**181** yield [%]	**182** yield [%]	**183** yield [%]	**179** yield [%][b]
1	5-Me **a**	97	86	76	89
2	6-Me **b**	-	68[a,b]	65	83
3	7-Me **c**	quant.	80	-	41[d]
4	8-Me **d**	-	68[a,b]	28	78
5	5-Br **e**	99	89	82	98
6	5-CF_3 **f**	-	44[b]	82	88
7	7-OMe **g**	quant.	-	42[b]	74
8	7-F **h**	99	77	75	77
9	3,3-dimethyl **i**	-	-	38[c]	72
10	4,4-cyclopropyl **j**	85	-	24[b]	84

[a] **182b** : **182d** = 2.6 : 1.0; [b] over two steps;; [c] over three steps;
[d] prepared from **182c** by DDQ oxidation in the presence of EtOH

Table 14. Summary of yields towards the synthesis of 1-ethoxyisochromans **179**.

Apart from 1-phenyl-1-(hydroxymethyl)cyclopropane **180j**, which was prepared quantitatively by reduction of 1-phenyl-1-cyclopropane-carboxylic acid,[154] all alcohols **180** were commercially available. MOM-protection with FDMA in the presence of 5 mol% of $Sc(Otf)_3$ gave MOM ethers **181** in excellent yields.[155] These underwent a Friedel Crafts cyclisation induced by $TiCl_4$,[156] or 10 mol% of TMSOTf,[114] to afford isochromans **182** in moderate to good yields. MOM ether **181b/d** gave a mixture of inseparable isochromans **182b** and **182d** in a 2.6 : 1.0 ratio (entries 2 and 4). The ratio reflects the steric hindrance in the Friedel Crafts cyclisation; thus the electrophilic substitution preferably occurs at the *para* position leading to isochroman **182b**, than at the *ortho* position, leading to isochroman **182d**. Oxidation to lactones **183** was achieved with $KMnO_4$ in the presence of a phase-transfer catalyst TEBAC.[157] Pleasingly, isochroman-1-ones **183b** and **183d** were now separable by column chromatography (entries 2 and 4). A smooth DIBALH-reduction led to lactols **184**, which were isolated but not characterised.[150] The crude products were instead stirred in EtOH with acidic Amberlite IR 120 beads to provide ethyl acetals **179** in good to excellent yields. Ethyl acetal **179c** was prepared by DDQ oxidation of isochroman **182c** in the presence of EtOH. In the same fashion, 1-ethoxyisobenzofuran **179k** was synthesised from commercially available phthalan **185** in a pleasing 89% yield (Scheme 52).



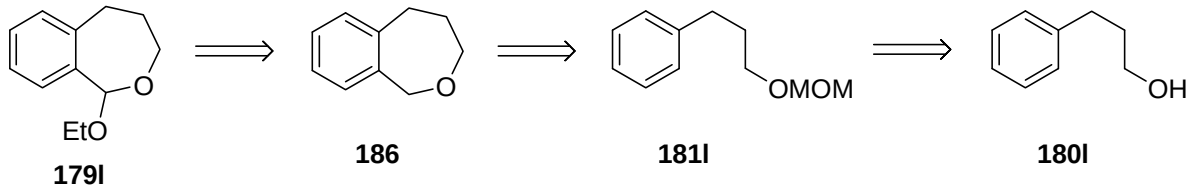
185 **179k**

Scheme 52. DDQ oxidation of phthalan **185** to obtain 1-ethoxyisobenzofuran **179k**.

Whilst the DDQ oxidation approach to isochroman acetals **179** is potentially more efficient in terms of number of steps, I did not favour this route for three reasons: first, the work-up on larger scale was very time-consuming; second, it was difficult to remove traces of unreacted

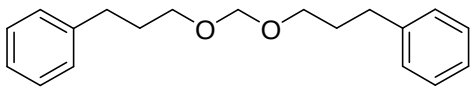
isochroman from the desired 1-ethoxy product by column chromatography since both compounds have similar polarity; third, the reaction is not particularly high yielding with sterically more hindered alcohols than MeOH. Therefore, we decided to use this route only where necessary.

We thought we might be able to employ a DDQ oxidation to prepare 1-ethoxy-3,4,5-trihydro-2-benzoxepin **179l** from benzoxepin **186** (Scheme 53). To this end, MOM ether **181l** was prepared from commercially available alcohol **180l** in 98% yield according to the general procedure.[155] Unfortunately, intramolecular cyclisation of MOM ether **181l** with either $TiCl_4$ or TMSOTf failed and the product mixture contained unreacted starting material together with acetal **187** and only trace amounts of the desired product (Figure 24).



179l **186** **181l** **180l**

Scheme 53. Retrosynthesis of 1-ethoxy-3,4,5-trihydro-2-benzoxepin **179l**.

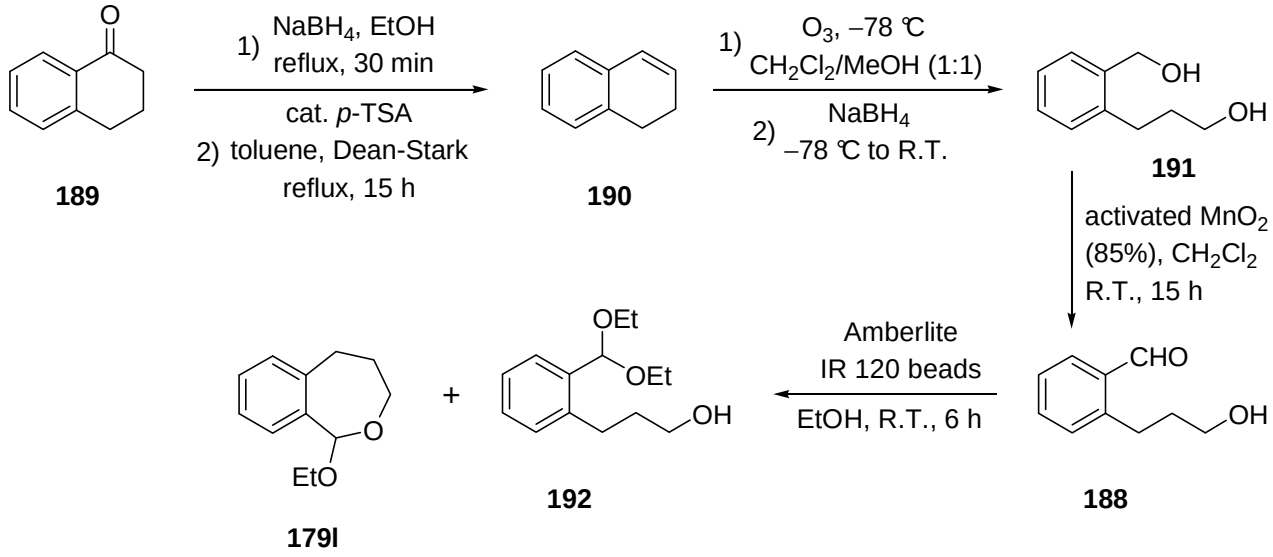


187

Figure 24. Formaldeyde diphenpropyl acetal **187**.

Considering an alternative route to 1-ethoxybenzoxepin **179l**, we postulated that aldehyde **188** should undergo cyclisation and acetalisation when stirring in EtOH in the presence of an acid catalyst. For the preparation of **188**, we were able to find a literature procedure starting with 1-tetralone **189**, which underwent a reduction–dehydration sequence to provide 1,2-dihydronaphthalene **190** in 87% overall yield (Scheme 54).[158] Ozonolysis and subsequent

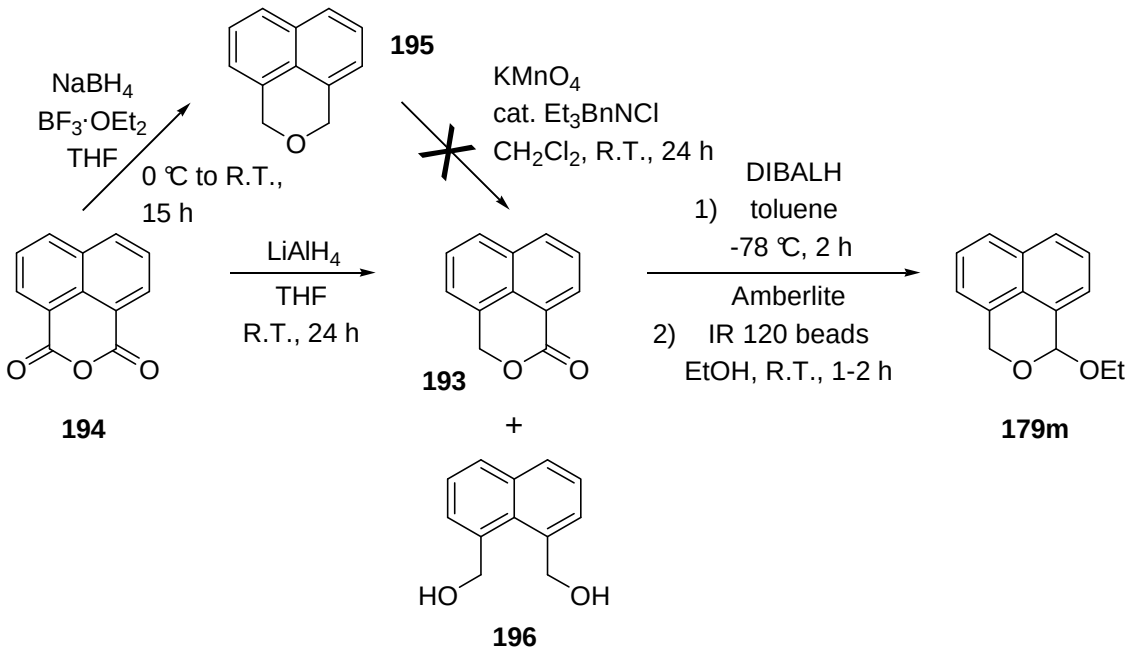
reduction of the intermediate ozonide led to 2-(3'-hydroxypropyl)benzyl alcohol **191** in 76% yield.[159] Activated MnO_2 (85%) chemoselectively oxidised the benzylic alcohol in **191** to afford 2-(3'-hydroxypropyl)benzaldeyde **188** in 86% yield.[159] Finally, hydroxyl aldehyde **188**, which exists in $CDCl_3$ 100% in the open form, was stirred in EtOH with Amberlite IR 120 beads to provide a mixture of the desired 1-ethoxy-3,4,5-trihydro-2-benzoxepin **179l** (56%) and 2-(3'-hydroxypropyl)benzaldehyde diethyl acetal **192** (12%) as a by-product, along with unreacted starting material (12%).



Scheme 54. Synthetic route to 1-ethoxy-3,4,5-trihydro-2-benzoxepin **179l** starting from 1-tetralone **189**.

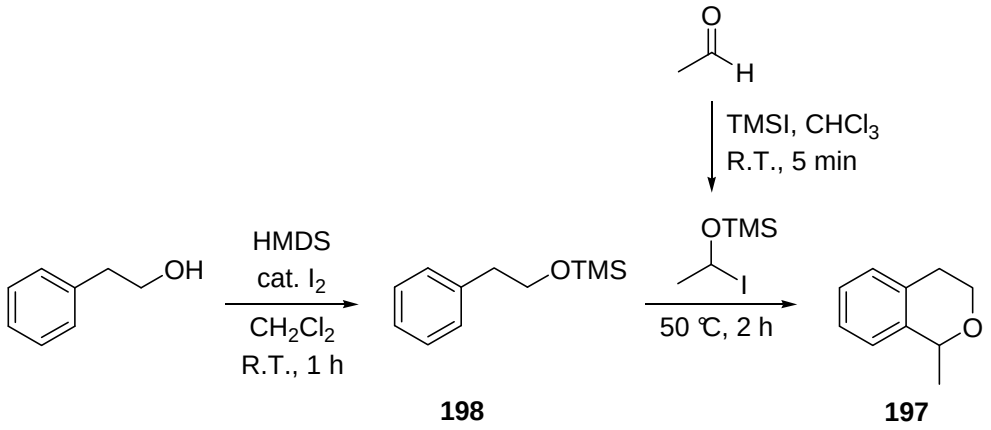
To avoid a DDQ oxidation, we planned to prepare 1-ethoxy-3*H*-naphtho[1,8-cd]pyran **179m** from 1*H*,3*H*-naphtho[1,8-cd]pyran-1-one **193** (Scheme 55). In a first attempt, 1,8-naphthalic anhydride **194** was reduced with $NaBH_4$ and $BF_3{\cdot}OEt_2$ to provide 1*H*,3*H*-naphtho[1,8-cd]pyran **195** in 74% yield. Its partial oxidation to pyran-1-one **193** using $KMnO_4$ in the presence of a phase-transfer catalyst TEBAC failed and led instead to anhydride **194**. Fortunately, a literature procedure reported **193** as a "by-product" in the $LiAlH_4$ reduction of 1,8-naphthalic anhydride **194**.[160] Using these conditions provided 1,8-dihydroxymethylnaphthalene **196** in 24% and desired pyran-1-one **193** in 41% yield.

Subsequent DIBALH reduction and conversion of the lactol to the ethyl acetal as before afforded 1-ethoxy-3*H*-naphtho[1,8-cd]pyran **179m** in 84% yield.



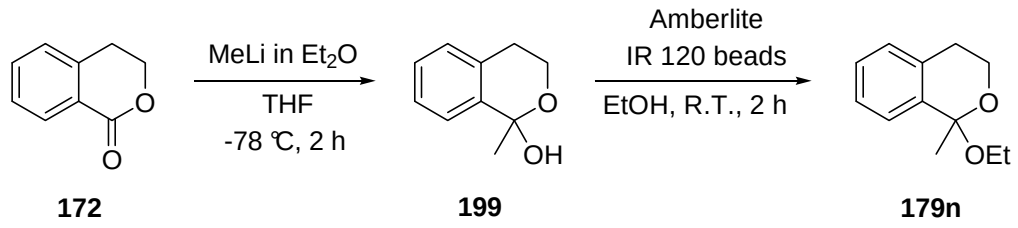
Scheme 55. Synthetic route to 1-ethoxy-3*H*-naphtho[1,8-cd]pyran **179m** starting from 1,8-naphthalic anhydride **194**.

I also wanted to synthesise 1-ethoxy-1-methylisochroman **179n** by DDQ oxidation of 1-methylisochroman **197**, expecting oxidation of this electron-rich starting material would give the desired acetal in a good yield. A literature procedure suggested the cyclisation of 2-phenylethyl trimethylsilyl ether **198**, which was prepared by TMS protection of 2-phenylethyl alcohol in 98% yield, with TMSI-masked acetaldehyde would provide the isochroman **197** (Scheme 56).[161] Unfortunately, the desired product was obtained in impure form in only 32% yield after difficult column chromatography because several other products with similar polarity were formed during the reaction.



Scheme 56. Attempt to 1-methylisochroman **197**.

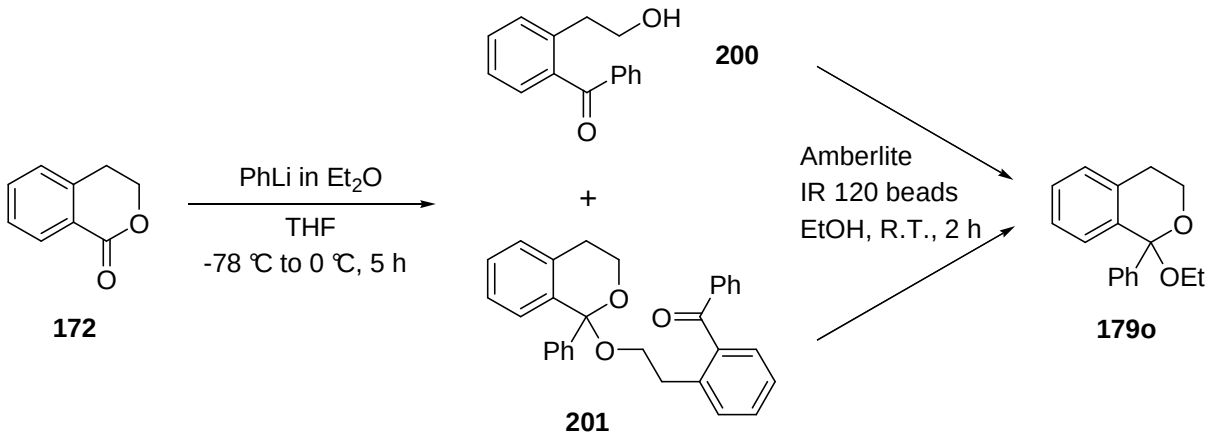
Therefore, I decided to carry out a nucleophilic addition of MeLi on to lactone **172** (Scheme 57), which was synthesised by oxidation of isochroman with fuming nitric acid in 99% yield.[162] The resulting lactol **199** was isolated, but not characterised, and stirred in EtOH with acidic Amberlite beads to afford 1-ethoxy-1-methylisochroman **179n** in 60% yield. The material was not stored but freshly prepared when employed for the asymmetric allylation since it proved to be unstable and rapidly formed the corresponding dimer with adventitious H_2O.



Scheme 57. Preparation of 1-ethoxy-1-methylisochroman **179n**.

Finally, 1-ethoxy-1-phenylisochroman **179o** was prepared in a similar fashion to its 1-methyl analogue, by addition of PhLi to lactone **172** (Scheme 58). Two products were obtained after column chromatography, namely benzophenones **200** and **201**. Stirring both compounds in

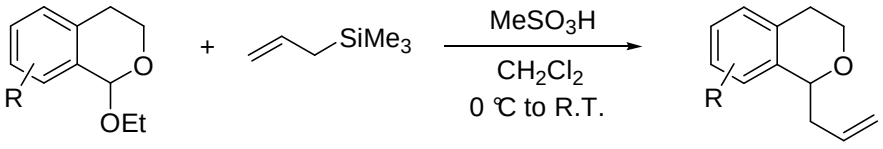
EtOH with acidic Amberlite beads provided 1-ethoxy-1-phenylisochroman **179o** (40% yield in case of **200** as the starting material).



Scheme 58. Preparation of 1-ethoxy-1-phenylisochroman **179o**.

3.2.2.7.2 Asymmetric allylation

In order to be able to determine the e.r. of our allylation products, the retention times of both enantiomers were identified by first analysing racemic samples by chiral HPLC. For this purpose, all racemic products were prepared by carrying out a reaction of the 1-ethoxyisochromans **179** with allyltrimethylsilane in the presence of the achiral acid, methanesulfonic acid. In the case of 5-ring **202k**, a baseline separation of the two enantiomers was not possible. Therefore, an oxidative cleavage–reduction sequence according to Scheme 51 was carried out. It was possible to separate the two enantiomers of alcohol **203** by chiral HPLC. Table 15 summarises the isolated yields of the obtained 1-allylisochromans **202**.



179 **202**

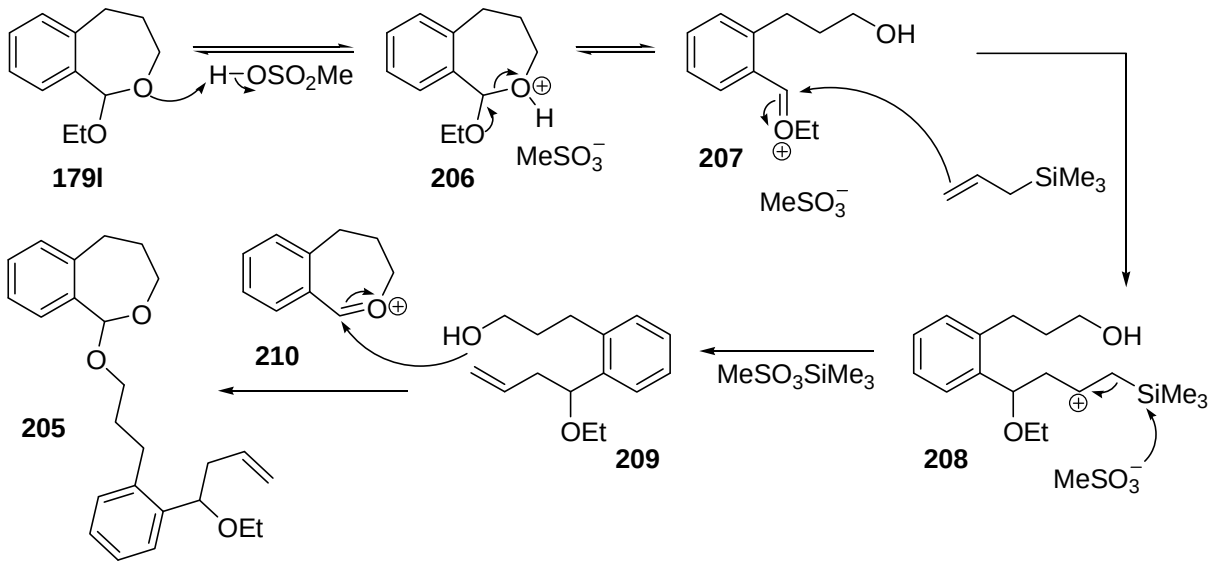
entry	Substrate	product	yield [%]
1	unsub. **166**	**163**	94[a]
2	5-Me **179a**	**202a**	95
3	6-Me **179b**	**202b**	95
4	7-Me **179c**	**202c**	91
5	8-Me **179d**	**202d**	57
6	5-Br **179e**	**202e**	62
7	5-CF_3 **179f**	**202f**	78
8	7-MeO **179g**	**202g**	72
9	7-F **179h**	**202h**	83
10	1-Me **179n**	**202n**	41
		204	38
11	1-Ph **179o**	**202o**	44
12	5-ring **179k**	**202k**	72[a]
13	7-ring **179l**	**202l**	26
		205	15
14	3,3-dimethyl **179i**	**202i**	88
15	4,4-cyclopropyl **179j**	**202j**	94
16	naphthopyran **179m**	**202m**	96

[a] reduced yield owing to volatility of the product

Table 15. Summary of yields of racemic allylation products **202**.

TLC results and comparison of the isolated yields of the allylation products gave an early indication of the reactivity of each substrate under Brønsted acid activation. Most products were prepared uneventfully in good to excellent yields (entries 1-4, 7-9, 12, 14-16). 8-Me **179d** was less reactive and the corresponding product **202d** was isolated in only 57% yield (entry 5), which is probably a consequence of the methyl group being close to the reactive

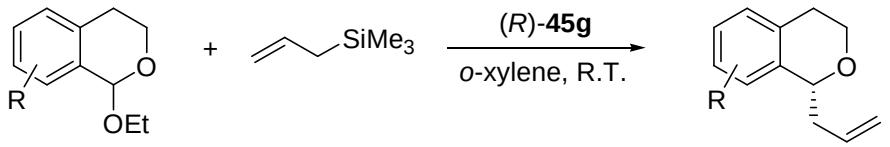
centre and increasing the steric hindrance for the nucleophilic attack. 5-Br **179e** was also less reactive due to the electron-withdrawing bromo substituent, and provided the allylation product in only 62% (entry 6). In 1-Me **179n**, the reactive centre is a quaternary carbon which also increases the steric hindrance and might explain the low product yield of 41% (entry 10). A second product **204** whose structure was not determined was also isolated in 38% as a mixture of diastereoisomers. 1-Ph **202o** was obtained in only 44% yield probably for the same reason as 1-Me **202n** (entry 11). Changing the six-membered ring in the isochroman system to a seven-membered ring had a negative influence on the reactivity of the ethyl acetal. 1-Allylbenzoxepin **202l** was isolated in only 26% together with by-product **205** in 15% yield. Scheme 59 outlines a possible mechanism for the formation of **205**.



Scheme 59. A possible mechanism for the formation of by-product **205**.

1-Ethoxybenzoxepin **179l** gets protonated on the ring oxygen and forms cation **206**. This ring opens through anchimeric assistance from the adjacent ethoxy group. The resulting planar oxacarbenium ion **207** gets attacked by allyltrimethylsilane to give the cationic intermediate **208** in which the positive charge is stabilised by the *β*-effect of silicon. Cleavage of the silyl electrofuge then provides alcohol **209** which attacks oxacarbenium **210** to lead to by-product **205** after deprotonation.

To investigate the scope and limitations of our asymmetric allylation method we reacted each substrate **179** with allyltrimethylsilane under the optimised reaction conditions. To ensure reproducibility, each reaction was repeated at least twice. Table 16 summarises the specific conditions regarding reaction time, concentration and catalyst loading, as well as the yields and e.r. values of the 1-allylisochroman products **202**.



179 **202**

entry	substrate	time [h]	concentration [mol/l]	catalyst loading [mol%]	product	yield [%]	e.r.
1	unsub. **166**	24	1.5	15	**163**	74[a]	90:10
2	5-Me **179a**	7	1.5	10	**202a**	84	92:8
3	6-Me **179b**	6	1	15	**202b**	79	87:13
4	7-Me **179c**	8	1.5	15	**202c**	71	87:13
5	8-Me **179d**	48	1.5	20	**202d**	52	79:21
6	5-Br **179e**	48	1.5	20	**202e**	45	83:17
7	5-CF_3 **179f**	48	1.5	20	**202f**	24	88:12
8	7-MeO **179g**	24	1.5	15	**202g**	65	79:21
9	7-F **179h**	48	1.5	15	**202h**	41	80:20
10	1-Me **179n**	24	1.5	15	**202n**	33	63:37
11	1-Ph **179o**	24	1.5	15	**202o**	16	51:49
12	5-ring **179k**	24	1.5	15	**202k**	61[a]	74:26
13	7-ring **179l**	48	1.5	20	**202l**	traces	n.d.
14	3,3-dimethyl **179i**	24	1.5	20	**202i**	67	57:43
15	4,4-cyclopropyl **179j**	8	1.5	20	**202j**	44	57:43
16	naphthopyran **179m**	24	1.15	15	**202m**	42	69:31

[a] reduced yield owing to volatility of the product

Table 16. Overview of the asymmetric allylation of 1-ethoxyisochromans **179**.

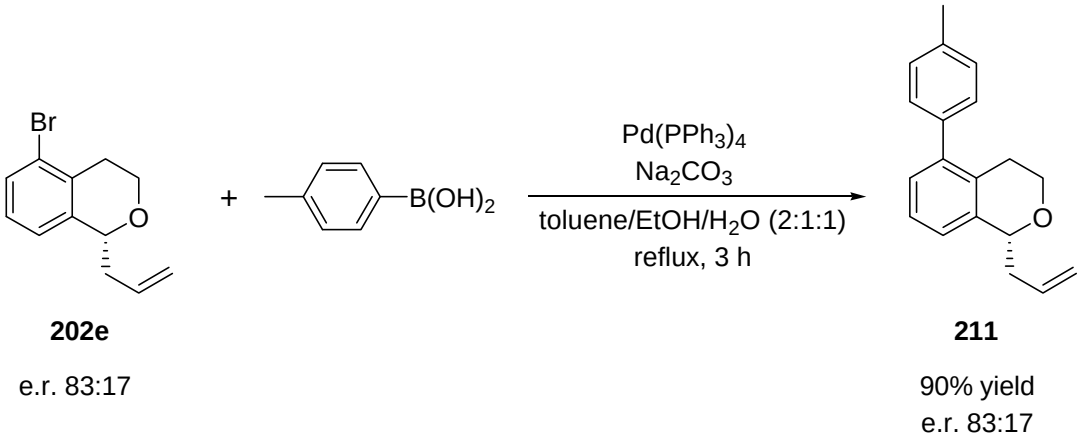
As already mentioned 1-ethoxyisochroman **166** led to a pleasing 90:10 enantiomeric ratio and the product **163** was isolated in 74% yield after 24 h. The volatility of the 1-allylisochroman led to a reduction in yield (entry 1). Introducing an electron-donating methyl group on to the aromatic ring led to an increase in the reaction rate in the case of **179a**, **179b** and **179c**, and a slower rate in the case of **179d**, which can be explained by the Me group increasing the steric hindrance close to the reacting centre (entries 2-5). A higher catalyst loading was necessary to achieve an acceptable yield with this substrate in a reasonable reaction time. The same explanation accounts for the decrease in yield going from 5-Me **202a** to 8-Me **202d**. The enantioselectivity also decreases in this order which is most likely due to the latter substrates not effectively fitting in the "chiral pocket" of the chiral counterion. It is noteworthy, that the highest enantioselectivity (e.r. 92:8) was obtained with 5-Me **179a**. **179e** and **179f** with an electron-withdrawing bromo- and trifluoromethyl group on the 5-position also led to good e.r. values (entries 6 and 7), which shows that substituents on the 5-position are well tolerated. However, in these two cases the low reactivity of both substrates warranted the use of a high catalyst loading and a longer reaction time for the products to be isolated in acceptable yields. The methoxy group on the 7-position gave 65% yield (entry 8), and the enantioselectivity (e.r. 79:21) was comparable with that obtained with the 7-F substrate **179h** (e.r. 80:20), which provided the product in 41% yield after 48 h (entry 9). These results suggest that sterics and not electronics might be key in controlling the enantioselectivity of these allylations. Having a quaternary carbon as the reactive centre led to a moderate enantioselectivity of 63:37 e.r. in the case of 1-Me **179n** and to no selectivity in the case of 1-Ph **179o** (entries 10 and 11). Both corresponding products were also isolated in low yields (33% and 16%, respectively). A change from the six-membered ring in the isochroman system to a five-membered ring also led to a significant drop in product enantioselectivity (e.r. 74:26) for 5-ring **202k** (entry 12). The yield of 61% was reduced due to the volatility of the product and is therefore not representative of the efficiency of this reaction. I did not determine the e.r. of the allylation

product derived from 7-ring **179l** because only traces of product were obtained even with a higher catalyst loading (entry 13). Introducing substituents on the 3- and 4-positions of the isochroman system was not tolerated: both substrates, 3,3-dimethyl **179i** and 4,4-cyclopropyl **179j**, reacted with very low enantioselectivity of 57:43 e.r. (entries 14 and 15), and with a high catalyst loading, yields of 67% and 44%, respectively, were achieved. Changing the whole structure of the starting material from an isochroman system to naphthopyran **179m** led to a product in moderate e.r. of 69:31 and a yield of 42% (entry 16).

In summary, the majority of the 1-ethoxyisochromans **179** gave moderate to good yields of the allylation product. Those substrates which led to low product yields can be explained by electronic and steric factors. In terms of enantioselectivity, substituents on the 5-position of the isochroman system were well tolerated while with substituents on the 7- and 8-positions a slight drop in selectivity was observed. This is most likely due to the substrate not effectively fitting in the "chiral pocket" of the chiral counterion meaning both enantiotopic faces are available for reaction. Converting the reactive centre into a quaternary carbon also led to a significant drop in the corresponding product e.r. values. Introducing substituents on to the 3- and 4-positions was also not tolerated very well, whilst a change of the whole isochroman structure resulted in moderate enantioselectivities at best.

3.2.2.8 Applications of the method

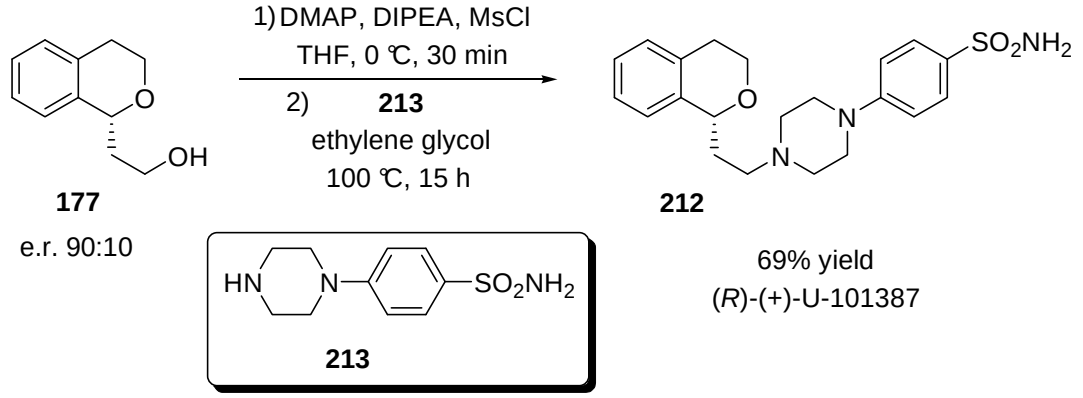
In order to demonstrate the synthetic utility of our developed allylation method, we employed the procedure in two applications. First, enantiomerically enriched 1-allyl-5-bromoisochroman **202e** underwent a Suzuki coupling with 4-tolylboronic acid to provide 1-allyl-5-tolylisochroman **211** in a pleasing 90% yield (Scheme 60).



Scheme 60. Suzuki coupling of enantiomerically enriched 1-allyl-5-bromoisochroman **202e** to provide 1-allyl-5-tolylisochroman **211**.

The e.r. of the starting material (83:17) used in this reaction was maintained in the product as revealed by chiral HPLC analysis. This reaction suggests enantiomerically enriched halogenated 1-allylisochromans can be used in cross-coupling reactions which opens the door to a broad range of transformations after the asymmetric allylation step.

In the second application, drug (*R*)-(+)-U-101387 **212** which is used for the treatment of psychosis especially schizophrenia, was synthesised from enantiomerically enriched alcohol **177** (Scheme 61).[153]



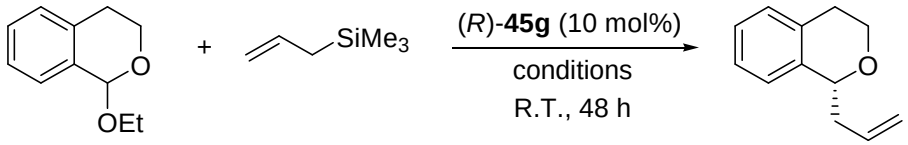
Scheme 61. Synthesis of drug (*R*)-(+)-U-101387 **212**.

177 was prepared from 1-allylisochroman **163** (e.r. 90:10) in an oxidative cleavage–reduction sequence as outlined in Scheme 51. The alcohol functionality in **177** was next converted into a good leaving group with MsCl. The resulting mesylate was not isolated but treated with piperazine **213** in a nucleophilic substitution. Drug **212** was isolated in 69% yield after column chromatography and the $[\alpha]_D^{21}$ = +41.1 (*c* 0.36, DMF) was a good match with the literature value of $[\alpha]_D$ = +48 (*c* 0.88, DMF) for an enantiomerically pure sample.[153]

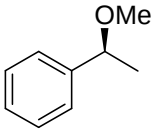
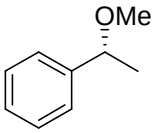
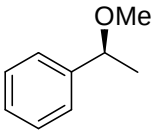
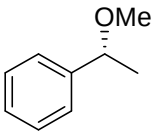
3.2.2.9 Understanding the origins of enantioselectivity

3.2.2.9.1 Additives and catalyst preparation

To shed some light on the origins of the observed enantioselectivity, a few test reactions and experiments were carried out. We decided to investigate the effect of different catalyst preparations and additives on the e.r. of the product. To do so, we reacted 1-ethoxyisochroman **166** was reacted with allyltrimethylsilane under conditions which vary from the optimised ones, changing one variable at a time. Table 17 summarises the employed conditions together with the corresponding e.r. value of product **163**. All of the reactions were carried out with the same batch of catalyst which gave 88:12 e.r. for the allylation product in a control experiment under optimised conditions.



166 **163**

entry	Conditions	e.r. of **163**
1	catalyst treated with toluene	66:34
2	catalyst treated with $MgSO_4$ and toluene	69:31
3	catalyst treated with 3 Å MS and toluene	69:31
4	catalyst HCl wash in Pr_2O	81:19
5	catalyst HCl wash in THF	84:16
6	catalyst HCl wash in THP	83:17
7	catalyst HCl wash in dioxane	80:20
8	*o*-xylene + H_2O (1 drop)	76:24
9	*o*-xylene + EtOH (1 drop)	87:13
10	*o*-xylene +  (1 eq)	88:12
11	*o*-xylene +  (1 eq)	87:13
12	 (solvent)	87:13
13	 (solvent)	86:14
14	anisol (solvent)	72:28
15	benzyl methyl ether (solvent)	66:34
16	Et_2O[a] (solvent)	71:29
17	DME (solvent)	55:45

[a] light yellow precipitate observed after stirring for 1 h

Table 17. Summary of the employed conditions together with the corresponding e.r. value of allylation product **163**.

First, I wanted to look at the preparation of the catalyst. The usual treatment includes washing with hydrochoric acid after column chromatography to ensure the Ca salt is protonated and enters the Et_2O phase. After drying the organic phase over $MgSO_4$ and removing the solvent under reduced pressure, the protonated phosphoramide (*R*)-**45g** was obtained as its ether solvate as analysed by ^{1}H-NMR spectroscopy and this was used in the asymmetric allylation reactions. Because the ether solvate was isolated, we questioned whether different methods of catalyst preparation might influence the enantioselectivity of the reaction. I started my investigation by treating a portion of the catalyst with dry toluene in order to try to remove the ether. To this end, the catalyst was dissolved in toluene and then the solvent was removed under reduced pressure. This procedure was repeated three times and after drying under reduced pressure, the catalyst was used in the asymmetric allylation under otherwise optimised conditions. 1H-NMR spectroscopy analysis proved that the Et_2O solvate molecules had been removed. Interestingly, a significant drop in product enantioselectivity (e.r. 66:34) was observed (entry 1) which is not obvious why this happens. Similar results were obtained by adding $MgSO_4$ or 3 Å MS to a solution of catalyst in dry toluene. After filtration, removal of the solvent and drying under reduced pressure, the phosphoramide was employed in the asymmetric allylation. In both cases, the product e.r. was 69:31 (entries 2 and 3). Clearly, the way in which the catalyst is isolated, plays a crucial role in determining the enantioselectivity of the reaction. A possible explanation is not immediately forthcoming at this stage and further experiments are necessary to draw conclusions from these results. Because the catalyst is used as its Et_2O solvate, we were also interested in investigating if and how other ethers would influence the product e.r. Therefore, we carried out the HCl (aq) wash in different ethers, namely Pr_2O, THF, THP and dioxane. The ^{1}H-NMR spectra revealed that in all four cases the catalyst was isolated as its corresponding ether solvate. In comparison to the optimised conditions using the Et_2O solvate (e.r. 88:12), a slight decrease in e.r. was observed

when employing each ether solvate in the allylation reaction (entries 4-7), again indicating that the preparation of the catalyst affects the e.r. of the allylation product.

I wanted to go a step further by investigating whether or not additives affected the enantioselectivity of the reaction. Adding one drop of H_2O to the reaction mixture led to a drop in the product e.r. (entry 8), which can be explained by the formation of dimer **171** from the starting material and additional H_2O as described in Chapter 3.2.2.4. Dimer **171** itself reacts in an essentially non-enantioselective fashion, and accounts for the overall reduction in enantioselectivity (Scheme 50). Adding one drop of EtOH had little effect on the product enantioselectivity giving a product with 87:13 e.r. (entry 9). To investigate the influence of a chiral additive (if there are interactions with the chiral catalyst in a match – mismatch fashion), in separate reactions, I added one equivalent of (*S*)-1-methoxyethylbenzene **214** (entry 10) and (*R*)-**214** (entry 11) to the reaction mixture; however this had no effect on the enantioselectivity. Employing both ether enantiomers as solvents did not show any significant change in enantioselectivity (entries 12 and 13), showing that at least these chiral solvent molecules did not influence the chiral catalyst and resulting contact ion pair to any great extent. Because of the structural similarity to **214**, I also decided to test anisol (entry 14) and benzyl methyl ether (entry 15) as solvents. Both led to a drop in enantioselectivity to 72:28 and 66:34, respectively, which is probably due to the difference in polarity in comparison to **214**. Anisol and benzyl methyl ether show more of an "ether polarity" where the oxygen atom splits the molecule in two halves while in **214** the methoxy group behaves more like a substituent on the ethylbenzene core. This explanation is strengthened by the fact that employing Et_2O and DME as solvents, both having an even higher polarity, also led to a decrease in product enantioselectivity (71:29 and 55:45, respectively) (entries 16 and 17).

This short study shows that the pre-treatment of the catalyst can have an effect on the enantioselectivity of the product. Different ether solvates led to slight changes in the e.r., whilst treatment of the catalyst with toluene and drying agents led to a larger drop in e.r. Chiral additives did not affect enantioselectivity, neither did their use as solvents.

3.2.2.9.2 Thiophosphoramide (*R*)-108

In order to probe the role of the oxygen in the P=O bond in the optimal catalyst, I synthesised its sulfur analogue (*R*)-**108** as described in Chapter 3.1 (Figure 25).

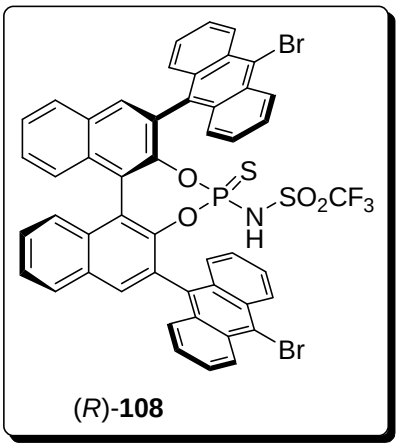


Figure 25. Thiophosphoramide (*R*)-**108**.

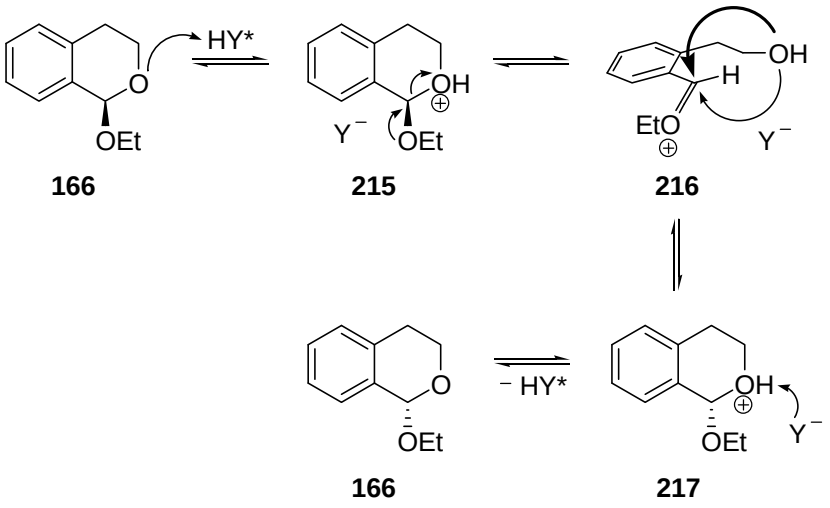
When employing (*R*)-**108** in the asymmetric allylation of 1-ethoxyisochroman **166** I observed two important changes in comparison to its oxygen analogue: i) The rate of the reaction was significantly higher, which fits with the fact that thiophosphoramides are more acidic than phosphoramides;[116] ii) the 1-allylisochroman product **163** was obtained as almost a racemic mixture. This drop in enantioselectivity from 90:10 with the phosphoramide catalyst (*R*)-**45g** to 55:45 with the thiophosphoramide catalyst (*R*)-**108** suggests that the oxygen in the P=O

bond plays an important role in the stereodetermining step. Most likely, a hydrogen bond is formed between the substrate/intermediate to the oxygen of the phosphoramide catalyst in the transition state which will be discussed further in Chapter 3.2.2.10. A hydrogen bond to sulfur is much weaker than to oxygen and therefore longer which leads to a looser association of catalyst and substrate and concomitant reduction in enantioselectivity.

3.2.2.9.3 Proof of a dynamic kinetic resolution

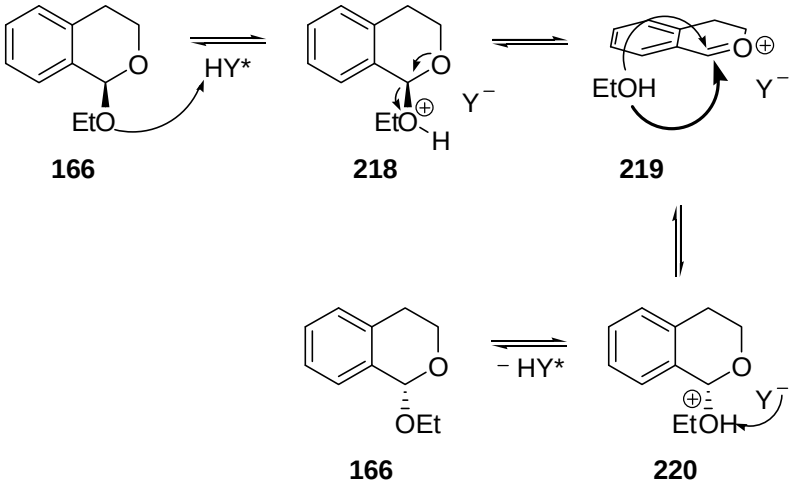
In order to probe the mechanism of our Brønsted acid-catalysed asymmetric allylation, we separated both enantiomers of 1-ethoxyisochroman **166** by chiral semi-preparative HPLC. Each enantiomer was exposed to 10 mol% of phosphoramide catalyst (*R*)-**45g** in *o*-xylene, aliquots were taken and the product e.r. was analysed by chiral HPLC. Aliquots were taken after 30 s, 1 min, 2 min, 5 min, 10 min, 20 min, 30 min, 40 min, 1 h, 2 h, 4 h, 8 h, 24 h and quenched with a few drops of NEt_3. A yellow precipitate was observed which most likely is the triethylammonium salt of the catalyst, and residual NEt_3 was evaporated under reduced pressure (~ 10 mmHg). A few drops of hexane were added and the resulting solution, which contained the product, was analysed by chiral HPLC. We also quenched three aliquots with a mixture of hexane and aqueous NaOH solution to demonstrate that the method of reaction sampling was not affecting the results. Thus, these three times, two aliquots were taken at the same time and quenched with the different methods. In each case, the measured e.r. values were the same. Investigation of the first enantiomer ($t_{R,\text{first}}$ = 8.6 min) revealed a rapid epimerisation within 30 s after addition of the chiral catalyst. Interestingly, each aliquot gave an e.r. value around 53:47 in favour of the first enantiomer instead of a 50:50 mixture. When analysing the second enantiomer ($t_{R,\text{second}}$ = 10.5 min), again rapid epimerisation was

observed, this time with e.r. values around 48:52 in favour of the second enantiomer. Scheme 62 outlines a possible mechanism for the epimerisation of the starting acetal.



Scheme 62. A possible mechanism for the epimerisation of the starting acetal.

Protonation of **166** on the ring-oxygen forms cation **215**, which ring opens through anchimeric assistance from the adjacent ethoxy group. The resulting planar oxacarbenium ion **216** can then be attacked by the free alcohol group from the *si*- or *re*-face. In the Scheme above, attack from the *re*-face provides cation **217**, which, after deprotonation by the conjugate base Y^-, gives enantiomer **166** with the opposite stereochemistry to the starting one. Another possible mechanism is shown in Scheme 63.



Scheme 63. A second possible mechanism for the epimerisation of the starting acetal.

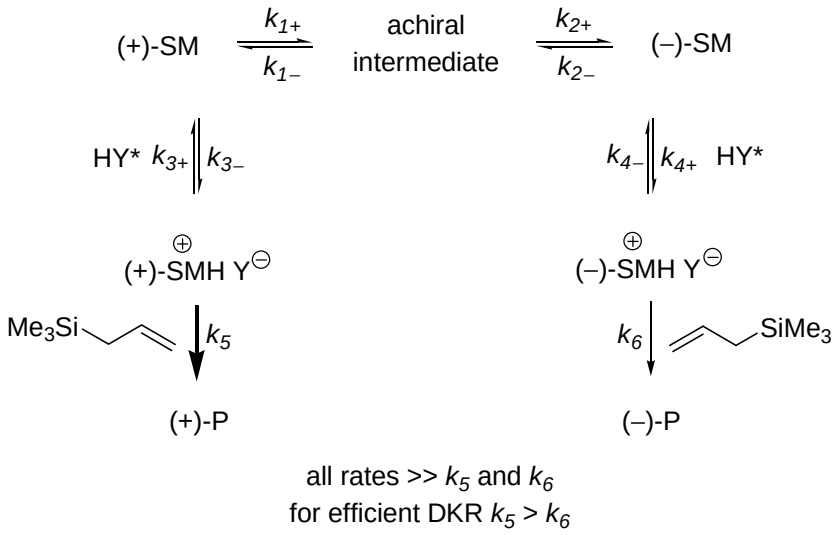
Protonation of enantiomer **166** may alternatively occur on the ethoxy oxygen to form cation **218**, which expels EtOH to leave oxacarbenium ion **219**. This can be attacked by the free EtOH from the *si*- or *re*-face. In the Scheme, attack from the *re*-face provides cation **220**, which after deprotonation by the conjugate base Y^-, gives enantiomer **166** with the opposite stereochemistry to the starting acetal.

In another experiment, the e.r. value of the product was followed throughout the reaction. Racemic 1-ethoxyisochroman **166** was exposed to allylsilane and 10 mol% of catalyst (*R*)-**45g**, and aliquots were taken over 48 h and in each case the e.r. of the product was analysed by chiral HPLC. Aliquots were taken after the times listed in Table 18 and quenched and analysed as described above.

time	e.r. of product	time	e.r. of product
1 min	88:12	2 h	89:11
2 min	86:14	2.5 h	89:11
5 min	89:11	3 h	89:11
10 min	89:11	4 h	89:11
20 min	89:11	5 h	89:11
30 min	89:11	8 h	88:12
40 min	90:10	24 h	89:11
1 h	89:11	48 h	89:11
1.5 h	89:11	after work-up and column	89:11

Table 18. Following the e.r. value throughout the reaction.

Considering, the error in the HPLC measurement is 1.5%, there is no significant change in the e.r. value of the product over the course of the reaction. These experiments suggest that the reaction may be a dynamic kinetic resolution (Scheme 64).



Scheme 64. Dynamic kinetic resolution.

It is therefore assumed, that the chiral Brønsted acid (*R*)-**45g** and both enantiomers of the ethyl acetal form two diastereomeric contact ion pairs. In the subsequent reaction with allyltrimethylsilane, one of the ion pairs reacts distinctly faster than its diastereomer. That is how complete conversion of the racemic substrate **166** into the allylation product **163** with high enantiomeric excess can be rationalised.

3.2.2.10 Proposed transition state

With all our results in hand, I am now able to propose a transition state for each enantiomer of the starting material (Figure 26) with **TS A** being lower in energy than **TS B** and accounting for the observed sense of induction.

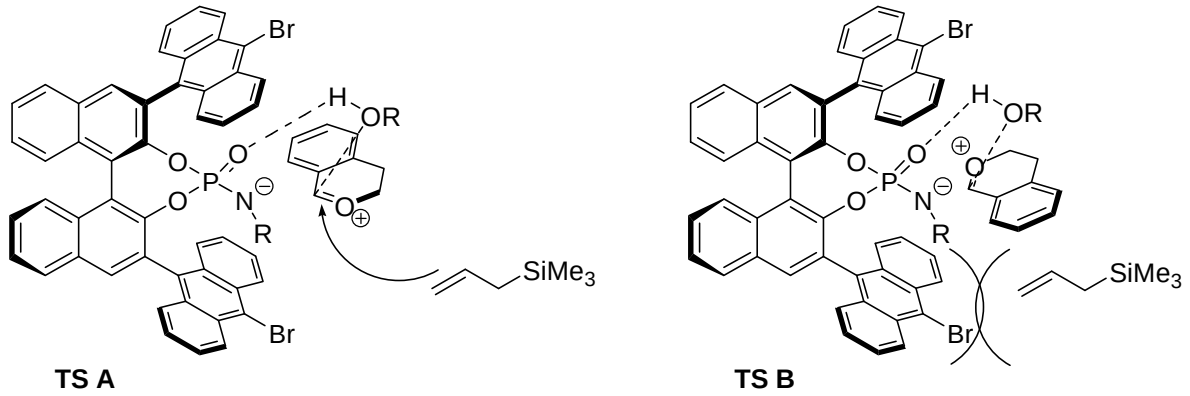


Figure 26. Proposed transition states **TS A** and **TS B**.

Brønsted acid (*R*)-**45g** protonates the alkoxy group of the acetal. Due to the observed leaving group effect, we reason that the alcohol leaving group is still "attached" or at least in close proximity to the oxacarbenium ion which is associated with the phosphoramide anion in a chiral contact ion pair. This is stabilised through intermolecular π-π stacking interactions as well as intermolecular electrostatic interactions. The two ions in the ion pair orientate in such a way that the positive charge of the oxacarbenium ion is compensated by the negative charge delocalised on the OPNTf system. I also invoke a hydrogen bond between the Lewis basic oxygen of the counterion and the hydrogen of the alcohol leaving group which is supported by the result with thiophosphoramide catalyst (*R*)-**108**. A sulfur atom forms a much weaker and therefore longer hydrogen bond than oxygen which results in a looser association of the substrate with the conjugate base. This explains the drop in enantioselectivity on exchanging the oxygen for a sulfur atom. Attack of allyltrimethylsilane occurs from the side opposite to the alcohol leaving group. Transition state **TS A** is favoured over **TS B** since the nucleophilic attack is sterically hindered by one of the 10-Br-anthracenyl-substituents in the latter one. This means the energy difference between **TS A** and **TS B** determines the enantioselectivity of the allylation step.

3.3 Synthesis of sulfonic acids

The outline study described in Chapter 3.2.1 had shown that a chiral Brønsted acid could be used to catalyse an enantioselective Hosomi Sakurai allylation of a simple acetal; however the very slow rate of reaction suggested that this was not going to be a particularly efficient process. At that time I decided to turn my attention to more reactive acetal systems, namely 1-alkoxyisochromans. After carrying out a detailed study on these substrates (Chapter 3.2.2), we again turned towards simple acyclic acetals and decided to investigate more acidic activators. Since sulfonic acids are effective activators for the allylation of acyclic acetals with allyltrimethylsilane,[69] we were interested in synthesising a range of enantiomerically pure chiral sulfonic acids. Whilst a few chiral sulfonic acids have been reported,[163,164] these approaches do not allow sufficient flexibility to generate the structural diversity that we desired, and which is invariably required for optimisation studies in asymmetric synthesis methodology. We therefore wanted to synthesise a new class of sulfonic acids based on the binaphthalene framework (Figure 27). When we started this project, sulfonic acids based on a binaphthalene framework were not known in the literature and we designed our own strategy towards their synthesis.

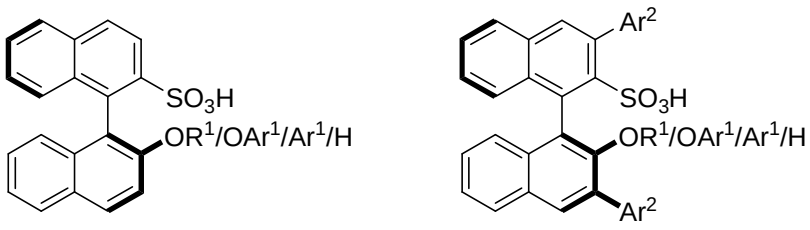
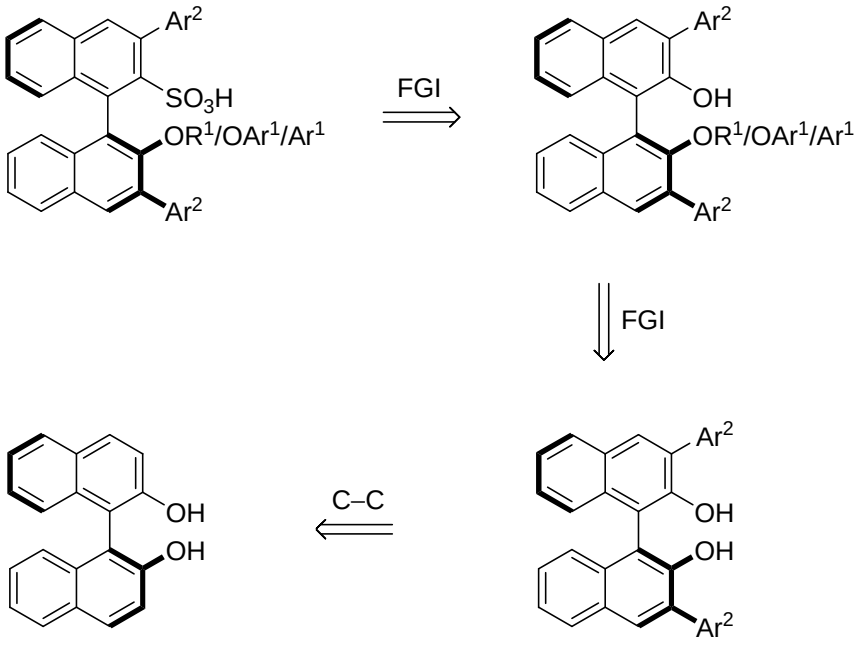


Figure 27. A new class of sulfonic acids.

In all cases, the sulfonic acid would be introduced at the 2-position of the binaphthalene framework; structural diversity would be introduced by functionalising the 2'-position. We

would also use the 3-position (and 3'-position for simplifying the synthesis) as a second site for introducing structural diversity. The retrosynthesis of these acids is summarised in Scheme 65: Substituents would be introduced to the 3,3'-positions by cross-coupling reactions. Then, the 2'-position would be derivatised. This can be achieved in a variety of ways. Simple alkyl ethers can be introduced by standard Williamson ether synthesis[165] or with Mitsunobu chemistry.[166] *O*-Arylation could be achieved by Ullmann[167] or Buchwald-Hartwig-type *O*-arylations,[168] whilst aryl substituents can be introduced by Suzuki coupling of the monotriflate with different boronic acid coupling partners.[169] Finally, manipulation of the remaining hydroxyl group at the 2-position would allow introduction of the sulfonic acid moiety.

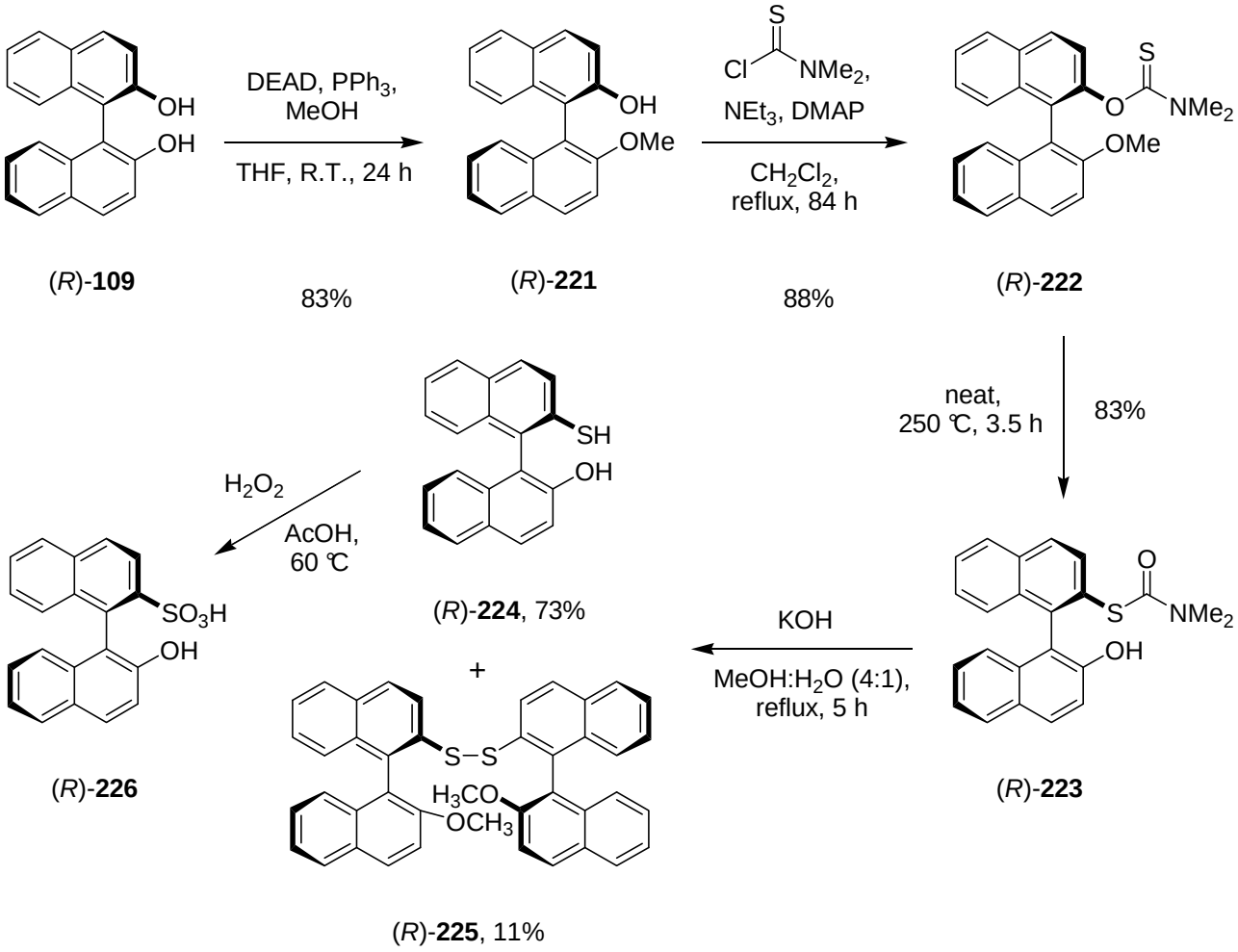


Scheme 65. Retrosynthesis of 3,3'-substituted chiral sulfonic acids.

A literature search identified an excellent procedure for carrying out the final part of the sequence. In 1997, Woodward developed a route to a 2-thiobinaphthol[170] which we proposed should be easily converted into a sulfonic acid by oxidation of the thiol moiety. This

transformation can be achieved with a variety of oxidants,[171,172] although most commonly with H_2O_2.[164,173,174] Since the route allows access to 5-10 g quantities of the product with excellent yields for all intermediates, and also delivers an enantiomerically pure end-product, we decided to follow this approach to our sulfonic acids.

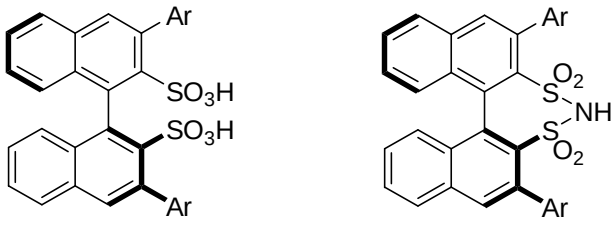
The synthesis of our first target is outlined in Scheme 66. For a first attempt we decided to convert the alcohol functionality at the 2'-position into a simple methoxy functionality. This would allow a simpler interpretation of NMR spectra since the chemical shift of a methoxy group is remote from the aromatic region where the signals for all the other protons and carbons in the molecule appear.



Scheme 66. Synthesis of sulfonic acid (*R*)-**226** starting from BINOL (*R*)-**109**.

Beginning with enantiomerically pure BINOL (*R*)- or (*S*)-**109**, I introduced the methoxy group into the 2'-position *via* Mitsunobu chemistry,[166] which gave the monomethyl ether (*R*)- or (*S*)-**221** in 83% yield. Flash column chromatography in 100% toluene allowed separation of the product from small amounts of bis-methyl ether and starting material. Reaction of the remaining hydroxyl group in (*R*)- or (*S*)-**221** with *N*,*N*-dimethylcarbamoyl chloride provided the corresponding thiocarbamate (*R*)- or (*S*)-**222** in 88% yield.[170] Noteworthy, *N*,*N*-dimethylcarbamoyl chloride was used as delivered by the supplier while Woodward recrystallised the reagent, and may explain why in our case the reaction time was twice as long and also required higher reaction temperature. Recrystallisation of the product from ethanol ensured the enantiomeric purity of (*R*)-**222** and (*S*)-**222**. Thermolysis of (*R*)- or (*S*)-**222** effected Newmann-Kwart rearrangement and provided carbamate (*R*)- or (*S*)-**223** in 83% yield.[166] Remarkably, despite the forcing conditions required to effect this transformation (250 °C, 3.5 h), the rearrangement proceeded with only slight erosion in enantiopurity; (*R*)-**223** and (*S*)-**223** were isolated in 97.5:2.5 e.r. and 98.7:1.3 e.r., respectively, as measured by chiral HPLC. Unfortunately, it was not possible to find suitable recrystallisation conditions. Since it is only my first attempt towards the sulfonic acids I decided not to improve the e.r. and instead choose to move on to the base-mediated hydrolysis of (*R*)-**223**, which provided thiol (*R*)-**224** in 73% yield.[170] Owing to the propensity for the thiol to undergo air oxidation, the disulfide (*R*,*R*)-**225** was also isolated in 11% yield. The last step in our synthesis involved the oxidation of thiol (*R*)-**224** to the sulfonic acid (*R*)-**226**. The most common oxidant for effecting this conversion is H_2O_2 in acetic acid at high temperature.[164,175] Following this approach, complete conversion of starting material occurred within 2 h. Unfortunately, purification of the crude product turned out to be a problem and could not be solved before the end of the laboratory work. The following strategies will help to find a way of successfully introducing the SO_3H moiety in my class of sulfonic acids.Recently, research groups have started to use 3,3'-disubstituted BINSA **227**[176-

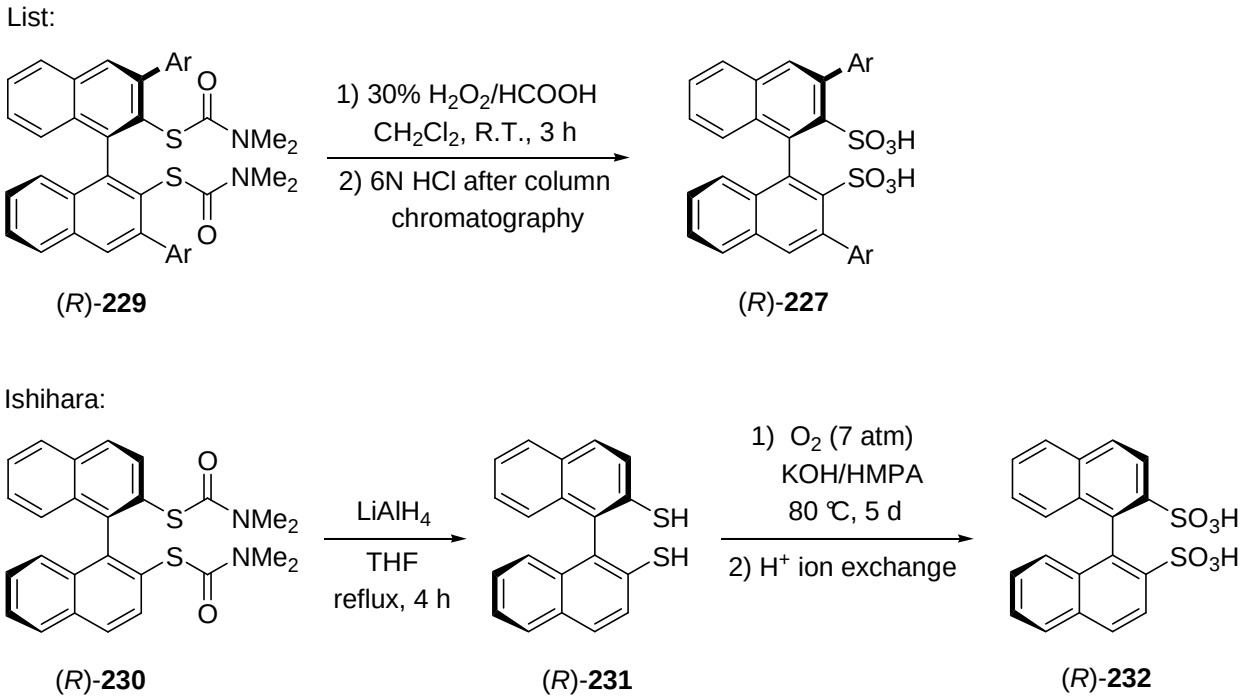
[180] and its disulfonimide derivative **228**[181,182] as strong chiral Brønsted acids in asymmetric organocatalysis (Figure 28).



227 **228**

Figure 28. 3,3'-Disubstituted BINSA **227** and its disulfonimide derivative **228**.

The first class was introduced independently by List and Ishihara who use different approaches for the introduction of the disulfonic acid motif. While List chose the direct oxidation of thiocarbamate **229** with performic acid to obtain BINSA **227**, Ishihara converted thiocarbamate **230** into bis-thiol **231** before oxidation to BINSA **232** under O_2 pressure in HMPA (Scheme 67).



Scheme 67. Different approaches for the introduction of the disulfonic acid motif.

4 Conclusions and Further Work

4.1 Summary

To confirm our hypothesis that a chiral Brønsted acid is able to impart stereoselectivity on the Hosomi-Sakurai reaction of acetals, I investigated the reaction of both acyclic dialkyl acetals as well as racemic cyclic acetals with allyltrimethylsilane, which was catalysed by different chiral Brønsted acids based on a binaphthyl core.

In the first section of the Results and Discussion (Chapter 3.1), the synthesis of a range of phosphoric acids and phosphoramides based on a BINOL core was described. I prepared some catalysts which were already known in the literature but also a selection of new chiral Brønsted acids. In particular, the previously unreported 10-Br-9-anthracenyl phosphoramide (*R*)-**45g** turned out to be the catalyst of choice for our isochroman actal investigation and may find application in other Brønsted acid-catalysed reactions.

In the second section of the Results and Discussion (Chapter 3.2), we employed our synthesised Brønsted acids as catalysts in the Hosomi-Sakurai reaction of acetals with allyltrimethylsilane. First, we started with acyclic acetals derived from benzaldehyde derivatives (Chapter 3.2.1). We tested 3,3'-unsubstituted racemic phosphoric acid *rac*-**143** and 3,3'-bis-tolyl-substituted phosphoric acid (*S*)-**32g** in the reaction of benzaldehyde

dimethyl acetal with allyltrimethylsilane under various reaction conditions; however no allylation product was observed. Since the employed phosphoric acids were not sufficiently acidic to induce the allylation reaction, I decided to turn my attention to more acidic phosphoramides. By employing tolyl-(*S*)-**45d**, allylation product was now formed and more pleasingly, with moderate enantioselectivity as analysed by chiral HPLC. A solvent screen, using tolyl-(*S*)-**45d**, was carried out with 4-chloro-acetal **159** as starting material. Cyclohexane and *p*-xylene, both solvents with a relatively low polarity, gave the best e.r. values, while acetonitrile led to a racemic mixture. This observation fits with the proposal that maintaining the contact ion pair in the reactive intermediate is critical for enantioselectivity. A selection of different dimethyl acetals was synthesised in excellent yields and investigated in the asymmetric allylation. We also examined other 3,3'-substituted phosphoramides and other dialkyl acetals. In this study, the best e.r. values were obtained by employing the tolyl-(*S*)-**45d** catalyst with the dimethyl acetal system. Whilst a low-polarity solvent had proven necessary to obtain noticeable enantioselectivity, conversion of the starting acetal was poor in these solvents. Decreasing the reaction temperature might have improved the enantioselectivity but it would likely also have led to a further reduction in the rate of the reaction. Therefore, we concluded that it would be necessary to investigate a more reactive acetal system and/or more acidic Brønsted acids.

I turned my primary attention to a more reactive acetal system, namely 1-alkoxyisochromans **164**, which proved more suitable for a detailed study of the asymmetric allylation (Chapter 3.2.2). A solvent screen with 1-methoxyisochroman **161** as starting material and tolyl-(*S*)-**45d** as catalyst, once again showed the best enantioselectivity was obtained with solvents of low polarity (*p*-xylene). In order to identify the optimal catalyst for our system, a selection of chiral Brønsted acids was screened. I varied the 3,3'-substituents, reduced the BINOL core to a H_8-BINOL system and replaced the NHTf group by a more acidic $NHSO_2C_6F_5$ group.

Overall, the 10-Br-9-anthracenyl phosphoramide (*R*)-**45g** turned out to give the highest enantioselectivities.

Further optimisation studies revealed that different catalyst loadings and reaction concentrations did not affect the enantioselectivity of the reaction but could be used to increase the reaction rate. Changing the temperature also affected the reaction rate but also the selectivity: increasing the temperature above R.T., a drop in enantioselectivity was observed, while a decrease in temperature did not lead to any improvement in selectivity and just served to reduce the rate. Employing other allylsilanes also failed to improve the enantioselectivity. Pleasingly, catalyst (*R*)-**45g** could be recovered and re-used without observing any decrease in enantioselectivity or activity. We also investigated the nature of the alkoxy leaving group. To this end, different 1-alkoxyisochromans **164** were exposed to the usual reaction conditions. To our surprise, the leaving group in the starting material was found to play a significant role in the product selectivity. Generally, the smaller the alkoxy leaving group, the higher was the e.r. of the product. 1-Methoxyisochroman **161** was an apparent exception to this rule; however in this particular case, reaction with adventitious water provides dimer **171**, which also reacts in a poorly enantioselective allylation and goes some way to accounting for the erosion in enantioselectivity in this case. 1-Ethoxyisochroman **166** together with catalyst (*R*)-**45g** gave the highest product enantioselectivity and provided the basis for investigating the scope and limitations of the developed method. To this end, differently substituted ethyl acetal substrates **179** were synthesised and reacted with allyltrimethylsilane in the presence of phosphoramide (*R*)-**45g**. The majority of these substrates gave moderate to good product yields. In terms of enantioselectivity, substituents on the 5-position of the isochroman system were well tolerated whilst with substituents at the 7- and 8-positions, a slight drop in selectivity was observed. This is most likely due to the substrate not effectively fitting in the “chiral pocket” of the chiral counterion meaning both enantiotopic faces are available for reaction. Converting the

reactive centre into a quaternary carbon also led to a significant drop in enantioselectivity. Introducing substituents into the 3- and 4-positions was not tolerated very well either, and changing the whole isochroman structure gave moderate enantioselectivities.

The absolute stereochemistry of 1-allylisochroman **163** was determined and the other reaction products were assigned by analogy. In order to demonstrate the synthetic utility of our developed method, we employed the procedure in two applications: the Suzuki coupling of enantiomerically enriched 5-brominated 1-allylisochroman **202e** and the synthesis of drug (*R*)-(+)-U-101387 **212**.

To shed light on the origins of the observed enantioselectivity, we decided to carry out some test reactions with different additives, although unfortunately these turned out not be particularly helpful. We also paid special attention to the catalyst preparation, which seems to play a significant role in the enantioselectivity. In another experiment, we employed the sulfur analogue of phosphoramide (*R*)-**45g** in the allylation reaction and a big drop in the e.r. value was observed. Therefore, we reasoned that the oxygen in the P=O bond plays an important role in the stereodetermining step, most likely forming a hydrogen bond to the substrate/intermediate in the transition state. Our Brønsted acid-catalysed asymmetric allylation may be a dynamic kinetic resolution. This is suggested by the rapid racemisation of both single enantiomers of 1-ethoxyisochroman **166** under the optimised reaction conditions and by following the e.r. value during the asymmetric allylation, which remained constant over the course of the reaction. Finally, all results and observations were brought together to generate a transition state model to account for the observed enantioselectivity (Chapter 3.2.2.10).

In the final section of the Results and Discussion (Chapter 3.3), we focused on chiral sulfonic acids. A possible pathway for the synthesis of two new classes of chiral sulfonic acids based on a binaphthyl core was outlined. The synthesis of our first target molecule was also described.

4.2 Further Work

After finishing the synthesis of the 3,3'-unsubstituted sulfonic acid (*R*)-**226** and its investigation in the asymmetric allylation of dimethyl acetals, a range of 3,3'-substituted sulfonic acids could be prepared (based on the knowledge transfer from the 3,3'-substituted phosphoramides) and their enantioselective catalytic potential investigated.

Other mechanistic studies of the isochroman based acetal system could be carried out:

- a cross-over experiment to investigate the mechanism of the acetal epimerisation;
- D-labelling on the 1-position of 1-ethoxyisochroman **166** and measurement of secondary KIEs to shed light on the nature of the reactive electrophile ($sp^3 \rightarrow S_N2$-like or $sp^2 \rightarrow$ oxacarbenium ion)

Computational modelling of the isochroman-based acetal system with a simplified phosphoramide would also be interesting.

Similar electrophiles to 1-alkoxyisochromans could be investigated (Figure 29).

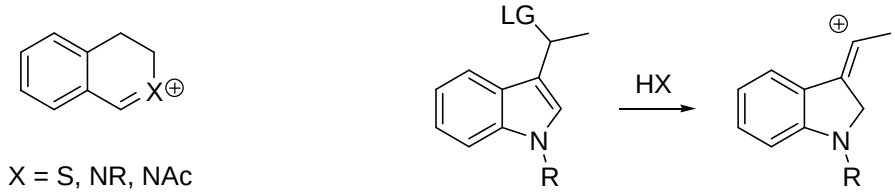


Figure 29. Possible electrophiles for investigation.

5 Experimental Section

5.1 Instrumentation

Elemental analyses were recorded on a Carlo Erba EA1110 simultaneous CHNS analyser and performed by the University of Birmingham microanalytical services. Infra red spectra were recorded either neat as thin films or as a $CHCl_3$ solution between NaCl discs, on a Perkin Elmer FT-IR PARAGON 1000 spectrometer. The intensity of each band is described as s (strong), m (medium), or w (weak) and with the prefix v (very) and suffix br (broad) where appropriate. ^{1}H-NMR spectra were recorded in $CDCl_3$ (unless stated otherwise) at ambient temperature on a Bruker AC-300 (300 MHz), Bruker AMX 400 (400 MHz) or Bruker DRX 500 (500 MHz) spectrometer, and are reported as follows: chemical shift δ(ppm), (number of protons, multiplicity, coupling constant *J* (Hz), assignment). Connectivities were deduced from COSY90, HSQC and HMBC experiments. The term "stack" is used to describe a region where resonances arising from non-equivalent nuclei are coincident, or, in the case of mixtures of compounds (*e.g.* diastereoisomers), to refer to the coincidence of an unresolved resonance proton(s) in both diastereoisomers. "Multiplet", m, is used to describe a region where resonances arising from a single nucleus (or equivalent nuclei) are coincident but coupling constants cannot be readily assigned. Fractional integrations are used when describing mixtures of diastereoisomers, when the resonance for the same proton in the two diastereoisomers does not coincide. Residual protic solvent $CHCl_3$ (δ_H = 7.26 ppm) was used

as an internal reference. ^{13}C-NMR spectra were recorded in $CDCl_3$ (unless stated otherwise) at ambient temperature on a Bruker AC-300 (75 MHz), Bruker AV-300 (75 MHz), Bruker AMX 400 (100 MHz) or Bruker DRX 500 (125 MHz) spectrometer, and are reported as follows: chemical shift δ (ppm), (multiplicity, assignment). The central resonance of $CDCl_3$ (δ_C = 77.0 ppm) was used as an internal reference. ^{31}P-NMR spectra were recorded in $CDCl_3$ (unless stated otherwise) at ambient temperature on a Bruker AV-300 (121 MHz) spectrometer, and are reported as follows: chemical shift δ (ppm), (multiplicity, assignment). ^{19}F-NMR spectra were recorded in $CDCl_3$ (unless stated otherwise) at ambient temperature on Bruker AV-300 (282 MHz) spectrometer, and are reported as follows: chemical shift δ (ppm), (multiplicity, assignment). EI (electron impact) and GC-MS mass spectra were recorded on a VG Prospec mass spectrometer, and TOF-ES+ mass spectra were recorded on a Micromass LCT spectrometer, and are reported as (m/z (%)). HRMS were recorded on a Micromass LCT spectrometer, using a lock mass incorporated into the mobile phase. Melting points were determined using open capillaries on a Gallenkamp MDP350 melting point apparatus and are uncorrected. Optical rotations were measured in chloroform (unless stated otherwise) using an Optical Activity PolAAr2001 automatic polarimeter. Analytical chiral HPLC was performed using a Daicel Chiral Pak AD DAIC19025 250 mm x 4.6 mm chiral column with a flow rate of 1 mL/min.

5.2 Chemicals and Reagents

All reagents were obtained from commercial sources and used without further purification unless stated otherwise. THF and Et_2O were freshly distilled from sodium benzophenone ketyl. Toluene was distilled from Na. MeOH was distilled from Mg + I_2 and stored under N_2 at room temperature over activated 4 Å molecular sieves (activated by heating under a

vacuum for 15 min with a Bunsen flame immediately before use). NEt_3 was distilled from CaH_2 and stored over 4 Å molecular sieves. All solutions are aqueous and saturated unless stated otherwise.

5.3 Reactions

All reactions were conducted in oven-dried (140 °C) or flame-dried glassware under a argon atmosphere, and at ambient temperature (19 to 25 °C) unless stated otherwise, with magnetic stirring. Volumes of 1 mL or less were measured and dispensed with Hamilton gastight syringes. Reactions were monitored by thin-layer chromatography (TLC) using pre-coated glass-backed silica-rapid plates (60A F_{254}) and visualised by UV detection (at 254 nm) and with ammonium molybdate(IV)-cerium(IV) sulfate or potassium manganate(VII) staining dip. Column chromatography was performed on Fluka 60 (40-60 μm mesh) silica gel. Evaporation and concentration under reduced pressure were performed at 50-500 mbar. Residual solvent was removed under high vacuum (< 1 mbar).

5.4 Characterisation

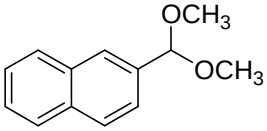
General procedure for the formation of dimethyl acetals derived from arylaldehydes

The dimethyl acetals **147**-**152** were prepared following a previously reported procedure for the preparation of 2-naphthaldehyde dimethyl acetal **147**:[144]

Trimethylorthoformate (0.82 mL, 7.50 mmol) and *p*TSA (5 mg, 0.028 mmol) were added to a solution of the aldehyde (5.00 mmol) in dry MeOH (1.5 mL). After stirring at R. T. for the specified time, $NaHCO_3$ solution (25 mL) and CH_2Cl_2 (25 mL) were added, and the layers

were separated. The organic layer was washed with brine (25 mL) and dried (Na_2SO_4). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product. Unless otherwise stated, the isolated crude product was sufficiently pure for characterisation and further use.

2-Naphthaldehyde dimethyl acetal 147

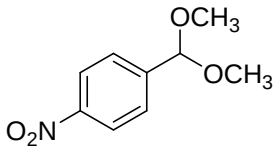


Chemical Formula: $C_{13}H_{14}O_2$
Exact Mass: 202.0994
Molecular Weight: 202.2491
Elemental Analysis: C, 77.20; H, 6.98; O, 15.82

Acetal **147** was prepared from 2-naphthaldehyde (781 mg, 5.00 mmol), trimethylorthoformate (0.82 mL, 7.50 mmol) and *p*TSA (5 mg, 0.028 mmol) in MeOH (1.5 mL) according to the general procedure. After 2 h, work-up afforded acetal **147** as a yellowish liquid (630 mg, 97%): δ_H(300 MHz) 3.38 (6H, s, CH(OC*H*$_3$)$_2$), 5.57 (1H, s, C*H*(OCH$_3$)$_2$), 7.44-7.59 (3H, stack, Ar*H*), 7.81-7.96 (4H, stack, Ar*H*); δ_C(75 MHz, C_6D_6) 52.1 (CH$_3$, OC*H*$_3$), 103.0 (CH, *C*H(OCH$_3$)$_2$), 125.1 (CH, Ar), 126.36 (CH, Ar), 126.40 (CH, Ar), 126.7 (CH, 2 × Ar, resonance overlap), 128.3 (CH, Ar), 128.7 (CH, Ar), 133.7 (quat. C, *ipso* Ar), 134.0 (quat. C, *ipso* Ar), 136.4 (quat. C, *ipso* Ar); m/*z* (EI) 202 ([M]$^+$, 16%), 171 (100, [M – OCH$_3$]$^+$), 155 (22), 127 (28), 75 (13).

Data were in agreement with those reported in the literature.[144]

4-Nitrobenzaldehyde dimethyl acetal 148

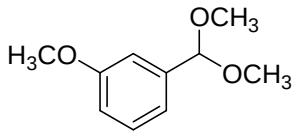


Chemical Formula: $C_9H_{11}NO_4$
Exact Mass: 197.0688
Molecular Weight: 197.1879
Elemental Analysis: C, 54.82; H, 5.62; N, 7.10; O, 32.46

Acetal **148** was prepared from 4-nitrobenzaldehyde (500 mg, 3.31 mmol), trimethylorthoformate (545 μL, 4.96 mmol) and *p*TSA (3 mg, 0.019 mmol) in MeOH (1.0 mL) according to the general procedure. After 3 h, work-up afforded acetal **148** as a yellow liquid (642 mg, 98%): δ_H(300 MHz) 3.33 (6H, s, CH(OC*H*$_3$)$_2$), 5.47 (1H, s, C*H*(OCH$_3$)$_2$), 7.64 (2H, d, *J* 8.6, Ar*H*), 8.23 (2H, d, *J* 8.6, Ar*H*); δ_C(75 MHz) 52.6 (CH$_3$, O*C*H$_3$), 101.5 (CH, *C*H(OCH$_3$)$_2$), 123.3 (CH, Ar), 127.7 (CH, Ar), 145.0 (quat. C, *ipso* Ar), 147.9 (quat. C, *ipso* Ar); m/*z* (EI) 196 ([M – H]$^+$, 13%), 166 (100, [M – OCH$_3$]$^+$), 120 (27), 75 (15).

Data were in agreement with those reported in the literature.[183]

3-Methoxybenzaldehyde dimethyl acetal 149

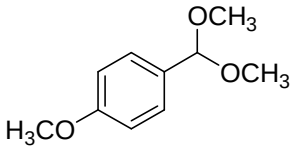


Chemical Formula: $C_{10}H_{14}O_3$
Exact Mass: 182.0943
Molecular Weight: 182.2164
Elemental Analysis: C, 65.91; H, 7.74; O, 26.34

Acetal **149** was prepared from 3-methoxybenzaldehyde (560 mg, 4.11 mmol), trimethylorthoformate (675 μL, 6.17 mmol) and *p*TSA (4 mg, 0.023 mmol) in MeOH (1.2 mL) according to the general procedure. After 2 h, work-up afforded acetal **149** as a pale orange liquid (749 mg, 100%): δ_H(300 MHz, C$_6$D$_6$) 3.14 (6H, s, CH(OC*H*$_3$)$_2$), 3.32 (3H, s,

ArOC*H*$_3$), 5.35 (1H, s, C*H*(OCH$_3$)$_2$), 6.75-6.82 (1H, m, Ar*H*), 7.10-7.29 (3H, stack, Ar*H*); δ_C(75 MHz, C_6D_6) 52.0 (CH$_3$, CH(O*C*H$_3$)$_2$), 54.8 (CH$_3$, ArO*C*H$_3$), 102.8 (CH, *C*H(OCH$_3$)$_2$), 112.7 (CH, Ar), 114.5 (CH, Ar), 119.6 (CH, Ar), 129.5 (CH, Ar), 140.6 (quat. C, *ipso* Ar), 160.3 (quat. C, *ipso* Ar); m/*z* (EI) 182 ([M]$^+$, 12%), 151 (100, [M – OCH$_3$]$^+$), 136 (12), 135 (12), 108 (9), 75 (14).

4-Methoxybenzaldehyde dimethyl acetal 150

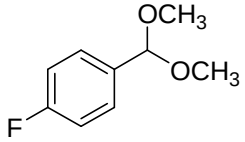


Chemical Formula: $C_{10}H_{14}O_3$
Exact Mass: 182.0943
Molecular Weight: 182.2164
Elemental Analysis: C, 65.91; H, 7.74; O, 26.34

Acetal **150** was prepared from 4-methoxybenzaldehyde (5.60 g, 41.1 mmol), trimethylorthoformate (6.75 mL, 61.7 mmol) and *p*TSA (44 mg, 0.230 mmol) in MeOH (12 mL) according to the general procedure. After 2 h, work-up with 2 M NaOH solution (100 mL) [instead of NaHCO$_3$ solution] afforded acetal **150** as a colourless liquid (7.49 g, 100%): δ_H(300 MHz, C_6D_6) 3.16 (6H, s, CH(OC*H*$_3$)$_2$), 3.29 (3H, s, ArOC*H*$_3$), 5.37 (1H, s, C*H*(OCH$_3$)$_2$), 6.81 (2H, d, *J* 8.6, Ar*H*), 7.50 (2H, d, *J* 8.6, Ar*H*); δ_C(75 MHz, C_6D_6) 51.9 (CH$_3$, CH(O*C*H$_3$)$_2$), 54.8 (CH$_3$, ArO*C*H$_3$), 102.9 (CH, *C*H(OCH$_3$)$_2$), 113.8 (CH, Ar), 128.5 (CH, Ar), 131.1 (quat. C, *ipso* Ar), 160.2 (quat. C, *ipso* Ar); m/*z* (EI) 182 ([M]$^+$, 7%), 151 (100, [M – OCH$_3$]$^+$), 135 (16).

Data were in agreement with those reported in the literature.[184]

4-Fluorobenzaldehyde dimethyl acetal 151

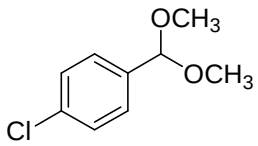


Chemical Formula: $C_9H_{11}FO_2$
Exact Mass: 170.0743
Molecular Weight: 170.1808
Elemental Analysis: C, 63.52; H, 6.52; F, 11.16; O, 18.80

Acetal **151** was prepared from 4-fluorobenzaldehyde (588 mg, 4.74 mmol), trimethylorthoformate (775 μL, 7.11 mmol) and *p*TSA (5 mg, 0.028 mmol) in MeOH (1.5 mL) according to the general procedure. After 8 h, work-up afforded acetal **151** as a colourless liquid (734 mg, 91%): δ_H(300 MHz) 3.31 (6H, s, CH(OC*H*$_3$)$_2$), 5.37 (1H, s, C*H*(OCH$_3$)$_2$), 7.00-7.10 (2H, m, Ar*H*), 7.39-7.46 (2H, m, Ar*H*); δ_C(75 MHz) 52.0 (CH$_3$, CH(O*C*H$_3$)$_2$), 101.9 (CH, *C*H(OCH$_3$)$_2$), 114.4 (CH, d, $^2J_{C\text{-}F}$ 21.4, Ar), 127.8 (CH, d, $^3J_{C\text{-}F}$ 8.3, Ar), 133.4 (quat. C, d, $^4J_{C\text{-}F}$ 3.1, *ipso* Ar), 162.1 (quat. C, d, $^1J_{C\text{-}F}$ 245.0, *ipso* Ar); δ_F(282 MHz) –114.2 (F, s, Ar*F*); m/z (EI) 170 ([M]$^+$, 4%), 139 (100, [M – OCH$_3$]$^+$), 123 (47), 109 (43), 95 (43), 91 (10), 75 (30).

Data were in agreement with those reported in the literature.[185]

4-Chlorobenzaldehyde dimethyl acetal 152



Chemical Formula: $C_9H_{11}ClO_2$
Exact Mass: 186.0448
Molecular Weight: 186.6354
Elemental Analysis: C, 57.92; H, 5.94; Cl, 19.00; O, 17.15

Acetal **152** was prepared from 4-chlorobenzaldehyde (15.0 g, 107 mmol), trimethylorthoformate (17.5 mL, 160 mmol) and *p*TSA (45 mg, 0.237 mmol) in MeOH (30

mL) according to the general procedure. After 8 h, work-up and purification by vacuum distillation (bp 90 °C/10 mmHg) afforded acetal **152** as a colourless liquid (18.2 g, 91%): δ_H(300 MHz) 3.31 (6H, s, CH(OC*H*$_3$)$_2$), 5.37 (1H, s, C*H*(OCH$_3$)$_2$), 7.31-7.42 (4H, stack, Ar*H*); δ_C(75 MHz) 52.5 (CH$_3$, O*C*H$_3$), 102.2 (CH, *C*H(OCH$_3$)$_2$), 128.1 (CH, Ar), 128.3 (CH, Ar), 134.2 (quat. C, *ipso* Ar), 136.6 (quat. C, *ipso* Ar); m/*z* (EI) 186 ([M – H]$^+$, 6%), 155 (100, [M – OCH$_3$]$^+$), 139 (20), 111 (14), 91 (32), 75 (22).

Data were in agreement with those reported in the literature.[184]

General procedure for the formation of homoallylic methylethers 153-159

Method A: Racemic allylation

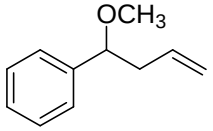
MeSO$_3$H (215 μL, 3.29 mmol) was added to a solution of the dimethyl acetal (3.29 mmol) and allyltrimethylsilane (575 μL, 3.61 mmol) in CH$_2$Cl$_2$ (16 mL) at 0 °C. After stirring at R.T. for the specified time, NaHCO$_3$ solution (50 mL) and CH$_2$Cl$_2$ (90 mL) were added, and the layers were separated. The aqueous phase was extracted with CH$_2$Cl$_2$ (15 mL) and the combined organic fractions were washed with brine (50 mL) and dried (Na$_2$SO$_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product, which was purified by flash column chromatography.

Method B: Asymmetric allylation

Phosphoric acid (*S*)-**32g** or phosphoramide (*R*)- or (*S*)-**45d**, respectively (0.033 mmol) was added to a solution of the dimethyl acetal (0.332 mmol) and allyltrimethylsilane (65 μL, 0.399 mmol) in a specified solvent (0.75 mL) and stirred at R.T. After the specified time, NaHCO$_3$ solution (10 mL) and CH$_2$Cl$_2$ (10 mL) were added, and the layers were separated. The

aqueous layer was extracted with CH_2Cl_2 (5 mL) and the combined organic layers were washed with brine (10 mL) and dried (Na_2SO_4). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product, which was purified by flash column chromatography.

4-Methoxy-4-phenyl-but-1-ene 153



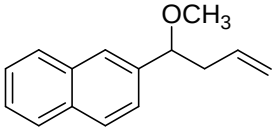
Chemical Formula: $C_{11}H_{14}O$
Exact Mass: 162.1045
Molecular Weight: 162.2283
Elemental Analysis: C, 81.44; H, 8.70; O, 9.86

Racemic ether **153** was prepared from benzaldehyde dimethyl acetal **146** (495 μL, 3.29 mmol), allyltrimethylsilane (575 μL, 3.61 mmol) and $MeSO_3H$ (215 μL, 3.29 mmol) in CH_2Cl_2 (16 mL) according to Method A. After 5 h, work-up and purification by flash column chromatography (95% hexane, 5% Et_2O) afforded methyl ether **153** as a colourless liquid (251 mg, 47% (reduced yield owing to volatility of the product)): R_f = 0.36 (95% hexane, 5% Et_2O); ν_{max}(film)/cm^{-1} 3076s (CH=CH_2), 3029m, 2980s (CH_2CH=CH_2), 2936s (CH_2CH=CH_2), 2854m, 2821s (OCH_3), 1951w, 1876w, 1829w, 1641s, 1602m (C=C aromatic), 1547w, 1494s (C=C aromatic), 1454s, 1440w, 1357m, 1339w, 1307m, 1288w, 1238m, 1198m, 1155w, 1101s, 1073w, 1042w, 1027w, 999m, 975m, 915s, 856m, 824w, 758s, 701s, 654m, 608m; δ_H(300 MHz) 2.36-2.47 (1H, m, CH_aH$_b$CH=CH_2), 2.52-2.64 (1H, m, CH$_a$$H_b$CH=$CH_2$), 3.23 (3H, s, O$CH_3$), 4.18 (1H, dd, *J* 7.2, 6.1, C*H*(OCH_3)), 5.00-5.11 (2H, stack, CH_2CH=CH_2), 5.70-5.86 (1H, m, CH_2C*H*=CH_2), 7.24-7.40 (5H, stack, Ph*H*); δ_C(75 MHz) 42.5 (CH_2, *C*H_2CH=CH_2), 56.6 (CH_3, O*C*H_3), 83.6 (CH, *C*H(OCH_3)), 116.8 (CH_2, CH_2CH=*C*H_2), 126.7 (CH, Ar), 127.5 (CH, Ar), 128.3 (CH, Ar), 134.8 (CH, CH_2*C*H=CH_2),

141.6 (quat. C, *ipso* Ar); m/*z* (EI) 121 ([M – C_3H_5]$^+$, 100%), 91 (21), 84 (14), 77 (36), 49 (19), 44 (54).

Data were in agreement with those reported in the literature.[50]

4-Methoxy-4-(2'-naphthyl)-but-1-ene 154

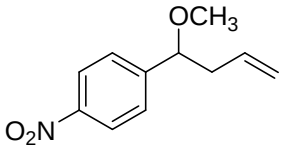


Chemical Formula: $C_{15}H_{16}O$
Exact Mass: 212.1201
Molecular Weight: 212.2869
Elemental Analysis: C, 84.87; H, 7.60; O, 7.54

Racemic ether **154** was prepared from 2-naphthaldehyde dimethyl acetal **147** (300 mg, 1.48 mmol), allyltrimethylsilane (260 μL, 1.63 mmol) and $MeSO_3H$ (95 μL, 1.48 mmol) in CH_2Cl_2 (7 mL) according to Method A. After 15 min at 0 °C, work-up and purification by flash column chromatography (95% hexane, 5% Et_2O) afforded methyl ether **154** as a colourless liquid (225 mg, 72%): R_f = 0.25 (95% hexane, 5% Et_2O); ν_{max}(film)/cm^{-1} 3057s (CH=CH_2), 2980s (CH_2CH=CH_2), 2934s (CH_2CH=CH_2), 2903m, 2853m, 2820s (OCH_3), 1922w, 1830w, 1641m, 1602m (C=C aromatic), 1508m, 1464m, 1444m, 1371m, 1322m, 1271m, 1236w, 1190m, 1170w, 1154w, 1098s, 1042w, 1019w, 998m, 982m, 950w, 916s, 857s, 820s, 747s, 717w, 665m, 620w; δ_H(300 MHz) 2.45-2.57 (1H, m, C$H_a$$H_b$CH=$CH_2$), 2.61-2.73 (1H, m, $CH_a$$H_b$CH=$CH_2$), 3.27 (3H, s, OC$H_3$), 4.35 (1H, app. t, *J* 6.8, C*H*(OCH_3)), 5.00-5.12 (2H, stack, CH_2CH=CH_2), 5.72-5.87 (1H, m, CH_2C*H*=CH_2), 7.43-7.54 (3H, stack, Ar*H*), 7.73 (1H, s, Ar*H*), 7.80-7.89 (3H, stack, Ar*H*); δ_C(75 MHz) 42.4 (CH_2, *C*H_2CH=CH_2), 56.7 (CH_3, O*C*H_3), 83.7 (CH, *C*H(OCH_3)), 117.0 (CH_2, CH_2CH=*C*H_2), 124.4 (CH, Ar), 125.7 (CH, Ar), 125.9 (CH, Ar), 126.0 (CH, Ar), 127.7 (CH, Ar), 127.8 (CH, Ar), 128.2 (CH, Ar), 133.07

(quat. C, *ipso* Ar), 133.14 (quat. C, *ipso* Ar), 134.6 (CH, $CH_2CH{=}CH_2$), 139.0 (quat. C, *ipso* Ar); m/*z* (TOF ES+) 425.1 ($[M + Na]^+$, 100%); HRMS: $C_{15}H_{16}ONa$ calcd 235.1099 ($[M + Na]^+$), obsd 235.1105.

4-Methoxy-4-(4'-nitrophenyl)-but-1-ene 155

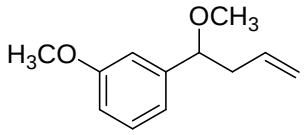


Chemical Formula: $C_{11}H_{13}NO_3$
Exact Mass: 207.0895
Molecular Weight: 207.2258
Elemental Analysis: C, 63.76; H, 6.32; N, 6.76; O, 23.16

Racemic ether **155** was prepared from 4-nitrobenzaldehyde dimethyl acetal **148** (300 mg, 1.52 mmol), allyltrimethylsilane (265 μL, 1.67 mmol) and $MeSO_3H$ (100 μL, 1.52 mmol) in CH_2Cl_2 (7 mL) according to Method A. After 17 h, work-up and purification by flash column chromatography (90% hexane, 10% Et_2O) afforded methyl ether **155** as a yellow-orange oil (78 mg, 25%): R_f = 0.19 (90% hexane, 10% Et_2O); ν_{max}(film)/cm^{-1} 3078m (CH=CH_2), 2983m ($CH_2CH{=}CH_2$), 2934s ($CH_2CH{=}CH_2$), 2825m (OCH_3), 2361w, 1641m, 1607s (C=C aromatic), 1522s (NO_2), 1491w, 1443w, 1416w, 1346s (NO_2), 1317w, 1290m, 1239w, 1198m, 1156w, 1106s, 1039w, 1014m, 999w, 982w, 920s, 855s, 842w, 777w, 754m, 722w, 701s, 666m; δ_H(300 MHz) 2.34-2.46 (1H, m, $CH_aH_bCH{=}CH_2$), 2.48-2.60 (1H, m, $CH_aH_bCH{=}CH_2$), 3.25 (3H, s, OCH_3), 4.29 (1H, app. t, *J* 6.4, $CH(OCH_3)$), 4.97-5.07 (2H, stack, $CH_2CH{=}CH_2$), 5.64-5.80 (1H, m, $CH_2CH{=}CH_2$), 7.45 (2H, d, *J* 8.6, Ar*H*), 8.21 (2H, d, *J* 8.6, Ar*H*); δ_C(75 MHz) 42.1 (CH_2, $CH_2CH{=}CH_2$), 57.1 (CH_3, OCH_3), 82.7 (CH, $CH(OCH_3)$), 117.8 (CH_2, $CH_2CH{=}CH_2$), 123.6 (CH, Ar), 127.4 (CH, Ar), 133.4 (CH, $CH_2CH{=}CH_2$), 147.4 (quat. C, *ipso* Ar), 149.4 (quat. C, *ipso* Ar); m/*z* (EI) 166 ($[M - C_3H_5]^+$,

100%), 136 (10), 120 (34), 108 (16), 91 (12), 77 (11), 51 (10); HRMS: $C_8H_8NO_3$ calcd 166.0504 ($[M - C_3H_5]^+$), obsd 166.0499.

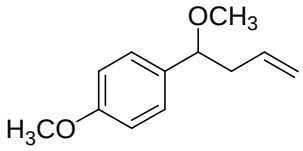
4-Methoxy-4-(3'-methoxyphenyl)-but-1-ene 156



Chemical Formula: $C_{12}H_{16}O_2$
Exact Mass: 192.115
Molecular Weight: 192.2542
Elemental Analysis: C, 74.97; H, 8.39; O, 16.64

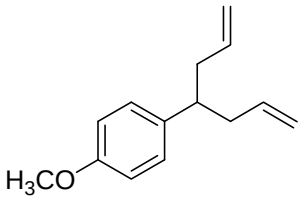
Racemic ether **156** was prepared from 3-methoxybenzaldehyde dimethyl acetal **149** (200 mg, 1.10 mmol), allyltrimethylsilane (190 μL, 1.21 mmol) and $MeSO_3H$ (70 μL, 1.10 mmol) in CH_2Cl_2 (5 mL) according to Method A. After 30 min stirring at 0 °C, work-up and purification by flash column chromatography (95% hexane, 5% Et_2O) afforded methyl ether **156** as a colourless liquid (129 mg, 61%): R_f = 0.14 (95% hexane, 5% Et_2O); ν_{max}(film)/cm^{-1} 3075m (CH=CH_2), 2979s (CH_2CH=CH_2), 2937s (CH_2CH=CH_2), 2835s, 2822s (OCH_3), 1839w, 1641m, 1601s (C=C aromatic), 1587s, 1499s, 1455m, 1435m, 1351m, 1316m, 1286s, 1258s, 1191m, 1155m, 1102s, 1050s, 996m, 983m, 917m, 876m, 826w, 784m, 755w, 735w, 702s, 666m; δ_H(300 MHz) 2.34-2.45 (1H, m, C$H_a$$H_b$CH=$CH_2$), 2.49-2.60 (1H, m, $CH_a$$H_b$CH=$CH_2$), 3.22 (3H, s, OC$H_3$), 3.81 (3H, s, ArOC$H_3$), 4.14 (1H, dd, *J* 7.5, 5.7, C*H*(OCH_3)), 4.98-5.11 (2H, stack, CH_2CH=CH_2), 5.69-5.84 (1H, m, CH_2C*H*=CH_2), 6.77-6.90 (3H, stack, Ar*H*), 7.20-7.30 (1H, m, Ar*H*); δ_C(75 MHz) 42.4 (CH_2, *C*H_2CH=CH_2), 55.1 (CH_3, CH(O*C*H_3) or ArO*C*H_3), 56.6 (CH_3, CH(O*C*H_3) or ArO*C*H_3), 83.5 (CH, *C*H(OCH_3)), 111.9 (CH, Ar), 112.9 (CH, Ar), 116.7 (CH_2, CH_2CH=*C*H_2), 119.1 (CH, Ar), 129.2 (CH, Ar), 134.7 (CH, CH_2*C*H=CH_2), 143.4 (quat. C, *ipso* Ar), 159.7 (quat. C, *ipso* Ar); m/*z* (EI) 151 ($[M - C_3H_5]^+$, 100%), 136 (9); HRMS: $C_9H_{11}O_2$ calcd 151.0759 ($[M - C_3H_5]^+$), obsd 151.0753.

4-Methoxy-4-(4'-methoxyphenyl)-but-1-ene 157 and 4-(4'-methoxyphenyl)-hepta-1,6-diene 160



Chemical Formula: $C_{12}H_{16}O_2$
Exact Mass: 192.115
Molecular Weight: 192.2542
Elemental Analysis: C, 74.97; H, 8.39; O, 16.64

157



Chemical Formula: $C_{14}H_{18}O$
Exact Mass: 202.1358
Molecular Weight: 202.2921
Elemental Analysis: C, 83.12; H, 8.97; O, 7.91

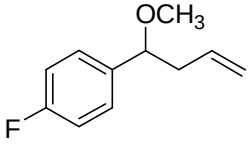
160

Racemic ether **157** was prepared from 4-methoxybenzaldehyde dimethyl acetal **150** (200 mg, 1.10 mmol), allyltrimethylsilane (190 μL, 1.21 mmol) and $MeSO_3H$ (70 μL, 1.10 mmol) in CH_2Cl_2 (5 mL) according to Method A. After 17 h, work-up and purification by flash column chromatography (95% hexane, 5% Et_2O) afforded, in order of elution, diene **160** as a colourless liquid (3 mg, 1%): R_f = 0.43 (95% hexane, 5% Et_2O); δ_H(300 MHz) 2.24-2.46 (4H, m, CH_2CH=CH_2), 2.69-2.73 (1H, m, CH($CH_2CH=CH_2$)$_2$), 3.79 (3H, s, ArOCH_3), 4.89-5.02 (4H, m, $CH_2CH=CH_2$), 5.58-5.74 (2H, stack, $CH_2CH=CH_2$), 6.83 (2H, d, *J* 8.5, Ar*H*), 7.07 (2H, d, *J* 8.5, Ar*H*); δ_C(75 MHz) 40.5 (CH_2, $CH_2CH=CH_2$), 44.7 (CH, $CH(CH_2CH=CH_2)_2$), 55.2 (CH_3, ArOCH_3), 113.6 (CH, Ar), 116.0 (CH_2, $CH_2CH=CH_2$), 128.6 (CH, Ar), 136.7 (quat. C, *ipso* Ar), 136.9 (CH, $CH_2CH=CH_2$), 157.8 (quat. C, *ipso* Ar); m/*z* (EI) 202 ($[M]^+$, 4%), 161 (100, $[M - C_3H_5]^+$), 146 (10), 91 (13); and then methyl ether **157** as a colourless liquid (150 mg, 71%): R_f = 0.14 (95% hexane, 5% Et_2O); ν_{max}(film)/cm^{-1} 3075m (CH=CH_2), 2979s (CH_2CH=CH_2), 2935s (CH_2CH=CH_2), 2904s, 2836s, 2820s (OCH_3), 2061w, 1885w,

1641m, 1612s (C=C aromatic), 1586m, 1513s (C=C aromatic), 1464m, 1442m, 1355m, 1303s, 1248s, 1173s, 1096s, 1036s, 999m, 976m, 916s, 862m, 832s, 812m, 771m, 740w, 632w; δ_H(300 MHz) 2.33-2.44 (1H, m, CH_aH$_b$CH=CH$_2$), 2.51-2.62 (1H, m, CH$_a$$H_b$CH=CH$_2$), 3.19 (3H, s, CH(OC$H_3$)), 3.81 (3H, s, ArOC$H_3$), 4.12 (1H, t, *J* 7.7, C*H*(OCH$_3$)), 4.98-5.10 (2H, stack, CH$_2$CH=CH_2), 5.67-5.83 (1H, m, CH$_2$C*H*=CH$_2$), 6.89 (2H, d, *J* 8.6, Ar*H*), 7.21 (2H, d, *J* 8.6, Ar*H*); δ_C(75 MHz) 42.4 (CH$_2$, *C*H$_2$CH=CH$_2$), 55.1 (CH$_3$, CH(O*C*H$_3$) or ArO*C*H$_3$), 56.3 (CH$_3$, CH(O*C*H$_3$) or ArO*C*H$_3$), 83.1 (CH, *C*H(OCH$_3$)), 113.6 (CH, Ar), 116.7 (CH$_2$, CH$_2$CH=*C*H$_2$), 127.8 (CH, Ar), 133.5 (quat. C, *ipso* Ar), 134.8 (CH, CH$_2$*C*H=CH$_2$), 159.0 (quat. C, *ipso* Ar); m/*z* (EI) 151 ([M – C$_3$H$_5$]$^+$, 100%), 136 (9); HRMS: C$_9$H$_{11}$O$_2$ calcd 151.0759 ([M – C$_3$H$_5$]$^+$), obsd 151.0753.

Data for both compounds were in agreement with those reported in the literature.[50,186]

4-(4'-Fluorophenyl)-4-methoxy-but-1-ene 158

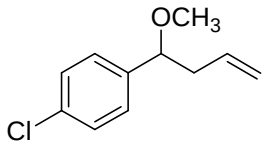


Chemical Formula: $C_{11}H_{13}FO$
Exact Mass: 180.095
Molecular Weight: 180.2187
Elemental Analysis: C, 73.31; H, 7.27; F, 10.54; O, 8.88

Racemic ether **158** was prepared from 4-fluorobenzaldehyde dimethyl acetal **151** (200 mg, 1.18 mmol), allyltrimethylsilane (205 μL, 1.29 mmol) and MeSO$_3$H (75 μL, 1.18 mmol) in CH$_2$Cl$_2$ (5 mL) according to Method A. After 3 h, work-up and purification by flash column chromatography (95% hexane, 5% Et$_2$O) afforded methyl ether **158** as a colourless liquid (75 mg, 36% (reduced yield owing to volatility of the product)): R_f = 0.20 (95% hexane, 5% Et$_2$O); ν_{max}(film)/cm^{-1} 3077m (CH=*CH$_2$*), 2982s (*CH$_2$*CH=CH$_2$), 2934s (*CH$_2$*CH=CH$_2$),

2905s, 2854m, 2822s (OCH_3), 1894w, 1642m, 1605s (C=C aromatic), 1509s (C=C aromatic), 1466w, 1443w, 1417w, 1347m, 1296m, 1223s (ArC–F), 1156s, 1102s, 1042w, 1014m, 999m, 978m, 918s, 864m, 836s, 783w, 740w, 722w, 649w, 631w, 568s; δ_H(300 MHz) 2.32-2.44 (1H, m, C$H_a$$H_b$CH=$CH_2$), 2.49-2.61 (1H, m, $CH_a$$H_b$CH=$CH_2$), 3.20 (3H, s, OC$H_3$), 4.15 (1H, app. t, *J* 6.6, C*H*(OCH_3)), 4.99-5.09 (2H, stack, CH_2CH=CH_2), 5.65-5.81 (1H, m, CH_2C*H*=CH_2), 6.99-7.08 (2H, stack, Ar*H*), 7.21-7.29 (2H, stack, Ar*H*); δ_C(75 MHz) 42.5 (CH_2, *C*H_2CH=CH_2), 56.6 (CH_3, O*C*H_3), 82.9 (CH, *C*H(OCH_3)), 115.2 (CH, d, $^2J_{C\text{-}F}$ 21.1, Ar), 117.1 (CH_2, CH_2CH=*C*H_2), 128.3 (CH, d, $^3J_{C\text{-}F}$ 8.3, Ar), 134.4 (CH, CH_2*C*H=CH_2), 137.3 (quat. C, d, $^4J_{C\text{-}F}$ 3.1, *ipso* Ar), 162.2 (quat. C, d, $^1J_{C\text{-}F}$ 243.9, *ipso* Ar); δ_F(282 MHz) – 115.5 (F, s, Ar*F*); m/*z* (EI) 139 ([M – C_3H_5]$^+$, 100%), 109 (17); HRMS: C_8H_8FO calcd 139.0559 ([M – C_3H_5]$^+$), obsd 139.0556.

4-(4'-Chlorophenyl)-4-methoxy-but-1-ene 159



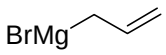
Chemical Formula: $C_{11}H_{13}ClO$
Exact Mass: 196.0655
Molecular Weight: 196.6733
Elemental Analysis: C, 67.18; H, 6.66; Cl, 18.03; O, 8.14

Racemic ether **159** was prepared from 4-chlorobenzaldehyde dimethyl acetal **152** (200 mg, 1.07 mmol), allyltrimethylsilane (185 μL, 1.18 mmol) and $MeSO_3H$ (70 μL, 1.07 mmol) in CH_2Cl_2 (5 mL) according to Method A. After 3 h, work-up and purification by flash column chromatography (95% hexane, 5% Et_2O) afforded methyl ether **159** as a colourless liquid (116 mg, 55%): R_f = 0.31 (95% hexane, 5% Et_2O); (Found: C, 67.27; H, 6.73. $C_{11}H_{13}ClO$ requires C, 67.18; H, 6.66%); ν_{max}(film)/cm^{-1} 3077m (CH=*CH*$_2$), 2981s (*CH*$_2$CH=CH_2), 2933s (*CH*$_2$CH=CH_2), 2904m, 2851m, 2822s (OCH_3), 1906w, 1642m, 1598m (C=C

aromatic), 1490s (C=C aromatic), 1464w, 1442w, 1409m, 1346m, 1277w, 1236w, 1187m, 1105s, 1090s, 1041w, 1014s, 999w, 979m, 917s, 856m, 827s (ArC–Cl), 786m, 743w, 666w; δ_H(300 MHz) 2.31-2.44 (1H, m, CH_aH$_b$CH=CH$_2$), 2.48-2.60 (1H, m, CH$_a$$H_b$CH=CH$_2$), 3.21 (3H, s, OC$H_3$), 4.15 (1H, app. t, *J* 6.6, C*H*(OCH$_3$)), 4.96-5.09 (2H, stack, CH$_2$CH=CH_2), 5.65-5.82 (1H, m, CH$_2$C*H*=CH$_2$), 7.20-7.28 (2H, stack, Ar*H*), 7.29-7.36 (2H, stack, Ar*H*); δ_C(75 MHz) 42.4 (CH$_2$, *C*H$_2$CH=CH$_2$), 56.7 (CH$_3$, O*C*H$_3$), 82.9 (CH, *C*H(OCH$_3$)), 117.2 (CH$_2$, CH$_2$CH=*C*H$_2$), 128.1 (CH, Ar), 128.5 (CH, Ar), 133.2 (quat. C, *ipso* Ar), 134.2 (CH, CH$_2$*C*H=CH$_2$), 140.2 (quat. C, *ipso* Ar); m/*z* (EI) 155 ([M – C$_3$H$_5$]$^+$, 100%); HRMS: C$_8$H$_8$ClO calcd 155.0264 ([M – C$_3$H$_5$]$^+$), obsd 155.0259.

Data were in agreement with those reported in the literature.[53]

Allylmagnesium bromide in Et$_2$O[187]

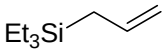


Chemical Formula: C$_3$H$_5$BrMg
Exact Mass: 143.9425
Molecular Weight: 145.2808
Elemental Analysis: C, 24.80; H, 3.47; Br, 55.00; Mg, 16.73

A 250 mL three-neck round-bottom flask, equipped with a reflux condenser and a dropping funnel, was charged with Mg turnings (7.00 g, 288 mmol). Sufficient Et$_2$O (~ 15 mL) was added to cover the Mg turnings under fast stirring. A few I$_2$ crystals were added and the brown colour disappeared within 1 min indicating the activation of the Mg. A solution of allyl bromide (9.95 mL, 115 mmol) in Et$_2$O (90 mL) was then added dropwise (1 drop every 3 seconds) until the reaction started and then the addition rate was increased to maintain a gentle reflux (1-2 drops every second). After the addition was finished, the suspension was

stirred for an additional 30 min and then left to settle. The ethereal solution was filtered and transferred *via* cannula (fitted with an oven-dried Whatman 1 filter paper) into a flask equipped with a septum, and then stored at 4 °C.

Allyltriethylsilane

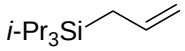


Chemical Formula: $C_9H_{20}Si$
Exact Mass: 156.1334
Molecular Weight: 156.3406
Elemental Analysis: C, 69.14; H, 12.89; Si, 17.96

Chlorotriethylsilane (1.54 mL, 9.20 mmol) was added dropwise over 1 min to a vigorously stirred solution of allylmagnesium bromide in Et_2O (0.92 M, 20 mL, 18.4 mmol). After heating at reflux overnight, the pale yellow suspension was cooled to 0 °C and a mixture of aqueous NH_4Cl/NH_3 solution (1:1, 25 mL) was added over a period of 3 min. The layers were separated and the aqueous phase was extracted with Et_2O (20 mL). The combined organic fractions were washed with brine (30 mL) and dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product. Purification by silica plug (100% pentane) afforded allyltriethylsilane as a colourless liquid (753 mg, 52%): R_f = 0.80 (100% pentane); δ_H(300 MHz) 0.52 (6H, q, *J* 7.7, $Si(CH_2CH_3)_3$), 0.93 (9H, t, *J* 7.7, $Si(CH_2CH_3)_3$), 1.51-1.57 (2H, m, $SiCH_2CH=CH_2$), 4.76-4.89 (2H, stack, $SiCH_2CH=CH_2$), 5.71-5.88 (1H, m, $SiCH_2CH=CH_2$); δ_C(75 MHz) 3.1 (CH_2, $Si(CH_2CH_3)_3$), 7.3 (CH_3, $Si(CH_2CH_3)_3$), 19.5 (CH_2, $SiCH_2CH=CH_2$), 112.4 (CH_2, $SiCH_2CH=CH_2$), 135.4 (CH, $SiCH_2CH=CH_2$); m/*z* (EI) 156 (11, $[M]^+$), 115 (100, $[M - C_3H_5]^+$), 99 (11), 87 (50).

Data were in agreement with those reported in the literature.[188]

Allyltriisopropylsilane

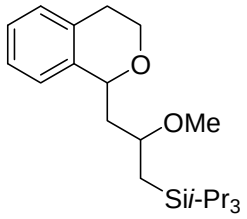


Chemical Formula: $C_{12}H_{26}Si$
Exact Mass: 198.1804
Molecular Weight: 198.4203
Elemental Analysis: C, 72.64; H, 13.21; Si, 14.15

Chlorotriisopropylsilane (1.00 mL, 4.67 mmol) was added dropwise over 1 min to a vigorously stirred solution of allylmagnesium bromide in Et_2O (0.92 M, 7.60 mL, 7.01 mmol). After heating at reflux overnight, the pale yellow suspension was cooled to 0 °C and a mixture of aqueous NH_4Cl/NH_3 solution (1:1, 10 mL) was added over a period of 3 min. The layers were separated and the aqueous phase was extracted with Et_2O (15 mL). The combined organic fractions were washed with brine (20 mL) and dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product. Purification by silica plug (100% hexane) afforded allyltriisopropylsilane as a colourless liquid (390 mg, 42%): R_f = 0.85 (100% hexane); δ_H(300 MHz) 0.90-1.12 (21H, stack, $Si(CH(CH_3)_2)_3$, 1.58-1.67 (2H, m, $SiCH_2CH=CH_2$), 4.75-4.95 (2H, stack, $SiCH_2CH=CH_2$), 5.78-5.96 (1H, m, $SiCH_2CH=CH_2$); δ_C(75 MHz) 11.0 (CH, $Si(CH(CH_3)_2)_3$), 17.3 (CH_2, $SiCH_2CH=CH_2$), 18.7 (CH_3, $Si(CH(CH_3)_2)_3$), 112.8 (CH_2, $SiCH_2CH=CH_2$), 136.2 (CH, $SiCH_2CH=CH_2$); m/z (EI) 198 (3, $[M]^+$), 157 (100, $[M - C_3H_5]^+$), 115 (50), 99 (13), 87 (39), 85 (43), 73 (42), 59 (77), 43 (30) .

Data were in agreement with those reported in the literature.[188]

1-(2'-Methoxy-3'-triisopropylsilyl-propyl)isochroman 175

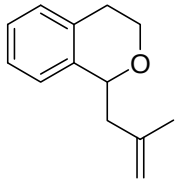


Chemical Formula: $C_{22}H_{38}O_2Si$
Exact Mass: 362.2641
Molecular Weight: 362.6214
Elemental Analysis: C, 72.87; H, 10.56; O, 8.82; Si, 7.75

Racemic phosphoramide **162** (9 mg, 0.018 mmol) was added to a solution of 1-methoxyisochroman (30 mg, 0.183 mmol) and allyltriisopropylsilane (65 μL, 0.274 mmol) in *p*-xylene (360 μL). After stirring at R.T. for 24 h, $NaHCO_3$ solution (15 mL) and Et_2O (15 mL) were added. The two phases were separated and the aqueous phase was extracted with Et_2O (10 mL). The combined organic fractions were washed with brine (15 mL) and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product. Purification by flash column chromatography afforded isochroman **175** as a colourless liquid (17 mg, 26%; single diastereoisomer; stereochemistry not determined) amongst a range of unidentified by-products: R_f = 0.31 (90% hexane, 10% Et_2O); ν_{max}(film)/cm^{-1} 2942m, 2864m, 1497w, 1455m, 1382m, 1231w, 1104s, 1066m, 987m, 944m, 873m, 743s; δ_H(500 MHz) 1.03-1.12 (23H, stack, CH_2Si(CH(CH_3)$_2$)$_3$), 1.79 (1H, ddd, *J* 13.6, 9.0, 3.0, CH_aH$_b$), 2.32 (1H, ddd, *J* 13.6, 10.3, 3.4, CH$_a$$H_b$), 2.71 (1H, app. dt, *J* 16.2, 3.9, CH_aH$_b$CH$_2$O), 2.99 (1H, ddd, *J* 15.7, 9.4, 5.3, CH$_a$$H_bCH_2$O), 3.27 (3H, s, OC$H_3$), 3.64-3.71 (1H, m, C$HOCH_3$), 3.75 (1H, ddd, *J* 11.3, 9.4, 3.9, CH$_2$CH_aH$_b$O), 4.12 (1H, ddd, *J* 11.3, 5.3, 4.1, CH$_2$CH$_a$$H_b$O), 4.81 (1H, app. d, *J* 9.0, CHO), 7.07-7.21 (4H, stack, ArH); δ_C(125 MHz) 11.5 (CH, Si(*C*H(CH$_3$)$_2$)$_3$), 15.4 (CH$_2$, Si*C*H$_2$), 18.8 (CH$_3$, Si(CH(*C*H$_3$)$_a$(CH$_3$)$_b$)$_3$), 18.9 (CH$_3$, Si(CH(CH$_3$)$_a$(*C*H$_3$)$_b$)$_3$), 29.0 (CH$_2$, *C*H$_2$CH$_2$O), 42.3 (CH$_2$, CH_2), 55.6 (CH$_3$, O*C*H$_3$), 63.0 (CH$_2$, *C*H$_2$O), 73.6 (CH, *C*HO), 75.9 (CH, *C*HOCH$_3$), 124.6 (CH, Ar), 126.1 (CH, Ar), 126.2 (CH, Ar), 128.9 (CH, Ar), 133.7

(quat. C, *ipso* Ar), 138.6 (quat. C, *ipso* Ar); m/*z* (TOF ES+) 385.3 ([M + Na]$^+$, 100%); HRMS: $C_{22}H_{38}O_2SiNa$ calcd 385.2539 ([M + Na]$^+$), obsd 385.2531.

1-(2'-Methallyl)isochroman 176



Chemical Formula: $C_{13}H_{16}O$
Exact Mass: 188.1201
Molecular Weight: 188.2655
Elemental Analysis: C, 82.94; H, 8.57; O, 8.50

Racemic allylation:

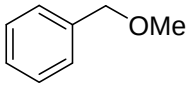
$MeSO_3H$ (50 μL, 0.74 mmol) was added to a solution of 1-ethoxyisochroman **166** (120 mg, 0.673 mmol) and 2-methallyltrimethylsilane (177 μL, 1.01 mmol) in CH_2Cl_2 (1.35 mL) at 0 °C. A colour change from colourless to orange was observed. After stirring at R.T. for 20 min, $NaHCO_3$ solution (15 mL) and Et_2O (15 mL) were added. The two phases were separated and the aqueous phase was extracted with Et_2O (15 mL). The combined organic fractions were washed with brine (15 mL) and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product. Purification by flash column chromatography (99% hexane, 1% Et_2O) afforded racemic isochroman **176** as a colourless liquid (56 mg, 44%): R_f = 0.30 (90% hexane, 10% Et_2O); ν_{max}(film)/cm^{-1} 2965m, 2922m, 1649w, 1491m, 1452m, 1374m, 1279w, 1107s, 1067m, 1040m, 886s, 743s; δ_H(300 MHz) 1.85 (3H, s, C(C*H*$_3$)=CH$_2$), 2.46-2.78 (3H, stack, C*H*$_2$C(CH$_3$)=CH$_2$ and C*H*$_a$H$_b$CH$_2$O), 2.98 (1H, ddd, *J* 15.8, 9.3, 5.5, CH$_a$*H*$_b$CH$_2$O), 3.78 (1H, ddd, *J* 11.4, 9.3, 4.1, CH$_2$C*H*$_a$H$_b$O), 4.15 (1H, app. td, *J* 11.4, 4.4, CH$_2$CH$_a$*H*$_b$O), 4.81-4.97 (3H, stack, C*H*CH$_2$C(CH$_3$)=C*H*$_2$), 7.06-7.20 (4H, stack, Ar*H*); δ_C(100 MHz) 22.5 (CH$_3$, *C*H$_3$), 29.0 (CH$_2$, *C*H$_2$CH$_2$O), 44.4 (CH$_2$, C*H*$_2$C(CH$_3$)=CH$_2$), 62.9 (CH$_2$, CH$_2$*C*H$_2$O), 74.1 (CH,

*C*HO), 112.8 (CH_2, $CH_2C(CH_3)=CH_2$), 124.9 (CH, Ar), 126.0 (CH, Ar), 126.2 (CH, Ar), 128.9 (CH, Ar), [133.9, 138.3, 142.8 (quat. C, $CH_2C(CH_3)=CH_2$) and 2 × (quat. C, *ipso* Ar)]; m/*z* (EI) 188 ($[M]^+$, 4%), 170 (56), 133 (100, $[M - C_4H_7]^+$), 129 (30), 116 (20), 104 (31), 90 (12); HRMS: $C_{13}H_{16}O$ calcd 188.1201 ($[M]^+$), obsd 188.1203.

Asymmetric allylation:

The phosphoramide catalyst (*R*)-**45g** (18 mg, 0.018 mmol) was added to a solution of the 1-alkoxyisochroman (0.183 mmol) and allyltrimethylsilane (50 μL, 0.27 mmol) in *o*-xylene (360 μL). After stirring for 24 h at R.T., $NaHCO_3$ solution (15 mL) and Et_2O (15 mL) were added. The two phases were separated and the aqueous phase was extracted with Et_2O (10 mL). The combined organic fractions were washed with brine (15 mL) and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude methallylisochroman product. After purification by flash column chromatography the e.r. was determined by chiral HPLC: Chiralpak AD, 1.0 mL/min, 100% hexane, λ = 210 nm, $t_{R,\text{minor}}$ = 9.5 min, $t_{R,\text{major}}$ = 12.9 min; e.r. (using 1-methoxyisochroman as starting material) = 40:60; e.r. (using 1-ethoxyisochroman as starting material) = 41:59.

Benzyl methyl ether



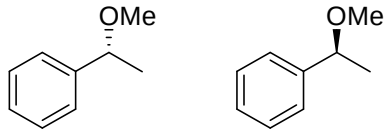
Chemical Formula: $C_8H_{10}O$
Exact Mass: 122.0732
Molecular Weight: 122.1644
Elemental Analysis: C, 78.65; H, 8.25; O, 13.10

Benzyl alcohol (1.50 g, 13.9 mmol) was added to a suspension of NaH (666 mg of a 60 wt % suspension in mineral oil, 16.6 mmol) in DMF (50 mL) at 0 °C. The mixture was stirred for 2

h at R.T. and then cooled to 0 °C. MeI (1.10 mL, 18.0 mmol) was added and the mixture was warmed to R.T. overnight. NH_4Cl solution (50 mL) and Et_2O (50 mL) were added and the layers were separated. The organic phase was washed sequentially with $NaHCO_3$ solution (30 mL), H_2O (30 mL) and brine (30 mL), and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product. Purification by flash column chromatography (gradient: 99% pentane, 1% Et_2O → 95% pentane, 5% Et_2O) afforded benzyl methyl ether as a colourless liquid (1.02 g, 60%, reduced yield owing to product volatility): R_f = 0.34 (90% hexane, 10% Et_2O); δ_H(300 MHz) 3.41 (3H, s, OC*H*$_3$), 4.48 (2H, s, C*H*$_2$O), 7.27-7.41 (5H, stack, Ar*H*); δ_C(100 MHz) 58.0 (CH_3, O*C*H$_3$), 74.7 (CH_2, *C*H$_2$O), 127.6 (CH, Ar), 127.7 (CH, Ar), 128.4 (CH, Ar), 138.2 (quat. C, *ipso* Ar); m/*z* (EI) 122 ($[M]^+$, 75%), 121 (65, $[M - H]^+$), 91 (100, ($[M - OCH_3]^+$), 77 (31, $[C_6H_5]^+$).

Data were in agreement with those reported in the literature.[189]

(*R*)- and (*S*)-1-Methoxyethylbenzene (*R*)- and (*S*)-214



Chemical Formula: $C_9H_{12}O$
Exact Mass: 136.0888
Molecular Weight: 136.191
Elemental Analysis: C, 79.37; H, 8.88; O, 11.75

(*S*)-2-Phenyl ethanol (1.50 g, 12.3 mmol) was added to a suspension of NaH (540 mg of a 60 wt % suspension in mineral oil, 13.5 mmol) in DMF (50 mL) at 0 °C. The mixture was stirred for 2 h at R.T. and then cooled to 0 °C. MeI (920 μL, 14.7 mmol) was added and the mixture was warmed to R.T. overnight. NH_4Cl solution (50 mL) and Et_2O (50 mL) were added and

the layers were separated. The organic phase was washed sequentially with $NaHCO_3$ solution (30 mL), H_2O (30 mL) and brine (30 mL), and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product. Purification by flash column chromatography (gradient: 99% pentane, 1% Et_2O → 95% pentane, 5% Et_2O) afforded (*S*)-ether **214** as a colourless liquid (1.04 g, 62%, reduced yield owing to product volatility): R_f = 0.38 (90% pentane, 10% Et_2O); $[\alpha]_D^{20}$ = –118.3 (neat) (lit.[190] $[\alpha]_D^{26}$ = –114.0 (neat); δ_H(300 MHz) 1.44 (3H, d, *J* 6.5, C*H*$_3$), 3.23 (3H, s, OC*H*$_3$), 4.30 (1H, q, *J* 6.5, ArC*H*O), 7.24-7.39 (5H, stack, Ar*H*); δ_C(100 MHz) 23.9 (CH_3, *C*H_3), 56.4 (CH_3, O*C*H_3), 79.6 (CH, *C*HO), 126.1 (CH, Ar), 127.4 (CH, Ar), 128.4 (CH, Ar), 143.5 (quat. C, *ipso* Ar); m/*z* (EI) 121 ($[M - CH_3]^+$, 100%).

The same protocol was followed for the preparation of the (*R*)-enantiomer: $[\alpha]_D^{20}$ = +117.6 (neat) (lit.[191] $[\alpha]_D^{25}$ = +120.0 (neat)).

Data were in agreement with those reported in the literature.[192]

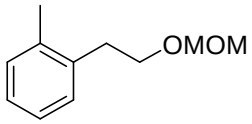
General procedure for the MOM-protection of different phenethyl alcohols

The MOM-protected phenethyl alcohols **181** were prepared following a previously reported procedure for the preparation of [2-(methoxymethoxy)ethyl]benzene:[155]

$Sc(OTf)_3$ (191 mg, 0.389 mmol) was added to a solution of the alcohol (7.78 mmol) in FDMA (27 mL, 389 mmol) and $CHCl_3$ (27 mL). The resulting mixture was heated at 75 °C. After the specified time, deionised H_2O (20 mL) was added, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic fractions were washed with brine (30 mL) and dried ($MgSO_4$). [Removal of the H_2O from the aqueous

phase allows recovery of the $Sc(OTf)_3$, which can be reused]. The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product. Unless otherwise stated, the isolated crude product was sufficiently pure for characterisation and further use.

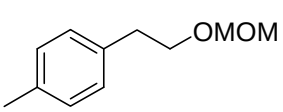
1-[2-(Methoxymethoxy)ethyl]-2-methylbenzene 181a



Chemical Formula: $C_{11}H_{16}O_2$
Exact Mass: 180.115
Molecular Weight: 180.2435
Elemental Analysis: C, 73.30; H, 8.95; O, 17.75

Acetal **181a** was prepared from 2-methylphenethyl alcohol (1.06 g, 7.78 mmol), FDMA (27 mL, 389 mmol) and $Sc(OTf)_3$ (191 mg, 0.389 mmol) in $CHCl_3$ (27 mL) according to the general procedure. After 24 h, work-up afforded MOM ether **181a** as a colourless liquid (1.40 g, 97%): R_f = 0.23 (90% hexane, 10% Et_2O); δ_H(300 MHz, C_6D_6) 2.13 (3H, s, ArCH_3), 2.79 (2H, t, *J* 7.2, C$H_2$$CH_2O$), 3.09 (3H, s, OC$H_3$), 3.60 (2H, t, *J* 7.2, CH_2CH_2O), 4.44 (2H, s, OC$H_2$$OCH_3$), 6.98-7.11 (4H, stack, Ar*H*); δ_C(75 MHz, C_6D_6) 19.4 (CH_3, Ar*C*H_3), 33.9 (CH_2, *C*H_2CH_2O), 54.8 (CH_3, O*C*H_3), 67.9 (CH_2, CH_2*C*H_2O), 96.5 (CH_2, O*C*H_2OCH_3), 126.3 (CH, Ar), 126.7 (CH, Ar), 129.9 (CH, Ar), 130.4 (CH, Ar), 136.5 (quat. C, *ipso* Ar), 137.5 (quat. C, *ipso* Ar); m/*z* (EI) 148 ($[M - H - OCH_3]^+$, 13%), 119 (43, $[M - OCH_2OCH_3]^+$), 118 (100, $[M - H - OCH_2OCH_3]^+$), 105 (63, $[M - CH_2OCH_2OCH_3]^+$), 91 (12, $[M - H - CH_2CH_2OCH_2OCH_3]^+$), 77 (10, $[C_6H_5]^+$).

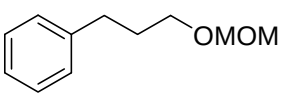
1-[2-(Methoxymethoxy)ethyl]-4-methylbenzene 181c



Chemical Formula: $C_{11}H_{16}O_2$
Exact Mass: 180.115
Molecular Weight: 180.2435
Elemental Analysis: C, 73.30; H, 8.95; O, 17.75

Acetal **181c** was prepared from 4-methylphenethyl alcohol (1.76 g, 12.9 mmol), FDMA (45 mL, 645 mmol) and $Sc(OTf)_3$ (317 mg, 0.645 mmol) in $CHCl_3$ (45 mL) according to the general procedure. After 24 h, work-up afforded MOM ether **181c** as a pale brown liquid (2.46 g, quant): R_f = 0.25 (90% hexane, 10% Et_2O); δ_H(300 MHz, C_6D_6) 2.13 (3H, s, ArC*H*$_3$), 2.78 (2H, t, *J* 6.9, C*H*$_2$CH$_2$O), 3.10 (3H, s, OC*H*$_3$), 3.63 (2H, t, *J* 6.9, CH$_2$C*H*$_2$O), 4.45 (2H, s, OC*H*$_2$OCH$_3$), 6.98 (2H, d, *J* 8.0, Ar*H*), 7.05 (2H, d, *J* 8.0, Ar*H*); δ_C(100 MHz, C_6D_6) 21.1 (CH$_3$, Ar*C*H$_3$), 36.4 (CH$_2$, *C*H$_2$CH$_2$O), 54.9 (CH$_3$, O*C*H$_3$), 68.9 (CH$_2$, CH$_2$*C*H$_2$O), 96.6 (CH$_2$, O*C*H$_2$OCH$_3$), 129.2 (CH, Ar), 129.3 (CH, Ar), 135.6 (quat. C, *ipso* Ar), 136.5 (quat. C, *ipso* Ar); m/*z* (EI) 119 ([M – OCH_2OCH_3]$^+$, 39%), 118 (90, [M – H – OCH_2OCH_3]$^+$), 105 (100, [M – $CH_2OCH_2OCH_3$]$^+$).

[3-(Methoxymethoxy)propyl]benzene 181l

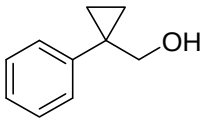


Chemical Formula: $C_{11}H_{16}O_2$
Exact Mass: 180.115
Molecular Weight: 180.2435
Elemental Analysis: C, 73.30; H, 8.95; O, 17.75

Acetal **181l** was prepared from phenpropyl alcohol (2.00 mL, 14.8 mmol), FDMA (65 mL, 740 mmol) and $Sc(OTf)_3$ (364 mg, 0.740 mmol) in $CHCl_3$ (65 mL) according to the general procedure. After 24 h, work-up afforded MOM ether **181l** as a colourless liquid (2.62 g,

98%): R_f = 0.24 (90% hexane, 10% Et_2O); δ_H(300 MHz) 1.91-2.03 (2H, m, $ArCH_2CH_2$), 2.76 (2H, t, *J* 7.5, $ArCH_2CH_2$), 3.42 (3H, s, OCH_3), 3.60 (2H, t, *J* 6.4, CH_2CH_2O), 4.68 (2H, s, OCH_2OCH_3), 7.19-7.38 (5H, stack, Ar*H*); δ_C(100 MHz) 31.4 (CH_2, $ArCH_2$ or $ArCH_2CH_2$), 32.4 (CH_2, $ArCH_2$ or $ArCH_2CH_2$), 55.1 (CH_3, OCH_3), 67.1 (CH_2, CH_2CH_2O), 96.4 (CH_2, OCH_2OCH_3), 125.8 (CH, *p*-Ar), 128.3 (CH, Ar), 128.4 (CH, Ar), 141.8 (quat. C, *ipso* Ar); m/*z* (EI) 148 ($[M - H - OCH_3]^+$, 18%), 118 (34, $[M - H - OCH_2OCH_3]^+$), 117 (31), 105 (29, $[M - CH_2OCH_2OCH_3]^+$), 92 (25), 91 (100, $[M - H - CH_2CH_2OCH_2OCH_3]^+$).

1-Phenyl-1-(hydroxymethyl)cyclopropane 180j[154]



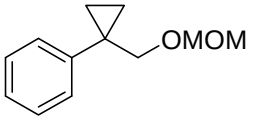
Chemical Formula: $C_{10}H_{12}O$
Exact Mass: 148.0888
Molecular Weight: 148.2017
Elemental Analysis: C, 81.04; H, 8.16; O, 10.80

$NaBH_4$ (620 mg, 16.5 mmol) was added to a solution of 1-phenyl-1-cyclopropane-carboxylic acid (2.00 g, 12.3 mmol) in THF (7 mL) at 0 °C (caution: gas formation!). A solution of $BF_3{\cdot}OEt_2$ (2.70 mL, 21.8 mmol) in THF (5 mL) was added over 3 min at 0 °C and the reaction mixture was stirred for 1 h at R.T. A mixture of THF/H_2O (1:1, 30 mL) was then added carefully (caution: gas formation), followed by the addition of more H_2O (20 mL). The two phases were separated and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic fractions were washed with brine (30 mL), and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude alcohol **180j** as a colourless liquid (1.83 g, quantitative), which was sufficiently pure for characterisation and further use: R_f = 0.45 (70% hexane, 30% EtOAc); δ_H(300 MHz) 0.81-0.94 (4H, stack, CH_2CH_2), 1.72 (1H, br s, O*H*), 3.65 (2H, s, CH_2OH),

7.19-7.41 (5H, stack, Ar*H*); δ_C(100 MHz) 11.3 (CH_2, cyclopropyl *C*H_2), 28.0 (quat. C, cyclopropyl *C*), 70.6 (CH_2, *C*H_2OH), 126.5 (CH, Ar), 128.3 (CH, Ar), 128.9 (CH, Ar), 142.7 (quat. C, *ipso* Ar); m/*z* (EI) 148 ($[M]^+$, 40%), 133 (19), 130 (35), 117 (100, $[M - CH_2OH]^+$), 105 (23), 91 (92), 77 (19, $[C_6H_5]^+$), 65 (16), 51 (20).

Data were in agreement with those reported in the literature.[193]

1-Phenyl-1-(methoxymethoxy)methylcyclopropane 181j

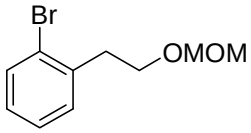


Chemical Formula: $C_{12}H_{16}O_2$
Exact Mass: 192.115
Molecular Weight: 192.2542
Elemental Analysis: C, 74.97; H, 8.39; O, 16.64

Acetal **181j** was prepared from 1-phenyl-1-(hydroxymethyl)cyclopropane **180j** (2.00 mL, 14.8 mmol), FDMA (65 mL, 740 mmol) and $Sc(OTf)_3$ (364 mg, 0.740 mmol) in $CHCl_3$ (65 mL) according to the general procedure. After 24 h, work-up and purification by flash column chromatography (gradient: 98% hexane, 2% Et_2O → 95% hexane, 5% Et_2O) afforded MOM ether **181j** as a colourless liquid (2.50 g, 85%): R_f = 0.19 (90% hexane, 10% Et_2O); ν_{max}(film)/cm^{-1} 2884m, 1603w, 1497w, 1446w, 1384w, 1213w, 1149m, 1103m, 1046s, 1017s, 974m, 917m, 857w, 758m, 697s; δ_H(300 MHz) 0.90-1.00 (4H, stack, cyclopropyl*CH*$_2$), 3.29 (3H, s, OC*H*$_3$), 3.70 (2H, s, C*H*$_2$O), 4.62 (2H, s, OC*H*$_2$OCH$_3$), 7.20-7.44 (5H, stack, Ar*H*); δ_C(75 MHz) 11.9 (CH_2, cyclopropyl*C*H_2), 25.1 (quat. C, cyclopropyl*C*), 55.0 (CH_3, O*C*H_3), 74.9 (CH_2, *C*H_2OCH$_2$OCH$_3$), 96.0 (CH_2, *C*H_2OCH$_3$), 126.1 (CH, *p*-Ar), 128.1 (CH, Ar), 128.4 (CH, Ar), 143.3 (quat. C, *ipso* Ar); m/*z* (EI) 192 ($[M]^+$, 7%), 132 (44), 131 (55, $[M - OCH_2OCH_3]^+$), 130 (96, $[M - H - OCH_2OCH_3]^+$), 129 (58), 117 (100), 115 (57, [M –

$CH_2OCH_2OCH_3]^+$), 104 (33), 103 (34), 91 (50), 77 (18, $[C_6H_5]^+$), 45 (39, $[CH_2OCH_3]^+$); HRMS: $C_{12}H_{16}O_2$ calcd 192.1150 ($[M]^+$), obsd 192.1155.

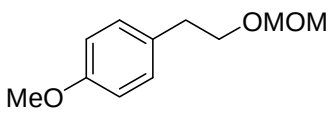
1-Bromo-2-[2-(methoxymethoxy)ethyl]benzene 181e



Chemical Formula: $C_{10}H_{13}BrO_2$
Exact Mass: 244.0099
Molecular Weight: 245.113
Elemental Analysis: C, 49.00; H, 5.35; Br, 32.60; O, 13.05

Acetal **181e** was prepared from 2-bromophenethyl alcohol (5.04 mL, 25.1 mmol), FDMA (88 mL, 1.25 mol) and $Sc(OTf)_3$ (617 mg, 1.25 mmol) in $CHCl_3$ (88 mL) according to the general procedure. After 48 h, work-up afforded MOM ether **181e** as a colourless liquid (6.06 g, 99%): R_f = 0.28 (90% hexane, 10% Et_2O); δ_H(300 MHz, C_6D_6) 2.95 (2H, t, *J* 6.9, C*H*$_2$$CH_2O$), 3.08 (3H, s, OC*H*$_3$), 3.64 (2H, t, *J* 6.9, CH_2C*H*$_2$O), 4.41 (2H, s, OC*H*$_2$$OCH_3$), 6.68 (1H, app. t, *J* 7.6, Ar*H*), 6.89 (1H, app. t, *J* 7.5, Ar*H*), 7.01 (1H, dd, *J* 7.6, 1.7, Ar*H*), 7.36 (1H, dd, *J* 8.0, 1.2, Ar*H*); δ_C(75 MHz, C_6D_6) 36.5 (CH_2, *C*$H_2$$CH_2O$), 54.5 ($CH_3$, O*C*$H_3$), 66.4 ($CH_2$, CH_2*C*H_2O), 96.0 (CH_2, O*C*$H_2$$OCH_3$), 124.7 (quat. C, *ipso* ArBr), 127.1 (CH, Ar), 127.8 (CH, Ar), 131.1 (CH, Ar), 132.6 (CH, Ar), 138.4 (quat. C, *ipso* Ar); m/*z* (EI) 246 ($[M]^+$, 1%), 244 ($[M]^+$, 1%), 216 (12), 214 (18), 212 (12), 186 (12), 185 (43), 184 (71), 183 (47), 182 (69), 171 (28), 169 (29), 158 (16), 156 (16), 135 (100), 105 (22), 104 (43), 103 (37), 91 (11), 90 (16), 89 (16), 77 (26, $[C_6H_5]^+$), 45 (58, $[CH_2OCH_3]^+$); HRMS: $C_{10}H_{13}O_2{}^{79}Br$ calcd 244.0099 ($[M]^+$), obsd 244.0094.

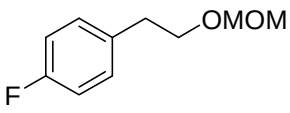
1-Methoxy-4-[2-(methoxymethoxy)ethyl]benzene 181g



Chemical Formula: $C_{11}H_{16}O_3$
Exact Mass: 196.1099
Molecular Weight: 196.2429
Elemental Analysis: C, 67.32; H, 8.22; O, 24.46

Acetal **181g** was prepared from 4-methoxyphenethyl alcohol (2.00 g, 13.1 mmol), FDMA (46 mL, 657 mmol) and $Sc(OTf)_3$ (323 mg, 0.657 mmol) in $CHCl_3$ (46 mL) according to the general procedure. After 15 h, work-up afforded MOM ether **181g** as a colourless oil (2.58 g, quant): R_f = 0.20 (90% hexane, 10% Et_2O); δ_H(300 MHz, C_6D_6) 2.76 (2H, t, *J* 7.0, C*H*$_2$CH$_2$O), 3.11 (3H, s, CH$_2$OC*H*$_3$), 3.32 (3H, s, ArOC*H*$_3$), 3.62 (2H, t, *J* 7.0, CH$_2$C*H*$_2$O), 4.47 (2H, s, OC*H*$_2$OCH$_3$), 6.74-6.83 (2H, m, Ar*H*), 6.99-7.07 (2H, m, Ar*H*); δ_C(100 MHz, C_6D_6) 35.9 (CH$_2$, *C*H$_2$CH$_2$O), 54.8 (CH$_3$, CH$_2$O*C*H$_3$ or ArO*C*H$_3$), 54.9 (CH$_3$, CH$_2$O*C*H$_3$ or ArO*C*H$_3$), 69.0 (CH$_2$, CH$_2$*C*H$_2$O), 96.5 (CH$_2$, O*C*H$_2$OCH$_3$), 114.1 (CH, Ar), 130.2 (CH, Ar), 131.5 (quat. C, *ipso* Ar), 158.8 (quat. C, *ipso* ArOMe); m/*z* (EI) 196 ([M]$^+$, 7%), 134 (50, [M – H – OCH$_2$OCH$_3$]$^+$), 121 (100, [M – CH$_2$OCH$_2$OCH$_3$]$^+$), 45 (36, [CH$_2$OCH$_3$]$^+$).

1-Fluoro-4-[2-(methoxymethoxy)ethyl]benzene 181h



Chemical Formula: $C_{10}H_{13}FO_2$
Exact Mass: 184.09
Molecular Weight: 184.2074
Elemental Analysis: C, 65.20; H, 7.11; F, 10.31; O, 17.37

Acetal **181h** was prepared from 4-fluorophenethyl alcohol (2.00 g, 14.3 mmol), FDMA (50 mL, 714 mmol) and $Sc(OTf)_3$ (351 mg, 0.714 mmol) in $CHCl_3$ (50 mL) according to the general procedure. After 48 h, work-up afforded MOM ether **181h** as a colourless liquid (2.61

g, 99%): R_f = 0.19 (90% hexane, 10% Et_2O); δ_H(300 MHz, C_6D_6) 2.60 (2H, t, *J* 6.8, C*H*$_2$CH$_2$O), 3.06 (3H, s, OC*H*$_3$), 3.49 (2H, t, *J* 6.8, CH$_2$C*H*$_2$O), 4.41 (2H, s, OC*H*$_2$OCH$_3$), 6.74-6.89 (4H, stack, Ar*H*); δ_C(100 MHz, C_6D_6) 35.8 (CH_2, *C*H$_2$CH$_2$O), 54.8 (CH_3, CH$_2$O*C*H$_3$), 68.5 (CH_2, CH$_2$*C*H$_2$O), 96.5 (CH_2, O*C*H$_2$OCH$_3$), 115.2 (CH, d, $^2J_{C\text{-}F}$ 21.0, Ar), 130.7 (CH, d, $^3J_{C\text{-}F}$ 7.6, Ar), 135.3 (quat. C, d, $^4J_{C\text{-}F}$ 2.4, *ipso* Ar), 162.0 (quat. C, d, $^1J_{C\text{-}F}$ 241.9, *ipso* Ar); δ_F(282 MHz, C_6D_6) –117.3- –117.1 (m, Ar*F*); m/*z* (EI) 122 (100, [M – H – OCH_2OCH_3]$^+$), 109 (61, [M – $CH_2OCH_2OCH_3$]$^+$), 45 (10, [CH_2OCH_3]$^+$).

General procedure for the formation of isochromans 182 *via* Friedel Crafts cyclisation of MOM-protected phenethyl alcohols 181

Isochromans **182** were prepared by modification of previously reported procedures for the preparation of different substituted isochromans *via* cyclisation of MOM- or MEM-protected phenethyl alcohols:

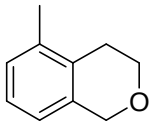
Method A[114]

TMSOTf (0.694 or 1.39 mmol (see specific experimental details)) was added to a solution of MOM-protected phenethyl alcohol (6.94 mmol) in MeCN (35 mL) at 0 °C. After stirring at R.T. for 15 h, $NaHCO_3$ solution (10 mL) was added and the MeCN was removed under reduced pressure. Et_2O (20 mL) and more $NaHCO_3$ solution (10 mL) were added to the residue and the layers were separated. The aqueous phase was extracted with Et_2O (2 × 20 mL) and the combined organic fractions were washed with brine (25 mL) and dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product, which was purified by flash column chromatography.

Method B[156,194]

A solution of $TiCl_4$ in CH_2Cl_2 (1 M, 2.40 mL, 2.40 mmol) was added dropwise over 5 min to a solution of MOM-protected phenethyl alcohol (2.00 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After stirring at R.T. for 15 h, MeOH (1 mL) was added and the brown colouration disappeared. Hydrochloric acid (1 M, 25 mL) was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic fractions were washed with brine (25 mL) and dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product, which was purified by flash column chromatography.

5-Methylisochroman 182a[114]



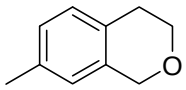
Chemical Formula: $C_{10}H_{12}O$
Exact Mass: 148.0888
Molecular Weight: 148.2017
Elemental Analysis: C, 81.04; H, 8.16; O, 10.80

Isochroman **182a** was prepared from MOM ether **181a** (1.36 g, 7.55 mmol) and TMSOTf (273 μL, 1.51 mmol) in MeCN (35 mL) according to Method A. After 15 h, work-up and purification by flash column chromatography (gradient: 99% hexane, 1% Et_2O → 95% hexane, 5% Et_2O) afforded isochroman **182a** as a colourless liquid (0.96 g, 86%): R_f = 0.25 (90% hexane, 10% Et_2O); δ_H(300 MHz) 2.29 (3H, s, CH_3), 2.76 (2H, t, *J* 5.8, CH_2CH_2O), 4.07 (2H, t, *J* 5.8, CH_2CH_2O), 4.82 (2H, s, ArCH_2O), 6.89 (1H, d, *J* 7.2, Ar*H*), 7.06-7.18 (2H, stack, Ar*H*); δ_C(75 MHz) 18.7 (CH_3, CH_3), 26.0 (CH_2, CH_2CH_2O), 65.4 (CH_2, CH_2CH_2O or ArCH_2O), 68.2 (CH_2, CH_2CH_2O or ArCH_2O), 121.9 (CH, Ar), 125.5 (CH, Ar), 127.6 (CH,

Ar), 131.6 (quat. C, *ipso* Ar), 134.7 (quat. C, *ipso* Ar), 136.3 (quat. C, *ipso* Ar); m/*z* (EI) 148 ($[M]^+$, 100%), 133 (37, $[M - CH_3]^+$), 118 (67, $[M - OCH_2]^+$), 91 (12).

Data were in agreement with those reported in the literature.[114]

7-Methylisochroman 182c[114]

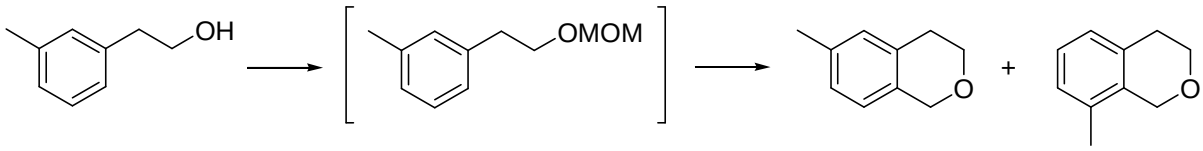


Chemical Formula: $C_{10}H_{12}O$
Exact Mass: 148.0888
Molecular Weight: 148.2017
Elemental Analysis: C, 81.04; H, 8.16; O, 10.80

Isochroman **182c** was prepared from MOM ether **181c** (2.38 g, 13.2 mmol) and TMSOTf (239 μL, 1.32 mmol) in MeCN (67 mL) according to Method A. After 15 h, work-up and purification by flash column chromatography (gradient: 99% hexane, 1% Et_2O → 95% hexane, 5% Et_2O) afforded isochroman **182c** as a colourless oil (1.57 g, 80%): R_f = 0.30 (90% hexane, 10% Et_2O); δ_H(300 MHz) 2.32 (3H, s, C*H*$_3$), 2.83 (2H, t, *J* 5.7, C*H*$_2$CH$_2$O), 3.98 (2H, t, *J* 5.7, CH$_2$C*H*$_2$O), 4.76 (2H, s, ArC*H*$_2$O), 6.81 (1H, s, Ar*H*), 6.96-7.15 (2H, stack, Ar*H*); δ_C(100 MHz) 21.0 (CH$_3$, *C*H$_3$), 28.0 (CH$_2$, *C*H$_2$CH$_2$O), 65.5 (CH$_2$, CH$_2$*C*H$_2$O or Ar*C*H$_2$O), 67.9 (CH$_2$, CH$_2$*C*H$_2$O or Ar*C*H$_2$O), 124.8 (CH, Ar), 127.1 (CH, Ar), 128.7 (CH, Ar), 130.1 (quat. C, *ipso* Ar), 134.7 (quat. C, *ipso* Ar), 135.4 (quat. C, *ipso* Ar); m/*z* (EI) 148 ($[M]^+$, 71%), 133 (24, $[M - CH_3]^+$), 118 (100, $[M - OCH_2]^+$), 103 (14, $[M - CH_3 - OCH_2]^+$), 91 (35), 77 (12, $[C_6H_5]^+$).

Data were in agreement with those reported in the literature.[114]

6-Methylisochroman 182b and 8-methylisochroman 182d[114]



2.6 : 1.0

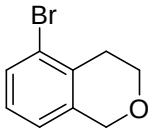
Chemical Formula: $C_{10}H_{12}O$
Exact Mass: 148.0888
Molecular Weight: 148.2017
Elemental Analysis:
C, 81.04; H, 8.16; O, 10.80

$Sc(OTf)_3$ (191 mg, 0.389 mmol) was added to a solution of 3-methylphenethyl alcohol (3.00 g, 22.0 mmol) in FDMA (85 mL, 1.10 mol) and $CHCl_3$ (85 mL). The resulting mixture was heated at 75 °C to generate the corresponding MOM ethers **181b** and **181d**. After 48 h, the solvents were evaporated at 75 °C, which effected cyclisation to isochromans **182b** and **182d**. The dark-brown oil was cooled to R.T. CH_2Cl_2 (40 mL) and deionised H_2O (40 mL) were added, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic fractions were washed with brine (50 mL) and dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product. Purification by flash column chromatography (gradient: 99% hexane, 1% Et_2O → 95% hexane, 5% Et_2O) afforded a mixture of isochromans **182b** and **182d** as a colourless oil (2.22 g, 68% from 3-methylphenethyl alcohol, **182b : 182d** = 2.6 : 1.0): R_f = 0.30 (90% hexane, 10% Et_2O); δ_H(300 MHz) [2.19 (3H, s, C*H*$_3$, minor), 2.36 (3H, s, C*H*$_3$, major)], 2.83-2.94 (2H, stack, C*H*$_2$CH$_2$O, both isomers), 3.96-4.05 (2H, stack, CH$_2$C*H*$_2$O, both isomers), [4.77 (2H, s, ArC*H*$_2$O, minor), 4.80 (2H, s, ArC*H*$_2$O, major)], 6.88-7.18 (3H, stack, Ar*H*, both isomers); δ_C(75 MHz) 17.7 (CH_3, *C*H$_3$, minor), 21.0 (CH_3, *C*H$_3$, major), 28.2 (CH_2, *C*H$_2$CH$_2$O, major), 28.6 (CH_2, *C*H$_2$CH$_2$O, minor), 64.8 (CH_2, CH$_2$*C*H$_2$O or Ar*C*H$_2$O, minor), 65.3 (CH_2, CH$_2$*C*H$_2$O or Ar*C*H$_2$O, major), 66.4 (CH_2, CH$_2$*C*H$_2$O or

Ar*C*H_2O, minor), 67.8 (CH_2, CH_2*C*H_2O or Ar*C*H_2O, major), 124.2 (CH, Ar, major), 126.0 (CH, Ar, minor), 126.4 (CH, Ar, minor), 126.7 (CH, Ar, major), 127.4 (CH, Ar, minor), 129.3 (CH, Ar, major), 131.8 (quat. C, *ipso* Ar, major), 132.9 (quat. C, *ipso* Ar, major), 133.0 (quat. C, *ipso* Ar, minor), 133.1 (quat. C, *ipso* Ar, minor), 133.3 (quat. C, *ipso* Ar, minor), 135.7 (quat. C, *ipso* Ar, major); m/*z* GC-MS (EI) $t_{R,\text{major}}$ = 5.85 min: 148 ($[M]^+$, 100%), 133 (94, $[M - CH_3]^+$), 118 (80, $[M - OCH_2]^+$), 103 (22, $[M - CH_3 - OCH_2]^+$), 91 (36), 77 (21, $[C_6H_5]^+$); $t_{R,\text{minor}}$ = 5.97 min: 148 ($[M]^+$, 100%), 133 (100, $[M - CH_3]^+$), 118 (92, $[M - OCH_2]^+$), 103 (25, $[M - CH_3 - OCH_2]^+$), 91 (61), 77 (22, $[C_6H_5]^+$).

Data were in agreement with those reported in the literature.[114]

5-Bromoisochroman 182e[195]



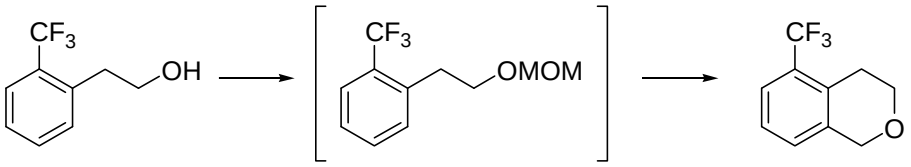
Chemical Formula: C_9H_9BrO
Exact Mass: 211.9837
Molecular Weight: 213.0712
Elemental Analysis: C, 50.73; H, 4.26; Br, 37.50; O, 7.51

Isochroman **182e** was prepared from MOM ether **181e** (5.07 g, 20.7 mmol) and a solution of $TiCl_4$ in CH_2Cl_2 (24.8 mL, 24.8 mmol) in CH_2Cl_2 (200 mL) according to Method B. After 15 h, work-up and purification by flash column chromatography (gradient: 99% hexane, 1% Et_2O → 95% hexane, 5% Et_2O) afforded isochroman **182e** as a white crystalline solid (3.91 g, 89%): mp 152-154 °C; R_f = 0.30 (90% hexane, 10% Et_2O); δ_H(300 MHz) 2.81 (2H, t, *J* 5.8, C*H*$_2$CH$_2$O), 3.99 (2H, t, *J* 5.8, CH$_2$C*H*$_2$O), 4.73 (2H, s, ArC*H*$_2$O), 6.94 (1H, d, *J* 7.5, Ar*H*), 7.04 (1H, app. t, *J* 7.7, Ar*H*), 7.43 (1H, d, *J* 7.7, Ar*H*); δ_C(100 MHz, C_6D_6) 29.5 (CH_2, *C*H$_2$CH$_2$O), 65.2 (CH_2, CH$_2$*C*H$_2$O or Ar*C*H$_2$O), 67.8 (CH_2, CH$_2$*C*H$_2$O or Ar*C*H$_2$O), 121.9

(CH, Ar), 125.5 (CH, Ar), 127.6 (CH, Ar), 131.6 (quat. C, *ipso* Ar), 134.7 (quat. C, *ipso* Ar), 136.3 (quat. C, *ipso* Ar); m/*z* (EI) 214 ($[M]^+$, 53%), 212 (61, $[M]^+$), 184 (83, $[M - OCH_2]^+$), 182 (84, $[M - OCH_2]^+$), 133 (100, $[M - Br]^+$), 103 (59, $[M - Br - OCH_2]^+$), 77 (17, $[C_6H_5]^+$).

Data were in agreement with those reported in the literature.[195]

5-Trifluoromethylisochroman 182f

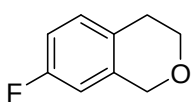


Chemical Formula: $C_{10}H_9F_3O$
Exact Mass: 202.0605
Molecular Weight: 202.1731
Elemental Analysis:
C, 59.41; H, 4.49; F, 28.19; O, 7.91

MOM ether **181f** was prepared from 2-trifluoromethylphenethyl alcohol (2.00 g, 10.5 mmol), FDMA (37 mL, 526 mmol) and $Sc(OTf)_3$ (259 mg, 0.526 mmol) in $CHCl_3$ (37 mL) according to the general procedure for the MOM-protection of different phenethyl alcohols. After 48 h, work-up afforded the MOM ether as a colourless liquid (2.44 g, 10.4 mmol) which was used directly and without purification in the preparation of isochroman **182f** from a solution of $TiCl_4$ in CH_2Cl_2 (12.5 mL, 12.5 mmol) in CH_2Cl_2 (100 mL) according to Method B. After 15 h, work-up and purification by flash column chromatography (gradient: 99% hexane, 1% Et_2O → 95% hexane, 5% Et_2O) afforded isochroman **182f** as a colourless liquid (934 mg, 44% over two steps): R_f = 0.25 (90% hexane, 10% Et_2O); ν_{max}(film)/cm^{-1} 2944w, 2894w, 1497w (C=C aromatic), 1322s, 1307s, 1263w, 1200w, 1186m, 1157s, 1102s, 1075s, 1063s,

1011m, 973m, 957m, 925m, 845w, 794s, 727m, 690m, 653m; δ_H(300 MHz) 3.01 (2H, t, *J* 5.7, C*H*$_2$CH$_2$O), 3.99 (2H, t, *J* 5.7, CH$_2$C*H*$_2$O), 4.82 (2H, s, ArC*H*$_2$O), 7.15 (1H, d, *J* 7.7, Ar*H*), 7.21-7.30 (1H, m, Ar*H*), 7.51 (1H, d, *J* 7.5, Ar*H*); δ_C(100 MHz) 25.3 (CH$_2$, *C*H$_2$CH$_2$O), 64.7 (CH$_2$, CH$_2$*C*H$_2$O or Ar*C*H$_2$O), 68.0 (CH$_2$, CH$_2$*C*H$_2$O or Ar*C*H$_2$O), 124.13 (CH, q, $^3J_{C\text{-}F}$ 5.6, Ar), 124.4 (quat. C, q, $^1J_{C\text{-}F}$ 272.4, Ar*C*F$_3$), 125.8 (CH, Ar), 128.2 (CH, Ar), 128.8 (quat. C, q, $^2J_{C\text{-}F}$ 28.4, *ipso* Ar), 132.1 (quat. C, *ipso* Ar), 136.4 (quat. C, *ipso* Ar); δ_F(282 MHz) – 61.5 (s, ArC*F*$_3$); m/*z* (EI) 202 ([M]$^+$, 26%), 172 (100, [M – OCH$_2$]$^+$), 151 (18), 133 (32, [M – CF$_3$]$^+$), 103 (14); HRMS: $C_{10}H_9OF_3$ calcd 202.0605 ([M]$^+$), obsd 202.0600.

7-Fluoroisochroman 182h



Chemical Formula: C_9H_9FO
Exact Mass: 152.0637
Molecular Weight: 152.1656
Elemental Analysis: C, 71.04; H, 5.96; F, 12.49; O, 10.51

Isochroman **182h** was prepared from MOM ether **181h** (2.51 g, 13.6 mmol) and a solution of $TiCl_4$ in CH_2Cl_2 (16.4 mL, 16.4 mmol) in CH_2Cl_2 (135 mL) according to Method B. After 15 h, work-up and purification by flash column chromatography (gradient: 99% hexane, 1% Et_2O → 95% hexane, 5% Et_2O) afforded isochroman **182h** as a pale yellow liquid (1.59 g, 77%): R_f = 0.26 (90% hexane, 10% Et_2O); ν_{max}(film)/cm^{-1} 2935w, 2857w, 282w, 1617m, 1400s (C=C aromatic), 1430m, 1259m, 1248m, 1223s, 1202m, 1114m, 1094s, 1069m, 1005w, 993m, 949m, 931s, 856s, 809s 747m, 736s; δ_H(300 MHz) 2.81 (2H, t, *J* 5.7, C*H*$_2$CH$_2$O), 3.95 (2H, t, *J* 5.7, CH$_2$C*H*$_2$O), 4.73 (2H, s, ArC*H*$_2$O), 6.68 (1H, dd, $^3J_{H\text{-}F}$ 9.1, $^4J_{H\text{-}H}$ 2.6, Ar*H*), 6.86 (1H, app. td, $^3J_{H\text{-}H}$ and $^3J_{H\text{-}F}$ 8.5, $^4J_{H\text{-}H}$ 2.6, Ar*H*), 7.07 (1H, dd, $^3J_{H\text{-}H}$ 8.5, $^4J_{H\text{-}F}$ 5.6, Ar*H*); δ_C(75 MHz) 27.5 (CH$_2$, *C*H$_2$CH$_2$O), 65.3 (CH$_2$, CH$_2$*C*H$_2$O or Ar*C*H$_2$O), 67.6

(CH_2, CH_2CH_2O or $ArCH_2O$), 110.8 (CH, d, $^2J_{C\text{-}F}$ 21.4, Ar), 113.4 (CH, d, $^2J_{C\text{-}F}$ 21.3, Ar), 128.62 (quat. C, d, $^4J_{C\text{-}F}$ 2.2, *ipso* Ar), 130.2 (CH, d, $^3J_{C\text{-}F}$ 7.6, Ar), 136.6 (quat. C, d, $^3J_{C\text{-}F}$ 6.5, *ipso* Ar), 161.0 (quat. C, d, $^1J_{C\text{-}F}$ 242.9, *ipso* Ar); δ_F(282 MHz) –116.6- –116.4 (m, Ar*F*); m/*z* (EI) 152 ($[M]^+$, 17%), 128 (21), 122 (100, $[M - OCH_2]^+$), 96 (11); HRMS: C_9H_9OF calcd 152.0637 ($[M]^+$), obsd 152.0636.

General procedure for the formation of isochroman-1-ones 183

Substituted isochroman-1-ones **183** were prepared following two previously reported procedures for the preparation of isochroman-1-one **172**:

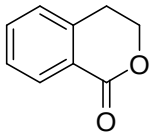
Method A[162]

A solution of fuming nitric acid (100%) (2.97 mL, 71.6 mmol) in CH_2Cl_2 (5 mL) was added dropwise *via* dropping funnel over 10 min to a cooled (0 °C) solution of the isochroman (23.9 mmol) in CH_2Cl_2 (5 mL). A colour change of the colourless solution *via* green to orange was observed. After the addition was complete, the homogeneous reaction mixture was warmed to R.T. and stirring was continued for 1 h. The solution was then diluted with CH_2Cl_2 (50 mL) and $NaHCO_3$ solution (30 mL) was added *via* pipette (caution: rapid gas formation!). The layers were separated, and the organic phase was washed with $NaHCO_3$ solution (30 mL) and brine (30 mL) and dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product, which was purified by a silica plug or flash column chromatography as appropriate.

Method B[157]

$KMnO_4$ (4.74 g, 30.0 mmol) was added to a solution of the isochroman (10.0 mmol) and TEBAC (342 mg, 1.50 mmol) in CH_2Cl_2 (100 mL). The heterogeneous purple solution was stirred for 24 h at R.T. The solvent was evaporated, and the residue was loaded on to a column with a minimum amount of CH_2Cl_2 and the crude product was purified by flash column chromatography.

Isochroman-1-one 172[130162]

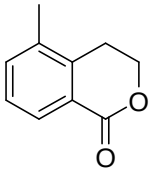


Chemical Formula: $C_9H_8O_2$
Exact Mass: 148.0524
Molecular Weight: 148.1586
Elemental Analysis: C, 72.96; H, 5.44; O, 21.60

Isochroman-1-one **172** was prepared from isochroman (3.20 g, 23.9 mmol) in CH_2Cl_2 (5 mL) and fuming nitric acid (100%) (2.97 mL, 71.6 mmol) in CH_2Cl_2 (5 mL) according to Method A. Work-up and purification by silica plug (60% hexane, 40% EtOAc) afforded isochroman-1-one **172** as a pale yellow viscous oil (3.50 g, 99%): R_f = 0.25 (60% hexane, 40% EtOAc); δ_H(300 MHz, C_6D_6) 2.03-2.24 (2H, stack, C$H_2$$CH_2$O), 3.64-3.83 (2H, stack, CH_2CH_2O), 6.63 (1H, d, *J* 7.0 Ar*H*), 6.86-7.08 (2H, stack, Ar*H*), 8.19 (1H, d, *J* 7.5, Ar*H*); δ_C(100 MHz, C_6D_6) 27.6 (CH_2, *C*$H_2$$CH_2$O), 66.8 ($CH_2$, CH_2*C*H_2O), 126.2 (quat. C, *ipso* Ar), 127.3 (CH, Ar), 127.6 (CH, Ar), 130.4 (CH, Ar), 133.2 (CH, Ar), 140.0 (quat. C, *ipso* Ar), 164.4 (quat. C, *C*=O); m/*z* (EI) 148 ($[M]^+$, 59%), 118 (100, $[M - OCH_2]^+$), 90 (69, $[M - CO - OCH_2]^+$), 63 (14).

Data were in agreement with those reported in the literature.[196]

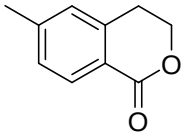
5-Methylisochroman-1-one 183a



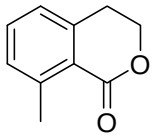
Chemical Formula: $C_{10}H_{10}O_2$
Exact Mass: 162.0681
Molecular Weight: 162.1852
Elemental Analysis: C, 74.06; H, 6.21; O, 19.73

Isochroman-1-one **183a** was prepared from isochroman **182a** (962 mg, 6.49 mmol), $KMnO_4$ (3.08 g, 19.5 mmol) and TEBAC (222 mg, 0.974 mmol) in CH_2Cl_2 (65 mL) according to Method B. Purification by flash column chromatography (gradient: 90% hexane, 10% EtOAc → 80% hexane, 20% EtOAc) afforded isochroman-1-one **183a** as a white crystalline solid (801 mg, 76%): mp 67-68 °C; R_f = 0.30 (70% hexane, 30% EtOAc); (Found: C, 74.01; H, 5.92. $C_{10}H_{10}O_2$ requires C, 74.06; H, 6.21%); ν_{max}(film)/cm^{-1} 2994w, 2963w, 2910w, 1700s (C=O), 1477m (C=C aromatic), 1396m, 1302m, 1279s, 1258m, 1170m, 1123s, 1084m, 1071m, 1045s, 1037s, 1011m, 951m, 824m, 768s, 760s, 706m; δ_H(300 MHz) 2.31 (3H, s, C*H*$_3$), 2.95 (2H, t, *J* 6.1, C*H*$_2$CH$_2$O), 4.50 (2H, t, *J* 6.2, CH$_2$C*H*$_2$O), 7.26 (1H, dd, *J* 7.7, 7.2, Ar*H*), 7.38 (1H, d, *J* 7.2, Ar*H*), 7.94 (1H, d, *J* 7.7, Ar*H*); δ_C(100 MHz) 18.8 (CH$_3$, *C*H$_3$), 24.8 (CH$_2$, *C*H$_2$CH$_2$O), 66.6 (CH$_2$, CH$_2$*C*H$_2$O), 125.2 (quat. C, *ipso* Ar), 127.0 (CH, Ar), 128.1 (CH, Ar), 134.9 (CH, Ar), 135.0 (quat. C, *ipso* Ar), 138.1 (quat. C, *ipso* Ar), 165.4 (quat. C, *C*=O); m/*z* (EI) 162 ([M]$^+$, 93%), 132 (100, [M – OCH$_2$]$^+$), 104 (58, [M – CO – OCH$_2$]$^+$).

6-Methylisochroman-1-one 183b and 8-methylisochroman-1-one 183d



Chemical Formula: $C_{10}H_{10}O_2$
Exact Mass: 162.0681
Molecular Weight: 162.1852
Elemental Analysis: C, 74.06; H, 6.21; O, 19.73



Chemical Formula: $C_{10}H_{10}O_2$
Exact Mass: 162.0681
Molecular Weight: 162.1852
Elemental Analysis: C, 74.06; H, 6.21; O, 19.73

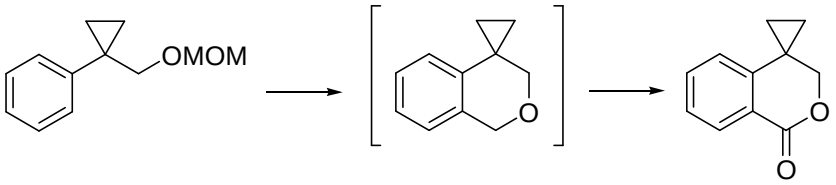
Isochroman-1-ones **183b** and **183d** were prepared from the mixture of isochromans **182b** and **182d** (1.98 g, 13.4 mmol) in CH_2Cl_2 (2.8 mL) and fuming nitric acid (100%) (1.66 mL, 40.1 mmol) in CH_2Cl_2 (2.8 mL) according to Method A. Work-up and purification by careful[3] column chromatography (gradient: 95% hexane, 5% EtOAc → 90% hexane, 10% EtOAc) afforded, in order of elution, 8-methylisochroman-1-one **183d** as a white solid (598 mg, 28%): mp 64-65 °C; R_f = 0.24 (80% hexane, 20% EtOAc); ν_{max}(film)/cm^{-1} 2963w, 2925m, 1710s (C=O), 1595m, 1470m (C=C aromatic), 1419m, 1386m, 1379m, 1277s, 1232s, 1187m, 1115s, 1078m, 1057s, 1046m, 1028s, 978m, 923m, 787m, 768s, 697s, 654m; δ_H(300 MHz) 2.60 (3H, s, C*H*$_3$), 2.95 (2H, t, *J* 5.9, C*H*$_2$CH$_2$O), 4.37 (2H, t, *J* 5.9, CH$_2$C*H*$_2$O), 7.04 (1H, d, *J* 7.6, Ar*H*), 7.13 (1H, d, *J* 7.6, Ar*H*), 7.31 (1H, app. t, *J* 7.6, Ar*H*); δ_C(75 MHz) 21.9 (CH$_3$, *C*H$_3$), 28.7 (CH$_2$, *C*H$_2$CH$_2$O), 66.5 (CH$_2$, CH$_2$*C*H$_2$O), 123.5 (quat. C, *ipso* Ar), 124.8 (CH, Ar), 130.8 (CH, Ar), 132.3 (CH, Ar), 140.5 (quat. C, *ipso* Ar), 142.6 (quat. C, *ipso* Ar), 164.2 (quat. C, *C*=O); m/*z* (EI) 162 ([M]$^+$, 89%), 147 (20, [M – CH$_3$]$^+$), 132 (100, [M – OCH$_2$]$^+$), 119 (24), 115 (15), 104 (45, [M – CO – OCH$_2$]$^+$), 91 (10), 78 (14), 77 (15); HRMS: $C_{10}H_{10}O_2$ calcd 162.0681 ([M]$^+$), obsd 162.0678; and then 6-methylisochroman-1-one **183b** as a white solid (1.40 g, 65%): mp 52-53 °C; R_f = 0.18 (80% hexane, 20% EtOAc); ν_{max}(film)/cm^{-1} 2991m, 2904w, 1708s (C=O), 1614s, 1470m (C=C aromatic), 1419m, 1397m, 1288m, 1243s, 1200w, 1161m, 1127m, 1090s, 1060m, 1030s, 958m, 908m, 894w, 837s, 772s, 730w, 710s, 678m; δ_H(300 MHz) 2.34 (3H, s, C*H*$_3$), 2.95 (2H, t, *J* 6.0, C*H*$_2$CH$_2$O), 4.44 (2H, t, *J* 6.0, CH$_2$C*H*$_2$O), 7.02 (1H, s, Ar*H*), 7.13 (1H, d, *J* 8.0, Ar*H*), 7.90 (1H, d, *J* 8.0, Ar*H*); δ_C(100

[3] in total three columns were carried out to fully separate the two compounds

MHz) 21.5 (CH_3, *C*H_3), 27.6 (CH_2, *C*H_2CH_2O), 67.1 (CH_2, CH_2*C*H_2O), 122.3 (quat. C, *ipso* Ar), 127.6 (CH, Ar), 128.3 (CH, Ar), 130.1 (CH, Ar), 139.4 (quat. C, *ipso* Ar), 144.4 (quat. C, *ipso* Ar), 165.0 (quat. C, *C*=O); m/*z* (EI) 162 ($[M]^+$, 81%), 132 (100, $[M - OCH_2]^+$), 104 (49, $[M - CO - OCH_2]^+$), 78 (13), 77 (12); HRMS: $C_{10}H_{10}O_2$ calcd 162.0681 ($[M]^+$), obsd 162.0683.

Data were in agreement with those reported in the literature.[197]

Spiro[isochroman-1-one-4,1'-cyclopropane] 183j

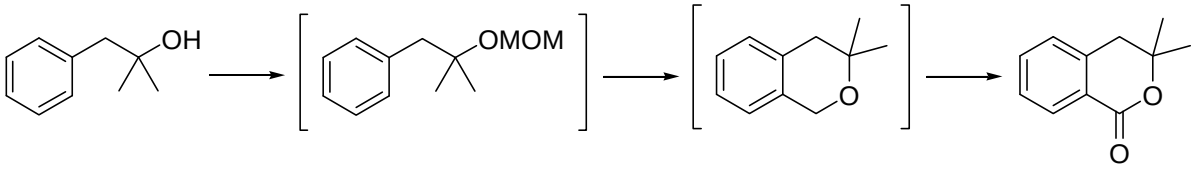


Chemical Formula: $C_{11}H_{10}O_2$
Exact Mass: 174.0681
Molecular Weight: 174.1959
Elemental Analysis:
C, 75.84; H, 5.79; O, 18.37

Isochroman **182j** was prepared from MOM ether **181j** (2.47 g, 12.8 mmol) and TMSOTf (233 μL, 1.28 mmol) in MeCN (65 mL) according to Method A for the formation of different isochromans *via* cyclisation of MOM-protected phenethyl alcohols. After 15 h, work-up and purification by flash column chromatography (gradient: 98% hexane, 2% Et_2O → 90% hexane, 10% Et_2O) afforded crude isochroman **182j** as a colourless liquid, which was used without further purification for the preparation of isochroman-1-one **183j** from $KMnO_4$ (2.14 g, 13.6 mmol) and TEBAC (154 mg, 0.678 mmol) in CH_2Cl_2 (45 mL) according to Method B. Purification by flash column chromatography (gradient: 90% hexane, 10% EtOAc → 85%

hexane, 15% EtOAc) afforded isochroman-1-one **183j** as a colourless oil (524 mg, 24% over two steps): R_f = 0.20 (80% hexane, 20% EtOAc); ν_{max}(film)/cm^{-1} 3004w, 2886w, 1712s (C=O), 1605m, 1487m, 1460m, 1427w, 1394m, 1270s, 1220m, 1165w, 1108s, 1074m, 1037m, 1008m, 941m, 828w, 801w, 755s, 719m, 695s, 656m; δ_H(300 MHz) 0.97-1.13 (4H, stack, cyclopropylC*H*$_2$), 4.19 (2H, s, C*H*$_2$O), 6.83 (1H, d, *J* 7.8, Ar*H*), 7.25 (1H, app. t, *J* 7.8, Ar*H*), 7.45 (1H, app. t, *J* 7.8, Ar*H*), 8.02 (1H, d, *J* 7.8, Ar*H*); δ_C(100 MHz) 13.2 (CH_2, *C*H_2), 18.1 (quat. C, *C*CH_2O), 73.8 (CH_2, *C*H_2O), 120.8 (CH, Ar), 125.5 (quat. C, *ipso* Ar), 126.4 (CH, Ar), 130.2 (CH, Ar), 133.8 (CH, Ar), 143.3 (quat. C, *ipso* Ar), 165.1 (quat. C, *C*=O); m/*z* (EI) 174 ([M]$^+$, 48%), 146 (70, [M – CH_2CH_2]$^+$), 145 (100), 131 (11), 118 (66, [M – CO – CH_2CH_2]$^+$), 115 (61), 90 (22), 69 (11), 63 (11); HRMS: $C_{11}H_{10}O_2$ calcd 174.0681 ([M]$^+$), obsd 174.0677.

3,3-Dimethylisochroman-1-one 183i

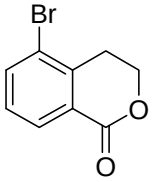


Chemical Formula: $C_{11}H_{12}O_2$
Exact Mass: 176.0837
Molecular Weight: 176.2118
Elemental Analysis:
C, 74.98; H, 6.86; O, 18.16

$Sc(OTf)_3$ (191 mg, 0.389 mmol) was added to a solution of 3-methyl-1-phenyl-2-propanol (2.21 g, 14.7 mmol) in FDMA (65 mL, 736 mmol) and $CHCl_3$ (65 mL). The resulting mixture was heated at 75 °C to generate the corresponding MOM ether **181i**. After 48 h, the solvent was evaporated at 75 °C, which effected cyclisation to isochroman **182i**. The resulting dark-

brown oil was cooled to R.T. CH_2Cl_2 (30 mL) and deionised H_2O (30 mL) were added, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic fractions were washed with brine (40 mL) and dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product. Purification by flash column chromatography (gradient: 99% hexane, 1% Et_2O → 90% hexane, 10% Et_2O) afforded crude isochroman **182i** as a colourless oil which was used without further purification for the preparation of isochroman-1-one **183i** from $KMnO_4$ (3.62 g, 22.9 mmol) and TEBAC (261 mg, 1.15 mmol) in CH_2Cl_2 (75 mL) according to Method B. Purification by flash column chromatography (gradient: 99% hexane, 1% EtOAc → 80% hexane, 20% EtOAc) afforded isochroman-1-one **183i** as a colourless oil (983 mg, 38% from 3-methyl-1-phenyl-2-propanol): R_f = 0.25 (80% hexane, 20% EtOAc); ν_{max}(film)/cm^{-1} 2921m, 1708s (C=O), 1607m, 1459m, 1388m, 1373m, 1290s, 1260m, 1211m, 1199m, 1180m, 1107s, 1079s, 1031m, 943m, 907w, 800m, 740s, 717s, 691m; δ_H(300 MHz) 1.38-1.48 (6H, stack, C*H*$_3$), 2.99 (2H, s, C*H*$_2$), 7.19 (1H, d, *J* 7.5, Ar*H*), 7.29-7.39 (1H, m, Ar*H*), 7.46-7.55 (1H, m, Ar*H*), 8.05 (1H, dd, *J* 7.7, 1.2, Ar*H*); δ_C(100 MHz) 27.4 (CH_3, *C*H_3), 39.3 (CH_2, *C*H_2), 80.6 (quat. C, *C*$(CH_3)_2$), 124.6 (quat. C, *ipso* Ar), 127.4 (CH, Ar), 127.9 (CH, Ar), 129.8 (CH, Ar), 133.7 (CH, Ar), 138.0 (quat. C, *ipso* Ar), 165.0 (quat. C, *C*=O); m/*z* (EI) 176 ([M]$^+$, 32%), 161 (37, [M – CH_3]$^+$), 133 (46, [M – CO – CH_3]$^+$), 118 (100, [M – CO – 2 × CH_3]$^+$), 115 (21), 105 (13), 90 (73), 63 (13); HRMS: $C_{11}H_{12}O_2$ calcd 176.0837 ([M]$^+$), obsd 176.0842.

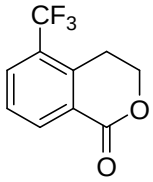
5-Bromoisochroman-1-one 183e



Chemical Formula: $C_9H_7BrO_2$
Exact Mass: 225.9629
Molecular Weight: 227.0547
Elemental Analysis: C, 47.61; H, 3.11; Br, 35.19; O, 14.09

Isochroman-1-one **183e** was prepared from isochroman **182e** (1.00 g, 4.69 mmol), $KMnO_4$ (2.23 g, 14.1 mmol) and TEBAC (160 mg, 0.704 mmol) in CH_2Cl_2 (47 mL) according to Method B. Purification by flash column chromatography (gradient: 90% hexane, 10% EtOAc → 80% hexane, 20% EtOAc) afforded isochroman-1-one **183e** as a white crystalline solid (864 mg, 82%): mp 83-84 °C; R_f = 0.23 (80% hexane, 20% EtOAc); (Found: C, 47.88; H, 3.29. $C_9H_7O_2Br$ requires C, 47.61; H, 3.11%); ν_{max}(film)/cm^{-1} 2969w, 1716s (C=O), 1446m, 1397m, 1295m, 1274s, 1240s, 1210m, 1179m, 1141m, 1095s, 1059s, 1030s, 954m, 811m, 775m, 741s, 696m; δ_H(300 MHz) 3.13 (2H, t, *J* 6.1, C*H*$_2$CH$_2$O), 4.54 (2H, t, *J* 6.1, CH$_2$C*H*$_2$O), 7.28 (1H, app. t, *J* 7.9, Ar*H*), 7.77 (1H, dd, *J* 7.9, 1.2, Ar*H*), 8.07 (1H, dd, *J* 7.9, 1.2, Ar*H*); δ_C(75 MHz) 28.0 (CH$_2$, *C*H$_2$CH$_2$O), 66.5 (CH$_2$, CH$_2$*C*H$_2$O), 122.8 (quat. C, *ipso* Ar), 127.2 (quat. C, *ipso* Ar), 128.7 (CH, Ar), 129.6 (CH, Ar), 137.3 (CH, Ar), 139.3 (quat. C, *ipso* Ar), 164.1 (quat. C, *C*=O); m/*z* (EI) 228 ([M]$^+$, 54%), 226 ([M]$^+$, 57%), 198 (100, [M – OCH$_2$]$^+$), 196 (100, [M – OCH$_2$]$^+$), 170 (54, [M – CO – OCH$_2$]$^+$), 168 (52, [M – CO – OCH$_2$]$^+$), 89 (47), 63 (20); HRMS: $C_9H_7O_2{}^{79}Br$ calcd 225.9626 ([M]$^+$), obsd 225.9623.

5-Trifluoromethylisochroman-1-one 183f

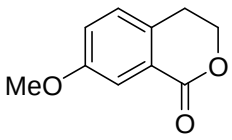


Chemical Formula: $C_{10}H_7F_3O_2$
Exact Mass: 216.0398
Molecular Weight: 216.1566
Elemental Analysis: C, 55.56; H, 3.26; F, 26.37; O, 14.80

Isochroman-1-one **183f** was prepared from isochroman **182f** (914 mg, 4.52 mmol), $KMnO_4$ (2.14 g, 13.6 mmol) and TEBAC (154 mg, 0.678 mmol) in CH_2Cl_2 (47 mL) according to Method B. Purification by flash column chromatography (gradient: 90% hexane, 10% EtOAc → 80% hexane, 20% EtOAc) afforded isochroman-1-one **183f** as a white crystalline solid (864 mg, 82%): mp 54-55 °C; R_f = 0.23 (80% hexane, 20% EtOAc); ν_{max}(film)/cm^{-1} 3016w,

2916w, 1726s (C=O), 1475m, 1397m, 1325m, 1307m, 1287m, 1246m, 1224m, 1160s, 1133s, 1091s, 1074s, 1064s, 1041m, 959m, 831m, 757s, 711m; δ_H(300 MHz) 3.19 (2H, t, *J* 6.0, C*H*$_2$CH$_2$O), 4.52 (2H, t, *J* 6.0, CH$_2$C*H*$_2$O), 7.48 (1H, app. t, *J* 7.8, Ar*H*), 7.82 (1H, d, *J* 7.8, Ar*H*), 8.26 (1H, d, *J* 7.8, Ar*H*); δ_C(75 MHz) 24.9 (CH$_2$, *C*H$_2$CH$_2$O), 66.4 (CH$_2$, CH$_2$*C*H$_2$O), 123.6 (quat. C, q, $^1J_{C\text{-}F}$ 272.2, Ar*C*F$_3$), 125.8 (CH, Ar), 127.5 (quat. C, *ipso* Ar), 128.4 (quat. C, q, $^2J_{C\text{-}F}$ 46.4, *ipso* Ar), 130.6 (CH, q, $^3J_{C\text{-}F}$ 5.1, Ar), 134.0 (CH, Ar), 138.2 (quat. C, *ipso* Ar), 163.8 (quat. C, *C*=O); δ_F(282 MHz) –60.9 (s, ArC*F*$_3$); m/*z* (EI) 216 ([M]$^+$, 52%), 186 (100, [M – OCH$_2$]$^+$), 158 (79, [M – CO – OCH$_2$]$^+$), 138 (16); HRMS: $C_{10}H_7O_2F_3$ calcd 216.0398 ([M]$^+$), obsd 216.0402.

7-Methoxyisochroman-1-one 183g

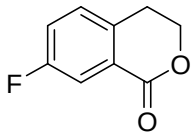


Chemical Formula: $C_{10}H_{10}O_3$
Exact Mass: 178.063
Molecular Weight: 178.1846
Elemental Analysis: C, 67.41; H, 5.66; O, 26.94

Isochroman-1-one **183g** was prepared from isochroman **182g** (565 mg, 3.44 mmol), $KMnO_4$ (1.63 g, 10.3 mmol) and TEBAC (118 mg, 0.516 mmol) in CH_2Cl_2 (35 mL) according to Method B. Purification by flash column chromatography (gradient: 90% hexane, 10% EtOAc → 75% hexane, 25% EtOAc) afforded isochroman-1-one **183g** as a white solid (260 mg, 42%): mp 53-54 °C; R_f = 0.20 (70% hexane, 30% EtOAc); ν_{max}(film)/cm^{-1} 2994w, 2913w, 1706s (C=O), 1500m, 1426m, 1324m, 1283m, 1268m, 1242s, 1220m, 1190m, 1177m, 1131m, 1084s, 1024s, 875m, 820s, 784s, 747m, 715m; δ_H(300 MHz) 2.98 (2H, t, *J* 6.0, C*H*$_2$CH$_2$O), 3.83 (3H, s, OC*H*$_3$), 4.50 (2H, t, *J* 6.0, CH$_2$C*H*$_2$O), 7.05-7.22 (2H, stack, Ar*H*), 7.57 (1H, s, Ar*H*); δ_C(100 MHz) 26.9 (CH$_2$, *C*H$_2$CH$_2$O), 55.6 (CH$_3$, O*C*H$_3$), 67.6 (CH$_2$,

CH_2CH_2O), 112.9 (CH, Ar), 121.6 (CH, Ar), 126.0 (quat. C, *ipso* Ar), 128.4 (CH, Ar), 131.8 (quat. C, *ipso* Ar), 158.9 (quat. C, *ipso* Ar), 165.2 (quat. C, *C*=O); m/*z* (EI) 178 ($[M]^+$, 100%), 148 (73, $[M - OCH_2]^+$), 120 (86, $[M - CO - OCH_2]^+$), 105 (11), 91 (21), 77 (16); HRMS: $C_{10}H_{10}O_3$ calcd 178.0630 ($[M]^+$), obsd 178.0628.

7-Fluoroisochroman-1-one 183h



Chemical Formula: $C_9H_7FO_2$
Exact Mass: 166.043
Molecular Weight: 166.1491
Elemental Analysis: C, 65.06; H, 4.25; F, 11.43; O, 19.26

Isochroman-1-one **183h** was prepared from isochroman **182h** (1.57 g, 10.3 mmol), $KMnO_4$ (4.89 g, 31.0 mmol) and TEBAC (353 mg, 1.55 mmol) in CH_2Cl_2 (100 mL) according to Method B. Purification by flash column chromatography (gradient: 90% hexane, 10% EtOAc → 70% hexane, 30% EtOAc) afforded isochroman-1-one **183h** as a white crystalline solid (1.28 g, 75%): mp 50-51 °C; R_f = 0.21 (70% hexane, 30% EtOAc); (Found: C, 64.80; H, 4.25. $C_9H_7O_2F$ requires C, 65.06; H, 4.25%); ν_{max}(film)/cm^{-1} 3069w, 2926w, 1713s (C=O), 1493s, 1435s, 1307m, 1273s, 1261s, 1237s, 1124s, 1083s, 1061m, 1028m, 927m, 886s, 852m, 841m, 779s, 745m, 716m; δ_H(300 MHz) 3.02 (2H, t, *J* 6.0, C*H*$_2$CH$_2$O), 4.52 (2H, t, *J* 6.0, CH$_2$C*H*$_2$O), 7.18-7.29 (2H, stack, Ar*H*), 7.72 (1H, dd, *J* 8.3, 1.9, Ar*H*); δ_C(75 MHz) 27.0 (CH_2, *C*H$_2$CH$_2$O), 67.4 (CH_2, CH$_2$*C*H$_2$O), 116.5 (CH, d, $^2J_{C\text{-}F}$ 23.0, Ar), 121.0 (CH, d, $^2J_{C\text{-}F}$ 21.8, Ar), 126.8 (quat. C, d, $^3J_{C\text{-}F}$ 7.4, *ipso* Ar), 129.1 (CH, d, $^3J_{C\text{-}F}$ 7.3, Ar), 135.2 (quat. C, d, $^4J_{C\text{-}F}$ 2.5, *ipso* Ar), 161.7 (quat. C, d, $^1J_{C\text{-}F}$ 245.5, *ipso* Ar), 164.0 (quat. C, *C*=O); δ_F(282 MHz) –113.3 - –113.1 (m, Ar*F*); m/*z* (EI) 166 ($[M]^+$, 62%), 136 (76, $[M - OCH_2]^+$), 108 (100, $[M - CO - OCH_2]^+$); HRMS: $C_9H_7O_2F$ calcd 166.0430 ($[M]^+$), obsd 166.0425.

General procedure for the formation of 1-alkoxyisochromans 164

1-Alkoxyisochromans **164** were prepared by a modification of previously reported procedures for the preparation of different 1-substituted isochromans:

Method A for 1-ethoxyisochromans[150]

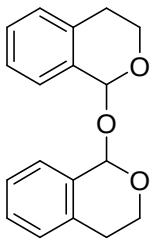
DIBALH (1.5 M solution in toluene, 20.2 mL, 30.3 mmol) was added over 10 min to a solution of the isochroman-1-one (10.1 mmol) in toluene (25 mL) at –78 °C. After stirring at –78 °C for 2 h, a saturated solution of Rochelle's salt (25 mL) was added and the mixture was warmed up to R.T. overnight. The mixture was transferred to a separating funnel, and without shaking, the two layers were separated.[4] The aqueous phase was extracted with Et_2O (2 × 15 mL), and the combined organic fractions were washed with NH_4Cl solution (25 mL) and brine (25 mL) and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude 1-hydroxyisochroman product, which was of sufficient purity to be used directly in the next step. The 1-hydroxyisochroman, obtained from the previous step, was dissolved in EtOH (20 mL) and stirred with Amberlite (IR 120 beads, teaspoon) at R.T. for 2 h. The beads were filtered off and washed with Et_2O (15 mL). $NaHCO_3$ solution (20 mL) was added and the Et_2O and EtOH were evaporated. The residue was extracted with Et_2O (2 × 20 mL) and the combined organic fractions were washed with brine (30 mL) and dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude acetal product, which was purified by flash column chromatography.

[4] with this method, no problems with Al salts did arise

Method B for 1-alkoxyisochromans[114,149]

The isochroman (7.95 mmol) and anhydrous alcohol (9.54 mmol) were added to a yellow suspension of DDQ (2.17 g, 9.54 mmol) in CH_2Cl_2 (50 mL). While vigorously stirring at R.T. for 24 h, the colour of the mixture changed from bright red to pale red-brown. More alcohol (9.54 mmol) was added, and the mixture was stirred at R.T. for another 24 h. The reaction was quenched by addition of $NaHCO_3$ solution (60 mL) (caution: gas formation!) and then CH_2Cl_2 (50 mL) was added. The two phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic fractions were washed with $NaHCO_3$ solution (50 mL) and with brine (50 mL), and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude acetal product, which was purified by flash column chromatography.

1,1-Oxodiisochroman 171



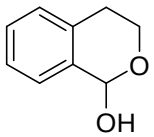
Chemical Formula: $C_{18}H_{18}O_3$
Exact Mass: 282.1256
Molecular Weight: 282.3337
Elemental Analysis: C, 76.57; H, 6.43; O, 17.00

1,1-Oxodiisochroman **171** was prepared according to a modification of Method B: Isochroman (0.50 mL, 3.98 mmol) and H_2O (1.00 mL, 55.5 mmol) were added to a yellow suspension of DDQ (1.13 g, 4.97 mmol) in CH_2Cl_2 (20 mL). After stirring for 24 h at R.T., the reaction was quenched by addition of $NaHCO_3$ solution (30 mL) (caution: gas formation!) and then CH_2Cl_2 (25 mL) was added. The two phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic fractions were washed with

$NaHCO_3$ solution (25 mL) and with brine (25 mL), and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude acetal product. Purification by flash column chromatography (gradient: 98% hexane, 2% Et_2O → 90% hexane, 10% Et_2O) afforded oxodiisochroman **171** as a white crystalline solid (436 mg, 78%; single diastereoisomer; stereochemistry not determined): mp 138-141 °C (lit.[198] mp 135-137 °C); R_f = 0.18 (90% hexane, 10% Et_2O); ν_{max}(neat)/cm^{-1} 2962m, 2925m, 2881m, 2814w, 1489m, 1469w, 1455m, 1421m, 1381m, 1355m, 1320m, 1273m, 1201m, 1118m, 1088s, 1068s, 1032m, 997s, 973w, 955s, 911w, 881w, 865m, 792m, 779w, 740s; δ_H(300 MHz) 2.66 (2H, app. dd, *J* 16.5, 2.5, C$H_a$$H_b$$CH_2O$), 3.13 (2H, ddd, *J* 17.0, 12.4, 6.1, $CH_a$$H_b$$CH_2O$), 4.09 (2H, ddd, *J* 11.1, 6.1, 1.2, CH_2C$H_a$$H_b$O), 4.36 (2H, app. td, *J* 11.6, 3.2, $CH_2CH_a$$H_b$O), 6.14 (2H, s, C*H*(O)O), 7.08-7.29 (8H, stack, Ar*H*); δ_C(75 MHz) 27.9 (CH_2, *C*H_2CH_2O), 58.1 (CH_2, CH_2*C*H_2O), 92.7 (CH, *C*H(O)O), 126.3 (CH, Ar), 127.5 (CH, Ar), 128.0 (CH, Ar), 128.4 (CH, Ar), 133.8 (quat. C, *ipso* Ar), 134.1 (quat. C, *ipso* Ar); m/*z* (TOF ES+) 305 ([M + $Na]^+$, 100%); HRMS: $C_{18}H_{18}O_3Na$ calcd 305.1154 ([M + $Na]^+$), obsd 305.1145.

The two enantiomers of the single diastereoisomer were separated by chiral HPLC for a mechanistic study: Lux 5u Cellulose-2, 3 mL/min, 1% IPA in hexane, λ = 210 nm, $t_{R,first}$ = 30.1 min, $t_{R,second}$ = 39.7 min.

1-Hydroxyisochroman 170[150]

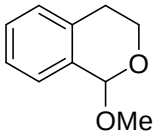


Chemical Formula: $C_9H_{10}O_2$
Exact Mass: 150.0681
Molecular Weight: 150.1745
Elemental Analysis: C, 71.98; H, 6.71; O, 21.31

1-Hydroxyisochroman **170** was prepared according to a modification of Method A: DIBALH (1.5 M solution in toluene, 13.5 mL, 20.3 mmol) was added over 10 min to a solution of isochroman-1-one **172** (2.00 g, 13.5 mmol) in toluene (30 mL) at –78 °C. After stirring at –78 °C for 2 h, a saturated solution of Rochelle's salt (30 mL) was added and the mixture was warmed up to R.T. overnight. The mixture was transferred to a separating funnel, and without shaking, the two layers were separated. The aqueous phase was extracted with Et_2O (2 × 15 mL), and the combined organic fractions were washed with NH_4Cl solution (25 mL) and brine (25 mL) and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude hemiacetal **170** as a white solid (2.03, quantitative), which was sufficiently pure for characterisation and further use: mp 72-75 °C (lit.[199] mp 73-74 °C); R_f = 0.15 (60% hexane, 40% Et_2O); ν_{max}(neat)/cm^{-1} 3357s br (OH), 3029w, 2988m, 2883w, 1607m, 1494m, 1459m, 1423w, 1384m, 1289w, 1270m, 1116m, 1092w, 1078m, 1065s, 1007s, 982s, 949s, 936s, 883s, 868s, 825m, 784s, 738s, 718w; δ_H(300 MHz) 2.65 (1H, app. dt, *J* 16.5, 3.0, C$H_a$$H_b$$CH_2$O), 2.96 (1H, ddd, *J* 16.5, 11.0, 5.7, $CH_a$$H_b$$CH_2$O), 3.91 (1H, ddd, *J* 11.4, 5.7, 2.7, CH_2C$H_a$$H_b$O), 4.02 (1H, d, *J* 5.5, O*H*), 4.19 (1H, app. td, *J* 11.2, 3.6, $CH_2CH_a$$H_b$O), 5.92 (1H, d, *J* 5.5, C*H*OH), 7.08-7.34 (4H, stack, Ar*H*); δ_C(75 MHz) 28.0 (CH_2, *C*H_2CH_2O), 58.3 (CH_2, CH_2*C*H_2O), 91.4 (CH, *C*HOH), 126.4 (CH, Ar), 127.2 (CH, Ar), 128.1 (CH, Ar), 128.4 (CH, Ar), 134.0 (quat. C, *ipso* Ar), 135.0 (quat. C, *ipso* Ar); m/*z* (EI) 150 ($[M]^+$, 40%), 149 (78, $[M - H]^+$), 132 (93, $[M - H_2O]^+$), 119 (99), 104 (76), 91 (100), 77 (47), 65 (37), 51 (34).

Data were in agreement with those reported in the literature.[150]

1-Methoxyisochroman 161[114]

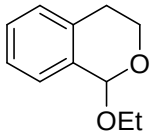


Chemical Formula: $C_{10}H_{12}O_2$
Exact Mass: 164.0837
Molecular Weight: 164.2011
Elemental Analysis: C, 73.15; H, 7.37; O, 19.49

1-Methoxyisochroman **161** was prepared from isochroman (1.60 g, 11.9 mmol), DDQ (3.25 g, 14.3 mmol) and anhydrous MeOH (2 × 482 μL, 2 × 11.9 mmol) in CH_2Cl_2 (75 mL) according to Method B. Purification by flash column chromatography (gradient: 100% hexane → 98% hexane, 2% Et_2O) afforded acetal **161** as a colourless liquid (1.45 g, 74%): R_f = 0.19 (90% hexane, 10% Et_2O); ν_{max}(film)/cm^{-1} 2935w, 2881m, 2827w, 1492m, 1457m, 1382m, 1343m, 1275m, 1204m, 1186m, 1118w, 1093m, 1073s, 1047s, 1031s, 993m, 953s, 936w, 897m, 779m, 745s; δ_H(300 MHz, C_6H_6) 2.10 (1H, ddd, *J* 16.5, 3.3, 1.6, CH_aH$_b$CH$_2$O), 2.72 (1H, ddd, *J* 16.5, 12.0, 6.0, CH$_a$$H_bCH_2$O), 3.35 (3H, s, OC$H_3$), 3.61 (1H, ddd, *J* 11.1, 6.0, 1.6, CH$_2$CH_aH$_b$O), 3.98 (1H, app. td with unresolved fine coupling, *J* 11.1, 3.3, CH$_2$CH$_a$$H_b$O), 5.39 (1H, d, C*H*O), 6.78-6.86 (1H, m, Ar*H*), 6.98-7.06 (2H, stack, Ar*H*), 7.12-7.21 (1H, m, Ar*H*); δ_C(75 MHz, C_6H_6) 28.4 (CH$_2$, *C*H$_2$CH$_2$O), 55.2 (CH$_3$, OCH$_3$), 57.9 (CH$_2$, CH$_2$*C*H$_2$O), 98.3 (CH, *C*HO), 126.4 (CH, Ar), 128.1 (CH, Ar), 128.2 (CH, Ar), 128.6 (CH, Ar), 134.6 (quat. C, *ipso* Ar), 135.2 (quat. C, *ipso* Ar); m/*z* (EI) 164 ([M]$^+$, 21%), 163 (39, [M – H]$^+$), 133 (100, [M – OCH$_3$]$^+$), 119 (13), 105 (40), 91 (25), 77 (28), 65 (12), 51 (16).

Data were in agreement with those reported in the literature.[114]

1-Ethoxyisochroman 166



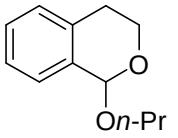
Chemical Formula: $C_{11}H_{14}O_2$
Exact Mass: 178.0994
Molecular Weight: 178.2277
Elemental Analysis: C, 74.13; H, 7.92; O, 17.95

1-Ethoxyisochroman **166** was prepared from isochroman (1.00 mL, 7.95 mmol), DDQ (2.17 g, 9.54 mmol) and anhydrous EtOH (2 × 556 μL, 2 × 9.54 mmol) in CH_2Cl_2 (50 mL) according to Method B. Purification by flash column chromatography (gradient: 100% hexane → 98% hexane, 2% Et_2O) afforded acetal **166** as a colourless liquid (827 mg, 58%): R_f = 0.28 (90% hexane, 10% Et_2O); ν_{max}(film)/cm^{-1} 2973m, 2880m, 1493w, 1457m, 1382m, 1331m, 1274m, 1204m, 1094m, 1073s, 1049s, 991s, 956m, 919m, 876w, 775m, 744s; δ_H(300 MHz) 1.31 (3H, t, *J* 7.1, OCH_2CH_3), 2.63 (1H, ddd, *J* 17.1, 3.4, 1.6, $CH_aH_bCH_2O$), 3.03 (1H, ddd, *J* 17.1, 11.9, 6.1, $CH_aH_bCH_2O$), 3.72 (1H, dq, *J* 9.7, 7.1, $OCH_aH_bCH_3$), 3.91 (1H, ddd, *J* 11.4, 6.1, 1.6, $CH_2CH_aH_bO$), 3.95 (1H, dq, *J* 9.7, 7.1, $OCH_aH_bCH_3$), 4.17 (1H, app. td with unresolved fine coupling, *J* 11.4, 3.4, $CH_2CH_aH_bO$), 5.58 (1H, s, CHO), 7.09-7.16 (1H, m, ArH), 7.19-7.28 (3H, stack, ArH); δ_C(75 MHz) 15.3 (CH_3, OCH_2CH_3), 28.0 (CH_2, CH_2CH_2O), 57.8 (CH_2, CH_2CH_2O), 63.4 (CH_2, OCH_2CH_3), 96.5 (CH, CHO), 126.3 (CH, Ar), 127.4 (CH, Ar), 128.0 (CH, Ar), 128.4 (CH, Ar), 134.0 (quat. C, *ipso* Ar), 134.3 (quat. C, *ipso* Ar); m/*z* (EI) 178 ([M]$^+$, 19%), 177 (26, [M – H]$^+$), 149 (93, [M – CH_2CH_3]$^+$), 133 (100, [M – OCH_2CH_3]$^+$), 105 (29), 91 (17), 77 (22).

The two enantiomers were separated by chiral HPLC (5 mg per 0.5 mL run): Lux 5u Cellulose-2, 3 mL/min, 1% IPA in hexane, λ = 210 nm, $t_{R,first}$ = 8.6 min, $[\alpha]_D^{20}$ = +59.4 (*c* 0.99, CH_2Cl_2, e.r. 100:0); $t_{R,second}$ = 10.5 min, $[\alpha]_D^{20}$ = –54.9 (*c* 0.99, CH_2Cl_2, e.r. 0:100).

Data were in agreement with those reported in the literature.[200]

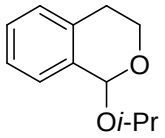
1-*n*-Propoxyisochroman 167



Chemical Formula: $C_{12}H_{16}O_2$
Exact Mass: 192.115
Molecular Weight: 192.2542
Elemental Analysis: C, 74.97; H, 8.39; O, 16.64

1-*n*-Propoxyisochroman **167** was prepared from isochroman (0.50 mL, 3.98 mmol), DDQ (1.35 g, 5.96 mmol) and anhydrous *n*-PrOH (2 × 892 μL, 2 ×11.9 mmol) in CH_2Cl_2 (25 mL) according to Method B. Purification by flash column chromatography (gradient: 100% hexane → 98% hexane, 2% Et_2O) afforded acetal **167** as a colourless liquid (373 mg, 49%): R_f = 0.31 (90% hexane, 10% Et_2O); ν_{max}(film)/cm^{-1} 2963m, 2877m, 1457m, 1381m, 1334m, 1274m, 1205m, 1093m, 1073s, 1050m, 1019s, 993s, 954m, 782m, 744s; δ_H(300 MHz) 0.99 (3H, t, *J* 7.4, $OCH_2CH_2CH_3$), 1.70 (2H, app. sextet, *J* 7.3, $OCH_2CH_aH_bCH_3$), 2.63 (1H, ddd, *J* 16.6, 3.2, 1.6, $CH_aH_bCH_2O$), 3.03 (1H, ddd, *J* 16.6, 11.9, 6.0, $CH_aH_bCH_2O$), 3.61 (1H, app. dt, *J* 9.6, 6.7, $OCH_aH_bCH_2CH_3$), 3.84 (1H, app. dt, *J* 9.6, 6.7, $OCH_aH_bCH_2CH_3$), 3.90 (1H, ddd, *J* 11.4, 6.0, 1.6, $CH_2CH_aH_bO$), 4.17 (1H, app. td with unresolved fine coupling, *J* 11.4, 3.2, $CH_2CH_aH_bO$), 5.56 (1H, s, CHO), 7.09-7.16 (1H, m, ArH), 7.19-7.28 (3H, stack, ArH); δ_C(75 MHz) 10.8 (CH_3, $OCH_2CH_2CH_3$), 23.0 (CH_2, $OCH_2CH_2CH_3$), 28.0 (CH_2, CH_2CH_2O), 57.8 (CH_2, CH_2CH_2O), 69.9 (CH_2, $OCH_2CH_2CH_3$), 96.8 (CH, CHO), 126.3 (CH, Ar), 127.4 (CH, Ar), 128.0 (CH, Ar), 128.4 (CH, Ar), 134.1 (quat. C, *ipso* Ar), 134.4 (quat. C, *ipso* Ar); m/*z* (EI) 192 ($[M]^+$, 11%), 191 (13, $[M - H]^+$), 149 (13, $[M - CH_2CH_2CH_3]^+$), 133 (100, $[M - OCH_2CH_2CH_3]^+$), 105 (15), 77 (10); HRMS: $C_{12}H_{16}O_2$ calcd 192.1150 ($[M]^+$), obsd 192.1140.

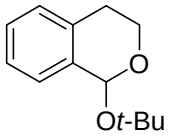
1-*i*-Propoxyisochroman 168



Chemical Formula: $C_{12}H_{16}O_2$
Exact Mass: 192.115
Molecular Weight: 192.2542
Elemental Analysis: C, 74.97; H, 8.39; O, 16.64

1-*i*-Propoxyisochroman **168** was prepared from isochroman (0.50 mL, 3.98 mmol), DDQ (1.08 g, 4.77 mmol) and anhydrous *i*-PrOH (2 × 365 μL, 2 × 4.77 mmol) in CH_2Cl_2 (25 mL) according to Method B. Purification by flash column chromatography (gradient: 100% hexane → 98% hexane, 2% Et_2O) afforded acetal **168** as a colourless liquid (400 mg, 52%): R_f = 0.33 (90% hexane, 10% Et_2O); ν_{max}(film)/cm^{-1} 2970m, 2935w, 2885w, 1494w, 1456m, 1378m, 1322m, 1274m, 1205m, 1178w, 1124m, 1085m, 1070m, 1016s, 990s, 958w, 945m, 928m, 870w, 821w, 769m, 744s; δ_H(300 MHz) 1.25 (3H, d, *J* 6.2, OCH(CH_3)$_a$(CH_3)$_b$), 1.27 (3H, d, *J* 6.2, OCH(CH_3)$_a$(CH_3)$_b$), 2.62 (1H, ddd, *J* 16.6, 3.1, 1.5, CH_aH$_b$$CH_2$O), 3.02 (1H, ddd, *J* 16.6, 12.0, 6.0, $CH_a$$H_b$$CH_2$O), 3.89 (1H, ddd, *J* 11.3, 6.0, 1.5, CH_2CH_aH$_b$O), 4.08-4.25 (2H, stack, OCH(CH_3)$_2$ and $CH_2$$CH_a$$H_b$O), 5.65 (1H, s, C$H$O), 7.07-7.15 (1H, m, Ar$H$), 7.16-7.25 (3H, stack, ArH); δ_C(75 MHz) 21.9 (CH_3, OCH(*C*H_3)$_a$(CH_3)$_b$), 23.6 (CH_3, OCH(CH_3)$_a$(*C*H_3)$_b$), 28.0 (CH_2, *C*$H_2$$CH_2$O), 57.6 ($CH_2$, CH_2*C*H_2O), 69.4 (CH, O*C*H(CH_3)$_a$(CH_3)$_b$), 94.9 (CH, *C*HO), 126.2 (CH, Ar), 127.3 (CH, Ar), 127.8 (CH, Ar), 128.4 (CH, Ar), 134.1 (quat. C, *ipso* Ar), 134.5 (quat. C, *ipso* Ar); m/*z* (EI) 192 ([M]$^+$, 6%), 191 (7, [M – H]$^+$), 149 (14, [M – CH(CH_3)$_2$]$^+$), 133 (100, [M – OCH(CH_3)$_2$]$^+$), 105 (15), 77 (14); HRMS: $C_{12}H_{16}O_2$ calcd 192.1150 ([M]$^+$), obsd 192.1141.

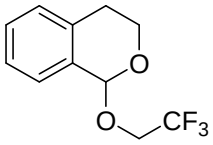
1-*t*-Butoxyisochroman 169



Chemical Formula: $C_{13}H_{18}O_2$
Exact Mass: 206.1307
Molecular Weight: 206.2808
Elemental Analysis: C, 75.69; H, 8.80; O, 15.51

1-*t*-Butoxyisochroman **169** was prepared from isochroman (0.50 mL, 3.98 mmol), DDQ (1.35 g, 5.96 mmol) and anhydrous *t*-BuOH (2 × 760 μL, 2 × 7.96 mmol) in CH_2Cl_2 (25 mL) according to Method B. Purification by flash column chromatography (gradient: 100% hexane → 98% hexane, 2% Et_2O) afforded acetal **169** as a colourless liquid (180 mg, 22%): R_f = 0.35 (90% hexane, 10% Et_2O); (Found: C, 75.29; H, 8.65. $C_{13}H_{18}O_2$ requires C, 75.69; H, 8.80%); ν_{max}(film)/cm^{-1} 2973m, 2932w, 1456m, 1367m, 1341m, 1273w, 1255w, 1192m, 1087m, 1072m, 1040m, 1009s, 989s, 959m, 918m, 864w, 833w, 789m, 742s; δ_H(300 MHz, C_6D_6) 1.30 (9H, s, OC(CH_3)$_3$), 2.17 (1H, ddd, *J* 16.1, 3.3, 1.5, CH_aH$_b$CH$_2$O), 2.77 (1H, ddd, *J* 16.1, 12.1, 6.1, CH$_a$$H_bCH_2$O), 3.65 (1H, ddd, *J* 11.1, 6.1, 1.5, CH$_2$CH_aH$_b$O), 4.16 (1H, app. td with unresolved fine coupling, *J* 11.8, 3.3, CH$_2$CH$_a$$H_b$O) 5.86 (1H, s, C*H*O), 6.83-6.91 (1H, m, Ar*H*), 7.01-7.21 (3H, stack, Ar*H*); δ_C(75 MHz, C_6D_6) 28.5 (CH$_2$, *C*H$_2$CH$_2$O), 29.3 (CH$_3$, OC(*C*H$_3$)$_3$), 57.6 (CH$_2$, CH$_2$*C*H$_2$O), 74.4 (quat. C, O*C*(CH$_3$)$_3$), 91.9 (CH, *C*HO), [126.3, 127.6, 128.7 (CH, Ar), the fourth CH, Ar was not observed owing to overlap with the solvent signals], 134.9 (quat. C, *ipso* Ar), 136.7 (quat. C, *ipso* Ar); m/*z* (EI) 133 ([M – OC(CH$_3$)$_3$]$^+$, 98%), 132 (98, [M – H – OC(CH$_3$)$_3$]$^+$), 118 (16), 115 (17), 104 (100), 90 (12), 77 (52), 63 (12), 51 (18), 45 (16); HRMS: C_9H_9O calcd 133.0653 ([M – OC(CH$_3$)$_3$]$^+$), obsd 133.0649.

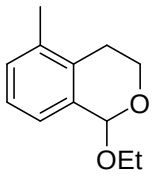
1-(2',2',2'-Trifluoroethoxy)isochroman 174



Chemical Formula: $C_{11}H_{11}F_3O_2$
Exact Mass: 232.0711
Molecular Weight: 232.199
Elemental Analysis: C, 56.90; H, 4.77; F, 24.55; O, 13.78

1-(2',2',2'-Trifluoroethoxy)isochroman **174** was prepared from isochroman (1.00 mL, 7.95 mmol), DDQ (2.17 g, 9.54 mmol) and anhydrous 2,2,2-trifluoroethanol (2 × 695 μL, 2 × 9.54 mmol) in CH_2Cl_2 (50 mL) according to Method B. Purification by flash column chromatography (gradient: 100% hexane → 98% hexane, 2% Et_2O) afforded acetal **174** as a yellow oil (970 mg, 52%): R_f = 0.33 (90% hexane, 10% Et_2O); ν_{max}(film)/cm^{-1} 2956m, 2904m, 1434m, 1275m, 1214w, 1170s, 1117m, 1103m, 1076s, 1059s, 1031m, 991s, 969s, 954s, 904m, 870m, 851w, 827w, 784m, 744s, 727w, 670m; δ_H(300 MHz) 2.03 (1H, app. d, *J* 16.5, 2.4, C$H_a$$H_b$$CH_2$O), 2.65 (1H, ddd, *J* 16.5, 12.3, 6.0, $CH_a$$H_b$$CH_2$O), 3.51 (1H, ddd, *J* 11.2, 6.0, 1.4, CH_2C$H_a$$H_b$O), 3.58 (1H, dq, *J* 12.4, 8.9, OC$H_a$$H_b$$CF_3$), 3.76 (1H, dq, *J* 12.4, 9.0, $OCH_a$$H_b$$CF_3$), 3.82 (1H, app. td, *J* 11.7, 3.2, $CH_2CH_a$$H_b$O), 5.34 (1H, s, C*H*O), 6.74-6.83 (1H, m, Ar*H*), 6.95-7.06 (2H, stack, Ar*H*), 7.10-7.15 (1H, m, Ar*H*); δ_C(100 MHz) 28.0 (CH_2, *C*H_2CH_2O), 58.2 (CH_2, CH_2*C*H_2O), 64.6 (CH_2, q, $^2J_{C\text{-}F}$ 34.1, O*C*H_2CF_3), 97.5 (CH, *C*HO), 124.9 (quat. C, q, $^1J_{C\text{-}F}$ 276.3, *C*F_3), 126.7 (CH, Ar), 128.2 (CH, Ar), 128.6 (CH, Ar), 128.7 (CH, Ar), 133.2 (quat. C, *ipso* Ar), 134.4 (quat. C, *ipso* Ar); δ_F(282 MHz, C_6D_6) –73.9 (s, C*F*$_3$); m/*z* (EI) 232 ($[M]^+$, 19%), 231 (26, $[M - H]^+$), 204 (16), 133 (100, $[M - OCH_2CF_3]^+$), 105 (31), 91 (16), 77 (13); HRMS: $C_{11}H_{11}O_2F_3$ calcd 232.0711 ($[M]^+$), obsd 232.0694.

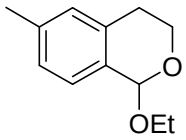
1-Ethoxy-5-methylisochroman 179a



Chemical Formula: $C_{12}H_{16}O_2$
Exact Mass: 192.115
Molecular Weight: 192.2542
Elemental Analysis: C, 74.97; H, 8.39; O, 16.64

1-Ethoxyisochroman **179a** was prepared by DIBALH reduction (3.10 mL, 4.63 mmol) of isochroman-1-one **183a** (500 mg, 3.09 mmol), followed by acetalisation using Amberlite and EtOH (6.2 mL) according to Method A. Purification by flash column chromatography (gradient: 98% hexane, 2% Et_2O → 90% hexane, 10% Et_2O) afforded 1-ethoxyisochroman **179a** as a colourless liquid (529 mg, 89% over two steps): R_f = 0.24 (80% hexane, 20% Et_2O); ν_{max}(film)/cm^{-1} 2974m, 2881m, 1471w, 1385w, 1332w, 1105m, 1074s, 1046s, 998s, 932m, 854w, 779s, 742m, 711w; δ_H(300 MHz, C_6D_6) 1.19 (3H, t, *J* 7.1, OCH_2CH_3), 1.91 (3H, s, $ArCH_3$), 2.03 (1H, app. d with unresolved fine coupling, *J* 16.7, $CH_aH_bCH_2O$), 2.48 (1H, ddd, *J* 17.3, 11.9, 6.3, $CH_aH_bCH_2O$), 3.54 (1H, dq, *J* 9.6, 7.1, $OCH_aH_bCH_3$), 3.72 (1H, ddd, *J* 11.2, 6.3, 1.5, $CH_2CH_aH_bO$), 3.92 (1H, dq, *J* 9.6, 7.1, $OCH_aH_bCH_3$), 4.10 (1H, app. td, *J* 11.7, 3.7, $CH_2CH_aH_bO$), 5.58 (1H, s, CHO), 6.95 (1H, d, *J* 7.3, ArH), 7.04 (1H, app. t, *J* 7.6, ArH), 7.13 (1H, d, *J* 7.7, ArH); δ_C(75 MHz, C_6D_6) 15.6 (CH_3, OCH_2CH_3), 18.8 (CH_3, $ArCH_3$), 26.0 (CH_2, CH_2CH_2O), 57.7 (CH_2, CH_2CH_2O), 63.4 (CH_2, OCH_2CH_3), 97.3 (CH, CHO), 126.0 (CH, Ar), 128.4 (CH, Ar), 129.3 (CH, Ar), 133.0 (quat. C, *ipso* Ar), 135.2 (quat. C, *ipso* Ar), 135.7 (quat. C, *ipso* Ar); m/*z* (EI) 192 ($[M]^+$, 19%), 191 (21, $[M - H]^+$), 163 (12, $[M - CH_2CH_3]^+$), 147 (100, $[M - OCH_2CH_3]^+$), 133 (18, $[M - CH_3 - OCH_2CH_3]^+$), 117 (36), 115 (23), 105 (12), 103 (10), 91 (18); HRMS: $C_{12}H_{16}O_2$ calcd 192.1150 ($[M]^+$), obsd 192.1145.

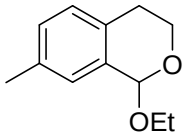
1-Ethoxy-6-methylisochroman 179b



Chemical Formula: $C_{12}H_{16}O_2$
Exact Mass: 192.115
Molecular Weight: 192.2542
Elemental Analysis: C, 74.97; H, 8.39; O, 16.64

1-Ethoxyisochroman **179b** was prepared by DIBALH reduction (7.35 mL, 11.0 mmol) of isochroman-1-one **183b** (1.19 g, 7.35 mmol), followed by acetalisation using Amberlite and EtOH (15 mL) according to Method A. Purification by flash column chromatography (gradient: 98% hexane, 2% Et_2O → 95% hexane, 5% Et_2O) afforded 1-ethoxyisochroman **179b** as a colourless liquid (1.17 g, 83% over two steps): R_f = 0.23 (90% hexane, 10% Et_2O); (Found: C, 74.94; H, 8.14. $C_{12}H_{16}O_2$ requires C, 74.97; H, 8.39%); ν_{max}(film)/cm^{-1} 2974m, 2876m, 1619w, 1425w, 1381m, 1328m, 1275m, 1203w, 1133m, 1090m, 1073s, 1046s, 1005s, 985m, 960m, 918m, 902w, 863w, 824m, 803m; δ_H(300 MHz, C_6D_6) 1.18 (3H, t, *J* 7.1, OCH_2CH_3), 2.10 (3H, s, $ArCH_3$), 2.17 (1H, d with unresolved fine coupling, *J* 16.7, $CH_aH_bCH_2O$), 2.78 (1H, ddd, *J* 16.7, 12.0, 6.0, $CH_aH_bCH_2O$), 3.53 (1H, dq, *J* 9.7, 7.1, $OCH_aH_bCH_3$), 3.69 (1H, ddd, *J* 11.0, 6.0, 1.7, $CH_2CH_aH_bO$), 3.91 (1H, dq, *J* 9.7, 7.1, $OCH_aH_bCH_3$), 4.09 (1H, app. td, *J* 11.5, 3.4, $CH_2CH_aH_bO$), 5.58 (1H, s, CHO), 6.67 (1H, s, ArH), 6.89 (1H, d, *J* 7.7, ArH), 7.16 (1H, d, *J* 7.7, ArH); δ_C(75 MHz, C_6D_6) 15.6 (CH_3, OCH_2CH_3), 21.2 (CH_3, $ArCH_3$), 28.5 (CH_2, CH_2CH_2O), 57.9 (CH_2, CH_2CH_2O), 63.4 (CH_2, OCH_2CH_3), 97.1 (CH, CHO), 127.2 (CH, Ar), 128.1 (CH, Ar), 129.1 (CH, Ar), 132.7 (quat. C, *ipso* Ar), 134.4 (quat. C, *ipso* Ar), 137.4 (quat. C, *ipso* Ar); m/*z* (EI) 192 ([M]$^+$, 14%), 191 (34, [M – H]$^+$), 147 (100, [M – OCH_2CH_3]$^+$); HRMS: $C_{12}H_{16}O_2$ calcd 192.1150 ([M]$^+$), obsd 192.1149.

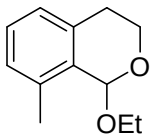
1-Ethoxy-7-methylisochroman 179c



Chemical Formula: $C_{12}H_{16}O_2$
Exact Mass: 192.115
Molecular Weight: 192.2542
Elemental Analysis: C, 74.97; H, 8.39; O, 16.64

1-Ethoxyisochroman **179c** was prepared from isochroman **182c** (1.56 g, 10.5 mmol), DDQ (2.87 g, 12.6 mmol) and EtOH (2 × 735 μL, 2 × 12.6 mmol) in CH_2Cl_2 (65 mL) according to Method B. Purification by flash column chromatography (gradient: 98% hexane, 2% Et_2O → 95% hexane, 5% Et_2O) afforded 1-ethoxyisochroman **179c** as a yellow crystalline solid (833 mg, 41%): mp 39-40 °C; R_f = 0.36 (80% hexane, 20% Et_2O); ν_{max}(film)/cm^{-1} 2973m, 2886m, 1504m, 1375m, 1332m, 1273w, 1155m, 1118w, 1090m, 1073s, 1075s, 1049s, 1004s, 990s, 958m, 936m, 902m, 883m, 851m, 811s, 737w; δ_H(300 MHz, C_6D_6) 1.19 (3H, t, *J* 7.1, OCH_2CH_3), 2.10 (3H, s, $ArCH_3$), 2.18 (1H, d with unresolved fine coupling, *J* 16.5, $CH_aH_bCH_2O$), 2.78 (1H, ddd, *J* 16.5, 12.1, 6.0, $CH_aH_bCH_2O$), 3.54 (1H, dq, *J* 9.6, 7.1, $OCH_aH_bCH_3$), 3.68 (1H, ddd, *J* 11.0, 6.0, 1.6, $CH_2CH_aH_bO$), 3.91 (1H, dq, *J* 9.6, 7.1, $OCH_aH_bCH_3$), 4.07 (1H, app. td with unresolved fine coupling, *J* 11.6, 3.3, $CH_2CH_aH_bO$), 5.55 (1H, s, CHO), 6.81 (1H, d, *J* 7.8, ArH), 6.90 (1H, dd, *J* 7.8, 1.5, ArH), 7.04 (1H, s, ArH); δ_C(100 MHz, C_6D_6) 15.6 (CH_3, OCH_2CH_3), 21.1 (CH_3, $ArCH_3$), 28.1 (CH_2, CH_2CH_2O), 58.0 (CH_2, CH_2CH_2O), 63.4 (CH_2, OCH_2CH_3), 97.2 (CH, CHO), 128.5 (CH, Ar), 128.7 (CH, Ar), 128.9 (CH, Ar), 131.5 (quat. C, *ipso* Ar), 135.2 (quat. C, *ipso* Ar), 135.5 (quat. C, *ipso* Ar); m/*z* (EI) 192 ([M]$^+$, 29%), 191 (33, [M – H]$^+$), 163 (17, [M – CH_2CH_3]$^+$), 147 (100, [M – OCH_2CH_3]$^+$), 133 (12, [M – CH_3 – OCH_2CH_3]$^+$), 117 (23), 115 (12), 105 (13), 91 (13); HRMS: $C_{12}H_{16}O_2$ calcd 192.1150 ([M]$^+$), obsd 192.1146.

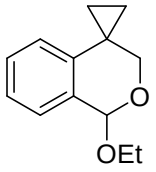
1-Ethoxy-8-methylisochroman 179d



Chemical Formula: $C_{12}H_{16}O_2$
Exact Mass: 192.115
Molecular Weight: 192.2542
Elemental Analysis: C, 74.97; H, 8.39; O, 16.64

1-Ethoxyisochroman **179d** was prepared by DIBALH reduction (3.30 mL, 4.94 mmol) of isochroman-1-one **183d** (533 mg, 3.29 mmol), followed by acetalisation using Amberlite and EtOH (6.6 mL) according to Method A. Purification by flash column chromatography (gradient: 98% hexane, 2% Et_2O → 95% hexane, 5% Et_2O) afforded 1-ethoxyisochroman **179d** as a pale yellow solid (494 mg, 78% over two steps): mp 35-36 °C; R_f = 0.24 (80% hexane, 20% Et_2O); (Found: C, 75.31; H, 8.26. $C_{12}H_{16}O_2$ requires C, 74.97; H, 8.39%); ν_{max}(film)/cm^{-1} 2973m, 2879m, 1479m, 1471m, 1332m, 1206m, 1123m, 1101m, 1078m, 1052s, 1036m, 993s, 973m, 918m, 901w, 892w, 866w, 775s, 747w, 715m; δ_H(300 MHz, C_6D_6) 1.14 (3H, t, *J* 7.1, OCH_2CH_3), 2.12-2.23 (4H, stack, $CH_aH_bCH_2O$ and $ArCH_3$), 2.86 (1H, ddd, *J* 16.6, 12.8, 6.4, $CH_aH_bCH_2O$), 3.44 (1H, dq, *J* 9.5, 7.1, $OCH_aH_bCH_3$), 3.67 (1H, ddd, *J* 11.0, 6.4, 1.1, $CH_2CH_aH_bO$), 3.90 (1H, dq, *J* 9.5, 7.1, $OCH_aH_bCH_3$), 4.14 (1H, dddd, *J* 12.7, 11.0, 3.4, 0.5, $CH_2CH_aH_bO$), 5.53 (1H, s, CHO), 6.78 (1H, d, *J* 7.5, ArH), 6.90 (1H, d, *J* 7.4, ArH), 7.04 (1H, app. t, *J* 7.5, ArH); δ_C(75 MHz, C_6D_6) 15.5 (CH_3, OCH_2CH_3), 18.4 (CH_3, $ArCH_3$), 28.6 (CH_2, CH_2CH_2O), 57.3 (CH_2, CH_2CH_2O), 63.1 (CH_2, OCH_2CH_3), 95.7 (CH, CHO), 126.5 (CH, Ar), 127.9 (CH, Ar), 128.5 (CH, Ar), 133.5 (quat. C, *ipso* Ar), 134.3 (quat. C, *ipso* Ar), 136.6 (quat. C, *ipso* Ar); m/*z* (EI) 192 ([M]$^+$, 11%), 147 (100, [M – OCH_2CH_3]$^+$), 119 (17), 91 (11); HRMS: $C_{12}H_{16}O_2$ calcd 192.1150 ([M]$^+$), obsd 192.1153.

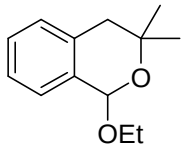
Spiro[1-ethoxyisochroman-4,1'-cyclopropane] 179j



Chemical Formula: $C_{13}H_{16}O_2$
Exact Mass: 204.115
Molecular Weight: 204.2649
Elemental Analysis: C, 76.44; H, 7.90; O, 15.67

1-Ethoxyisochroman **179j** was prepared by DIBALH reduction (2.95 mL, 4.40 mmol) of isochroman-1-one **183j** (510 mg, 2.93 mmol), followed by acetalisation using Amberlite and EtOH (6.5 mL) according to Method A. Purification by flash column chromatography (gradient: 98% hexane, 2% Et_2O → 95% hexane, 5% Et_2O) afforded 1-ethoxyisochroman **179j** as a colourless oil (502 mg, 84% over two steps): R_f = 0.23 (90% hexane, 10% Et_2O); ν_{max}(film)/cm^{-1} 2974m, 2870m, 1493w, 1465w, 1383w, 1330m, 1244m, 1206m, 1099m, 1083m, 1049s, 1003s, 963m, 929m, 855w, 827m, 753s, 721m, 674w; δ_H(300 MHz, C_6D_6) 0.36-0.46 (1H, m, cyclopropylC*H*), 0.59-0.68 (1H, m, cyclopropylC*H*), 0.77-0.94 (2H, stack, cyclopropylC*H*), 1.18 (3H, t, *J* 7.1, OCH_2CH_3), 2.91 (1H, d, *J* 11.3, CH_aH_bO), 3.53 (1H, dq, *J* 9.5, 7.0, $OCH_aH_bCH_3$), 3.92 (1H, dq, *J* 9.5, 7.0, $OCH_aH_bCH_3$), 4.46 (1H, d, *J* 11.3, CH_aH_bO), 5.66 (1H, s, C*H*O), 6.40-6.48 (1H, m, Ar*H*), 6.97-7.06 (2H, stack, Ar*H*), 7.14-7.22 (1H, m, Ar*H*); δ_C(75 MHz, C_6D_6) 10.5 (CH_2, cyclopropylCH_2), 15.6 (CH_3, OCH_2CH_3), 18.4 (quat. C, CCH_2O), 20.4 (CH_2, cyclopropyl CH_2), 63.4 (CH_2, CH_2O), 66.0 (CH_2, CH_2O), 98.1 (CH, CHO), 121.1 (CH, Ar), 125.4 (CH, Ar), 127.8 (CH, Ar), 128.5 (CH, Ar), 135.4 (quat. C, *ipso* Ar), 139.3 (quat. C, *ipso* Ar); m/*z* (EI) 204 ([M]$^+$, 13%), 176 (10, [M – CH_2CH_2]$^+$), 159 (48, [M – OCH_2CH_3]$^+$), 157 (76), 148 (23), 129 (100), 119 (16), 115 (58), 102 (39), 91 (31), 77 (15), 51 (11); HRMS: $C_{13}H_{16}O_2$ calcd 204.1150 ([M]$^+$), obsd 204.1152.

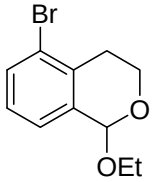
3,3-Dimethyl-1-ethoxyisochroman 179i



Chemical Formula: $C_{13}H_{18}O_2$
Exact Mass: 206.1307
Molecular Weight: 206.2808
Elemental Analysis: C, 75.69; H, 8.80; O, 15.51

1-Ethoxyisochroman **179i** was prepared by DIBALH reduction (4.00 mL, 5.96 mmol) of isochroman-1-one **183i** (700 mg, 3.97 mmol) followed by acetalisation using Amberlite and EtOH (8 mL) according to Method A. Purification by flash column chromatography (gradient: 98% hexane, 2% Et_2O → 95% hexane, 5% Et_2O) afforded 1-ethoxyisochroman **179i** as a colourless oil (590 mg, 72% over two steps): R_f = 0.46 (90% hexane, 10% Et_2O); (Found: C, 75.42; H, 8.82. $C_{13}H_{18}O_2$ requires C, 75.69; H, 8.80%); ν_{max}(film)/cm^{-1} 2973m, 2869w, 1456w, 1384m, 1370m, 1335m, 1257w, 1212m, 1183m, 1086m, 1048s, 1030s, 1006s, 947w, 927m, 874w, 804w, 759s, 734m, 723m; δ_H(300 MHz, C_6D_6) 1.17 (3H, t, *J* 7.1, OCH_2CH_3), 1.23 (3H, s, CH_3), 1.30 (3H, s, CH_3), 2.44-2.63 (2H, stack, CH_2), 3.52 (1H, dq, *J* 9.5, 7.1, $OCH_aH_bCH_3$), 3.97 (1H, dq, *J* 9.5, 7.1, $OCH_aH_bCH_3$), 5.67 (1H, s, CHO), 6.86-6.94 (1H, m, ArH), 7.06-7.14 (2H, stack, ArH), 7.30-7.38 (1H, m, ArH); δ_C(100 MHz, C_6D_6) 15.6 (CH_3, OCH_2CH_3), 27.7 (CH_3, $C(CH_3)_a(CH_3)_b$), 29.7 (CH_3, $C(CH_3)_a(CH_3)_b$), 40.5 (CH_2, CH_2CO), 63.1 (CH_2, OCH_2CH_3), 71.4 (quat. C, $C(CH_3)_2$), 97.2 (CH, CHO), 126.5 (CH, Ar), 127.6 (CH, Ar), 128.2 (CH, Ar), 128.6 (CH, Ar), 134.0 (quat. C, *ipso* Ar), 135.0 (quat. C, *ipso* Ar); m/*z* (EI) 206 ($[M]^+$, 32%), 205 (44, $[M - H]^+$), 161 (79, $[M - OCH_2CH_3]^+$), 159 (45), 148 (22), 145 (100), 142 (79), 133 (35), 128 (39), 119 (50), 115 (74), 104 (30), 91 (83), 77 (17), 65 (16); HRMS: $C_{13}H_{18}O_2$ calcd 206.1307 ($[M]^+$), obsd 206.1301.

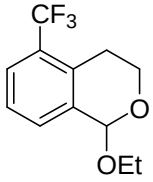
5-Bromo-1-ethoxyisochroman 179e



Chemical Formula: $C_{11}H_{13}BrO_2$
Exact Mass: 256.0099
Molecular Weight: 257.1237
Elemental Analysis: C, 51.38; H, 5.10; Br, 31.08; O, 12.44

1-Ethoxyisochroman **179e** was prepared by DIBALH reduction (2.20 mL, 3.30 mmol) of isochroman-1-one **183e** (500 mg, 2.20 mmol), followed by acetalisation using Amberlite and EtOH (4.4 mL) according to Method A. Purification by flash column chromatography (gradient: 99% hexane, 1% Et_2O → 95% hexane, 5% Et_2O) afforded 1-ethoxyisochroman **179e** as a white crystalline solid (555 mg, 98% over two steps): mp 27-28 °C; R_f = 0.34 (90% hexane, 10% Et_2O); ν_{max}(film)/cm^{-1} 2969m, 2891m, 1442m, 1329m, 1381m, 1339m, 1096m, 1077m, 1071m, 1044s, 1010s, 996s, 969m, 955m, 927m, 896m, 843m, 774s, 720m, 689m; δ_H(300 MHz, C_6D_6) 1.13 (3H, t, *J* 7.1, OCH_2CH_3), 2.41 (1H, ddd, *J* 17.4, 3.8, 1.5, $CH_aH_bCH_2O$), 2.61 (1H, ddd, *J* 17.4, 11.7, 6.2, $CH_aH_bCH_2O$), 3.43 (1H, dq, *J* 9.6, 7.1, $OCH_aH_bCH_3$), 3.57 (1H, ddd, *J* 11.3, 6.2, 1.5, $CH_2CH_aH_bO$), 3.80 (1H, dq, *J* 9.6, 7.1, $OCH_aH_bCH_3$), 3.90 (1H, app. td, *J* 11.5, 3.8, $CH_2CH_aH_bO$), 5.37 (1H, s, CHO), 6.69 (1H, app. t, *J* 7.8, ArH), 6.98 (1H, d, *J* 7.6, ArH), 7.30 (1H, d, *J* 7.9, ArH); δ_C(100 MHz, C_6D_6) 15.1 (CH_3, OCH_2CH_3), 28.9 (CH_2, CH_2CH_2O), 57.1 (CH_2, CH_2CH_2O), 63.1 (CH_2, OCH_2CH_3), 96.0 (CH, CHO), 124.5 (quat. C, *ipso* ArBr), 126.8 (CH, Ar), 127.2 (CH, Ar), 131.5 (CH, Ar), 134.2 (quat. C, *ipso* Ar), 137.4 (quat. C, *ipso* Ar); m/z (EI) 258 ([M]$^+$, 10%), 257 (11, [M – H]$^+$), 256 (10, [M]$^+$), 255 (11, [M – H]$^+$), 213 (100, [M – OCH_2CH_3]$^+$), 211 (100, [M – OCH_2CH_3]$^+$), 184 (26), 182 (26), 132 (30), 103 (39), 77 (29); HRMS: $C_{11}H_{13}O_2{}^{79}Br$ calcd 256.0099 ([M]$^+$), obsd 256.0092.

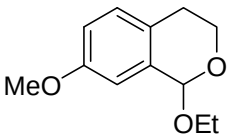
5-Trifluoromethyl-1-ethoxyisochroman 179f



Chemical Formula: $C_{12}H_{13}F_3O_2$
Exact Mass: 246.0868
Molecular Weight: 246.2256
Elemental Analysis: C, 58.54; H, 5.32; F, 23.15; O, 13.00

1-Ethoxyisochroman **179f** was prepared by DIBALH reduction (2.30 mL, 3.47 mmol) of isochroman-1-one **183f** (500 mg, 2.31 mmol), followed by acetalisation using Amberlite and EtOH (4.6 mL) according to Method A. Purification by flash column chromatography (gradient: 99% hexane, 1% Et_2O → 95% hexane, 5% Et_2O) afforded 1-ethoxyisochroman **179f** as a colourless liquid (503 mg, 88% over two steps): R_f = 0.31 (90% hexane, 10% Et_2O); ν_{max}(film)/cm^{-1} 2976w, 2888w, 1315s, 1263w, 1199m, 1187m, 1156m, 1115s, 1103m, 1074s, 1047s, 1003m, 969m, 936m, 850m, 805m, 794m, 748w, 726m, 692m; δ_H(300 MHz, C_6D_6) 1.13 (3H, t, *J* 7.1, OCH_2CH_3), 2.61 (1H, d with unresolved fine coupling, *J* 17.4, $CH_aH_bCH_2O$), 2.84 (1H, ddd, *J* 17.4, 11.9, 6.1, $CH_aH_bCH_2O$), 3.43 (1H, dq, *J* 9.6, 7.1, $OCH_aH_bCH_3$), 3.52 (1H, ddd, *J* 11.3, 6.0, 1.2, $CH_2CH_aH_bO$), 3.74-3.93 (2H, stack, $OCH_aH_bCH_3$ and $CH_2CH_aH_bO$), 5.36 (1H, s, CHO), 6.80 (1H, app. t, *J* 7.7, ArH), 7.10 (1H, d, *J* 7.7, ArH), 7.33 (1H, d, *J* 7.7, ArH); δ_C(100 MHz, C_6D_6) 15.4 (CH_3, OCH_2CH_3), 25.5 (CH_2, CH_2CH_2O), 57.0 (CH_2, CH_2CH_2O), 63.5 (CH_2, OCH_2CH_3), 96.5 (CH, CHO), 125.1 (quat. C, q, $^1J_{C-F}$ 272.0, $ArCF_3$), 125.7 (CH, q, $^3J_{C-F}$ 5.2, Ar), 126.0 (CH, Ar), 128.4 (quat. C, q, $^2J_{C-F}$ 28.4, *ipso* Ar), 132.0 (CH, Ar), 133.6 (quat. C, *ipso* Ar), 136.8 (quat. C, *ipso* Ar); δ_F(282 MHz) –61.1 (s, $ArCF_3$); m/*z* (EI) 246 ([M]$^+$, 4%), 245 (11, [M – H]$^+$), 201 (100, [M – OCH_2CH_3]$^+$), 172 (17), 151 (13), 133 (14); HRMS: $C_{12}H_{13}O_2F_3$ calcd 246.0868 ([M]$^+$), obsd 246.0863.

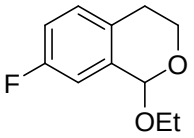
7-Methoxy-1-ethoxyisochroman 179g



Chemical Formula: $C_{12}H_{16}O_3$
Exact Mass: 208.1099
Molecular Weight: 208.2536
Elemental Analysis: C, 69.21; H, 7.74; O, 23.05

1-Ethoxyisochroman **179g** was prepared by DIBALH reduction (1.40 mL, 2.10 mmol) of isochroman-1-one **183g** (250 mg, 1.40 mmol), followed by acetalisation using Amberlite and EtOH (3 mL) according to Method A. Purification by flash column chromatography (gradient: 99% hexane, 1% Et_2O → 90% hexane, 10% Et_2O) afforded 1-ethoxyisochroman **179g** as a colourless liquid (217 mg, 74% over two steps): R_f = 0.23 (90% hexane, 10% Et_2O); ν_{max}(film)/cm^{-1} 2973m, 2879m, 1615w, 1503m, 1330m, 1318m, 1273m, 1263m, 1237m, 1165w, 1092m, 1074m, 1049s, 1035s, 997s, 958m, 933w, 866w, 848m, 814m, 802m; δ_H(300 MHz, C_6D_6) 1.18 (3H, t, *J* 7.1, OCH_2CH_3), 2.17 (1H, ddd, *J* 16.1, 3.2, 1.6, $CH_aH_bCH_2O$), 2.76 (1H, ddd, *J* 16.1, 12.0, 5.9, $CH_aH_bCH_2O$), 3.31 (3H, s, OCH_3), 3.52 (1H, dq, *J* 9.6, 7.1, $OCH_aH_bCH_3$), 3.69 (1H, ddd, *J* 11.0, 5.9, 1.6, $CH_2CH_aH_bO$), 3.91 (1H, dq, *J* 9.6, 7.1, $OCH_aH_bCH_3$), 4.07 (1H, app. td, *J* 11.5, 3.2, $CH_2CH_aH_bO$), 5.57 (1H, s, CHO), 6.74-6.84 (2H, stack, ArH), 6.89 (1H, s, ArH); δ_C(100 MHz, C_6D_6) 15.6 (CH_3, OCH_2CH_3), 27.7 (CH_2, CH_2CH_2O), 54.8 (CH_3, OCH_3), 58.3 (CH_2, CH_2CH_2O), 63.4 (CH_2, OCH_2CH_3), 97.2 (CH, CHO), 112.6 (CH, Ar), 115.1 (CH, Ar), 126.6 (quat. C, *ipso* Ar), 129.6 (CH, Ar), 136.3 (quat. C, *ipso* Ar), 158.6 (quat. C, *ipso* Ar); m/*z* (EI) 208 ($[M]^+$, 18%), 207 (8, $[M - H]^+$), 180 (14), 163 (63, $[M - OCH_2CH_3]^+$), 134 (100), 121 (20), 103 (12), 91 (23); HRMS: $C_{12}H_{16}O_3$ calcd 208.1099 ($[M]^+$), obsd 208.1103.

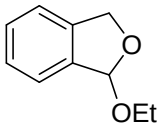
7-Fluoro-1-ethoxyisochroman 179h



Chemical Formula: $C_{11}H_{13}FO_2$
Exact Mass: 196.09
Molecular Weight: 196.2181
Elemental Analysis: C, 67.33; H, 6.68; F, 9.68; O, 16.31

1-Ethoxyisochroman **179h** was prepared by DIBALH reduction (4.20 mL, 6.32 mmol) of isochroman-1-one **183h** (700 mg, 4.21 mmol), followed by acetalisation using Amberlite and EtOH (7.3 mL) according to Method A. Purification by flash column chromatography (gradient: 98% hexane, 2% Et_2O → 95% hexane, 5% Et_2O) afforded 1-ethoxyisochroman **179h** as a pale yellow oil (639 mg, 77% over two steps): R_f = 0.23 (90% hexane, 10% Et_2O); ν_{max}(film)/cm^{-1} 2976w, 2882w, 1499m, 1433m, 1326w, 1257m, 1234m, 1112w, 1189m, 1075s, 1047s, 1001s, 961m, 942m, 904m, 864m, 855m, 815m, 804m, 739m; δ_H(300 MHz, C_6D_6) 1.11 (3H, t, *J* 7.1, OCH_2CH_3), 2.02 (1H, app. d, *J* 16.2, $CH_aH_bCH_2O$), 2.59 (1H, ddd, *J* 16.6, 12.0, 5.9, $CH_aH_bCH_2O$), 3.42 (1H, dq, *J* 9.6, 7.1, $OCH_aH_bCH_3$), 3.59 (1H, ddd, *J* 11.1, 5.9, 1.7, $CH_2CH_aH_bO$), 3.82 (1H, dq, *J* 9.6, 7.1, $OCH_aH_bCH_3$), 3.92 (1H, app. td, *J* 11.7, 3.4, $CH_2CH_aH_bO$), 5.37 (1H, s, C*H*O), 6.59 (1H, dd, $^3J_{H\text{-}H}$ 8.4, $^4J_{H\text{-}F}$ 5.7, Ar*H*), 6.72 (1H, app. td, $^3J_{H\text{-}H}$ and $^3J_{H\text{-}F}$ 8.4, $^4J_{H\text{-}H}$ 2.5, Ar*H*), 6.92 (1H, dd, $^3J_{H\text{-}F}$ 9.1, $^4J_{H\text{-}H}$ 2.5, Ar*H*); δ_C(75 MHz, C_6D_6) 15.5 (CH_3, OCH_2CH_3), 27.6 (CH_2, CH_2CH_2O), 57.9 (CH_2, CH_2CH_2O), 63.6 (CH_2, OCH_2CH_3), 96.5 (CH, CHO), 114.6 (CH, d, $^2J_{C\text{-}F}$ 21.3, Ar), 115.3 (CH, d, $^2J_{C\text{-}F}$ 21.3, Ar), 130.1 (CH, d, $^3J_{C\text{-}F}$ 7.2, Ar), 137.1 (quat. C, d, $^4J_{C\text{-}F}$ 6.5, *ipso* Ar), 161.6 (quat. C, d, $^1J_{C\text{-}F}$ 237.1, *ipso* Ar), the third quat. C, *ipso* Ar was not observed; δ_F(282 MHz) –116.6 - –116.3 (m, Ar*F*); m/*z* (EI) 196 ([M]$^+$, 7%), 195 (8, [M – H]$^+$), 151 (100, [M – OCH_2CH_3]$^+$), 122 (21), 109 (11), 103 (10); HRMS: $C_{11}H_{13}O_2F$ calcd 196.0900 ([M]$^+$), obsd 196.0901.

1-Ethoxyisobenzofuran 179k[201]

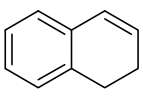


Chemical Formula: $C_{10}H_{12}O_2$
Exact Mass: 164.0837
Molecular Weight: 164.2011
Elemental Analysis: C, 73.15; H, 7.37; O, 19.49

1-Ethoxyisobenzofuran **179k** was prepared from phthalan **185** (0.50 mL, 4.57 mmol), DDQ (1.24 g, 5.48 mmol) and EtOH (2 × 320 μL, 2 × 5.48 mmol) in CH_2Cl_2 (29 mL) according to Method B. Purification by flash column chromatography (gradient: 100% hexane → 98% hexane, 2% Et_2O) afforded 1-ethoxyisobenzofuran **179k** as a pale yellow liquid (669 mg, 89%): R_f = 0.28 (90% hexane, 10% Et_2O); δ_H(300 MHz) 1.29 (3H, t, *J* 7.1, OCH_2CH_3), 3.70 (1H, dq, *J* 9.4, 7.1, $OCH_aH_bCH_3$), 3.82 (1H, dq, *J* 9.4, 7.1, $OCH_aH_bCH_3$), 5.06 (1H, d, *J* 12.7, CH_aH_bO), 5.26 (1H, dd, *J* 12.7, 1.9, CH_aH_bO), 6.29 (1H, d, *J* 1.9, C*H*O), 7.25-7.47 (4H, stack, Ar*H*); δ_C(100 MHz) 15.4 (CH_3, OCH_2CH_3), 62.9 (CH_2, CH_2O), 72.1 (CH_2, CH_2O), 106.7 (CH, *C*HO), 121.0 (CH, Ar), 122.9 (CH, Ar), 127.6 (CH, Ar), 129.1 (CH, Ar), 137.7 (quat. C, *ipso* Ar), 139.9 (quat. C, *ipso* Ar); m/*z* (EI) 163 ($[M - H]^+$, 9%), 135 (15, $[M - OCH_2CH_3]^+$), 119 (100), 91 (34), 77 (16).

Data were in agreement with those reported in the literature.[201]

1,2-Dihydronaphthalene 190[158]

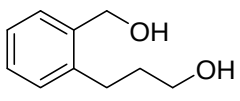


Chemical Formula: $C_{10}H_{10}$
Exact Mass: 130.0783
Molecular Weight: 130.1864
Elemental Analysis: C, 92.26; H, 7.74

$NaBH_4$ (569 mg, 15.1 mmol) was added in small portions to a solution of 1-tetralone **189** (4.40 g, 30.1 mmol) in EtOH (75 mL). After heating under reflux for 30 min, the solution was cooled to 0 °C and H_2O (75 mL) was added. The EtOH was removed under reduced pressure and the aqueous phase was extracted with toluene (2 × 75 mL). The combined organic fractions were washed with brine (75 mL) and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate was concentrated to a volume of 100 mL. *p*TSA (29 mg, 0.15 mmol) was added to the resulting solution of 1,2,3,4-tetrahydronaphthalen-1-ol in toluene and the mixture was heated under reflux with azeotropic removal of H_2O (Dean-Stark) for 15 h. After cooling to R.T., $NaHCO_3$ solution (30 mL) was added and the layers were separated. The organic phase was washed with $NaHCO_3$ solution (30 mL) and brine (40 mL) and dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product. Purification by a silica plug (100% hexane) afforded 1,2-dihydronaphthalene **190** as a colourless liquid (3.40 g, 87%): R_f = 0.50 (100% hexane); δ_H(300 MHz) 2.30-2.41 (2H, stack, CH=CHC*H*$_2$), 2.84 (2H, app. t, *J* 8.2, ArC*H*$_2$), 6.02-6.11 (1H, m, CH=C*H*CH_2), 6.47-6.55 (1H, m, C*H*=$CHCH_2$), 7.02-7.24 (4H, stack, Ar*H*); δ_C(100 MHz) 23.2 (CH_2, Ar*C*H_2CH_2 or $ArCH_2CH_2$), 27.5 (CH_2, Ar*C*H_2CH_2 or $ArCH_2CH_2$), [125.9, 126.4, 126.8, 127.5, 127.8, 128.6 (CH, 4 × Ar, *C*H=*C*H)], 134.1 (quat. C, *ipso* Ar), 135.4 (quat. C, *ipso* Ar); m/*z* (EI) 130 ($[M]^+$, 100%), 115 (43), 64 (14), 51 (13).

Data were in agreement with those reported in the literature.[158]

2-(3'-Hydroxypropyl)benzyl alcohol 191[159]

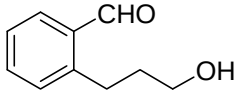


Chemical Formula: $C_{10}H_{14}O_2$
Exact Mass: 166.0994
Molecular Weight: 166.217
Elemental Analysis: C, 72.26; H, 8.49; O, 19.25

A solution of 1,2-dihydronaphthalene (3.27 g, 25.1 mmol) in CH_2Cl_2/MeOH (1:1, 130 mL) was cooled to –78 °C. O_3 was bubbled through the solution until a blue colour developed. The excess O_3 was then removed by bubbling N_2 through the solution until the blue colour had dissipated. $NaBH_4$ (1.90 g, 50.2 mmol) was added slowly over 5 min and the mixture was warmed to R.T. After stirring for 1.5 h at R.T., the reaction was quenched by the addition of NH_4Cl solution (80 mL) (caution: gas formation!). CH_2Cl_2 (50 mL) was added and the two phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic fractions were washed with brine (50 mL), and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude diol **191** as a colourless viscous oil (3.17 g, 76%), which was sufficiently pure for characterisation and further use: R_f = 0.20 (20% hexane, 80% EtOAc); δ_H(300 MHz) 1.79-1.91 (2H, stack, C*H*$_2$CH$_2$OH), 2.77 (2H, t, *J* 7.4, ArC*H*$_2$), 3.49 (2H, t, *J* 5.9, CH$_2$C*H*$_2$OH), 3.75 (1H, br s, O*H*), 4.04 (1H, br s, O*H*), 4.61 (2H, s, C*H*$_2$OH), 7.13-7.31 (4H, stack, Ar*H*); δ_C(75 MHz) 27.3 (CH$_2$, ArCH$_2$*C*H$_2$), 33.5 (CH$_2$, Ar*C*H$_2$CH$_2$), [60.7, 63.0 (CH$_2$, Ar*C*H$_2$OH, CH$_2$*C*H$_2$OH)], 126.0 (CH, Ar), 128.1 (CH, Ar), 129.3 (CH, 2 × Ar, resonance overlap), 138.3 (quat. C, *ipso* Ar), 140.2 (quat. C, *ipso* Ar); m/*z* (EI) 166 ([M]$^+$, 18%), 148 (40), 130 (100), 117 (99), 105 (53), 91 (74), 77 (28), 65 (12).

Data were in agreement with those reported in the literature.[159]

2-(3'-Hydroxypropyl)benzaldeyde 188[159]

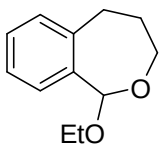


Chemical Formula: $C_{10}H_{12}O_2$
Exact Mass: 164.0837
Molecular Weight: 164.2011
Elemental Analysis: C, 73.15; H, 7.37; O, 19.49

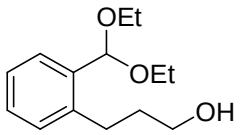
Activated MnO_2 85% (4.31 g, 42.1 mmol) was added to a solution of diol **191** (1.00 g, 6.02 mmol) in CH_2Cl_2 (13 mL). After stirring for 12 h at R.T., more MnO_2 (1.85 g, 18.1 mmol) was added and the stirring was continued for 2 h. Another portion of MnO_2 (1.85 g, 18.1 mmol) was added and the stirring was continued. After 1 h, the MnO_2 was removed by filtration over Celite, and the Celite was washed with CH_2Cl_2 (150 mL). The filtrate was concentrated under reduced pressure to provide the crude aldehyde **188** as a colourless viscous oil (851 mg, 86%), which was sufficiently pure for characterisation and further use: R_f = 0.20 (40% hexane, 60% EtOAc); δ_H(300 MHz) 1.82-1.94 (2H, stack, CH_2CH$_2$OH), 2.25 (1H, br s, O*H*), 3.13 (2H, t, *J* 7.6, ArCH_2), 3.66 (2H, t, *J* 6.1, CH$_2$CH_2OH), 7.31 (1H, d, *J* 7.6, Ar*H*), 7.38 (1H, app. td, *J* 7.5, 1.2, Ar*H*), 7.51 (1H, app. td, *J* 7.5, 1.2, Ar*H*), 7.81 (1H, dd, *J* 7.6, 1.5 Ar*H*), 10.22 (1H, s, C*H*O); δ_C(100 MHz) [28.7, 34.6 (CH$_2$, ArCH_2CH_2)], 61.7 (CH$_2$, CH_2OH), 126.6 (CH, Ar), 131.2 (CH, Ar), 133.0 (CH, Ar), 133.8 (CH, Ar), 144.6 (quat. C, *ipso* Ar), 193.1 (CH, *C*HO), the second *ipso* Ar resonance was not observed; m/*z* (EI) 164 ([M]$^+$, 14%), 146 (20), 131 (36), 118 (100, [M – CHO – OH]$^+$), 105 (20), 91 (45), 77 (26), 65 (20), 55 (10), 51 (14).

Data were in agreement with those reported in the literature.[159]

1-Ethoxy-3,4,5-trihydro-2-benzoxepin 179l and 2-(3'-hydroxypropyl)benzaldehyde diethyl acetal 192



Chemical Formula: $C_{12}H_{16}O_2$
Exact Mass: 192.115
Molecular Weight: 192.2542
Elemental Analysis: C, 74.97; H, 8.39; O, 16.64

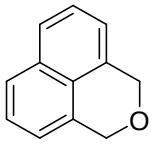


Chemical Formula: $C_{14}H_{22}O_3$
Exact Mass: 238.1569
Molecular Weight: 238.3227
Elemental Analysis: C, 70.56; H, 9.30; O, 20.14

A solution of 2-(3'-hydroxypropyl)benzaldehyde **188** (610 mg, 3.72 mmol) in EtOH (8 mL) was stirred with Amberlite (IR 120 beads, spatula tip) at R.T. After 6 h, the beads were filtered off and washed with Et_2O (15 mL). $NaHCO_3$ solution (20 mL) was added and the Et_2O and EtOH were evaporated. The residue was extracted with Et_2O (2 × 20 mL) and the combined organic fractions were washed with brine (30 mL) and dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure. Purification of the residue by column chromatography (gradient: 98% hexane, 2% Et_2O → 50% hexane, 50% Et_2O) afforded, in order of elution, benzoxepin **179l** as a colourless liquid (466 mg, 56%): R_f = 0.58 (50% hexane, 50% Et_2O); ν_{max}(film)/cm^{-1} 2933m, 1455m, 1373w, 1346m, 1288w, 1222m, 1196w, 1142m, 1104m, 1085s, 1069s, 1050s, 1019s, 963m, 947m, 906m, 876m, 851w, 770m, 746s; δ_H(300 MHz, C_6D_6) 1.18 (3H, t, *J* 7.1, OCH_2CH_3), 1.41-1.62 (2H, stack, $CH_2CH_2CH_2O$), 2.62-2.84 (2H, stack, $CH_2CH_2CH_2O$), 3.38 (1H, dq, *J* 9.4, 7.1, $OCH_aH_bCH_3$), 3.58 (1H, ddd, *J* 11.8, 7.2, 4.1, $CH_2CH_aH_bO$), 3.91 (1H, dq, *J* 9.4, 7.1, $OCH_aH_bCH_3$), 4.06 (1H, ddd, *J* 11.8, 6.0, 4.4, $CH_2CH_aH_bO$), 5.42 (1H, s, C*H*O), 6.92-6.99 (1H, m, Ar*H*), 7.02-7.13 (2H, stack, Ar*H*), 7.62-7.70 (1H, m, Ar*H*); δ_C(100 MHz, C_6D_6) 15.3 (CH_3, OCH_2CH_3), [29.9, 34.5 (CH_2, $CH_2CH_2CH_2O$], [63.6, 67.7 (CH_2, $CH_2CH_2CH_2O$ and OCH_2CH_3)], 103.8 (CH, CHO), 126.3 (CH, Ar), 127.0 (CH, Ar), 128.2 (CH, Ar), 129.6 (CH, Ar), 140.1 (quat. C, *ipso* Ar), 141.0 (quat. C, *ipso* Ar); m/*z* (EI) 192 ([M]$^+$, 3%), 191 (9, [M – H]$^+$), 161 (10), 147 (100, [M – OCH_2CH_3]$^+$), 133 (21), 129 (32), 117 (96), 115 (25), 105 (11), 91 (47), 77 (16), 65 (11); HRMS: $C_{12}H_{16}O_2$ calcd 192.1150 ([M]$^+$), obsd 192.1154; and then diethyl acetal **192** as a colourless oil (124 mg, 12%): R_f = 0.35 (50% hexane, 50% Et_2O); ν_{max}(film)/cm^{-1} 3421m br (OH), 2974m, 2877m, 1452w, 1374m, 1353m, 1285w, 1216m,

1048s, 953m, 915m, 753s; δ_H(300 MHz) 1.25 (6H, t, *J* 7.1, OCH_2CH_3), 1.85-1.97 (2H, stack, $CH_2CH_2CH_2OH$), 2.61 (1H, br s, O*H*), 2.86 (2H, t, *J* 7.3, $CH_2CH_2CH_2OH$), 3.50-3.70 (6H, stack, OCH_2CH_3, $CH_2CH_2CH_2OH$), 5.65 (1H, s, $CH(OEt)_2$), 7.17-7.33 (3H, stack, Ar*H*), 7.53-7.61 (1H, m, Ar*H*); δ_C(100 MHz) 15.0 (CH_3, OCH_2CH_3), 27.4 (CH_2, $CH_2CH_2CH_2OH$), 33.9 (CH_2, $CH_2CH_2CH_2OH$), [61.49, 61.52 (CH_2, $CH_2CH_2CH_2OH$ and OCH_2CH_3)], 100.3 (CH, $CH(OEt)_2$), 125.5 (CH, Ar), 126.8 (CH, Ar), 128.4 (CH, Ar), 129.5 (CH, Ar), 136.2 (quat. C, *ipso* Ar), 139.8 (quat. C, *ipso* Ar); m/*z* (TOF ES+) 261 ($[M + Na]^+$, 100%); HRMS: $C_{14}H_{22}O_3Na$ calcd 261.1467 ($[M + Na]^+$), obsd 261.1463; and then recovered starting material (85 mg, 12%): R_f = 0.25 (50% hexane, 50% Et_2O).

1*H*,3*H*-naphtho[1,8-cd]pyran 195



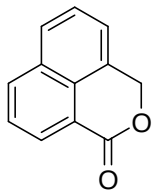
Chemical Formula: $C_{12}H_{10}O$
Exact Mass: 170.0732
Molecular Weight: 170.2072
Elemental Analysis: C, 84.68; H, 5.92; O, 9.40

$NaBH_4$ (239 mg, 6.31 mmol) was added to a solution of 1,8-naphthalic anhydride **194** (500 mg, 2.52 mmol) in THF (1 mL) at 0 °C (caution: gas formation!). A solution of $BF_3{\cdot}OEt_2$ (935 mL, 7.57 mmol) in THF (0.8 mL) was added over 3 min at 0 °C and the reaction mixture was stirred at R.T overnight. A mixture of THF/H_2O (1:1, 5 mL) was added carefully (caution: gas formation) followed by the addition of more H_2O (10 mL). The two phases were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic fractions were washed with brine (20 mL), and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product**.** Purification by flash column chromatography (gradient: 100% hexane → 99%

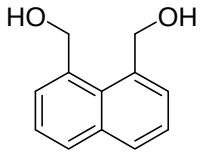
hexane, 1% Et_2O) afforded pyran **195** as a white crystalline solid (319 mg, 74%): mp 84-85 °C (lit.[202] mp 83-83.5 °C); R_f = 0.25 (90% hexane, 10% Et_2O); (Found: C, 84.68; H, 5.98. $C_{12}H_{10}O$ requires C, 84.68; H, 5.92%); δ_H(300 MHz) 5.10 (4H, s, C*H*$_2$O), 7.19 (2H, d, *J* 6.9, Ar*H*), 7.46 (2H, app. t, *J* 7.4, Ar*H*), 7.76 (2H, d, *J* 8.3, Ar*H*); δ_C(100 MHz) 69.3 (CH_2, *C*H_2O), 119.9 (CH, Ar), 125.6 (CH, Ar), 126.3 (CH, Ar), 126.7 (quat. C, *ipso* Ar), 132.5 (quat. C, *ipso* Ar), 132.8 (quat. C, *ipso* Ar); m/*z* (EI) 170 ([M]$^+$, 97%), 152 (21), 141 (100), 115 (19).

Data were in agreement with those reported in the literature.[202]

1*H*,3*H*-naphtho[1,8-cd]pyran-1-one 193 and 1,8-dihydroxymethylnaphthalene 196[160]



Chemical Formula: $C_{12}H_8O_2$
Exact Mass: 184.0524
Molecular Weight: 184.1907
Elemental Analysis: C, 78.25; H, 4.38; O, 17.37



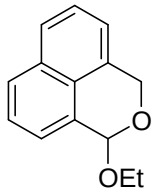
Chemical Formula: $C_{12}H_{12}O_2$
Exact Mass: 188.0837
Molecular Weight: 188.2225
Elemental Analysis: C, 76.57; H, 6.43; O, 17.00

1,8-Naphthalic anhydride **194** (5.00 g, 25.2 mol) was added in 1 g portions to a suspension of $LiAlH_4$ (1.92 g, 50.5 mol) in THF (125 mL) over 1 h. After stirring overnight at R.T., the reaction was quenched by the cautious addition of a saturated solution of Rochelle's salt (50 mL) (caution: gas formation!) at 0 °C. The THF was removed under reduced pressure and then CH_2Cl_2 (100 mL) and H_2SO_4 (1 M, 100 mL) were added. The two layers were separated

and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic fractions were washed with NaOH solution (1 M, 50 mL) and brine (50 mL) and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure. Purification of the residue by flash column chromatography (residue pre-adsorbed on silica, gradient: 80% hexane, 10% EtOAc, 10% toluene → 70% hexane, 20% EtOAc, 10% toluene) afforded, in order of elution, pyran-1-one **193** as a white crystalline solid (1.88 g, 41%): mp 158-159 °C (lit.[203] mp 156-157 °C); R_f = 0.28 (70% hexane, 20% EtOAc, 10% toluene); (Found: C, 78.28; H, 4.36. $C_{12}H_8O_2$ requires C, 78.25; H, 4.38%); δ_H(300 MHz) 5.80 (2H, s, CH_2O), 7.31-7.39 (1H, m, Ar*H*), 7.53 (1H, dd, *J* 8.3, 7.1, Ar*H*), 7.62 (1H, dd, *J* 8.3, 7.4, Ar*H*), 7.83 (1H, dd, *J* 8.3, 0.7, Ar*H*), 8.08 (1H, dd, *J* 8.3, 1.1, Ar*H*), 8.36 (1H, dd, *J* 7.3, 1.1, Ar*H*); δ_C(75 MHz) 70.0 (CH_2, *C*H_2O), 120.1 (quat. C, *ipso* Ar), 121.4 (CH, Ar), 126.4 (CH, 2 × Ar, resonance overlap), 126.6 (CH, Ar), 127.1 (quat. C, *ipso* Ar), 128.2 (quat. C, *ipso* Ar), 129.0 (CH, Ar), 131.9 (quat. C, *ipso* Ar), 133.4 (CH, Ar), 164.1 (quat. C, *C*=O); m/*z* (EI) 184 ($[M]^+$, 85%), 155 (100), 139 (11), 127 (82), 77 (10), 63 (13); and then (gradient: 50% hexane, 50% EtOAc → 10% hexane, 90% EtOAc) diol **196** as a white crystalline solid (1.14 g, 24%): mp 155-156 °C (lit.[204] mp 157-158 °C); R_f = 0.15 (50% hexane, 50% EtOAc); δ_H(300 MHz, CD_3OD) 4.90 (2H, s, O*H*), 5.23 (4H, s, CH_2O), 7.44 (2H, dd, *J* 8.1, 7.1, Ar*H*), 7.61 (2H, dd, *J* 7.1, 1.3, Ar*H*), 7.86 (2H, dd, *J* 8.1, 1.3, Ar*H*); δ_C(75 MHz, CD_3OD) 66.3 (CH_2, *C*H_2OH), 126.2 (CH, Ar), 130.8 (CH, Ar), 131.1 (CH, Ar), 131.9 (quat. C, *ipso* Ar), 137.3 (quat. C, *ipso* Ar), 138.3 (quat. C, *ipso* Ar); m/*z* (EI) 188 ($[M]^+$, 30%), 170 (100), 153 (39), 141 (83), 128 (32), 115 (39), 84 (32), 63 (10), 49 (39).

Data were in agreement with those reported in the literature.[197,205]

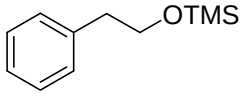
1-Ethoxy-3*H*-naphtho[1,8-cd]pyran 179m



Chemical Formula: $C_{14}H_{14}O_2$
Exact Mass: 214.0994
Molecular Weight: 214.2598
Elemental Analysis: C, 78.48; H, 6.59; O, 14.93

Naphthopyran **179m** was prepared by DIBALH reduction (3.80 mL, 5.70 mmol) of pyran-1-one **193** (700 mg, 3.80 mmol), followed by acetalisation using Amberlite and EtOH (6.7 mL) according to Method A. Purification by flash column chromatography (gradient: 98% hexane, 2% Et_2O → 95% hexane, 5% Et_2O) afforded 1-ethoxynaphthopyran **179m** as a colourless oil (684 mg, 84% over two steps): R_f = 0.25 (90% hexane, 10% Et_2O); ν_{max}(film)/cm^{-1} 2976w, 2894w, 1372m, 1331m, 1316w, 1176m, 1162w, 1128m, 1107w, 1076m, 1041s, 1013s, 985m, 933m, 902w, 833m, 817s, 797m, 771s, 735m; δ_H(300 MHz, C_6D_6) 1.17 (3H, t, *J* 7.1, OCH_2CH_3), 3.58 (1H, dq, *J* 9.6, 7.1, $OCH_aH_bCH_3$), 3.96 (1H, dq, *J* 9.6, 7.1, $OCH_aH_bCH_3$), 4.73 (1H, d, *J* 14.4, CH_aH_bO), 5.26 (1H, d, *J* 14.4, CH_aH_bO), 5.84 (1H, s, CHO), 6.80-6.86 (1H, m, Ar*H*), 7.13-7.26 (3H, stack, Ar*H*), 7.49-7.60 (2H, stack, Ar*H*); δ_C(75 MHz, C_6D_6) 15.5 (CH_3, OCH_2CH_3), 61.5 (CH_2, CH_2O), 63.6 (CH_2, CH_2O), 98.5 (CH, CHO), 120.6 (CH, Ar), 123.3 (CH, Ar), 125.7 (CH, Ar), 125.9 (CH, Ar), 126.5 (CH, Ar), 128.1 (CH, Ar), [132.3 (quat. C, *ipso* Ar), 133.1 (quat. C, *ipso* Ar), resonance overlap]; m/*z* (EI) 214 ([M]$^+$, 15%), 169 (79, [M – OCH_2CH_3]$^+$), 152 (24), 141 (100), 139 (21), 115 (24); HRMS: $C_{14}H_{14}O_2$ calcd 214.0994 ([M]$^+$), obsd 214.0993.

2-Phenylethyl trimethylsilyl ether 198[143]

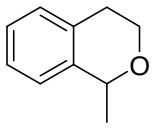


Chemical Formula: $C_{11}H_{18}OSi$
Exact Mass: 194.1127
Molecular Weight: 194.3455
Elemental Analysis: C, 67.98; H, 9.34; O, 8.23; Si, 14.45

I_2 (508 mg, 2.00 mmol) was added to a solution of 2-phenylethyl alcohol (2.40 mL, 20.0 mmol) in CH_2Cl_2 (80 mL). A solution of HMDS (3.30 mL, 16.00 mmol) in CH_2Cl_2 (20 mL) was added dropwise over 5 min to the dark purple solution. After stirring for 1 h, the reaction was quenched by the addition of $Na_2S_2O_3$ solution (60 mL), and the mixture was stirred until the solution turned colourless. The phases were separated and the organic phase was washed with brine (40 mL), and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude silyl ether **198** as a pale yellow liquid (3.79 g, 98%), which was sufficiently pure for characterisation and further use: δ_H(300 MHz) 0.10 (9H, s, Si(C*H*$_3$)$_3$), 2.87 (2H, t, *J* 7.3, ArC*H*$_2$), 3.81 (2H, t, *J* 7.3, C*H*$_2$OTMS), 7.19-7.36 (5H, stack, Ar*H*).

Data were in agreement with those reported in the literature.[206]

1-Methylisochroman 197[161]



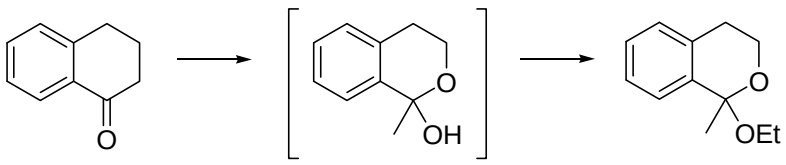
Chemical Formula: $C_{10}H_{12}O$
Exact Mass: 148.0888
Molecular Weight: 148.2017
Elemental Analysis: C, 81.04; H, 8.16; O, 10.80

TMSI (1.00 mL, 7.07 mmol) was added to a solution of freshly distilled acetaldehyde (400 μL, 7.07 mmol) in $CHCl_3$ (1 mL) at R.T. After stirring for 5 min, silyl ether **198** (1.92 g, 9.90 mmol) was added and the mixture was warmed to 50 °C for 2 h. After cooling to R.T., Et_2O (20 mL) was added. The organic phase was washed with $Na_2S_2O_3$ solution (3 × 20 mL), H_2O (10 mL) and brine (10 mL) and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product.

Purification by flash column chromatography (99% hexane, 1% Et_2O) afforded isochroman **197** as a colourless liquid (340 mg, 32%): R_f = 0.30 (90% hexane, 10% Et_2O); δ_H(300 MHz) 1.58 (3H, d, *J* 6.5, CH_3), 2.72 (1H, app. dt, *J* 16.3, 3.3, CH_aH$_b$CH$_2$O), 3.07 (1H, ddd, *J* 15.9, 10.1, 5.6, CH$_a$$H_bCH_2$O), 3.84 (1H, ddd, *J* 11.3, 10.1, 3.3, CH$_2$CH_aH$_b$O), 4.20 (1H, ddd, *J* 11.3, 5.6, 3.3, CH$_2$CH$_a$$H_b$O), 4.90 (1H, q, *J* 6.5, C*H*CH$_3$), 7.08-7.27 (4H, stack, Ar*H*); δ_C(75 MHz) 21.8 (CH$_3$, *C*H$_3$), 29.0 (CH$_2$, *C*H$_2$CH$_2$O), 63.6 (CH$_2$, CH$_2$*C*H$_2$O), 72.3 (CH, *C*HO), 124.7 (CH, Ar), 126.1 (CH, Ar), 126.2 (CH, Ar), 128.8 (CH, Ar), 133.4 (quat. C, *ipso* Ar), 139.5 (quat. C, *ipso* Ar); m/*z* (EI) 148 ([M]$^+$, 15%), 147 (15, [M – H]$^+$), 133 (100, [M – CH$_3$]$^+$), 117 (11), 115 (12), 105 (26), 91 (10), 77 (11).

Data were in agreement with those reported in the literature.[161]

1-Ethoxy-1-methylisochroman 179n

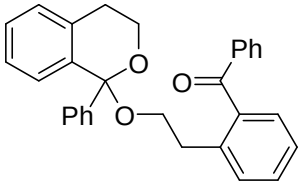


Chemical Formula: $C_{12}H_{16}O_2$
Exact Mass: 192.115
Molecular Weight: 192.2542
Elemental Analysis:
C, 74.97; H, 8.39; O, 16.64

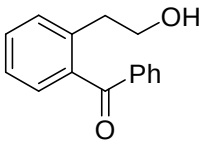
MeLi (1.6 M solution in Et_2O, 5.10 mL, 8.18 mmol) was added over 10 min to a solution of isochroman-1-one **172** (1.10 g, 7.43 mmol) in THF (37 mL) at –78 °C. After stirring at –78 °C for 2 h, AcOH (470 μL, 8.18 mmol) was added and the mixture was stirred for 15 min. The mixture was poured into ice-water (100 mL) and transferred to a separating funnel. The

phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic fractions were washed with brine (30 mL) and dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude hemiacetal product, which was of sufficient purity for it to be used directly in the next step: 1-Hydroxy-1-methylisochroman was dissolved in EtOH (15 mL) and stirred with Amberlite (IR 120 beads, tea spoon) at R.T. for 2 h. The beads were filtered off and washed with Et_2O (15 mL). $NaHCO_3$ solution (20 mL) was added and the Et_2O and EtOH were evaporated. The residue was extracted with Et_2O (2 × 20 mL) and the combined organic fractions were washed with brine (30 mL) and dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure. Purification of the residue by flash column chromatography (gradient: 99% hexane, 1% NEt_3 → 95% hexane, 4% Et_2O, 1% NEt_3) afforded 1-ethoxy-1-methylisochroman **179n** as a colourless oil (857 mg, 60% over two steps): R_f = 0.28 (90% hexane, 10% Et_2O); ν_{max}(film)/cm^{-1} 2974m, 2933m, 2880m, 1492w, 1451w, 1427w, 1388w, 1372m, 1304w, 1289m, 1267m, 1252m, 1160m, 1121s, 1096s, 1084s, 1069s, 1047s, 1029s, 973w, 941m, 907m, 872m, 840w, 789w, 758s, 732m; δ_H(300 MHz, C_6D_6) 1.15 (3H, app. t, *J* 7.1, OCH_2CH_3), 1.64 (3H, s, CCH_3), 2.24 (1H, app. dt, *J* 16.1, 3.2, $CH_aH_bCH_2O$), 2.70 (1H, ddd, *J* 16.1, 10.6, 5.4, $CH_aH_bCH_2O$), 3.55 (1H, app. q, *J* 7.1, OCH_2CH_3), 3.66 (1H, ddd, *J* 11.0, 5.4, 3.0, $CH_2CH_aH_bO$), 3.91 (1H, app. td, *J* 10.9, 3.5, $CH_2CH_aH_bO$), 6.82-6.91 (1H, m, Ar*H*), 7.00-7.12 (2H, stack, Ar*H*), 7.33-7.41 (1H, m, Ar*H*); δ_C(75 MHz, C_6D_6) 16.0 (CH_3, OCH_2CH_3), 26.1 (CH_3, CCH_3), 29.2 (CH_2, CH_2CH_2O), 56.8 (CH_2, CH_2O), 59.5 (CH_2, CH_2O), 98.9 (quat. C, CCH_3O), 126.6 (CH, Ar), 127.2 (CH, Ar), 127.5 (CH, Ar), 128.5 (CH, Ar), 134.2 (quat. C, *ipso* Ar), 139.8 (quat. C, *ipso* Ar); m/z (TOF ES+) 215.1 ([M + Na]$^+$, 100%); HRMS: $C_{12}H_{16}O_2Na$ calcd 215.1048 ([M + Na]$^+$), obsd 215.1041.

2-(2’-(1’’-Oxo-1’’-phenyl-isochroman)ethyl)benzophenone 201 and 2-(2’-hydroxyethyl)benzophenone 200[207]



Chemical Formula: $C_{30}H_{26}O_3$
Exact Mass: 434.1882
Molecular Weight: 434.5256
Elemental Analysis: C, 82.92; H, 6.03; O, 11.05



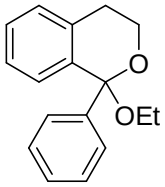
Chemical Formula: $C_{15}H_{14}O_2$
Exact Mass: 226.0994
Molecular Weight: 226.2705
Elemental Analysis: C, 79.62; H, 6.24; O, 14.14

PhLi (1.8 M solution in Et_2O, 3.50 mL, 6.26 mmol) was added over 10 min to a solution of isochroman-1-one **172** (842 mg, 5.69 mmol) in THF (28 mL) at –78 °C. After stirring at –78 °C for 1 h, the mixture was warmed up to 0 °C over 5 h. AcOH (360 μL, 6.26 mmol) was added and the mixture was stirred for 15 min. The mixture was poured into ice-water (100 mL) and transferred to a separating funnel. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic fractions were washed with brine (30 mL) and dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure. Purification of the residue by flash column chromatography (gradient: 95% hexane, 4% EtOAc, 1% NEt_3 → 92% hexane, 7% EtOAc, 1% NEt_3) afforded, in order of elution, 2-(2’-(1’’-oxo-1’’-phenyl-isochroman)ethyl)benzophenone **201** as a pale yellow solid (593 mg, 48%): mp 109-110 °C; R_f = 0.55 (70% hexane, 30% EtOAc); ν_{max}(film)/cm^{-1} 2883w, 1660s (C=O), 1447m, 1312m, 1285m, 1262m, 1196m, 1175m, 1075m, 1068m, 1048s, 1006m, 1000m, 986m, 939m, 925s, 769s, 752s, 732m, 703s, 660m; δ_H(300 MHz, C_6D_6) 2.23 (1H, app. dt, *J* 16.2, 3.2, C*H*$_a$H$_b$CH$_2$O), 2.76 (1H, ddd, *J* 16.1, 10.7, 5.5, CH$_a$*H*$_b$CH$_2$O), 3.11-3.31 (2H, stack,

OCH_2CH_2Ar), 3.70 (1H, ddd, *J* 11.0, 5.5, 3.0, $CH_2CH_aH_bO$), 3.75-3.96 (3H, stack, $CH_2CH_aH_bO$, OCH_2CH_2Ar), 6.75-7.31 (14H, stack, Ar*H*), 7.58-7.65 (2H, stack, Ar*H*), 7.71-7.78 (2H, stack, Ar*H*); δ_C(100 MHz, C_6D_6) 28.9 (CH_2, CH_2CH_2O), 34.2 (CH_2, CH_2CH_2O), 59.8 (CH_2, CH_2CH_2O), 64.0 (CH_2, CH_2CH_2O), 101.1 (quat. C, *C*Ph), [125.7 (CH, Ar), 126.6 (CH, Ar), 127.4 (CH, Ar), 127.6 (CH, Ar), 128.4 (CH, Ar), 128.5 (CH, Ar), 128.9 (CH, Ar), 129.0 (CH, Ar), 130.1 (CH, Ar), 130.5 (CH, Ar), 131.5 (CH, Ar), 132.8 (CH, Ar), resonance overlap], 134.0 (quat. C, *ipso* Ar), 138.3 (quat. C, *ipso* Ar), 138.6 (quat. C, *ipso* Ar), 139.0 (quat. C, *ipso* Ar), 139.8 (quat. C, *ipso* Ar), 143.4 (quat. C, *ipso* Ar), 197.6 (quat. C, *C*=O); m/*z* (TOF ES+) 457 ($[M + Na]^+$, 100%); HRMS: $C_{30}H_{26}O_3Na$ calcd 457.1780 ($[M + Na]^+$), obsd 457.1775; and then 2-(2'-hydroxyethyl)benzophenone **200** (gradient: 80% hexane, 19% EtOAc, 1% NEt_3 → 70% hexane, 29% EtOAc, 1% NEt_3) as a pale orange viscous oil (288 mg, 22%): R_f = 0.23 (70% hexane, 30% EtOAc); δ_H(300 MHz, C_6D_6) 2.79 (2H, t, *J* 6.4, CH_2CH_2OH), 3.71 (2H, t, *J* 6.4, CH_2CH_2OH), 6.75-7.22 (7H, stack, Ar*H*), 7.67-7.81 (2H, stack, Ar*H*); δ_C(100 MHz, C_6D_6) 36.8 (CH_2, CH_2CH_2OH), 63.9 (CH_2, CH_2CH_2OH), 125.6 (CH, Ar), 128.6 (CH, Ar), 129.2 (CH, Ar), 130.6 (CH, Ar), 130.7 (CH, Ar), 131.4 (CH, Ar), 133.1 (CH, Ar), 138.3 (quat. C, *ipso* Ar), 139.3 (quat. C, *ipso* Ar), 139.5 (quat. C, *ipso* Ar), 198.4 (quat. C, *C*=O); m/*z* (EI) 226 ($[M]^+$, 10%), 208 (100), 195 (95, $[M - CH_2OH]^+$), 179 (32), 165 (39), 152 (13), 131 (20), 119 (10), 105 (35), 91 (17), 77 (51), 51 (16).

Data were in agreement with those reported in the literature.[207]

1-Ethoxy-1-phenylisochroman 179o



Chemical Formula: $C_{17}H_{18}O_2$
Exact Mass: 254.1307
Molecular Weight: 254.3236
Elemental Analysis: C, 80.28; H, 7.13; O, 12.58

2-(2'-Hydroxyethyl)benzophenone **200** (288 mg, 1.25 mmol) was dissolved in EtOH (2.5 mL) and stirred with Amberlite (IR 120 beads, spatula tip) at R.T. for 2 h. The beads were filtered off and washed with Et_2O (15 mL). $NaHCO_3$ solution (15 mL) was added and the Et_2O and EtOH were evaporated. The residue was extracted with Et_2O (2 × 15 mL) and the combined organic fractions were washed with brine (25 mL) and dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure. Purification of the residue by flash column chromatography (gradient: 99% hexane, 1% NEt_3 → 97% hexane, 2% Et_2O, 1% NEt_3) afforded 1-ethoxy-1-phenylisochroman **179o** as a colourless oil (130 mg, 40%): R_f = 0.46 (90% hexane, 10% Et_2O); ν_{max}(film)/cm^{-1} 2973m, 2935w, 2886w, 1489m, 1448m, 1259w, 1239m, 1201m, 1121m, 1089m, 1080m, 1068s, 1048s, 1001s, 970m, 958m, 943m, 920m, 763s, 748s, 730m, 700s, 659m; δ_H(300 MHz, C_6D_6) 1.21 (3H, app. t, *J* 7.1, OCH_2CH_3), 2.32 (1H, app. dt, *J* 16.2, 3.2, $CH_aH_bCH_2O$), 2.83 (1H, ddd, *J* 16.2, 10.8, 5.6, $CH_aH_bCH_2O$), 3.49-3.70 (2H, stack, OCH_2CH_3), 3.66-3.78 (1H, ddd, *J* 11.0, 5.5, 2.9, $CH_2CH_aH_bO$), 4.02 (1H, app. td, *J* 10.9, 3.5, $CH_2CH_aH_bO$), 6.81-6.99 (3H, stack, Ar*H*), 7.05-7.25 (3H, stack, Ar*H*), 7.36-7.43 (1H, m, Ar*H*), 7.72-7.79 (2H, stack, Ar*H*); δ_C(100 MHz, C_6D_6) 15.8 (CH_3, OCH_2CH_3), 29.0 (CH_2, CH_2CH_2O), 58.3 (CH_2, CH_2O), 59.8 (CH_2, CH_2O), 101.2 (quat. C, *C*PhO), 126.6 (CH, Ar), 127.4 (CH, Ar), 127.7 (CH, Ar), 128.0 (CH, Ar), 128.3 (CH, Ar), 128.6 (CH, Ar), 129.1 (CH, Ar), 134.0 (quat. C, *ipso* Ar), 138.7 (quat. C, *ipso* Ar), 143.7 (quat. C, *ipso* Ar); m/*z* (EI) 209 ([M – OCH_2CH_3]$^+$, 100%), 194 (18), 177 (29, [M – C_6H_5]$^+$), 165 (12), 149 (16), 77 (14); HRMS: $C_{15}H_{13}O$ calcd 209.0966 ([M – OCH_2CH_3]$^+$), obsd 209.0960.

General procedure for the formation of 1-allylisochromans 202

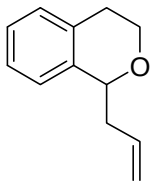
Method A: Racemic allylation

$MeSO_3H$ (32 μL, 0.49 mmol) was added to a solution of the 1-ethoxyisochroman (0.490 mmol) and allyltrimethylsilane (117 μL, 0.734 mmol) in CH_2Cl_2 (1 mL) at 0 °C. A colour change from colourless to a bright colour (depending on the 1-ethoxyisochroman) was observed. After stirring at R.T. for 30 min, $NaHCO_3$ solution (15 mL) and Et_2O (15 mL) were added. The two phases were separated and the aqueous phase was extracted with Et_2O (10 mL). The combined organic fractions were washed with brine (15 mL) and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude 1-allylisochroman product, which was purified by flash column chromatography.

Method B: Asymmetric allylation

The phosphoramide catalyst (*R*)-**45g** (0.049, 0.074 or 0.098 mmol (see specific experimental details)) was added to a solution of the 1-ethoxyisochroman (0.490 mmol) and allyltrimethylsilane (117 μL, 0.735 mmol) in *o*-xylene (327 or 490 μL (see specific experimental details)). After stirring at R.T. for the specified time, $NaHCO_3$ solution (15 mL) and Et_2O (15 mL) were added. The two phases were separated and the aqueous phase was extracted with Et_2O (10 mL). The combined organic fractions were washed with brine (15 mL) and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude 1-allylisochroman product, which was purified by flash column chromatography.

1-Allylisochroman 163[208]



Chemical Formula: $C_{12}H_{14}O$
Exact Mass: 174.1045
Molecular Weight: 174.239
Elemental Analysis: C, 82.72; H, 8.10; O, 9.18

Racemic 1-allylisochroman **163** was prepared from 1-ethoxyisochroman **166** (87 mg, 0.49 mmol), allyltrimethylsilane (120 μL, 0.74 mmol) and $MeSO_3H$ (32 μL, 0.49 mmol) in CH_2Cl_2 (1 mL) according to Method A. Purification by flash column chromatography (99% hexane, 1% Et_2O) afforded 1-allylisochroman **163** as a colourless liquid (80 mg, 94%): R_f = 0.37 (90% hexane, 10% Et_2O); ν_{max}(film)/cm^{-1} 3077w, 3024w, 2965w, 2926m, 2852m, 1641w, 1492m, 1453m, 1428m, 1375w, 1340w, 1280m, 1105s, 1038m, 987m, 910s, 852w, 742s; δ_H(300 MHz) 2.53-2.82 (3H, stack, CH_2CH=CH_2, C$H_a$$H_b$$CH_2O$), 3.03 (1H, ddd, *J* 15.7, 9.7, 5.4, $CH_a$$H_b$$CH_2O$), 3.80 (1H, ddd, *J* 11.3, 9.7, 3.7, CH_2C$H_a$$H_b$O), 4.19 (1H, ddd, *J* 11.3, 5.4, 3.6, $CH_2CH_a$$H_b$O), 4.87 (1H, dd, *J* 7.4, 2.9, C*H*O), 5.05-5.23 (2H, stack, CH=CH_2), 5.94 (1H, ddt, *J* 17.1, 10.2, 6.8, C*H*=CH_2), 7.03-7.28 (4H, stack, Ar*H*); δ_C(75 MHz) 29.0 (CH_2, *C*H_2CH_2O), 40.3 (CH_2, CH_2CH=CH_2), 63.3 (CH_2, CH_2*C*H_2O), 75.5 (CH, *C*HO), 116.9 (CH_2, CH_2CH=*C*H_2), 124.8 (CH, Ar), 126.0 (CH, Ar), 126.2 (CH, Ar), 128.8 (CH, Ar), 134.0 (quat. C, *ipso* Ar), 135.0 (CH, CH_2*C*H=CH_2), 137.7 (quat. C, *ipso* Ar); m/*z* (EI) 133 ([M – C_3H_5]$^+$, 100%), 115 (24), 105 (49), 91 (14), 77 (31), 55 (11); HRMS: C_9H_9O calcd 133.0653 ([M – C_3H_5]$^+$), obsd 133.0651.

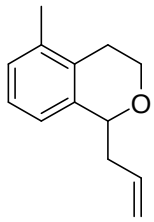
Asymmetric allylation:

Enantiomerically enriched 1-allylisochroman **163** was prepared from 1-ethoxyisochroman **166** (87 mg, 0.49 mmol), allyltrimethylsilane (120 μL, 0.74 mmol) and the phosphoramide catalyst (*R*)-**45g** (48.5 mg, 0.049 mmol) in *o*-xylene (327 μL) according to Method B. After

stirring for 24 h and work-up, purification by flash column chromatography (99% hexane, 1% Et_2O) afforded enantiomerically enriched 1-allylisochroman **163** (70 mg, 82%): $[\alpha]_D^{20}$ = +88.1 (*c* 0.74, $CHCl_3$, e.r. 10:90); Chiralpak AD, 1.0 mL/min, 100% hexane, λ = 210 nm, $t_{R,minor}$ = 11.5 min, $t_{R,major}$ = 12.6 min.

Data were in agreement with those reported in the literature.[208]

1-Allyl-5-methylisochroman 202a



Chemical Formula: $C_{13}H_{16}O$
Exact Mass: 188.1201
Molecular Weight: 188.2655
Elemental Analysis: C, 82.94; H, 8.57; O, 8.50

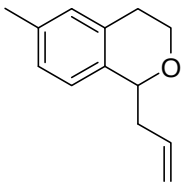
Racemic 1-allylisochroman **202a** was prepared from 1-ethoxyisochroman **179a** (94 mg, 0.49 mmol), allyltrimethylsilane (120 μL, 0.73 mmol) and $MeSO_3H$ (32 μL, 0.49 mmol) in CH_2Cl_2 (1 mL) according to Method A. Purification by flash column chromatography (99% hexane, 1% Et_2O) afforded 1-allylisochroman **202a** as a colourless liquid (88 mg, 95%): R_f = 0.39 (90% hexane, 10% Et_2O); (Found: C, 82.90; H, 8.50. $C_{13}H_{16}O$ requires C, 82.94; H, 8.57%); ν_{max}(film)/cm^{-1} 3074w, 2918m, 2854m, 1640w, 1469m, 1432w, 1379w, 1330w, 1263w, 1113s, 1088m, 1057m, 991m, 911s, 804w, 778s, 751m, 738m, 705w; δ_H(300 MHz) 2.26 (3H, s, CH_3), 2.54-2.90 (4H, stack, CH_2CH=CH_2, C$H_2$$CH_2$O), 3.82 (1H, ddd, *J* 11.4, 9.5, 4.2, $CH_2CH_aH_bO$), 4.23 (1H, ddd, *J* 11.4, 5.6, 3.6, $CH_2CH_aH_bO$), 4.86 (1H, dd, *J* 8.1, 3.6, C*H*O), 5.08-5.22 (2H, stack, CH=CH_2), 5.94 (1H, ddt, *J* 17.1, 10.3, 6.8, C*H*=CH_2), 6.99 (1H, d, *J* 7.6, Ar*H*), 7.04-7.17 (2H, stack, Ar*H*); δ_C(75 MHz) 19.0 (CH_3, *C*H_3), 26.6 (CH_2, *C*H_2CH_2O), 40.3

(CH_2, C*H*$_2$CH=CH_2), 63.1 (CH_2, *C*H_2O), 75.7 (CH, *C*HO), 116.8 (CH_2, CH=*C*H_2), 122.4 (CH, Ar), 125.6 (CH, Ar), 127.6 (CH, Ar), 132.6 (quat. C, *ipso* Ar), 135.1 (CH, *C*H=CH_2), 136.2 (quat. C, *ipso* Ar), 137.6 (quat. C, *ipso* Ar); m/*z* (EI) 188 ($[M]^+$, 3%), 147 (100, $[M - C_3H_5]^+$), 132 (16, $[M - C_3H_5 - CH_3]^+$), 129 (48), 119 (66), 117 (50), 115 (53), 105 (65), 91 (62), 77 (18), 65 (10); HRMS: $C_{13}H_{16}O$ calcd 188.1201 ($[M]^+$), obsd 188.1205.

Asymmetric allylation:

Enantiomerically enriched 1-allylisochroman **202a** was prepared from 1-ethoxyisochroman **179a** (77 mg, 0.40 mmol), allyltrimethylsilane (95 μL, 0.60 mmol) and the phosphoramide catalyst (*R*)-**45g** (39.6 mg, 0.040 mmol) in *o*-xylene (267 μL) according to Method B. After stirring for 7 h and work-up, purification by flash column chromatography (99% hexane, 1% Et_2O) afforded enantiomerically enriched 1-allylisochroman **202a** (63 mg, 84%): $[\alpha]_D^{20}$ = +93.9 (*c* 1.15, $CHCl_3$, e.r. 8:92); Chiralpak AD, 1.0 mL/min, 100% hexane, λ = 210 nm, $t_{R,minor}$ = 11.9 min, $t_{R,major}$ = 16.5 min.

1-Allyl-6-methylisochroman 202b



Chemical Formula: $C_{13}H_{16}O$
Exact Mass: 188.1201
Molecular Weight: 188.2655
Elemental Analysis: C, 82.94; H, 8.57; O, 8.50

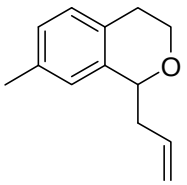
Racemic 1-allylisochroman **202b** was prepared from 1-ethoxyisochroman **179b** (100 mg, 0.52 mmol), allyltrimethylsilane (125 μL, 0.78 mmol) and $MeSO_3H$ (34 μL, 0.52 mmol) in CH_2Cl_2 (1 mL) according to Method A. Purification by flash column chromatography (99% hexane, 1% Et_2O) afforded 1-allylisochroman **202b** as a colourless oil (93 mg, 95%): R_f = 0.43 (90%

hexane, 10% Et_2O); (Found: C, 82.61; H, 8.91. $C_{13}H_{16}O$ requires C, 82.94; H, 8.57%); ν_{max}(film)/cm^{-1} 3072w, 2920m, 2850m, 1641w, 1617w, 1503m, 1428m, 1376m, 1331m, 1283m, 1251w, 1105s, 1063m, 987m, 908s, 872w, 847w, 815s, 778m, 713w; δ_H(300 MHz) 2.35 (3H, s, CH_3), 2.54-2.81 (3H, stack, CH_2CH=CH_2, C$H_a$$H_b$$CH_2O$), 3.01 (1H, ddd, *J* 16.0, 9.8, 5.4, $CH_a$$H_b$$CH_2O$), 3.80 (1H, ddd, *J* 11.3, 9.8, 3.8, CH_2C$H_a$$H_b$O), 4.19 (1H, ddd, *J* 11.3, 5.4, 3.4, $CH_2CH_a$$H_b$O), 4.85 (1H, dd, *J* 7.9, 3.4, C*H*O), 5.09-5.24 (2H, stack, CH=CH_2), 5.96 (1H, ddt, *J* 17.1, 10.3, 6.8, CH_2C*H*=CH_2), 6.95-7.06 (3H, stack, Ar*H*); δ_C(100 MHz) 20.9 (CH_3, *C*H_3), 29.0 (CH_2, *C*H_2CH_2O), 40.3 (CH_2, CH_2CH=CH_2), 63.4 (CH_2, *C*H_2O), 75.4 (CH, *C*HO), 116.8 (CH_2, CH=*C*H_2), 124.6 (CH, Ar), 126.8 (CH, Ar), 129.4 (CH, Ar), 133.8 (quat. C, *ipso* Ar), 134.7 (quat. C, *ipso* Ar), 135.1 (CH, *C*H=CH_2), 135.7 (quat. C, *ipso* Ar); m/*z* (EI) 188 ($[M]^+$, 2%), 147 (100, $[M - C_3H_5]^+$), 129 (11), 119 (19), 117 (17), 115 (13), 91 (21); HRMS: $C_{13}H_{16}O$ calcd 188.1201 ($[M]^+$), obsd 188.1204.

Asymmetric allylation:

Enantiomerically enriched 1-allylisochroman **202b** was prepared from 1-ethoxyisochroman **179b** (77 mg, 0.40 mmol), allyltrimethylsilane (95 μL, 0.60 mmol) and the phosphoramide catalyst (*R*)-**45g** (59.4 mg, 0.060 mmol) in *o*-xylene (400 μL) according to Method B. After stirring for 6 h and work-up, purification by flash column chromatography (99% hexane, 1% Et_2O) afforded enantiomerically enriched 1-allylisochroman **202b** (60 mg, 79%): $[\alpha]_D^{20}$ = +98.1 (*c* 1.04, $CHCl_3$, e.r. 13:87); Chiralcel OD, 1.0 mL/min, 100% hexane, λ = 210 nm, $t_{R,minor}$ = 12.9 min, $t_{R,major}$ = 14.9 min.

1-Allyl-7-methylisochroman 202c



Chemical Formula: $C_{13}H_{16}O$
Exact Mass: 188.1201
Molecular Weight: 188.2655
Elemental Analysis: C, 82.94; H, 8.57; O, 8.50

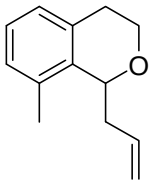
Racemic 1-allylisochroman **202c** was prepared from 1-ethoxyisochroman **179c** (100 mg, 0.52 mmol), allyltrimethylsilane (125 μL, 0.78 mmol) and $MeSO_3H$ (34 μL, 0.52 mmol) in CH_2Cl_2 (1 mL) according to Method A. Purification by flash column chromatography (99% hexane, 1% Et_2O) afforded 1-allylisochroman **202c** as a yellow oil (89 mg, 91%): R_f = 0.35 (90% hexane, 10% Et_2O); ν_{max}(film)/cm^{-1} 3076w, 2922m, 2855m, 1728w, 1641w, 1504m, 1429m, 1373w, 1327w, 1277w, 1250w, 1155w, 1105s, 1041m, 988m, 911s, 877m, 810s, 713w, 666w; δ_H(300 MHz) 2.35 (3H, s, CH_3), 2.54-2.81 (3H, stack, CH_2CH=CH_2, C$H_a$$H_b$$CH_2$O), 2.98 (1H, ddd, *J* 15.7, 9.6, 5.3, $CH_a$$H_b$$CH_2$O), 3.78 (1H, ddd, *J* 11.2, 9.7, 3.8, CH_2C$H_a$$H_b$O), 4.18 (1H, ddd, *J* 11.2, 5.3, 3.5, $CH_2CH_a$$H_b$O), 4.83 (1H, dd, *J* 8.2, 3.5, C*H*O), 5.09-5.24 (2H, stack, CH=CH_2), 5.96 (1H, ddt, *J* 17.1, 10.3, 6.8, C*H*=CH_2), 6.92-7.07 (3H, stack, Ar*H*); δ_C(100 MHz) 21.3 (CH_3, *C*H_3), 28.7 (CH_2, *C*H_2CH_2O), 40.4 (CH_2, CH_2CH=CH_2), 63.5 (CH_2, *C*H_2O), 75.6 (CH, *C*HO), 116.9 (CH_2, CH=*C*H_2), 125.3 (CH, Ar), 127.2 (CH, Ar), 128.8 (CH, Ar), 131.0 (quat. C, *ipso* Ar), 135.2 (CH, *C*H=CH_2), 135.6 (quat. C, *ipso* Ar), 137.6 (quat. C, *ipso* Ar); m/*z* (EI) 188 ($[M]^+$, 1%), 147 (100, $[M - C_3H_5]^+$), 119 (13), 117 (10), 91 (12); HRMS: $C_{13}H_{16}O$ calcd 188.1201 ($[M]^+$), obsd 188.1191.

Asymmetric allylation:

Enantiomerically enriched 1-allylisochroman **202c** was prepared from 1-ethoxyisochroman **179c** (77 mg, 0.40 mmol), allyltrimethylsilane (95 μL, 0.60 mmol) and the phosphoramide catalyst (*R*)-**45g** (59.4 mg, 0.060 mmol) in *o*-xylene (267 μL) according to Method B. After

stirring for 8 h and work-up, purification by flash column chromatography (99% hexane, 1% Et_2O) afforded enantiomerically enriched 1-allylisochroman **202c** (53 mg, 71%): $[\alpha]_D^{20}$ = +120.0 (*c* 0.98, $CHCl_3$, e.r. 13:87); Chiralpak AD, 1.0 mL/min, 100% hexane, λ = 210 nm, $t_{R,minor}$ = 10.3 min, $t_{R,major}$ = 12.4 min.

1-Allyl-8-methylisochroman 202d



Chemical Formula: $C_{13}H_{16}O$
Exact Mass: 188.1201
Molecular Weight: 188.2655
Elemental Analysis: C, 82.94; H, 8.57; O, 8.50

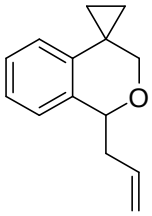
Racemic 1-allylisochroman **202d** was prepared from 1-ethoxyisochroman **179d** (100 mg, 0.52 mmol), allyltrimethylsilane (125 μL, 0.78 mmol) and $MeSO_3H$ (34 μL, 0.52 mmol) in CH_2Cl_2 (1 mL) according to Method A. Purification by flash column chromatography (99% hexane, 1% Et_2O) afforded 1-allylisochroman **202d** as a colourless oil (56 mg, 57%): R_f = 0.40 (90% hexane, 10% Et_2O); (Found: C, 82.68; H, 8.40. $C_{13}H_{16}O$ requires C, 82.94; H, 8.57%); ν_{max}(film)/cm^{-1} 3071w, 2920m, 2849m, 1639m, 1590w, 1464m, 1430m, 1374w, 1338w, 1267m, 1222w, 1194w, 1103s, 1080m, 1062m, 1029m, 999m, 910s, 850w, 768s, 736w, 711w; δ_H(300 MHz) 2.27 (3H, s, CH_3), 2.42-2.99 (4H, stack, CH_2CH=CH_2, C$H_2$$CH_2$O), 3.82 (1H, app. dt, *J* 11.3, 5.1, $CH_2CH_aH_bO$), 4.11 (1H, ddd, *J* 11.3, 8.1, 4.6, $CH_2CH_aH_bO$), 4.97 (1H, dd, *J* 9.3, 2.3, C*H*O), 5.09-5.22 (2H, stack, CH=CH_2), 5.99 (1H, ddt, *J* 17.1, 10.2, 6.9, C*H*=CH_2), 6.94-7.16 (3H, stack, Ar*H*); δ_C(100 MHz) 19.0 (CH_3, *C*H_3), 29.0 (CH_2, *C*$H_2$$CH_2$O), 38.0 ($CH_2$, C$H_2$CH=$CH_2$), 59.5 ($CH_2$, *C*$H_2$O), 73.3 (CH, *C*HO), 116.5 (CH_2, CH=*C*H_2), 126.2 (CH, Ar), 126.6 (CH, Ar), 128.5 (CH, Ar), 133.5 (quat. C, *ipso* Ar), 133.7

(quat. C, *ipso* Ar), 135.3 (CH, *C*H=CH_2), 136.2 (quat. C, *ipso* Ar); m/*z* (EI) 188 ($[M]^+$, 1%), 147 (100, $[M - C_3H_5]^+$); HRMS: $C_{13}H_{16}O$ calcd 188.1201 ($[M]^+$), obsd 188.1195.

Asymmetric allylation:

Enantiomerically enriched 1-allylisochroman **202d** was prepared from 1-ethoxyisochroman **179d** (67 mg, 0.35 mmol), allyltrimethylsilane (85 μL, 0.53 mmol) and the phosphoramide catalyst (*R*)-**45g** (69.3 mg, 0.070 mmol) in *o*-xylene (233 μL) according to Method B. After stirring for 48 h and work-up, purification by careful[5] column chromatography (99% hexane, 1% Et_2O) afforded enantiomerically enriched 1-allylisochroman **202d** (34 mg, 52%): $[\alpha]_D^{20}$ = +53.0 (*c* 0.37, $CHCl_3$, e.r. 21:79); Chiralcel OD, 1.0 mL/min, 100% hexane, λ = 210 nm, $t_{R,\text{minor}}$ = 12.8 min, $t_{R,\text{major}}$ = 15.2 min.

Spiro[1-allylisochroman-4,1'-cyclopropane] 202j



Chemical Formula: $C_{14}H_{16}O$
Exact Mass: 200.1201
Molecular Weight: 200.2762
Elemental Analysis: C, 83.96; H, 8.05; O, 7.99

Racemic 1-allylisochroman **202j** was prepared from 1-ethoxyisochroman **179j** (100 mg, 0.49 mmol), allyltrimethylsilane (120 μL, 0.73 mmol) and $MeSO_3H$ (32 μL, 0.49 mmol) in CH_2Cl_2 (0.95 mL) according to Method A. Purification by flash column chromatography (99% hexane, 1% Et_2O) afforded 1-allylisochroman **202j** as a colourless oil (92 mg, 94%): R_f = 0.34 (90% hexane, 10% Et_2O); ν_{max}(film)/cm^{-1} 3075w, 2948w, 2843m, 1641w, 1605w, 1492m,

[5] in total, two long columns were carried out to obtain a pure product

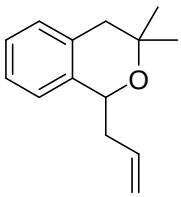
1454w, 1430m, 1379m, 1336w, 1254m, 1146w, 1093s, 1033m, 997m, 910s, 856w, 830m, 751s, 712m; δ_H(300 MHz) 0.84 (1H, ddd, *J* 9.4, 6.0, 4.4, cyclopropylCH_aH$_b$), 0.94-1.14 (3H, stack, cyclopropylCH$_a$$H_bCH_2$), 2.64-2.84 (2H, stack, CH_2CH=CH$_2$), 3.62 (1H, d, *J* 11.5, CH_aH$_b$O), 3.85 (1H, dd, *J* 11.5, 1.1, CH$_a$$H_b$O), 4.98 (1H, dd, *J* 8.2, 3.9, C*H*O), 5.09-5.24 (2H, stack, CH=CH_2), 5.98 (1H, ddt, *J* 17.1, 10.3, 6.8, C*H*=CH$_2$), 6.71-6.78 (1H, m, Ar*H*), 7.08-7.22 (3H, stack, Ar*H*); δ_C(100 MHz) [13.4, 17.8 (CH$_2$, cyclopropyl*C*H$_2$)], 18.9 (quat. C, *C*CH$_2$O), 40.0 (CH$_2$, CH_2CH=CH$_2$), 71.4 (CH$_2$, *C*H$_2$O), 76.6 (CH, *C*HO), 116.9 (CH$_2$, CH=*C*H$_2$), 121.3 (CH, Ar), 124.4 (CH, Ar), 125.1 (CH, Ar), 126.8 (CH, Ar), 135.1 (CH, *C*H=CH$_2$), 137.7 (quat. C, *ipso* Ar), 138.7 (quat. C, *ipso* Ar); m/*z* (EI) 159 ([M – C_3H_5]$^+$, 100%), 131 (25), 129 (25), 115 (19), 103 (17), 91 (16), 77 (11); HRMS: $C_{11}H_{11}O$ calcd 159.0810 ([M – C_3H_5]$^+$), obsd 159.0801.

Asymmetric allylation:

Enantiomerically enriched 1-allylisochroman **202j** was prepared from 1-ethoxyisochroman **179j** (82 mg, 0.40 mmol), allyltrimethylsilane (95 μL, 0.60 mmol) and the phosphoramide catalyst (*R*)-**45g** (79.2 mg, 0.080 mmol) in *o*-xylene (267 μL) according to Method B. After stirring for 8 h and work-up, purification by careful[6] column chromatography (99% hexane, 1% Et$_2$O) afforded enantiomerically enriched 1-allylisochroman **202j** (35 mg, 44%): $[\alpha]_D^{20}$ = +5.1 (*c* 0.35, $CHCl_3$, e.r. 43:57); Chiralpak AD, 1.0 mL/min, 1% IPA in hexane, λ = 210 nm, $t_{R,minor}$ = 5.9 min, $t_{R,major}$ = 7.4 min.

[6] in total, two long columns were carried out to obtain a pure product

1-Allyl-3,3-dimethylisochroman 202i



Chemical Formula: $C_{14}H_{18}O$
Exact Mass: 202.1358
Molecular Weight: 202.2921
Elemental Analysis: C, 83.12; H, 8.97; O, 7.91

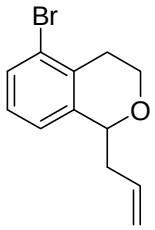
Racemic 1-allylisochroman **202i** was prepared from 1-ethoxyisochroman **179i** (100 mg, 0.485 mmol), allyltrimethylsilane (120 μL, 0.73 mmol) and methanesulfonic acid (31 μL, 0.485 mmol) in CH_2Cl_2 (0.95 mL) according to Method A. Purification by flash column chromatography (gradient: 100% hexane → 99% hexane, 1% Et_2O) afforded 1-allylisochroman **202i** as a colourless oil (86 mg, 88%): R_f = 0.40 (95% hexane, 5% Et_2O); ν_{max}(film)/cm^{-1} 3073w, 2973m, 2900w, 1493w, 1453w, 1431w, 1380m, 1367m, 1337m, 1255w, 1234w, 1206w, 1180m, 1110m, 1069s, 1040m, 992m, 910s, 801w, 739s, 712w; δ_H(300 MHz) 1.17 (3H, s, CH_3), 1.38 (3H, s, CH_3), 2.53 (1H, d, *J* 15.7, CH_aH$_b$), 2.53-2.65 (1H, m, CH_aH$_b$CH=CH$_2$), 2.68-2.79 (1H, m, CH$_a$$H_b$CH=CH$_2$), 2.88 (1H, d, *J* 15.7, CH$_a$$H_b$), 4.83-4.90 (1H, m, C*H*O), 5.00-5.15 (2H, stack, CH=CH_2), 5.88 (1H, ddt, *J* 17.2, 10.3, 6.8, C*H*=CH$_2$), 7.04-7.24 (4H, stack, Ar*H*); δ_C(100 MHz) [23.3, 30.1 (CH$_3$, C(*C*H$_3$)$_a$(*C*H$_3$)$_b$], [40.5, 40.7 (CH$_2$, *C*H$_2$CO, CH_2CH=CH$_2$)], 70.8 (quat. C, CH$_2$*C*O), 71.2 (CH, *C*HO), 116.6 (CH$_2$, CH=*C*H$_2$), 124.3 (CH, Ar), 125.9 (CH, Ar), 126.2 (CH, Ar), 128.9 (CH, Ar), 133.8 (quat. C, *ipso* Ar), 135.0 (CH, *C*H=CH$_2$), 137.0 (quat. C, *ipso* Ar); m/*z* (EI) 161 ([M – C_3H_5]$^+$, 100%), 143 (85), 128 (10); HRMS: $C_{11}H_{13}O$ calcd 161.0966 ([M – C_3H_5]$^+$), obsd 161.0969.

Asymmetric allylation:

Enantiomerically enriched 1-allylisochroman **202i** was prepared from 1-ethoxyisochroman **179i** (82.5 mg, 0.400 mmol), allyltrimethylsilane (95 μL, 0.60 mmol) and the phosphoramide

catalyst (*R*)-**45g** (79.2 mg, 0.080 mmol) in *o*-xylene (267 μL) according to Method B. After stirring for 24 h and work-up, purification by flash column chromatography (99% hexane, 1% Et_2O) afforded enantiomerically enriched 1-allylisochroman **202i** (54 mg, 67%): $[\alpha]_D^{21}$ = – 10.0 (*c* 0.96, $CHCl_3$, e.r. 43:57); Chiralcel OD, 1.0 mL/min, 100% hexane, λ = 210 nm, $t_{R,\text{minor}}$ = 7.3 min, $t_{R,\text{major}}$ = 9.1 min.

1-Allyl-5-bromoisochroman 202e



Chemical Formula: $C_{12}H_{13}BrO$
Exact Mass: 252.015
Molecular Weight: 253.135
Elemental Analysis: C, 56.94; H, 5.18; Br, 31.57; O, 6.32

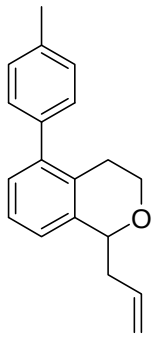
Racemic 1-allylisochroman **202e** was prepared from 1-ethoxyisochroman **179e** (100 mg, 0.39 mmol), allyltrimethylsilane (95 μL, 0.58 mmol) and $MeSO_3H$ (25 μL, 0.39 mmol) in CH_2Cl_2 (0.75 mL) according to Method A. Purification by flash column chromatography (gradient: 100% hexane → 99% hexane, 1% Et_2O) afforded 1-allylisochroman **202e** as a colourless oil (61 mg, 62%): R_f = 0.45 (90% hexane, 10% Et_2O); ν_{max}(film)/cm^{-1} 2933m, 2858m, 1640w, 1563m, 1461m, 1439s, 1377w, 1329m, 1255w, 1177w, 1113s, 1076m, 988s, 913s, 861w, 813w, 771s, 744m, 717m, 675m; δ_H(300 MHz) 2.51-2.95 (4H, stack, C*H*$_2$CH=CH_2, C*H*$_2$$CH_2$O), 3.77 (1H, ddd, *J* 11.5, 9.2, 4.4, C*H*$_a$$H_b$O), 4.19 (1H, ddd, *J* 11.5, 5.6, 3.8, CH_aH_bO), 4.80 (1H, dd, *J* 7.9, 3.8, C*H*O), 5.06-5.19 (2H, stack, CH=C*H*$_2$), 5.88 (1H, ddt, *J* 17.1, 10.3, 6.8, C*H*=CH_2), 7.02-7.11 (2H, stack, Ar*H*), 7.40-7.48 (1H, m, Ar*H*); δ_C(100 MHz) 29.8 (CH_2, *C*$H_2$$CH_2$O), 40.1 ($CH_2$, C*H*$_2$CH=$CH_2$), 63.1 ($CH_2$, *C*$H_2$O), 75.3 (CH, *C*HO), 117.2 (CH_2, CH=*C*H_2), 123.9 (CH, Ar), 125.3 (quat. C, *ipso* Ar), 127.2 (CH, Ar), 130.3 (CH, Ar),

133.9 (quat. C, *ipso* Ar), 134.5 (CH, *C*H=CH_2), 140.4 (quat. C, *ipso* Ar); m/*z* (EI) 213 ([M – C_3H_5]$^+$, 100%), 211 (10, [M – C_3H_5]$^+$), 132 (41), 104 (17), 103 (17), 77 (11); HRMS: $C_9H_8O^{79}Br$ calcd 210.9759 ([M – C_3H_5]$^+$), obsd 210.9764.

Asymmetric allylation:

Enantiomerically enriched 1-allylisochroman **202e** was prepared from 1-ethoxyisochroman **179e** (77 mg, 0.30 mmol), allyltrimethylsilane (70 μL, 0.45 mmol) and the phosphoramide catalyst (*R*)-**45g** (59.4 mg, 0.060 mmol) in *o*-xylene (200 μL) according to Method B. After stirring for 48 h and work-up, purification by careful[7] column chromatography (99% hexane, 1% Et_2O) afforded enantiomerically enriched 1-allylisochroman **202e** (34 mg, 45%): $[\alpha]_D^{20}$ = +53.8 (*c* 0.74, $CHCl_3$, e.r. 17:83); Chiralcel OD, 1.0 mL/min, 1% IPA in hexane, λ = 210 nm, $t_{R,\text{minor}}$ = 5.4 min, $t_{R,\text{major}}$ = 6.0 min.

1-Allyl-5-tolylisochroman 211



Chemical Formula: $C_{19}H_{20}O$
Exact Mass: 264.1514
Molecular Weight: 264.3615
Elemental Analysis: C, 86.32; H, 7.63; O, 6.05

Racemic 1-allyl-5-bromoisochroman **202e** (150 mg, 0.593 mmol), 4-tolylboronic acid (161 mg, 1.19 mmol) and Na_2CO_3 (530 mg, 5.00 mmol) were dissolved in a mixture of degassed toluene/EtOH/H_2O (2:1:1, 10 mL). $Pd(PPh_3)_4$ (68 mg, 0.059 mmol) was added, and the

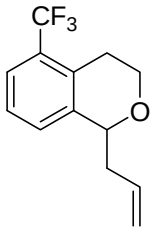
[7] in total, two long columns were carried out to obtain a pure product

mixture was heated under reflux for 3 h. The black suspension was cooled to R.T., the solvents were removed under reduced pressure and the resulting solid was dissolved in CH_2Cl_2 (20 mL). H_2O (20 mL) was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (10 mL). The combined organic fractions were washed with brine (20 mL), and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product. Purification by flash column chromatography (99.5% hexane, 0.5% Et_2O) afforded 1-allyl-5-tolylisochroman **211** as a colourless oil (152 mg, 97%): R_f = 0.31 (90% hexane, 10% Et_2O); ν_{max}(film)/cm^{-1} 2927m, 2855m, 1643w, 1515m, 1463m, 1377w, 1338w, 1110s, 990m, 911s, 822s, 790s, 736s; δ_H(300 MHz) 2.32 (3H, s, CH_3), 2.43 (1H, app. dt, *J* 16.6, 3.4, C*H*$_a$H$_b$CH$_2$O), 2.49-2.74 (2H, stack, C*H*$_2$CH=CH$_2$), 2.82 (1H, ddd, *J* 16.6, 9.6, 5.3, CH$_a$*H*$_b$CH$_2$O), 3.58 (1H, ddd, *J* 11.2, 9.6, 3.5, C*H*$_a$H$_b$O), 3.98 (1H, ddd, *J* 11.2, 5.3, 3.6, CH$_a$*H*$_b$O), 4.83 (1H, dd, *J* 7.9, 3.3, C*H*O), 5.00-5.17 (2H, stack, CH=C*H*$_2$), 5.88 (1H, ddt, *J* 17.1, 10.2, 6.8, C*H*=CH$_2$), 7.00-7.09 (2H, stack, Ar*H*), 7.10-7.22 (5H, stack, Ar*H*); δ_C(100 MHz) 21.1 (CH_3, ArCH_3), 28.3 (CH_2, *C*H$_2$CH$_2$O), 40.9 (CH_2, C*H*$_2$CH=CH$_2$), 63.4 (CH_2, *C*H$_2$O), 75.8 (CH, *C*HO), 117.0 (CH_2, CH=*C*H$_2$), 123.9 (CH, Ar), 125.8 (CH, Ar), 127.7 (CH, Ar), 128.8 (CH, Ar), 129.1 (CH, Ar), 132.0 (quat. C, *ipso* Ar), 135.1 (CH, *C*H=CH$_2$), 136.7 (quat. C, 2 × *ipso* Ar), 138.0 (quat. C, *ipso* Ar), 141.8 (quat. C, *ipso* Ar); m/*z* (EI) 223 ([M – C_3H_5]$^+$, 100%), 195 (40), 180 (29), 179 (25), 178 (27), 167 (24), 165 (34); HRMS: $C_{19}H_{20}O$ calcd 264.1514 ([M]$^+$), obsd 264.1526.

The same protocol was followed for the preparation of enantiomerically enriched 1-allyl-5-tolylisochroman **211** from enantiomerically enriched 1-allyl-5-bromoisochroman **202e** (17.0 mg, 0.067 mmol, e.r. 17:83), 4-tolylboronic acid (18 mg, 0.134 mmol), Na_2CO_3 (60 mg, 0.565 mmol) and $Pd(PPh_3)_4$ (7.7 mg, 0.007 mmol) in degassed toluene/EtOH/H_2O (2:1:1, 1.13 mL). Purification by flash column chromatography (99.5% hexane, 0.5% Et_2O) afforded enantiomerically enriched 1-allylisochroman **211** (16.0 mg, 90%): $[\alpha]_D^{20}$ = +22.6 (*c* 0.46,

$CHCl_3$, e.r. 17:83); Lux 5u Cellulose-2, 3 mL/min, 0.5% IPA in hexane, λ = 254 nm, $t_{R,major}$ = 8.9 min, $t_{R,major}$ = 10.4 min.

1-Allyl-5-trifluoromethylisochroman 202f



Chemical Formula: $C_{13}H_{13}F_3O$
Exact Mass: 242.0918
Molecular Weight: 242.2369
Elemental Analysis: C, 64.46; H, 5.41; F, 23.53; O, 6.60

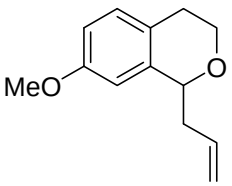
Racemic 1-allylisochroman **202f** was prepared from 1-ethoxyisochroman **179f** (100 mg, 0.41 mmol), allyltrimethylsilane (100 μL, 0.61 mmol) and $MeSO_3H$ (25 μL, 0.41 mmol) in CH_2Cl_2 (0.80 mL) according to Method A. Purification by flash column chromatography (gradient: 100% hexane → 99.5% hexane, 0.5% Et_2O) afforded 1-allylisochroman **202f** as a colourless oil (77 mg, 78%): R_f = 0.46 (90% hexane, 10% Et_2O); ν_{max}(film)/cm^{-1} 3070w, 2969w, 2860w, 1469w, 1458w, 1429w, 1316s, 1261w, 1183w, 1156s, 1112s, 1078s, 1046m, 995m, 969w, 914m, 801m, 755m, 742m, 727m, 675m; δ_H(300 MHz) 2.54-2.78 (2H, stack, CH_2CH=CH_2), 2.85-2.98 (1H, m, C$H_a$$H_b$$CH_2$O), 3.00-3.14 (1H, m, $CH_a$$H_b$$CH_2$O), 3.77 (1H, ddd, *J* 11.5, 9.4, 3.9, C$H_a$$H_b$O), 4.17 (1H, ddd, *J* 11.5, 5.3, 3.9, $CH_a$$H_b$O), 4.89 (1H, dd, *J* 7.7, 3.9, C*H*O), 5.06-5.19 (2H, stack, CH=CH_2), 5.88 (1H, ddt, *J* 17.1, 10.3, 6.8, C*H*=CH_2), 7.22-7.33 (2H, stack, Ar*H*), 7.48-7.56 (1H, m, Ar*H*); δ_C(100 MHz) 25.9 (CH_2, *C*$H_2$$CH_2$O), 40.5 ($CH_2$, C$H_2$CH=$CH_2$), 62.5 ($CH_2$, *C*$H_2$O), 75.4 (CH, *C*HO), 117.3 (CH_2, CH=*C*H_2), 124.0 (CH, q, $^3J_{C-F}$ 5.5, Ar), 124.4 (quat. C, q, $^1J_{C-F}$ 272.6, Ar*C*F_3), 125.7 (CH, Ar), 128.5 (quat. C, *ipso* Ar), 128.7 (CH, Ar), 133.1 (quat. C, *ipso* Ar), 134.4 (CH, *C*H=CH_2), 139.3 (quat. C, *ipso* Ar);

δ_F(282 MHz) –61.2 (s, ArC*F*$_3$); m/*z* (EI) 201 ([M – C_3H_5]$^+$, 100%), 181 (16), 153 (10), 151 (10), 133 (15); HRMS: $C_{10}H_8OF_3$ calcd 201.0527 ([M – C_3H_5]$^+$), obsd 201.0523.

Asymmetric allylation:

Enantiomerically enriched 1-allylisochroman **202f** was prepared from 1-ethoxyisochroman **179f** (98.5 mg, 0.40 mmol), allyltrimethylsilane (95 μL, 0.60 mmol) and the phosphoramide catalyst (*R*)-**45g** (59.4 mg, 0.060 mmol) in *o*-xylene (267 μL) according to Method B. After stirring for 48 h and work-up, purification by careful[8] column chromatography (99% hexane, 1% Et_2O) afforded enantiomerically enriched 1-allylisochroman **202f** (23 mg, 24%): $[\alpha]_D^{20}$ = +43.8 (*c* 0.78, $CHCl_3$, e.r. 88:12); Lux 5u Cellulose-2, 3 mL/min, 0.5% IPA in hexane, λ = 250 nm, $t_{R,major}$ = 6.0 min, $t_{R,minor}$ = 7.2 min.

1-Allyl-7-methoxyisochroman 202g



Chemical Formula: $C_{13}H_{16}O_2$
Exact Mass: 204.115
Molecular Weight: 204.2649
Elemental Analysis: C, 76.44; H, 7.90; O, 15.67

Racemic 1-allylisochroman **202g** was prepared from 1-ethoxyisochroman **179g** (70 mg, 0.34 mmol), allyltrimethylsilane (80 μL, 0.50 mmol) and $MeSO_3H$ (22 μL, 0.34 mmol) in CH_2Cl_2 (0.65 mL) according to Method A. Purification by flash column chromatography (gradient: 99% hexane, 1% Et_2O → 90% hexane, 10% Et_2O) afforded 1-allylisochroman **202g** as a colourless oil (50 mg, 72%): R_f = 0.23 (90% hexane, 10% Et_2O); ν_{max}(film)/cm^{-1} 3075w, 2919w, 2835w, 1612m, 1502s, 1464m, 1428m, 1314m, 1281s, 1255s, 1207m, 1161w, 1107s,

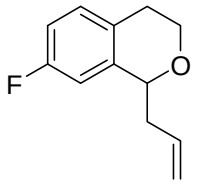
[8] in total, two long columns were carried out to obtain a pure product

1037s, 989m, 912m, 866w, 848w, 804m, 733w, 709w; δ_H(300 MHz) 2.53-2.77 (3H, stack, C*H*$_2$CH=CH$_2$, C*H*$_a$H$_b$CH$_2$O), 2.93 (1H, ddd, *J* 15.7, 9.7, 5.4, CH$_a$*H*$_b$CH$_2$O), 3.70-3.82 (4H, stack, CH$_2$C*H*$_a$H$_b$O, OC*H*$_3$), 4.16 (1H, ddd, *J* 11.3, 5.4, 3.7, CH$_a$*H*$_b$O), 4.81 (1H, dd, *J* 7.8, 3.7, C*H*O), 5.07-5.22 (2H, stack, CH=C*H*$_2$), 5.93 (1H, ddt, *J* 17.1, 10.1, 6.8, C*H*=CH$_2$), 6.65 (1H, d, *J* 2.5, Ar*H*), 6.75 (1H, dd, *J* 8.4, 2.5, Ar*H*), 7.04 (1H, d, *J* 8.4, Ar*H*); δ_C(75 MHz) 28.2 (CH$_2$, *C*H$_2$CH$_2$O), 40.3 (CH$_2$, C*H*$_2$CH=CH$_2$), 55.2 (CH$_3$, OC*H*$_3$), 63.6 (CH$_2$, *C*H$_2$O), 75.5 (CH, *C*HO), 110.0 (CH, Ar), 112.2 (CH, Ar), 116.9 (CH$_2$, CH=*C*H$_2$), 126.1 (quat. C, *ipso* Ar), 129.7 (CH, Ar), 135.0 (CH, *C*H=CH$_2$), 138.7 (quat. C, *ipso* Ar), 157.8 (quat. C, *ipso* Ar); m/*z* (EI) 204 ([M]$^+$, 3%), 163 (100, ([M – C$_3$H$_5$]$^+$), 121 (24), 105 (12); HRMS: C$_{13}$H$_{16}$O$_2$ calcd 204.1150 ([M]$^+$), obsd 204.1153.

Asymmetric allylation:

Enantiomerically enriched 1-allylisochroman **202g** was prepared from 1-ethoxyisochroman **179g** (90 mg, 0.432 mmol), allyltrimethylsilane (105 μL, 0.648 mmol) and the phosphoramide catalyst (*R*)-**45g** (64.3 mg, 0.065 mmol) in *o*-xylene (290 μL) according to Method B. After stirring for 24 h and work-up, purification by column chromatography (99% hexane, 1% Et$_2$O) afforded enantiomerically enriched 1-allylisochroman **202g** (57 mg, 65%): $[\alpha]_D^{20}$ = +64.6 (*c* 1.27, CHCl$_3$, e.r. 21:79); Chiralpak AD, 1.0 mL/min, 10% IPA in hexane, λ = 230 nm, $t_{R,minor}$ = 4.2 min, $t_{R,major}$ = 4.9 min.

1-Allyl-7-fluoroisochroman 202h



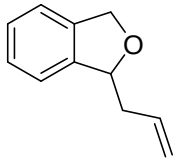
Chemical Formula: $C_{12}H_{13}FO$
Exact Mass: 192.095
Molecular Weight: 192.2294
Elemental Analysis: C, 74.98; H, 6.82; F, 9.88; O, 8.32

Racemic 1-allylisochroman **202h** was prepared from 1-ethoxyisochroman **179h** (100 mg, 0.51 mmol), allyltrimethylsilane (120 μL, 0.76 mmol) and $MeSO_3H$ (33 μL, 0.51 mmol) in CH_2Cl_2 (1 mL) according to Method A. Purification by flash column chromatography (gradient: 100% hexane → 99.5% hexane, 0.5% Et_2O) afforded 1-allylisochroman **202h** as a colourless oil (81 mg, 83%): R_f = 0.33 (90% hexane, 10% Et_2O); ν_{max}(film)/cm^{-1} 2930w, 2855w, 1616w, 1592w, 1497s, 1427m, 1249m, 1201m, 1108s, 992m, 938m, 914m, 866m, 811s, 736m; δ_H(300 MHz) 2.50-2.75 (3H, stack, CH_2CH=CH_2, CH_aH$_b$CH_2O), 2.88-3.01 (1H, m, CH$_a$$H_bCH_2$O), 3.74 (1H, ddd, *J* 11.3, 9.8, 3.8, CH_aH$_b$O), 4.16 (1H, ddd, *J* 11.3, 5.4, 3.4, CH$_a$$H_b$O), 4.79 (1H, dd, *J* 7.6, 3.6, C*H*O), 5.06-5.21 (2H, stack, CH=CH_2), 5.89 (1H, ddt, *J* 17.1, 10.3, 6.8, C*H*=CH_2), 6.77-6.92 (2H, stack, Ar*H*), 7.07 (1H, dd, *J* 8.3, 5.8, Ar*H*); δ_C(75 MHz) 28.3 (CH_2, *C*H_2CH_2O), 40.1 (CH_2, CH_2CH=CH_2), 63.5 (CH_2, *C*H_2O), 75.3 (CH, *C*HO), 111.4 (CH, d, $^2J_{C\text{-}F}$ 21.8, Ar), 113.4 (CH, d, $^2J_{C\text{-}F}$ 21.2, Ar), 117.3 (CH_2, CH=*C*H_2), 129.5 (quat. C, *ipso* Ar), 130.2 (CH, d, $^3J_{C\text{-}F}$ 7.5, Ar), 134.5 (CH, *C*H=CH_2), 139.5 (quat. C, d, $^4J_{C\text{-}F}$ 6.1, *ipso* Ar), 161.1 (quat. C, d, $^1J_{C\text{-}F}$ 242.2, *ipso* Ar); δ_F(282 MHz) –116.2 - –116.0 (F, m, Ar*F*); m/z (EI) 151 ($[M - C_3H_5]^+$, 100%), 133 (20), 109 (13), 103 (18); HRMS: C_9H_8OF calcd 151.0559 ($[M - C_3H_5]^+$), obsd 151.0552.

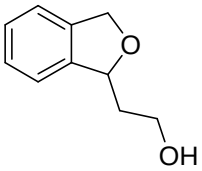
Asymmetric allylation:

Enantiomerically enriched 1-allylisochroman **202h** was prepared from 1-ethoxyisochroman **179h** (98.1 mg, 0.500 mmol), allyltrimethylsilane (120 μL, 0.750 mmol) and the phosphoramide catalyst (*R*)-**45g** (74.2 mg, 0.075 mmol) in *o*-xylene (333 μL) according to Method B. After stirring for 48 h and work-up, purification by column chromatography (99% hexane, 1% Et_2O) afforded enantiomerically enriched 1-allylisochroman **202h** (39 mg, 41%): $[\alpha]_D^{21}$ = +76.7 (*c* 0.67, $CHCl_3$, e.r. 20:80); Lux 5u Cellulose-2, 3 mL/min, 0.5% IPA in hexane, λ = 210 nm, $t_{R,major}$ = 8.5 min, $t_{R,minor}$ = 9.1 min.

1-Allylphthalan 202k and 1-(2'-hydroxyethyl)phthalan 203[151]



Chemical Formula: $C_{11}H_{12}O$
Exact Mass: 160.0888
Molecular Weight: 160.2124
Elemental Analysis: C, 82.46; H, 7.55; O, 9.99



Chemical Formula: $C_{10}H_{12}O_2$
Exact Mass: 164.0837
Molecular Weight: 164.2011
Elemental Analysis: C, 73.15; H, 7.37; O, 19.49

Racemic 1-allylphthalan **202k** was prepared from 1-ethoxyphthalan **179k** (100 mg, 0.61 mmol), allyltrimethylsilane (145 μL, 0.91 mmol) and $MeSO_3H$ (40 μL, 0.61 mmol) in CH_2Cl_2 (1.2 mL) according to Method A. Purification by flash column chromatography (99% pentane, 1% Et_2O) afforded 1-allylphthalan **202k** as a colourless liquid (70 mg, 72%, reduced yield owing to product volatility): R_f = 0.28 (90% pentane, 10% Et_2O); ν_{max}(film)/cm^{-1} 3076w, 2899w, 2851m, 1641m, 1479m, 1461m, 1415w, 1365m, 1350w, 1317w, 1259w, 1107w, 1043s, 1021m, 996m, 964m, 913s, 881w, 865w, 841m, 821w, 746s, 729s, 717s, 693m; δ_H(300 MHz) 2.50-2.75 (2H, stack, C*H*$_2$CH=CH_2), 5.06-5.26 (4H, stack, C*H*$_2$O, CH=C*H*$_2$), 5.31-5.39 (1H, m, C*H*O), 5.92 (1H, ddt, *J* 17.1, 10.2, 6.9, C*H*=CH_2), 7.20-7.36 (4H, stack, Ar*H*); δ_C(100 MHz) 40.6 (CH_2, C*H*$_2$CH=CH_2), 72.6 (CH_2, *C*H_2O), 83.1 (CH, *C*HO), 117.5 (CH_2, CH=*C*H_2), 120.9 (CH, Ar), 121.2 (CH, Ar), 127.1 (CH, Ar), 127.4 (CH, Ar), 134.0 (CH, *C*H=CH_2), 139.4 (quat. C, *ipso* Ar) 141.5 (quat. C, *ipso* Ar); m/*z* (EI) 160 ($[M]^+$, 1%), 119 (100, $[M - C_3H_5]^+$), 91 (57), 65 (8); HRMS: $C_{11}H_{12}O$ calcd 160.0888 ($[M]^+$), obsd 160.0889.

Racemic 1-(2'-hydroxyethyl)phthalan **203** was prepared from 1-allylphthalan **202k** by a one-pot oxidative cleavage–reduction sequence. $NaIO_4$ (915 mg, 4.28 mmol), 2,6-lutidine (250 μL, 2.14 mmol) and OsO_4 (a small crystal) were added to a mixture of the starting material (171 mg, 1.07 mmol) in dioxane/H_2O (3:1, 10.7 mL) at 0 °C. After stirring at R.T. for 2 h, $NaBH_4$ (202 mg, 5.35 mmol) was added in small portions over a period of 5 min. The mixture was stirred for additional 10 min, and then quenched with NH_4Cl solution (15 mL) at 0 °C. The two phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic fractions were washed with brine (20 mL) and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product as a dark-red liquid. Purification by flash column chromatography (gradient: 90% hexane, 10% EtOAc → 50% hexane, 50% EtOAc) afforded alcohol **203** as a colourless[9] viscous oil (129 mg, 73%): R_f = 0.18 (50% hexane, 50% EtOAc); δ_H(300 MHz) 1.88-2.02 (1H, m, CH_aH$_b$CH$_2$OH), 2.11-2.24 (1H, m, CH$_a$$H_bCH_2$OH), 3.13 (1H, br s, O*H*), 3.80-3.95 (2H, stack, CH$_2$CH_2OH), 5.03-5.20 (2H, stack, ArCH_2O), 5.40-5.49 (1H, m, C*H*O), 7.13-7.35 (4H, stack, Ar*H*); δ_C(100 MHz) 37.9 (CH$_2$, *C*H$_2$CH$_2$OH), 60.4 (CH$_2$, CH$_2$*C*H$_2$OH), 72.4 (CH$_2$, Ar*C*H$_2$O), 83.2 (CH, *C*HO), 120.8 (CH, Ar), 120.9 (CH, Ar), 127.3 (CH, Ar), 127.5 (CH, Ar), 138.8 (quat. C, *ipso* Ar), 141.4 (quat. C, *ipso* Ar); m/*z* (EI) 164 ([M]$^+$, 17%), 119 (100, [M – CH_2CH_2OH]$^+$), 91 (33); HRMS: $C_{10}H_{12}O_2$ calcd 164.0837 ([M]$^+$), obsd 164.0839.

Asymmetric allylation:

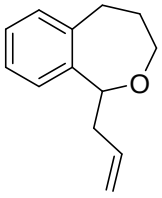
Enantiomerically enriched 1-allylphthalan **202k** was prepared from 1-ethoxyphthalan **179k** (98.5 mg, 0.600 mmol), allyltrimethylsilane (145 μL, 0.900 mmol) and the phosphoramide catalyst (*R*)-**45g** (89.1 mg, 0.090 mmol) in *o*-xylene (400 μL) according to Method B. After stirring for 24 h, a few drops of NEt_3 were added and from the resulting wet solid the *o*-xylene

[9] in total, two columns were carried out to obtain a pure colourless product

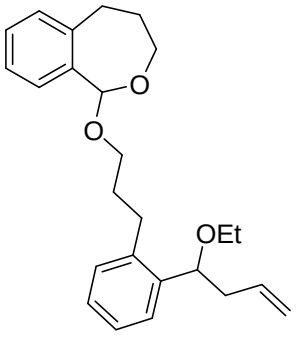
was removed under reduced pressure. Purification by column chromatography (99% hexane, 1% Et_2O) afforded enantiomerically enriched 1-allylisochroman **202k** (59 mg, 61%, reduced yield owing to product volatility): $[\alpha]_D^{20}$ = +25.0 (*c* 1.31, $CHCl_3$); no baseline separation of the two enantiomers by chiral HPLC.

Enantiomerically enriched 1-(2'-hydroxyethyl)phthalan **203** was prepared from enantiomerically enriched 1-allylphthalan **202k** (59 mg, 0.368 mmol), $NaIO_4$ (315 mg, 1.47 mmol), 2,6-lutidine (80 μL, 0.737 mmol), OsO_4 (a small crystal) and then $NaBH_4$ (70 mg, 1.84 mmol) in dioxane/H_2O (3:1, 370 μL). Work-up and purification by column chromatography (gradient: 90% hexane, 10% EtOAc → 50% hexane, 50% EtOAc) afforded enantiomerically enriched alcohol **203** (42 mg, 70%): $[\alpha]_D^{20}$ = +**???** (*c* **???**, $CHCl_3$, e.r. 26:74); Chiralpak AD, 1.0 mL/min, 0.5% IPA in hexane, λ = 210 nm, $t_{R,\text{major}}$ = 13.8 min, $t_{R,\text{minor}}$ = 15.3 min.

1-Allyl-3,4,5-trihydro-2-benzoxepin 202l and 1-(1'-ethoxy-but-3'-ene)-2-(3''-(1'''-oxo-3''',4''',5'''-trihydro-2-benzoxepin)propyl)benzene 205



Chemical Formula: $C_{13}H_{16}O$
Exact Mass: 188.1201
Molecular Weight: 188.2655
Elemental Analysis: C, 82.94; H, 8.57; O, 8.50



Chemical Formula: $C_{25}H_{32}O_3$
Exact Mass: 380.2351
Molecular Weight: 380.5198
Elemental Analysis: C, 78.91; H, 8.48; O, 12.61

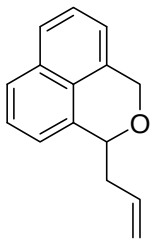
Racemic 1-allylbenzoxepin **202l** was prepared from 1-ethoxybenzoxepin **179l** (100 mg, 0.52 mmol), allyltrimethylsilane (125 μL, 0.78 mmol) and $MeSO_3H$ (35 μL, 0.52 mmol) in CH_2Cl_2 (1 mL) according to Method A. Purification by flash column chromatography (gradient: 99% hexane, 1% Et_2O → 90% hexane, 10% Et_2O) afforded, in order of elution, benzoxepin **202l** as a colourless liquid (25 mg, 26%): R_f = 0.33 (90% hexane, 10% Et_2O); ν_{max}(film)/cm^{-1} 3075w, 2934m, 2846m, 1641w, 1490w, 1454m, 1335w, 1281w, 1096s, 1021m, 998m, 980m, 911s, 876w, 851w, 807w, 763s, 744s; δ_H(300 MHz) 1.70-1.97 (2H, stack, $CH_2CH_2CH_2O$), 2.61-2.81 (2H, stack, $CH_2CH{=}CH_2$), 3.02 (2H, app. t, *J* 6.0, $CH_aH_bCH_2CH_2O$), 3.82 (1H, ddd, *J* 12.1, 11.2, 3.6, CH_aH_bO), 4.22 (1H, ddd, *J* 12.1, 4.8, 2.7, CH_aH_bO), 4.65 (1H, dd, *J* 8.4, 5.2, C*H*O), 5.08-5.23 (2H, stack, $CH{=}CH_2$), 5.99 (1H, ddt, *J* 17.1, 10.3, 6.7, $CH{=}CH_2$), 7.12-7.25 (4H, stack, Ar*H*); δ_C(75 MHz) 29.5 (CH_2, $CH_2CH_2CH_2O$), 33.9 (CH_2, $CH_2CH_2CH_2O$), 38.5 (CH_2, $CH_2CH{=}CH_2$), 72.2 (CH_2, CH_2O), 81.0 (CH, CHO), 116.7 (CH_2, $CH{=}CH_2$), 125.4 (CH, Ar), 126.0 (CH, Ar), 127.4 (CH, Ar), 129.5 (CH, Ar), 135.6 (CH, $CH{=}CH_2$), 141.5 (quat. C, *ipso* Ar), 141.6 (quat. C, *ipso* Ar); m/*z* (EI) 147 ($[M - C_3H_5]^+$, 100%), 129 (59), 115 (15), 91 (24); HRMS: $C_{10}H_{11}O$ calcd 147.0810 ($[M - C_3H_5]^+$), obsd 147.0809; and then benzoxepin **205** (15 mg, 15%): R_f = 0.23 (90% hexane, 10% Et_2O); ν_{max}(film)/cm^{-1} 3071w, 2930m, 1640w, 1454m, 1349m, 1281w, 1224w, 1140m, 1085s, 1020s, 964m, 946m, 913m, 876w, 852w, 747s; δ_H(300 MHz) 1.13-1.19 (3H, m, OCH_2CH_3), 1.74-2.08 (4H, stack, 2 × $CH_2CH_2CH_2O$), 2.26-2.42 (1H, m, $CH_aH_bCH{=}CH_2$), 2.46-2.60 (1H, m, $CH_aH_bCH{=}CH_2$), 2.69-3.06 (4H, stack, 2 × $CH_2CH_2CH_2O$), 3.23-3.43 (2H, stack, OCH_2CH_3), 3.59 (1H, app. dt, *J* 9.5, 6.0, $CH_2CH_2CH_aH_bO$), 3.89 (1H, ddd, *J* 11.9, 7.4, 4.7, $CH_2CH_2CH_aH_bO$), 3.97-4.07 (1H, m, $CH_2CH_2CH_aH_bO$), 4.21-4.32 (1H, m, $CH_2CH_2CH_aH_bO$), 4.62 (1H, app. dt, *J* 8.1, 4.7, C*H*O), 4.97-5.12 (2H, stack, $CH{=}CH_2$), 5.53 (1H, s, acetal C*H*), 5.75-5.92 (1H, m, $CH{=}CH_2$), 7.10-7.29 (6H, stack, Ar*H*), 7.42-7.56 (2H, stack, Ar*H*); δ_C(100 MHz) 15.3 (CH_3, OCH_2CH_3), 29.0 (CH_2), 29.5 (CH_2), 31.4 (CH_2), 34.2 (CH_2), 42.5 (CH_2), 64.0 (CH_2, CH_2O), 67.7 (CH_2,

CH_2O), 68.4 (CH_2, *C*H_2O), 77.5 (CH, *C*HOEt), 103.5 (CH, acetal *C*H), 116.5 (CH_2, CH=*C*H_2), 126.1 (CH, 2 × Ar), 126.1 (CH, Ar), 126.4 (CH, Ar), 127.1 (CH, Ar), 128.1 (CH, Ar), 129.3 (CH, Ar), 129.4 (CH, Ar), 135.3 (CH, *C*H=CH_2), 139.2 (quat. C, *ipso* Ar), 139.7 (quat. C, *ipso* Ar), 139.9 (quat. C, *ipso* Ar), 140.3 (quat. C, *ipso* Ar); m/*z* (TOF ES+) 403 ([M + Na]$^+$, 100%); HRMS: $C_{25}H_{32}O_3Na$ calcd 403.2249 ([M + Na]$^+$), obsd 403.2240.

Asymmetric allylation:

Enantiomerically enriched 1-allylbenzoxepin **202l** was prepared from 1-ethoxybenzoxepin **179l** (76.9 mg, 0.400 mmol), allyltrimethylsilane (95 μL, 0.600 mmol) and the phosphoramide catalyst (*R*)-**45g** (79.2 mg, 0.080 mmol) in *o*-xylene (267 μL) according to Method B. After stirring for 48 h and work-up, purification by column chromatography (99% hexane, 1% Et_2O) afforded traces of enantiomerically enriched 1-allylbenzoxepin **202l**.

1-Allyl-3*H*-naphtho[1,8-cd]pyran 202m



Chemical Formula: $C_{15}H_{14}O$
Exact Mass: 210.1045
Molecular Weight: 210.2711
Elemental Analysis: C, 85.68; H, 6.71; O, 7.61

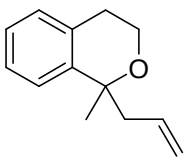
Racemic 1-allylpyran **202m** was prepared from 1-ethoxypyran **179m** (100 mg, 0.47 mmol), allyltrimethylsilane (110 μL, 0.70 mmol) and $MeSO_3H$ (45 μL, 0.47 mmol) in CH_2Cl_2 (0.9 mL) according to Method A. Purification by flash column chromatography (gradient: 100% hexane → 99% hexane, 1% Et_2O) afforded 1-allylpyran **202m** as a colourless oil (94 mg, 96%): R_f = 0.34 (90% hexane, 10% Et_2O); δ_H(300 MHz) 2.76-2.97 (2H, stack, CH_2CH=CH_2),

5.02-5.33 (5H, stack, CH_2O, CHO, CH=CH_2), 6.08 (1H, ddt, *J* 17.1, 10.3, 6.8, CH=CH_2), 7.17-7.24 (1H, m, Ar*H*), 7.25-7.32 (1H, m, Ar*H*), 7.41-7.53 (2H, stack, Ar*H*), 7.73-7.82 (2H, stack, ArH); δ_C(75 MHz) 38.3 (CH_2, CH_2CH=CH_2), 66.7 (CH_2, CH_2O), 76.2 (CH, CHO), 117.3 (CH_2, CH=CH_2), 120.0 (CH, Ar), 120.1 (CH, Ar), 125.5 (CH, 2 × Ar), 126.4 (CH, Ar), 126.5 (CH, Ar), 126.7 (quat. C, *ipso* Ar), 132.4 (quat. C, *ipso* Ar), 132.9 (quat. C, *ipso* Ar), 134.6 (CH, CH=CH_2), 135.1 (quat. C, *ipso* Ar); m/*z* (EI) 210 ($[M]^+$, 4%), 169 (100, $[M - C_3H_5]^+$), 141 (43), 115 (18); HRMS: $C_{15}H_{14}O$ calcd 210.1025 ($[M]^+$), obsd 210.1046.

Asymmetric allylation:

Enantiomerically enriched 1-allylpyran **202m** was prepared from 1-ethoxypyran **179m** (85.7 mg, 0.400 mmol), allyltrimethylsilane (95 μL, 0.600 mmol) and the phosphoramide catalyst (*R*)-**45g** (59.4 mg, 0.060 mmol) in *o*-xylene (348 μL) according to Method B. After stirring for 24 h and work-up, purification by column chromatography (99% hexane, 1% Et_2O) afforded enantiomerically enriched 1-allylpyran **202m** (35 mg, 42%): $[\alpha]_D^{20}$ = +56.3 (*c* 0.67, $CHCl_3$, e.r. 31:69); Chiralcel OD, 1.0 mL/min, 100% hexane, 10% IPA in hexane, λ = 210 nm, $t_{R,minor}$ = 5.4 min, $t_{R,major}$ = 5.9 min.

1-Allyl-1-methylisochroman 202n



Chemical Formula: $C_{13}H_{16}O$
Exact Mass: 188.1201
Molecular Weight: 188.2655
Elemental Analysis: C, 82.94; H, 8.57; O, 8.50

Racemic 1-allylisochroman **202n** was prepared from 1-ethoxyisochroman **179n** (120 mg, 0.61 mmol), allyltrimethylsilane (145 μL, 0.92 mmol) and $MeSO_3H$ (40 μL, 0.61 mmol) in CH_2Cl_2

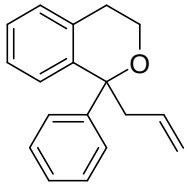
(1.2 mL) according to Method A. Purification by flash column chromatography (gradient: 99% hexane, 1% Et_2O → 90% hexane, 10% Et_2O) afforded, in order of elution, 1-allylisochroman **202n** as a colourless oil (47 mg, 41%): R_f = 0.36 (90% hexane, 10% Et_2O); ν_{max}(film)/cm^{-1} 3076w, 2975m, 2930m, 1639w, 1490m, 1447m, 1428m, 1372m, 1285m, 1159w, 1094s, 1058m, 1036m, 997m, 973w, 910s, 827w, 790w, 758s, 734s, 659m; δ_H(300 MHz) 1.51 (3H, s, CH_3), 2.51 (1H, dd, *J* 14.4, 7.7, C$H_a$$H_b$$CH_2O$), 2.64-2.94 (3H, stack, $CH_aH_bCH_2O$, CH_2CH=CH_2), 3.87-4.05 (2H, stack, CH_2O), 5.00-5.12 (2H, stack, CH=CH_2), 5.72-5.88 (1H, m, CH=CH_2), 7.06-7.25 (4H, stack, ArH); δ_C(75 MHz) 27.4 (CH_3, CH_3), 29.5 (CH_2, CH_2CH_2O), 46.6 (CH_2, CH_2CH=CH_2), 59.5 (CH_2, CH_2CH_2O), 76.2 (quat. C, *C*O), 117.4 (CH_2, CH=CH_2), 125.4 (CH, Ar), 125.9 (CH, Ar), 126.1 (CH, Ar), 128.7 (CH, Ar), 133.6 (quat. C, *ipso* Ar), 134.1 (CH, CH=CH_2), 141.9 (quat. C, *ipso* Ar); m/*z* (EI) 147 ([M – C_3H_5]$^+$, 100%), 129 (30); HRMS: $C_{10}H_{11}O$ calcd 147.0810 ([M – C_3H_5]$^+$), obsd 147.0811; and then a second product **204** whose structure was not determined as a colourless wax (39 mg, 38%, mixture of diastereoisomers): selected data: R_f = 0.15 (90% hexane, 10% Et_2O); ν_{max}(film)/cm^{-1} 3073w, 3019w, 2928m, 2858w, 1489m, 1448m, 1427m, 1370m, 1341w, 1285m, 1188w, 1157w, 1094s, 1057m, 1037m, 986w, 910m, 811w, 755s, 735s, 674w; m/*z* (TOF ES+) 357 ([M + Na]$^+$, 100%); HRMS: $C_{23}H_{26}O_2Na$ calcd 357.1831 ([M + Na]$^+$), obsd 357.1838.

Asymmetric allylation:

Enantiomerically enriched 1-allylisochroman **202n** was prepared from 1-ethoxyisochroman **179n** (76.9 mg, 0.400 mmol), allyltrimethylsilane (95 μL, 0.600 mmol) and the phosphoramide catalyst (*R*)-**45g** (59.4 mg, 0.060 mmol) in *o*-xylene (270 μL) according to Method B. After stirring for 24 h and work-up, purification by column chromatography (99% hexane, 1% Et_2O) afforded enantiomerically enriched 1-allylisochroman **202n** (25 mg, 33%):

$[\alpha]_D^{21}$ = +43.4 (*c* 0.73, $CHCl_3$, e.r. 37:63); Chiralcel OD, 1.0 mL/min, 100% hexane, λ = 210 nm, $t_{R,minor}$ = 8.9 min, $t_{R,major}$ = 10.9 min.

1-Allyl-1-phenylisochroman 202o



Chemical Formula: $C_{18}H_{18}O$
Exact Mass: 250.1358
Molecular Weight: 250.3349
Elemental Analysis: C, 86.36; H, 7.25; O, 6.39

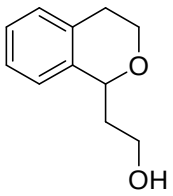
Racemic 1-allylisochroman **202o** was prepared from 1-ethoxyisochroman **179o** (60 mg, 0.24 mmol), allyltrimethylsilane (55 μL, 0.35 mmol) and $MeSO_3H$ (15 μL, 0.24 mmol) in CH_2Cl_2 (0.5 mL) according to Method A. Purification by flash column chromatography (gradient: 100% hexane → 98% hexane, 2% Et_2O) afforded 1-allylisochroman **202o** as a white crystalline solid (26 mg, 44%): mp 65-66 °C; R_f = 0.43 (90% hexane, 10% Et_2O); ν_{max}(film)/cm^{-1} 3064w, 2935w, 2914m, 2883w, 1488m, 1442m, 1429m, 1161w, 1097s, 1080m, 1069m, 1036m, 1013m, 994m, 973m, 942m, 920s, 886w, 849w, 759s, 733m, 701s, 671m; δ_H(300 MHz) 2.62 (1H, app. dt, *J* 16.4, 3.6, C$H_a$$H_b$$CH_2$O), 2.94 (1H, ddt, *J* 15.7, 6.5, 2.0, $CH_a$$H_b$$CH_2$O), 3.01-3.15 (2H, stack, CH_2CH=CH_2), 3.66 (1H, ddd, *J* 11.4, 10.8, 3.6, CH_2C$H_a$$H_b$O), 3.92 (1H, ddd, *J* 11.4, 6.5, 2.0, $CH_2CH_a$$H_b$O), 4.94-5.11 (2H, stack, CH=CH_2), 5.71 (1H, ddt, *J* 17.2, 10.3, 6.7, C*H*=CH_2), 7.14-7.42 (9H, stack, Ar*H*); δ_C(100 MHz) 29.0 (CH_2, *C*H_2CH_2O), 47.0 (CH_2, CH_2CH=CH_2), 60.0 (CH_2, *C*H_2O), 80.7 (quat. C, *C*O), 117.3 (CH_2, CH=*C*H_2), 125.4 (CH, Ar), 126.5 (CH, Ar), 127.2 (CH, Ar), 127.3 (CH, Ar), 127.8 (CH, Ar), 128.0 (CH, Ar), 129.2 (CH, Ar), 134.4 (CH, *C*H=CH_2), 134.7 (quat. C, *ipso* Ar), 137.8 (quat. C, *ipso* Ar), 145.6 (quat. C, *ipso* Ar); m/*z* (EI) 209 ([M – C_3H_5]$^+$, 100%), 194

(52), 165 (15), 103 (11), 77 (13); HRMS: $C_{15}H_{13}O$ calcd 209.0966 ($[M - C_3H_5]^+$), obsd 209.0960.

Asymmetric allylation:

Enantiomerically enriched 1-allylisochroman **202o** was prepared from 1-ethoxyisochroman **179o** (102 mg, 0.400 mmol), allyltrimethylsilane (95 μL, 0.600 mmol) and the phosphoramide catalyst (*R*)-**45g** (59.4 mg, 0.060 mmol) in *o*-xylene (270 μL) according to Method B. After stirring for 24 h and work-up, purification by column chromatography (99% hexane, 1% Et_2O) afforded enantiomerically enriched 1-allylisochroman **202o** (16 mg, 16%): $[\alpha]_D$ not recorded; e.r. 49:51; Chiralcel OD, 1.0 mL/min, 100% hexane, λ = 210 nm, $t_{R,\text{minor}}$ = 14.3 min, $t_{R,\text{major}}$ = 16.2 min.

1-(2'-Hydroxyethyl)isochroman 177[151]



Chemical Formula: $C_{11}H_{14}O_2$
Exact Mass: 178.0994
Molecular Weight: 178.2277
Elemental Analysis: C, 74.13; H, 7.92; O, 17.95

Racemic 1-(2'-hydroxyethyl)isochroman **177** was prepared by bubbling O_3 through a cooled (–78 °C) solution of 1-allylisochroman **163** (100 mg, 0.58 mmol) in CH_2Cl_2/MeOH (1:1, 6 mL) until a blue colour persisted. The excess O_3 was then removed by bubbling N_2 through the solution until the blue colour had dissipated. $NaBH_4$ (141 mg, 3.73 mmol) was added slowly over 2 min and the mixture was warmed to R.T. After stirring for 30 min, the reaction was quenched by the addition of NH_4Cl solution (10 mL) (caution: gas formation!). Et_2O (10 mL) was added and the two phases were separated. The aqueous phase was extracted with

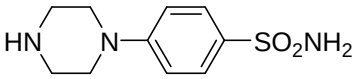
Et_2O (2 × 5 mL). The combined organic fractions were washed with brine (10 mL), and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product. Purification by flash column chromatography (gradient: 95% hexane, 5% EtOAc → 60% hexane, 40% EtOAc) afforded alcohol **177** as a colourless viscous oil (70 mg, 68%): R_f = 0.15 (60% hexane, 40% EtOAc); δ_H(300 MHz) 1.98-2.30 (2H, stack, CH_2CH$_2$OH), 2.69 (1H, app. dt, *J* 16.2, 3.1, CH_aH$_b$CH$_2$O), 2.95 (1H, br s, O*H*), 3.03 (1H, ddd, *J* 15.9, 10.0, 5.5, CH$_a$$H_bCH_2$O), 3.78 (1H, ddd, *J* 11.2, 10.0, 3.7, CH$_2$CH_aH$_b$O), 3.85 (2H, t, *J* 5.1, CH$_2$CH_2OH), 4.17 (1H, ddd, *J* 11.2, 5.5, 3.1, CH$_2$CH$_a$$H_b$O), 4.99 (1H, dd, *J* 8.5, 1.7, C*H*O), 6.98-7.24 (4H, stack, Ar*H*); δ_C(100 MHz) 28.9 (CH$_2$, *C*H$_2$CH$_2$O), 37.6 (CH$_2$, *C*H$_2$CH$_2$OH) [60.8, 63.6 (CH$_2$, *C*H$_2$O)], 76.0 (CH, *C*HO), 124.4 (CH, Ar), 126.2 (CH, Ar), 126.4 (CH, Ar), 128.9 (CH, Ar), 133.6 (quat. C, *ipso* Ar), 137.4 (quat. C, *ipso* Ar); m/*z* (EI) 178 ([M]$^+$, 6%), 133 (100, [M – CH$_2$CH$_2$OH]$^+$), 115 (13), 105 (18), 77 (13).

Enantiomerically enriched 1-(2'-hydroxyethyl)isochroman **177** was prepared from enantiomerically enriched 1-allylisochroman **163** by a one-pot oxidative cleavage – reduction sequence. $NaIO_4$ (354 mg, 1.66 mmol), 2,6-lutidine (95 μL, 0.828 mmol) and OsO_4 (a small crystal) were added to a mixture of the starting material (72 mg, 0.414 mmol, e.r. 82:18) in dioxane/H_2O (3:1, 4 mL) at 0 °C. After stirring at R.T. for 2 h, $NaBH_4$ (78 mg, 2.07 mmol) was added in small portions over a period of 2 min. The mixture was stirred for additional 10 min, and then quenched with NH_4Cl solution (8 mL) at 0 °C. The two phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic fractions were washed with brine (20 mL) and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product as a dark-red liquid. Purification by flash column chromatography (gradient: 95%

hexane, 5% EtOAc → 60% hexane, 40% EtOAc) afforded alcohol **177** as a colourless[10] viscous oil (57 mg, 77%): $[\alpha]_D^{20}$ = +102.2 (*c* 1.08, CH_2Cl_2, e.r. 82:18); Chiralcel OD, 1.0 mL/min, 10% IPA in hexane, λ = 210 nm, $t_{R,major}$ = 8.8 min, $t_{R,minor}$ = 10.1 min; (lit.[152] $[\alpha]_D^{28}$ = +43.5 (*c* 0.20, CH_2Cl_2, e.r. 80:20)).[11]

Data were in agreement with those reported in the literature.[153]

4-Piperazin-1-yl-benzenesulfonamide 213[209]



Chemical Formula: $C_{10}H_{15}N_3O_2S$
Exact Mass: 241.0885
Molecular Weight: 241.31
Elemental Analysis: C, 49.77; H, 6.27; N, 17.41; O, 13.26; S, 13.29

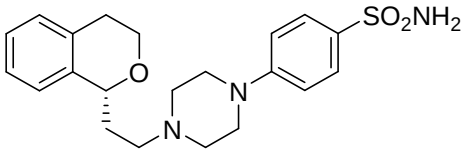
A mixture of 4-fluorobenzenesulfonamide (1.00 g, 5.71 mmol) and piperazine (2.46 g, 28.5 mmol) in H_2O (12 mL) was heated at 100 °C for 24 h. The resulting precipitate was collected by filtration and washed with H_2O (50 mL) and toluene (50 mL). The white solid was dried under reduced pressure to provide sulfonamide **213** (1.38 g, 95%): mp 217-219 °C (lit.[153] mp 219-221 °C); ν_{max}(neat)/cm^{-1} 3307m, 3097m, 3069m, 2949m, 2929m, 2863w, 2824m, 1592m, 1496m, 1458m, 1446m, 1438m, 1413w, 1379m, 1330s, 1308m, 1294m, 1261w, 1229m, 1187w, 1152s, 1135s, 1122s, 1097s, 1041w, 1023m, 976w, 936w, 882s, 815s, 754s, 725m, 679s; δ_H(300 MHz, DMSO-d_6) 2.31 (1H, br s, N*H*), 2.76-2.86 (4H, stack, CH_2N), 3.12-3.21 (4H, stack, CH_2N), 6.99 (2H, d, *J* 9.0, Ar*H*), 7.05 (2H, br s, SO_2NH_2), 7.60 (2H, d, *J* 9.0,

[10] in total, two columns were carried out to obtain a pure colourless product
[11] the (*R*)-(+)-correlation has been established in[153]

Ar*H*); δ_C(100 MHz) [45.4, 48.2 (CH_2, *C*H_2N)], 113.5 (CH, Ar), 127.1 (CH, Ar), 132.5 (quat. C, *ipso* Ar), 153.4 (quat. C, *ipso* Ar); m/*z* (TOF ES+) 242.1 ($[M + H]^+$, 100%).

Data were in agreement with those reported in the literature.[209]

(*R*)-(+)-4-[4-[2-(Isochroman-1-yl)ethyl]piperazin-1-yl]benzenesulfonamide (*R*)-212 [153]



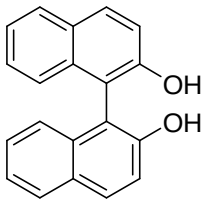
Chemical Formula: $C_{21}H_{27}N_3O_3S$
Exact Mass: 401.1773
Molecular Weight: 401.5224
Elemental Analysis: C, 62.82; H, 6.78; N, 10.47; O, 11.95; S, 7.99

DMAP (1.3 mg, 0.010 mmol), DIPEA (90 μL, 0.520 mmol) and MsCl (20 μL, 0.230 mmol) were added to a solution of (*R*)-(+)-1-(2'-hydroxyethyl)isochroman **177** (37 mg, 0.208 mmol, e.r. 82:18) in THF (235 μL) at 0 °C. After stirring for 30 min, 4-piperazin-1-yl-benzenesulfonamide **213** (58 mg, 0.239 mmol) and ethylene glycol (235 μL) were added and the mixture was heated at 100 °C for 15 h. After cooling to R.T., H_2O (3 mL) and CH_2Cl_2 (3 mL) were added. The phases were separated and the aqueous phase was extracted again with CH_2Cl_2 (5 mL). The combined organic fractions were washed with brine (10 mL), and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product. Purification by flash column chromatography (gradient: 100% CH_2Cl_2 → 95% CH_2Cl_2, 5% MeOH) afforded (*R*)-(+)-U-101387 **212** as a white solid (57 mg, 69%): mp 192-194 °C (lit.[153] mp 189-190 °C); R_f = 0.15 (95% CH_2Cl_2, 5% MeOH); $[\alpha]_D^{21}$ = +41.1 (*c* 0.36, DMF) (lit.[153] $[\alpha]_D$ = +48 (*c* 0.88, DMF); ν_{max}(neat)/cm^{-1} 2921m, 2835m, 1594m, 1496m, 1453m, 1390w, 1330s, 1306m, 1297m, 1245m, 1152s, 1112s, 1098s, 1083m, 1062w, 1016w, 1004m, 925m, 907m, 850w, 829s,

809m, 758s, 739s, 688w, 652w; δ_H(300 MHz) 1.80-1.97 (1H, m, CH_aH$_b$), 2.02-2.18 (1H, m, CH$_a$$H_b$), 2.31-2.73 (7H, stack, 3 × CH_2N and ArCH_aH$_b$), 2.78-2.93 (1H, m, ArCH$_a$$H_b$), 3.19-3.31 (4H, stack, 2 × CH_2NAr), 3.60-3.73 (1H, m, CH_aH$_b$O), 3.98-4.09 (1H, m, CH$_a$$H_b$O), 4.76 (1H, app. d, *J* 7.2, C*H*O), 6.96-7.28 (8H, stack, 6 × Ar*H* and SO_2NH_2), 7.61 (2H, d, *J* 8.7, Ar*H*); δ_C(100 MHz) 28.5 (CH_2, *C*H_2), 32.6, (CH_2, Ar*C*H_2), [47.1, 52.6 (CH_2, 2 × *C*H_2N)], 54.2 (CH_2, *C*H_2NAr), 62.2 (CH_2, *C*H_2O), 73.6 (CH, *C*HO), 113.6 (CH, Ar), 124.7 (CH, Ar), 126.0 (CH, Ar), 126.1 (CH, Ar), 127.1 (CH, Ar), 128.7 (CH, Ar), 132.7 (quat. C, *ipso* Ar), 133.6 (quat. C, *ipso* Ar), 138.1 (quat. C, *ipso* Ar), 152.8 (quat. C, *ipso* Ar); m/*z* (TOF ES+) 402.2 ([M + H]$^+$, 100%); HRMS: $C_{21}H_{28}N_3O_3S$ calcd 402.1851 ([M + H]$^+$), obsd 402.1841.

Data were in agreement with those reported in the literature.[153]

(±)-2,2'-Dihydroxy-1,1'-binaphthyl *rac*-109[126]



Chemical Formula: $C_{20}H_{14}O_2$
Exact Mass: 286.0994
Molecular Weight: 286.3240
Elemental Analysis: C, 83.90; H, 4.93; O, 11.18

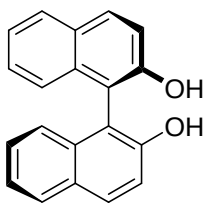
(±)-2,2'-Dihydroxy-1,1'-binaphthyl *rac*-**109** was prepared using a variation of a previously reported method:[125,126]

A solution of $FeCl_3$ (10.2 g, 62.9 mmol) in H_2O (90 mL) was added dropwise over 5 min to a solution of 2-naphthol (9.0 g, 62.4 mmol) in H_2O (1.2 L) at 100 °C. A further portion of 2-naphthol (9.0 g, 62.4 mmol) was added and the reaction mixture was stirred for 10 min at 100 °C before another solution of $FeCl_3$ (10.2 g, 62.9 mmol) in H_2O (90 mL) was added dropwise

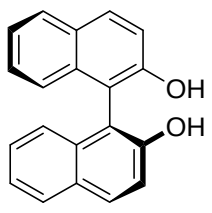
over 5 min. These additions and time delays were repeated with further portions of 2-naphthol (3 × 9.0 g) and solutions of $FeCl_3$ (3 × 10.2 g in 90 mL H_2O). The reaction was stirred for a further 30 min at 100 °C before the brown precipitate was filtered off and washed with boiling H_2O (6 × 500 mL). The solid residue was dissolved in Et_2O (750 mL) and activated charcoal (30 g) was added. The suspension was heated at reflux for 3 h. Removal of the charcoal by filtration and concentration of the filtrate under reduced pressure provided the crude product as a pale brown solid. Recrystallisation from toluene afforded BINOL *rac*-**109** as a fluffy white solid (34.4 g, 77%): mp 219-222 °C (lit.[126] mp 216-218 °C); (Found: C, 83.77; H, 4.87. $C_{20}H_{14}O_2$ requires C, 83.90; H, 4.93%); ν_{max}(film)/cm^{-1} 3532s (OH), 3484s (OH), 3398s (OH), 1957w, 1618s (C=C aromatic), 1597s (C=C aromatic), 1517s (C=C aromatic), 1470m, 1436w, 1382s, 1345m, 1314m, 1272m, 1182w, 1144s, 1125m, 978w, 960w, 930m, 863m, 625s; δ_H(300 MHz, CD_3CN) 6.62 (2H, br s, O*H*), 7.00 (2H, d, *J* 8.5, Ar*H*), 7.20-7.36 (6H, stack, Ar*H*), 7.90 (2H, d, *J* 8.1, Ar*H*), 7.96 (2H, d, *J* 9.2, Ar*H*); δ_C(75 MHz, CD_3CN) 114.5 (quat. C, *ipso* Ar), 119.3 (CH, Ar), 124.2 (CH, Ar), 125.1 (CH, Ar), 127.6 (CH, Ar), 129.1 (CH, Ar), 130.2 (quat. C, *ipso* Ar), 131.1 (CH, Ar), 135.3 (quat. C, *ipso* Ar), 154.2 (quat. C, *ipso* Ar); m/*z* (EI) 286 ([M]$^+$, 100%), 257 (14), 239 (14), 120 (13).

Data were in agreement with those reported in the literature.[126]

Resolution of (±)-2,2'-dihydroxy-1,1'-binaphthyl *rac*-109[127]



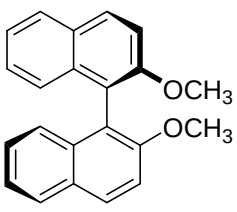
(*R*)-**109**



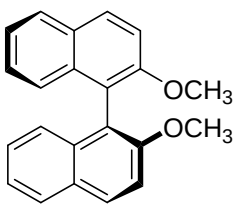
(*S*)-**109**

N-Benzylcinchonidinium chloride **111** (18.6 g, 44.2 mmol) was added to a solution of (±)-2,2'-dihydroxy-1,1'-binaphthyl *rac*-**109** (23.0 g, 80.3 mmol) in CH_3CN (300 mL) and the resulting suspension was heated at reflux for 4 h. After cooling to R.T. and stirring for 12 h, the mixture was cooled to 0 °C, kept at this temperature for 2 h, and then filtered. The filtrate was concentrated to dryness, redissolved in EtOAc (300 mL), and washed with 1 M hydrochloric acid (2 × 100 mL) and then brine (100 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford (*S*)-BINOL (*S*)-**109** as a light brown solid (10.90 g, 95%): $[\alpha]_D^{20}$ = –33.3 (*c* 1.0, THF, e.r. 0.4:99.6); Chiralpak AD column, 1.0 mL/min, 10% IPA in hexane, λ = 280 nm, $t_{R,\text{minor}}$ = 28.2 min, $t_{R,\text{major}}$ = 32.8 min; (lit.[127] $[\alpha]_D^{21}$ = –34.0 (*c* 1.0, THF, e.r. 0.5:99.5)). The solid was washed with CH_3CN (50 mL) and heated at reflux in MeOH (100 mL) for 24 h. After cooling to R. T., the mixture was filtered, and the solid was washed with MeOH (20 mL). The resulting solid was suspended in a mixture of EtOAc (300 mL) and 1 M hydrochloric acid (150 mL) and stirred until it was completely dissolved. The organic layer was washed with 1 M hydrochloric acid (150 mL) and then brine (150 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford (*R*)-BINOL (*R*)-**109** as a white solid (10.92 g, 95%): $[\alpha]_D^{20}$ = +33.0 (*c* 1.0, THF, e.r. 99.5:0.5); Chiralpak AD column, 1.0 mL/min, 10% IPA in hexane, λ = 280 nm, $t_{R,\text{minor}}$ = 29.0 min, $t_{R,\text{major}}$ = 32.2 min; (lit.[127] $[\alpha]_D^{21}$ = +34.3 (*c* 1.0, THF, e.r. > 99.9:0.1).

(*R*)- and (*S*)-2,2'-Dimethoxy-1,1'-binaphthyl (*R*)- and (*S*)-112[128,129]



(*R*)-**112**



(*S*)-**112**

Chemical Formula: $C_{22}H_{18}O_2$
Exact Mass: 314.1307
Molecular Weight: 314.3771
Elemental Analysis:
C, 84.05; H, 5.77; O, 10.18

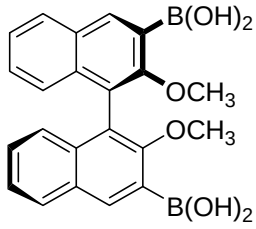
A suspension of (*S*)-BINOL (*S*)-**109** (5.10 g, 17.8 mmol) in acetone (150 mL) was heated until all of the starting material had dissolved. K_2CO_3 (8.29, 60.0 mmol) and MeI (4.36 mL, 70.0 mmol) were added, and the mixture was heated under reflux for 24 h. After adding more MeI (1.87 mL, 30.0 mmol), the heating was continued for another 12 h. The mixture was cooled to R.T. and concentrated under reduced pressure to 1/5 of its volume. H_2O (160 mL) was added and the suspension was stirred for 8 h. The resulting solid was filtered, washed with H_2O (2 × 50 mL) and dried to afford (*S*)-dimethyl ether (*S*)-**112** as a white powder (5.43 g, 97%). The crude product is usually used directly in the next step; however it can be further purified by recrystallisation from hexane/toluene (1:1) to afford the pure product as a cream-coloured powder (4.76 g, 85%): mp 227-230 °C (lit.[210] mp 222.9-227.0 °C); $[\alpha]_D^{21}$ = –54.0 (*c* 0.43, $CHCl_3$);[12] (Found: C, 84.02; H, 5.86. $C_{22}H_{18}O_2$ requires C, 84.05; H, 5.77%); ν_{max}(film)/cm^{-1} 2838w, 1616m (C=C aromatic), 1589s (C=C aromatic), 1506s (C=C aromatic), 1459m, 1353w, 1264s, 1147m, 1131w, 1090s, 1062s, 1018m, 894w; δ_H(300 MHz) 3.76 (6H, s, OC*H*$_3$), 7.10 (2H, d, *J* 8.5, Ar*H*), 7.16-7.34 (4H, stack, Ar*H*), 7.46 (2H, d, *J* 9.2, Ar*H*), 7.86 (2H, d, *J* 8.1, Ar*H*), 7.97 (2H, d, *J* 9.2, Ar*H*); δ_C(75 MHz) 56.9 (CH_3, OCH_3), 114.2 (CH, Ar), 119.6 (quat. C, *ipso* Ar), 123.5 (CH, Ar), 125.2 (CH, Ar), 126.3 (CH, Ar), 127.9 (CH, Ar), 129.2 (quat. C, *ipso* Ar), 129.4 (CH, Ar), 134.0 (quat. C, *ipso* Ar), 154.9 (quat. C, *ipso* Ar); m/*z* (EI) 314 ([M]$^+$, 100%), 268 (51), 239 (14), 237 (14), 199 (16), 181 (11), 163 (13), 119 (9), 69 (9).

The same protocol was followed for the preparation of the (*R*)-enantiomer (*R*)-**112**: $[\alpha]_D^{21}$ = +55.8 (*c* 0.43, $CHCl_3$) (lit.[210] $[\alpha]_D^{21}$ = +54.9 (*c* 1.0, $CHCl_3$).[12]

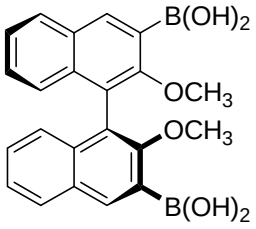
Data were in agreement with those reported in the literature.[210]

[12] the ee-value could not be determined by chiral HPLC owing to poor resolution of the racemic mixture

(*R*)- and (*S*)-3,3'-Bis(dihydroxyborane)-2,2'-dimethoxy-1,1'-binaphthyl (*R*)- and (*S*)-113[128,211,212]



(*R*)-**113**



(*S*)-**113**

Chemical Formula: $C_{22}H_{20}B_2O_6$
Exact Mass: 402.1446
Molecular Weight: 402.0126
Elemental Analysis:
C, 65.73; H, 5.01; B, 5.38; O, 23.88

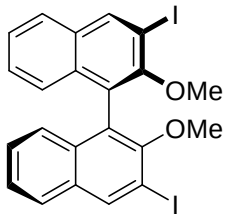
^{n}BuLi (19.1 mL of a 2.50 M solution in hexane, 47.7 mmol) was added to a solution of TMEDA (7.15 mL, 47.7 mmol) in Et_2O (250 mL) at R.T. The solution was stirred for 30 min, and then (*S*)-2,2'-dimethoxy-1,1'-binaphthyl (*S*)-**112** (5.00 g, 15.9 mmol) was added in one portion, and the mixture was stirred for 3.5 h. The resulting light brown suspension was cooled to –78 °C, and $B(OEt)_3$ (18.9 mL, 111 mmol) was added over 15 min. After warming to R.T., the suspension was stirred overnight at R.T. The mixture was cooled to 0 °C, 1 M hydrochloric acid (125 mL) was added, and the resulting solution was stirred vigoriously for 3.5 h at R.T. The organic layer was washed with 1 M hydrochloric acid (125 mL) and brine (125 mL), and then dried (Na_2SO_4). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product. The pale yellow solid was recrystallised from cyclohexane/toluene (2:1) to afford (*S*)-boronic acid (*S*)-**113** as a white powder (3.53 g, 55%): δ_H(300 MHz, CD_3CN) 3.37 (6H, s, OC*H*$_3$), 6.56 (4H, s, B(O*H*)$_2$), 7.07 (2H, d, *J* 8.5, Ar*H*), 7.26-7.36 (2H, m, Ar*H*), 7.44 (2H, app. t, *J* 7.0, Ar*H*), 8.02 (2H, d, *J* 8.1, Ar*H*), 8.51 (2H, s, Ar*H*); δ_C(75 MHz, $(CD_3)_2CO$) 61.8 (CH_3, O*C*H$_3$), 124.2 (quat. C, *ipso* Ar), 125.7 (CH, Ar), 126.3 (CH, Ar), 128.2 (CH, Ar), 129.6 (CH, Ar), 131.4 (quat. C, *ipso* Ar), 136.6 (quat. C, *ipso* Ar), 139.0 (CH, Ar), 161.1 (quat. C, *ipso* Ar), (quat. C, *ipso C*B(OH)$_2$) not observed because peak is too broad due to adjacent quadrupole boron

nucleus (^{11}B: I = 3/2) resulting in the resonance being lost in the noise; m/z (TOF ES+) 481 ([M – 4 × OH + 4 × OMe + Na]$^+$, 100%).

The same protocol was followed for the preparation of the (*R*)-enantiomer (*R*)-**113**.

Data were in agreement with those reported in the literature.[128,211,212]

(*R*)-3,3'-Diiodo-2,2'-dimethoxy-[1,1']-binaphthalenyl (*R*)-114[130]



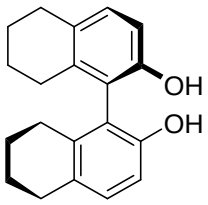
Chemical Formula: $C_{22}H_{16}I_2O_2$
Exact Mass: 565.924
Molecular Weight: 566.1702
Elemental Analysis: C, 46.67; H, 2.85; I, 44.83; O, 5.65

^{n}BuLi (28.6 mL of a 2.5 M solution in hexane, 71.6 mmol) was added to a solution of TMEDA (5.40 g, 35.8 mmol) in Et_2O (250 mL), and the mixture was stirred for 30 min before adding the solid dimethoxy binaphthalenyl (*R*)-**112** (7.50 g, 23.9 mmol). After stirring overnight at R.T., the mixture was cooled to –78 °C and a solution of I_2 (15.1 g, 59.6 mmol) in THF (30 mL) was added dropwise over 15 min *via* syringe. The reaction mixture was stirred for 1 h at –78 °C, and then warmed up to R.T. overnight. $Na_2S_2O_3$ solution (150 mL) was added and stirring was continued for 2 h. The layers were separated, and the aqueous phase was extracted with Et_2O/THF (1:1, 3 × 80 mL). The combined organic fractions were washed with $Na_2S_2O_3$ solution (100 mL), H_2O (100 mL) and brine (100 mL), and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product. Et_2O (30 mL) was added, and the suspension

was stirred vigorously for 1 h. Filtration provided a yellow powder. Recrystallisation from Et_2O/CH_2Cl_2 (3:2) afforded diiodo binaphthalenyl (*R*)-**114** as a cream-coloured solid (9.07 g, 67%): δ_H(300 MHz) 3.41 (6H, s, OC*H*$_3$), 7.07 (2H, d, *J* 8.5, Ar*H*), 7.22-7.31 (2H, stack, Ar*H*), 7.37-7.45 (2H, stack, Ar*H*), 7.80 (2H, d, *J* 8.1, Ar*H*), 8.54 (2H, s, Ar*H*); δ_C(75 MHz) 61.1 (CH_3, O*C*H$_3$), 92.3 (quat. C, *ipso* Ar), 125.3 (quat. C, *ipso* Ar), 125.6 (CH, Ar), 125.7 (CH, Ar), 126.9 (CH, Ar), 127.0 (CH, Ar), 132.1 (quat. C, *ipso* Ar), 133.8 (quat. C, *ipso* Ar), 139.9 (CH, Ar), 154.4 (quat. C, *ipso* Ar); m/*z* (TOF ES+) 589.0 ([M + Na]$^+$, 100%).

Data were in agreement with those reported in the literature.[130]

(*R*)-2,2'-Dihydroxy-5,6,7,8,5',6',7',8'-octahydro-[1,1']-binaphthalenyl (*R*)-H$_8$-115[131]



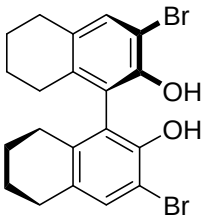
Chemical Formula: $C_{20}H_{22}O_2$
Exact Mass: 294.162
Molecular Weight: 294.3875
Elemental Analysis: C, 81.60; H, 7.53; O, 10.87

PtO_2 (286 mg, 1.26 mmol) was added to a solution of (*R*)-BINOL (*R*)-**109** (3.00 g, 10.5 mmol) in AcOH (84 mL). The atmosphere of the flask was purged under vacuum and flushed with H_2 three times. The reaction mixture was stirred under a balloon pressure of H_2 for 48 h and then filtered through a bed of Celite, washing with $CHCl_3$ (150 mL) and H_2O (200 mL). The layers were separated and the organic phase was washed with H_2O (150 mL), $NaHCO_3$ solution (300 mL) and brine (300 mL), and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude diol (*R*)-H$_8$-**115** as a white solid (3.19 g, quantitative), which was sufficiently pure for

characterisation and further use: mp 164-166 °C (lit.[213] mp 165-166 °C); $[\alpha]_D^{19}$ = +49.6 (*c* 1.00, $CHCl_3$) (lit.[213] $[\alpha]_D^{26}$ = +47.1 (*c* 1.04, $CHCl_3$); δ_H(300 MHz) 1.56-1.81 (8H, stack, $CH_2CH_2CH_2CH_2$), 2.08-2.36 (4H, stack, $ArCH_2$), 2.67-2.80 (4H, stack, $ArCH_2$), 4.66 (2H, s, O*H*), 6.81 (2H, d, *J* 8.5, Ar*H*), 7.04 (2H, d, *J* 8.5, Ar*H*); δ_C(75 MHz) 22.92 (CH_2, $CH_2CH_2CH_2CH_2$), 22.98 (CH_2, $CH_2CH_2CH_2CH_2$), 27.1 (CH_2, $ArCH_2$), 29.2 (CH_2, $ArCH_2$), 112.9 (CH, Ar), 118.9 (quat. C, *ipso* Ar), 130.0 (quat. C, *ipso* Ar), 130.1 (CH, Ar), 137.1 (quat. C, *ipso* Ar), 151.3 (quat. C, *ipso* Ar); m/*z* (TOF ES–) 293 ($[M - H]^-$, 100%).

Data were in agreement with those reported in the literature.[131]

(*R*)-3,3'-Dibromo-2,2'-dihydroxy-5,6,7,8,5',6',7',8'-octahydro-[1,1']-binaphthalenyl (*R*)-116[132]



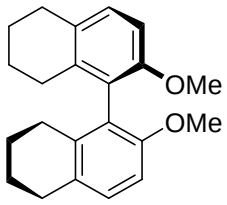
Chemical Formula: $C_{20}H_{20}Br_2O_2$
Exact Mass: 449.983
Molecular Weight: 452.1796
Elemental Analysis: C, 53.12; H, 4.46; Br, 35.34; O, 7.08

Br_2 (150 μL, 2.89 mmol) was added to a solution of (*R*)-H_8-BINOL (*R*)-H_8-**115** (370 mg, 1.26 mmol) in CH_2Cl_2 (12.5 mL) at –30 °C. After stirring for 30 min at –30 °C, the brown solution was warmed to –10 °C and $Na_2S_2O_3$ solution (15 mL) was added. The mixture was warmed to R.T. and diluted with CH_2Cl_2 (15 mL) and H_2O (15 mL). The layers were separated and the organic phase was washed with $NaHCO_3$ solution (20 mL) and brine (20 mL), and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product. Purification by flash column chromatography

(90% hexane, 10% Et_2O) afforded diol (*R*)-H_8-**116** as a white crystalline solid (0.467 g, 82%): mp 125-127 °C (lit.[213] mp 142-143 °C); $[\alpha]_D^{20}$ = +24.4 (*c* 1.0, $CHCl_3$) (lit.[213] $[\alpha]_D^{25}$ = +29.2 (*c* 1.05, $CHCl_3$); δ_H(300 MHz) 1.56-1.78 (8H, stack, $CH_2CH_2CH_2CH_2$), 2.00-2.15 (2H, m, $ArCH_aH_b$), 2.21-2.36 (2H, m, $ArCH_aH_b$), 2.65-2.80 (4H, stack, $ArCH_2$), 5.01 (2H, s, O*H*), 7.27 (2H, s, Ar*H*); δ_C(75 MHz) 22.7 (CH_2, $CH_2CH_2CH_2CH_2$), 22.8 (CH_2, $CH_2CH_2CH_2CH_2$), 26.9 (CH_2, $ArCH_2$), 29.0 (CH_2, $ArCH_2$), 107.1 (quat. C, *ipso* Ar), 122.1 (quat. C, *ipso* Ar), 131.5 (quat. C, *ipso* Ar), 132.5 (CH, Ar), 136.7 (quat. C, *ipso* Ar), 147.1 (quat. C, *ipso* Ar); m/*z* (TOF ES+) 475 ($[M + Na]^+$, 100%).

Data were in agreement with those reported in the literature.[213]

(*R*)-2,2'-Dimethoxy-5,6,7,8,5',6',7',8'-octahydro-[1,1']-binaphthalenyl (*R*)-H_8-117[133]



Chemical Formula: $C_{22}H_{26}O_2$
Exact Mass: 322.1933
Molecular Weight: 322.4406
Elemental Analysis: C, 81.95; H, 8.13; O, 9.92

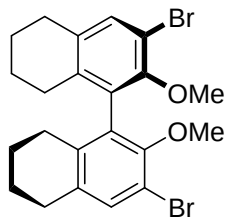
(*R*)-2,2'-Dimethoxy-5,6,7,8,5',6',7',8'-octahydro-[1,1']-binaphthalenyl (*R*)-H_8-**117** was prepared employing the procedure used for the methylation of BINOL.[128,129]

A suspension of (*R*)-H_8-BINOL (*R*)-H_8-**115** (3.08 g, 10.5 mmol) in acetone (100 mL) was heated until all of the starting material had dissolved. K_2CO_3 (7.24 g, 52.4 mmol) and MeI (2.45 mL, 39.4 mmol) were added, and the mixture was heated under reflux for 24 h. After adding more MeI (2.45 mL, 39.4 mmol), heating was continued for another 12 h. The mixture was cooled to R.T. and concentrated under reduced pressure to 1/5 of its volume. H_2O (120

mL) was added and the suspension was stirred for 8 h. The resulting solid was filtered, washed with H_2O (2 × 50 mL) and dissolved in CH_2Cl_2 (150 mL). Brine (50 mL) was added and the layers were separated. The organic phase was dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product in quantitative yield. Recrystallisation from toluene/hexane (1:1) afforded (*R*)-H_8-**117** as a white crystalline solid (2.91 g, 85%): δ_H(300 MHz) 1.56-1.80 (8H, stack, $CH_2CH_2CH_2CH_2$), 2.01-2.15 (2H, m, $ArCH_aH_b$), 2.20-2.34 (2H, m, $ArCH_aH_b$), 2.68-2.87 (4H, stack, $ArCH_2$), 3.38 (6H, s, OCH_3), 6.79 (2H, d, *J* 8.1, Ar*H*), 7.07 (2H, d, *J* 8.1, Ar*H*); δ_C(75 MHz) 23.1 (CH_2, $CH_2CH_2CH_2CH_2$), 23.2 (CH_2, $CH_2CH_2CH_2CH_2$), 27.1 (CH_2, $ArCH_2$), 29.4 (CH_2, $ArCH_2$), 55.9 (CH_3, OCH_3), 108.7 (CH, Ar), 125.8 (quat. C, *ipso* Ar), 128.7 (CH, Ar), 129.4 (quat. C, *ipso* Ar), 136.7 (quat. C, *ipso* Ar), 154.6 (quat. C, *ipso* Ar); m/*z* (TOF ES+) 345 ($[M + Na]^+$, 100%).

Data were in agreement with those reported in the literature.[133]

(*R*)-3,3'-Dibromo-2,2'-dimethoxy-5,6,7,8,5',6',7',8'-octahydro-[1,1']-binaphthalenyl (*R*)-H_8-118[131]



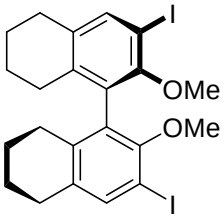
Chemical Formula: $C_{22}H_{24}Br_2O_2$
Exact Mass: 478.0143
Molecular Weight: 480.2328
Elemental Analysis: C, 55.02; H, 5.04; Br, 33.28; O, 6.66

Br_2 (990 μL, 19.3 mmol) was added to a solution of (*R*)-H_8-BINOL derivative (*R*)-H_8-**117** (2.70 g, 8.37 mmol) in CH_2Cl_2 (85 mL) at –30 °C. After stirring for 30 min at –30 °C,

$Na_2S_2O_3$ solution (70 mL) was added and the mixture was warmed to R.T. over 1 h. CH_2Cl_2 (30 mL) and H_2O (30 mL) were added and the layers were separated. The organic phase was washed with $NaHCO_3$ solution (40 mL), H_2O (40 mL) and brine (20 mL), and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product (*R*)-H_8-**118** as a cream-white solid (4.01 g, quantitative), which was sufficiently pure for characterisation and further use: mp 138-140 °C; $[\alpha]_D^{20}$ = –20.8 (*c* 1.0, $CHCl_3$); δ_H(300 MHz) 1.53-1.79 (8H, stack, $CH_2CH_2CH_2CH_2$), 1.98-2.13 (2H, m, $ArCH_aH_b$), 2.18-2.36 (2H, m, $ArCH_aH_b$), 2.65-2.83 (4H, stack, $ArCH_2$), 3.57 (6H, s, OCH_3), 7.32 (2H, s, Ar*H*); δ_C(75 MHz) 22.68 (CH_2, $CH_2CH_2CH_2CH_2$), 22.71 (CH_2, $CH_2CH_2CH_2CH_2$), 27.4 (CH_2, $ArCH_2$), 29.2 (CH_2, $ArCH_2$), 60.5 (CH_3, OCH_3), 113.9 (quat. C, *ipso* Ar), 132.1 (quat. C, *ipso* Ar), 133.0 (CH, Ar), 134.9 (quat. C, *ipso* Ar), 136.1 (quat. C, *ipso* Ar), 151.7 (quat. C, *ipso* Ar); m/*z* (TOF ES+) 503 ($[M + Na]^+$, 100%).

Data were in agreement with those reported in the literature.[133]

(*R*)-3,3'-Diiodo-2,2'-dimethoxy-5,6,7,8,5',6',7',8'-octahydro-[1,1']-binaphthalenyl (*R*)-H_8-119[133]



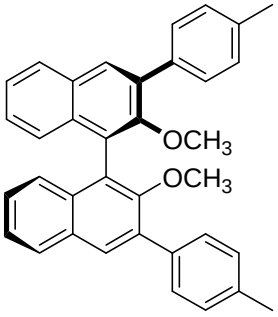
Chemical Formula: $C_{22}H_{24}I_2O_2$
Exact Mass: 573.9866
Molecular Weight: 574.2337
Elemental Analysis: C, 46.02; H, 4.21; I, 44.20; O, 5.57

^{t}BuLi (10.4 mL of a 1.7 M solution in pentane, 17.7 mmol) was added to a solution of binaphthalenyl (*R*)-H_8-**117** (2.00 g, 4.16 mmol) in Et_2O (100 mL) at –78 °C. The orange

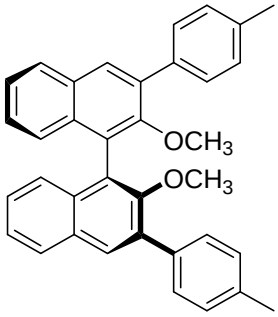
mixture was warmed to 0 °C over 30 min, after which time, a solution of I_2 (2.43 g, 9.58 mmol) in Et_2O (20 mL) was added. After warming up to R.T. overnight, the mixture was poured into $Na_2S_2O_3$ solution (100 mL) and stirred for 2 h. The layers were separated and the aqueous phase was extracted with Et_2O (2 × 100 mL). The combined organic fractions were washed with H_2O (150 mL) and brine (150 mL), and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product. Purification by flash column chromatography (70% hexane, 30% toluene) afforded binaphthalenyl (*R*)-H_8-**119** as a white solid (1.69 g, 71%): mp 123-125 °C; R_f = 0.23 (70% hexane, 30% toluene); $[\alpha]_D^{20}$ = –50.4 (*c* 1.0, $CHCl_3$); δ_H(300 MHz) 1.57-1.78 (8H, stack, $CH_2CH_2CH_2CH_2CH_2$), 2.01-2.14 (2H, m, $ArCH_aH_b$), 2.20-2.34 (2H, m, $ArCH_aH_b$), 2.68-2.79 (4H, stack, $ArCH_2$), 3.49 (6H, s, OCH_3), 7.56 (2H, s, Ar*H*); δ_C(75 MHz) 22.6 (CH_2, $CH_2CH_2CH_2CH_2$), 22.7 (CH_2, $CH_2CH_2CH_2CH_2$), 27.4 (CH_2, $ArCH_2$), 29.0 (CH_2, $ArCH_2$), 60.4 (CH_3, OCH_3), 88.3 (quat. C, *ipso* Ar), 131.4 (quat. C, *ipso* Ar), 135.5 (quat. C, *ipso* Ar), 137.2 (quat. C, *ipso* Ar), 139.1 (CH, Ar), 154.3 (quat. C, *ipso* Ar); m/*z* (TOF ES+) 597.0 ([M + Na]$^+$, 100%).

Data were in agreement with those reported in the literature.[133]

(*R*)- and (*S*)-3,3'-Bis(4-methylphenyl)-2,2'-dimethoxy-1,1'-binaphthyl (*R*)- and (*S*)-123 and (*R*)- and (*S*)-3-(4-methylphenyl)-2,2'-dimethoxy-1,1'-binaphthyl (*R*)- and (*S*)-124

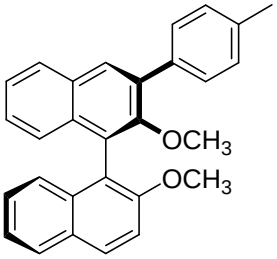


(*R*)-**123**

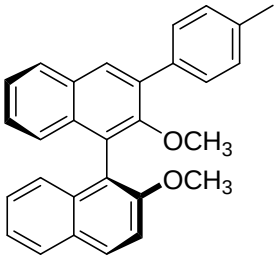


(*S*)-**123**

Chemical Formula: $C_{36}H_{30}O_2$
Exact Mass: 494.2246
Molecular Weight: 494.6222
Elemental Analysis:
C, 87.42; H, 6.11; O, 6.47



(*R*)-**124**



(*S*)-**124**

Chemical Formula: $C_{29}H_{24}O_2$
Exact Mass: 404.1776
Molecular Weight: 404.4997
Elemental Analysis:
C, 86.11; H, 5.98; O, 7.91

(*R*)- and (*S*)-3,3'-Bis(4-methylphenyl)-2,2'-dimethoxy-1,1'-binaphthyl (*R*)- and (*S*)-**123** And the by-products (*R*)- and (*S*)-3-(4-methylphenyl)-2,2'-dimethoxy-1,1'-binaphthyl (*R*)- and (*S*)-**124** were prepared using a previously reported general procedure for the formation of different 3,3'-bis-aryl-2,2'-dimethoxy-1,1'-binaphthyl compounds:[128]

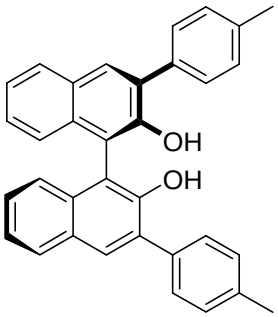
4-Bromotoluene (0.370 mL, 3.00 mmol), $Ba(OH)_2$ (946 mg, 3.00 mmol) and $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) were added to a solution of bis-boronic acid (*S*)-**113** (402 mg, 1.00 mmol) in a mixture of degassed dioxane/H_2O (3:1, 8 mL). The mixture was heated under reflux for 3 h and then cooled to room temperature. The solvents were removed under reduced pressure, and the resulting grey residue was redissolved in CH_2Cl_2 (25 mL) and 1 M hydrochloric acid (25 mL). The organic layer was washed with 1 M hydrochloric acid (25 mL) and brine (25 mL),

and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product. Purification by flash column chromatography (60% hexane, 40% toluene) afforded, in order of elution, bis-coupled product (*S*)-**123** as a white foamy solid (300 mg, 61%): mp 204-207 °C; R_f = 0.40 (60% hexane, 40% toluene); $[\alpha]_D^{20}$ = +19.2 (*c* 1.0, $CHCl_3$); (Found: C, 87.59; H, 6.27. $C_{36}H_{30}O_2$ requires C, 87.42; H, 6.11%); ν_{max}(film)/cm^{-1} 3054m, 3012m, 2934m, 2863w, 1907w, 1806w, 1620w (C=C aromatic), 1591w (C=C aromatic), 1514s (C=C aromatic), 1492m, 1456s, 1398s, 1352m, 1330w, 1308w, 1249s, 1186w, 1172w, 1148m, 1139w, 1131w, 1112w, 1079w, 1039s, 1016s, 979m, 954w, 936w, 916m, 893m, 856w, 822s, 691w, 638w, 615m, 573w; δ_H(300 MHz) 2.44 (6H, s, ArC*H*$_3$), 3.22 (6H, s, OC*H*$_3$), 7.23-7.32 (8H, stack, Ar*H*), 7.38-7.45 (2H, stack, Ar*H*), 7.70 (4H, d, *J* 8.1, Ar*H*), 7.92 (2H, d, *J* 8.1, Ar*H*), 7.98 (2H, s, Ar*H*); δ_C(75 MHz) 21.2 (CH_3, Ar*C*H_3), 60.4 (CH_3, O*C*H_3), 124.9 (CH, Ar), 125.7 (CH, Ar), 125.9 (quat. C, *ipso* Ar), 126.1 (CH, Ar), 127.9 (CH, Ar), 129.0 (CH, Ar), 129.1 (CH, Ar), 130.3 (CH, Ar), 130.8 (quat. C, *ipso* Ar), 133.5 (quat. C, *ipso* Ar), 134.9 (quat. C, *ipso* Ar), 136.0 (quat. C, *ipso* Ar), 136.9 (quat. C, *ipso* Ar), 154.1 (quat. C, *ipso* Ar); m/z (TOF ES+) 517.3 ([M + Na]$^+$, 100%), 495.3 (55, [M]$^+$); HRMS: $C_{36}H_{30}O_2Na$ calcd 517.2144 ([M + Na]$^+$), obsd 517.2161; and after increasing the polarity of the eluent (40% hexane, 60% toluene), mono-coupled product (*S*)-**124** as a white foamy solid (73 mg, 18%): mp 90-92 °C; R_f = 0.20 (40% hexane, 60% toluene); $[\alpha]_D^{22}$ = –103.4 (*c* 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 3055m, 3009m, 2935m, 2838w, 1622m (C=C aromatic), 1594m (C=C aromatic), 1511s (C=C aromatic), 1456s, 1432w, 1398m, 1356m, 1334m, 1267s, 1249s, 1181w, 1147m, 1131w, 1112w, 1089s, 1057m, 1037m, 1018s, 973w, 954w, 924w, 901m, 894m, 865w, 822s, 808m, 706w, 689w, 609m; δ_H(300 MHz) 2.46 (3H, s, ArC*H*$_3$), 3.17 (3H, s, OC*H*$_3$), 3.85 (3H, s, OC*H*$_3$), 7.16-7.46 (8H, stack, Ar*H*), 7.51 (1H, d, *J* 8.1, Ar*H*), 7.72 (2H, d, *J* 8.8, Ar*H*), 7.93 (2H, t, *J* 7.9, Ar*H*), 7.98-8.07 (2H, stack, Ar*H*); δ_C(75 MHz) 21.2 (CH_3, Ar*C*H_3), 56.5 (CH_3, O*C*H_3), 60.3 (CH_3,

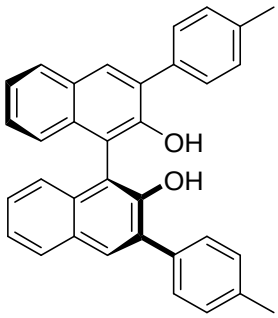
OCH_3), 113.6 (CH, Ar), 119.6 (quat. C, *ipso* Ar), 123.5 (CH, Ar), 124.8 (CH, Ar), 125.3 (CH, Ar), 125.5 (CH, Ar), 125.6 (quat. C, *ipso* Ar), 126.0 (CH, Ar), 126.5 (CH, Ar), 127.87 (CH, Ar), 127.94 (CH, Ar), 128.9 (CH, tolyl Ar), 129.0 (quat. C, *ipso* Ar), 129.2 (CH, tolyl Ar), 129.5 (CH, Ar), 130.1 (CH, Ar), 130.8 (quat. C, *ipso* Ar), 133.3 (quat. C, *ipso* Ar), 134.1 (quat. C, *ipso* Ar), 134.9 (quat. C, *ipso* Ar), 135.9 (quat. C, *ipso* Ar), 136.8 (quat. C, *ipso* Ar), 154.1 (quat. C, *ipso* Ar), 154.8 (quat. C, *ipso* Ar); m/*z* (TOF ES+) 427 ($[M + Na]^+$, 100%); HRMS: $C_{29}H_{24}O_2Na$ calcd 427.1674 ($[M + Na]^+$), obsd 427.1681.

The same protocol was followed for the preparation of the (*R*)-enantiomers (*R*)-**123**: $[\alpha]_D^{20} = -19.0$ (*c* 1.0, $CHCl_3$); and (*R*)-**124**: $[\alpha]_D^{21} = +100.8$ (*c* 1.0, $CHCl_3$).

(*R*)- and (*S*)-3,3'-Bis(4-methylphenyl)-2,2'-dihydroxy-1,1'-binaphthyl (*R*)- and (*S*)-125



(*R*)-**125**



(*S*)-**125**

Chemical Formula: $C_{34}H_{26}O_2$
Exact Mass: 466.1933
Molecular Weight: 466.569
Elemental Analysis:
C, 87.52; H, 5.62; O, 6.86

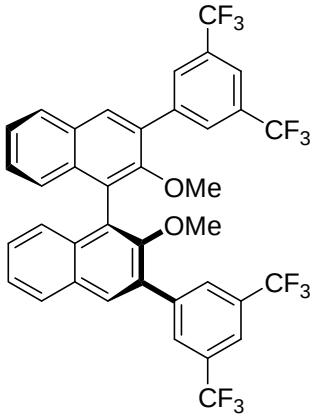
(*R*)- and (*S*)-3,3'-Bis(4-methylphenyl)-2,2'-dihydroxy-1,1'-binaphthyl (*R*)- and (*S*)-**125** were prepared using a previously reported general procedure for the deprotection of different 3,3'-bis-aryl-2,2'-dimethoxy-1,1'-binaphthyl compounds:[128]

A solution of BBr_3 in CH_2Cl_2 (1.0 M, 5.90 mL, 5.90 mmol) was added to a solution of bis-ether (*S*)-**123** (587 mg, 1.19 mmol) in CH_2Cl_2 (100 mL) at 0 °C and the mixture was warmed

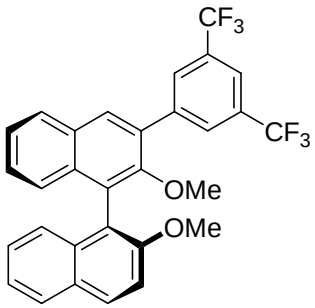
to R.T. overnight. H_2O (4 mL) was added at 0 °C and the mixture was poured into CH_2Cl_2/H_2O (1:1, 200 mL). After stirring for 30 min, the layers were separated and the organic fraction was washed with brine (150 mL), and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product. Purification by flash column chromatography (80% hexane, 20% Et_2O) afforded diol (*S*)-**125** as a white foamy solid (537 mg, 97%): mp 115-125 °C; R_f = 0.33 (80% hexane, 20% Et_2O); $[\alpha]_D^{23}$ = –58.4 (*c* 1.0, $CHCl_3$, e.r. 100:0); Chiralpak AD column, 1.0 mL/min, 10% IPA in hexane, λ = 254 nm, t_R = 22.0 min; (Found: C, 87.24; H, 5.64. $C_{34}H_{26}O_2$ requires C, 87.52; H, 5.62%); ν_{max}(film)/cm^{-1} 3519s (OH), 3056m, 3016m, 2921w (CH_3), 2866w (OCH_3), 1907w, 1802w, 1621m (C=C aromatic), 1597m (C=C aromatic), 1514m (C=C aromatic), 1498m, 1436s, 1403s, 1384m, 1360m, 1335w, 1318m, 1292w, 1238s, 1197w, 1170m, 1147m, 1128s, 1066m, 1022m, 996m, 973w, 951w, 933w, 899m, 879w, 820s, 691m, 638w, 614m; δ_H(300 MHz) 2.45 (6H, s, ArC*H*$_3$), 5.38 (2H, s, O*H*), 7.21-7.45 (10H, stack, Ar*H*), 7.65 (4H, d, *J* 7.7, Ar*H*), 7.93 (2H, d, *J* 7.7, Ar*H*), 8.03 (2H, s, Ar*H*); δ_C(75 MHz) 21.2 (CH_3, Ar*C*H$_3$), 112.4 (quat. C, *ipso* Ar), 124.2 (CH, Ar), 124.3 (CH, Ar), 127.1 (CH, Ar), 128.3 (CH, Ar), 129.2 (CH, Ar), 129.4 (CH, Ar), 130.6 (quat. C, *ipso* Ar), 131.1 (CH, Ar), 132.8 (quat. C, *ipso* Ar), 134.5 (quat. C, *ipso* Ar), 137.5 (quat. C, 2 × *ipso* Ar), 150.2 (quat. C, *ipso* Ar); m/*z* (TOF ES+) 489.2 ([M + Na]$^+$, 100%); HRMS: $C_{34}H_{26}O_2Na$ calcd 489.1831 ([M + Na]$^+$), obsd 489.1825.

The same protocol was followed for the preparation of the (*R*)-enantiomer: $[\alpha]_D^{20}$ = +55.8 (*c* 1.0, $CHCl_3$, e.r. 2:98); Chiralpak AD column, 1.0 mL/min, 10% IPA in hexane, λ = 254 nm, $t_{R,minor}$ = 22.7 min, $t_{R,major}$ = 27.4 min.

(*S*)-3,3'-Bis-(3'',5''-di(trifluoromethyl)phenyl)-2,2'-dimethoxy-[1,1']-binaphthalenyl (*S*)-127 and (*S*)-3-(3'',5''-di(trifluoromethyl)phenyl)-2,2'-dimethoxy-1,1'-binaphthyl (*S*)-128[135]



Chemical Formula: $C_{38}H_{22}F_{12}O_2$
Exact Mass: 738.1428
Molecular Weight: 738.5609
Elemental Analysis: C, 61.80; H, 3.00; F, 30.87; O, 4.33



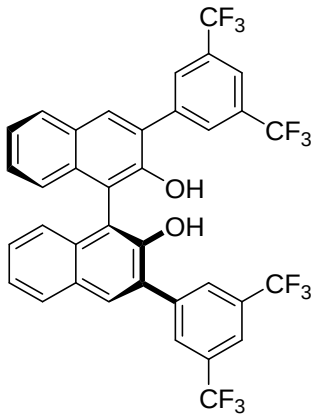
Chemical Formula: $C_{30}H_{20}F_6O_2$
Exact Mass: 526.1367
Molecular Weight: 526.469
Elemental Analysis: C, 68.44; H, 3.83; F, 21.65; O, 6.08

3,5-Bis(trifluoromethyl) iodobenzene (490 μL, 2.75 mmol) and $Pd(PPh_3)_4$ (63 mg, 0.055 mmol) were added sequentially to a solution of bis-boronic acid (*S*)-**113** (368 mg, 0.915 mmol) and Na_2CO_3 (291 mg, 2.75 mmol) in degassed DME/EtOH/H_2O (5.5:1.0:1.4, 7.9 mL). The mixture was heated under reflux for 24 h. After cooling to R.T., the solvents were removed under reduced pressure and the resulting solid was dissolved in CH_2Cl_2 (25 mL). Hydrochloric acid (1 M, 25 mL) was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic fractions were washed with H_2O (30 mL) and brine (30 mL), and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product as a pale yellow oil. Purification by flash column chromatography (gradient: 100% hexane →

80% hexane, 20% toluene) afforded, in order of elution, bis-ether (*S*)-**127** as a white fluffy solid (330 mg, 49%, 7:1 impurity of $Ph_3P=O$): R_f = 0.35 (80% hexane, 20% toluene); $[\alpha]_D$ was not determined; ν_{max}(film)/cm^{-1} 3061m, 3012m, 2941m, 2836w, 1955w, 1806w, 1621m (C=C aromatic), 1594m (C=C aromatic), 1496m, 1464m, 1444m, 1406m, 1378s, 1353w, 1327m, 1279s, 1248m, 1174s br, 1134s br, 1108w, 1085m, 1048s, 1034w, 1018m, 998m, 960m, 924m, 893s, 870w, 845s, 707s, 682s, 669m, 620m; δ_H(300 MHz) 3.21 (6H, s, OC*H*$_3$), 7.27 (2H, d, *J* 8.5, Ar*H*), 7.31-7.55 (4H, stack, Ar*H* and Ar*H* from 12.5 mol% $Ph_3P=O$), 7.94 (2H, s, Ar*H*), 8.00 (2H, d, *J* 8.1, Ar*H*), 8.07 (2H, s, Ar*H*), 8.28 (4H, s, Ar*H*); δ_C(75 MHz) 60.9 (CH_3, O*C*H$_3$), 121.1 (CH, septet, $^3J_{C\text{-}F}$ 4.0, Ar), 123.4 (quat. C, q, $^1J_{C\text{-}F}$ 271.0, Ar*C*F$_3$), 125.7 (CH, Ar), 125.8 (CH, Ar), 125.9 (quat. C, *ipso* Ar), 127.4 (CH, Ar), 128.4 (CH, Ar), 129.5-129.8 (CH, m, Ar), 130.7 (quat. C, 2 × *ipso* Ar), 131.1 (CH, Ar), 131.8 (quat. C, q, $^2J_{C\text{-}F}$ 33.1, *ipso* Ar), 134.2 (quat. C, *ipso* Ar), 140.7 (quat. C, *ipso* Ar), 153.4 (quat. C, *ipso* Ar); δ_F(282 MHz) –63.09 (s, ArC*F*$_3$); m/*z* (TOF ES+) 760.9 ([M + Na]$^+$, 100%); HRMS: $C_{38}H_{22}O_2F_{12}Na$ calcd 761.1326 ([M + Na]$^+$), obsd 761.1335; and then mono-ether (*S*)-**128** as a white foamy solid (50 mg, 10%): mp 145-148 °C; R_f = 0.15 (80% hexane, 20% toluene); $[\alpha]_D$ was not determined; ν_{max}(film)/cm^{-1} 2937w, 2840w, 1622m (C=C aromatic), 1594m (C=C aromatic), 1510m, 1463m, 1444w, 1432w, 1377s, 1355m, 1326m, 1279s, 1249m, 1181s br, 1139s br, 1107w, 1090m, 1061m, 1038m, 1021m, 990w, 929w, 902m, 892m, 845m, 809m, 708m, 682m; δ_H(300 MHz) 3.71 (3H, s, OC*H*$_3$), 3.86 (3H, s, OC*H*$_3$), 7.17-7.55 (7H, stack, Ar*H*), 7.88-8.10 (5H, stack, Ar*H*), 8.30 (2H, s, Ar*H*); δ_C(75 MHz) 56.5 (CH_3, O*C*H$_3$), 60.6 (CH_3, O*C*H$_3$), 113.4 (CH, Ar), 118.7 (quat. C, *ipso* Ar), 120.9 (CH, septet, $^3J_{C\text{-}F}$ 4.0, Ar), 123.5 (quat. C, q, $^1J_{C\text{-}F}$ 271.0, Ar*C*F$_3$), 123.7 (CH, Ar), 125.0 (CH, Ar), 125.5 (CH, Ar), 125.6 (CH, Ar), 126.3 (quat. C, *ipso* Ar), 126.8 (CH, Ar), 127.0 (CH, Ar), 128.1 (CH, Ar), 128.2 (CH, Ar), 129.1 (quat. C, *ipso* Ar), 129.3-129.7 (CH, m, Ar), 130.0 (CH, Ar), 130.4 (CH, Ar), 130.7 (quat. C, *ipso* Ar), 131.5 (quat. C, q, $^2J_{C\text{-}F}$ 33.1, *ipso* Ar), 132.0 (quat. C, *ipso* Ar), 133.9

(quat. C, *ipso* Ar), 134.3 (quat. C, *ipso* Ar), 141.0 (quat. C, *ipso* Ar), 153.4 (quat. C, *ipso* Ar), 154.8 (quat. C, *ipso* Ar); δ_F(282 MHz) –62.99 (s, ArC*F*$_3$); m/*z* (TOF ES+) 549.0 ([M + Na]$^+$, 100%); HRMS: $C_{30}H_{20}O_2F_6Na$ calcd 549.1265 ([M + Na]$^+$), obsd 549.1274.

(*S*)-3,3'-Bis-(3'',5''-di(trifluoromethyl)phenyl)-2,2'-dihydroxy-[1,1']-binaphthalenyl (*S*)-126[135]



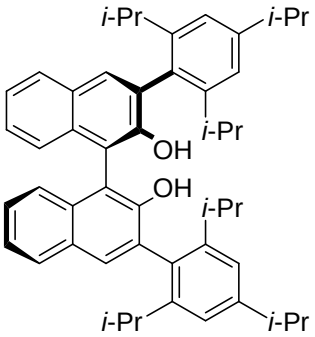
Chemical Formula: $C_{36}H_{18}F_{12}O_2$
Exact Mass: 710.1115
Molecular Weight: 710.5078
Elemental Analysis: C, 60.86; H, 2.55; F, 32.09; O, 4.50

A solution of BBr_3 in CH_2Cl_2 (1.0 M, 1.60 mL, 1.60 mmol) was added to a solution of bis-ether (*S*)-**127** (295 mg, 0.399 mmol) in CH_2Cl_2 (13 mL) at 0 °C and the mixture was warmed to R.T. overnight. H_2O (5 mL) was slowly added over a period of 2 min at 0 °C and the mixture was poured into CH_2Cl_2/H_2O (1:1, 30 mL). After stirring for 30 min, the layers were separated and the organic fraction was washed with brine (10 mL), and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product. Purification by flash column chromatography (gradient: 100% hexane → 80% hexane, 20% toluene) afforded diol (*S*)-**126** as a white fluffy solid (275 mg, 97%): mp 212-215 °C; R_f = 0.20 (80% hexane, 20% toluene); $[\alpha]_D^{19}$ = –51.2 (*c* 1.0, $CHCl_3$) (lit.[134] (*R*)-enantiomer: $[\alpha]_D^{26}$ = +45.3 (*c* 1.06, $CHCl_3$); ν_{max}(film)/cm^{-1} 3534s (OH),

3064m, 1809w, 1621m (C=C aromatic), 1598m (C=C aromatic), 1503m (C=C aromatic), 1473m, 1463m, 1427m, 1378s, 1359m, 1336m, 1279s, 1236m, 1174s br, 1135s br, 1036m, 1022m, 990m, 954w, 936m, 896s, 872m, 845m, 705s, 682m; δ_H(300 MHz) 5.41 (2H, s, O*H*), 7.26 (2H, d, *J* 7.4, Ar*H*), 7.40-7.54 (4H, stack, Ar*H*), 7.94 (2H, br s, Ar*H*), 8.02 (2H, d, *J* 8.1, Ar*H*), 8.14 (2H, br s, Ar*H*), 8.27 (4H, br s, Ar*H*); δ_C(75 MHz) 111.8 (quat. C, *ipso* Ar), 121.3 (CH, septet, $^3J_{C\text{-}F}$ 4.0, Ar), 123.4 (quat. C, q, $^1J_{C\text{-}F}$ 271.0, Ar*C*F_3), 124.0 (CH, Ar), 125.2 (CH, Ar), 127.7 (quat. C, *ipso* Ar), 128.7 (CH, Ar), 128.9 (CH, Ar), 129.5 (quat. C, *ipso* Ar), 129.7-130.1 (CH, m, Ar), 131.6 (quat. C, q, $^2J_{C\text{-}F}$ 32.8, *ipso* Ar), 132.3 (CH, Ar), 133.2 (quat. C, *ipso* Ar), 139.5 (quat. C, *ipso* Ar), 149.9 (quat. C, *ipso* Ar); δ_F(282 MHz) –63.13 (s, ArCF_3); m/*z* (TOF ES–) 709 ([M – H]$^-$, 100%); HRMS: $C_{36}H_{17}O_2F_{12}$ calcd 709.1037 ([M – H]$^-$), obsd 709.1030.

Data were in agreement with those reported in the literature.[134]

(*R*)-3,3'-Bis-(2'',4'',6''-triisopropylphenyl)-2,2'-dihydroxy-[1,1']-binaphthalenyl (*R*)-129[136]



Chemical Formula: $C_{50}H_{58}O_2$
Exact Mass: 690.4437
Molecular Weight: 690.9943
Elemental Analysis: C, 86.91; H, 8.46; O, 4.63

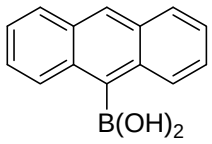
^{n}BuLi (500 μL of a 2.5 M solution in hexane, 1.24 mmol) was added to a solution of 1-bromo-2,4,6-triisopropylbenzene (310 μL, 1.22 mmol) in THF (0.8 mL) at –78 °C. After stirring for

20 min, a solution of $ZnBr_2$ (320 mg, 1.42 mmol) in THF (1.4 mL) was added at –78 °C *via* cannula. The mixture was warmed to R.T. over 5 h, and then the solvent was removed under reduced pressure (~ 10 mmHg) and the colourless oil was dried under reduced pressure (~ 10 mmHg) for 2 h. THF (4.2 mL), diiodo binaphthalenyl (*R*)-**114** (300 mg, 0.530 mmol) and $Pd(P^tBu_3)_2$ (2.7 mg, 5.3 μmol) were added, and the resulting mixture was heated at 60 °C overnight. After cooling to R.T., Et_2O (15 mL) and hydrochloric acid (1 M, 10 mL) were added, and the layers were separated. The aqueous phase was extracted with Et_2O (2 × 10 mL). The combined organic fractions were washed with H_2O (15 mL) and brine (15 mL), and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product which was redissolved in CH_2Cl_2 (15 mL). A solution of BBr_3 in CH_2Cl_2 (1.0 M, 2.65 mL, 2.65 mmol) was added at 0 °C and the mixture was warmed to R.T. overnight. H_2O (5 mL) was added at 0 °C and the mixture was poured into CH_2Cl_2/H_2O (1:1, 30 mL). After stirring for 30 min, the layers were separated and the organic fraction was washed with brine (10 mL), and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product. Purification by flash column chromatography (gradient: 90% hexane, 10% toluene → 70% hexane, 30% toluene) afforded diol (*R*)-**129** as a white fluffy solid (194 mg, 53% over two steps): mp 128-131 °C; R_f = 0.23 (70% hexane, 30% toluene); $[\alpha]_D^{20}$ = +71.8 (*c* 1.0, $CHCl_3$) (lit.[136] $[\alpha]_D^{27}$ = +88.8 (*c* 3.03, THF); ν_{max}(film)/cm^{-1} 3522s (OH), 2961s, 2927w, 2869m, 1604m (C=C aromatic), 1497m (C=C aromatic), 1460s, 1423s, 1383m, 1362m, 1318m, 1257m, 1171m, 1148m, 1016m, 1067m, 994w, 936m, 896m, 879m, 855m, 692m; δ_H(300 MHz) 1.10 (6H, d, *J* 7.0, 2 × CH_3 of ^{i}Pr), 1.16 (6H, d, *J* 6.6, 2 × CH_3 of ^{i}Pr), 1.18 (6H, d, *J* 7.0, 2 × CH_3 of ^{i}Pr), 1.27 (6H, d, *J* 6.6, 2 × CH_3 of ^{i}Pr), 1.38 (12H, d, *J* 7.0, 4 × CH_3 of ^{i}Pr), 2.77 (2H, septet, *J* 6.7, C*H*$(CH_3)_2$), 2.92 (2H, septet, *J* 6.7, C*H*$(CH_3)_2$), 3.03 (2H, septet, *J* 6.7, C*H*$(CH_3)_2$), 5.00 (2H, s, O*H*), 7.16-7.24 (4H, stack, Ar*H*), 7.33-7.48 (6H, stack, Ar*H*), 7.84 (2H, s, Ar*H*), 7.93 (2H, d, *J* 7.7, Ar*H*); δ_C(75 MHz) [23.7, 23.9, 24.0, 24.1,

24.29, 24.32 (CH_3, 3 × CH(*C*H_3)(*C*H_3))], [30.8, 30.9, 34.3 (CH, *C*H(CH_3)$_2$)], 113.1 (quat. C, *ipso* Ar), 121.15 (CH, Ar), 121.21 (CH, Ar), 123.8 (CH, Ar), 124.5 (CH, Ar), 126.6 (CH, Ar), 128.2 (CH, Ar), 129.0 (quat. C, *ipso* Ar), 129.1 (quat. C, *ipso* Ar), 130.4 (quat. C, *ipso* Ar), 130.6 (CH, Ar), 133.4 (quat. C, *ipso* Ar), 147.7 (quat. C, *ipso* Ar), 147.8 (quat. C, *ipso* Ar), 149.1 (quat. C, *ipso* Ar), 150.6 (quat. C, *ipso* Ar); m/*z* (TOF ES+) 713.5 ($[M + Na]^+$, 100%); HRMS: $C_{50}H_{58}O_2Na$ calcd 713.4335 ($[M + Na]^+$), obsd 713.4343.

Data were in agreement with those reported in the literature.[136]

9-Anthracene boronic acid 121[137]



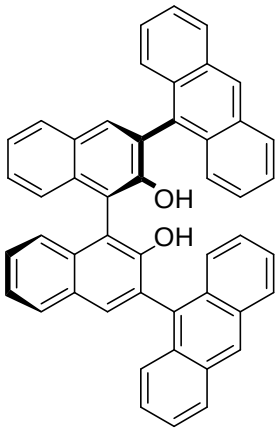
Chemical Formula: $C_{14}H_{11}BO_2$
Exact Mass: 222.0852
Molecular Weight: 222.0469
Elemental Analysis: C, 75.73; H, 4.99; B, 4.87; O, 14.41

*n*BuLi (2.50 mL of a 2.36 M solution in hexane, 5.83 mmol) was added to a solution of 9-bromoanthracene (1.00 g, 3.89 mmol) in THF (32 mL) at –78 °C. The reaction mixture was stirred for 1 h, over which time, the pale brown solution turned orange. $B(OMe)_3$ (650 μL, 5.83 mmol) was added dropwise over 2 min, and the mixture was warmed to R.T. overnight. Hydrochloric acid (2 M, 30 mL) was added at 0 °C and the mixture was stirred at R.T. for 3 h. The layers were separated, and the THF was removed under reduced pressure. The resulting solid was dissolved in EtOAc (50 mL) and washed with $NaHCO_3$ solution (30 mL) and brine (30mL), and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product **121** as a red-orange powder (900 mg, quantitative), which was used without further purification and characterisation.

General procedure for the formation of binaphthalenyl diols (*R*)-H_8-122, (*R*)-130 and (*R*)-133-136[134]

The diiodo binaphthalenyl starting material (3.53 mmol), the boronic acid (14.1 mmol) and Na_2CO_3 (3.03 g, 28.2 mmol) were dissolved in a mixture of degassed toluene/EtOH/H_2O (2:1:1, 58 mL). $Pd(PPh_3)_4$ (404 mg, 0.35 mmol) was added, and the mixture was heated under reflux for 24 h. After cooling to R.T., the solvents were removed under reduced pressure and the resulting solid was dissolved in CH_2Cl_2 (100 mL). Hydrochloric acid (1 M, 100 mL) was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic fractions were washed with H_2O (50 mL) and brine (50 mL), and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product, which was redissolved in CH_2Cl_2 (125 mL). A solution of BBr_3 in CH_2Cl_2 (1.0 M, 17.7 mL, 17.7 mmol) was added at 0 °C and the mixture was warmed to R.T. overnight. H_2O (20 mL) was added at 0 °C and the mixture was poured into CH_2Cl_2/H_2O (1:1, 200 mL). After stirring for 30 min, the layers were separated and the organic fraction was washed with brine (100 mL), and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude diol product, which was purified by flash column chromatography.

(*R*)-3,3’-Bis-(9’’-anthracenyl)-2,2’-dihydroxy-[1,1’]-binaphthalenyl (*R*)-130



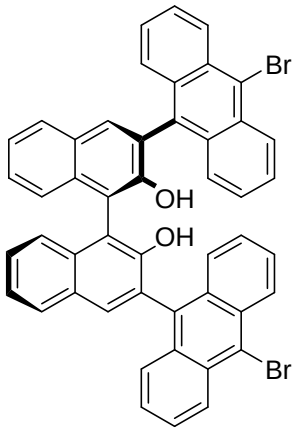
Chemical Formula: $C_{48}H_{30}O_2$
Exact Mass: 638.2246
Molecular Weight: 638.7506
Elemental Analysis: C, 90.26; H, 4.73; O, 5.01

Diol (*R*)-**130** was prepared by Suzuki coupling of (*R*)-3,3’-diiodo-2,2’-dimethoxy-[1,1’]-binaphthalenyl (*R*)-**114** (400 mg, 0.707 mmol) with crude 9-anthracene boronic acid (628 mg, 2.82 mmol), followed by demethylation with BBr_3 in CH_2Cl_2 (1.0 M, 2.80 mL, 2.80 mmol) according to the general procedure. Purification by flash column chromatography (30% hexane, 70% toluene) afforded diol (*R*)-**130** as a pale brown solid (420 mg, 93% over two steps): mp >330 °C; R_f = 0.20 (30% hexane, 70% toluene); $[\alpha]_D^{20}$ = +193.2 (*c* 1.0, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3529s (OH), 3053w, 3009w, 2926w, 1624m (C=C aromatic), 1498m, 1441s, 1401w, 1380w, 1355m, 1333w, 1247s, 1193s, 1148s, 1094m, 1014m, 947m, 931w, 890s, 850s, 796m, 787m, 777w, 736s; δ_H(300 MHz) 5.09 (2H, s, O*H*), 7.22-7.31 (2H, m, Ar*H*), 7.37-7.72 (14H, stack, Ar*H*), 7.83-7.97 (4H, stack, Ar*H*), 8.00-8.14 (6H, stack, Ar*H*), 8.58 (2H, s, Ar*H*); δ_C(75 MHz) 113.5 (quat. C, *ipso* Ar), 124.3 (CH, Ar), 124.8 (CH, Ar), 125.3 (CH, 2 × Ar), 126.1 (CH, Ar), 126.15 (CH, 2 × Ar), 126.20 (CH, Ar), 127.1 (quat. C, *ipso* Ar), 127.4 (CH, Ar), 127.8 (CH, Ar), 128.47 (CH, Ar), 128.54 (CH, Ar), 128.7 (CH, Ar), 129.3 (quat. C, *ipso* Ar), 130.7 (quat. C, *ipso* Ar), 130.76 (quat. C, *ipso* Ar), 130.83 (quat. C, *ipso* Ar), 131.4 (quat. C, *ipso* Ar), 131.5 (quat. C, *ipso* Ar), 133.0 (CH, Ar), 133.9 (quat. C,

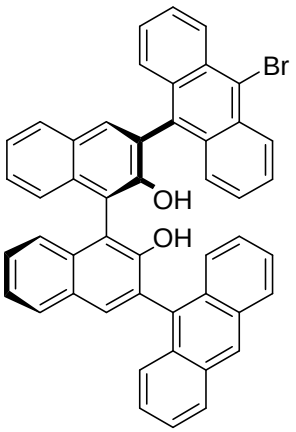
ipso Ar), 151.0 (quat. C, *ipso* Ar); m/*z* (TOF ES–) 637.1 ([M – H]$^-$, 100%); HRMS: $C_{48}H_{29}O_2$ calcd 636.2168 ([M – H]$^-$), obsd 637.2160.

Data were in agreement with those reported in the literature.[134]

(*R*)-3,3'-Bis-(10''-bromoanthracenyl-9''-yl)-2,2'-dihydroxy-[1,1']-binaphthalenyl (*R*)-134 and (*R*)-3-(9''-anthracenyl)-3'-(10''-bromoanthracenyl-9''-yl)-2,2'-dihydroxy-[1,1']-binaphthyl (*R*)-135



Chemical Formula: $C_{48}H_{28}Br_2O_2$
Exact Mass: 794.0456
Molecular Weight: 796.5427
Elemental Analysis: C, 72.38; H, 3.54; Br, 20.06; O, 4.02

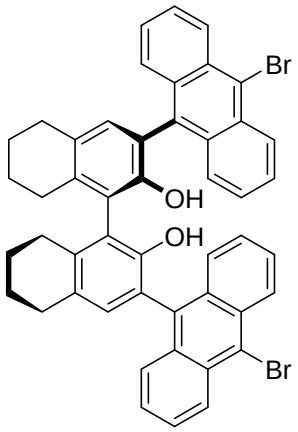


Chemical Formula: $C_{48}H_{29}BrO_2$
Exact Mass: 716.1351
Molecular Weight: 717.6467
Elemental Analysis: C, 80.33; H, 4.07; Br, 11.13; O, 4.46

Diol (*R*)-**134** was prepared by Suzuki coupling of (*R*)-3,3'-diiodo-2,2'-dimethoxy-[1,1']-binaphthalenyl (*R*)-**114** (2.00 g, 3.53 mmol) with 10-bromoanthracene-9-boronic acid **120** (4.25 g, 14.1 mmol) followed by deprotection with BBr_3 in CH_2Cl_2 (1.0 M, 17.7 mL, 17.7 mmol) according to the general procedure. Purification by flash column chromatography (gradient: 90% hexane, 10% toluene → 70% hexane, 30% toluene) afforded, in order of elution, diol (*R*)-**134** as a yellow crystalline solid (2.65 g, 75% over two steps): mp 245-248 °C; R_f = 0.25 (60% hexane, 40% toluene); $[\alpha]_D^{20}$ = +116.0 (*c* 1.0, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3526m (OH), 1622m (C=C aromatic), 1498m, 1438m, 1363w, 1345m, 1329m, 1256m, 1207s, 1149m, 1093m, 1026m, 936m, 890s, 784m, 751s, 735s; δ_H(300 MHz) 5.08 (2H, s, O*H*), 7.24-7.33 (2H, m, Ar*H*), 7.43-7.72 (14H, stack, Ar*H*), 7.83-7.98 (4H, stack, Ar*H*), 8.02 (2H, s, Ar*H*), 8.62 (2H, d, *J* 8.8, Ar*H*), 8.67 (2H, d, *J* 8.8, Ar*H*); δ_C(75 MHz) 113.2 (quat. C, *ipso* Ar), 124.1 (quat. C, *ipso* Ar), 124.5 (CH, Ar), 124.7 (CH, Ar), 126.3 (CH, Ar), 126.4 (CH, Ar), 126.57 (CH, Ar), 126.62 (CH, Ar), 126.8 (quat. C, *ipso* Ar), 127.12 (CH, Ar), 127.14 (CH, Ar), 127.7 (CH, Ar), 128.1 (CH, Ar), 128.2 (CH, Ar), 128.6 (CH, Ar), 129.2 (quat. C, *ipso* Ar), 130.37 (quat. C, *ipso* Ar), 130.42 (quat. C, *ipso* Ar), 131.4 (quat. C, *ipso* Ar), 131.5 (quat. C, *ipso* Ar), 131.7 (quat. C, *ipso* Ar), 133.2 (CH, Ar), 133.9 (quat. C, *ipso* Ar), 150.9 (quat. C, *ipso* Ar); m/*z* (TOF ES–) 795.3 ($[M - H]^-$, 100%); HRMS: $C_{48}H_{27}O_2{}^{79}Br^{81}Br$ calcd 795.0357 ($[M - H]^-$), obsd 795.0341; and then after increasing the polarity of the eluents (gradient: 70% hexane, 30% toluene → 40% hexane, 60% toluene) diol (*R*)-**135** as a pale orange crystalline solid (481 mg, 19%): mp 245-247 °C; R_f = 0.15 (60% hexane, 40% toluene); $[\alpha]_D^{21}$ = +159.6 (*c* 1.05, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3521m (OH), 3050w, 1622w, 1496w, 1438m, 1381w, 1347m, 1258m, 1207m, 1145m, 1093w, 1024w, 935w, 892s, 859m, 843m, 784m, 749s, 730s, 681m; δ_H(300 MHz) 5.07 (1H, s, O*H*), 5.12 (1H, s, O*H)*, 7.27-7.33 (2H, stack, Ar*H*), 7.40-7.75 (14H, stack, Ar*H*), 7.84-8.15 (8H, stack, Ar*H*), 8.58-8.72 (3H, stack, Ar*H*); δ_C(75 MHz) 112.9 (quat. C, *ipso* Ar), 113.8 (quat. C, *ipso* Ar), 123.9 (quat. C, *ipso* Ar), [124.4 (CH, Ar),

124.7 (CH, Ar), 124.9 (CH, Ar), 125.4 (CH, Ar), 125.9 (CH, Ar), 126.0 (CH, Ar), 126.2 (CH, Ar), 126.28 (CH, Ar), 126.33 (CH, Ar), 126.8 (CH, Ar), 127.1 (CH, Ar), 127.5 (CH, Ar), 127.97 (CH, Ar), 128.04 (CH, Ar), 128.2 (CH, Ar), 128.49 (CH, Ar), 128.53 (CH, Ar), 128.6 (CH, Ar), 128.7 (CH, Ar), resonance overlap], 129.2 (quat. C, *ipso* Ar), 129.3 (quat. C, *ipso* Ar), 130.2 (quat. C, *ipso* Ar), 130.37 (quat. C, *ipso* Ar), 130.42 (quat. C, *ipso* Ar), 130.8 (quat. C, *ipso* Ar), 130.9 (quat. C, *ipso* Ar), 131.4 (quat. C, *ipso* Ar), 131.5 (CH, Ar), 132.2 (quat. C, *ipso* Ar), 133.0 (CH, Ar), 133.3 (CH, Ar), 133.9 (quat. C, *ipso* Ar), 150.8 (quat. C, *ipso* Ar), 151.1 (quat. C, *ipso* Ar), resonance overlap of 5 × (quat. C, *ipso* Ar); m/*z* (TOF ES–) 715.2 ([M – H]$^-$, 100%); HRMS: $C_{48}H_{28}O_2{}^{79}Br$ calcd 715.1273 ([M – H]$^-$), obsd 715.1270.

(*R*)-3,3’-Bis-(10’’-bromoanthracenyl-9’’-yl)-2,2’-dihydroxy-5,6,7,8,5’,6’,7’,8’-octahydro-[1,1’]-binaphthalenyl (*R*)-H_8-122

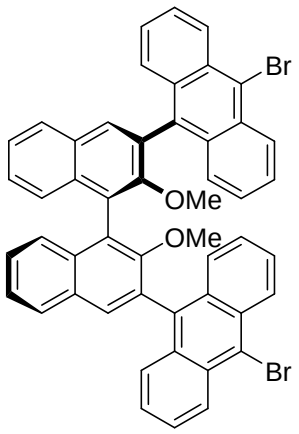


Chemical Formula: $C_{48}H_{36}Br_2O_2$
Exact Mass: 802.1082
Molecular Weight: 804.6062
Elemental Analysis: C, 71.65; H, 4.51; Br, 19.86; O, 3.98

Diol (*R*)-H_8-**122** was prepared by Suzuki coupling of (*R*)-3,3’-diiodo-2,2’-dimethoxy-5,6,7,8,5’,6’,7’,8’-octahydro-[1,1’]-binaphthalenyl (*R*)-H_8-**119** (500 mg, 0.871 mmol) with 10-bromoanthracene-9-boronic acid **120** (1.05 g, 3.48 mmol) followed by deprotection with BBr_3 in CH_2Cl_2 (1.0 M, 3.50 mL, 3.50 mmol). Purification by flash column chromatography

(60% hexane, 40% toluene) afforded diol (*R*)-H_8-**122** as a yellow solid (118 mg, 17% over two steps): mp 190-192 °C; R_f = 0.16 (60% hexane, 40% toluene); $[\alpha]_D^{20}$ = –26.0 (*c* 1.0, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3525m (OH), 2926s (CH_2), 2855w, 1720w br, 1608w (C=C aromatic), 1438s, 1346m, 1256s, 1217s, 1157s, 1088w, 1027m, 968w, 929m, 893s, 860w, 788m, 756s; δ_H(300 MHz) 1.80-1.98 (8H, stack, $CH_2CH_2CH_2CH_2CH_2$), 2.54-2.88 (8H, stack, $ArCH_2$), 4.59 (2H, s, O*H*), 7.07 (2H, s, Ar*H*), 7.23-7.35 (2H, m, Ar*H*), 7.45-7-73 (8H, stack, Ar*H*), 7.83 (2H, d, *J* 8.8, Ar*H*), 8.59 (2H, d, *J* 8.8, Ar*H*), 8.64 (2H, d, *J* 8.8, Ar*H*); δ_C(75 MHz) 23.0 (CH_2, $CH_2CH_2CH_2CH_2CH_2$), 23.2 (CH_2, $CH_2CH_2CH_2CH_2CH_2$), 27.4 (CH_2, $ArCH_2$), 29.2 (CH_2, $ArCH_2$), 120.6 (quat. C, *ipso* Ar), 122.0 (quat. C, *ipso* Ar), 123.4 (quat. C, *ipso* Ar), 125.9 (CH, Ar), 126.1 (CH, Ar), 126.95 (CH, Ar), 126.97 (CH, 2 × Ar), 127.1 (CH, Ar), 127.9 (CH, Ar), 128.1 (CH, Ar), 130.2 (quat. C, *ipso* Ar), 130.4 (quat. C, *ipso* Ar), 130.5 (quat. C, *ipso* Ar), 131.3 (quat. C, *ipso* Ar), 131.4 (quat. C, *ipso* Ar), 132.8 (quat. C, *ipso* Ar), 133.2 (CH, Ar), 137.5 (quat. C, *ipso* Ar), 149.2 (quat. C, *ipso* Ar); m/*z* (TOF ES+) 827 ([M + Na]$^+$, 100%); HRMS: $C_{48}H_{36}{}^{79}Br^{81}BrO_2Na$ calcd 827.0959 ([M + Na]$^+$), obsd 827.0978.

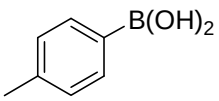
(*R*)-3,3'-Bis-(10''-bromoanthracenyl-9''-yl)-2,2'-dimethoxy-[1,1']-binaphthalenyl (*R*)-131



Chemical Formula: $C_{50}H_{32}Br_2O_2$
Exact Mass: 822.0769
Molecular Weight: 824.5959
Elemental Analysis: C, 72.83; H, 3.91; Br, 19.38; O, 3.88

Binaphthalenyl (*R*)-**131** was prepared by Suzuki coupling of (*R*)-3,3'-diiodo-2,2'-dimethoxy-[1,1']-binaphthalenyl (*R*)-**114** (720 mg, 1.27 mmol) with 10-bromoanthracene-9-boronic acid **120** (1.53 g, 5.09 mmol) according to the general procedure. After work-up and removal of solvent, the residue was redissolved in toluene (50 mL) and passed through a silica plug (100% toluene). The solvent was removed under reduced pressure to afford a shiny yellow solid which was stirred in CH_2Cl_2 (10 mL) for 1 h. Filtration afforded binaphthalenyl (*R*)-**131** as a cream white solid (839 mg, 80%): mp 338-341 °C; $[\alpha]_D^{19}$ = +182.4 (*c* 0.25, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3068w, 2933m, 2840w, 1907w, 1622w (C=C aromatic), 1493m, 1439m, 1398m, 1347m, 1319m, 1256m, 1233s, 1146m, 1099s, 1028m, 1014s, 937m, 894s, 783m, 757s, 729s; δ_H(300 MHz, $C_6D_5CD_3$) 2.73 (6H, s, OC*H*$_3$), 6.81-7.34 (12H, stack, Ar*H*), 7.59-7.68 (6H, stack, Ar*H*), 7.77 (2H, d, *J* 8.8, Ar*H*), 8.02 (2H, d, *J* 8.8 Ar*H*), 8.62 (2H, d, *J* 8.8, Ar*H*), 8.70 (2H, d, *J* 8.8, Ar*H*); δ_C(75 MHz, CD_2Cl_2) 61.4 (CH_3, O*C*H$_3$), 123.7 (quat. C, *ipso* Ar), 126.0 (CH, Ar), 126.1 (quat. C, *ipso* Ar), 126.37 (CH, Ar), 126.43 (CH, Ar), 126.6 (CH, Ar), 127.5 (CH, Ar), 127.68 (CH, Ar), 127.72 (CH, Ar), 127.90 (CH, Ar), 127.93 (CH, Ar), 128.4 (CH, Ar), 128.5 (CH, Ar), 128.9 (CH, Ar), 130.90 (quat. C, *ipso* Ar), 130.92 (quat. C, *ipso* Ar), 131.3 (quat. C, *ipso* Ar), 131.9 (quat. C, *ipso* Ar), 132.0 (quat. C, *ipso* Ar), 132.4 (quat. C, *ipso* Ar), 133.5 (CH, Ar), 134.97 (quat. C, *ipso* Ar), 135.0 (quat.C, *ipso* Ar), 156.0 (quat. C, *ipso* Ar); m/*z* (TOF ES+) 795.3 ($[M + Na]^+$, 100%); HRMS: $C_{50}H_{32}O_2{}^{79}Br^{81}BrNa$ calcd 847.0646 ($[M + Na]^+$), obsd 847.0668.

4-Tolylboronic acid 132[139]

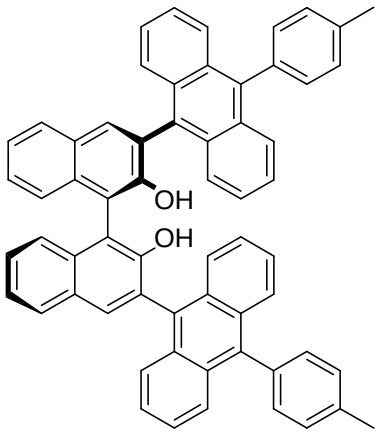


Chemical Formula: $C_7H_9BO_2$
Exact Mass: 136.0696
Molecular Weight: 135.9562
Elemental Analysis: C, 61.84; H, 6.67; B, 7.95; O, 23.54

^{n}BuLi (7.0 mL of a 2.50 M solution in hexane, 17.5 mmol) was slowly added over a period of 7 min to a solution of 4-bromotoluene (2.50 g, 14.6 mmol) in THF (25 mL) at –78 °C. After stirring for 20 min, a solution of $B(OMe)_3$ (2.40 mL, 21.9 mmol) in THF (10 mL) was added. While warming up to R.T. overnight, the clear solution became a white suspension. The mixture was cooled to 0 °C, hydrochloric acid (2 M, 25 mL) was added, and the resulting solution was stirred vigorously at R.T for 3 h. The layers were separated and the solvent was removed under reduced pressure from the organic phase. The resulting white residue was redissolved in EtOAc (50 mL) and washed with $NaHCO_3$ solution (30 mL) and brine (30 mL) and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product. The white solid was recrystallised from H_2O to afford boronic acid **132** as a white powder (1.44 g, 72%): mp 248-250 °C (lit.[214] mp 245-247 °C); δ_H(300 MHz) 2.45 (3H, s, ArC*H*$_3$), 7.32 (2H, d, *J* 8.0, Ar*H*), 8.13 (2H, d, *J* 8.0, Ar*H*); δ_C(75 MHz) 21.9 (CH_3, Ar*C*H_3), 128.8 (CH, Ar), 135.7 (CH, Ar), 142.9 (quat. C, *ipso C*CH_3), (quat. C, *ipso C*$B(OH)_2$) not observed because peak is very broad due to adjacent quadrupole boron nucleus (^{11}B: I = 3/2) resulting in the resonance being lost in the noise.

Data were in agreement with those reported in the literature.[134]

(*R*)-3,3'-Bis-(10''-(4'''-methylphenyl)-anthracenyl-9''-yl)-2,2'-dihydroxy-[1,1']-binaphthalenyl (*R*)-133



Chemical Formula: $C_{62}H_{42}O_2$
Exact Mass: 818.3185
Molecular Weight: 818.9957
Elemental Analysis: C, 90.92; H, 5.17; O, 3.91

Diol (*R*)-**133** was prepared using a modification of the previously reported Suzuki coupling used for similar coupling partners:[138]

Dibromo binaphthalenyl (*R*)-**131** (300 mg, 0.364 mmol), 4-tolylboronic acid **132** (198 mg, 1.46 mmol), tri(3-tolyl)phosphine (17 mg, 0.055 mmol) and K_2CO_3 (96 mg, 0.691 mmol) were dissolved in a mixture of degassed toluene/DME/H_2O (2:2:1, 7.5 mL). $Pd(OAc)_2$ (4 mg, 0.018 mmol) was added, and the mixture was heated under reflux for 24 h. After cooling to R.T., the solvents were removed under reduced pressure and the resulting solid was dissolved in CH_2Cl_2 (30 mL). Hydrochloric acid (1 M, 30 mL) was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic fractions were washed with H_2O (25 mL) and brine (25 mL), and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product which was redissolved in CH_2Cl_2 (13 mL). A solution of BBr_3 in CH_2Cl_2 (1.0 M, 1.5 mL, 1.5 mmol) was added at 0 °C and the mixture was warmed to R.T. overnight. H_2O (5 mL) was added at 0 °C and the mixture was poured into CH_2Cl_2/H_2O (1:1, 30 mL). After stirring for 30 min, the layers were separated and the organic fraction was

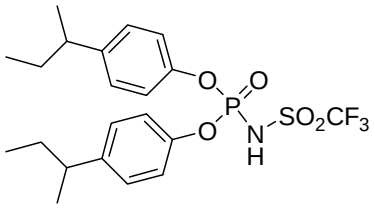
washed with brine (20 mL), and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude diol product. Purification by flash column chromatography (60% hexane, 40% toluene) afforded diol (*R*)-**133** as a yellow solid (286 mg, 96% over two steps): mp 270-272 °C; R_f = 0.31 (60% hexane, 40% toluene); $[\alpha]_D^{20}$ = +45.6 (*c* 1.0, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3526m (OH), 3060w, 3033w, 1623w (C=C aromatic), 1497m, 1439s, 1379s, 1209s, 1144m, 1023m, 944m, 908m, 814s, 768s, 747s; δ_H(300 MHz) 2.55 (6H, s, ArC*H*$_3$), 5.20 (2H, s, O*H*), 7.16-7.56 (20H, stack, Ar*H*), 7.60-7.66 (2H, m, Ar*H*), 7.69-7.82 (6H, stack, Ar*H*), 7.88-7.99 (4H, stack, Ar*H*), 8.08 (2H, s, Ar*H*); δ_C(75 MHz) 19.8 (CH_3, Ar*C*H_3), 111.9 (quat. C, *ipso* Ar), 122.7 (CH, Ar), 123.3 (CH, Ar), 123.5 (CH, 2 × Ar), 124.2 (CH, Ar), 124.3 (CH, Ar), 124.55 (CH, Ar), 124.62 (CH, Ar), 125.75 (CH, Ar), 125.79 (CH, Ar), 125.86 (CH, Ar), 125.91 (quat. C, *ipso* Ar), 126.9 (CH, Ar), 127.49 (CH, Ar), 127.51 (CH, Ar), 127.8 (quat. C, *ipso* Ar), 128.57 (quat. C, *ipso* Ar), 128.63 (quat. C, *ipso* Ar), 128.88 (quat. C, *ipso* Ar), 128.94 (quat. C, *ipso* Ar), 128.98 (quat. C, *ipso* Ar), 129.49 (CH, Ar), 129.53 (CH, Ar), 131.6 (CH, Ar), 132.3 (quat. C, *ipso* Ar), 134.1 (quat. C, *ipso* Ar), 135.6 (quat. C, *ipso* Ar), 136.9 (quat. C, *ipso* Ar), 149.5 (quat. C, *ipso* Ar); m/*z* (TOF ES+) 841.3 ($[M + Na]^+$, 100%); HRMS: $C_{62}H_{42}O_2Na$ calcd 841.3083 ($[M + Na]^+$), obsd 841.3087.

General procedure for the formation of chiral *N*-triflyl phosphoramides 45[87]

NEt_3 (1.85 mL, 13.3 mmol), $POCl_3$ (210 μL, 2.27 mmol) and DMAP (463 mg, 3.79 mmol) were added to a solution of the diol (1.90 mmol) in CH_2Cl_2 (9.5 mL) at 0 °C. After stirring for 2 h at R.T., EtCN (9.5 mL) and $TfNH_2$ (565 mg, 3.79 mmol) were added and the mixture was heated under reflux for 15 h. After cooling to R.T., the reaction was quenched with H_2O (5 mL). Et_2O (40 mL) and hydrochloric acid (4 M, 30 mL) were added, and the layers were

separated. The aqueous phase was extracted with Et_2O (2 × 20 mL), and the combined organic fractions were dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure. Purifiation of the crude product by flash column chromatography afforded the phosphoramide which may be a salt. The product was extracted with Et_2O (40 mL) and hydrochloric acid (4 M, 2 × 25 mL), and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the desired phosphoramide.

4-*sec*-Butylphenoxy-*N*-*tri*flyl posphoramide 162

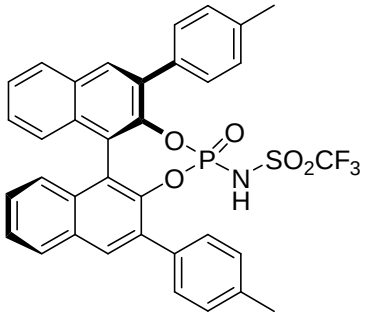


Chemical Formula: $C_{21}H_{27}F_3NO_5PS$
Exact Mass: 493.13
Molecular Weight: 493.4768
Elemental Analysis: C, 51.11; H, 5.51; F, 11.55; N, 2.84; O, 16.21; P, 6.28; S, 6.50

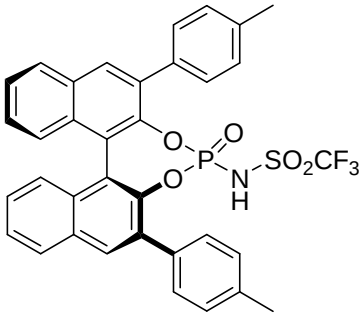
Phosphoramide **162** was prepared from 4-*sec*-butylphenol (360 mg, 2.40 mmol) according to the general procedure. Purification by flash column chromatography (gradient: 60% CH_2Cl_2, 40% EtOAc → 40% CH_2Cl_2, 60% EtOAc) afforded phosphoramide **162** as a yellow wax which changes its colour to purple after the HCl-wash (285 mg, 48%): R_f = 0.18 (50% CH_2Cl_2, 50% EtOAc); ν_{max}(film)/cm^{-1} 2962m, 2925m, 2876w, 1504m (C=C aromatic), 1434m, 1378m, 1272m, 1187s, 1162s, 1139s, 1095m, 935s, 835m; δ_H(300 MHz) 0.79 (6H, t, *J* 7.4, CH_2CH_3), 1.19 (6H, d, *J* 6.9, $CHCH_3$), 1.46-1.63 (4H, stack, CH_2), 2.57 (2H, app. sextet, *J* 7.1, C*H*), 7.04-7.20 (8H, stack, Ar*H*); δ_C(75 MHz) 12.1 (CH_3, CH_3), 21.7 (CH_3, CH_3), 31.1 (CH_2, CH_2), 41.0 (CH, ArCH), 119.1 (quat. C, q, $^1J_{C-F}$ 319.3, $S(O)_2CF_3$), 119.8 (CH, Ar), 128.4 (CH, Ar), 145.7 (quat. C, *ipso* Ar), 147.6 (quat. C, d, J_{C-P} 7.5, *ipso* Ar);

δ_P(121 MHz) –14.95 (s, *P*(O)NH); δ_F(282 MHz) –77.34 (s, C*F*$_3$); m/*z* (TOF ES–) 492.0 ([M – H]$^-$, 100%); HRMS: $C_{21}H_{26}NO_5F_3PS$ calcd 492.1221 ([M – H]$^-$), obsd 492.1223.

(*R*)- and (*S*)-[3,3'-Bis(4-methylphenyl)-1,1'-binaphthalen-2,2'-yl]-*N*-triflyl phosphoramide (*R*)- and (*S*)-45d



(*R*)-**45d**



(*S*)-**45d**

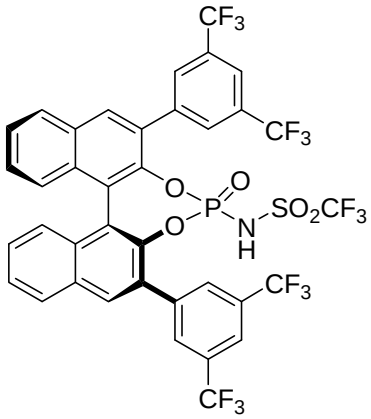
Chemical Formula: $C_{35}H_{25}F_3NO_5PS$
Exact Mass: 659.1143
Molecular Weight: 659.6107
Elemental Analysis: C, 63.73; H, 3.82; F, 8.64; N, 2.12; O, 12.13; P, 4.70; S, 4.86

Phosphoramide (*S*)-**45d** was prepared from diol (*S*)-**125** (280 mg, 0.600 mmol) according to the general procedure. Purification by flash column chromatography (10% EtOAc, 10% toluene, 80% CH_2Cl_2) afforded phosphoramide (*S*)-**45d** as a white solid (351 mg, 89%): mp 257-260 °C; R_f = 0.28 (20% EtOAc, 80% CH_2Cl_2); $[\alpha]_D^{20}$ = +366 (*c* 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 2924w (CH_3), 1614w (C=C aromatic), 1516m (C=C aromatic), 1497w, 1423m, 1290s, 1191s, 1150s, 1097m, 1078w, 1023w, 996m, 974s, 898s, 845m, 820s, 610m; δ_H(300 MHz) 2.29 (6H, s, ArC*H*$_3$), 6.43 (1H, br s, N*H*), 7.00-7.14 (3H, stack, Ar*H*), 7.20-7.48 (8H, stack, Ar*H*), 7.51-7.62 (3H, stack, Ar*H*), 7.87-8.01 (3H, stack, Ar*H*), 8.09 (1H, s, Ar*H*); δ_C(75 MHz) 20.96 (CH_3, Ar*C*H$_3$), 21.01 (CH_3, Ar*C*H$_3$), 118.7 (quat. C, q, $^1J_{C-F}$ 317.9,

$S(O)_2CF_3$), 122.06 (quat. C, d, $J_{C\text{-}P}$ 2.9, *ipso* Ar), 122.17 (quat. C, d, $J_{C\text{-}P}$ 2.9, *ipso* Ar), 126.1 (CH, Ar), 126.4 (CH, Ar), 126.5 (CH, Ar), 126.65 (CH, Ar), 126.68 (CH, Ar), 127.1 (CH, Ar), 128.3 (CH, Ar), 128.4 (CH, Ar), 128.8 (CH, 2 × Ar), 129.3 (CH, 2 × Ar), 129.6 (CH, 2 × Ar), 129.9 (CH, 2 × Ar), 131.4 (CH, Ar), 131.65 (CH, Ar), 131.66 (quat. C, d, $J_{C\text{-}P}$ 5.1, *ipso* Ar), 131.9 (quat. C, d, $J_{C\text{-}P}$ 4.4, *ipso* Ar), 133.01 (quat. C, *ipso* Ar), 133.03 (quat. C, *ipso* Ar), 133.5 (quat. C, d, $J_{C\text{-}P}$ 3.1, *ipso* Ar), 133.8 (quat. C, d, $J_{C\text{-}P}$ 2.6, *ipso* Ar), 137.7 (quat. C, 2 × *ipso* Ar), 137.9 (quat. C, 2 × *ipso* Ar), 142.9 (quat. C, d, $J_{C\text{-}P}$ 9.4, *ipso* Ar), 143.6 (quat. C, d, $J_{C\text{-}P}$ 11.4, *ipso* Ar); δ_P(121 MHz) –1.74 (s, *P*(O)NH); δ_F(282 MHz) –78.97 (s, $S(O)_2CF_3$); m/*z* (TOF ES+) 682.0 ($[M + Na]^+$, 100%); HRMS: $C_{35}H_{25}NO_5F_3PSNa$ calcd 682.1041 ($[M + Na]^+$), obsd 682.1058.

The same protocol was followed for the preparation of the (*R*)-enantiomer: $[\alpha]_D^{20}$ = –372 (*c* 1.0, $CHCl_3$).

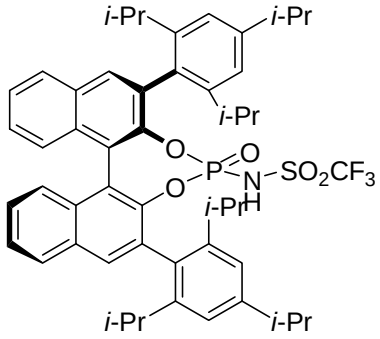
(*S*)-[3,3'-Bis(3'',5''-di(trifluoromethyl)phenyl)-[1,1']-binaphthalen-2,2'-yl]-*N*-triflyl phosphoramide (*S*)-45e



Chemical Formula: $C_{37}H_{17}F_{15}NO_5PS$
Exact Mass: 903.0326
Molecular Weight: 903.5494
Elemental Analysis: C, 49.18; H, 1.90; F, 31.54; N, 1.55; O, 8.85; P, 3.43; S, 3.55

Phosphoramide (*S*)-**45e** was prepared from diol (*S*)-**26** (460 mg, 0.647 mmol) according to the general procedure. Purification by flash column chromatography (gradient: 100% CH_2Cl_2 → 90% CH_2Cl_2, 10% EtOAc) afforded phosphoramide (*S*)-**45e** as a pale purple solid (532 mg, 91%): mp 174-177 °C; R_f = 0.10 (2% EtOAc, 98% CH_2Cl_2); $[\alpha]_D^{19}$ = +225 (*c* 0.5, $CHCl_3$); ν_{max}(film)/cm^{-1} 3385m br (NH), 1693w (C=C aromatic), 1621w, 1503m (C=C aromatic), 1475w, 1380m, 1280s, 1141s, 1082m, 991m, 965m, 925m, 889m, 874w, 845m, 705w, 696w, 681m, 669s; δ_H(300 MHz) 6.01 (1H, br s, N*H*), 7.33-7.72 (7H, stack, Ar*H*), 7.88 (1H, br s, Ar*H*), 8.00-8.16 (8H, stack, Ar*H*); δ_C(75 MHz) 118.4 (quat. C, dq, $^1J_{C\text{-}F}$ 317.9, $^3J_{C\text{-}P}$ 2.0, $S(O)_2CF_3$), 121.6-121.8 (CH, m, Ar), 121.9-122.2 (CH, m, Ar), 122.5 (quat. C, d, $J_{C\text{-}P}$ 2.6, *ipso* Ar), 122.7 (quat. C, d, $J_{C\text{-}P}$ 2.3, *ipso* Ar), 123.08 (quat. C, q, $^1J_{C\text{-}F}$ 271.3, 2 × ArCF_3), 123.10 (quat. C, q, $^1J_{C\text{-}F}$ 271.3, 2 × ArCF_3), 126.9 (CH, Ar), 127.1 (CH, 2 × Ar), 127.4 (CH, Ar), 127.97 (CH, Ar), 128.03 (CH, Ar), 128.8 (CH, Ar), 128.9 (CH, Ar), 129.7 (CH, stack, 2 ×Ar), 130.1 (CH, stack, 2 × Ar), 130.5 (quat. C, d, $J_{C\text{-}P}$ 3.4, *ipso* Ar), 130.9 (quat. C, d, $J_{C\text{-}P}$ 2.6, *ipso* Ar), 131.7-131.9 (quat. C, m, *ipso* Ar), 131.80 (quat. C, q, $^2J_{C\text{-}F}$ 33.4, 2 × *ipso* Ar), 131.9 (quat. C, q, $^2J_{C\text{-}F}$ 33.4, 2 × *ipso* Ar), 132.2-132.4 (quat. C, m, *ipso* Ar), 132.5 (CH, Ar), 132.7 (CH, Ar), 137.75 (quat. C, 2 × *ipso* Ar), 137.83 (quat. C, 2 × *ipso* Ar), 141.6 (quat. C, *ipso* Ar), 141.7 (quat. C, *ipso* Ar), 142.7 (quat. C, *ipso* Ar), 142.9 (quat. C, *ipso* Ar); δ_P(121 MHz) –4.13 (s, *P*(O)NH); δ_F(282 MHz) –63.26 (s, 2 × ArCF_3), –63.566 (s, ArCF_3), –63.570 (s, ArCF_3), –78.74 (s, $S(O)_2CF_3$); m/*z* (TOF ES–) 902.2 ($[M - H]^-$, 100%); HRMS: $C_{37}H_{16}NO_5F_{15}PS$ calcd 902.0247 ($[M - H]^-$), obsd 902.0253.

(*R*)-[3,3'-Bis(2'',4'',6''-triisopropylphenyl)-[1,1']-binaphthalen-2,2'-yl]-*N*-triflyl phosphoramide (*R*)-45a



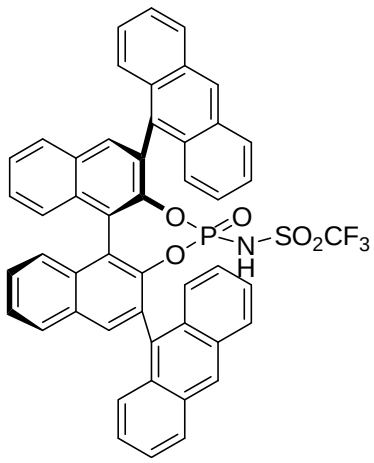
Chemical Formula: $C_{51}H_{57}F_3NO_5PS$
Exact Mass: 883.3647
Molecular Weight: 884.036
Elemental Analysis: C, 69.29; H, 6.50; F, 6.45; N, 1.58; O, 9.05; P, 3.50; S, 3.63

Phosphoramide (*R*)-**45a** was prepared from diol (*R*)-**129** (334 mg, 0.483 mmol) according to the general procedure. Purification by flash column chromatography (gradient: 100% CH_2Cl_2 → 90% CH_2Cl_2, 10% EtOAc) afforded phosphoramide (*R*)-**45a** as a pale brown solid (355 mg, 83%): mp 158-161 °C; R_f = 0.20 (5% EtOAc, 95% CH_2Cl_2); $[\alpha]_D^{21}$ = +33.3 (*c* 0.42, CH_2Cl_2) (lit.[87] $[\alpha]_D^{27.9}$ = +29.9 (*c* 0.42, CH_2Cl_2); ν_{max}(film)/cm^{-1} 3424m br (NH), 2962s (CH_3), 2870w, 1606m (C=C aromatic), 1567w (C=C aromatic), 1496w, 1462m, 1412w, 1384w, 1363m, 1315m, 1195s, 1149m, 1116m, 998m, 976m, 940w, 901m, 878w, 856w, 805w, 666m, 598w; δ_H(300 MHz) 0.95 (3H, d, *J* 7.0, 1 × CH_3 of ^{i}Pr), 1.01 (3H, d, *J* 7.0, 1 × CH_3 of ^{i}Pr), 1.06-1.33 (30H, stack, 10 × CH_3 of ^{i}Pr), 2.47-2.67 (2H, stack, C*H*(CH_3)$_2$), 2.68-2.84 (2H, stack, C*H*(CH_3)$_2$), 2.85-3.02 (2H, stack, C*H*(CH_3)$_2$), 4.85 (1H, br s, N*H*), 7.05 (1H, br s, Ar*H*), 7.10-7.19 (3H, stack, Ar*H*), 7.26-7.42 (4H, stack, Ar*H*), 7.52-7.62 (2H, stack Ar*H*), 7.92-7.83 (4H, stack, Ar*H*); δ_C(75 MHz) 22.76 (CH_3, CH_3 of ^{i}Pr), 22.85 (CH_3, CH_3 of ^{i}Pr), 22.91 (CH_3, CH_3 of ^{i}Pr), 23.0 (CH_3, CH_3 of ^{i}Pr), 23.87 (CH_3, CH_3 of ^{i}Pr), 23.94 (CH_3, CH_3 of ^{i}Pr), 24.0 (CH_3, CH_3 of ^{i}Pr), 24.1 (CH_3, CH_3 of ^{i}Pr), 25.1 (CH_3, CH_3 of ^{i}Pr), 25.5 (CH_3, CH_3 of ^{i}Pr), 26.8 (CH_3, CH_3 of ^{i}Pr), 26.9 (CH_3, CH_3 of ^{i}Pr), 30.4 (CH, *C*H(CH_3)$_2$), 31.1 (CH, 2 × *C*H(CH_3)$_2$), 31.5 (CH, *C*H(CH_3)$_2$), 34.4 (CH, *C*H(CH_3)$_2$), 34.5 (CH, *C*H(CH_3)$_2$), 118.7 (quat. C, q, $^1J_{C-F}$ 320.4, S(O)$_2$*C*F$_3$), 120.3 (CH, Ar), 121.0 (quat. C, d, J_{C-P} 1.7, *ipso* Ar),

121.3 (CH, Ar), 121.4 (CH, Ar), 121.7 (quat. C, d, $J_{C\text{-}P}$ 2.6, *ipso* Ar), 121.8 (CH, Ar), 126.4 (CH, Ar), 126.5 (CH, Ar), 126.7 (CH, Ar), 126.8 (CH, Ar), 127.3 (CH, 2 × Ar), 128.4 (CH, 2 × Ar), 129.7 (quat. C, *ipso* Ar), 130.0 (quat.C, *ipso* Ar), 130.3 (quat. C, d, $J_{C\text{-}P}$ 4.3, *ipso* Ar), 131.2 (quat. C, d, $J_{C\text{-}P}$ 0.9, *ipso* Ar), 131.6 (quat. C, d, $J_{C\text{-}P}$ 1.1, *ipso* Ar), 132.08 (quat. C, d, $J_{C\text{-}P}$ 0.8, *ipso* Ar), 132.1 (quat. C, d, $J_{C\text{-}P}$ 1.7, *ipso* Ar), 132.5 (quat. C, d, $J_{C\text{-}P}$ 2.9, *ipso* Ar), 132.9 (CH, Ar), 133.2 (CH, Ar), 144.6 (quat. C, $J_{C\text{-}P}$ 8.9, *ipso* Ar), 145.4 (quat. C, $J_{C\text{-}P}$ 11.1, *ipso* Ar), 146.2 (quat. C, *ipso* Ar), 146.9 (quat. C, *ipso* Ar), 147.7 (quat. C, *ipso* Ar), 148.0 (quat. C, *ipso* Ar), 149.0 (quat. C, *ipso* Ar), 149.8 (quat. C, *ipso* Ar); δ_P(121 MHz) –3.79 (s, *P*(O)NH); δ_F(282 MHz) –77.40 (s, C*F*$_3$); m/*z* (TOF ES–) 882.1 ([M – H]$^-$, 100%); HRMS: $C_{51}H_{56}NO_5F_3PS$ calcd 882.3569 ([M – H]$^-$), obsd 882.3564.

Data were in agreement with those reported in the literature.[87]

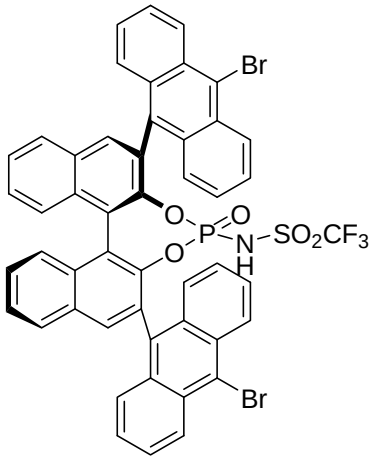
(*R*)-[3,3'-Bis(anthracen-9''-yl)-[1,1']-binaphthalen-2,2'-yl]-*N*-triflyl phosphoramide (*R*)-45f



Chemical Formula: $C_{49}H_{29}F_3NO_5PS$
Exact Mass: 831.1456
Molecular Weight: 831.7922
Elemental Analysis: C, 70.75; H, 3.51; F, 6.85; N, 1.68; O, 9.62; P, 3.72; S, 3.85

Phosphoramide (*R*)-**45f** was prepared from diol (*R*)-**130** (330 mg, 0.517 mmol) according to the general procedure. Purification by flash column chromatography (gradient: 100% CH_2Cl_2 → 90% CH_2Cl_2, 10% EtOAc) afforded phosphoramide (*R*)-**45f** as its ether solvate **45f**·0.55 Et_2O as a brown solid (340 mg, 75%): mp 250-253 °C °C; R_f = 0.11 (100% Et_2O); $[\alpha]_D^{20}$ = +9.6 (*c* 0.83, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3308w, 3053w, 2933w, 2832w, 1594w, 1497w, 1445w, 1402w, 1380w, 1329m, 1308m, 1296m, 1262w, 1226m, 1194m, 1151s, 1135m, 1123m, 1098s, 1024w, 953w, 883s, 839m, 818m, 788m, 775w, 751m, 727s, 706w, 677m, 655w; δ_H(300 MHz, C_6D_6) 0.64 (0.55 × 6H, t, *J* 6.8, $O(CH_2CH_3)_2$), 2.88 (0.55 × 4H, q, *J* 6.8, $O(CH_2CH_3)_2$), 6.80-8.06 (26H, stack, Ar*H*), 8.17 (1H, s, Ar*H*), 8.23 (1H, s, Ar*H*), N*H* was not observed; δ_C(100 MHz, C_6D_6) 14.5 (CH_3, $O(CH_2CH_3)_2$), 66.1 (CH_2, $O(CH_2CH_3)_2$), 122.3 (quat. C, *ipso* Ar), 122.8 (quat. C, *ipso* Ar), 125.1-129.1 (stack, CH, Ar, resonance overlap), 130.6-133.1 (stack, quat. C, $S(O)_2CF_3$ and *ipso* Ar, resonance overlap), 134.8 (CH, Ar), 135.2 (CH, Ar), 146.3 (quat. C, *ipso* Ar), 146.9 (quat. C, *ipso* Ar); δ_P(121 MHz) –3.36 (s, *P*(O)NH); δ_F(282 MHz) –78.58 (s, CF_3); m/*z* (TOF ES–) 830 ($[M - H]^-$, 100%); HRMS: $C_{49}H_{28}NO_5F_3PS$ calcd 830.1378 ($[M - H]^-$), obsd 830.1381.

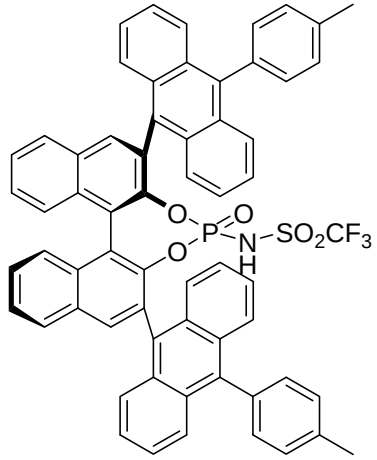
(*R*)-[3,3'-Bis(10''-bromoanthracen-9''-yl)-[1,1']-binaphthalen-2,2'-yl]-*N*-triflyl phosphoramide (*R*)-45g



Chemical Formula: $C_{49}H_{27}Br_2F_3NO_5PS$
Exact Mass: 986.9666
Molecular Weight: 989.5844
Elemental Analysis: C, 59.47; H, 2.75; Br, 16.15; F, 5.76; N, 1.42; O, 8.08; P, 3.13; S, 3.24

Phosphoramide (*R*)-**45g** was prepared from diol (*R*)-**134** (1.52 g, 1.91 mmol) according to the general procedure. Purification by flash column chromatography (gradient: 100% CH_2Cl_2 → 85% CH_2Cl_2, 15% EtOAc) afforded phosphoramide (*R*)-**45g** as its ether solvate **45g**·1.79 Et_2O as a pale brown solid (1.49 g, 70%): mp 245-250 °C (dec.); R_f = 0.25 (100% Et_2O); $[\alpha]_D^{21}$ = +16.2 (*c* 1.06, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3074w, 2926w, 1622w, 1497w, 1441m, 1347w, 1259w, 1195s, 1148w, 1086s, 1029m, 952s, 906s, 881m, 802w, 751s, 713w; δ_H(300 MHz) 0.87 (1.79 × 6H, t, *J* 7.1, $O(CH_2CH_3)_2$), 3.25 (1.79 × 4H, t, *J* 7.1, $O(CH_2CH_3)_2$), 7.08-7.76 (18H, stack, N*H* and Ar*H*), 7.89 (1H, d, *J* 8.7, Ar*H*), 8.01-8.09 (2H, stack, Ar*H*), 8.11-8.17 (2H, stack, Ar*H*), 8.43 (1H, d, *J* 8.7, Ar*H*), 8.53-8.63 (3H, stack, Ar*H*), N*H* not observed; δ_C(100 MHz) 14.4 (CH_3, $O(CH_2CH_3)_2$), 66.0 (CH_2, $O(CH_2CH_3)_2$), 118.4 (quat. C, q, $^1J_{C\text{-}F}$ 319.7, $S(O)_2CF_3$), 121.9 (quat. C, *ipso* Ar), 122.3 (quat. C, *ipso* Ar), 124.0 (quat. C, *ipso* Ar), 124.2 (quat. C, *ipso* Ar), 125.2 (CH, Ar), 126.3 (CH, Ar), 126.36 (CH, Ar), 126.38 (CH, Ar), 126.5 (CH, Ar), [126.6, 126.7 (CH, Ar), resonance overlap], 126.9 (CH, Ar), 127.0 (CH, Ar), [127.5, 127.57, 127.62, 127.7 (CH, Ar), resonance overlap], 127.9 (CH, Ar), 128.1 (CH, Ar), 128.7 (CH, Ar), 128.8 (CH, Ar), 129.8 (quat. C, 2 × *ipso* Ar), 130.0 (quat. C, *ipso* Ar), 130.2 (quat. C, 3 × *ipso* Ar), 130.5 (quat. C, *ipso* Ar), 130.9 (quat. C, *ipso* Ar), 131.08 (quat. C, *ipso* Ar), 131.14 (quat. C, *ipso* Ar), 131.5 (quat. C, *ipso* Ar), 131.6 (quat. C, *ipso* Ar), 131.66 (quat. C, *ipso* Ar), 131.74 (quat. C, *ipso* Ar), 132.7 (quat. C, 2 × *ipso* Ar), 134.4 (CH, Ar), 134.6 (CH, Ar), 145.3 (quat. C, d $J_{C\text{-}P}$ 9.8, *ipso* Ar), 145.8 (quat. C, d, $J_{C\text{-}P}$ 10.5, *ipso* Ar); δ_P(121 MHz) –2.21 (s, *P*(O)NH); δ_F(282 MHz) –79.24 (s, CF_3); m/*z* (TOF ES–) 988.3 ($[M - H]^-$, 100%); HRMS: $C_{49}H_{26}NO_5F_3PS^{79}Br^{81}Br$ calcd 987.9568 ($[M - H]^-$), obsd 987.9572.

(*R*)-[3,3'-Bis(10''-tolylanthracen-9''-yl)-[1,1']-binaphthalen-2,2'-yl]-*N*-triflyl phosphoramide (*R*)-45h

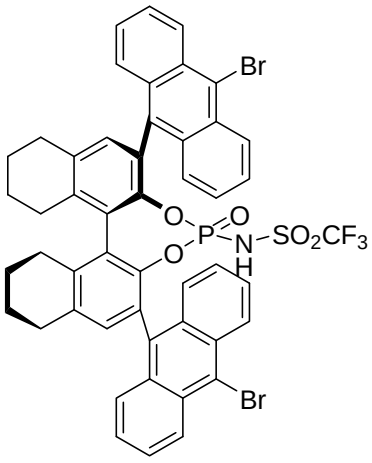


Chemical Formula: $C_{63}H_{41}F_3NO_5PS$
Exact Mass: 1011.2395
Molecular Weight: 1012.0373
Elemental Analysis: C, 74.77; H, 4.08; F, 5.63; N, 1.38; O, 7.90; P, 3.06; S, 3.17

Phosphoramide (*R*)-**45h** was prepared from diol (*R*)-**133** (265 mg, 0.324 mmol) according to the general procedure. Purification by flash column chromatography (gradient: 100% CH_2Cl_2 → 80% CH_2Cl_2, 20% EtOAc) afforded phosphoramide (*R*)-**45h** as a brown glittery solid (207 mg, 63%): mp 273-278 °C (dec.); R_f = 0.18 (20% hexane, 80% Et_2O); $[\alpha]_D^{21}$ = –5.6 (*c* 1.00, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3065w, 2922w, 2867w, 1515w, 1441m, 1382m, 1321m br, 1196s, 1150w, 1135w, 1100m, 1030m, 956m, 902s, 815s, 767s, 751w, 727s; δ_H(300 MHz) 2.55 (6H, s, C*H*$_3$), 7.13-7.88 (30H, stack, Ar*H*), 8.09 (1H, d, *J* 9.5 Ar*H*), 8.12 (1H, d, *J* 9.2, Ar*H*), 8.26 (1H, s, Ar*H*), 8.31 (1H, s, Ar*H*); δ_C(75 MHz) 21.4 (CH_3, 2 × Ar*C*H_3), 118.3 (quat. C, q, $^1J_{C\text{-}F}$ 320.1, $^3J_{C\text{-}P}$ 1.4, $S(O)_2CF_3$), 121.9 (quat. C, d, $J_{C\text{-}P}$ 1.7, *ipso* Ar), 122.3 (quat. C, d, $J_{C\text{-}P}$ 2.6, *ipso* Ar), 124.6 (CH, Ar), 124.76 (CH, Ar), 124.78 (CH, Ar), 125.0 (CH, Ar), 125.1 (CH, Ar), 125.2 (CH, Ar), 125.6 (CH, Ar), 125.7 (CH, Ar), 125.97 (CH, Ar), 126.03 (CH, Ar), 126.7 (CH, 2 × Ar), 127.1-127.5 (CH, stack, 8 × Ar), 127.6 (CH, Ar), 127.8 (CH, Ar), 128.6 (CH, Ar), 128.76 (CH, Ar), 128.84 (CH, Ar), 128.9 (CH, Ar), 129.13 (CH, Ar), 129.15 (CH, Ar), 129.57 (quat. C, *ipso* Ar), 129.59 (quat. C, *ipso* Ar), 129.7 (quat. C, *ipso* Ar), 129.8 (quat. C, *ipso* Ar), 128.98 (quat. C, *ipso* Ar), 130.04 (quat. C, *ipso* Ar), 130.06 (quat. C, *ipso* Ar),

130.09 (quat. C, *ipso* Ar), 130.1 (quat. C, *ipso* Ar), 130.17 (quat. C, *ipso* Ar), 130.22 (quat. C, *ipso* Ar), 130.5 (quat. C, *ipso* Ar), 130.8 (CH, Ar), 130.9 (CH, Ar), 131.2 (CH, 2 × Ar), 131.7 (quat. C, d, $J_{C\text{-}P}$ 0.9, *ipso* Ar), 132.0 (quat. C, d, $J_{C\text{-}P}$ 1.1, *ipso* Ar), 132.5 (quat. C, d, $J_{C\text{-}P}$ 1.4, *ipso* Ar), 132.7 (quat. C, d, $J_{C\text{-}P}$ 0.6, *ipso* Ar), 134.5 (CH, 2 × Ar), 135.5 (quat. C, *ipso* Ar), 136.0 (quat. C, *ipso* Ar), 136.9 (quat. C, *ipso* Ar), 137.1 (quat. C, *ipso* Ar), 138.5 (quat. C, *ipso* Ar), 138.9 (quat. C, *ipso* Ar), 145.3 (quat. C, d $J_{C\text{-}P}$ 9.1, *ipso* Ar), 146.1 (quat. C, d, $J_{C\text{-}P}$ 11.4, *ipso* Ar); δ_P(121 MHz) –3.68 (s, *P*(O)NH); δ_F(282 MHz) –78.72 (s, C*F*$_3$); m/*z* (TOF ES–) 1010.0 ([M – H]$^-$, 100%); HRMS: $C_{63}H_{40}NO_5F_3PS$ calcd 1010.2317 ([M – H]$^-$), obsd 1010.2311.

(*R*)-[3,3'-Bis(10''-bromoanthracen-9''-yl)-5,6,7,8,5',6',7',8'-octahydro-[1,1']-binaphthalen-2,2'-yl]-*N*-triflyl phosphoramide (*R*)-H$_8$-45j

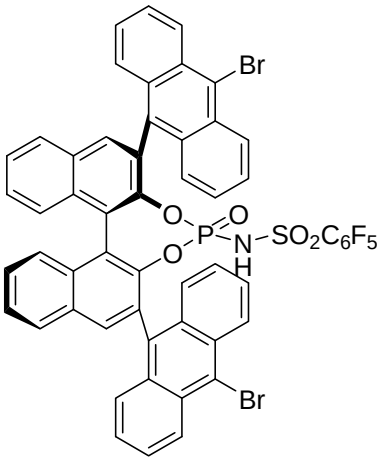


Chemical Formula: $C_{49}H_{35}Br_2F_3NO_5PS$
Exact Mass: 995.0292
Molecular Weight: 997.6479
Elemental Analysis: C, 58.99; H, 3.54; Br, 16.02; F, 5.71; N, 1.40; O, 8.02; P, 3.10; S, 3.21

Phosphoramide (*R*)-H$_8$-**45j** was prepared from diol (*R*)-H$_8$-**122** (118 mg, 0.147 mmol) according to the general procedure. Purification by flash column chromatography (gradient: 90% CH_2Cl_2, 10% EtOAc → 70% CH_2Cl_2, 30% EtOAc) afforded phosphoramide (*R*)-H$_8$-**45j** as its ether solvate **45j**·0.49 Et_2O as brown solid (106 mg, 70%): mp 195-198 °C; R_f = 0.09

(95% CH_2Cl_2, 5% EtOAc); $[\alpha]_D^{21}$ = –128.9 (*c* 0.76, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2925m, 2852m, 1699m, 1605w, 1523w, 1440m, 1407w, 1296m, 1259m, 1193s, 1134m, 1089m, 1029m, 941s, 906s, 885s, 860m, 785m, 755s, 726m, 682m, 662w; δ_H(300 MHz) 1.25 (0.49 × 6H, t, *J* 7.1, $O(CH_2CH_3)_2$), 1.95-2.07 (8H, stack, $CH_2CH_2CH_2CH_2$), 2.59-3.12 (8H, stack, $ArCH_2$), 4.09 (0.49 × 4H, q, *J* 7.1, $O(CH_2CH_3)_2$), 7.26-7.65 (10H, stack, Ar*H*), 7.77 (1H, d, *J* 8.9, Ar*H*), 7.86 (1H, d, *J* 8.5, Ar*H*), 8.21 (2H, br s, Ar*H*), 8.49 (1H, d, *J* 8.9, Ar*H*), 8.58 (3H, app. d, *J* 8.7, Ar*H*), N*H* not observed; δ_C(100 MHz) not recorded; δ_P(121 MHz, C_6D_6) –3.88 (s, *P*(O)NH); δ_F(282 MHz, C_6D_6) –78.97 (s, CF_3); m/*z* (TOF ES–) 996.0 ([M – H]$^-$, 100%); HRMS: $C_{49}H_{34}NO_5F_3PS^{79}Br^{81}Br$ calcd 994.0214 ([M – H]$^-$), obsd 994.0208.

(*R*)-[3,3'-Bis(10''-bromoanthracen-9''-yl)-[1,1']-binaphthalen-2,2'-yl]-*N*-pentafluorophenylsulfonyl phosphoramide (*R*)-107

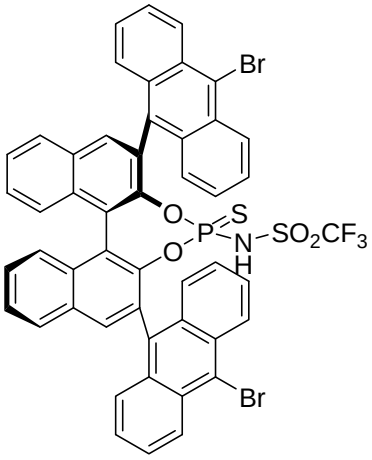


Chemical Formula: $C_{54}H_{27}Br_2F_5NO_5PS$
Exact Mass: 1084.9634
Molecular Weight: 1087.6347
Elemental Analysis: C, 59.63; H, 2.50; Br, 14.69; F, 8.73; N, 1.29; O, 7.36; P, 2.85; S, 2.95

Phosphoramide (*R*)-**107** was prepared from diol (*R*)-**134** (150 mg, 0.188 mmol) using a modification of the general procedure: $C_6F_5SO_2NH_2$ (93 mg, 0.377 mmol) was added instead of $TfNH_2$. Purification by flash column chromatography (gradient: 100% CH_2Cl_2 → 90% CH_2Cl_2, 10% EtOAc) afforded phosphoramide (*R*)-**107** as a yellow-brown crystalline solid

(160 mg, 78%): mp 255-260 °C (dec.); R_f = 0.23 (90% CH_2Cl_2, 10% EtOAc); $[\alpha]_D^{20}$ = +14.4 (*c* 1.00, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3068w, 1644w, 1520m, 1498s, 1441m, 1402m, 1346m, 1302m, 1259w, 1227m, 1206w, 1179m, 1147m, 1099m, 1029m, 991m, 976m, 954m, 936m, 906s, 889s, 807w, 785w, 775w, 752s, 713m, 681m; δ_H(300 MHz) 4.57 (1H, br s, N*H*), 7.12-7.80 (17H, stack, Ar*H*), 7.87 (1H, d, *J* 8.7, Ar*H*), 7.97-8.13 (3H, stack, Ar*H*), 8.20 (1H, s, Ar*H*), 8.51 (1H, d, *J* 8.7, Ar*H*), 8.58-8.73 (3H, stack, Ar*H*); δ_C(100 MHz) 121.8 (quat. C, *ipso* Ar), 122.4 (quat. C, *ipso* Ar), 124.0 (quat. C, *ipso* Ar), 124.8 (quat. C, *ipso* Ar), [125.3 (CH, Ar), 125.6 (CH, Ar), 125.8 (CH, Ar), 125.9 (CH, Ar), 126.4 (CH, Ar), 126.5 (CH, Ar), 126.7 (CH, Ar), 126.75-127.15 (CH, stack, Ar), 127.3 (CH, Ar), 127.6 (CH, Ar), 128.1 (CH, Ar), 128.2 (CH, Ar), 128.7 (CH, Ar), resonance overlap], 129.4 (quat. C, *ipso* Ar), 129.5 (quat.C, *ipso* Ar), 130.2 (quat. C, 2 × *ipso* Ar), 130.3 (quat. C, 2 × *ipso* Ar), 130.5 (quat. C, *ipso* Ar), 130.6 (quat. C, *ipso* Ar), 130.8 (quat. C, *ipso* Ar), 131.0 (quat. C, *ipso* Ar), 131.3 (quat. C, *ipso* Ar), 131.6 (quat. C, 2 × *ipso* Ar), 131.9 (quat. C, *ipso* Ar), 132.5 (quat. C, *ipso* Ar), 132.7 (quat. C, *ipso* Ar), 134.3 (CH, Ar), 134.4 (CH, Ar), 135.4 (quat. C, app. br s, *ipso* Ar*C*F), 137.9 (quat. C, app. br s, *ipso* Ar*C*F), 142.3 (quat. C, app. br s, *ipso* Ar*C*F), 144.3 (quat. C, d $J_{C\text{-}P}$ 8.3, *ipso* Ar), 144.9 (quat. C, app. br s, *ipso* Ar*C*F), 145.7 (quat. C, d, $J_{C\text{-}P}$ 11.8, *ipso* Ar); δ_P(121 MHz) –6.46 (s, *P*(O)NH); δ_F(282 MHz) –159.1- –158.4 (m, 2 × Ar*F*), –143.2- –142.8 (m, Ar*F*), –136.9- –136.4 (m, 2 × Ar*F*); m/*z* (TOF ES–) 1086.1 ($[M - H]^-$, 100%); HRMS: $C_{54}H_{26}NO_5F_5PS^{79}Br^{81}Br$ calcd 1085.9536 ($[M - H]^-$), obsd 1085.9517.

(*R*)-[3,3'-Bis(10''-bromoanthracen-9''-yl)-[1,1']-binaphthalen-2,2'-yl]-*N*-triflyl thiophosphoramide (*R*)-108

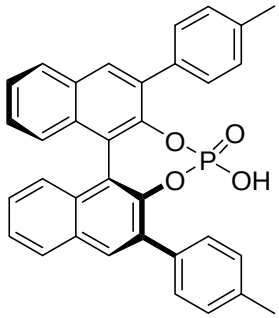


Chemical Formula: $C_{49}H_{27}Br_2F_3NO_4PS_2$
Exact Mass: 1002.9438
Molecular Weight: 1005.65
Elemental Analysis: C, 58.52; H, 2.71; Br, 15.89; F, 5.67; N, 1.39; O, 6.36; P, 3.08; S, 6.38

Thiophosphoramide (*R*)-**108** was prepared from diol (*R*)-**134** (188 mg, 0.236 mmol) using a modification of the general procedure: $PSCl_3$ (30 μL, 0.283 mmol) was added instead of $POCl_3$. Purification by flash column chromatography (gradient: 100% CH_2Cl_2 → 90% CH_2Cl_2, 10% EtOAc) afforded thiophosphoramide (*R*)-**108** as its ether solvate **108**·0.70 Et_2O as a brown-orange solid (116 mg, 46%): mp 247-252 °C; R_f = 0.20 (100% Et_2O); $[\alpha]_D^{20}$ = +25.1 (*c* 0.91, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3076w, 1440w, 1424w, 1311w, 1200s, 1133m, 1100w, 1081w, 955m, 931w, 907s, 882s, 866s, 805w, 752s, 720w, 710w, 675w, 652w; δ_H(300 MHz) 0.98 (0.70 × 6H, t, *J* 7.0, $O(CH_2CH_3)_2$), 3.27 (0.70 × 4H, q, *J* 7.0, $O(CH_2CH_3)_2$), 5.72 (1H, br s, P(S)N*H*), 7.27-7.78 (16H, stack, Ar*H*), 7.94-8.27 (6H, stack, Ar*H*), 8.54-8.73 (4H, stack, Ar*H*); δ_C(100 MHz) 14.7 (CH_3, $O(CH_2CH_3)_2$), 65.5 (CH_2, $O(CH_2CH_3)_2$), 118.0 (quat. C, q, $^1J_{C\text{-}F}$ 321.3, $S(O)_2CF_3$), 122.4 (quat. C, *ipso* Ar), 123.0 (quat. C, *ipso* Ar), 124.2 (quat. C, *ipso* Ar), 124.8 (quat. C, *ipso* Ar), 125.2 (CH, Ar), 126.0 (CH, Ar), 126.2 (CH, Ar), 126.3 (CH, Ar), 126.5 (CH, Ar), 126.7 (CH, Ar), 126.8 (CH, Ar), 126.9 (CH, 3 × Ar), 127.2 (CH, 2 × Ar), 127.3 (CH, Ar), 127.5 (CH, 2 × Ar), 127.6 (CH, 2 × Ar), 127.8 (CH, Ar), 128.0 (CH, Ar), 128.1 (CH, Ar), 128.5 (CH, Ar), 128.6 (CH, Ar), 128.7 (CH, 2 × Ar), 129.8 (quat. C, *ipso*

Ar), 130.1 (quat.C, *ipso* Ar), 130.4 (quat. C, br s, 4 × *ipso* Ar), 130.6 (quat. C, *ipso* Ar), 130.8 (quat. C, *ipso* Ar), 131.0 (quat. C, 2 × *ipso* Ar), 131.2 (quat. C, *ipso* Ar), 131.5 (quat. C, *ipso* Ar), 131.8 (quat. C, *ipso* Ar), 131.9 (quat. C, *ipso* Ar), 132.8 (quat. C, *ipso* Ar), 132.9 (quat. C, *ipso* Ar), 134.75 (CH, Ar), 134.82 (CH, Ar), 144.8 (quat. C, d $J_{C\text{-}P}$ 8.6, *ipso* Ar), 146.6 (quat. C, d, $J_{C\text{-}P}$ 15.7, *ipso* Ar); δ_P(121 MHz) 54.03 (s, *P*(S)NH); δ_F(282 MHz) –76.13 (s, C*F*$_3$); m/*z* (TOF ES–) 1004.3 ([M – H]$^-$, 100%); HRMS: $C_{49}H_{26}NO_4F_3PS_2{}^{79}Br^{81}Br$ calcd 1003.9339 ([M – H]$^-$), obsd 1003.9344.

(*S*)-[3,3'-Bis(4-methylphenyl)-1,1'-binaphthalen-2,2'-yl]-phosphoric acid (*S*)-32g



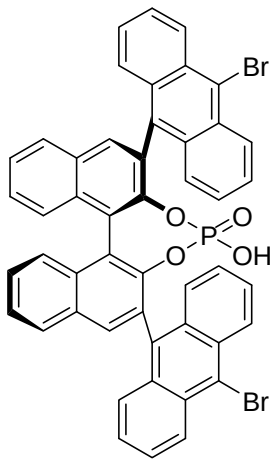
Chemical Formula: $C_{34}H_{25}O_4P$
Exact Mass: 528.1490
Molecular Weight: 528.5337
Elemental Analysis: C, 77.26; H, 4.77; O, 12.11; P, 5.86

Phosphoric acid (*S*)-**32g** was prepared using a previously reported general procedure for the formation of different BINOL-derived phosphoric acids:[90]

$POCl_3$ (80 µL, 0.857 mmol) was added to a solution of diol (*S*)-**125** (200 mg, 0.439 mmol) in pyridine (1 mL) at R.T. After stirring for 3 h at R.T., the reaction was quenched with H_2O (1 mL) and the resulting suspension was stirred overnight. CH_2Cl_2 (15 mL) was added and the pyridine was removed by reverse extraction with hydrochloric acid (1 M, 2 × 15 mL). The organic layer was dried (Na_2SO_4), the drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product. Purification by flash column chromatography (90% CH_2Cl_2, 10% EtOH) afforded the phosphoric acid as a white

solid. The product was extracted with hydrochloric acid (4 M, 20 mL) again, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford the desired phosphoric acid (*S*)-**32g** (201 mg, 87%): mp 230-265 °C (dec.); R_f = 0.38 (90% CH_2Cl_2, 10% EtOH); $[\alpha]_D^{21}$ = +167.5 (*c* 0.53, $CHCl_3$); ν_{max}(film)/cm^{-1} 2922m, 1615w, 1516s (C=C aromatic), 1497m, 1447w, 1419s, 1362w, 1332m, 1265s, 1244s, 1191s, 1151s, 1024s, 998w, 970s, 900m, 888w, 879w, 845m, 820s, 611m, 603w; δ_H(300 MHz) 2.18 (6H, s, ArC*H*$_3$), 7.08 (4H, d, *J* 7.7, Ar*H*), 7.24-7.39 (4H, stack, Ar*H*), 7.44-7.54 (6H, stack, Ar*H*), 7.94 (2H, d, *J* 8.5, Ar*H*), 7.99 (2H, s, Ar*H*), 9.47 (1H, br s, P(O)O*H*); δ_C(75 MHz) 20.7 (CH_3, Ar*C*H_3), 123.2 (quat. C, *ipso* Ar), 124.9 (CH, Ar), 125.8 (CH, Ar), 126.9 (CH, Ar), 128.1 (CH, Ar), 128.8 (CH, Ar), 129.7 (CH, Ar), 130.2 (CH, Ar), 130.9 (quat. C, *ipso* Ar), 132.2 (quat. C, *ipso* Ar), 134.6 (quat. C, *ipso* Ar), 134.9 (quat. C, *ipso* Ar), 136.6 (quat. C, *ipso* Ar), 146.8 (quat. C, d, $^2J_{P\text{-}C}$ 9.5, *ipso* Ar); δ_P(121 MHz) 4.00 (s, *P*(O)OH); m/*z* (TOF ES–) 527.1 ([M – H]$^-$, 100%); HRMS: $C_{34}H_{24}O_4P$ calcd 527.1412 ([M – H]$^-$), obsd 527.1414.

(*R*)-[3,3'-Bis(10''-bromoanthracen-9''-yl)-[1,1']-binaphthalen-2,2'-yl]-phosphoric acid (*R*)-32h

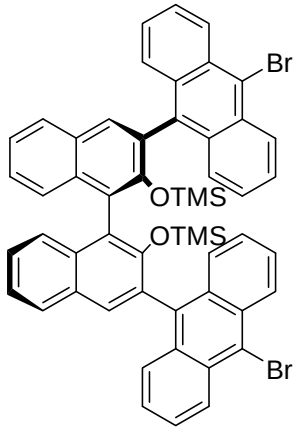


Chemical Formula: $C_{48}H_{27}Br_2O_4P$
Exact Mass: 856.0014
Molecular Weight: 858.5073
Elemental Analysis: C, 67.15; H, 3.17; Br, 18.61; O, 7.45; P, 3.61

Phosphoric acid (*S*)-**32h** was prepared using a previously reported general procedure for the formation of different BINOL-derived phosphoric acids:[90]

$POCl_3$ (50 μL, 0.502 mmol) was added to a solution of diol (*R*)-**134** (200 mg, 0.251 mmol) in pyridine (0.6 mL) at R.T. After stirring for 3 h at R.T., the reaction was quenched with H_2O (1 mL) and the resulting suspension was stirred overnight. CH_2Cl_2 (25 mL) was added and the pyridine was removed by reverse extraction with hydrochloric acid (1 M, 2 × 15 mL). The organic layer was dried ($MgSO_4$), the drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product. Purification by flash column chromatography (gradient: 100% CH_2Cl_2 → 95% CH_2Cl_2, 5% EtOH) afforded the phosphoric acid as a pale yellow crystalline solid. The product was extracted with hydrochloric acid (4 M, 20 mL) again, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford the desired phosphoric acid (*S*)-**32h** as a brown crystalline solid (200 mg, 93%): mp 252-257 °C (dec.); R_f = 0.19 (95% CH_2Cl_2, 5% EtOH); $[\alpha]_D^{20}$ = +70.5 (*c* 0.76, $CHCl_3$); ν_{max}(film)/cm^{-1} 3045w, 2924w, 1622w (C=C aromatic), 1599w, 1523w, 1497w, 1440m, 1419s, 1398w, 1346m, 1311m, 1259m, 1229m, 1183w, 1147m, 1102m, 1087m, 1017s, 972s, 948m, 937m, 903s, 884s, 840m, 783w, 775w, 749s, 714m, 682m, 669w; δ_H(300 MHz) 6.95 (1H, br s, O*H*), 7.10-7.19 (4H, stack, Ar*H*), 7.20-7.29 (2H, stack, Ar*H*), 7.39-7.75 (12H, stack, Ar*H*), 7.95 (2H, s, Ar*H*), 7.99 (2H, d, *J* 7.9, Ar*H*), 8.11-8.20 (2H, stack, Ar*H*), 8.43 (2H, d, *J* 8.9, Ar*H*); δ_C(100 MHz) 122.2 (quat. C, *ipso* Ar), 123.8 (quat. C, *ipso* Ar), 125.2 (CH, Ar), 126.0 (CH, Ar), 126.3 (CH, Ar), 126.4 (CH, Ar), 126.5 (CH, Ar), 126.6 (CH, Ar), 127.2 (CH, 2 × Ar), 127.4 (CH, Ar), 127.8 (CH, Ar), 127.9 (CH, Ar), 128.5 (CH, Ar), 129.8 (quat. C, *ipso* Ar), 130.1 (quat. C, *ipso* Ar), 130.4 (quat. C, *ipso* Ar), 131.0 (quat. C, *ipso* Ar), 131.2 (quat. C, *ipso* Ar), 131.3 (quat. C, *ipso* Ar), 131.4 (quat. C, *ipso* Ar), 132.7 (quat. C, *ipso* Ar), 134.0 (CH, Ar), 146.1 (quat. C, d, J_{C-P} 8.9, *ipso* Ar); δ_P(121 MHz) 0.57 (s, *P*(O)OH); m/*z* (TOF ES–) 857.0 ([M – H]$^-$, 100%); HRMS: $C_{48}H_{26}O_4P^{79}Br^{81}Br$ calcd 856.9915 ([M – H]$^-$), obsd 856.9926.

(*R*)-3,3'-Bis-(10''-bromoanthracenyl-9''-yl)-2,2'-ditrimethylsilyl-[1,1']-binaphthalenyl (*R*)-140



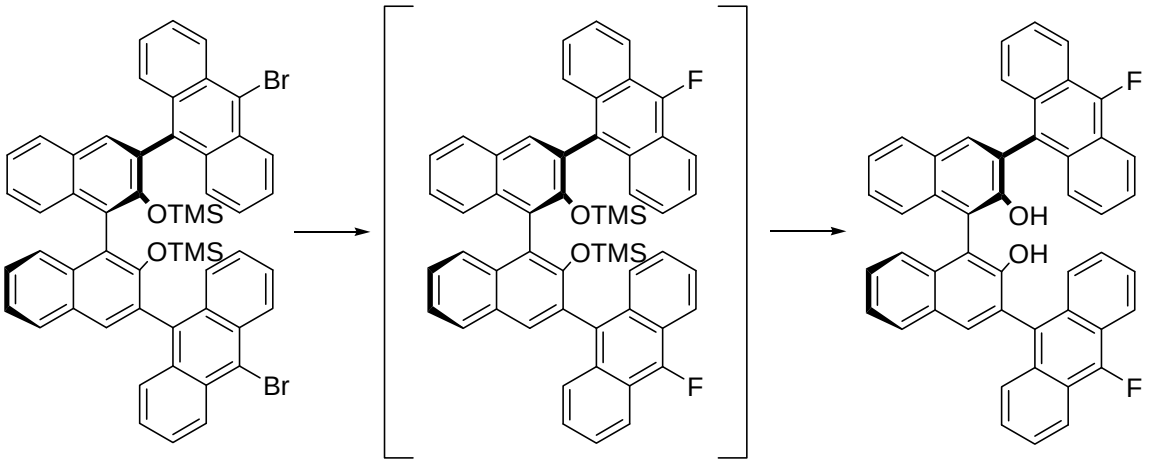
Chemical Formula: $C_{54}H_{44}Br_2O_2Si_2$
Exact Mass: 938.1247
Molecular Weight: 940.905
Elemental Analysis: C, 68.93; H, 4.71; Br, 16.98; O, 3.40; Si, 5.97

TMS-protected diol (*R*)-**140** was prepared using a general procedure for the TMS-protection of alcohols:[143]

I_2 (13 mg, 0.051 mmol) was added to a suspension of diol (*R*)-**134** (410 mg, 0.515 mmol) in CH_2Cl_2 (5.7 mL). HMDS (170 μL, 0.826 mmol) in CH_2Cl_2 (2.4 mL) was added dropwise over 2 min to the dark purple suspension, which turned to a solution during the addition. After stirring for 10 min, the reaction was quenched by the addition of $Na_2S_2O_3$ solution (10 mL), and the mixture was stirred until the solution turned yellow-orange. More CH_2Cl_2 (10 mL) was added and the layers were separated. The organic phase was washed with brine (15 mL), and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product. Purification by a silica plug (100% Et_2O) afforded the TMS-protected diol (*R*)-**140** as a yellow-orange solid (465 mg, 96%): mp 345-350 °C; R_f = 0.58 (60% hexane, 40% toluene); $[\alpha]_D^{20}$ = +147.3 (*c* 0.88, $CHCl_3$); ν_{max}(film)/cm^{-1} 3059w, 2961m, 2163w, 1947w, 1799w, 1703w, 1620w, 1589w, 1522w, 1489w, 1424m, 1403m, 1345m, 1325m, 1280m, 1260m, 1246s, 1203m, 1173w,

1150m, 1104m, 1041w, 1026m, 974s, 936m, 894s, 860s, 837s, 778m, 745s, 695m, 658m; δ_H(300 MHz, C_6D_6) –1.01 (18H, s, SiC*H*$_3$), 7.07-7.14 (2H, m, Ar*H*), 7.19-7.40 (10H, stack, Ar*H*), 7.62-7.80 (6H, stack, Ar*H*), 8.20 (2H, d, *J* 8.7, Ar*H*), 8.26 (2H, d, *J* 8.7, Ar*H*), 8.82 (4H, app. t, *J* 8.0, Ar*H*); δ_C(75 MHz, C_6D_6) –0.14 (CH_3, Si*C*H$_3$), 123.8 (quat. C, *ipso* Ar), 124.8 (CH, Ar), 125.9 (CH, Ar), 126.1 (CH, Ar), 126.3 (CH, Ar), 127.0 (CH, Ar), 127.3 (CH, Ar), 127.5 (CH, Ar), 128.1 (CH, Ar), 128.6 (CH, Ar), 128.7 (CH, Ar), 129.3 (CH, Ar), 130.2 (quat. C, *ipso* Ar), 131.1 (quat. C, *ipso* Ar), 131.2 (quat. C, *ipso* Ar), 131.4 (quat. C, *ipso* Ar), 132.1 (quat. C, *ipso* Ar), 132.2 (quat. C, *ipso* Ar), 133.2 (CH, Ar), 135.0 (quat. C, *ipso* Ar), 135.3 (quat.C, *ipso* Ar), 151.4 (quat. C, *ipso* Ar), one (CH, Ar) and one (quat. C, *ipso* Ar) were not observed; m/*z* (TOF ES+) 963.1 ([M + Na]$^+$, 100%); HRMS: $C_{54}H_{44}O_2Si_2{}^{79}Br^{81}BrNa$ calcd 963.1124 ([M + Na]$^+$), obsd 963.1120.

(*R*)-3,3'-Bis-(10''-fluoroanthracenyl-9''-yl)-2,2'-dihydroxy-[1,1']-binaphthalenyl (*R*)-139



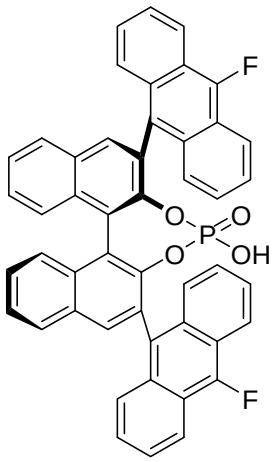
Chemical Formula: $C_{48}H_{28}F_2O_2$
Exact Mass: 674.2057
Molecular Weight: 674.7315
Elemental Analysis:
C, 85.44; H, 4.18; F, 5.63; O, 4.74

^{t}BuLi (940 μL of a 1.7 M solution in pentane, 1.59 mmol) was added dropwise over 2 min to a solution of TMEDA (95 μL, 0.638 mmol) and TMS-protected diol (*R*)-**140** (300 mg, 0.319 mmol) in THF (7.2 mL) at –78 °C. After stirring for 2 h at –78 °C, a solution of *N*-fluorodibenzenesulfonimide (402 mg, 1.28 mmol) in THF (2.4 mL) was added dropwise over 5 min over which time the solution changed its colour from black-green to orange. The syringe was washed with THF (2.4 mL) and the mixture was warmed to R.T. overnight. H_2O (10 mL), Et_2O (10 mL) and hydrochloric acid (1 M, 5 mL, for a better phase separation) were added and the layers were separated. The aqueous phase was extracted with Et_2O (10 mL) and the combined organic fractions were washed with brine (15 mL), and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product. Purification by flash column chromatography[13] (gradient: 100% hexane → 95% hexane, 5% toluene) afforded the TMS-protected diol (*R*)-**141** as a yellow solid (200 mg, 0.244 mmol, 77%) which was dissolved in THF (1.25 mL) and cooled to 0 °C. TBAF (535 μL of a 1 M solution in THF, 0.537 mmol) was added dropwise over 2 min and the mixture was stirred at R.T. for 30 min. H_2O (10 mL) and Et_2O (10 mL) were added and the layers were separated. The aqueous phase was extracted with Et_2O (10 mL) and the combined organic fractions were washed with brine (15 mL), and then dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product. Purification by flash column chromatography (60% hexane, 20% toluene, 20% CH_2Cl_2) afforded diol (*R*)-**139** as a yellow solid (90 mg, 55%): mp 228-231 °C; R_f = 0.16 (60% hexane, 20% toluene, 20% CH_2Cl_2); $[\alpha]_D^{20}$ = +121.0 (*c* 1.0, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3530m (OH), 1620m (C=C aromatic), 1498m, 1436m, 1364w, 1345m, 1327m, 1255m, 1223s (ArC–F), 1148m, 1093m, 1025m, 936m, 918s, 836s, 784m, 734s; δ_H(300 MHz) 5.08 (2H, s, O*H*), 7.26-7.34 (2H, m, Ar*H*), 7.42-7.72 (14H, stack, Ar*H*),

[13] the crude product was loaded onto the column with a few drops of CH_2Cl_2; in total, three long columns were carried out with the mixed fractions to be able to fully separate the product from the F-H- and H-H-diols

7.82-8.05 (6H, stack, Ar*H*), 8.35 (2H, d, *J* 8.6, Ar*H*), 8.40 (2H, d, *J* 8.6, Ar*H*); δ_C(75 MHz) 113.5 (quat. C, *ipso* Ar), 118.9 (quat. C, d, ^3J 4.8, *ipso* Ar), 119.0 (quat. C, d, ^3J 4.8, *ipso* Ar), 120.7 (CH, d, ^3J 4.4, Ar), 120.8 (CH, d, ^3J 4.4, Ar), 124.4 (CH, Ar), 124.7 (CH, Ar), 125.5 (CH, 2 × Ar), 125.9 (CH, 2 × Ar), 126.1 (quat. C, d, ^2J 6.5, *ipso* Ar), 126.6 (quat. C, d, ^2J 6.5, *ipso* Ar), 126.7 (CH, 2 × Ar), 127.5 (CH, Ar), 128.5 (CH, Ar), 129.3 (quat. C, *ipso* Ar), 131.17 (quat. C, *ipso* Ar), 131.20 (quat. C, *ipso* Ar), 133.4 (CH, Ar), 133.9 (quat. C, *ipso* Ar), 151.1 (quat.C, *ipso* Ar), 154.6 (quat. C, ^1J 257.3, *ipso* Ar); δ_F(282 MHz) –129.2 (s, Ar*F*); m/*z* (TOF ES+) 697.1 ($[M + Na]^+$, 100%); HRMS: $C_{48}H_{28}O_2F_2Na$ calcd 697.1955 ($[M + H]^+$), obsd 697.1956.

(*R*)-[3,3'-Bis(10''-fluoroanthracen-9''-yl)-[1,1']-binaphthalen-2,2'-yl]-phosphoric acid (*R*)-32i



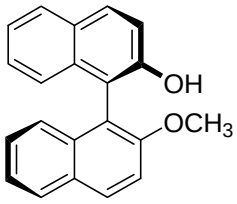
Chemical Formula: $C_{48}H_{27}F_2O_4P$
Exact Mass: 736.1615
Molecular Weight: 736.6961
Elemental Analysis: C, 78.26; H, 3.69; F, 5.16; O, 8.69; P, 4.20

Phosphoric acid (*R*)-**32i** was prepared using a previously reported general procedure for the formation of different BINOL-derived phosphoric acids:[90]

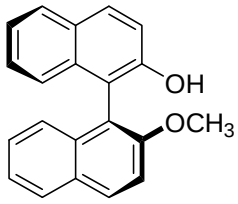
$POCl_3$ (20 μL, 0.238 mmol) was added to a solution of diol (*R*)-**139** (80 mg, 0.119 mmol) in pyridine (0.3 mL) at R.T. After stirring for 3 h at R.T., the reaction was quenched with H_2O (1

mL) and the resulting suspension was stirred overnight. CH_2Cl_2 (15 mL) was added and the pyridine was removed by reverse extraction with hydrochloric acid (1 M, 2 × 10 mL). The organic layer was dried ($MgSO_4$), the drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product. Purification by flash column chromatography (gradient: 100% CH_2Cl_2 → 95% CH_2Cl_2, 5% EtOH) afforded the phosphoric acid as a brown solid. The product was extracted with hydrochloric acid (4 M, 10 mL) again, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford the desired phosphoric acid (*R*)-**32i** as a brown solid (80 mg, 91%): mp 248-253 °C (dec.); R_f = 0.23 (95% CH_2Cl_2, 5% EtOH); $[\alpha]_D^{21}$ = +11.9 (*c* 0.47, $CHCl_3$); ν_{max}(film)/cm^{-1} 3058w, 2924w, 2852w, 1625w, 1562w, 1487w, 1441w, 1414w, 1379s, 1325m, 1277w, 1229m, 1184m, 1148m, 1096m, 1069m, 1021s, 971m, 947m, 888m, 849m, 822m, 786w, 763s, 749s, 701s, 675m; δ_H(300 MHz) 5.49 (1H, br s, O*H*), 7.06-7.76 (19H, stack, Ar*H*), 7.92-8.06 (5H, stack, Ar*H*), 8.18 (2H, d, *J* 8.5, Ar*H*); δ_C(100 MHz) 118.4 (d, $^2J_{C\text{-}F}$ 19.9, *ipso* Ar), 118.6 (d, $^2J_{C\text{-}F}$ 19.9, *ipso* Ar), 119.7 (d, $J_{C\text{-}F}$ 3.0), 120.5 (d, $J_{C\text{-}F}$ 4.0), 122.4, 125.0, 125.4, 125.8, 126.1, 126.3, 127.0, 127.3, 128.5, 130.3, 130.7, 131.1, 131.4, 132.7, 134.1, 146.5 (d, $J_{C\text{-}P}$ 9.2, *ipso* Ar), 154.2 (d, $^1J_{C\text{-}F}$ 256.3, *ipso* Ar), resonance overlap; δ_P(121 MHz) 0.82 (s, *P*(O)OH); δ_F(282 MHz) –130.1 (s, Ar*F*); m/*z* (TOF ES–) 735.1 ([M – H]$^-$, 100%); HRMS: $C_{48}H_{26}O_4PF_2$ calcd 735.1537 ([M – H]$^-$), obsd 735.1542.

(*R*)- and (*S*)-2-Hydroxy-2'-methoxy-1,1'-binaphthyl (*R*)- and (*S*)-221[166]



(*R*)-**221**



(*S*)-**221**

Chemical Formula: $C_{21}H_{16}O_2$
Exact Mass: 300.1150
Molecular Weight: 300.3505
Elemental Analysis:
C, 83.98; H, 5.37; O, 10.65

(*R*)- and (*S*)-2-Hydroxy-2'-methoxy-1,1'-binaphthyl (*R*)- and (*S*)-**221** were prepared using a variation of a previously reported procedure:[166]

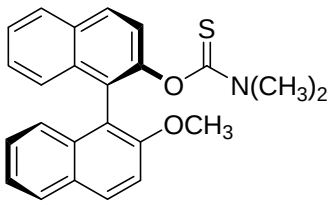
DEAD (785 μL, 5.00 mmol) was added dropwise over 2 min to a solution of (*S*)-BINOL (*S*)-**109** (1.43 g, 5.00 mmol), Ph_3P (1.31 g, 5.00 mmol) and anhydrous MeOH (1.0 mL, 24.7 mmol) in THF (50 mL) at R.T. After stirring for 24 h, the mixture was concentrated under reduced pressure. The resulting pale pink solid was dissolved in CH_2Cl_2 (30 mL) and hexane was added under vigorous stirring leading to precipitation of the by-product *N*,*N*-bis(ethoxycarbonyl)hydrazine. Removal of the white fluffy solid by filtration and concentration of the filtrate under reduced pressure provided the crude product as a pale pink foam. Purification by flash column chromatography (100% toluene) afforded (*S*)-monomethyl ether (*S*)-**221** as a white foamy solid (1.25 g, 83%): mp 69-71 °C (lit.[166] mp 89-91 °C); R_f = 0.15 (100% toluene); $[\alpha]_D^{21}$ = +53.6 (*c* 0.41, $CHCl_3$) (lit.[166] $[\alpha]_D^{28}$ = +44.8 (*c* 1.4, $CHCl_3$), 99.3% ee);[14] (Found: C, 84.06; H, 5.39. $C_{21}H_{16}O_2$ requires C, 83.98; H, 5.37%); ν_{max}(film)/cm^{-1} 3498m br (OH), 3422m br (OH), 3958m, 2937w, 2839m (OCH_3), 1954w, 1620s (C=C aromatic), 1592s (C=C aromatic), 1507s (C=C aromatic), 1462m, 1431w, 1380m, 1362w, 1346w, 1332m, 1300w, 1264s, 1248s, 1173m, 1147s, 1129m, 1083s, 1055m, 1020m, 972w, 940w, 905w, 863w, 813s, 708w, 573w; δ_H(300 MHz) 3.80 (3H, s, OC*H*$_3$), 4.94 (1H, br s, O*H*), 7.06 (1H, d, *J* 8.1, Ar*H*), 7.15-7.41 (6H, stack, Ar*H*), 7.48 (1H, d, *J* 9.2, Ar*H*), 7.84-7.94 (3H, stack, Ar*H*), 8.05 (1H, d, *J* 9.2, Ar*H*); δ_C(75 MHz) 56.6 (CH_3, O*C*H_3), 113.8 (CH, Ar), 115.0 (quat. C, *ipso* Ar), 115.3 (quat. C, *ipso* Ar), 117.4 (CH, Ar), 123.2 (CH, Ar), 124.1 (CH, Ar), 124.8 (CH, Ar), 124.9 (CH, Ar), 126.4 (CH, Ar), 127.3 (CH, Ar), 128.09 (CH, Ar), 128.10 (CH, Ar), 129.1 (quat. C, *ipso* Ar), 129.4 (quat. C, *ipso* Ar), 129.7 (CH, Ar), 131.0 (CH, Ar), 133.7 (quat. C, *ipso* Ar), 134.0 (quat. C, *ipso* Ar), 151.2 (quat. C, *ipso* Ar), 155.9 (quat. C, *ipso* Ar); m/*z* (EI) 300 ($[M]^+$, 100%), 285 (10, $[M - CH_3]^+$), 268 (19), 239 (18), 228 (10), 119 (12), 84 (20), 49 (25).

[14] the ee-value could not be determined by chiral HPLC owing to poor resolution of the racemic mixture

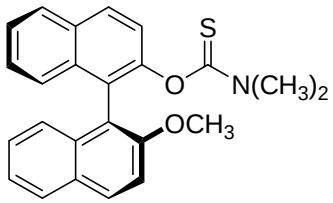
The same protocol was followed for the preparation of the (*R*)-enantiomer: $[\alpha]_D^{21} = -51.9$ (*c* 0.45, $CHCl_3$).

Data were in agreement with those reported in the literature.[166]

(*R*)- and (*S*)-2-(*N*,*N*-Dimethylthiocarbamoyloxy)-2'-methoxy-1,1'-binaphthyl (*R*)- and (*S*)-222[215]



(*R*)-**222**



(*S*)-**222**

Chemical Formula: $C_{24}H_{21}NO_2S$
Exact Mass: 387.1293
Molecular Weight: 387.4951
Elemental Analysis: C, 74.39; H, 5.46; N, 3.61; O, 8.26; S, 8.28

(*R*)- and (*S*)-2-(*N*,*N*-Dimethylthiocarbamoyloxy)-2'-methoxy-1,1'-binaphthyl (*R*)- and (*S*)-**222** were prepared using a previously reported procedure for the formation of (*R*)- and (*S*)-2-(*N*,*N*-dimethylthiocarbamoyloxy)-2'-hydroxy-1,1'-binaphthyl:[170]

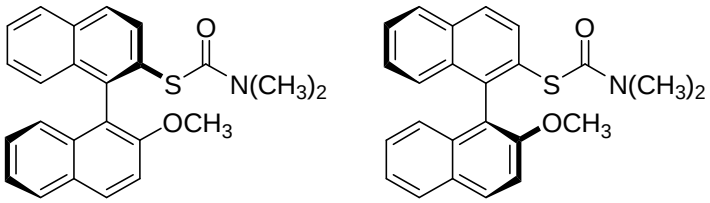
N,*N*-Dimethylcarbamoyl chloride (1.17 g, 9.47 mmol) was added to a solution of (*S*)-2-hydroxy-2'-methoxy-1,1'-binaphthyl (*S*)-**221** (2.47 g, 8.22 mmol), NEt_3 (1.38 mL, 9.90 mmol) and DMAP (251 mg, 2.05 mmol) in CH_2Cl_2 (80 mL) at R.T. After heating at reflux for 60 h, more *N*,*N*-dimethylcarbamoyl chloride (1.60 g, 12.9 mmol), NEt_3 (1.00 mL, 7.17 mmol) and DMAP (251 mg, 2.05 mmol) were added to the yellow mixture. After heating at reflux for another 24 h, CH_2Cl_2 (100mL) and hydrochloric acid (0.1M, 200 mL) were added to the

orange solution. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine (100 mL) and dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product. Recrystallisation from EtOH afforded (*S*)-thiocarbamate (*S*)-**222** as colourless crystals (2.81 g, 88%): mp 161-164 °C; $[\alpha]_D^{21}$ = –102.8 (*c* 1.0, $CHCl_3$, e.r. 0:100); Chiralpak AD column, 1.0 mL/min, 1% IPA in hexane, λ = 254 nm, t_R = 36.5 min; (Found: C, 74.35; H, 5.67; N, 3.33. $C_{24}H_{21}NO_2S$ requires C, 74.39; H, 5.46; N, 3.61%); ν_{max}(film)/cm^{-1} 3012m, 2838w (OCH_3), 1719w, 1622m (C=C aromatic), 1592m (C=C aromatic), 1533s (C=C aromatic), 1509s (C=C aromatic), 1475m, 1462m, 1430w, 1396s, 1359w, 1330w, 1289s, 1272s, 1261s, 1250s, 1194w, 1147s, 1128w, 1085m, 1056m, 1020m, 986w, 906w, 863w, 811s; δ_H(300 MHz) 2.50 (3H, s, NC*H*$_3$), 3.08 (3H, s, NC*H*$_3$), 3.75 (3H, s, OC*H*$_3$), 7.19-7.34 (5H, stack, Ar*H*), 7.37-7.48 (2H, stack, Ar*H*), 7.58 (1H, d, *J* 8.8, Ar*H*), 7.83 (1H, d, *J* 8.1, Ar*H*), 7.91-8.01 (3H, stack, Ar*H*); δ_C(75 MHz) 37.5 (CH_3, N*C*H$_3$), 42.6 (CH_3, N*C*H$_3$), 56.6 (CH_3, O*C*H$_3$), 113.5 (CH, Ar), 117.7 (quat. C, *ipso* Ar), 123.4 (CH, Ar), 123.6 (CH, Ar), 125.37 (CH, Ar), 125.45 (quat. C, *ipso* Ar), 125.9 (CH, Ar), 126.17 (CH, Ar), 126.21 (CH, Ar), 126.3 (CH, Ar), 127.5 (CH, Ar), 128.1 (CH, Ar), 128.2 (CH, Ar), 128.7 (quat. C, *ipso* Ar), 129.8 (CH, Ar), 131.7 (quat. C, *ipso* Ar), 133.6 (quat. C, *ipso* Ar), 133.8 (quat. C, *ipso* Ar), 149.5 (quat. C, *ipso* Ar), 155.0 (quat. C, *ipso* Ar), 186.5 (quat. C, *C*=S); m/*z* (EI) 387 ([M]$^+$, 100%), 284 (12, [M – (CH_3 + C(S)N(CH_3)$_2$)]$^+$), 268 (37), 239 (25), 226 (15); HRMS: $C_{24}H_{21}NO_2S$ calcd 387.1293 ([M]$^+$), obsd 387.1281.

The same protocol was followed for the preparation of the (*R*)-enantiomer: $[\alpha]_D^{21}$ = +100.8 (*c* 1.0, $CHCl_3$, e.r. 100:0); Chiralpak AD column, 1.0 mL/min, 1% IPA in hexane, λ = 254 nm, t_R = 29.2 min.

Data were in agreement with those reported in the literature.[215]

(*R*)- and (*S*)-2-(*N*,*N*-Dimethylcarbamoylthio)-2'-methoxy-1,1'-binaphthyl (*R*)- and (*S*)-223[215]



(*R*)-**223** (*S*)-**223**

Chemical Formula: $C_{24}H_{21}NO_2S$
Exact Mass: 387.1293
Molecular Weight: 387.4951
Elemental Analysis: C, 74.39; H, 5.46; N, 3.61; O, 8.26; S, 8.28

(*R*)- and (*S*)-2-(*N*,*N*-Dimethylcarbamoylthio)-2'-methoxy-1,1'-binaphthyl (*R*)- and (*S*)-**223** were prepared using a previously reported procedure for the formation of (*R*)- and (*S*)-2-(*N*,*N*-dimethylcarbamoyloxy)-2'-(*N*,*N*-dimethylcarbamoylthio)-1,1'-binaphthyl:[170]

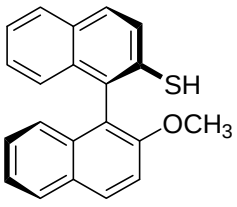
(*S*)-2-(*N*,*N*-Dimethylthiocarbamoyloxy)-2'-methoxy-1,1'-binaphthyl (*S*)-**222** (2.70 g, 6.97 mmol) was heated (3.5 h at 250 °C) under argon. After cooling to R.T., the dark-brown mass was dissolved in CH_2Cl_2 (50 mL) and activated charcoal (5 g) was added. The suspension was stirred for 6 h at R.T. Removal of the charcoal by filtration and concentration of the filtrate under reduced pressure provided the crude product as a yellow-brown foamy solid. Purification by flash column chromatography (100% CH_2Cl_2) afforded (*S*)-carbamate (*S*)-**223** as a white foamy solid (2.23 g, 83%): mp 80-83 °C; R_f = 0.16 (100% CH_2Cl_2); $[\alpha]_D^{21}$ = +19.2 (*c* 1.0, $CHCl_3$, e.r. 98.7:1.3); Chiralpak AD column, 1.0 mL/min, 10% IPA in hexane, λ = 254 nm, t_R = 13.2 min; ν_{max}(film)/cm^{-1} 3010m, 2935m, 2839w (OCH_3), 1661s (C=O), 1623w (C=C aromatic), 1594m (C=C aromatic), 1510m (C=C aromatic), 1462m, 1406w, 1364m, 1333w, 1270s, 1260s, 1251s, 1216s, 1179w, 1148m, 1096s, 1052m, 1020m, 952w, 908m, 869w, 811s, 691w; δ_H(300 MHz) 2.77 (6H, br s, N(CH_3)$_2$), 3.73 (3H, s, OCH_3), 7.05 (1H, d, *J*

8.5, Ar*H*), 7.11-7.34 (4H, stack, Ar*H*), 7.39-7.48 (2H, stack, Ar*H*), 7.79-8.01 (5H, stack, Ar*H*); δ_C(75 MHz) 36.7 (CH_3, N(CH_3)$_2$), 56.6 (CH_3, OCH_3), 113.6 (CH, Ar), 121.7 (quat. C, *ipso* Ar), 123.6 (CH, Ar), 125.5 (CH, Ar), 126.1 (CH, Ar), 126.4 (CH, Ar), 126.5 (CH, Ar), 126.6 (CH, Ar), 127.6 (CH, Ar), 127.9 (CH, Ar), 128.0 (CH, Ar), 128.3 (quat. C, *ipso* Ar), 128.8 (quat. C, *ipso* Ar), 129.7 (CH, Ar), 133.18 (CH, Ar), 133.20 (quat. C, *ipso* Ar), 133.4 (quat. C, *ipso* Ar), 133.7 (quat. C, *ipso* Ar), 138.7 (quat. C, *ipso* Ar), 154.8 (quat. C, *ipso* Ar), 166.5 (quat. C, *C*=O); m/*z* (TOF ES+) 410.0 ([M + Na]$^+$, 100%); HRMS: $C_{24}H_{21}NO_2SNa$ calcd 410.1191 ([M + Na]$^+$), obsd 410.1188.

The same protocol was followed for the preparation of the (*R*)-enantiomer: $[\alpha]_D^{20}$ = –18.1 (*c* 1.0, $CHCl_3$, e.r. 2.7:97.3); Chiralpak AD column, 1.0 mL/min, 10% IPA in hexane, λ = 254 nm, t_R = 28.5 min.

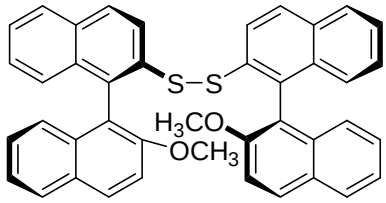
Data were in agreement with those reported in the literature.[215]

(*R*)-2-Mercapto-2'-methoxy-1,1'-binaphthyl (*R*)-224 and (*R*,*R*)-bis(2'-methoxy-1,1'-binaphthyl-2-yl)disulfide (*R*,*R*)-225



Chemical Formula: $C_{21}H_{16}OS$
Exact Mass: 316.0922
Molecular Weight: 316.4171
Elemental Analysis: C, 79.71; H, 5.10; O, 5.06; S, 10.13

(*R*)-**224**



Chemical Formula: $C_{42}H_{30}O_2S_2$
Exact Mass: 630.1687
Molecular Weight: 630.8184
Elemental Analysis: C, 79.97; H, 4.79; O, 5.07; S, 10.17

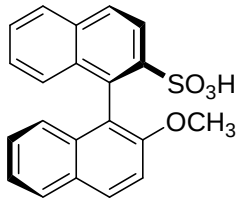
(*R*)-**225**

(*R*)-2-Mercapto-2'-methoxy-1,1'-binaphthyl (*R*)-**224** and (*R,R*)-bis(2'-methoxy-1,1'-binaphthyl-2-yl)disulfide (*R,R*)-**225** as a by-product were prepared using a variation of a previously reported procedure for the formation of 2-hydroxy-2'-mercapto-1,1'-binaphthyl:[170]

(*R*)-2-(*N,N*-Dimethylcarbamoylthio)-2'-methoxy-1,1'-binaphthyl (*R*)-**223** (814 mg, 2.10 mmol) was added to a solution of KOH (1.41 g, 25.2 mmol) in a mixture of degassed MeOH/H_2O (4:1, 40 mL) and the resulting suspension was heated at reflux for 5 h. After cooling to R.T., the mixture was evaporated to dryness under reduced pressure providing a pale yellow solid which was dissolved in deoxygenated H_2O (45 mL). After acidification with concentrated hydrochloric acid (3.5 mL), the product was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic layers were dried (Na_2SO_4). The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to provide the crude product. Purification by flash column chromatography (40% hexane, 60% toluene) afforded, in order of elution, thiol (*R*)-**224** as a white foamy solid (485 mg, 73%): mp 105-107 °C; R_f = 0.38 (40% hexane, 60% toluene); $[\alpha]_D^{23}$ = +6.3 (*c* 0.51, $CHCl_3$); (Found: C, 79.87; H, 4.91. $C_{21}H_{16}OS$ requires C, 79.71; H, 5.10%); ν_{max}(film)/cm^{-1} 3054m, 3006m, 2934m, 2838m (OCH_3), 2566w (SH), 1954w, 1814w, 1755w, 1621m (C=C aromatic), 1592s (C=C aromatic), 1562w, 1504s (C=C aromatic), 1472m, 1461m, 1431m, 1402w, 1352m, 1332m, 1271s, 1261s, 1250s, 1179m, 1148m, 1136w, 1126m, 1082s, 1052m, 1020m, 952w, 907m, 860m, 845w, 809s, 710w, 631w, 617w; δ_H(300 MHz) 3.26 (1H, s, S*H*), 3.81 (3H, s, OC*H*$_3$), 7.04

(1H, d, *J* 8.1, Ar*H*), 7.07 (1H, d, *J* 8.5, Ar*H*), 7.19-7.30 (2H, stack, Ar*H*), 7.32-7.41 (2H, stack, Ar*H*), 7.48 (1H, d, *J* 8.8, Ar*H*), 7.55 (1H, d, *J* 8.8, Ar*H*), 7.80-7.92 (3H, stack, Ar*H*), 8.04 (1H, d, *J* 9.2, Ar*H*); δ_C(75 MHz) 56.7 (CH_3, O*C*H_3), 113.9 (CH, Ar), 120.7 (quat. C, *ipso* Ar), 123.9 (CH, Ar), 124.6 (CH, Ar), 124.9 (CH, Ar), 125.3 (CH, Ar), 126.6 (CH, Ar), 127.01 (CH, Ar), 127.04 (CH, Ar), 128.0 (CH, Ar), 128.1 (CH, Ar), 128.2 (CH, Ar), 129.3 (quat. C, *ipso* Ar), 130.3 (CH, Ar), 130.8 (quat. C, *ipso* Ar), 130.9 (quat. C, *ipso* Ar), 131.6 (quat. C, *ipso* Ar), 133.0 (quat. C, *ipso* Ar), 133.6 (quat. C, *ipso* Ar), 154.7 (quat. C, *ipso* Ar); m/*z* (TOF ES+) 339 ($[M + Na]^+$, 100%); HRMS: $C_{21}H_{16}OSNa$ calcd 339.0820 ($[M + Na]^+$), obsd 339.0811; and then disulfide (*R*,*R*)-**225** as a pale yellow solid (73 mg, 11%): mp 269-273 °C; R_f = 0.23 (40% hexane, 60% toluene); $[\alpha]_D^{23}$ = –103.4 (*c* 1.0, $CHCl_3$); (Found: C, 79.93; H, 4.92. $C_{42}H_{30}O_2S_2$ requires C, 79.97; H, 4.79%); ν_{max}(film)/cm^{-1} 3056m, 3010m, 2935w, 2838w (OCH_3), 1951w, 1757w, 1622m (C=C aromatic), 1592s (C=C aromatic), 1562w, 1504s (C=C aromatic), 1461m, 1431m, 1402w, 1351m, 1331m, 1269s, 1247s, 1178w, 1149m, 1134w, 1121m, 1079s, 1050m, 1020m, 956w, 904m, 859m, 809s, 686w, 627w; δ_H(300 MHz) 3.80 (6H, s, OC*H*$_3$), 6.98 (2H, d, *J* 8.5, Ar*H*), 7.10 (2H, d, *J* 8.5, Ar*H*), 7.18-7.26 (4H, stack, Ar*H*), 7.32-7.41 (4H, stack, Ar*H*), 7.46 (2H, d, *J* 9.2, Ar*H*), 7.85-7.75 (4H, stack, Ar*H*), 7.81 (2H, d, *J* 8.1, Ar*H*), 7.90 (2H, d, *J* 8.1, Ar*H*), 8.04 (2H, d, *J* 9.2, Ar*H*); δ_C(75 MHz) 56.7 (CH_3, O*C*H_3), 113.9 (CH, Ar), 120.7 (quat. C, *ipso* Ar), 123.9 (CH, Ar), 124.6 (CH, Ar), 124.9 (CH, Ar), 125.3 (CH, Ar), 126.6 (CH, Ar), 127.01 (CH, Ar), 127.04 (CH, Ar), 128.0 (CH, Ar), 128.1 (CH, Ar), 128.2 (CH, Ar), 129.3 (quat. C, *ipso* Ar), 130.3 (CH, Ar), 130.8 (quat. C, *ipso* Ar), 130.9 (quat. C, *ipso* Ar), 131.6 (quat. C, *ipso* Ar), 133.0 (quat. C, *ipso* Ar), 133.6 (quat. C, *ipso* Ar), 154.7 (quat. C, *ipso* Ar); m/*z* (TOF ES+) 653 ($[M + Na]^+$, 100%); HRMS: $C_{42}H_{30}O_2S_2Na$ calcd 653.1585 ($[M + Na]^+$), obsd 653.1571.

(*R*)-2-Methoxy-2'-sulfonic-acid-1,1'-binaphthyl (*R*)-226



Chemical Formula: $C_{21}H_{16}O_4S$
Exact Mass: 364.0769
Molecular Weight: 364.4153
Elemental Analysis: C, 69.21; H, 4.43; O, 17.56; S, 8.80

(*R*)-2-Methoxy-2'-sulfonic-acid-1,1'-binaphthyl (*R*)-**226** was prepared using a previously reported procedure for a common formation of sulfonic acids:[164,175]

A suspension of (*R*)-2-mercapto-2'-methoxy-1,1'-binaphthyl (*R*)-**224** (100 mg, 0.316 mmol) in acetic acid (1 mL) was stirred at 60 °C for 15 min before it was treated with H_2O_2 (35% in water, 140 μL, 1.58 mmol) dropwise over 5 min. Over 20 min the white suspension darkened and the resulting clear dark brown solution was stirred for 3 h at 60 °C. After cooling to R.T., the acetic acid was removed azeotropically with toluene. An attempt to purify the product by recrystallisation from toluene afforded impure sulfonic acid (*R*)-**226** as a pale brown solid (14 mg, 12%): δ_H(300 MHz) 3.76 (3H, s, OC*H*$_3$), 6.82 (1H, d, *J* 8.1, Ar*H*), 6.95 (1H, br s, SO_3H), 7.09-7.41 (4H, stack, Ar*H*), 7.53-7.68 (2H, stack, Ar*H*), 7.91 (1H, d, *J* 8.1, Ar*H*), 8.03-8.28 (4H, stack, Ar*H*); m/*z* (TOF ES–) 363 ($[M - H]^-$, 100%); HRMS: $C_{21}H_{15}O_4S$ calcd 363.0691 ($[M - H]^-$), obsd 363.0706.

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