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DIASTEREOSELECTIVE INTRAMOLECULAR HYDRIDE TRANSFER

DHIKA ADITYA GANDAMANA

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

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SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

A thesis submitted to the Nanyang Technological
University in partial fulfilment of the requirement for the
degree of Doctor of Philosophy

2020

Statement of Originality

I hereby certify that the work embodied in this thesis is the result of original research done by me except where otherwise stated in this thesis. The thesis work has not been submitted for a degree or professional qualification to any other university or institution. I declare that this thesis is written by myself and is free of plagiarism and of sufficient grammatical clarity to be examined. I confirm that the investigations were conducted in accord with the ethics policies and integrity standards of Nanyang Technological University and that the research data are presented honestly and without prejudice.

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Prof. Shunsuke Chiba

Authorship Attribution Statement

This thesis contains material from 4 papers published in the following peer-reviewed journals where I am listed as the first and co-first author.

Chapter 2 is published as D. A. Gandamana, B. Wang, C. Tejo, B. Bolte, F. Gagosz, and S. Chiba. "Use of Alkyl Ethers as Traceless Hydride Donors in Brønsted Acid-Catalyzed Intramolecular Hydrogen Atom Transfer" *Angew. Chem., Int. Ed.* **2018**, *57*, 6181. DOI: 10.1002/anie.201801953. and B. Wang, D. A. Gandamana, F. Gagosz, and S. Chiba. "Diastereoselective Intramolecular Hydride Transfer under Brønsted Acid Catalysis" *Org. Lett.* **2019**, *21*, 2298. DOI: 10.1021/acs.orglett.9b00590.

The contribution of the co-authors are as follows:

- Prof. S. Chiba provided the initial project direction.
- The manuscript was prepared and revised by Prof. S. Chiba, Prof. F. Gagosz, Dr. C. Tejo, Dr. B. Wang and the author.
- Dr. C. Tejo, Dr. B. Wang and the author designed the study and performed all the experimental work at the NTU School of Physical and Mathematical Sciences.
- Dr. Li assisted in the interpretation of the X-ray absorption spectroscopy data

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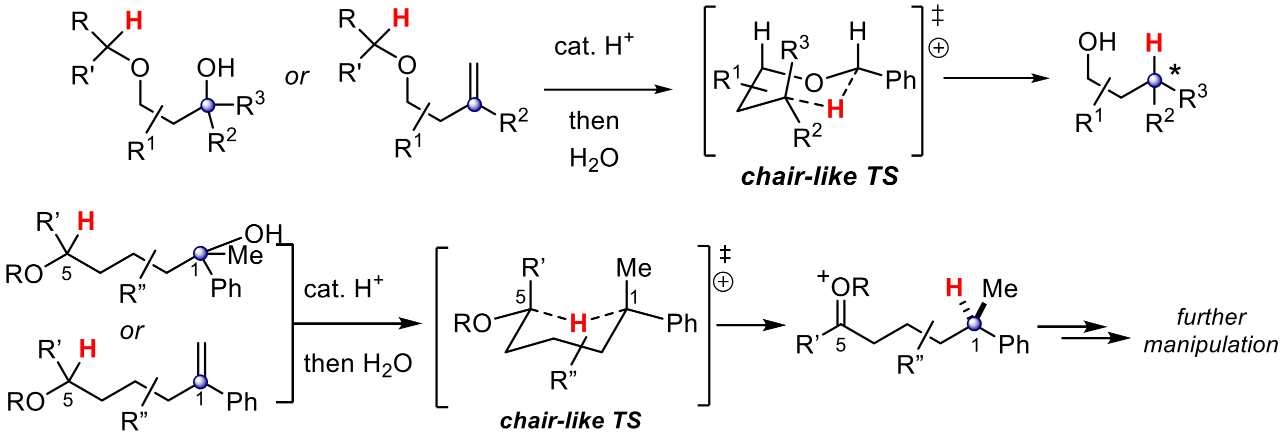
Abstract

This thesis focuses on the synthetic applications of diastereoselective 1,5-hydride transfer to undergo reduction of transient carbocation, which is generated upon electrophilic activation of alkenes or alcohols. Diastereoselective assembly of these stereogenic centers is enabled via the 6-membered chair-like transition state.

Chapter 1 of the thesis describes the recent updates and applications of 1,5-hydride transfer onto various electrophilic hydride acceptors, such as electro-deficient alkenes, carbonyl compounds/imines, transient carbocations and others.

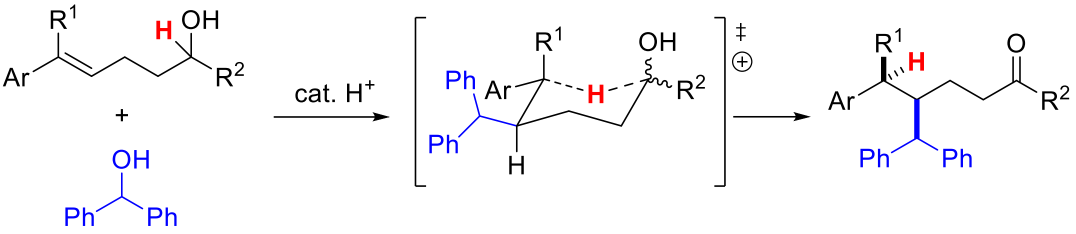
Chapter 2 describes the application of electron rich alkyl ethers as traceless hydride donors for the hydrogenation of alkenes and deoxygenation of alcohols under the Brønsted acid catalysis. The introduction of the substituents next to the transiently generated carbocation induces a well-ordered 6-membered ring chair-like transition state, which results in the formation of multiple stereogenic centers in high level of diastereoselectivity.

Chapter 2. Brønsted acid catalyzed 1,5-hydride transfer



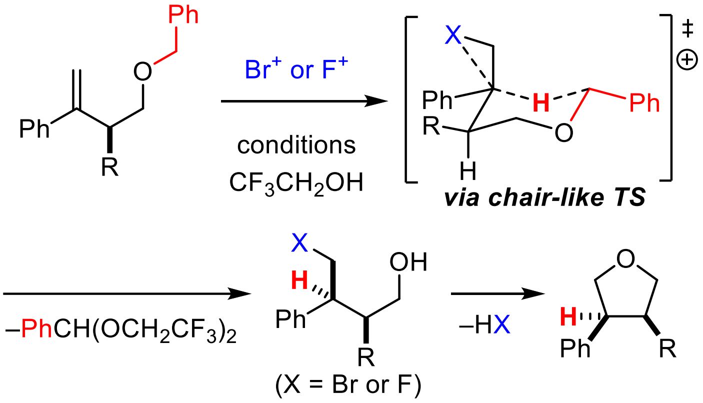
Chapter 3 of this thesis presents the use of prochiral *endo*-aryl alkenes for *anti*-Markovnikov hydroalkylation with *in-situ* generated external carbocations from activated alcohols. This method offers construction of two consecutive stereogenic centers through the sequence of electrophilic alkylation of alkenes and 1,5-hydride shift.

Chapter 3. *Anti*-Markovnikov diastereoselective hydroalkylation



In Chapter 4, utilization of electrophilic halogenation of arylalkenes by *N*-bromosuccinimide and Selectfluor to trigger 1,5-hydride shift is discussed. This protocol offers an efficient route to deliver *anti*-Markovnikov hydrohalogenation of alkenes upon the diastereoselective 1,5-hydride shift. The resulting haloalcohols finally furnish diastereomerically enriched multi-substituted tetrahydrofurans.

Chapter 4. *Anti*-Markovnikov hydroetherification of alkenes



Chapter 5 describes the experimental sections and the characterization data of the synthesized compounds in Chapters 2,3 and 4.

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List of Abbreviations

δ	chemical shift (ppm)
°C	degree centigrade
α	alpha
Ac	acetyl
AIBN	azobisisobutyronitrile
ATH	asymmetric transfer hydrogenation
Ar	aryl (substituted aromatic ring)
Β	beta
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BOMCl	benzyl chloromethyl ether
BQ	benzoquinone
brs	broad singlet
brsm	based on recovery of the starting material
Bu	butyl
cat.	catalytic
cm^{-1}	wave number
CSA	camphorsulfonic acid
d	doublet
dd	doublet of doublets
DCE	dichloroethane
DLP	dilauroyl peroxide
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMSO	dimethylsulfoxide
DNBA	dinitrobenzenesulfonic acid
d.r.	diastereomeric ratio
ee	enantiomeric excess
equiv.	equivalent
Et	ethyl
EWG	electron withdrawing group
FLP	frustrated Lewis pair

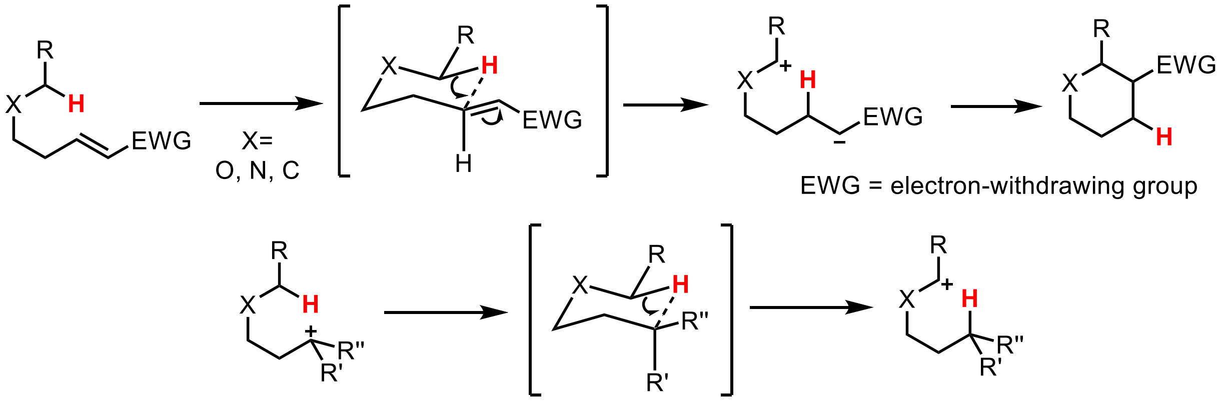
FTIR	Fourier Transform Infrared Spectroscopy
g	gram
GC	Gas Chromatography
1,5-H shift	1,5-hydride shift
h	hour
HFIP	hexafluoroisopropanol
HPLC	High-Performance Liquid Chromatography
Hz	hertz
*i*Pr	*iso*-propyl
J	coupling constants
KHMDS	potassium hexamethyldisilazane
LiHMDS	lithium hexamethyldisilazane
LDA	lithium diisopropylamide
LED	Light-Emitting Diode
M	concentration (mol dm^{-3})
m	multiplet
Me	methyl
Mes	mesityl
mg	miligram
MHz	megahertz
min	minutes
mL	milliliters
mmol	millimole
MS	molecular sieve
NADH	Nicotinamide adenine dinucleotide
NADPH	Nicotinamide adenine dinucleotide phosphate
NBA	*N*-bromoacetamide
NBS	*N*-bromosuccinimide
NBSH	*o*-nitrobenzenesulfonylhydrazine
NMR	nuclear magnetic resonance
n-Hex	*n*-Hexane
NPhth	phtalimide
Nu	nucleophile

OTf	trifluoromethanesulfonate
Ph	phenyl
PMB	*para*-methoxybenzyl
PPA	polyphosphoric acid
p-QM	*para*-quinonemethide
ppm	parts per million
py	pyridine
q	quartet
s	singlet
SET	single electron transfer
rt	room temperature
s-Bu	*sec*-butyl
sep	septet
t	triplet
*t*Bu	*tert*-butyl
td	triplet of doublet
tt	triplet of triplets
TBAI	tetrabutylammonium iodide
TFA	trifluoroacetic acid
TFE	trifluoroethanol
Tf_2NH	bistriflimide
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	*para*-toluenesulfonyl
TsOH	*para*-toluenesulfonic acid
TS	transition state

Chapter 1. General Introduction

1.1 Intramolecular Hydride Transfer

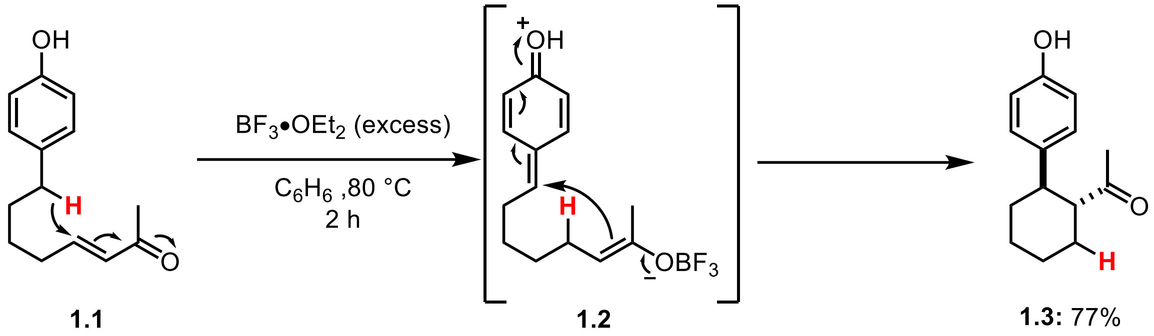
Intramolecular remote hydride transfer can be induced when the substrate has an electron-rich C-H bond and an electrophilic functionality in the appropriate position, producing a zwitterionic species having both carbocation and carbanion moieties (or their equivalents).[1] 1,5-Hydride shift *via* a 6-membered ring transition state is a typical mode of the operation, which has been utilized for the construction of carbo- and heterocyclic scaffolds from readily available substrates.



Scheme 1.1 General 1,5-hydride transfer

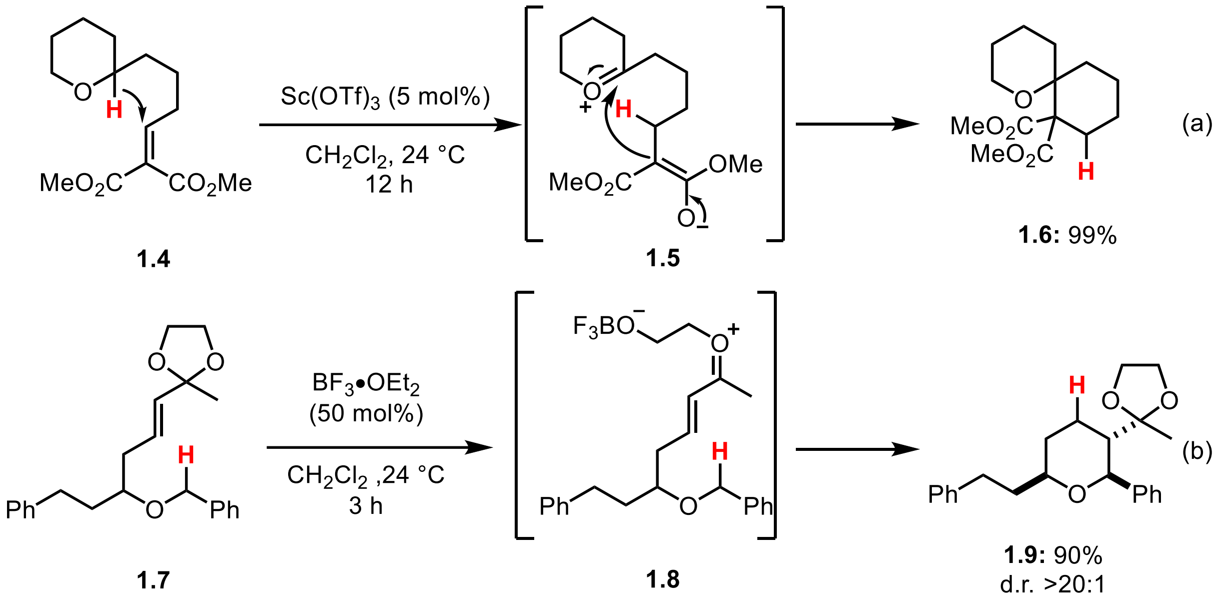
1.1.1 Hydride Transfer onto Electron-Deficient Olefins

The earliest example of synthetic application of 1,5-hydride shift was reported by Atkinson[2] in 1969. Treatment of (*p*-hydroxyphenyl)-substituted enone with excess BF_3•OEt_2 in benzene affords the 2-(*p*-hydoxyphenyl)cyclohexylethan-1-one in 77% yield as a single diastereomer (Scheme 1.2). The activation of enone **1.1** with BF_3•OEt_2 promotes the 1,5-benzylic hydride shift produce zwitterionic intermediate **1.2**. Subsequent ring-closure between enolate and methylene cyclohexadienone moieties furnishes cyclohexane product **1.3**.



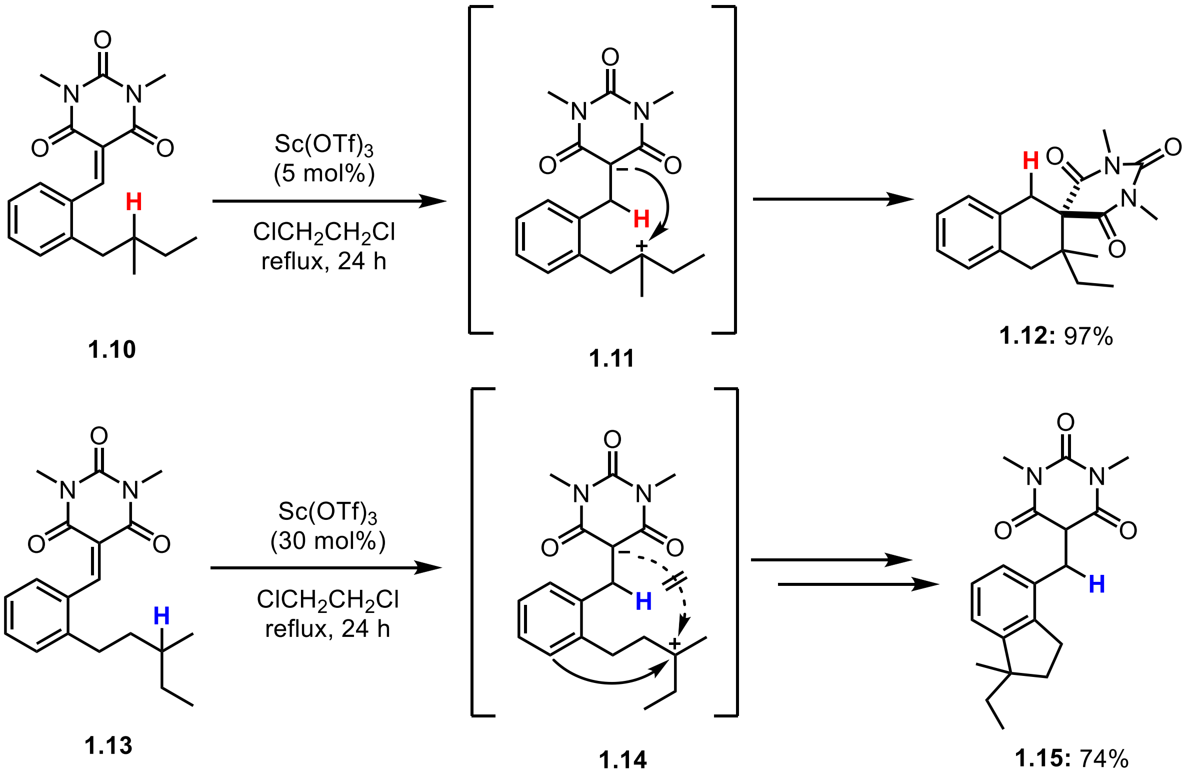
Scheme 1.2 Earliest example of 1,5-hydride shift reported by Atkinson

Sames[3] and co-workers developed $Sc(OTf)_3$-catalyzed conversion of tetrahydropyran **1.4** bearing a pendant alkylidenemalonate moiety into spirocyclic tetrahydropyran **1.6** *via* a key 1,5-hydride transfer step (Scheme 1.3a). Complexation between $Sc(OTf)_3$ and the carbonyl oxygen triggers the 1,5-hydride shift from the α-oxy tertiary carbon to electrophically activated alkenyl moiety to afford a zwitterionic intermediate **1.5**. The resulting metal enolate then reacts with the oxocarbenium ion to furnish the desired spirocyclic product **1.6**. In 2009, the same group[4] further extended the catalytic system to the cyclization of acetal **1.7** having a distal benzyl ether via the generation of conjugated oxocarbenium ion **1.8** in the addition of BF_3•OEt_2 through opening of the acetal. (Scheme 1.3b).



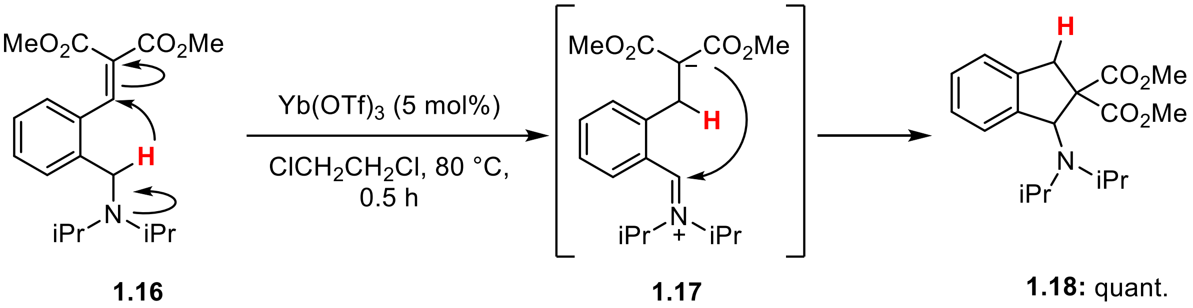
Scheme 1.3 Lewis Acid-mediated benzylic 1,5-hydride shift, followed by cyclization

In 2011, Mori and Akiyama[5] reported the earliest example of a hydride shift that occurs from a non-benzylic tertiary carbon position (Scheme 1.4). Treatment of benzylidene barbiturate **1.10** with 5 mol% of Sc(OTf)3 in 1,2-dichloroethane at reflux temperature yields the spirocyclic barbiturate **1.12** in 97% yield. In this case, a 1,5-hydride shift from the tertiary carbon onto the activated alkylidene barbiturate moiety occurs to form the enolate intermediate **1.11**, that in turn cyclizes to furnish the desired product **1.12**. Interestingly, the present reaction condition also enables a 1,6-hydride shift from substrate **1.13** to form the zwitterionic intermediate **1.14**. However, in this case, the resulting enolate does not cyclize with the carbocationic moiety. Instead, a Friedel-Crafts cyclization with the aromatic ring takes place affording the indane derivative **1.15** in 74% yield.



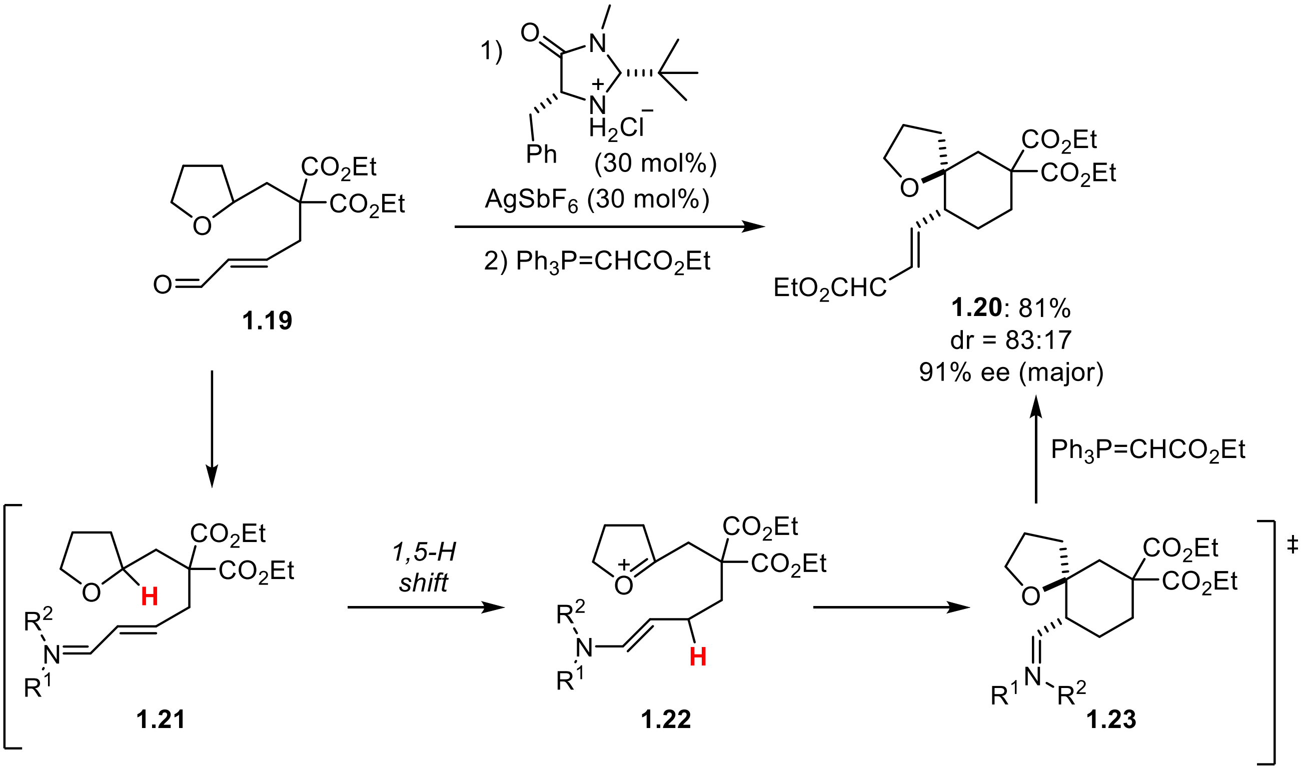
Scheme 1.4 1,5- and 1,6-hydride-shift from an aliphatic tertiary carbon

The same group also reported, in 2014, another example of hydride shift/cyclization process for synthesis of 1-aminoindane derivatives **1.18** (Scheme 1.5).[6] Interestingly, the treatment of benzylidene malonate **1.16** with catalytic amount of Yb(OTf)$_3$ allows a unique 1,4-hydride shift process from electron-rich benzyl C-H bond. It was realised that the presence of a bulky tertiary amine considerably enhances the reactivity as it controls the conformation of the benzylamine moiety in the key hydride transfer process.



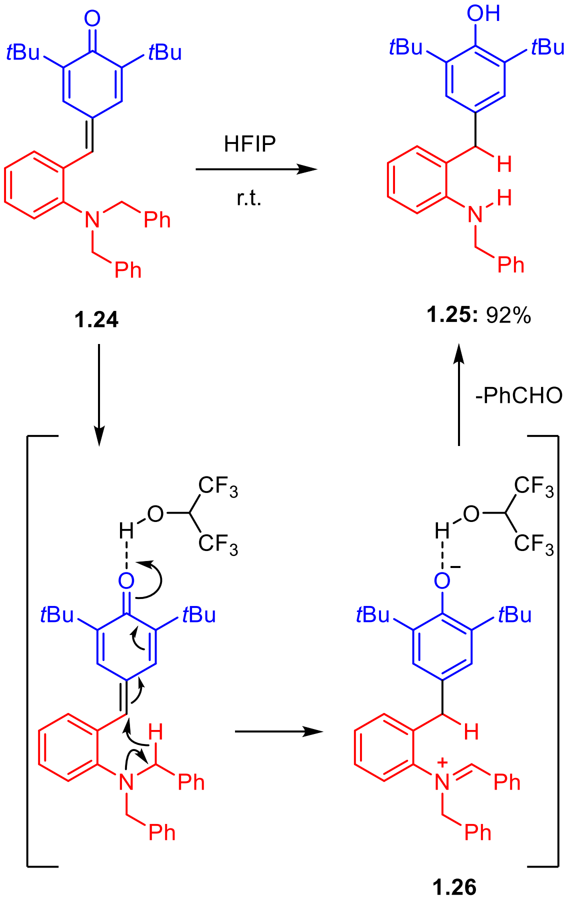
Scheme 1.5 Example of 1,4-hydride shift

Inspired by Sames's report in 2005 of the activation of α,β-unsaturated aldehyde with Lewis acid such as BF_3•OEt_2 and $Sc(OTf)_3$ to induce a redox 1,5-hydride transfer/cyclization process[3], Tu and coworkers[7] have developed an asymmetric catalytic variant with imidazolidinone salt (Scheme 1.6). Upon generation of an iminium ion **1.21** from the reaction of cyclic ether **1.19** consisting pendant *α,β*-unsaturated aldehyde moiety and the chiral organocatalyst, the 1,5-hydride shift would be initiated and the derived oxocarbenium moieties **1.22** and enamine would subsequently react to give chiral spiroether, which was further subjected *in situ* to the Wittig reaction to furnish the unsaturated ethylester **1.20** in good enantioseletictivity.



Scheme 1.6 Asymmetric Imidazolidinone-catalyzed 1,5-hydride transfer

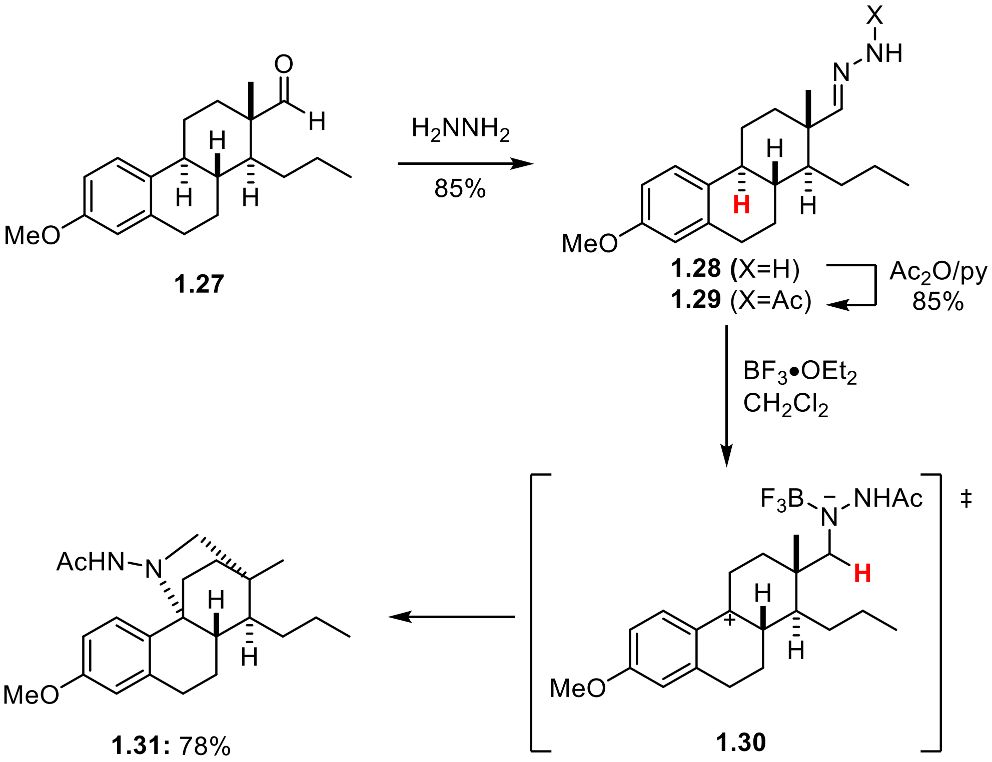
The Xiao's group has recently developed the use *p*-quinone methide (*p*-QM) as a hydride acceptor and the application of re-aromatization as the driving force for the 1,5-hydride transfer to take place (Scheme 1.7).[8] The activation of *p*-QM **1.24** is facilitated by hydrogenbonding clusters with hexafluoroisopropanol (HFIP), where HFIP behaves as a netted charge template to lower the electron density of conjugate *para*-quinonemethide. Subsequently, the innate tendency for re-aromatization initiated 1,5-hydride transfer which leads to the generation of zwitterion **1.26**. Lastly, hydrolysis of iminium intermediate would afford the secondary amine **1.25**.



Scheme 1.7 *para*-Quinone methides as hydride acceptor

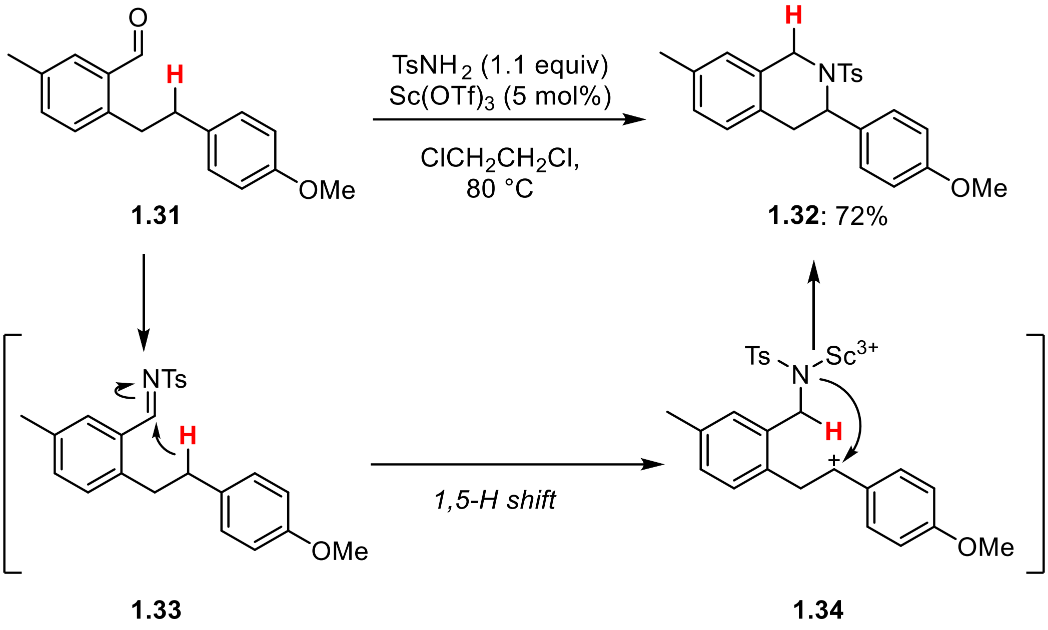
1.1.2 Hydride Transfer onto Activated Carbonyl/Imines

In 2009, Wölfling and coworkers reported an intramolecular hydro-*N*-alkylation of hydrazones for the synthesis of D-secoestrone isoquinuclidines (Scheme 1.8).[9] This synthesis is initiated from transformation of aldehyde **1.27** with hydrazine to form aldazine **1.28**, which is further acetylated to **1.29** due to the instability of aldazine **1.28** upon treatment with following BF_3•OEt_2. The acetylhydrazone **1.29** finally undergoes the following 1,5-hydride transfer and an ensuing intramolecular ring-closure step to finally furnish bridged steroidal azacycles **1.31**.



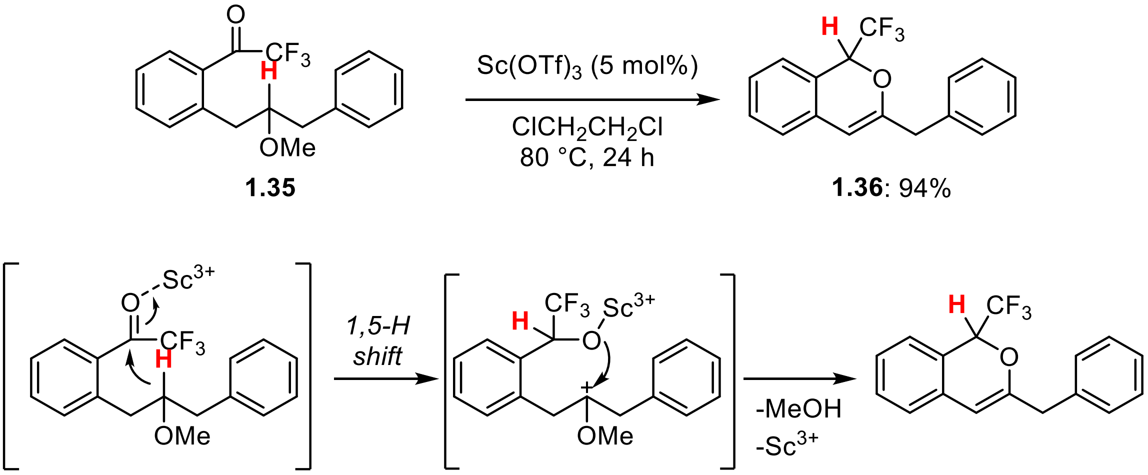
Scheme 1.8 Intramolecular hydro-*N*-alkylation of hydrazone

Similarly, Akiyama and coworkers^{10} developed another example of 1,5-hydride shift from an electron-rich benzylic C-H bond of a *p*-methoxyphenyl group onto in-situ generated aldimine **1.33** derived from the corresponding aldehyde **1.31** (Scheme 1.9). Treatment of **1.31** with tosylamine in the presence of sub-stoichiometric amount of $Sc(OTf)_3$ enabled one-pot imine formation, which followed by an internal redox reaction to give the desired cyclized isoquinoline product **1.32**.



Scheme 1.9 One-pot imine synthesis/1,5-hydride transfer/cyclization

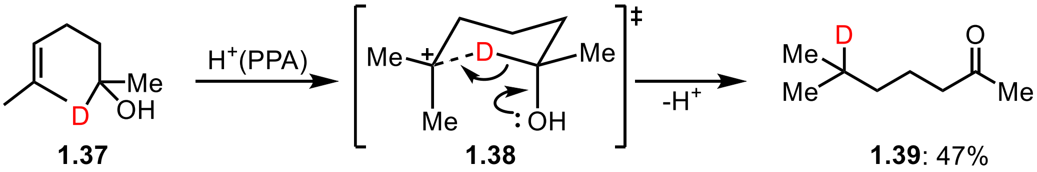
Synthesis of trifluoromethyl-substituted polycylic skeletons under catalytic amount of $Sc(OTf)_3$ was recently reported by Mori and coworkers (Scheme 1.10).[11] Treatment of trifluoromethyl ketone **1.35** having an *ortho*-phenetyl ether group with $Sc(OTf)_3$ triggers 1,5-hydride shift from electron-rich methyl ether C-H bond onto an activated carbonyl group. Subsequently, cyclization and elimination of MeOH affords trifluoromethylated isochromene **1.36**.



Scheme 1.10 Synthesis of trifluoromethyl-substituted isochromene

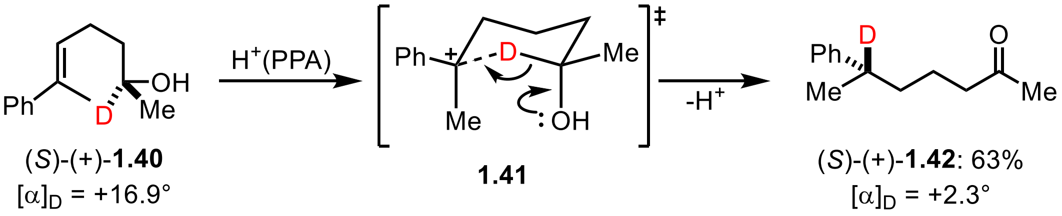
1.1.3 Hydride Transfer onto Carbocation

The mechanistic study of 1,5-hydride transfer has been earlier reported by Carlson and Hill in 1965 via the polyphosphoric acid (PPA) catalysed isomerization of 6-methylhept-5-en-2-ol **1.37** into saturated ketone **1.39** (Scheme 1.11).[12] Deuterium labelling signifies the migration of hydrogen attached to the carbinol carbon onto the *in-situ* generated carbocation **1.38**.



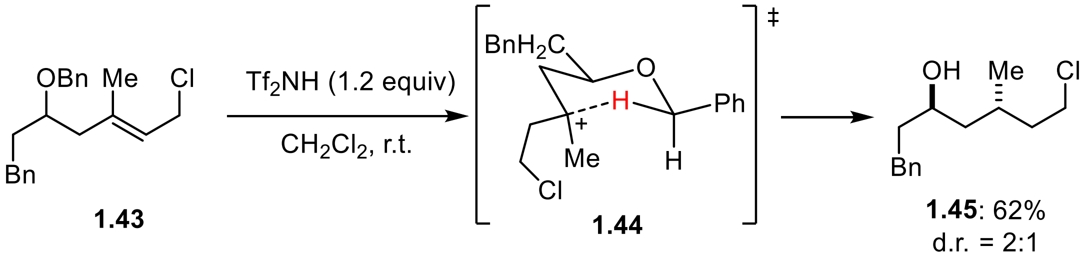
Scheme 1.11 Early example of 1,5-hydride transfer

More importantly, it was also indicated that the 6-membered ring transition state **1.41** is indeed involved in the hydride transfer mechanism. (Scheme 1.12) This mechanism was realized by the isomerization dextrorotatory isomer of **1.40** to ketone **1.42**, which proved to be optically active, having [α]D = +2.3°. Therefore, the 6-membered cyclic transition state **1.41** adopts a chair conformation, in which the sterically larger phenyl at C-6 is located in the pseudo equatorial position, whereas the smaller methyl being in pseudo axial position.



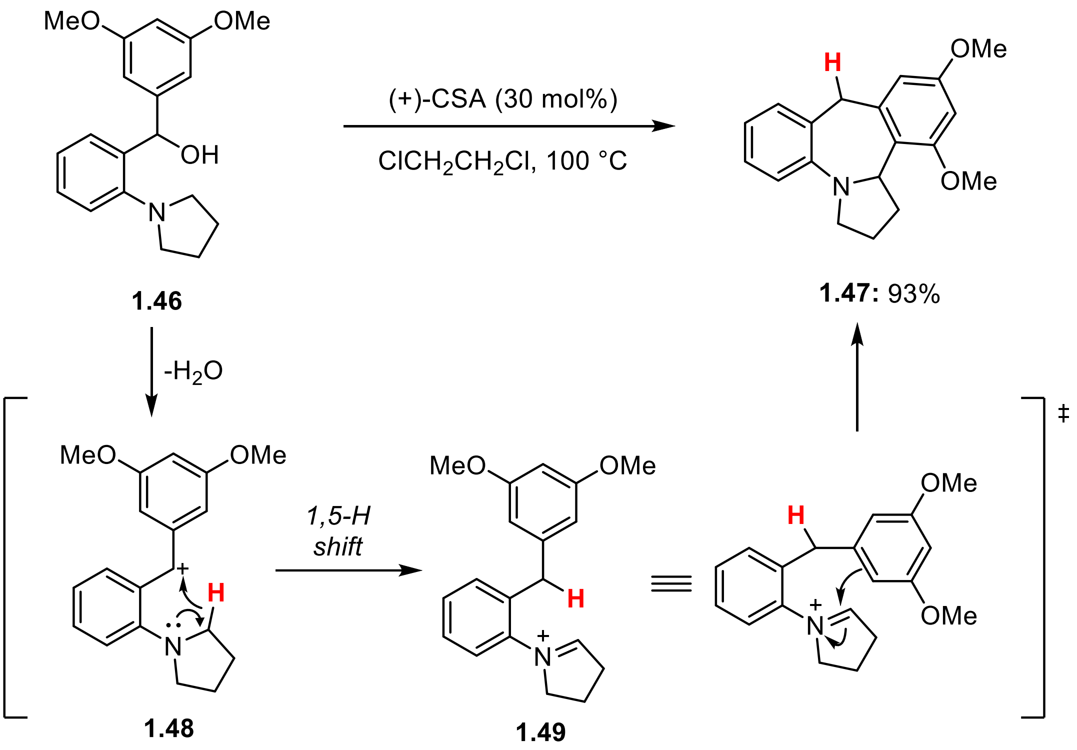
Scheme 1.12 Stereo-specificity study to determine 6-membered ring transition state

Taylor and coworkers reported in 2015 that the acidic activation of homoallylic *O*-benzyl ether **1.43** triggers a 1,5-hydride transfer and furnishes alcohol **1.45**, in *anti*-configuration as a result from the chair-like transition state **1.44** (Scheme 1.13).[13]



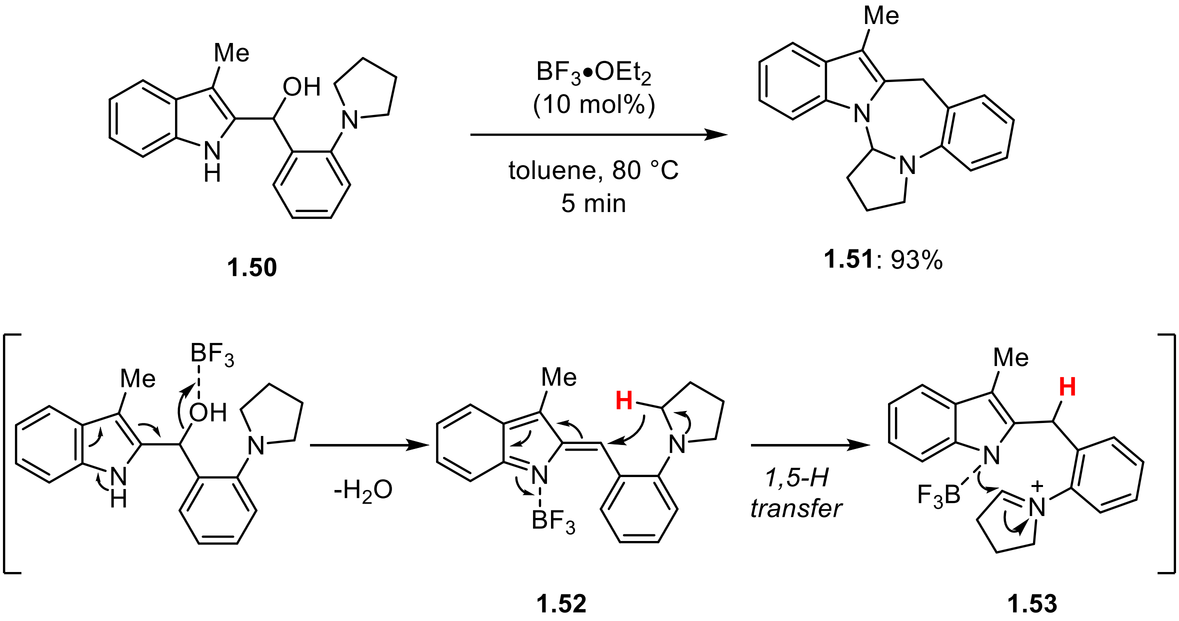
Scheme 1.13 Alkene as pro-carbocation as hydride acceptor

Subsequently, Xiao and coworkers reported the synthesis of dihydrobenzo[*b,e*]azepines by carbocation-initiated cascade 1,5-hydride transfer/cyclization and dimerization (Scheme 1.14).[14] Protonation of diarylmethanol moiety with (+)-camphorsulfonic acid (CSA) generates transient benzylic carbocation **1.48** which enables 1,5-hydride transfer process from electron-rich pyrrolidine **1.46** C-H bond leading to the formation of iminium ion **1.49**. Ultimately, the intramolecular Pictet-Spengler type reaction occurs to give the desired product **1.47**.



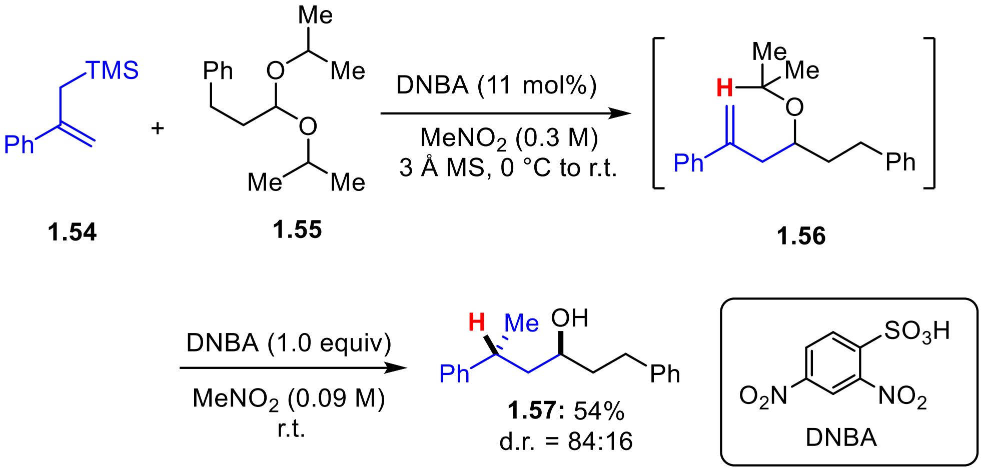
Scheme 1.14 Synthesis of dihydrodibenzoazepines

In the same year, Baomin and coworkers[15] also reported another example of 1,5-hydride transfer event triggered by dehydration of diarylmethanol **1.50**, followed by cyclization to furnish indolodiazepine product **1.51** (Scheme 1.15). In this case, the presence of indole moiety helps the protonation of alcohol to generate iminium **1.52** under Lewis acid catalysis, that is followed by the 1,5-hydride shift process and the formation of seven-membered ring closed at the nitrogen atom of indole **1.53**.



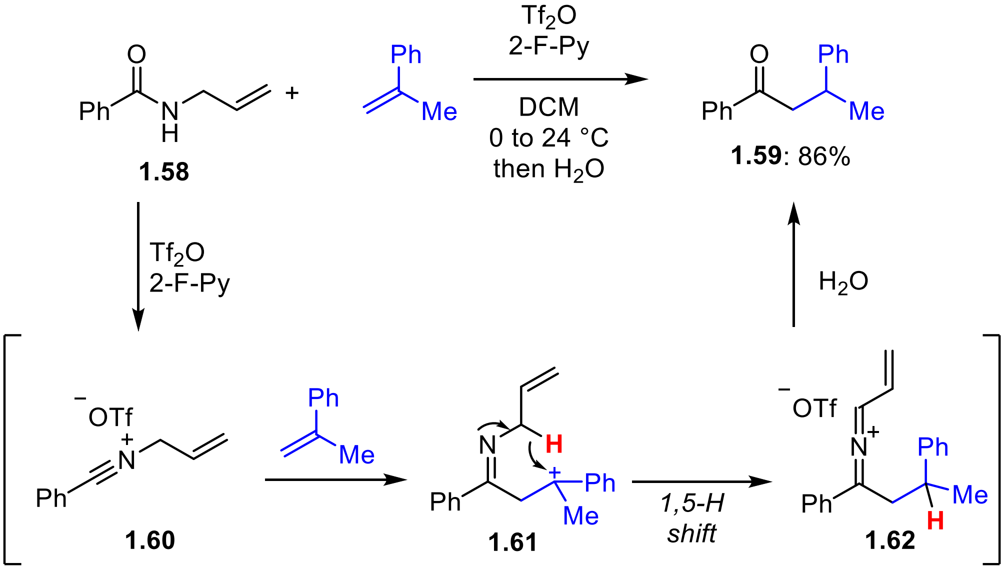
Scheme 1.15 Synthesis of indolodiazepines

In 2018, Maulide and coworkers reported a stereoselective reductive Hosomi-Sakurai reaction in the addition of a stoichiometric amount of Brønsted acid (Scheme 1.16).[16] At first, treatment of allylsilane **1.54** and acetal **1.55** with a catalytic amount of 2,4-dinitrobenzenesulfonic acid affords mixture of Hosomi-Sakurai product **1.56** and alcohol **1.57**. Further addition of a stoichiometric amount of acid was required to complete this internal redox process. Moreover, *anti*-product of **1.57** was obtained in good diastereoselectivity level, especially when the allylsilane nucleophilic part carries an aryl substituent.



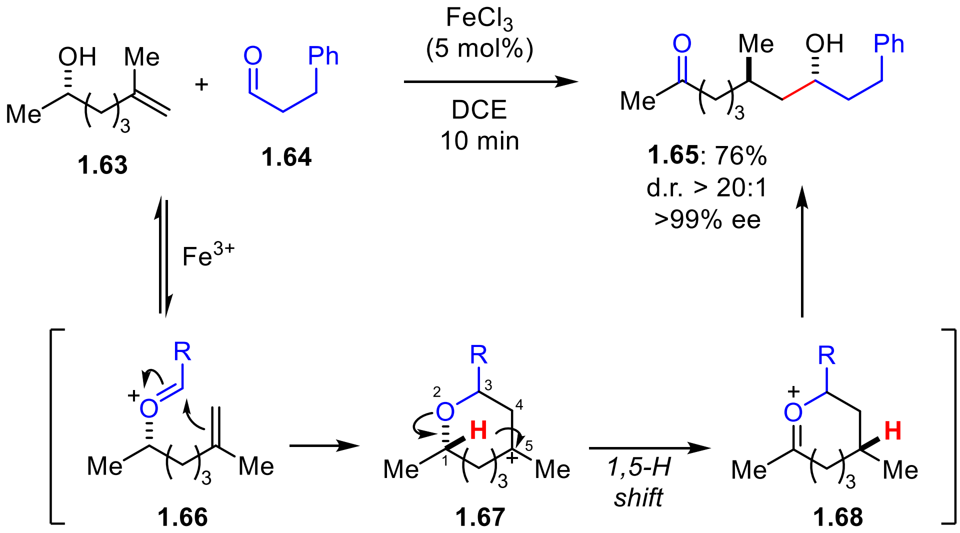
Scheme 1.16 Stereoselective Reductive Hosomi-Sakurai Reaction

Maulide's group recently demonstrated the direct synthesis of ketones by coupling of alkenes and amides (Scheme 1.17).[17] Activation of *N*-allylamide **1.58** with triflic anhydride and 2-fluoropyridine affords *N*-allylnitrilium species **1.60**, which is captured by the alkene partner to set up the intramolecular 1,5-hydride delivery from electron-rich *N*-allyl species to the transient carbocation **1.61**. This step simultaneously achieves reduction of the transient carbocation and formation of an azoniallene intermediate **1.62**, which upon hydrolysis results in the hydroacylated product **1.59**.



Scheme 1.17 Direct synthesis of ketones via coupling of alkenes and amides

The same group also recently disclosed another redox-neutral coupling reaction between aldehyde **1.64** and alkenes **1.63** to yield linear coupling ketone product **1.65** in excellent diastereoselectivity and enantioselectivity (Scheme 1.18).[18] The key of this transformation is the use of aldehyde reaction partner to bear the lower nucleophilicity of this unactivated alkenes. Therefore, the hydroxyl group on the alkene substrate **1.63** reacts with the aldehyde **1.64** to form oxocarbenium ion **1.66,** which undergoes intramolecular electrophilic attack from the alkene partner to generate a cylic, tertiary carbocation **1.67**. The resulting carbocation **1.67** is then reduced via 1,5-hydride shift event, which leads to the formation of stabilized oxocarbenium **1.68**, which is finally hydrolyzed to give the linear product **1.65**.

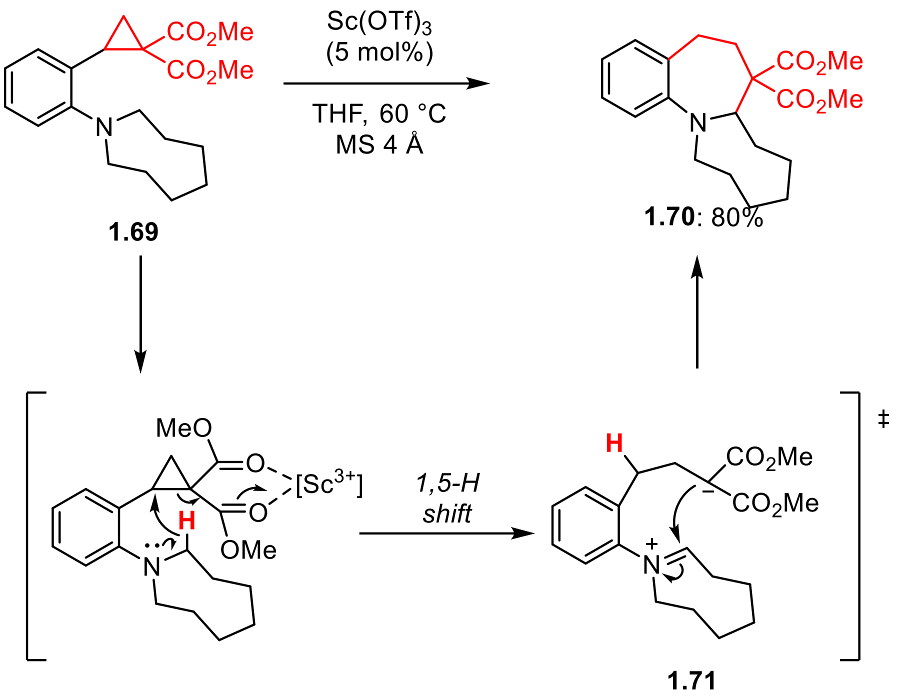


Scheme 1.18 Direct coupling of alkenols and aldehydes

1.1.4 Hydride Transfer onto Other Electrophiles

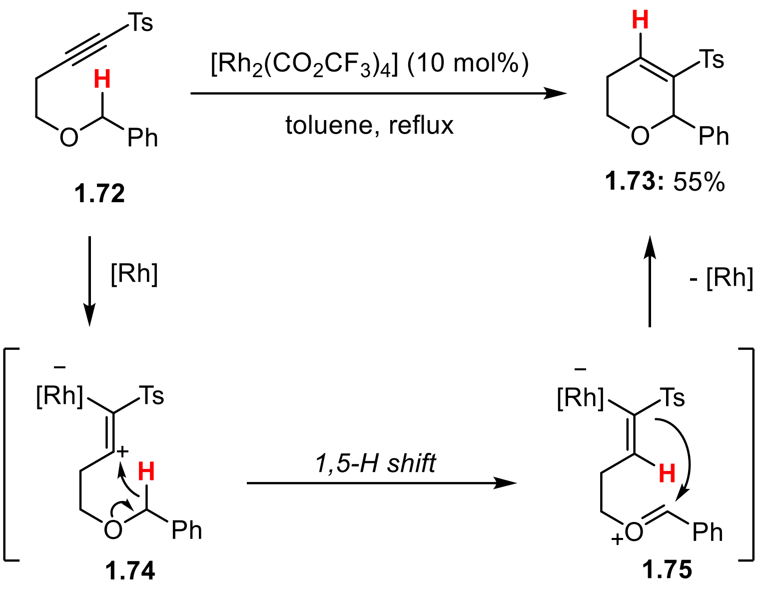
Besides the use of conventional electrophiles as described in previous sections, there were several reports on the use of other electrophiles as a possible hydride acceptor in the 1,5-hydride transfer process. For example, Kim and co-workers[19] reported the use of donor-acceptor cyclopropane **1.69** as hydride acceptor and a pendant cyclic amine as hydride donor

(Scheme 1.19). The process is initiated by the Lewis acid activation to trigger 1,5-hydride shift from C-H α to the nitrogen atom to form a zwitterion **1.71**. The following 7-endo cyclization finally furnishes the benzazepine **1.70**.



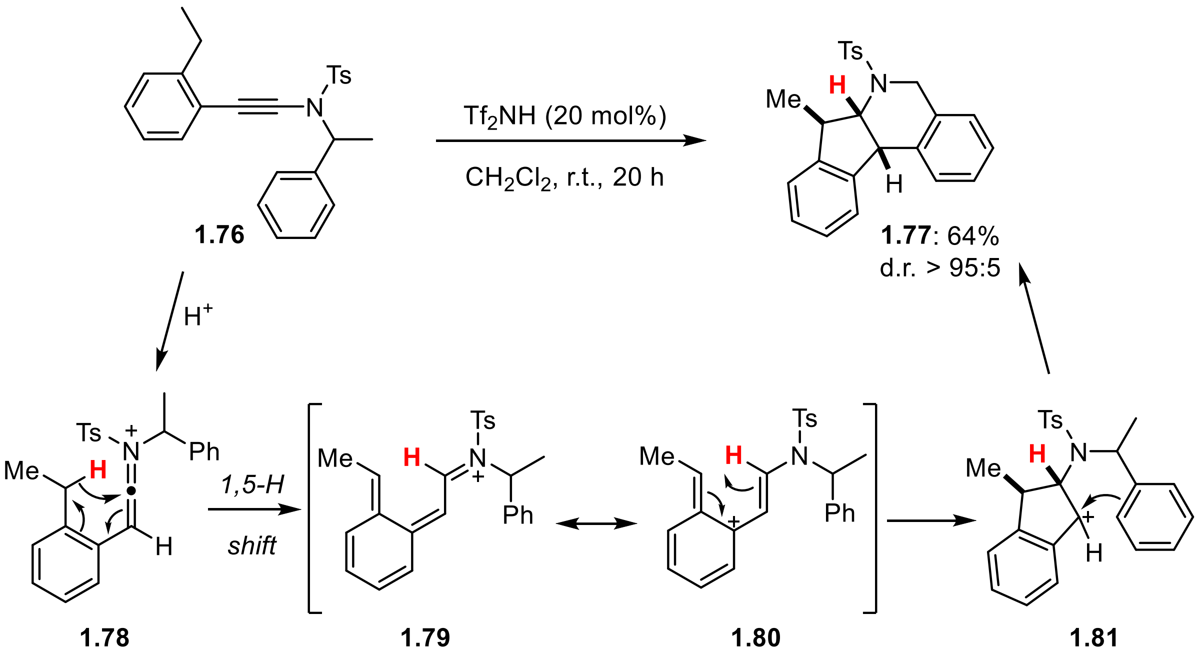
Scheme 1.19 Donor-Acceptor cyclopropanes as hydride acceptor

Urabe[20] and co-workers reported the use of the sulfonylacetylene **1.72** as an hydride acceptor through activation with a dinuclear rhodium(II) catalyst (Scheme 1.20). This process is initiated by the electrophilic activation of the acetylenic moiety by the dinuclear rhodium(II) catalyst to generate a zwitterionic intermediate **1.74**. This triggers a 1,5-hydride shift from the benzylic hydrogen onto the vinylic carbocation to form the oxocarbenium **1.75**. A subsequent ring closure furnishes the dihydropyran **1.73.**



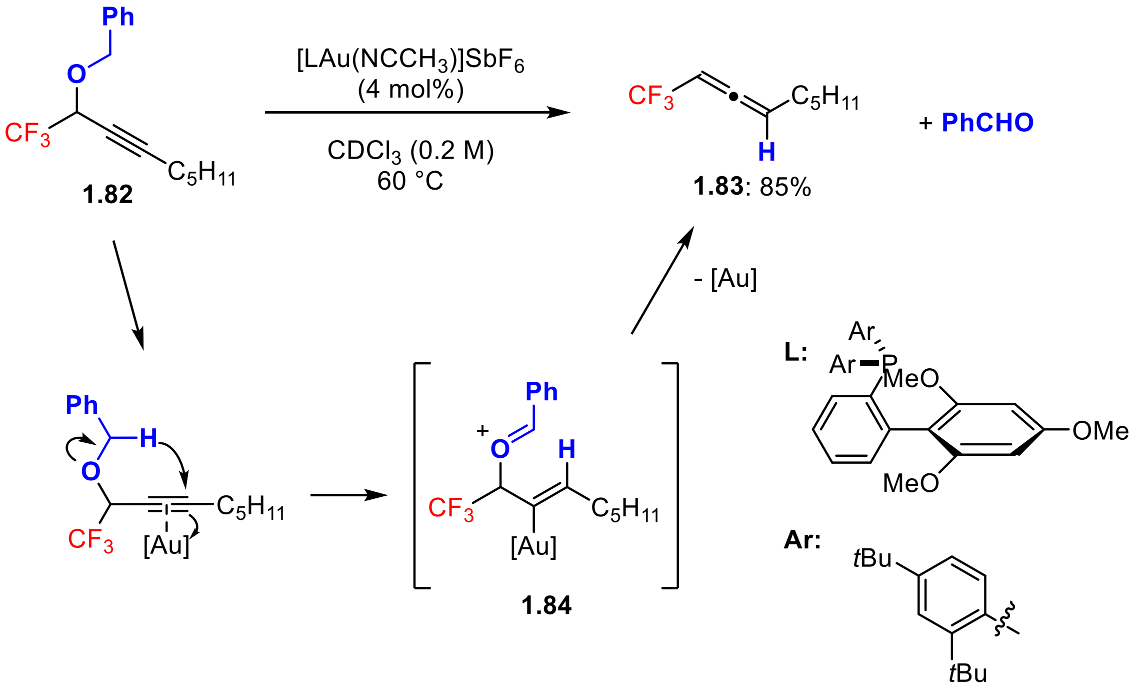
Scheme 1.20 Hydrofunctionalization of sulfonylacetylenes

Meanwhile, the Evano's group[21] has reported a keteniminium-initiated cationic cyclization to afford nitrogen heterocycles having three contiguous stereocenters from readily available ynamides (Scheme 1.21). The reaction is triggered upon protonation of ynamide **1.76** bearing an electron-rich alkyne to give exceptionally reactive *N*-tosyl-keteniminium **1.78**. The following 1,5-hydride shift then occurs from the benzylic C-H bond, generating conjugated iminium **1.79**, which is in the resonance form with the bis-allylic carbocationic intermediate **1.80**. This cyclic motif is generated via a 4π conrotatory electrocyclization to afford benzylic carbocation **1.81** which undergoes second cyclization with the arene subunit leading to the generation of polycycle **1.77**.



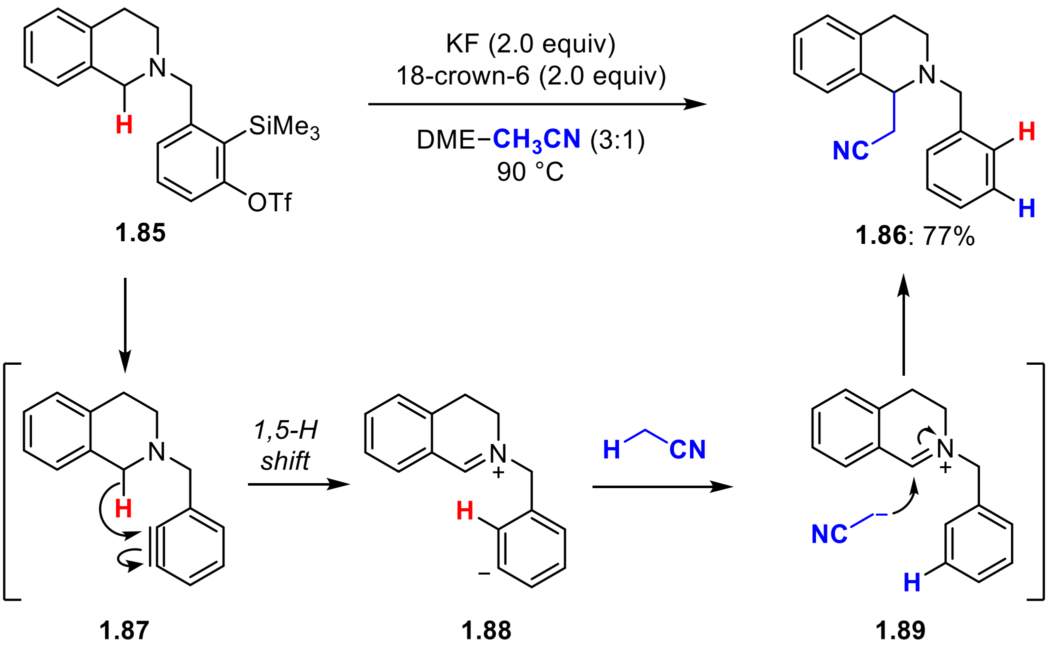
Scheme 1.21 Hydride transfer onto keteniminium

Gagosz and coworkers reported the synthesis of trifluoromethyl-allenes from α-trifluoromethyl-propargyl benzyl ether **1.82** by ensuing a gold-catalysed intramolecular hydride transfer (Scheme 1.22).[22] The electrophilic activation of alkyne with gold catalyst induces a 1,5-hydride transfer which leads to the generation of oxocarbenium **1.84**. The following elimination of benzaldehyde moiety with concomitant regeneration of the gold catalyst results in the formation of trifluoromethyl-allenes **1.83**.



Scheme 1.22 Gold-catalyzed synthesis of trifluoromethyl-allenes

Recently, Jones and co-workers developed an *α*-functionalization of amines, while using internal hydride acceptor such as arynes (Scheme 1.23).[23] The key 1,5-hydride transfer from electron-rich C-H bond α of the nitrogen atom onto *in-situ* generated benzyne **1.87** generates zwitterion intermediate **1.88**. Significantly, zwitterion **1.88** involves a basic aryl anion which can activate a pro-nucleophile such as acetonitrile inside the reaction mixture, thus undergoing Mannich-type addition to iminium ion **1.89** to furnish α-cyanomethylated amine **1.86**.

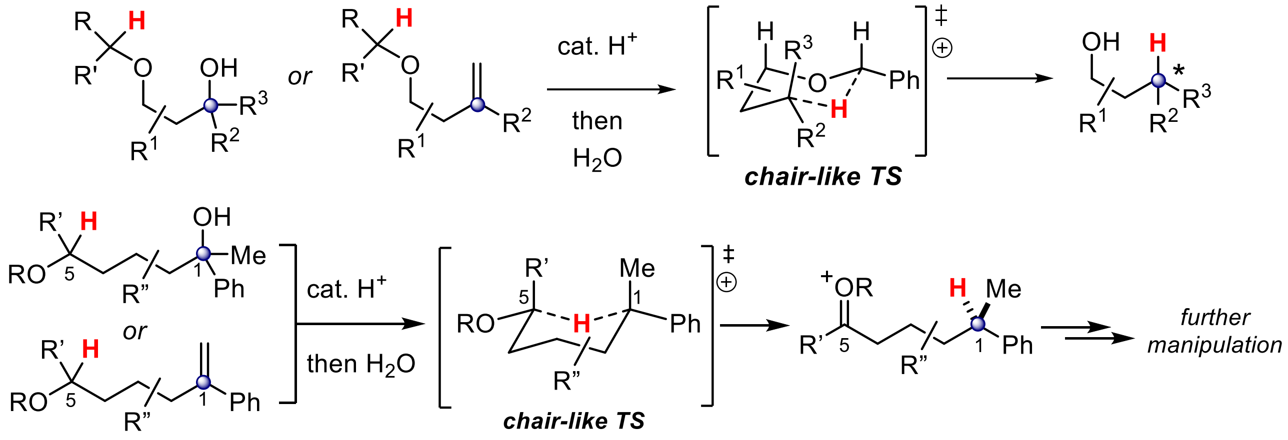


Scheme 1.23 *α*-Functionalization of amines using arynes as hydride acceptor

1.2 Perspective of the Thesis

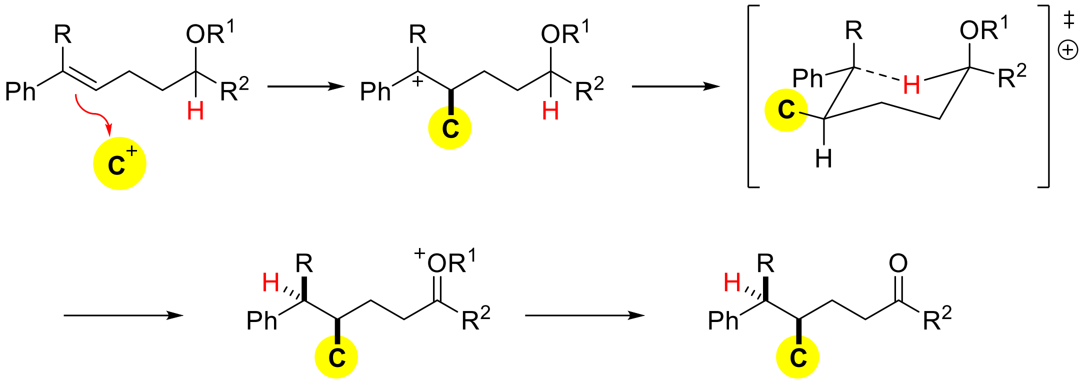
As described above, various applications of 1,5-hydride shift have been disclosed onto an array of hydride acceptors. Most of these works however have focused on the functionalization of aliphatic C-H bonds, whereas the application of this chemistry for the reductive event on the hydride acceptor remains elusive. More importantly, it continues to be a challenge to achieve predictable stereocontrol in the creation of consecutive stereogenic centers. Therefore, in this thesis, the author has aimed at the strategy development for the reduction of the transiently generated carbocation upon electrophilic activation of olefins or alcohols, while demonstrating the use of predictable 6-membered chair-like transition state to enable the diastereoselective construction of stereogenic centers.

In Chapter 2, the author demonstrated the application of alkyl ethers as traceless hydride donors for the hydrogenation of alkenes and the deoxygenation of alcohols under Brønsted acid catalysis. Various alkyl ethers, such as benzyl and isopropyl ether could be applied as a traceless hydrogen atom donor. Furthermore, distal methyl ethers or acetals were also described in the synthesis of aldehyde acetal, ester or ketone derivatives. The reductive process is relied on an intramolecular 1,5-hydride shift onto a transiently generated carbocation, obtained upon Brønsted acid protonation of alcohols and alkenes. As described in previous section, 1,5-hydride transfer step generally proceeds via a 6-membered ring chair-like transition state. Therefore, the construction of multiple stereogenic centers would be achieved with a high level of diastereoselectivity.



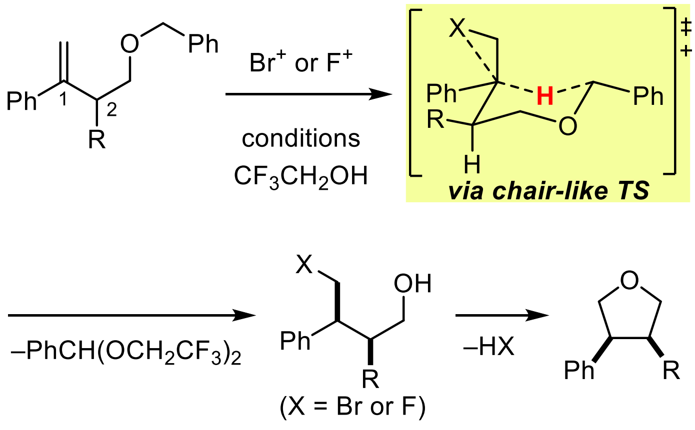
Scheme 1.24 Brønsted acid catalyzed 1,5-hydride transfer

The preinstalled stereogenic center of the *exo*-alkene substrate at the allylic position was used in Chapter 2 in the attempt to construct consecutive vicinal stereogenic centers. In Chapter 3, the author demonstrated the electrophilic alkylation of prochiral *endo*-aryl alkenes with external carbocations, formed from *in-situ* protonation of diaryl methanols with Brønsted acid. The resulting benzylic carbocations generated upon electrophilic alkylation could finally be acquired by the following key 1,5-hydride shift to furnish *anti*-Markovnikov hydroalkylated ketone or ester derivatives.



Scheme 1.25 Anti-Markovnikov diastereoselective hydroalkylation

In place of Brønsted acid catalysis for the electrophilic activation to initiate the 1,5-hydride shift described in previous chapters, the author also utilized *N*-bromosuccinimide (NBS) and Selectfluor for electrophilic halogenation of alkenes. The resulting haloniums then could undergo 1,5-hydride shift to deliver *anti*-Markovnikov hydrohalogenation of alkenes. Finally, intramolecular cyclization from the resulting haloalcohols would give the multi-substituted tetrahydrofurans in excellent diastereoselectivity.



Scheme 1.26 Anti-Markovnikov hydroetherification of alkenes

1.3 References

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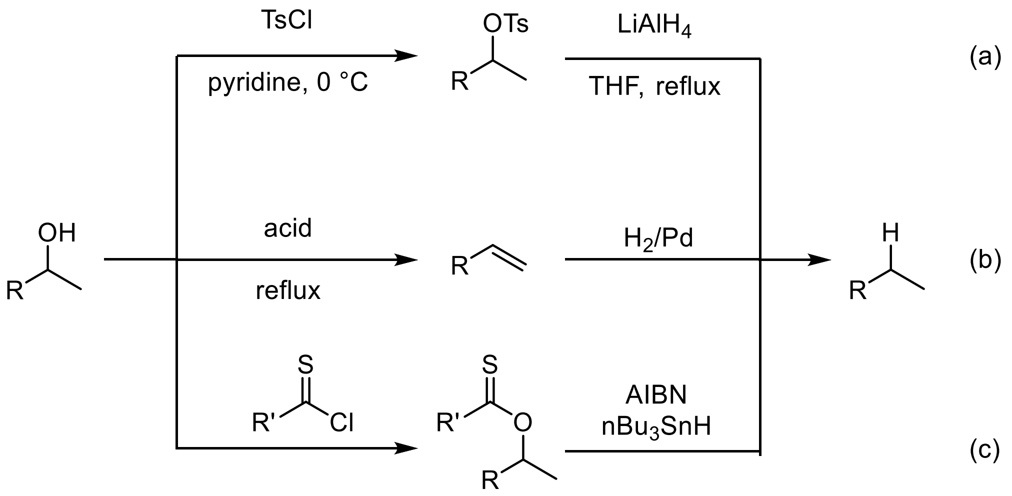
Chapter 2. Diastereoselective Intramolecular Hydride Transfer under Brønsted Acid Catalysis

2.1 Introduction

Intramolecular hydride transfer allows for a delivery of hydride to an electrophilic functional group such as activated carbonyl, electron deficient olefins and *in-situ* generated carbocation intermediates. The carbocation could potentially be derived from alcohols via dehydration and from olefins via protonation in the presence of Brønsted acids. Intramolecular hydride shift to the resulting carbocations allows for deoxygenation of alcohols and hydrogenation of alkenes to provide reduced alkanes. This introductory section will summarize and highlight general and recent synthetic methods for deoxygenation of alcohols and hydrogenation of alkenes.

2.l.1 Deoxygenation of Alcohols

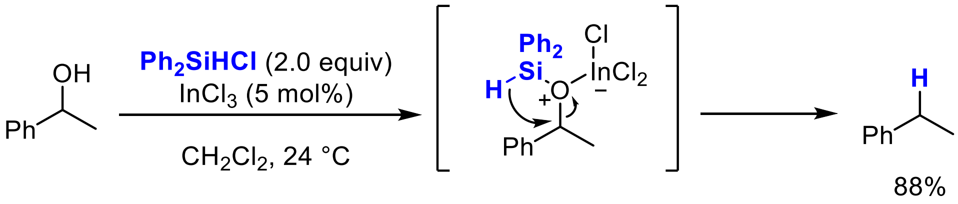
The deoxygenation of aliphatic alcohols is a broad research area in modern organic chemistry. However, due to the poor leaving ability of the hydroxy group, the reductive conversion of alcohols into alkanes is typically achieved by conversion of alcohols into (pseudo)halides in prior to their treatment under the appropriate hydridic reaction conditions (Scheme 2.1a). Another method for the deoxygenation involves acidic dehydration of alcohols followed by hydrogenation of the resulting C=C bond (Scheme 2.1b).



Scheme 2.1 Two-stepped deoxygenation of alcohols

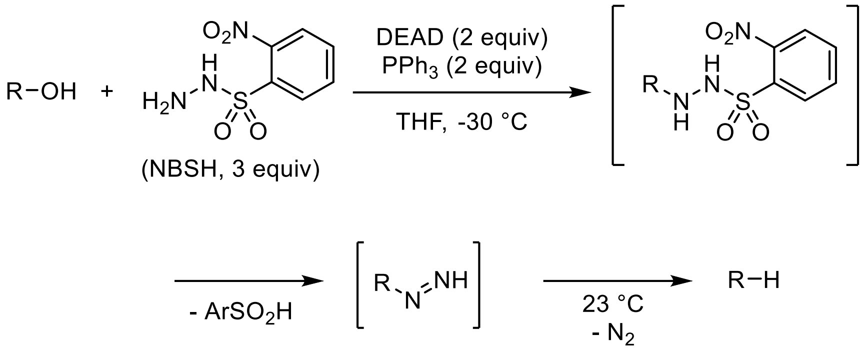
The other typical method of deoxygenation of aliphatic alcohols is the Barton-McCombie deoxygenation by their conversion into thioesters followed by radical deoxygenation using tributyltin hydride in the presence of radical initiators such as AIBN[1] (Scheme 2.1c). The use of stoichiometric amount of organotin-based reagent entails disadvantages, as these reagents are toxic and difficult to be removed from the reaction mixture. Therefore, the development of efficient catalytic systems for the direct reduction of alcohols is highly desirable from the synthetic and atom-economic points of view.

In 2001, Baba and co-workers developed a mild and general reducing system using indium trichloride and chlorodiphenylsilane.[2d] A variety of secondary and tertiary alcohols were effectively reduced to the corresponding alkanes. Since this discovery, several similar systems utilizing hydrosilanes as the reductant have been reported.[2]



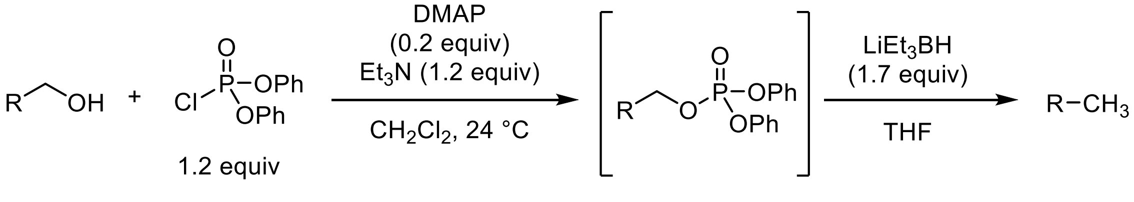
Scheme 2.2 $InCl_3$-catalyzed deoxygenation of alcohols

Zheng and co-workers developed the transformation of aliphatic alcohols into monoalkyl diazenes, the process involves the Mitsunobu displacement of the hydroxy group with *o*-nitrobenzenesulfonylhydrazine (NBSH) followed by elimination of an *o*-nitrobenzenesulfinic acid[3]. The resulting monoalkyl diazenes are finally decomposed under a free radical mechanism to form deoxygenated alkanes.



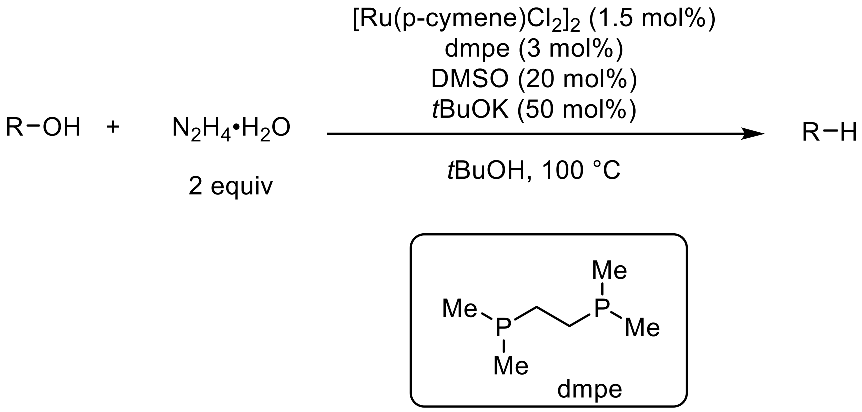
Scheme 2.3 Hydrazine mediated deoxygenation of alcohols

Recently, Standaert and co-workers showed that primary alcohols could also be deoxygenated by reduction of the corresponding diphenyl phosphate esters derived from primary alcohols with lithium triethylborohydride.[4]



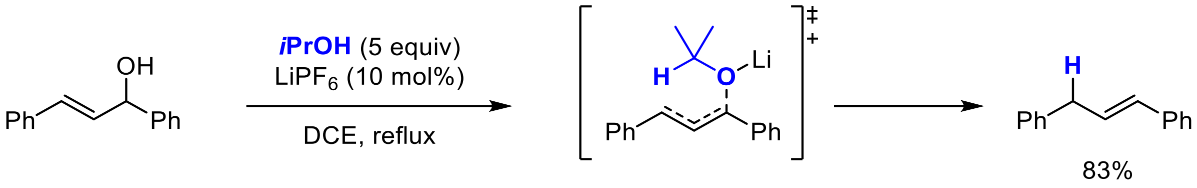
Scheme 2.4 Reduction of diphenyl phosphate ester

Li and co-workers reported a catalytic redox design using late-transition-metal catalysis on the basis of simultaneous dehydrogenation/the Wolff-Kishner reduction.[5] This synthetic utility tackles the challenges regarding selectivity and step economy, generating only N_2, H_2 and H_2O as the co-products. The catalytic system is consisted of [Ru(*p*-cymene)Cl_2]$_2$/bidentate phosphine ligand in 1,2-bis(dimethylphophino)ethane in the presence of sub-stoichiometric amount of DMSO and potassium *tert*-butoxide.



Scheme 2.5 Simultaneous dehydrogenation/Wolff-Kishner reduction

Isopropanol was utilized as a hydride donor in the direct reduction with lithium cation catalysis to undergo deoxygenation of allylic alcohols.[6] The hydride transfer of *in situ* generated lithium isopropoxide to the allylic cation intermediates is the key process in this transformation. The process offers good atom economy as only water and acetone are generated as co-products.

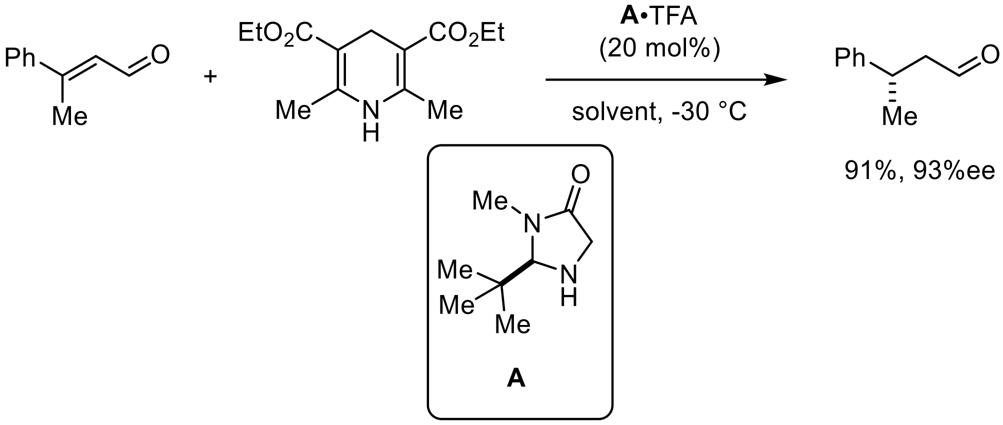


Scheme 2.6 Use of isopropanol as hydride donor

2.l.2 Hydrogenation of Alkenes

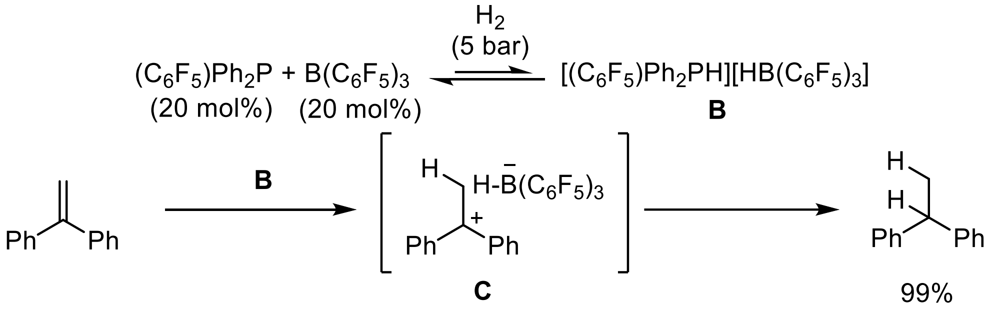
Various transition-metal complexes (typically Pd on carbon) have been employed for the catalytic hydrogenation of alkenes under a hydrogen atmosphere.[7] On the other hand, the development of alkenes hydrogenation without precious transition-metals would be attractive from the sustainability point of view.

Hantzsch esters and their related organic hydride donors have been widely utilized in biomimetic approaches of asymmetric transfer hydrogenation (ATH) reactions.[8] As nature is able to perform the ATH by taking advantage of enzymes such as NADH or NADPH,[9] many chemists were inspired to develop a similar process using organic hydride reagents. In this aspect, MacMillan and co-workers have developed an enantioselective organocatalytic transfer hydrogenation in 1,4-hydrogenation of *α,β*-unsaturated aldehyde upon subjection of the chiral imidazolinone catalyst in the presence of Hantzsch esters.[10]



Scheme 2.7 Hantzsch ester as hydride donor in Asymmetric Transfer Hydrogenation

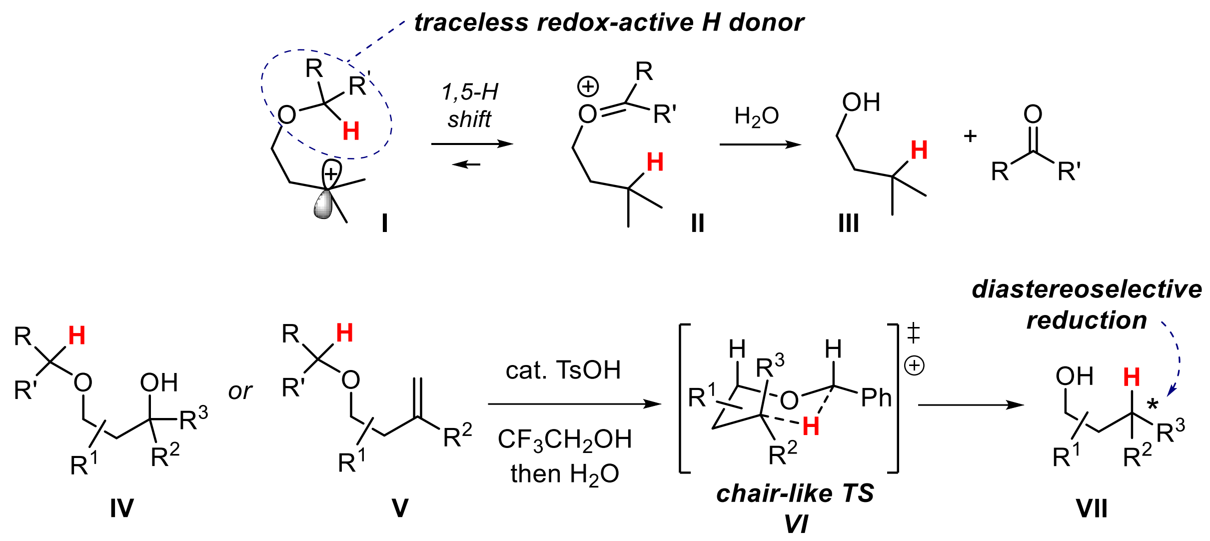
Stephan[11] has recently developed a metal-free process to activate molecular hydrogen (H_2) to perform alkene hydrogenation. This process is initiated by the reaction between pentafluorophenyl-phosphine and -borane through transient hydrogen activation to form the frustrated Lewis pair (FLP) complex **B** (Scheme 1.11). The FLP complex transfers a proton to the olefin to form the carbocation **C**, which is trapped by the hydridoborate to regenerate FLP catalyst along with the liberation of the hydrocarbon product in nearly quantitative yield**.**



Scheme 2.8 Frustrated Lewis Pair as a hydride donor

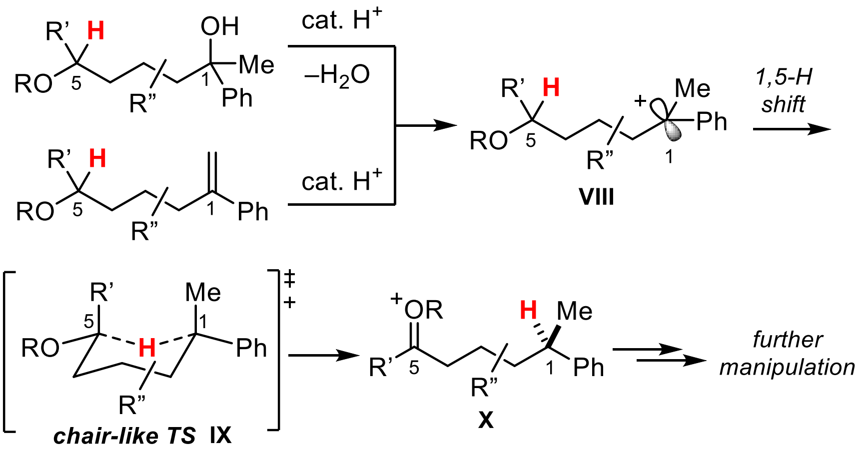
2.2 Working Hypothesis

The author wondered if alkyl ethers could be used as a traceless hydride donor in the reduction of a transiently generated carbocation **I**[12]. In this process, the electron-rich hydrogen atom α to the ethereal oxygen would be able to migrate to the carbocation to produce a relatively more stable oxocarbenium ion **II**. Subsequent hydrolysis would ultimately deliver alcohol **III** along with a carbonyl co-product derived from the hydride donor moiety. The precursors of the carbocations could be 1,3-diol mono alkyl ethers **IV** or homoallylic alcohol *O*-alkyl ethers **V**. As the 1,5-hydride shift takes places through a 6-membered ring chair-like transition state **VI**, overall process enables diastereoselective deoxygenation of alcohols **IV** or hydrogenation of alkenes **V** through a 6-membered ring chair-like transition state **VI**, furnishing the reduced alcohol **VII**. The details on the investigation of this process will be discussed in Section 2.3.



Scheme 2.9 Working Hypothesis-1

The author also envisioned that 1,5-hydride transfer process could occur at the carbocation intermediates **VIII** derived from 5-alkoxypentan-ols **X** or alkenes 6-alkoxyhex-1-enes having a distal alkyl ether moiety. Similarly, it could be proposed that the 1,5-hydride transfer enables the control of the diastereoselectivity through a 6-membered ring chair-like transition state **IX**. In this case, the resulting oxocarbenium ion **X** could be further transformed into useful oxygen functional groups, such as aldehyde acetal, ketone or ester derivatives. This chemistry will be discussed in Section 2.4.

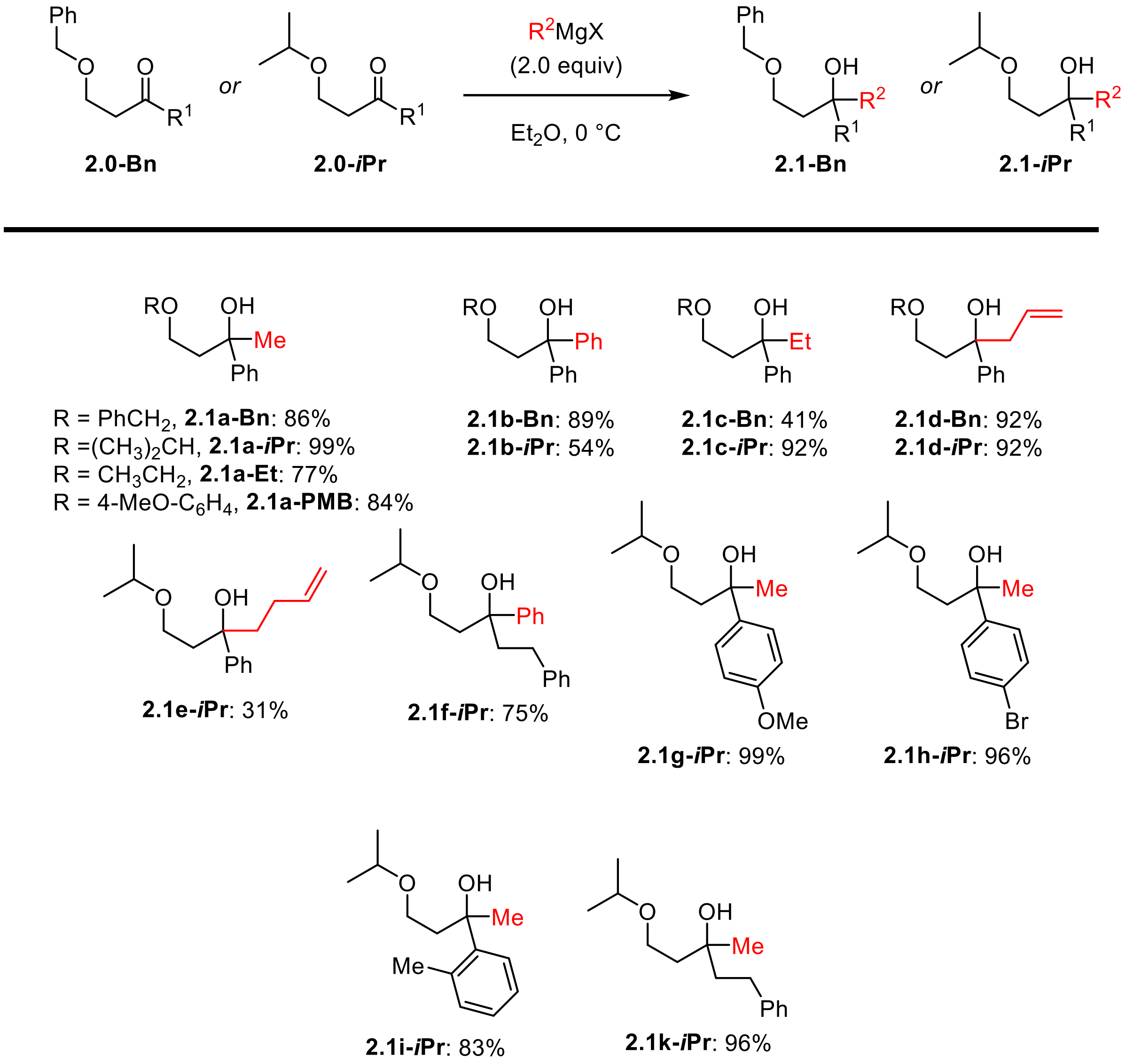


Scheme 2.10 Working Hypothesis-2

2.3 Result and Discussion - Alkyl Ethers as Traceless Hydride Donors

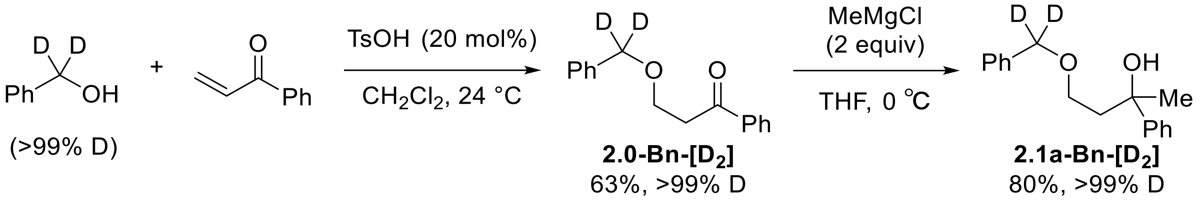
2.3.1 Substrate Synthesis

Substrate **2.1-Bn** and **2.1-*i*Pr** were synthesized from addition of the Grignard reagents into a known β-alkyloxy ketone **2.0-Bn** and **2.0-*i*Pr**[13] respectively. (Scheme 2.11).



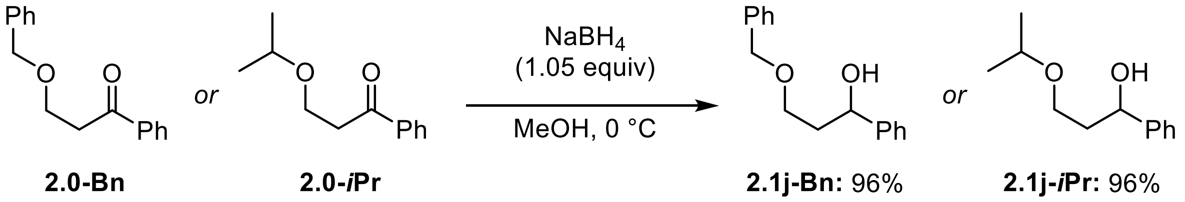
Scheme 2.11 Synthesis of substrates **2.1**

Deuterated labelled alcohol 2.1a-Bn-[D_2] was synthesized from 1,4-addition of benzyl alcohol-d_2 onto vinyl phenyl ketone to give benzyloxy ketone 2.0-Bn-[D_2][14], followed by addition of methylmagnesium chloride (Scheme 2.12).



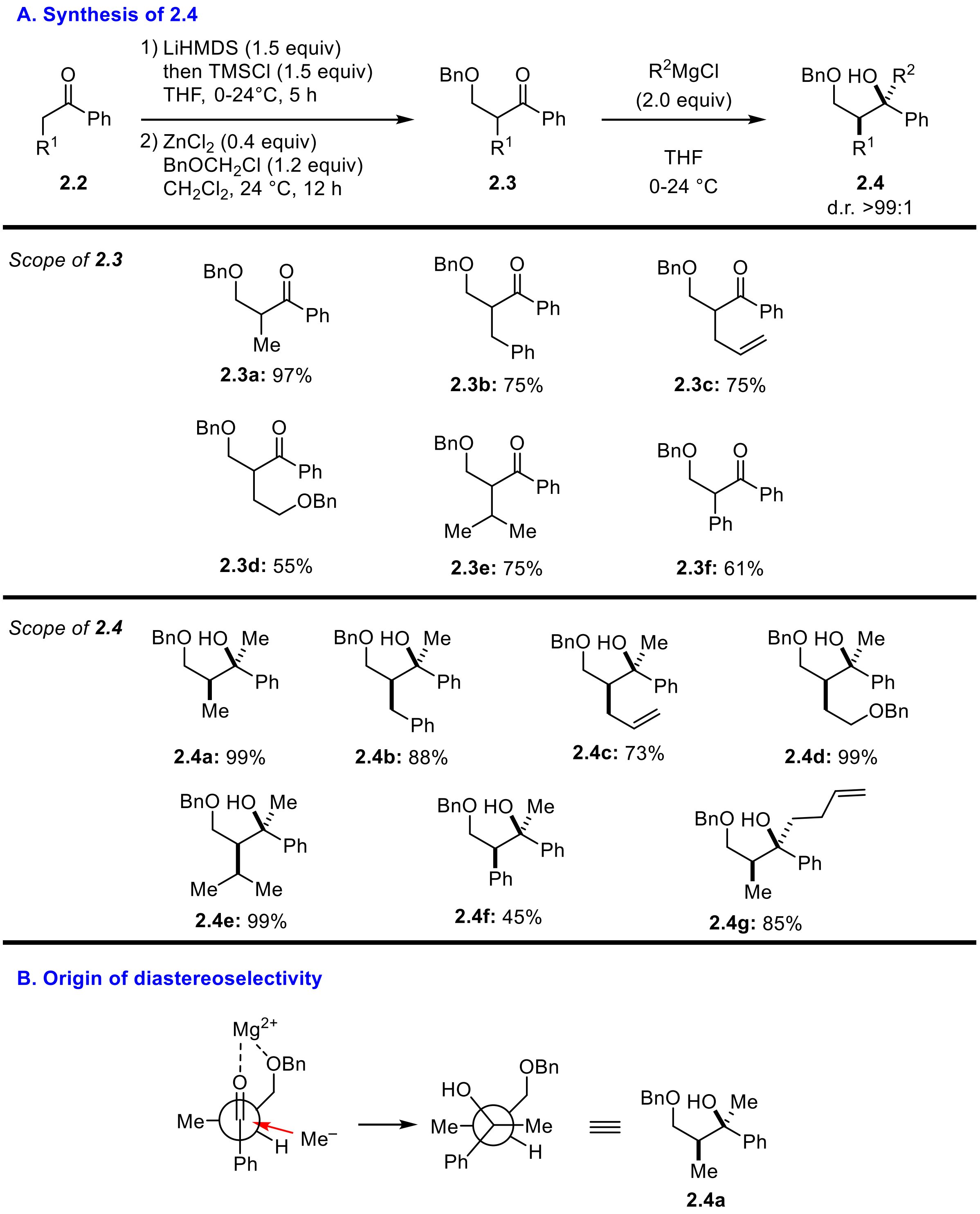
Scheme 2.12 Synthesis of deuterated substrate **2.1a-Bn-[D_2]**

For synthesis of **2.1j-Bn** and **2.1j-iPr**, the phenyl ketones **2.0** were reduced by $NaBH_4$ (Scheme 2.13).



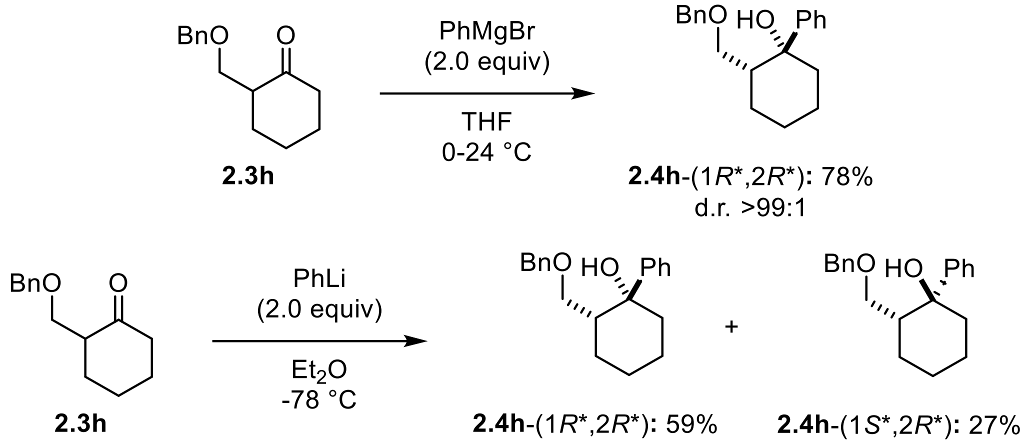
Scheme 2.13 Synthesis of substrate **2.1j**

The synthesis of tertiary alcohol substrates **2.4** was conducted through the following two-step synthesis: 1) $ZnCl_2$-catalyzed benzyloxy methylation[15] of lithium enolate derived from ketones **2.2**; 2) addition of the Grignard reagents to the resulting β-benzyloxy ketones **2.3** to afford tertiary alcohols **2.4a-2.4g** as a single diastereomer (Scheme 2.14A). The observed diastereoselectivity for the synthesis of **2.4a-2.4g** could be explained by invoking a chelation model, in which the carbonyl and benzyloxy moieties are linked with the magnesium ion as depicted in Scheme 2.14B.[16]



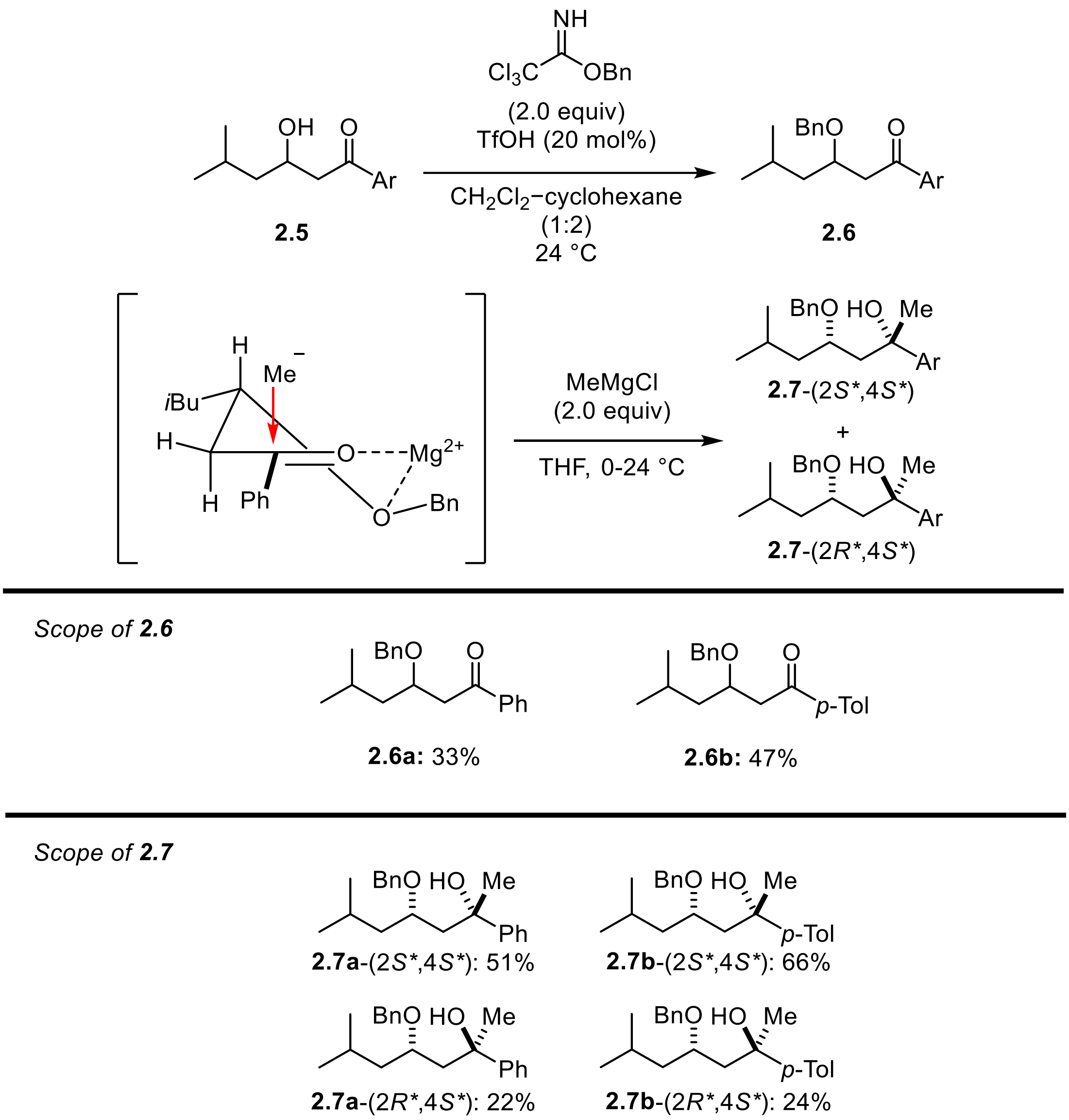
Scheme 2.14. Synthesis of substrates **2.4a-2.4g**

For the synthesis of cyclohexanol **2.4h**, the addition of phenylmagnesium bromide into cyclohexanone **2.3h** afforded single diastereomer of **2.4h**, whereas addition of phenyllithium gave a mixture of diastereomers of **2.4h** (Scheme 2.15).



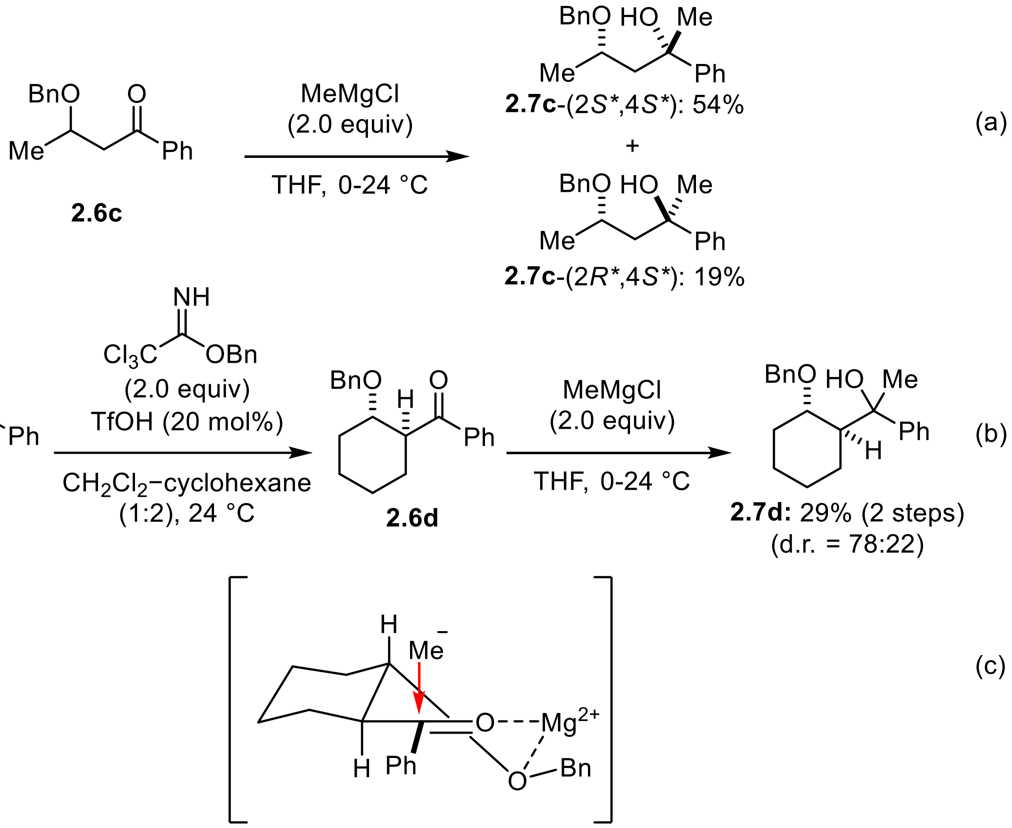
Scheme 2.15. Synthesis of substrates **2.4h**

The synthesis of substrates **2.7** was achieved by benzylation of β-hydroxy ketone **2.5** with benzyl 2,2,2-trichloroacetimidate followed by addition of methylmagnesium chloride to the resulting ketones **2.6** (Scheme 2.16). The origin of the diastereoselectivity could be explained via a chelation model between carbonyl and benzyl ether moiety, where the addition of Grignard reagent from top side would favor the formation of **2.7**-(2*S**,2*S**).



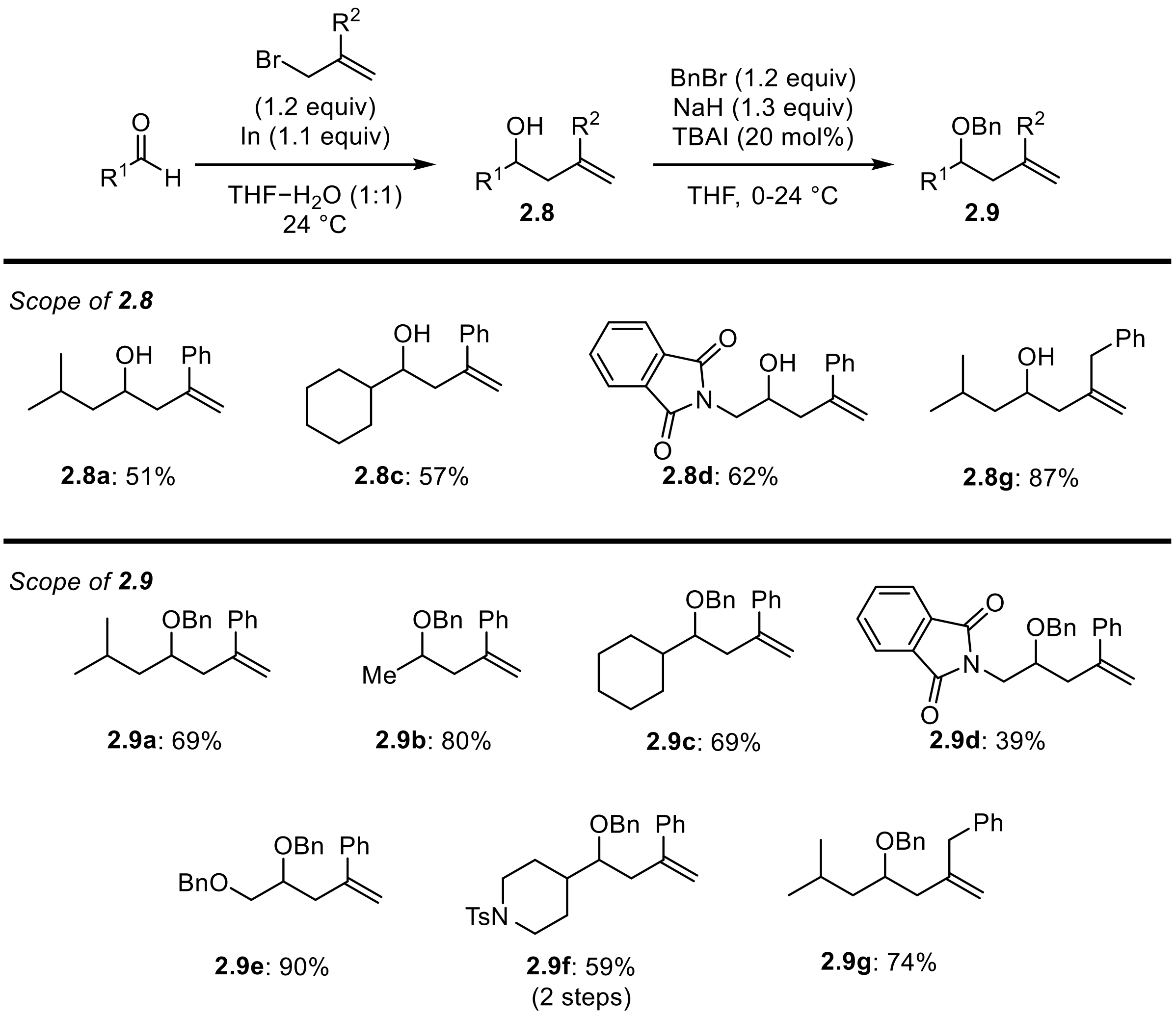
Scheme 2.16. Synthesis of substrates **2.7a** and **2.7b**

Alcohol **2.7c** was synthesized directly using known ketone **2.6c**[17] and methylmagnesium chloride (Scheme 2.17a). The synthesis of **2.7d** was achieved following 2-step synthesis from known β-hydroxyketone **2.5d**[18] (Scheme 2.17b)**.** The origin of the diastereoselectivity could be explained by a chelation model as depicted in Scheme 2.17c, where the structure of major diastereomer possessing a (*S**)-configuration at the carbinol center might be deduced.



Scheme 2.17. Synthesis of substrates **2.7c** and **2.7d**

Homoallylic alcohol *O*-benzyl ethers **2.9** were prepared by the two-step protocol composed of 1) the Barbier reaction of the corresponding aldehydes with allyl bromide in the presence of indium to give homoallylic alcohol **2.8**; 2) benzylation of alcohols **2.8** in the presence of NaH and tetrabutylammonium iodide (Scheme 2.18).

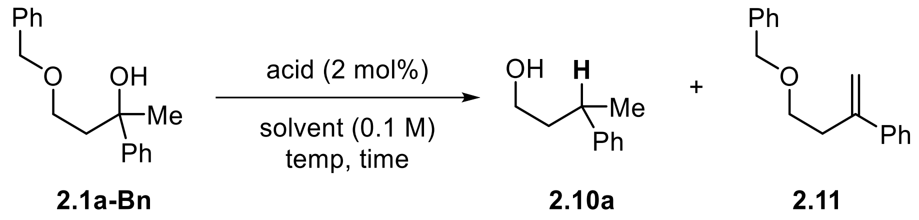


Scheme 2.18. Synthesis of substrates **2.9a-2.9g**

2.3.2 Optimization of reaction conditions

The author started our investigation with the optimization of the reaction conditions with model substrate **2.1a-Bn**, a tertiary alcohol having a benzyl ether moiety as a potential hydride donor in the presence of Brønsted acids. Treatment of **2.1a-Bn** with 2 mol% of *p*-toluenesulfonic acid (TsOH) in aprotic solvents such as 1,2-dichloroethane, acetonitrile and nitromethane at 50 °C gave good conversion of **2.1a-Bn** to provide desired deoxygenated alcohol **2.10** in moderate yields (entries 1-3). It should be noted that formation of alkene **2.11** was also observed in substantial amounts. It was observed that the reaction in EtOH resulted in full recovery of the starting material (entry 4). In sharp contrast, the reaction in 2,2,2-trifluoroethanol (TFE) rendered the desired transformation optimally performed to consume **2.1a-Bn** within 15 min at at 50 °C, affording alcohol **2.10a** in 85% yield (entry 5). The author observed that this transformation could also be achieved at 24 °C albeit lower yield and the formation of alkene in 7% yield (entry 6). Further screening of other Bronsted acids such as trifluoromethanesulfonic acid (TfOH), bistriflimide (Tf_2NH) and trifluoroacetic acid (TFA) gave lower yields of **2.10a** (entry 7-9).

Table 2.1. Optimization of the reaction conditions

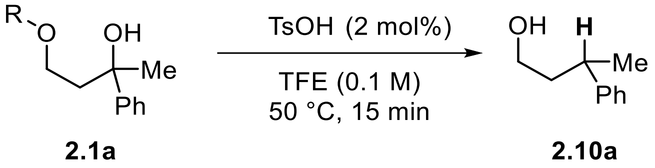


entry	acid	solvent	Temp. [°C]	Time [h]	Yield of **2.10a** [%][b]	Yield of **2.11** [%][b]
1	TsOH	$ClCH_2CH_2Cl$	50	18	33	8
2	TsOH	CH_3CN	50	18	35	32
3	TsOH	CH_3NO_2	50	1	54	18
4	TsOH	EtOH	50	17	0[c]	0
5	**TsOH**	**CF_3CH_2OH**	**50**	**0.25**	**87 (85)[d]**	**0**
6	TsOH	CF_3CH_2OH	24	0.25	80	7
7	TfOH	CF_3CH_2OH	50	0.25	80	0
8	Tf_2NH	CF_3CH_2OH	50	0.25	81	0
9	CF_3CO_2H	CF_3CH_2OH	50	1.5	44	4

[a] The reactions were conducted on a 0.3 mmol scale in 3 mL of the indicated solvent. [b] ^{1}H NMR yield determined using 1,1,2,2-tetrachloroethane as an internal standard. [c] **2.1a-Bn** recovered in >99% yield. [d] Isolated yield of **2.10a**.

The author then examined use of other alkyl ethers as alternative hydride donor (Table 2.2). It was noted that reaction of *p*-methoxybenzyl ether **2.1a-PMB** resulted in the formation of a mixture of unidentified compounds probably due to the undesired reactions of the electron-rich *p*-methoxyphenyl moiety under the acidic reaction conditions (entry 2). On the other hand, the reactions of isopropyl ethers **2.1a-iPr** and ethyl ether **2.1a-Et** were found to function as a hydride donor to form **2.10a** in 78% and 51% yields, respectively (entries 3 and 4).

Table 2.2. Investigation of the reactivity of alkyl ethers.



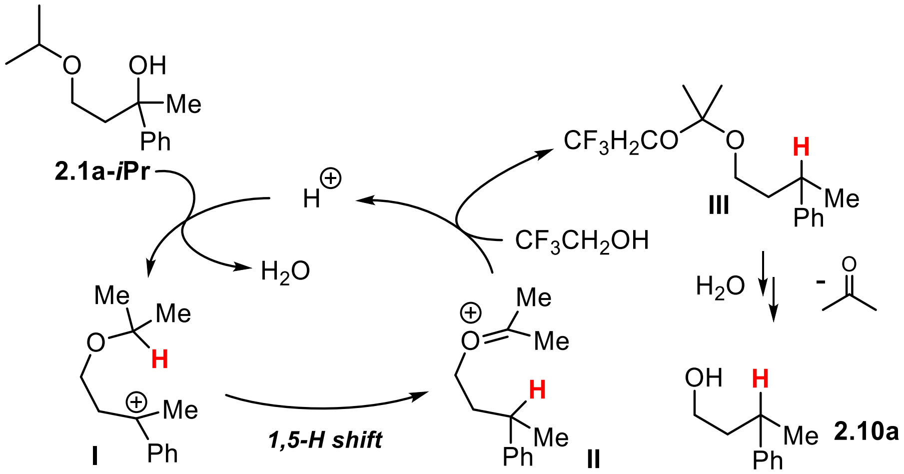
entry	substrates	R	Yield of **2.10a** [%][a][b]
1	**2.1a-Bn**	$PhCH_2$	85
2	**2.1a-PMB**	$4\text{-}MeOC_6H_4CH_2$	0[c]
3	**2.1a-*i*Pr**	*i*Pr	78
4	**2.1a-Et**	Et	51

[a]The reactions were conducted on a 0.3 mmol scale in 3 mL of TFE. [b] Isolated yield of **2.10a**. [c] A complex mixture of unidentified compounds was formed.

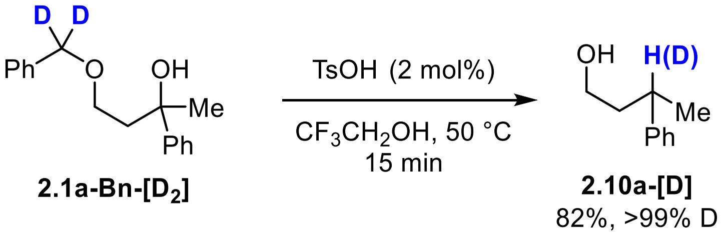
2.3.3 Proposed Reaction Mechanism

The mechanistic proposal for the formation of **2.10a** from **2.1a-iPr** is shown in Scheme 2.19A. The reaction of **2.1a-*i*Pr** with TsOH promotes its dehydration to afford the carbocation intermediate **I**. Subsequent 1,5-hydride transfer then leads to the formation of the oxocarbenium ion **II**, which is then trapped by 2,2,2-trifluoroethanol to deliver ketal **C**. The final step is accompanied by the regeneration of a proton to maintain the catalytic turnover. Ketal **III** is finally hydrolyzed under aqueous work-up to afford **2.10a** with concomitant elimination of acetone. A proof of the 1,5-hydride shift was ascertained by the reaction of deuterated substrate **2.1a-Bn-[D2]** resulted in deuterium incorporation of **2.10a-[D]**, thus unambiguously proving the 1,5-hydride shift process (Scheme 2.19B).

A. Proposed Reaction Mechanism



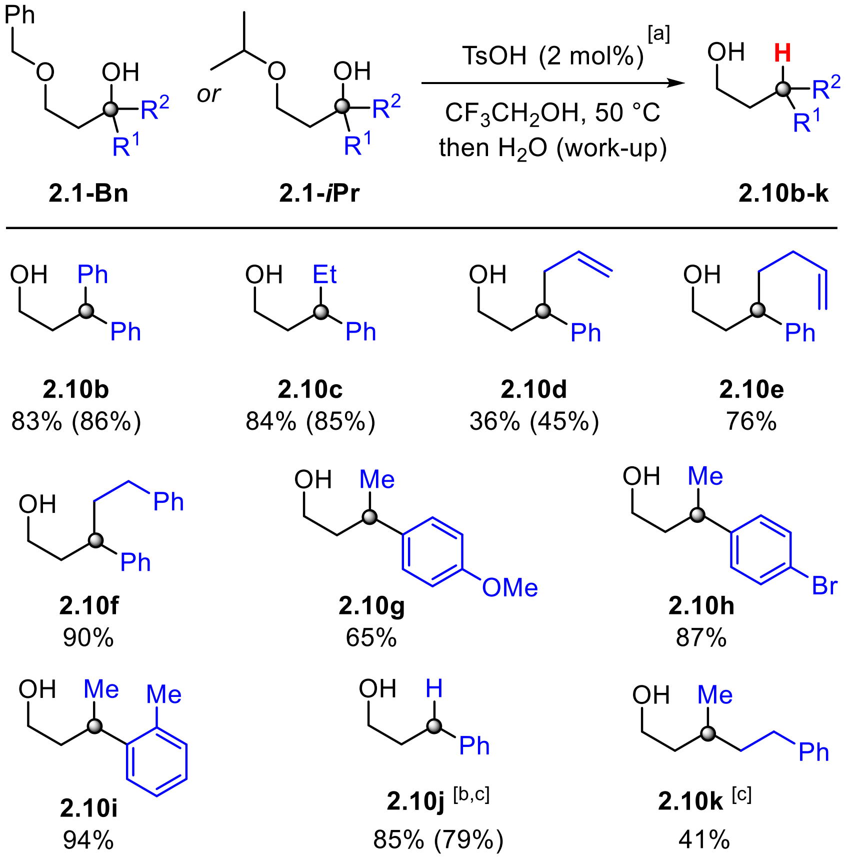
B. Deuterium labelling study



Scheme 2.19. Proposed reaction mechanism and deuterium labelling study

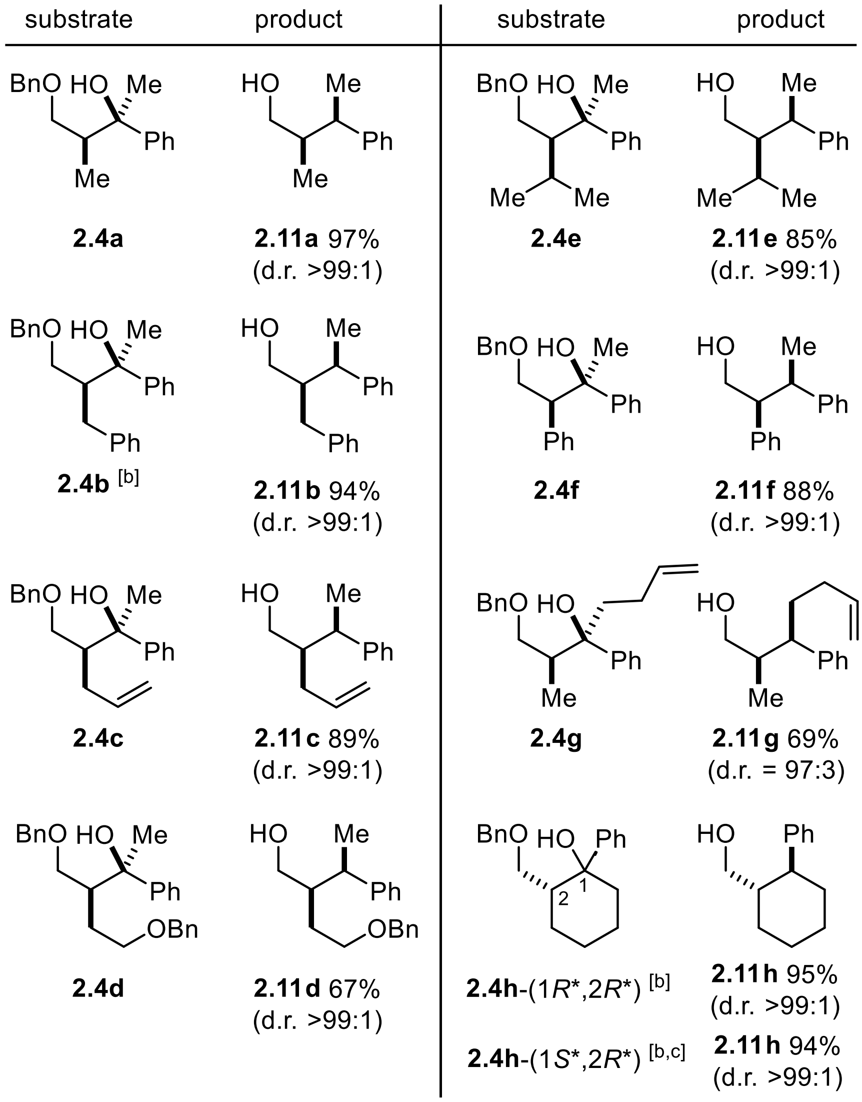
2.3.4 Scope and limitation

Having optimized the reaction conditions, the author next investigated the scope and limitations of this deoxygenative reaction using a variety of β-benzyloxy alcohols **2.1-Bn** or β-isopropoxy alcohols **2.1-*i*Pr** (Scheme 2.20). The method could be applied to the formation of mono or bis-benzylic tertiary carbon centers as exemplified by the formation of benzhydryl derivative **2.10b** and benzyl derivatives **2.10c-2.10f**. In these cases, the yields were generally high (>80%) except for the formation of allyl derivative **2.10d**. No significant difference in reactivity was observed among isopropyl and benzyl ethers as hydride donors (see formation of **2.10b-d**). The process tolerated substitution of different electronic nature on the aromatic ring (see **2.10g-i**) and was not influenced by the presence of a sterically demanding *o*-tolyl group at the carbinol center (see **2.10i**). The deoxygenation of secondary benzyl alcohol **2.1j** could also be achieved but an increase of the reaction temperature to 80 °C was required in this case. It was found that the reduction of a non-benzylic carbon center was possible (see **2.10k**) albeit with lower efficiency (41%).



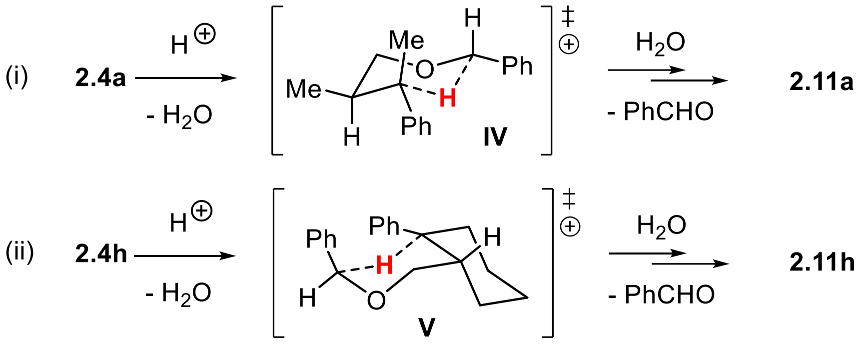
Scheme 2.20 Substrate scope: TsOH-catalyzed deoxygenation of alcohols **2.1-Bn** and **2.1-*i*Pr**. [a]Isolated yields are given. Yields in parentheses refer to the use of **2.1-Bn** as the substrates. Yields without parentheses refer to the use of **2.1-*i*Pr** as the substrates. [b]The reaction was conducted using 0.3 mmol of **2.1j**. [c]The reaction was conducted at 80 °C.

The substituent effect on the stereoselectivity of the transformation was next investigated (Scheme 2.21).[19] As discussed in the working hypothesis (section 2.2), the presence of a substituent at the position adjacent to the hydroxyl group would allow 1,2-diastereoinduction during the 1,5-hydride transfer step. As expected, the reaction of **2.4a** under the optimized reaction conditions proceeded smoothly to afford **2.11a** as a single diastereomer (Me groups in a relative *syn* configuration) in an excellent yield. High efficiencies and perfect 1,2-*syn* diastereoselectivity were also attained when structurally related substrates bearing a benzyl (for **2.11b**), an allyl (for **2.11c**), a benzyloxyethyl (for **2.11d**), an isopropyl (for **2.11e**) and a phenyl group (for **2.11f**) at the position adjacent to the hydroxyl group were employed. Interestingly, the reaction of **2.4d** having two benzyloxy groups as potential hydride donors proceeded selectively via a 1,5-shift (not via a 1,6-shift). The installation of a butenyl group at the carbinol position (**2.4g**) resulted in a slightly lower yield of **2.11g** (67%) but the diastereoselectivity remained high (97:3). Cyclohexanol derivative **2.4h** was also shown to be a suitable substrate for this transformation. It is worth noting that different diastereomers **2.4h**-(1*R**,2*R**) and **2.4h**-(1*S**,2*R**) furnished the identical single diastereomer of **2.11h** in excellent yields. These results attest of the stereoconvergence of the process, which is not affected by the stereochemistry at the carbinol centre.



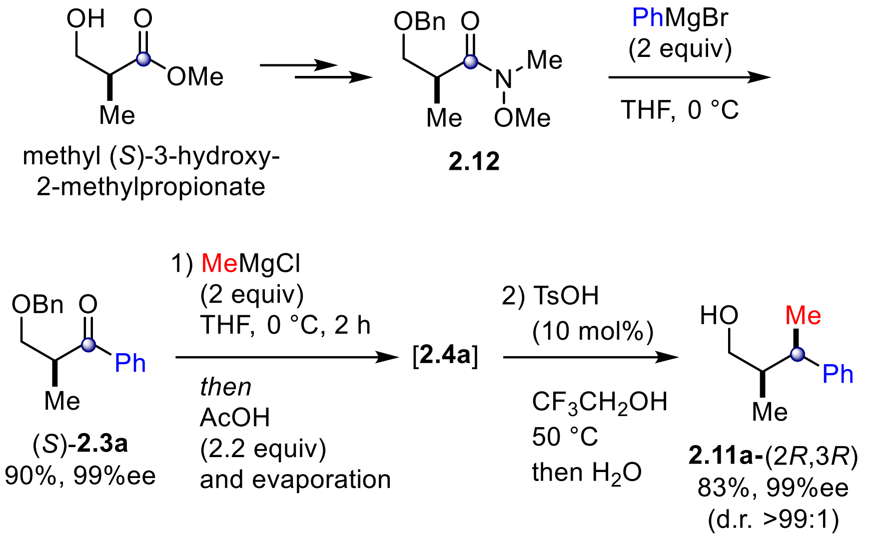
Scheme 2.21 1,2-Diasteroinduction in the deoxygenation of alcohols. [a]The reactions were conducted using 0.5 mmol of alcohol **2.4** as a single diastereomer and 2 mol% of TsOH in CF_3CH_2OH (0.1M) at 50 °C. Yields of the isolated products and diastereomeric ratios of **2.11** are given. [b]The reaction was conducted using 5 mol% of TsOH at 80 °C. [c]0.39 mmol of **2.4h**-(1*S**,2*R**) was used

The present 1,2-*syn* diastereoinduction could be rationalized by invoking a 6-membered ring chair-like transition state in the key 1,5-hydride transfer step. In this model, represented for substrate **2.4a** in Scheme 2.22, the more sterically demanding phenyl group[20] on the carbocation and the methyl group at the adjacent position would both adopt a pseudo-equatorial position (TS **IV**). For the formation of cyclohexane derivative **2.11h**, the selectivity could be explained by a transfer of the hydride onto a pseudo-axial position of the cyclohexyl moiety *via* a *cis* decalin type transition state **V**, in which the benzyloxymethyl tether would be lying in the pseudo-equatorial position.



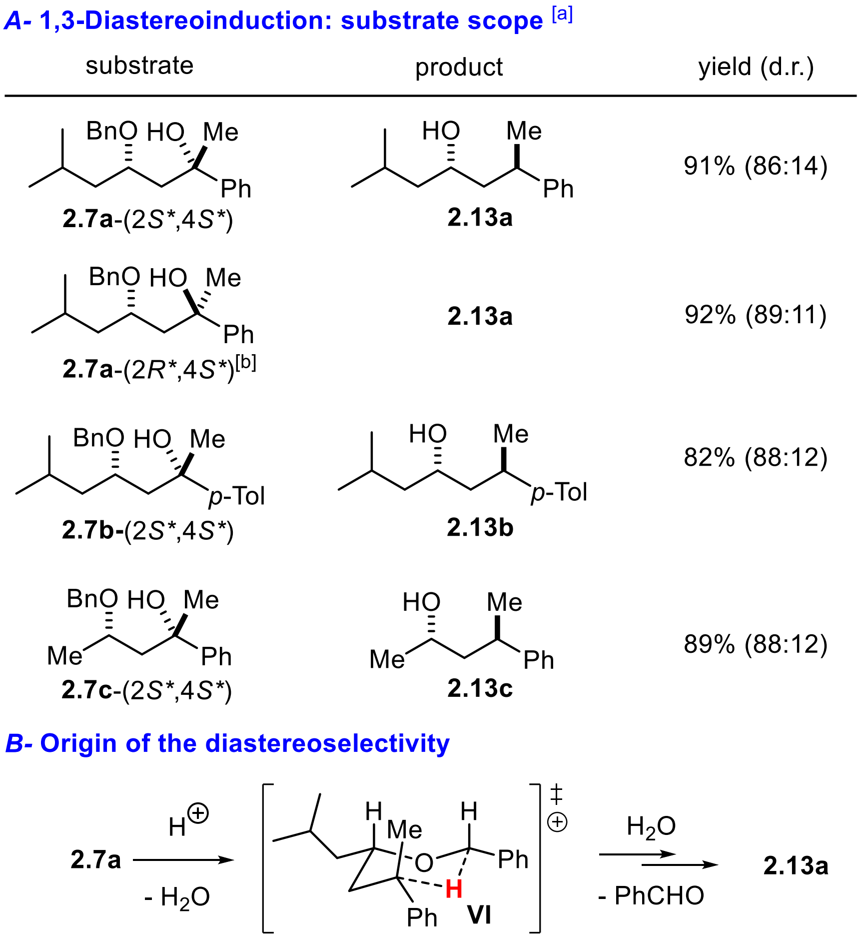
Scheme 2.22 Origin of the 1,2-diasteroselectivity in the deoxygenation of alcohols

The author also demonstrated construction of a new chiral centre by taking advantage of the diastereoselective nature of the present 1,5-hydride transfer (Scheme 2.23). The literature-known optically active Weinreb amide **2.12** (prepared from commercially available methyl (*S*)-3-hydroxy-2-methylpropionate)[21] was first treated with PhMgBr to afford the enantio-enriched β-benzyloxy phenyl ketone **2.3a**-(*S*) (99% ee). Its subsequent treatment with MeMgCl followed by an acidic work-up with a slight excess amount of AcOH delivered the crude methyl phenyl carbinol **2.4a**. The reaction of **2.4a** in the presence of TsOH (10 mol%) in trifluoroethanol at 50 °C furnished **2.11a**-(2*R*,3*R*) in 83% yield as a single diastereomer with a high degree of enantiopurity (99% ee). Overall, this one-pot conversion of **2.3a**-(*S*) into **2.11a**-(2*R*,3*R*) can be regarded as a stereoselective deoxygenative methylation of the ketone moiety.



Scheme 2.23 Synthesis of enantio-enriched **2.11a**-(2*R*,3*R*).

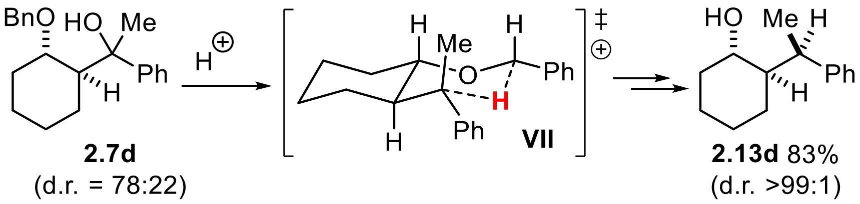
The author next examined the effect of a substituent located at the γ-position to the hydroxyl group (Scheme 2.24). The reaction of **2.7a**-(2*S**,4*S**) under the optimized reaction conditions afforded alcohol **2.13a** in 91% yield with a good 1,3-*anti* diastereoselectivity (86:14). It should be noted that the reaction of another diastereomer **2.7a**-(2*R**,4*S**) afforded identical outcomes in terms of yield and the diastereoselectivity. Installation of a *p*-tolyl group at the carbinol position in **2.7b** allowed for the synthesis of dihydro-*ar*turmerol **2.13b**, which was reported to exhibit acetylcholinesterase (AChE) inhibitory activity.[22] Replacement of the isobutyl substituent with a smaller methyl group did not affect the diastereoselectivity (for **2.7c**). The origin of the 1,3-*anti* diastereoinduction could be explained by the involvement of a 6-membered ring chair-like transition state such as **VI**, in which the most sterically demanding group occupies a pseudo-equatorial position (exemplified with **2.7a** in Scheme 2.24B).


A- 1,3-Diastereoinduction: substrate scope [a]

B- Origin of the diastereoselectivity

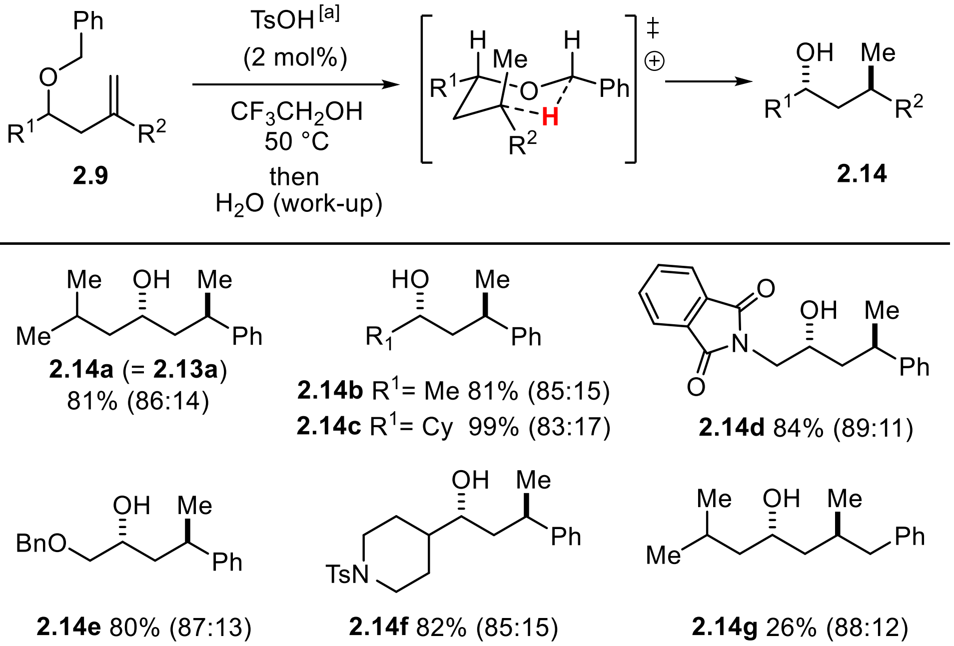
Scheme 2.24 Substrate Scope: 1,3-Diastereoinduction

Interestingly, the reaction of **2.7d**, which possesses two adjacent stereocenters in an *anti*-relationship on the cyclohexane fragment, afforded the deoxygenated compound **2.13d** in high yield (83%) as a single diastereomer (Scheme 2.25). This transformation might proceed *via* the rigid chair-like 6-membered ring transition state **VII** shown in Scheme 2.25.



Scheme 2.25 1,2,3-Diastereoinduction

The use of alkenes as alternative source of carbocations under the Brønsted acid catalysis was also examined. The optimized reaction conditions for the deoxygenation of alcohols were applicable to the hydrogenation of alkenes (Scheme 2.26). For instance, the reaction of homoallylic alcohol *O*-benzyl ether **2.9a** proceeded smoothly to produce **2.14a** (= **2.13a**) in 81% yield with a good 1,3-*anti* diastereoselectivity (d.r. = 86:14). This result is very similar to that obtained for the deoxygenation of **2.7a** (Scheme 2.24), indicating that both reactions proceed *via* the formation of a common carbocation intermediate. The investigation of the substrate scope revealed that various primary and secondary alkyl groups could be installed as R^1 to generate products (**2.14b-f**) in good yields and diastereoselectivity. Notably, nitrogen-containing substituents such as a phthalimide (**2.14d**) or a piperidine (**2.14f**) were tolerated. The transformation also exhibited selective 1,5-hydride shift over 1,6-shift in the case of **2.14e** having two benzyloxy groups. The reduction process could also be applied to benzyl substituted alkene **2.14g**, where the diastereoselectivity was similarly high despite a noticeable drop in the yield.

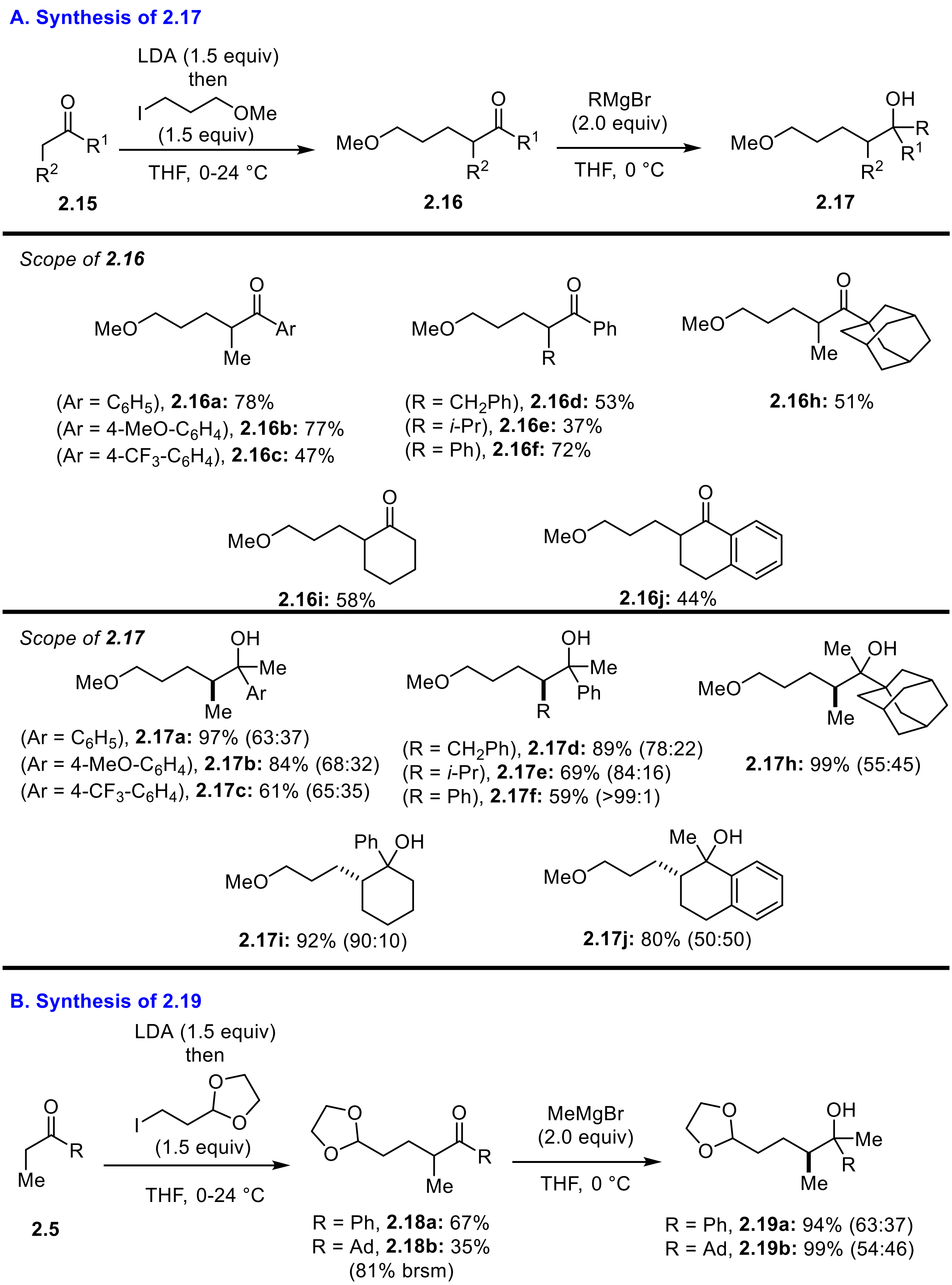


Scheme 2.26 Hydrogenation of alkenes **2.9.** [a]The reactions were conducted using 0.3-0.5 mmol of alkenes **2.9** and 2 mol% of TsOH in CF_3CH_2OH (0.1M) at 50 °C. Isolated yields and diastereomeric ratio (d.r.) of the products are given.

2.4 Result and Discussion - Distal Alkyl Ethers as Hydride Donors

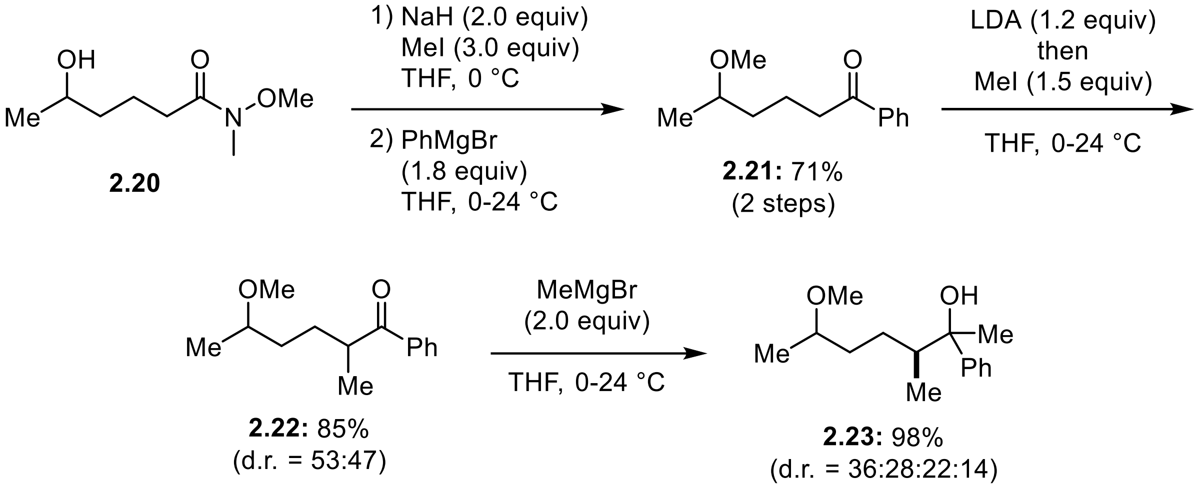
2.4.1 Substrate Synthesis

Synthesis of methyl ethers **2.17** were initiated by alkylation of lithium enolates of ketones **2.15**, with 1-iodo-3-methoxypropane, affording ketones **2.16**. Subsequently, treatment of the resulting ketones **2.16** with the Grignard reagents afforded tertiary alcohols **2.17** (Scheme 2.27A). The same protocol could be adopted for synthesis of tertiary alcohols **2.19** having a 1,3-dioxolane moiety (Scheme 2.27B).



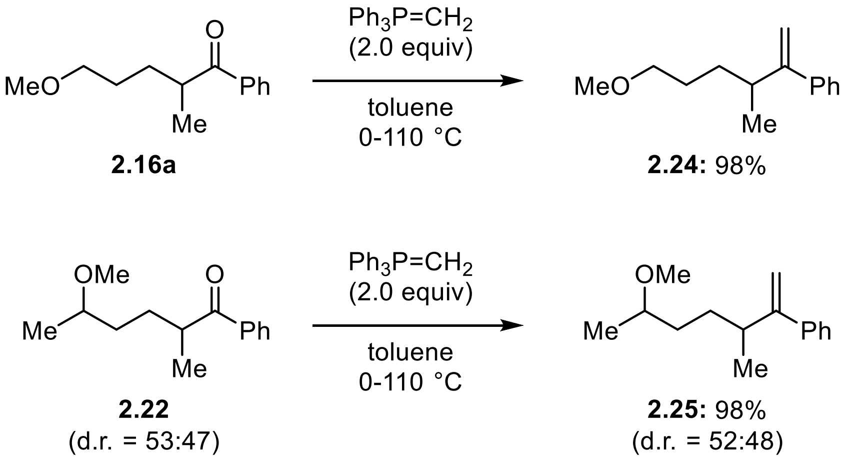
Scheme 2.27. Synthesis of substrates **2.17** and **2.19.** Diastereomeric ratio are given in parentheses.

Alcohol **2.23** was synthesized from the known Weinreb amide **2.20**[23] (Scheme 2.27). Methylation of the free hydroxy group of **2.20** followed by addition of phenylmagnesium bromide provided phenyl ketone **2.21** in 71% yield. Subsequent α-methylation of **2.21** and addition of methylmagnesium bromide furnished alcohol **2.23** as a mixture of diastereomers.



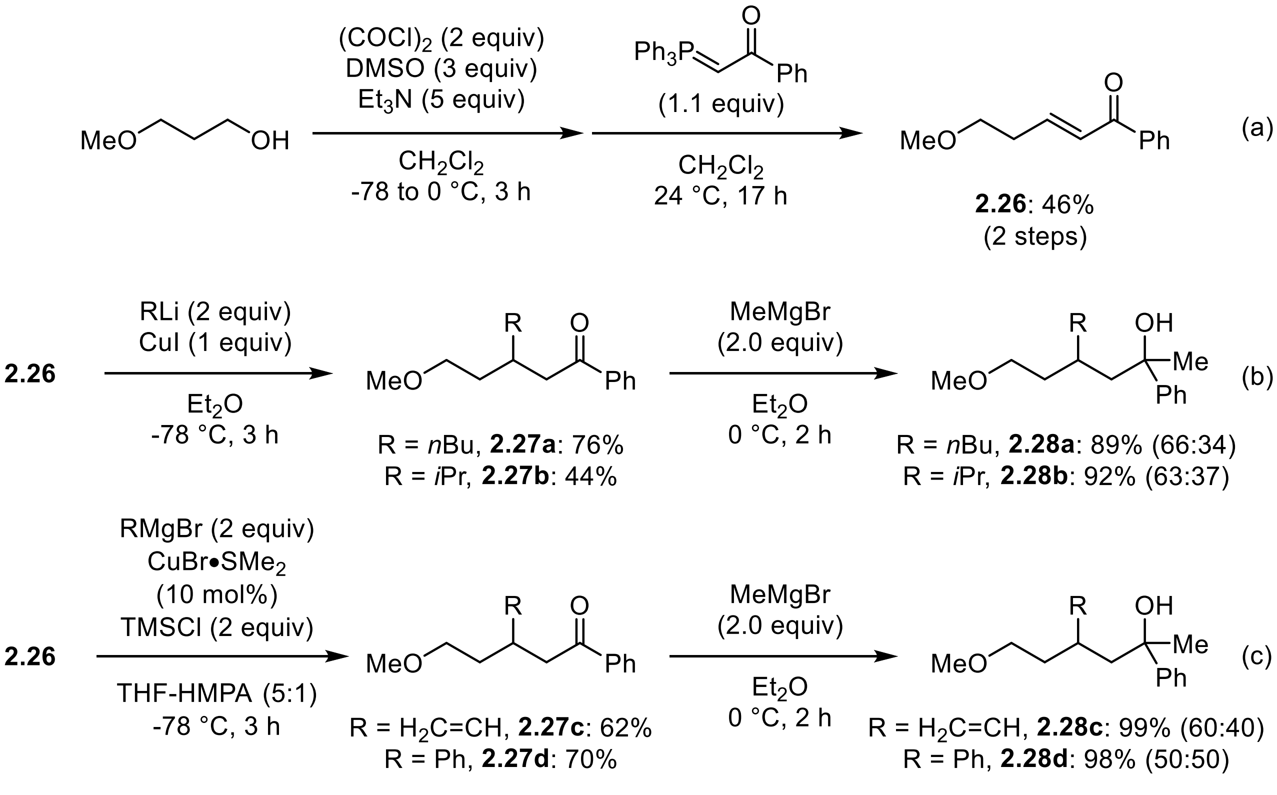
Scheme 2.28. Synthesis of substrate **2.23**

Synthesis of alkenyl ethers **2.24** and **2.25** was performed through by the Wittig reaction of ketones **2.16a** and **2.22** (Scheme 2.29).



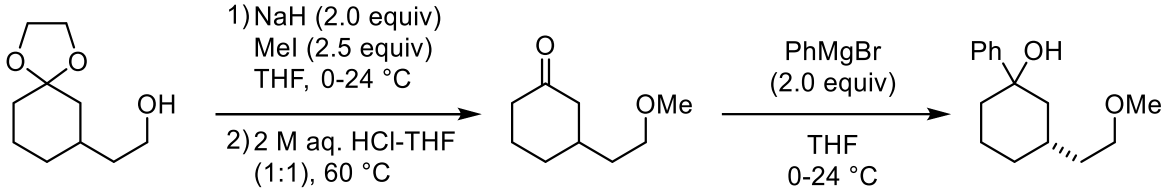
Scheme 2.29. Synthesis of substrates **2.24** and **2.25**

The synthetic scheme of alcohol substrates **2.28** was shown in Scheme 2.30. It was commenced with preparation of *α,β*-unsaturated ketone **2.26** via Swern oxidation of 3-methoxy-1-propanol followed by the Wittig reaction alkenylation (Scheme 2.30a). The resulting *α,β*-unsaturated ketone **2.26** was treated with alkyl cuprates derived from the corresponding butyl and isopropyllithium and CuI, providing saturated ketones **2.27a** and **2.27b**, which were converted into tertiary alcohols **2.22a** and **2.22b** by addition of methylmagnesium bromide (Scheme 2.30b). To install vinyl and phenyl moieties for synthesis of **2.28c** and **2.28d**, the corresponding Grignard reagents were used in the presence of a catalytic amount of CuBr•SMe$_2$ and TMSCl in THF-HMPA solvent system (Scheme 2.30c).[24]



Scheme 2.30. Synthesis of substrates **2.28a-2.28d.** Diastereomeric ratio are given in the parentheses.

Cyclohexanol **2.28e** having a methoxyethyl tether at C3 from the hydroxyl group was synthesized from known alcohol **2.29**[25] through methylation, removal of the acetal moiety, and addition of phenylmagnesium bromide (Scheme 2.31).



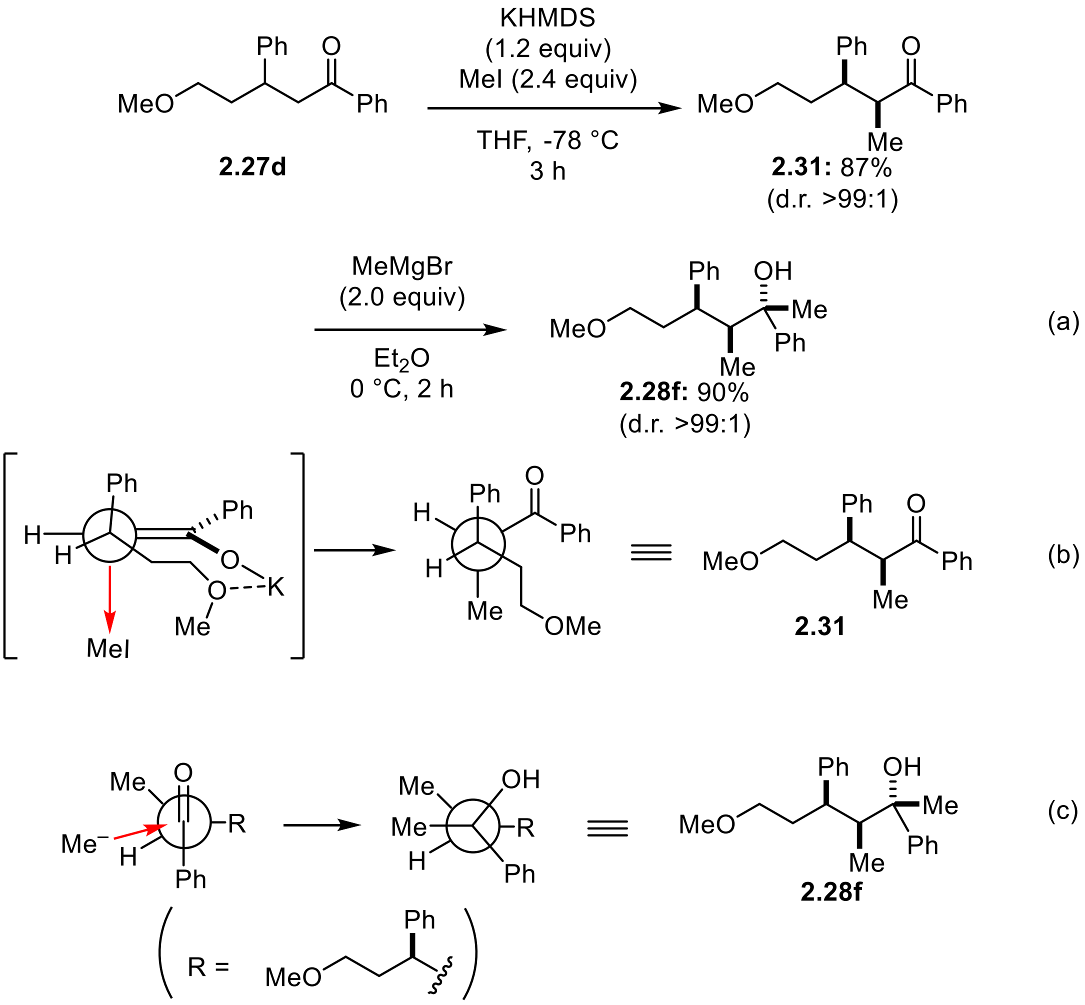
2.29

2.30: 87%
(2 steps)

2.28e: 86%
(d.r. = 71:29)

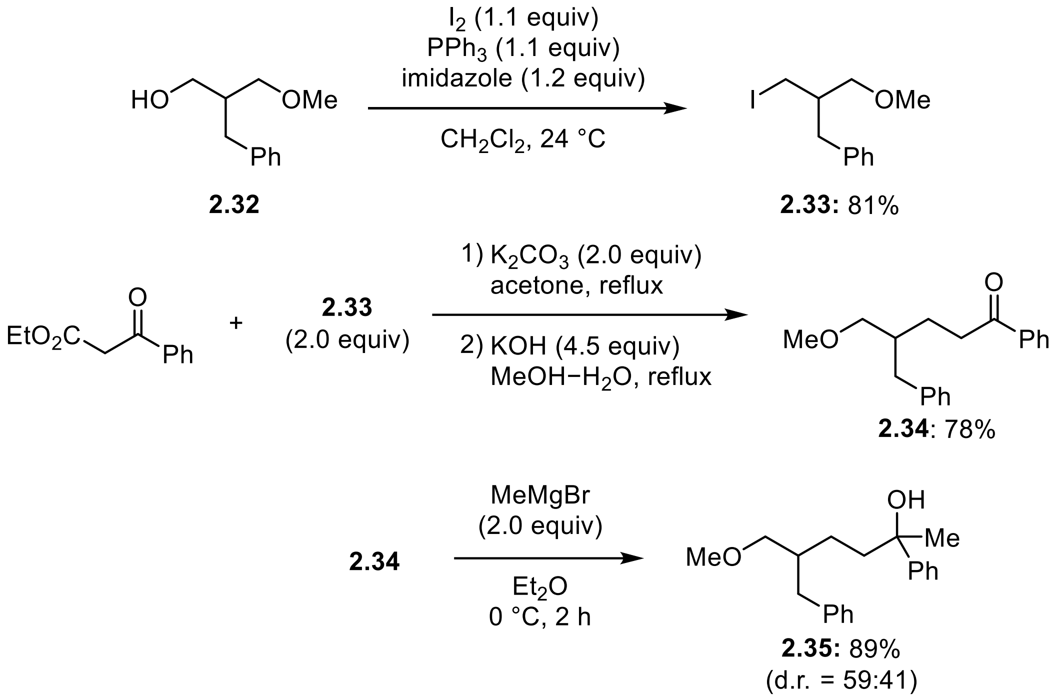
Scheme 2.31. Synthesis of substrate **2.28e**

Multi-substituted alcohol **2.28f** was obtained from ketone **2.27d** prepared in Scheme 2.32a. α-Methylation of ketone **2.27d** using KHMDS as a base afforded **2.31** as a single diastereomer. The observed diastereoselectivity could be explained by invoking a chelation model in which potassium enolate complexes the methoxy moiety, therefore rigidifying the structure (Scheme 2.32b). Finally, installation of a methyl group was conducted by addition of methylmagnesium bromide, providing alcohol **2.28f** again as a single diastereomer. The excellent diastereoselectivity here could be rationalized by a Felkin-Anh model as shown in Scheme 2.32c.



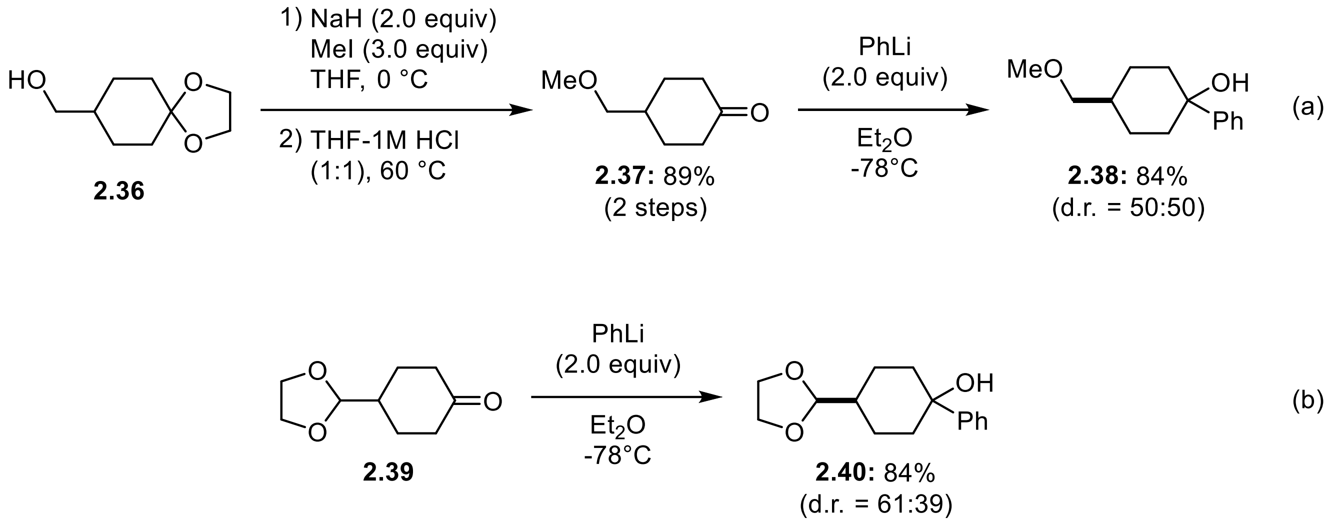
Scheme 2.32. Synthesis of substrate **2.28f**

The synthesis of tertiary alcohol **2.35** was conducted from ethyl benzoylacetate and iodide **2.33**, derived from known alcohol **2.32**[26] (Scheme 2.33). Namely, α-alkylation of ethyl benzoylacetate with **2.33** followed by basic hydrolysis-decarboxylation afforded ketone **2.34**, which was subsequently functionalized by the addition of methylmagnesium bromide to furnish alcohol **2.35**.



Scheme 2.33. Synthesis of substrate **2.35**

Cyclohexanol derivative **2.38** having a methoxymethyl moiety at C4 from the hydroxyl group was synthesized in 2 steps from known alcohol **2.36**[27] via methylation of the hydroxy group, removal of acetal, and addition of phenyllithium (Scheme 2.34a). Similarly, cyclohexanol **2.40** having a 1,3-dioxolane moiety was synthesized by addition of phenyllithium addition onto cyclohexanone **2.39**[28] (Scheme 2.34b).

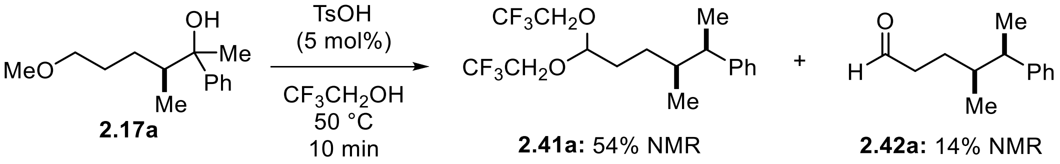


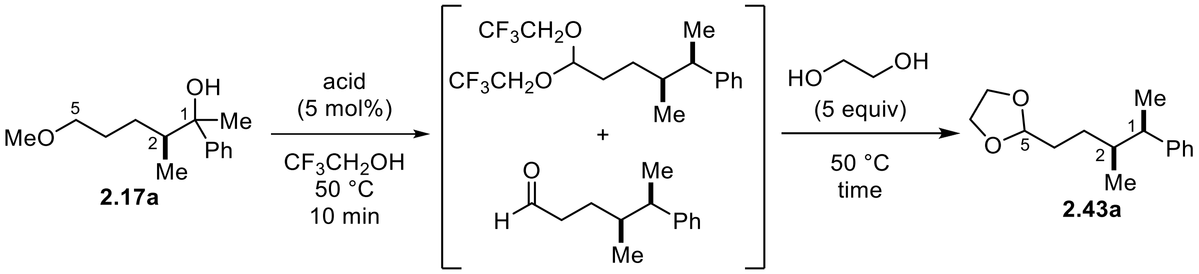
Scheme 2.34. Synthesis of substrates **2.38** and **2.40**

2.4.2 Optimization of the reaction conditions

Based on the working hypothesis shown in the section 2.2, the author examined the reactivity of methyl ether **2.17a** having a C1-tertiary alcohol and a methyl group at C2 position. It was observed that treatment of **2.17a** with 5 mol% of TsOH in trifluoroethanol at 50 °C results in rapid consumption within 10 min to form bis(trifluoroethyl) acetal **2.41a** and aldehyde **2.42a** in 54% and 14% yield, respectively. Because of the instability of **2.41a** and **2.42a**, the reaction mixture was subsequently treated with the addition of 5 equivalents of ethylene glycol to convert them into more stable 1,3-dioxolane **2.43a**, which was isolated in 80% yield after stirring at 50 °C for additional 18 h. Interestingly, high 1,2-*syn* diastereoselectivity (>98:2) was observed. It was found that the use of stronger Bronsted acid, bistriflimide (Tf_2NH)[29] instead of TsOH, could accelerate the acetal formation step to 8 h with similar yield of the desired product **2.43a**.

Table 2.3. Optimization of the reaction conditions[a]



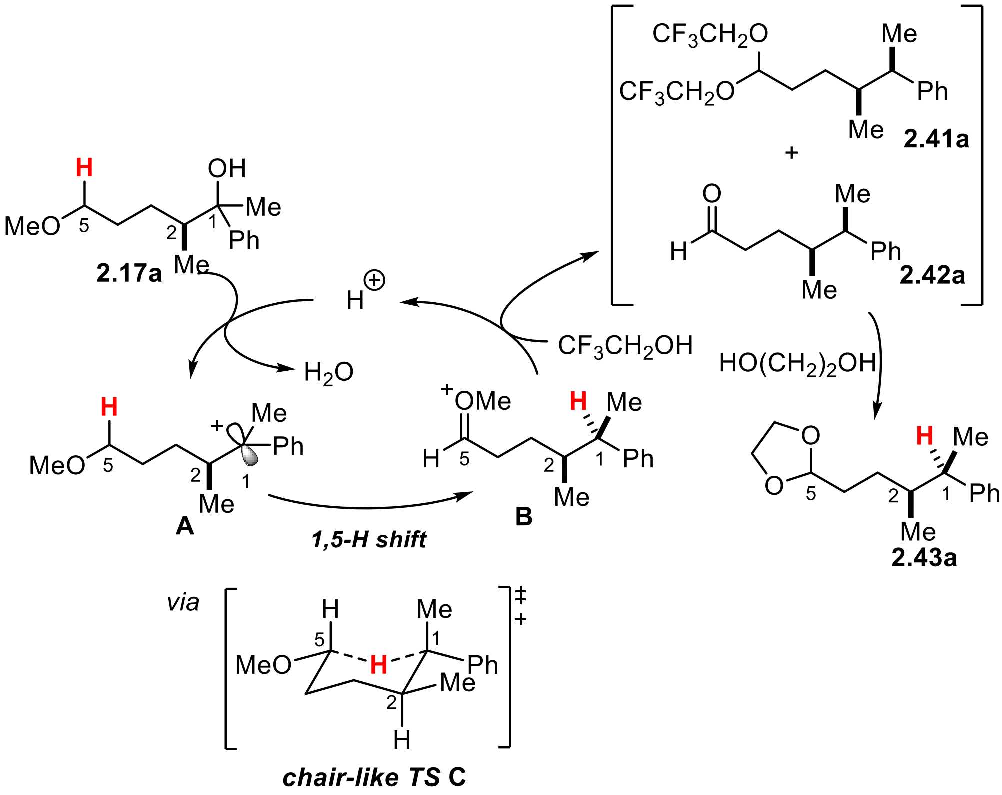


entry	acid	time	Yield of **2.43a** [%][b]	d.r.[c]
1	TsOH	18 h	80	>98:2
2	Tf_2NH	8 h	78	>98:2

[a]Reaction conditions: **2.17a** (0.5 mmol), acids (5 mol%), TFE (5 mL, 0.1 M), 50 °C 10 min, then ethylene glycol (5 equiv). [b]Isolated yields. [c]Diastereomeric ratio was determined based on ^{1}H NMR analysis.

2.4.3 Proposed Reaction Mechanism

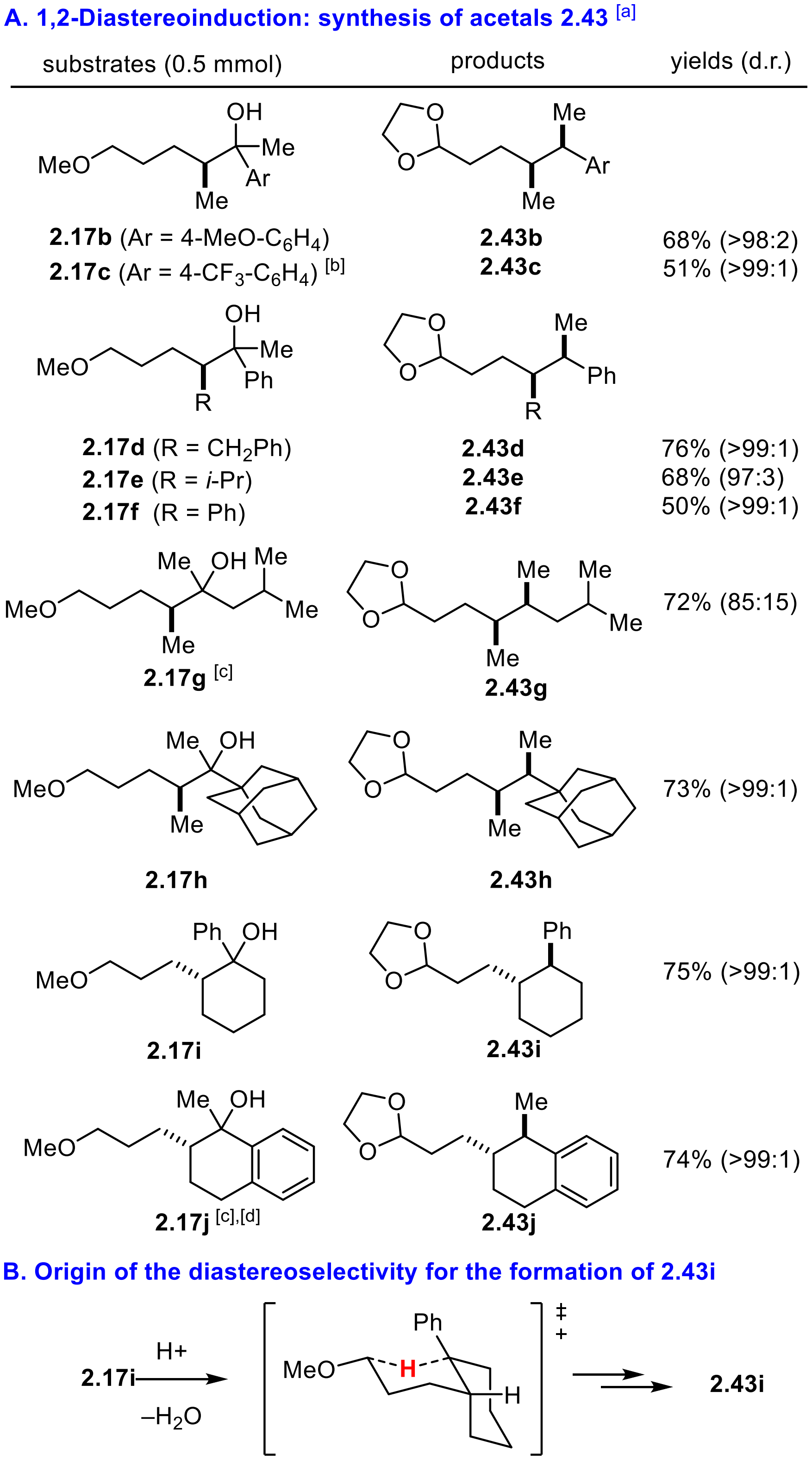
Similarly, with the reaction of benzyl ether **2.1** as described in section 2.3.3, this process is also initiated with the dehydration of tertiary alcohol **2.17a** through dehydration with the Bronsted acid to generate a transient carbocation **A** (Scheme 2.35). The following 1,5-hydride shift from distal alkyl ether generates oxocarbenium **B**, which is solvolyzed to give mixture of acetal **2.41a** and aldehyde **2.42a** together with proton regeneration. Further treatment with ethylene glycol affords the more stable dioxolane **2.43a**. The origin of the 1,2-*syn* diastereoselectivity could be rationalized by invoking a transient 6-membered ring transition state **C**, where larger substituents of Ph at C1 and Me at C2 would be placed in pseudo-equatorial positions.



Scheme 2.35. Proposed reaction mechanism

2.4.4 Substrate Scope

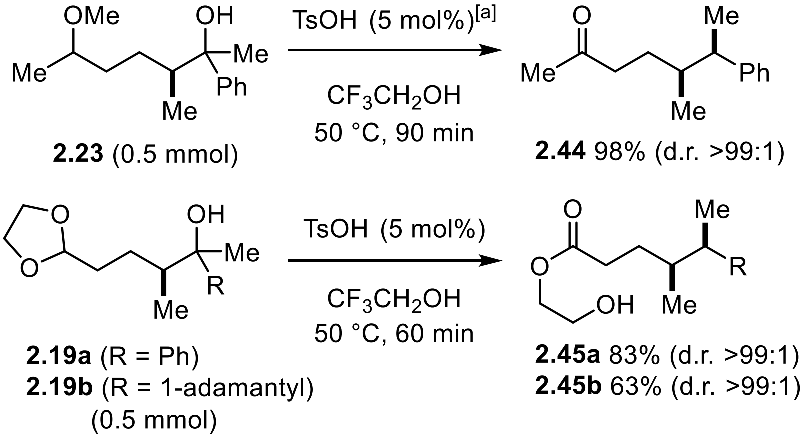
The substituent effect on the 1,2- diastereoinduction using various methyl ethers **2.17** (Scheme 2.36A) was then investigated. The process was not affected by the electronic nature of the aryl group at position C1: both electron-rich and -deficient arenes could be installed with high 1,2-*syn* diastereoselectivity (for **2.43b** and **2.43c**). As for the nature of C2 substituent, the sterically more demanding benzyl, isopropyl, and phenyl groups were tolerated (for **2.43d−f**) and no noticeable erosion of the diastereoselectivity was observed. It is noteworthy that the current protocol allows for the use of non-benzylic alcohols that are relatively less prone to electrophilic activation. Thus, alcohols **2.17g** and **2.17h** having isobutyl and 1-adamantyl groups, respectively, provided the corresponding 1,3-dioxolanes **2.43g** and **2.43h** in good yields despite the moderate diastereoselectivity observed in **2.43g** (d.r. = 85:15). The reactions of cyclic alcohols **2.17i** and **2.17j** proceeded smoothly to yield **2.43i** and **2.43j**, respectively. In both cases, a high 1,2-*trans* diastereoselectivity (>99:1) was obtained probably due to the involvement of a *cis*-decalin-like transition state (Scheme 2.36B).



Scheme 2.36 1,2-Diasteroinduction in the synthesis of acetals. [a]Reaction conditions: **2.17** (0.5 mmol), Tf_2NH (5 mol%), CF_3CH_2OH (5 mL, 0.1 M), 50 °C, 10 min, then ethylene glycol

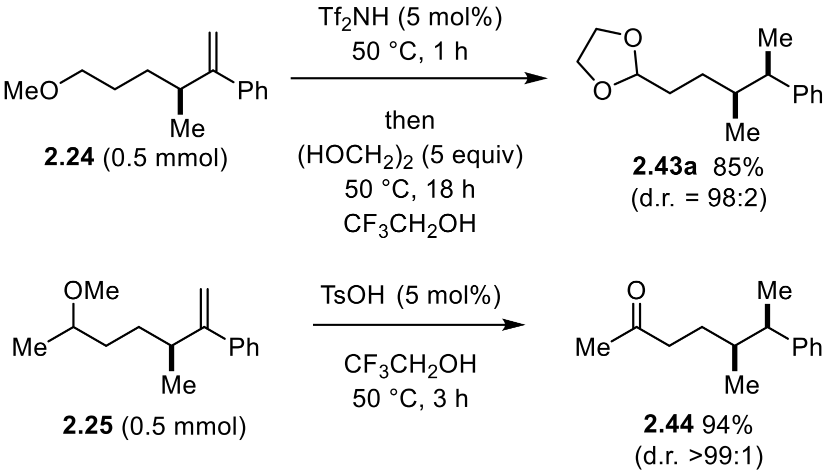
(5 equiv). Isolated yields and diastereomeric ratio of **2.43** are given. [b]80 °C. [c]24 °C. [d]With Tf_2NH (10 mol%).

The author also found that the method was applicable to the use of secondary alkyl ether **2.23** and 1,3- dioxolanes **2.19** as hydride donors for the efficient and highly diastereoselective construction of ketone **2.44** and glycol esters **2.45**, respectively (Scheme 2.37).



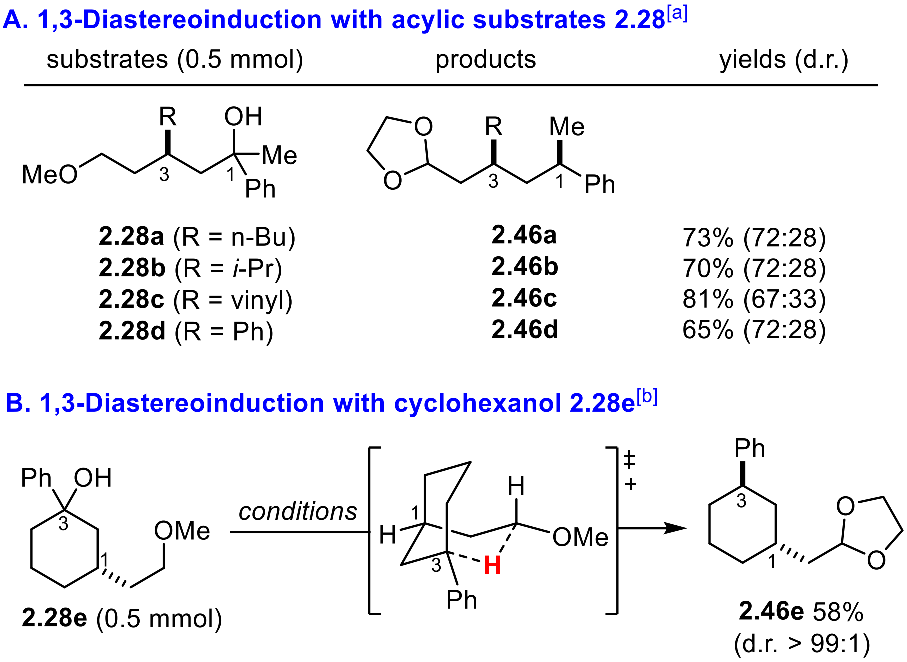
Scheme 2.37. Other application to the synthesis of ketone and esters. [a]Reaction conditions: **2.23** or **2.19** (0.5 mmol), TsOH (5 mol%), CF_3CH_2OH (5 mL, 0.1 M), 50 °C. Isolated yields and diastereomeric ratio of **2.44** and **2.45** are given.

Alkenes **2.24** and **2.25** were also proven to be viable sources of carbocations for the 1,5-hydride transfer process since the corresponding acetal **2.43a** and ketone **2.44** could be obtained in good yields and with high diastereoselectivity (Scheme 2.38).



Scheme 2.38 Diastereoselective 1,5-hydride transfer with alkenes

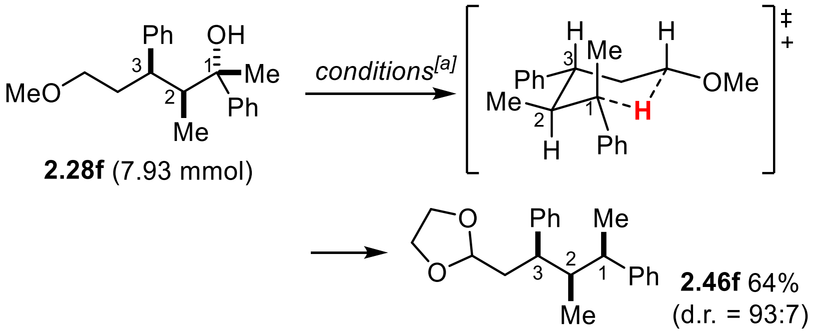
The presence of a substituent at position C3 could induce a 1,3-*syn* diastereoselectivity during the 1,5- hydride transfer process (Scheme 2.39A). While the reactions of acyclic alcohols **2.28a−d** were efficient (65−81%) and various groups (alkyl, aryl, or vinyl) could be tolerated, the observed diastereomeric ratios for the formation of products **2.46a−d** (67:33−72:28) were not as high as those obtained in the case of 1,2-stereoinduction (97:3−99:1). On the other hand, cyclohexanol derivative **2.28e** could be transformed into the diastereomerically pure 1,3-*trans* cyclohexane **2.46e** presumably through a rigid bicyclic chair/chair-like transition state (Scheme 2.39B).



substrates (0.5 mmol)	products	yields (d.r.)
2.28a (R = n-Bu)	**2.46a**	73% (72:28)
2.28b (R = *i*-Pr)	**2.46b**	70% (72:28)
2.28c (R = vinyl)	**2.46c**	81% (67:33)
2.28d (R = Ph)	**2.46d**	65% (72:28)

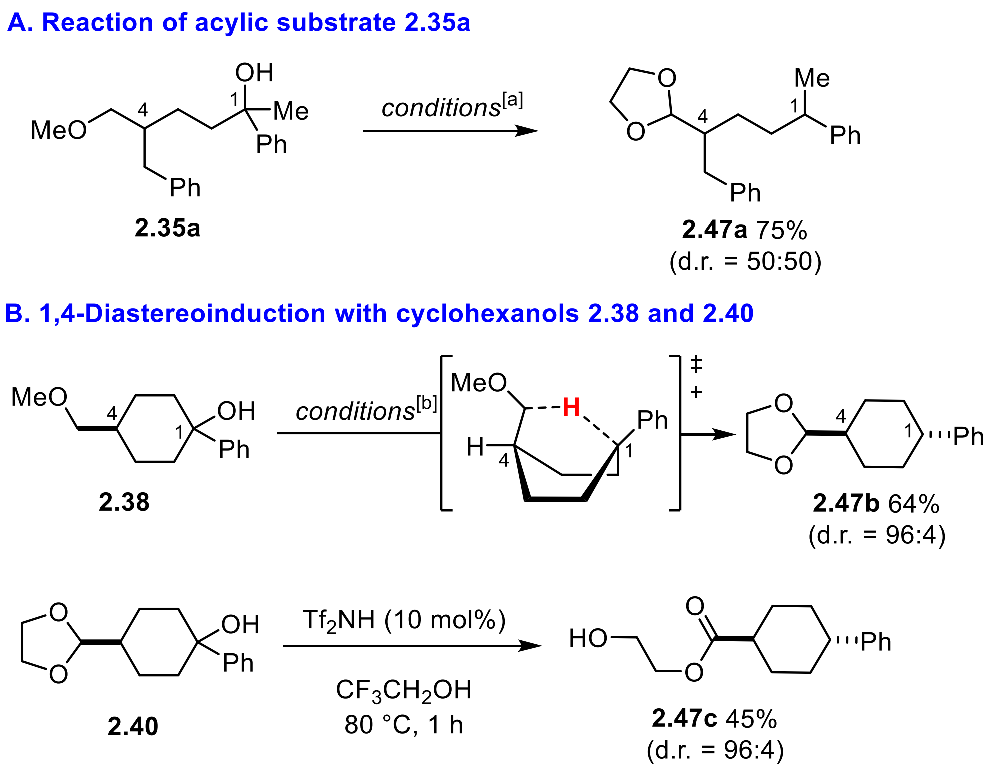
Scheme 2.39 1,3-Diastereoinduction of methyl ethers **2.22.** [a]Reaction conditions: **2.22** (0.5 mmol), Tf_2NH (5 mol%), CF_3CH_2OH (5 mL, 0.1 M), 50 °C, 10 min, then ethylene glycol (5 equiv). Isolated yields and diastereomeric ratio of **2.46** are given. [b]80 °C.

In addition, the author observed a higher diastereoselectivity of 93:7 in the conversion of alcohol **2.28f**, which possesses methyl and phenyl substituents at positions C2 and C3, respectively. The corresponding acetal **2.46f** was isolated in 64% yield (Scheme 2.40). Notably, this 1,2,3-diastereoselective induction could be attained in almost a 8 mmol scale, thus demonstrating the scalability of the present protocol.



Scheme 2.40. 1,2,3-Diastereoinduction with acylic substrate **2.28f**. [a]Reaction was conducted using 7.93 mmol (2.37 g) of **2.46f** with Tf_2NH (5 mol%) in CF_3CH_2OH (79 mL, 0.1 M) at 24 °C for 15 min, then ethylene glycol (5 equiv) at 50 °C.

At the final outset of our substrate compatibility study, the author examined the possibility to perform 1,4-diastereo induction with substrates possessing a substituent at position C4. The reaction with acyclic substrate **2.35a** proceeded smoothly to give acetal **2.47a** in 75% yield, but unfortunately with no diastereoinduction (Scheme 2.41A). In sharp contrast, the use of cyclohexanol derivative **2.38** having a methoxymethyl tether at position C4 resulted in the formation of cyclohexane **2.47b** with high 1,4-*trans* diastereoselectivity (95:5). Similarly, diastereoselective 1,5-hydride transfer took place in the conversion of 1,3-dioxolane **2.40** into ester **2.47c** (Scheme 2.41B). In these cases, the 1,5-hydride transfer step most likely proceeds via a boat-like transition state that would account for the observed 1,4-*trans* diastereoselectivity.



A. Reaction of acylic substrate 2.35a

B. 1,4-Diastereoinduction with cyclohexanols 2.38 and 2.40

Scheme 2.41. 1,4-Diastereoinduction. [a]Reaction conditions: **2.35a** (0.5 mmol), Tf_2NH (5 mol%), CF_3CH_2OH (5 mL, 0.1 M), 50 °C, 10 min, then ethylene glycol (5 equiv). Isolated yields and diastereomeric ratio of **2.47** are given. [b]80 °C, 1 h.

2.5 Conclusion

In this chapter, the author described the investigation on the use of alkyl ethers as a hydride donor for the deoxygenation of alcohols and the hydrogenation of alkenes under Brønsted acid catalysis. The reductive process described herein, which is based on an intramolecular 1,5-hydride shift onto a transient carbocation, exhibits high degree of efficiency and stereoselectivity. This redox neutral process allows for enhancement of the molecular complexity from rather simple and readily available starting materials.

2.6 References

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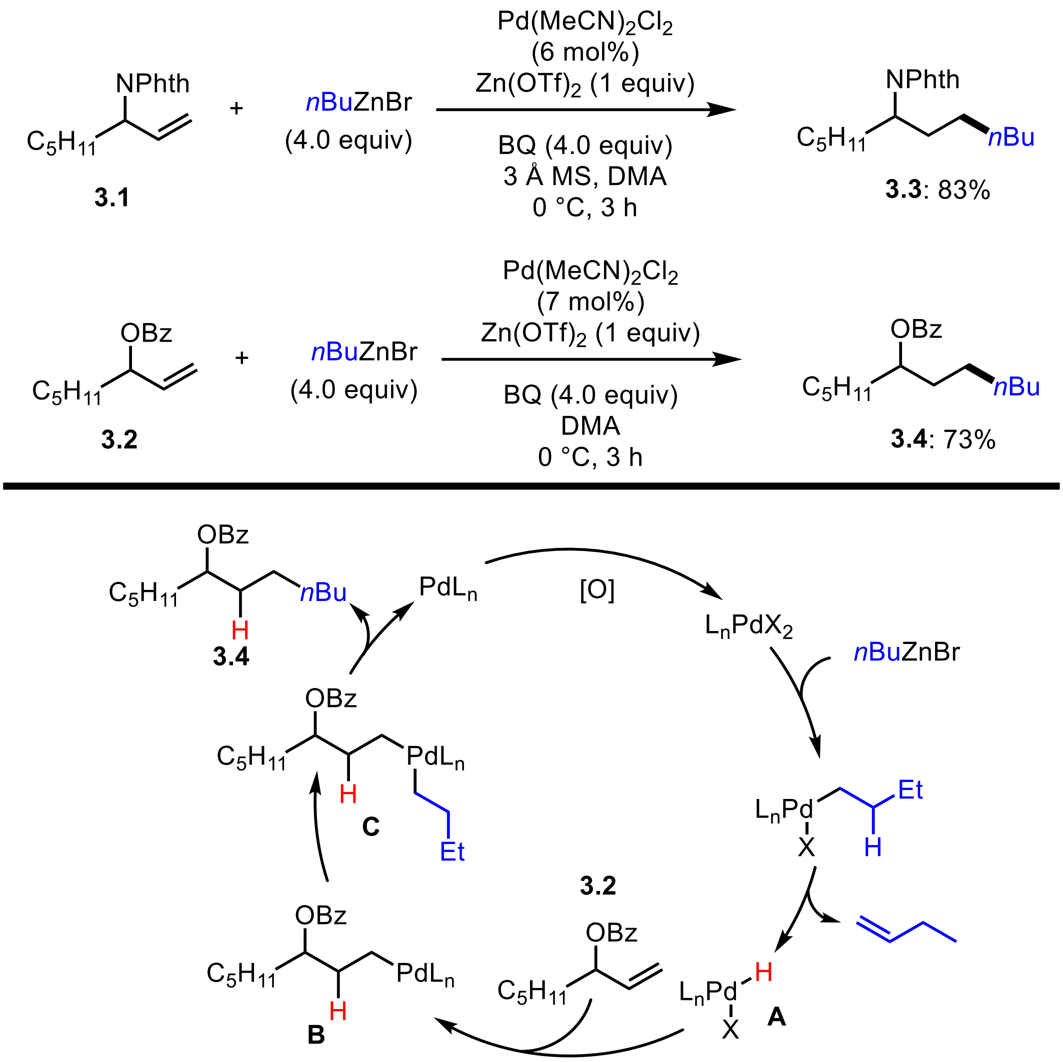
Chapter 3. Diastereoselective Hydroalkylation of Aryl Alkenes Enabled by Intramolecular Hydride Transfer

3.1 Introduction

Hydrofunctionalization of alkenes has received considerable interests among synthetic chemists.[1] In general, hydrofunctionalization of alkenes is categorized in three main mechanistic operations, namely transition metal catalysis, radical-mediated hydrofunctionalization and the process initiated by the electrophilic activation of alkenes. This introductory section will provide a brief review on recent development on the hydrofunctionalization of alkenes.

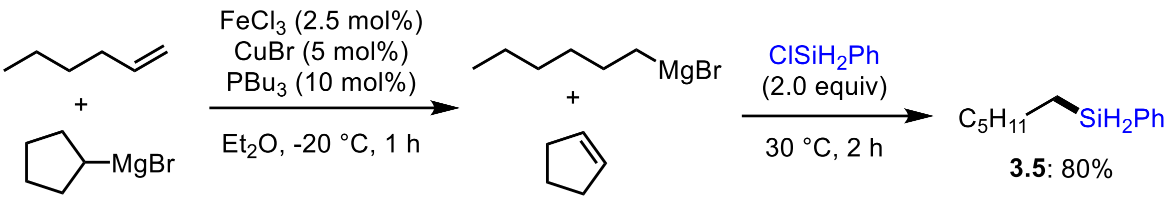
3.1.1 Transition Metal-Catalyzed Hydrofunctionalization

Sigman and coworkers developed a selective *anti*-Markovnikov palladium-catalyzed hydroalkylation of allylic amine **3.1** and alcohol derivatives **3.2** in the presence of alkylzinc reagents (Scheme 3.1).[2] This process is initiated by the generation of Pd(II)-hydride intermediate **A**, which undergoes migratory insertion to the olefin **3.2**. Another equivalent of an alkylzinc halide is used to perform transmetallation (**B** to **C**) followed by reductive elimination to furnish the hydroalkylated product.



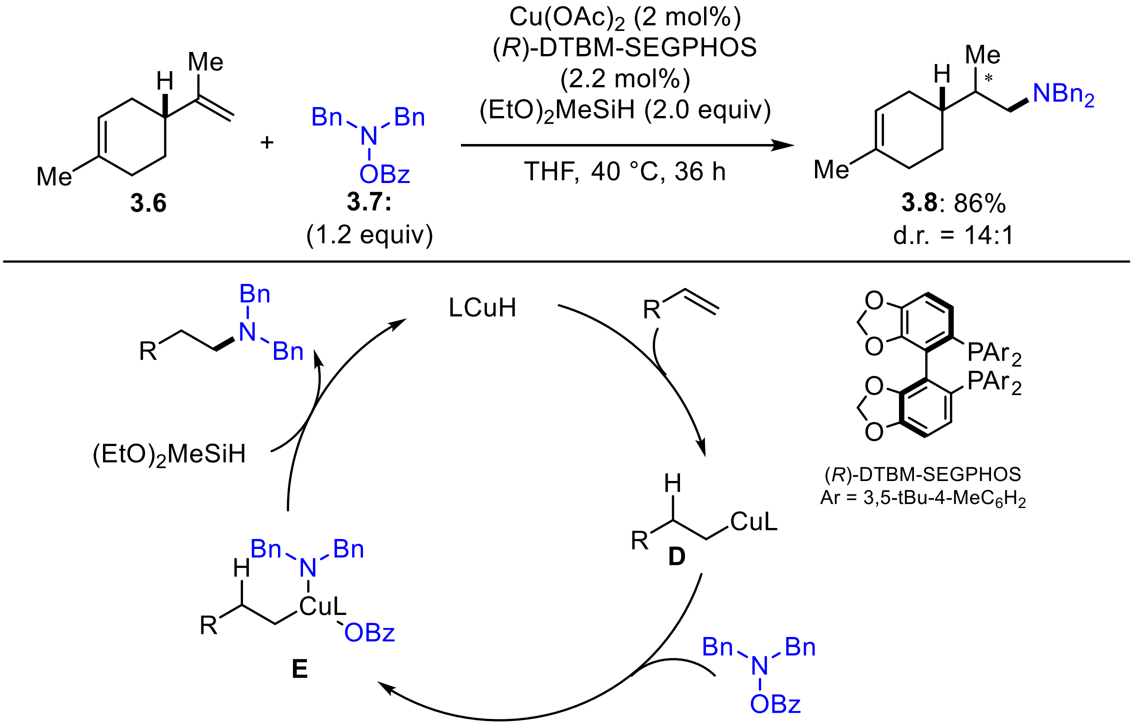
Scheme 3.1. Pd-catalyzed hydroalkylation of allyl amine and alcohol

The application of Fe-Cu cooperative catalysis for hydrosilylation of alkenes was reported by Hayashi and co-workers.[3] The process is comprised of the step-wise sequence involving 1) hydromagnesiation of alkenes with cyclopentylmagnesium bromide in the presence of $FeCl_3$ and CuBr catalysts with a PBu_3 ligand to form alkylmagnesium bromide; 2) trap of the carbanion with silylchloride (Scheme 3.2).



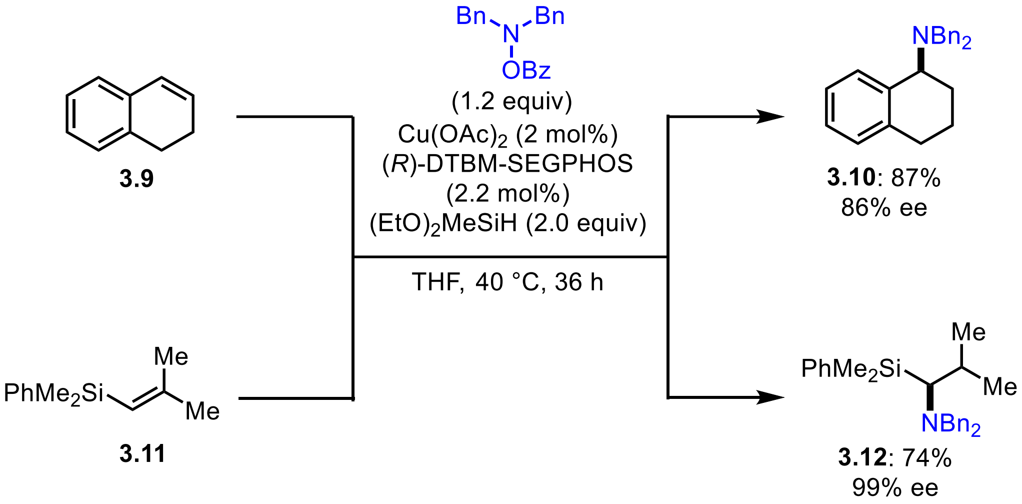
Scheme 3.2. Iron-copper catalysis for hydrofunctionalization of terminal olefin

Buchwald[4] has developed a series of hydroamination of alkenes by taking advantage of copper-hydride catalysis (Scheme 3.3). The catalytic cycle is initiated by the insertion of an alkene **3.6** into a ligand-bound LCu^IH species derived from the copper precatalyst and hydrosilane to furnish an alkyl-copper complex **D**. Oxidative addition of hydroxylamine **3.7** then occurs to give alkyl-aminocopper intermediate **E**, that is followed by C-N reductive elimination to provide the *anti*-Markovnikov hydroaminated olefin **3.8** with regeneration of LCu^IH species.



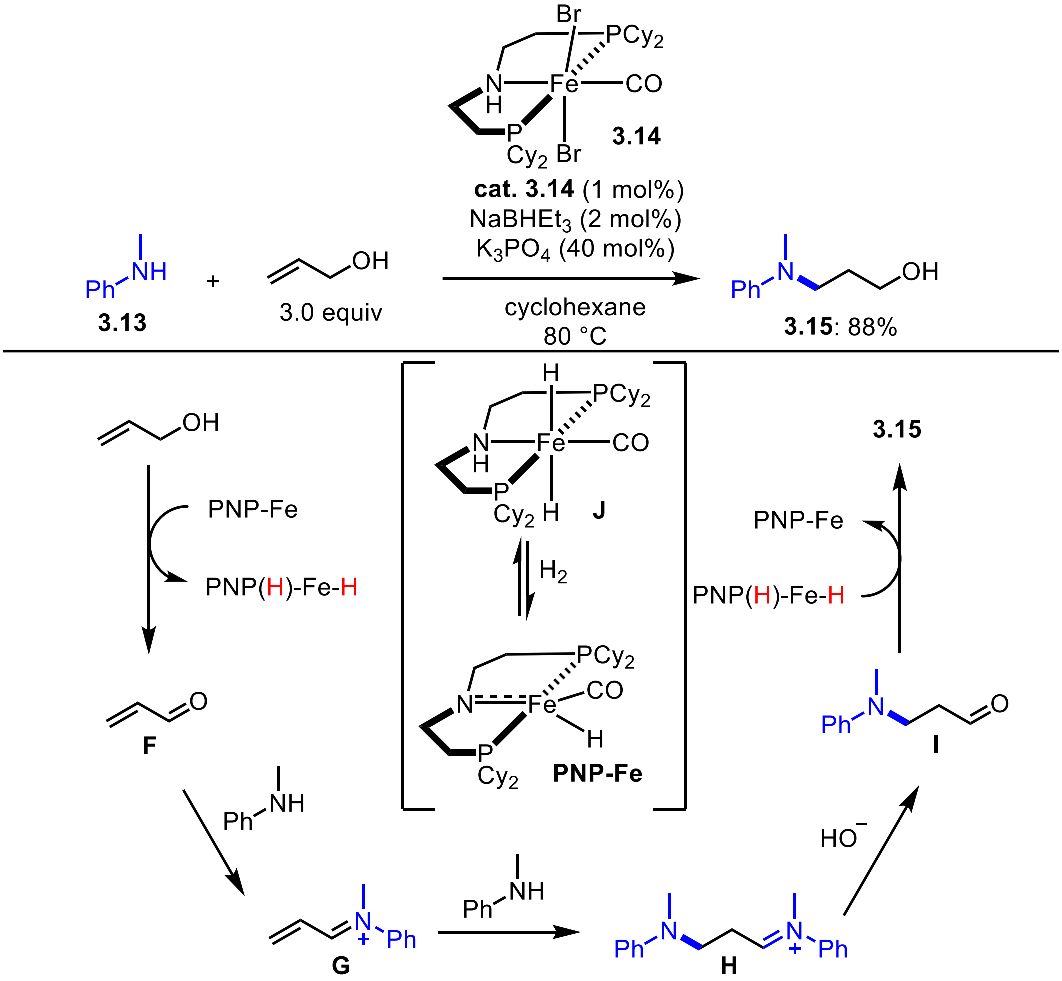
Scheme 3.3. Copper-catalyzed *anti*-Markovnikov hydroamination of aliphatic olefins

When styrene derivatives[5] and vinyl silanes[6] are subjected into the same copper-catalyzed hydroamination protocol, Markovnikov addition is predominantly observed (Scheme 3.4). This is due to the stability of benzylic amino-copper or α-silyl-alkylcopper intermediate.



Scheme 3.4. Copper-catalyzed Markovnikov hydroamination of benzylic and silylated olefins

In 2019, Wang and co-workers[7] developed an iron-catalyzed formal *anti*-Markovnikov hydroamination of allylic and homoallylic alcohols (Scheme 3.5). The catalytic system consists of a pincer Fe-PNP complex with a weak base such as K_3PO_4. This process is initiated by hydride reduction of pre-catalyst **3.14** with $NaBHEt_3$ to give Fe hydride complex **J**,[8] which is under equilibrium with the PNP-Fe complex through elimination and insertion of molecular H_2. The PNP-Fe complex induces dehydrogenative oxidation of allyl alcohol to acrolein **F**. The resulting acrolein **F** then undergoes condensation with 1-phenylethylamine **3.13** to form an iminium intermediate **G**, which is trapped with another amine through aza-Michael addition to give **H**. Subsequent hydrolysis of **H** affords aldehyde **I**, which is finally reduced by the iron-dihydride intermediate to furnish the hydroaminated product **3.15** with regeneration of the Fe-PNP catalyst species.

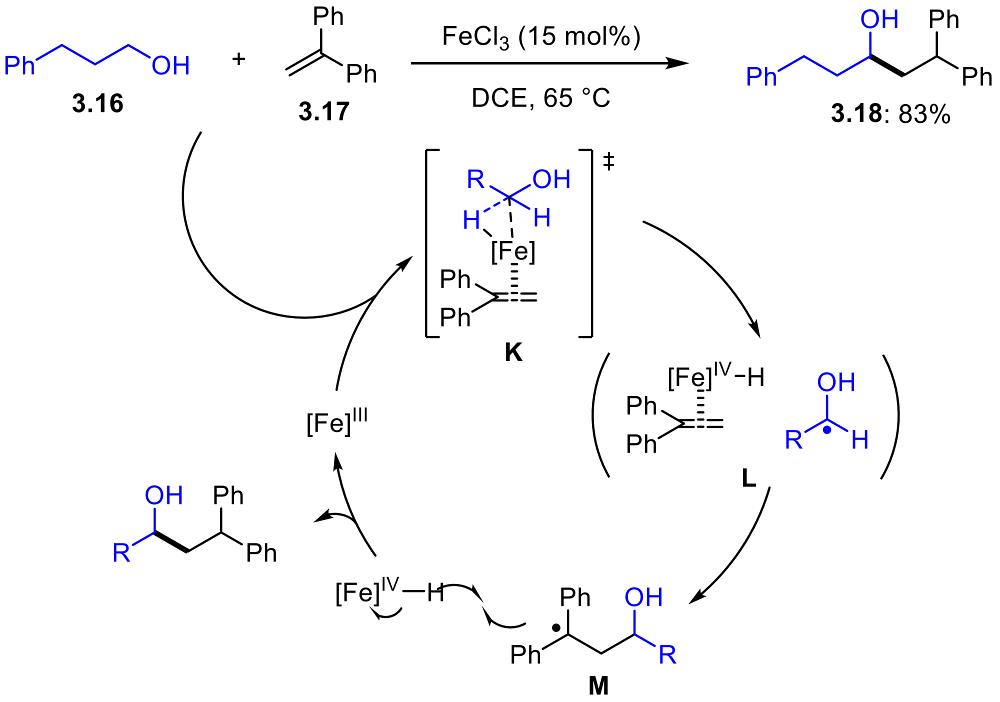


Scheme 3.5. Iron-catalyzed *anti*-Markovnikov hydroamination of allylic alcohols

3.1.2 Radical Mediated Hydrofunctionalization

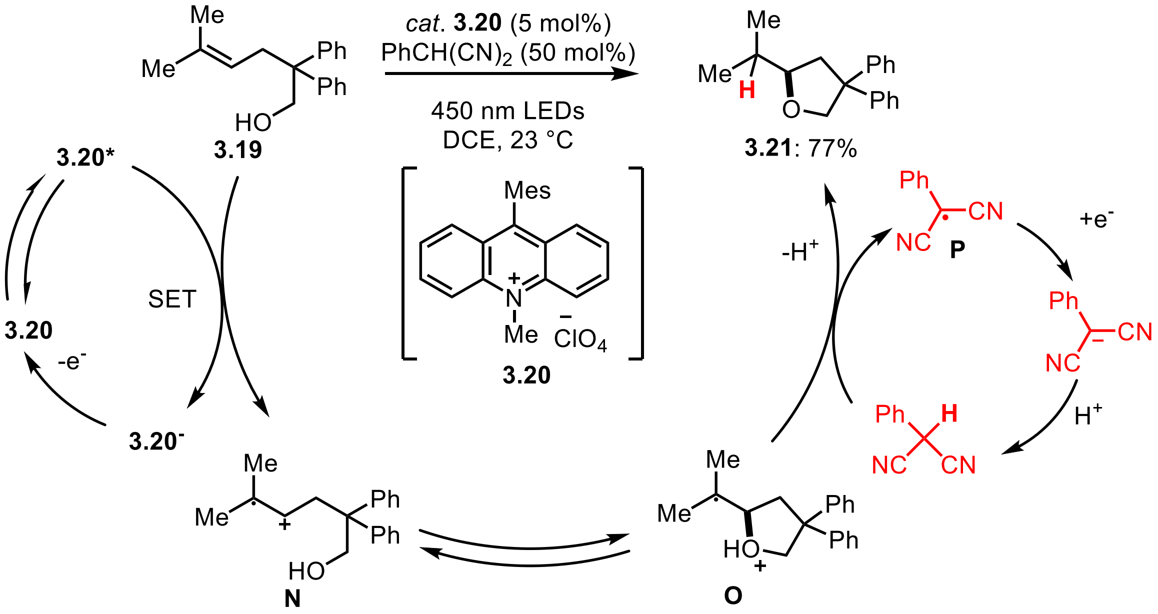
In 2009, Tu and co-workers[9] reported $FeCl_3$-catalyzed C(sp^3)-C(sp^3) bond forming cross-coupling reaction between alcohols and alkenes (Scheme 3.6). The reaction mechanism of this process was proposed to begin with Fe(III)-mediated assembly of alcohols **3.16** and alkenes **3.17** to induce homolytic cleavage of a C(sp^3)-H bond adjacent to the oxygen of alcohols **3.16** through transition-state **K**, forming a pair of α-hydroxy radical and alkene-

Fe(IV) hydride complex **L**. Subsequent radical addition onto the alkene allows for construction of a new C-C bond to form radical intermediate **M** and ensuing hydrogen atom transfer from Fe(IV) hydride furnishes the coupled product **3.18** with regeneration of the Fe(III) catalyst.



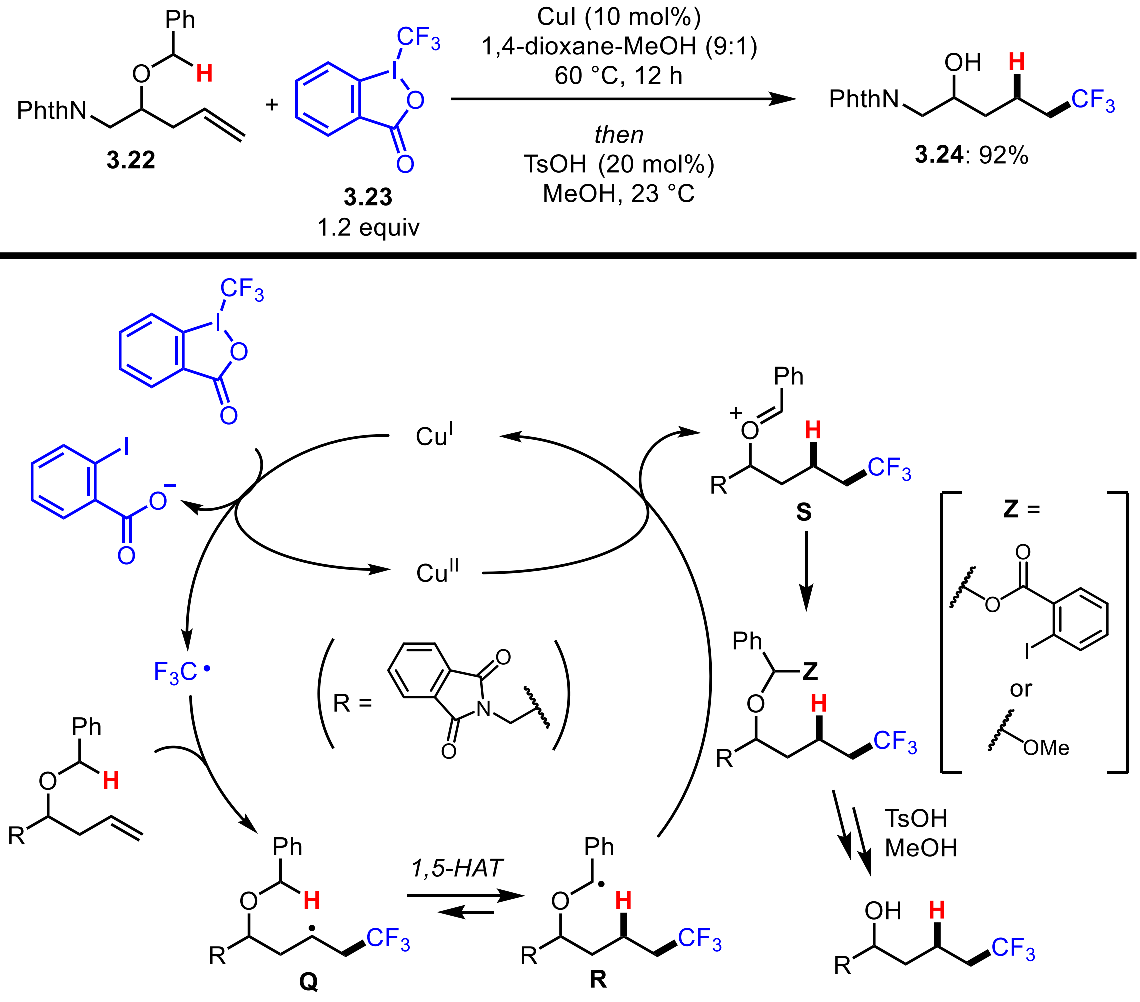
Scheme 3.6. $FeCl_3$-catalyzed cross-coupling of alkene and alcohol

The Nicewicz's group[10] reported an intramolecular *anti*-Markovnikov hydroetherification of alkenols **3.19** employing acridinium perchlorate **3.20** as photoredox catalyst and 2-phenylmalononitrile as a redox-cycling H-atom source under irradiation of blue light (450 nm) (Scheme 3.7). The process is initiated by the excitation of acridinium photocatalyst to **3.20***, which undergoes single-electron-oxidation of alkene **3.19** to form alkene cation radical **N**. Subsequent intramolecular etherification leads to the formation of tertiary radical **O** and ensuing H-atom transfer from 2-phenylmalononitrile delivers tetrahydrofuran product **3.21** with the formation of radical **P**, which serves as an oxidant for the regeneration of the ground state photooxidation catalyst.



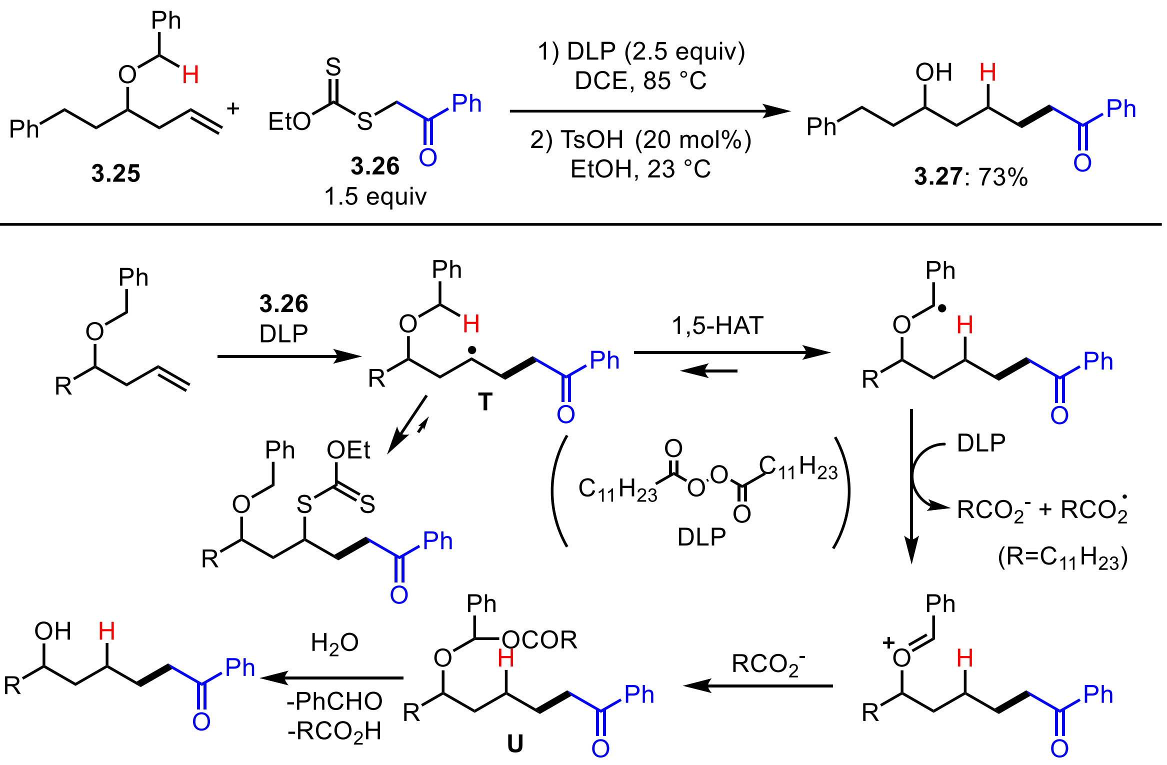
Scheme 3.7. Anti-Markovnikov hydroetherification of alkenols

Our group recently reported the use of a benzyl protecting group on homoallylic alcohol *O*-benzyl ethers as a traceless redox active hydrogen donor for the *anti*-Markovnikov hydrofunctionalization of alkenes.[11] In this work, treatment of homoallylic alcohol *O*-benzyl ether **3.22** with the Togni reagent **3.23** and a catalytic amount of CuI affords the hydrotrifluoromethylated alcohol **3.24** in 92% yield after acidic alkolysis (Scheme 3.8). This process is initiated by single-electron-reduction of the Togni reagent by the Cu^I species to generate a trifluoromethyl radical, which undergoes an *anti*-Markovnikov radical addition onto the alkenyl moiety. The resulting secondary carbon-centered radical **Q**[12] induces 1,5-hydrogen atom shift to form relatively more stable α-oxy benzyl radical **R**, which is then oxidized by the concomitant Cu^{II} species to furnish the oxocarbenium ion **S** along with the regeneration of the active Cu^I species. Oxocarbenium ion **S** is trapped by the iodobenzoic acid or MeOH to produce the corresponding acetals, which are finally converted into hydrotrifluoromethylated alcohol **3.24** by a simple acidic solvolysis.



Scheme 3.8. Copper-catalyzed anti-Markovnikov hydrofunctionalization of alkenes

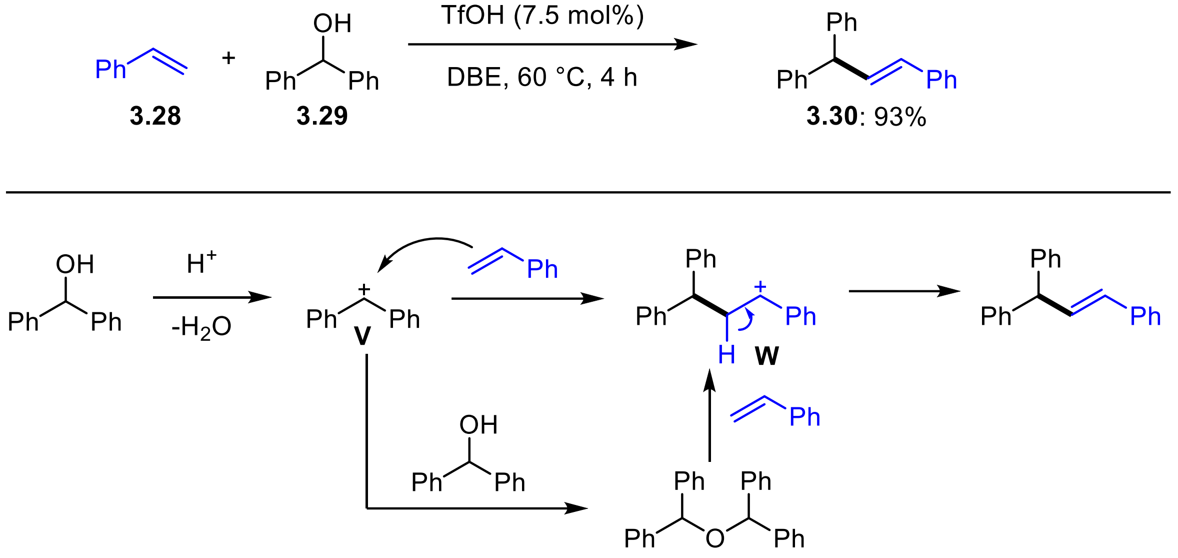
However, the use of hypervalent iodine reagents as carbon-radical precursors limits the possible functional groups that could be installed onto the alkenes. Therefore, our group continuously explored the use of readily available xanthates as a source of carbon radical with combination of dilauroyl peroxide (DLP) as the radical initiator and a stoichiometric oxidant (Scheme 3.9).[13] The presence of a benzyloxy group in the alkene **3.25** facilitates 1,5-hydrogen atom transfer to the carbon-centered radical **T**, which is oxidized to oxocarbenium ion with another DLP, and then converted into ketal **U**. This ketal intermediate is hydrolyzed to generate hydrofunctionalized alcohol **3.27** along with the formation of benzaldehyde and lauric acid as co-products.



Scheme 3.9. Anti-Markovnikov hydrofunctionalization of alkenes using xanthates

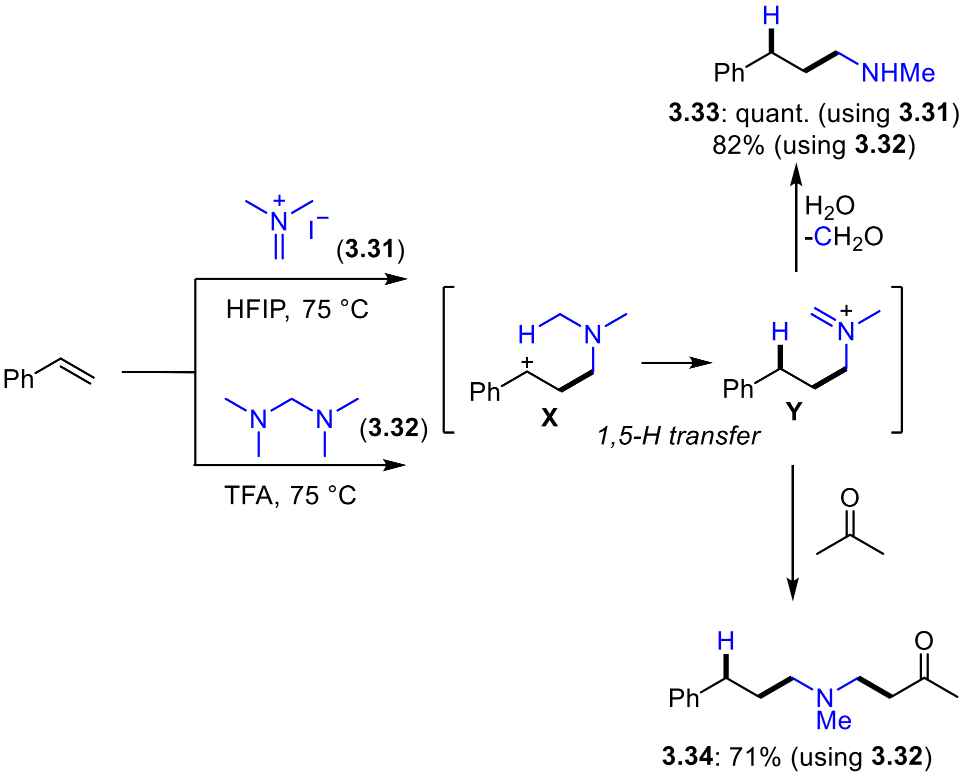
3.1.3 Electrophilic Hydrofunctionalization

In the past decade, dehydrative coupling of alcohols with alkenes under Brønsted or Lewis acid catalysts has been well developed to provide the construction of sp^3-sp^2 C-C bond via the corresponding carbocation intermediates.[14] For example, Ji and co-workers reported trifluoromethanesulfonic acid-catalyzed of cross-coupling between styrene (**3.28**) and diphenylmethanol (**3.29**). This process is initiated by protonation of diphenylmethanol **3.29** to generate benzylic carbocation **V**, which is then trapped by nucleophilic attack of styrene (**3.28**) to form another carbocation **W**. Alternative pathway involves the formation of diphenylmethyl ether, which is then protonated to form carbocation **W**. Subsequent deprotonation provides the alkene product **3.30**.



Scheme 3.10. TfOH-catalyzed coupling of alkenes and alcohols

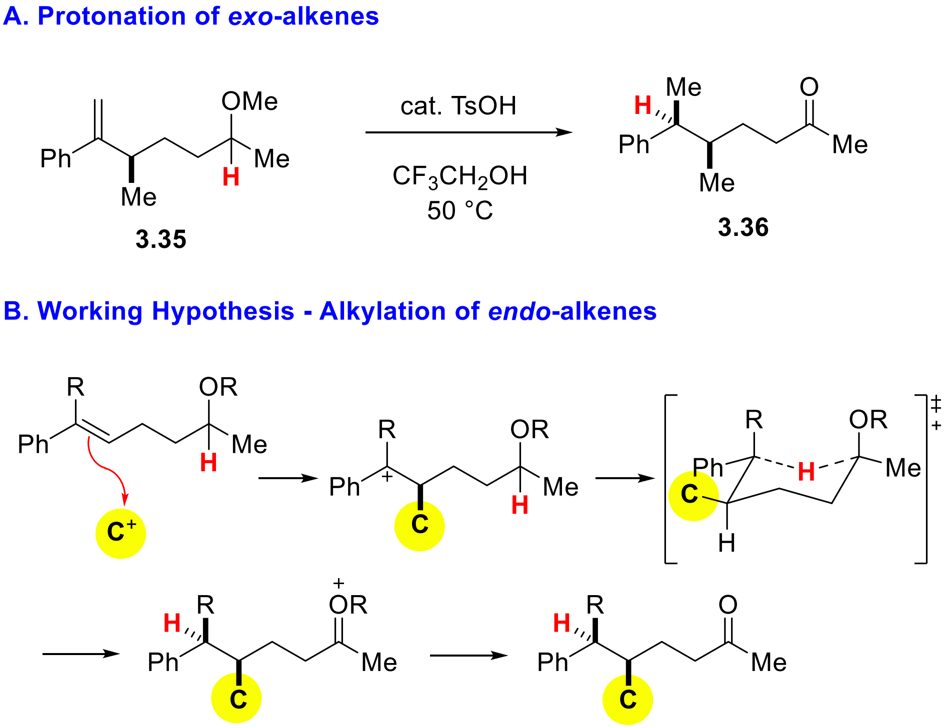
Maulide and co-workers reported an acid-mediated hydroaminomethylation of alkenes using Eschenmoser's salt **3.31** and aminal bis(dimethylamino)methane **3.32** as iminium ion precursors (Scheme 3.11).[15] The key of this transformation involves the nucleophilic addition of a olefins onto an iminium ion, which triggers an internal redox event by 1,5-hydride transfer to the resulting carbenium ion of intermediate **X**, affording the desired hydroaminomethylated product **3.33** after aqueous workup. Moreover, the iminium ion **Y** can also be engaged in domino functionalization processes with the addition of ketones (the Mannich reation) to furnish tertiary amine **3.34**.



Scheme 3.11. Anti-Markovnikov hydroaminomethylation of alkene

3.2 Working Hypothesis

In Chapter 2, the author described use of diastereoselective intramolecular hydride transfer from alkyl ethers to carbocations generated via protonation of alkenes under Brønsted Acid catalysis. However, this process could only be achieved by taking advantage of a preinstalled stereogenic center at the allylic position of the *exo*-alkene starting materials such as **3.35** to create a new stereogenic center in the final products such as **3.36** upon the 1,5-hydride shift event (Scheme 3.12A). Therefore, the author wondered if electrophilic alkylation of prochiral *endo*-aryl alkenes with *in-situ* generated external carbocations would generate benzylic carbocations, which could analogously be captured by ensuing 1,5-hydride shift (Scheme 3.12B). Therefore, the proposed process would allow for the construction of consecutive vicinal stereogenic centers by using readily accessible prochiral alkene starting materials.


A. Protonation of *exo*-alkenes

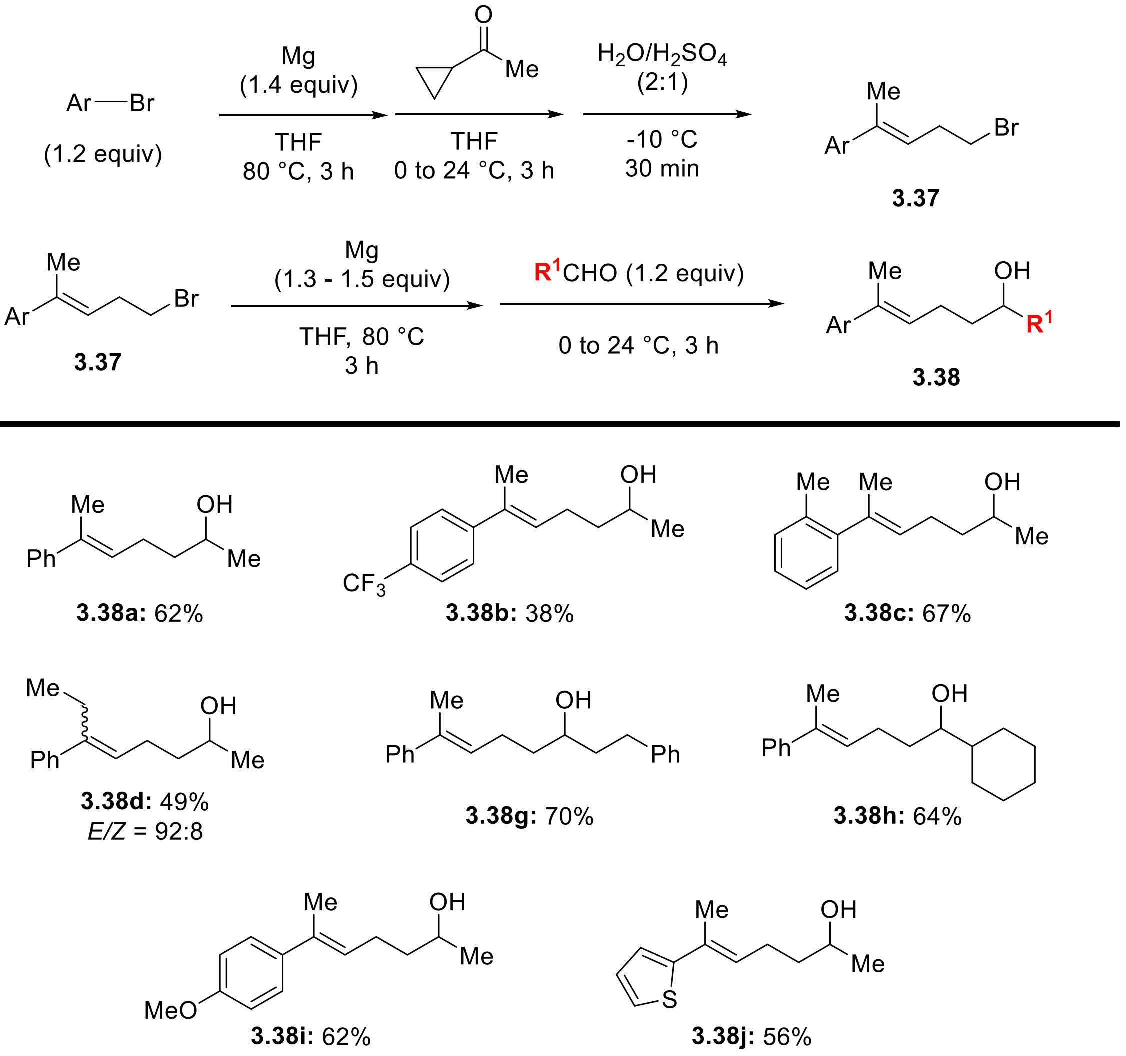
B. Working Hypothesis - Alkylation of *endo*-alkenes

Scheme 3.12. Working Hypothesis

3.3 Results and Discussions

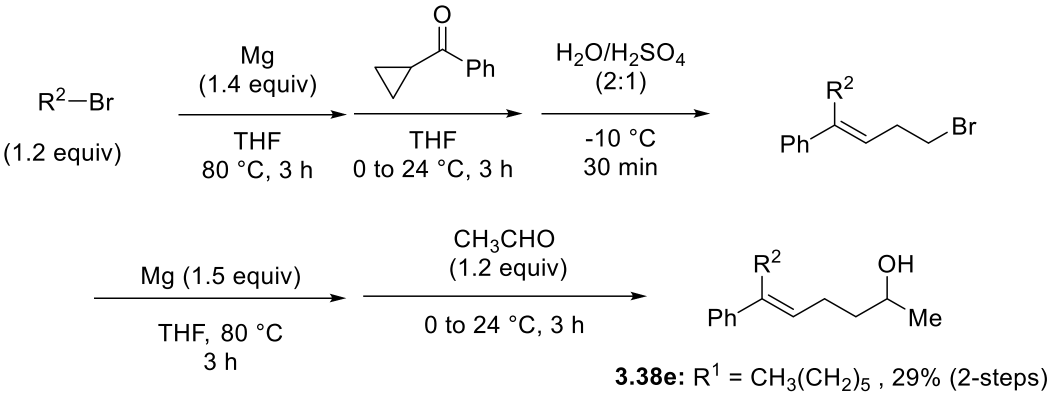
3.3.1 Substrate Synthesis

The alkenyl alcohols **3.38a** – **3.38h** were synthesized from known homoallylic bromides **3.37**,[16] which were synthesized through addition of aryl Grignard reagents to cyclopropyl methyl ketone followed by acid-mediated brominative ring-opening. These bromides were subsequently converted into the Grignard reagents and subjected to nucleophilic addition onto aliphatic aldehydes (Scheme 3.13).



Scheme 3.13. Synthesis of alkenols **3.38a - 3.38d** and **3.38g – 3.38j**

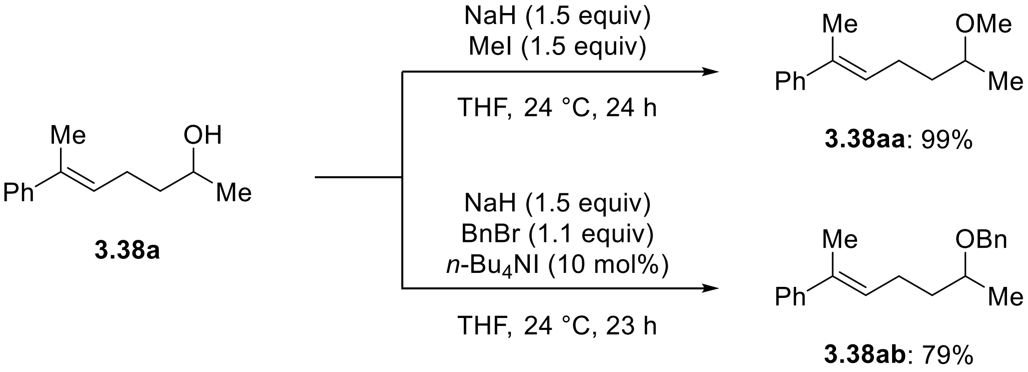
The alkenyl alcohols **3.38e** and **3.38f** were prepared by following the scheme 3.14. Homoallylic bromides were similarly prepared through the addition of alkyl Grignard reagents to cyclopropyl phenyl ketone followed by acid-mediated brominative ring-opening. These homoallylic bromides were converted into the Grignard reagents which were trapped with acetaldehyde to form **3.38e** and **3.38f**.



3.38e: $R^1 = CH_3(CH_2)_5$, 29% (2-steps)
3.38f: $R^1 = H_2C{=}CH(CH_2)_3$, 37% (2-steps)

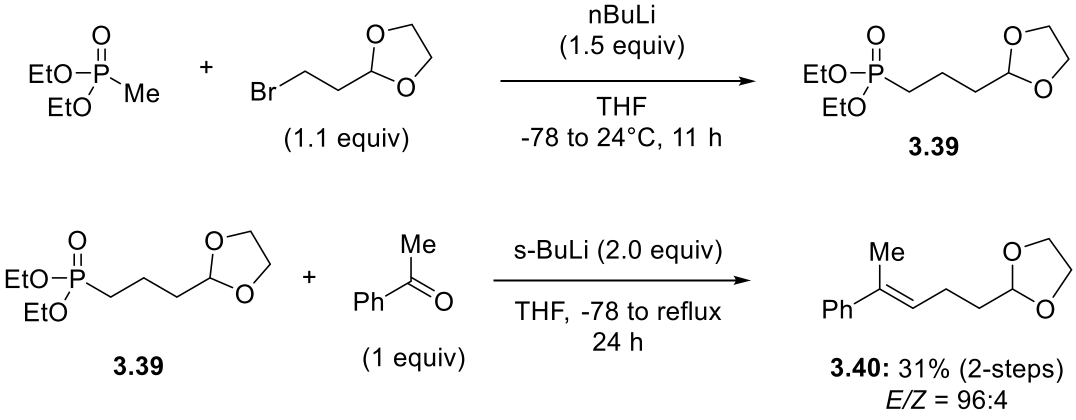
Scheme 3.14. Synthesis of alkenols **3.38e** and **3.38f**

Alkenes **3.38aa** and **3.38ab** were prepared respectively from methylation and benzylation of **3.38a** in the presence of NaH (Scheme 3.15).



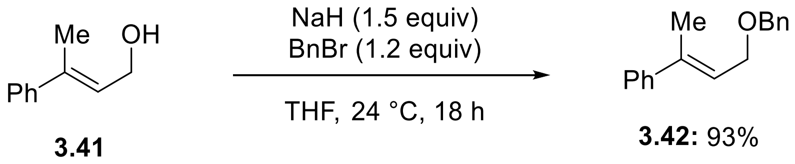
Scheme 3.15. Synthesis of alkenes **3.38aa** and **3.38ab**

Alkene **3.40** having a 1,3-dioxolane moiety was prepared through preparation of phosphonate **3.39** from diethyl methylphosphonate[17] and 2-(2-bromoethyl)-1,3-dioxolane followed by the Horner-Wadsworth-Emmons reaction with acetophenone in the presence of *sec*-butyllithium[18] (Scheme 3.16).



Scheme 3.16. Synthesis of alkenes 3.40

Allylic alcohol *O*-benzyl ether **3.42** was prepared by benzylation of allyl alcohol **3.41** (Scheme 3.17).



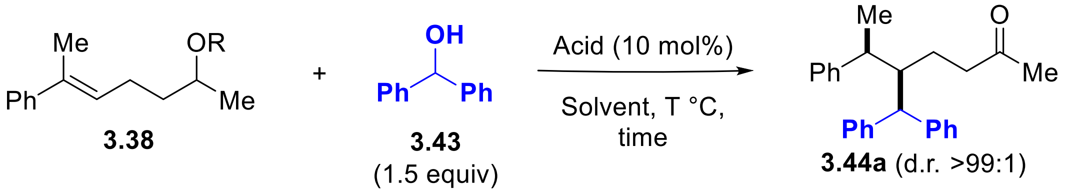
Scheme 3.17. Synthesis of alkenes 3.42

3.3.2 Optimization of the reaction conditions

Based on the working hypothesis described in section 3.2, the author began the investigation with the optimization of the reaction conditions using aryl alkene **3.38aa** having a methyl ether tether as a possible hydride donor and diphenylmethanol **3.43** as a source of carbocation (Table 1, entry 1). Treatment of **3.38** and 1.5 equiv of **3.43** with 10 mol% of *p*-toluenesulfonic acid (TsOH) in 2,2,2-trifluoroethanol (TFE) at 50 °C gave good conversion of alkene **3.38aa** within 2 h and provided the desired hydroalkylated ketone **3.44a** in 80% yield as a pure diastereomer. It was observed that the use of a benzyl protecting group on ether **3.38ab** did not improve the yield of **3.44a** (entry 2). On the other hand, interestingly, the reaction of unprotected alcohol **3.38a** was found to be a faster process (0.5 h), providing **3.44a** in 73% yield (entry 3).

As the direct use of alcohol **3.38a** as the hydride donor would be beneficial from the viewpoints of overall process efficiency, we further screened a series of Brønsted acids using alcohol **3.38a** as the substrate. Among the Brønsted acids tested (entries 4-6), the reaction with bistriflimide resulted in the formation of **3.44a** (Tf_2NH) in the highest yield in 88% yield within 20 min (entry 5). The reactions in other solvents such as dichloromethane and nitromethane ($MeNO_2$) provided the desired ketone **3.44a** in lower yield (entry 7-8). Lowering the reaction temperature to 24 °C provided 65% yield of **3.44a** (entry 9), whereas higher temperature at 80 °C gave the similar yield of 84% (entry 10).

Table 3.1. Optimization of the reaction conditions

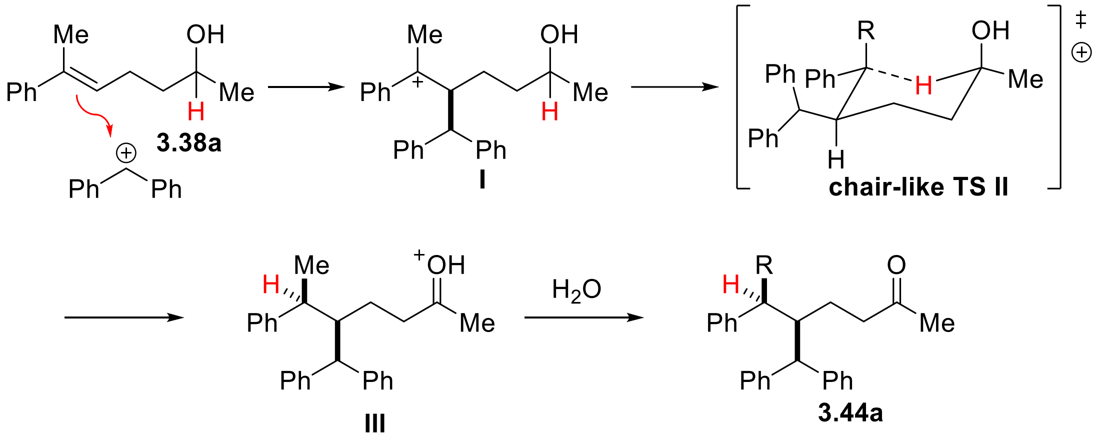


entry[a]	R	acid	solvent	T	time	yield[b]
1	Me (aa)	TsOH	TFE	50	2 h	80 (77)
2	Bn (ab)	TsOH	TFE	50	3 h	69
3	H (a)	TsOH	TFE	50	30 min	73 (71)
4	H	TfOH	TFE	50	20 min	75 (67)
5	**H**	**Tf_2NH**	**TFE**	**50**	**20 min**	**88 (80)**
6	H	TFA	TFE	50	19 h	50
7	H	Tf_2NH	CH_2Cl_2	50	3 h	56
8	H	Tf_2NH	$MeNO_2$	50	3 h	70
9	H	Tf_2NH	TFE	24	20 min	65
10	H	Tf_2NH	TFE	80	20 min	84

[a]The reactions were conducted using 0.3 mmol of **3.38** in solvent (0.1 M). [b]Isolated yield is in parentheses

3.3.3 Proposed Reaction Mechanism

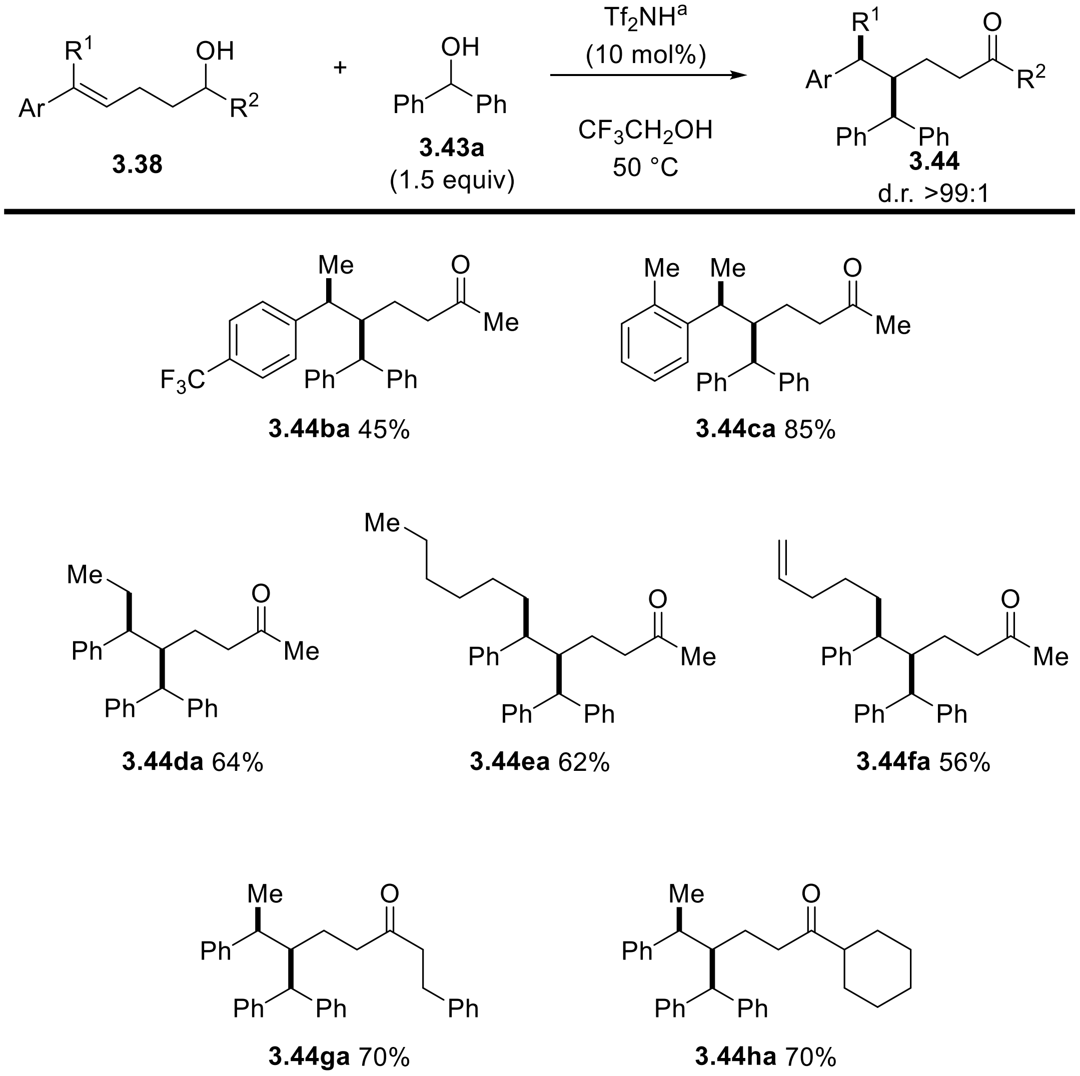
The process is proposed to be initiated by electrophilic alkylation of prochiral *endo*-aryl alkenes **3.38a** with *in-situ* generated dibenzylic carbocation to form benzylic carbocation **I**, which then undergoes 1,5-hydride shift from the electron-rich carbinol hydride via 6-membered chair-like transition state **II** to provide diastereomerically pure *anti*-Markovnikov hydroalkylated products **III**. The resulting oxocarbenium ion moiety of **III** could finally be hydrolyzed to furnish the corresponding ketone **3.44a** (Scheme 3.18).



Scheme 3.18. Proposed Reaction Mechanism

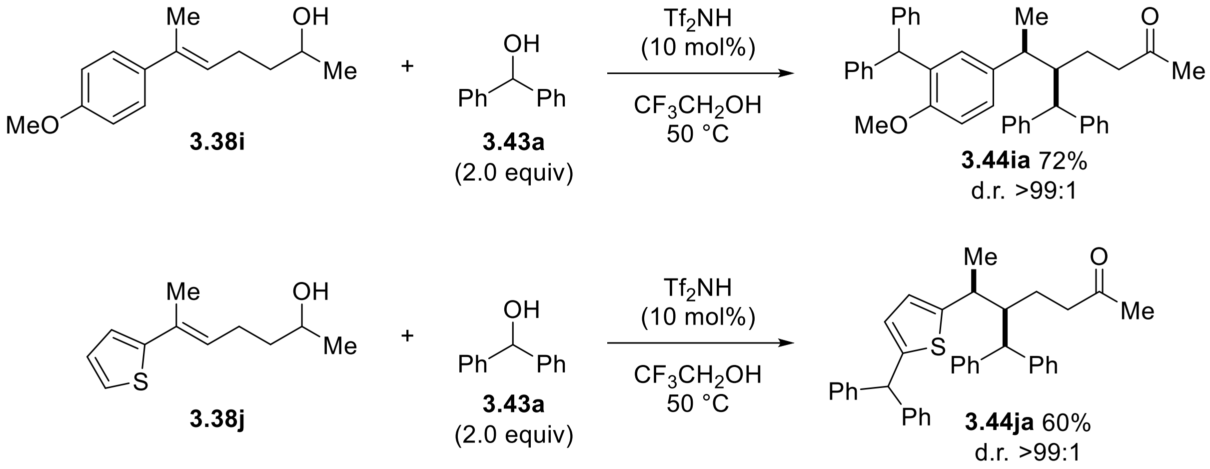
3.3.4 Scope and limitation

Using the optimized reaction conditions (Table 3.1, entry 5), the author started the investigation for the substituent compatibility of the reaction between the aryl alkenes **3.38** with diphenylmethanol **3.43a** (Scheme 3.19). The reaction of alkene **3.38b** having an electron-deficient 4-trifluoromethylphenyl group provided **3.44ba** in moderate yield (45%), whereas this reaction condition allowed the presence of a bulkier group such as 2-methylphenyl group (for **3.44ca**). As for the substituent on R^1, ethyl, *n*-hexyl, and pentenyl groups could be installed, affording **3.44da**, **3.44ea**, and **3.44fa**, respectively, as single diastereomers. It was noted that installation of bulkier phenethyl and cyclohexyl groups at the carbinol position (for **3.44ga** and **3.44ha**) would not disturb the overall efficiency of the transformation including the diastereoselectivity.



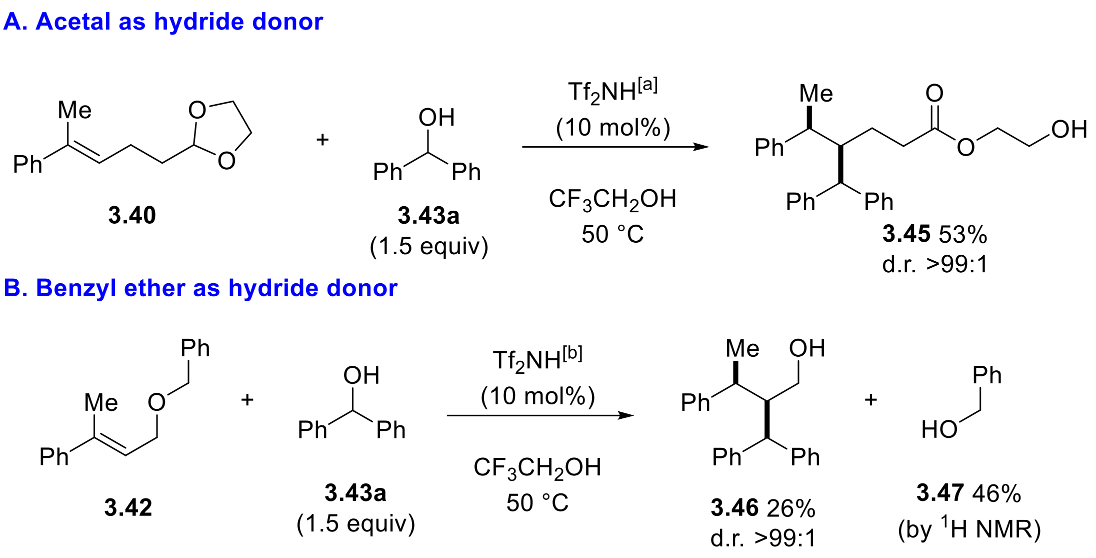
Scheme 3.19. Substrate scope of aryl alkenes **3.38**. [a]The reactions were conducted using 0.3 mmol of aryl alkenol **3.38** within 30 min. Single diastereomers of **3.44** were obtained from all substrates

Interestingly, the reactions of the substrates **3.38i** and **3.38j** having an electron-rich aryl group on the alkenyl moiety induced an additional Friedel-Crafts type aromatic C-H alkylation with the transient carbocation derived from alcohol **3.43a** to give the corresponding products **3.44ia** and **3.44ja** in 72% and 60% yields, respectively (Scheme 3.20).



Scheme 3.20. The reactions of **3.38i** and **3.38j** having electron-rich aryl group on alkenyl moiety. [a]The reactions were conducted using 0.3 mmol of aryl alkenol **3.38** within 30 min.

As for the compatibility on the hydride donor moiety, a 1,3-dioxolane moiety in substrate **3.40** was found capable of inducing the diastereoselective hydroalkylation with alcohol **3.43a**. Under the optimized reaction conditions, the process led to the formation of ester **3.45** in 53% yield (Scheme 3.21A). The reaction of allylic alcohol *O*-benzyl ether **3.42** also resulted in formation of **3.46** as a pure diastereomer through debenzylation despite a poor yield (26%) (Scheme 3.21B). The formation of several side-products including benzyl alcohol (**3.47**) in 46% yield was observed, probably due to more acid-sensitive character of the allyl benzyl ether motif of substrate **3.42**.

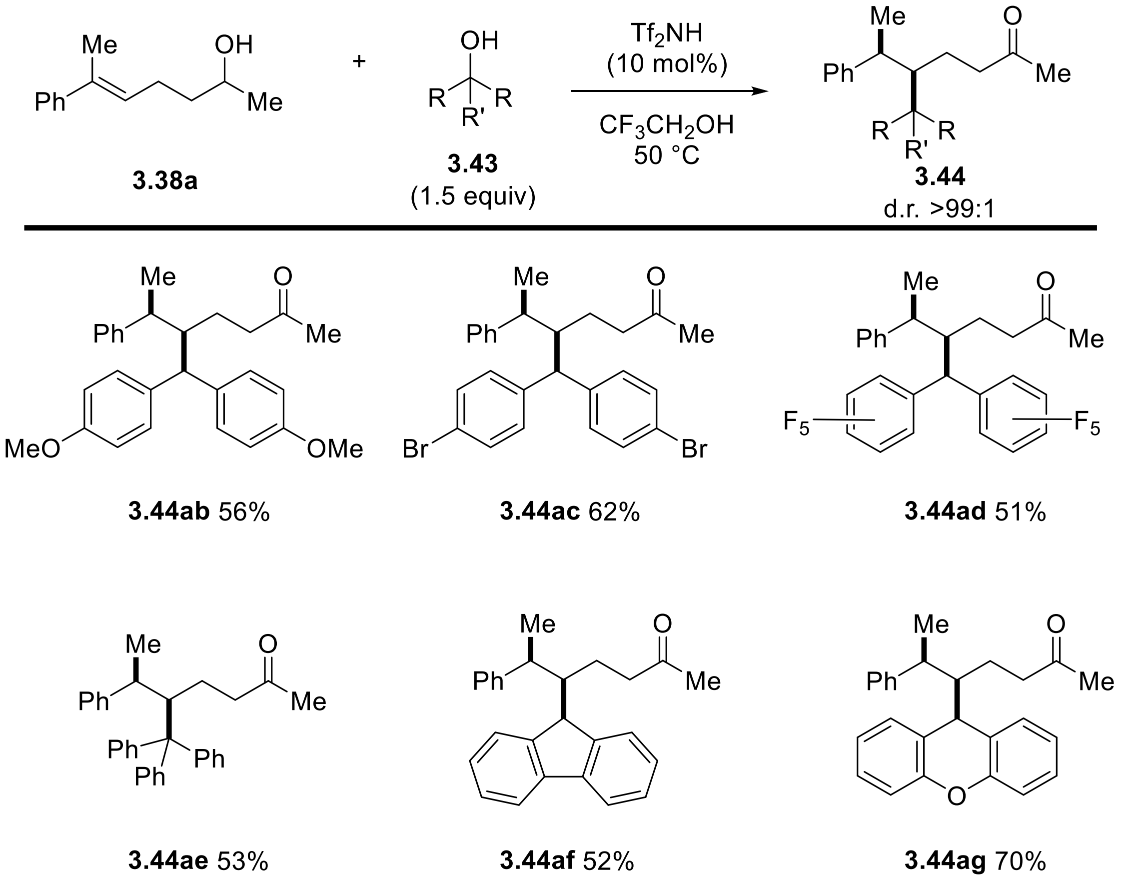


A. Acetal as hydride donor

B. Benzyl ether as hydride donor

Scheme 3.21 The use of other hydride donors. [a]The reactions were conducted using 0.3 mmol of aryl alkene **3.40** within 2 h. [b]The reactions were conducted using 0.3 mmol of aryl alkene **3.42** within 20 min.

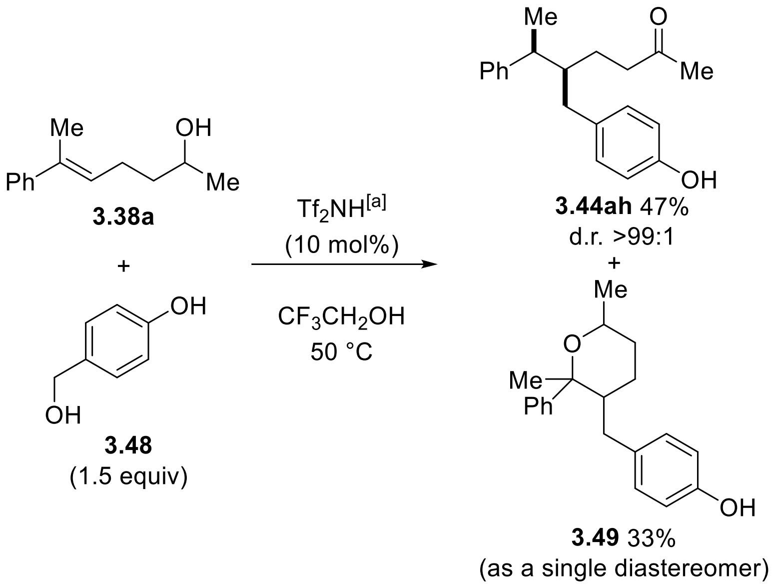
The author next screened various alcohols as the potential carbocation source (Scheme 3.22). Symmetrical bisarylmethanols **3.43b-3.43d** including 4-methoxyphenyl, 4-bromophenyl or pentafluorophenyl motifs were found to be suitable reaction partners, leading to the formation of the corresponding hydroalkylated products **3.44ab-3.44ad**, respectively in good to moderate yields. The reaction with triphenylmethanol **3.43e** delivered **3.44ae** having a trityl group in 53% yield. The method would also allow installation of fluorene and xanthene moieties, as shown by the formation of **3.44af** and **3.44ag**, in 52% and 70% yields, respectively.



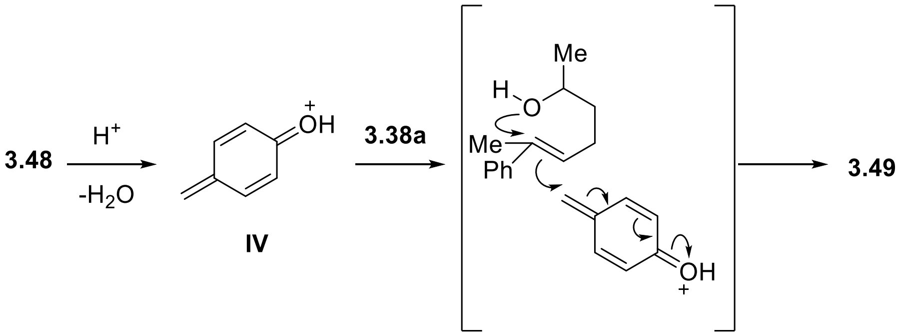
Scheme 3.22 Substrate scope of alcohols **3.43** as carbocation sources. [a]The reactions were conducted using 0.3 mmol of aryl alkenol **3.38a** within 30 min.

The reaction of aryl alkene **3.38a** with 4-hydroxybenzyl alcohol (**3.48**) provided not only the expected hydrobenzylated product **3.44ah** in 47% yield but also tetrahydropyran **3.49** in 33% yield as a single diastereomer under the optimized reaction conditions (Scheme 3.23A). It is proposed that this process was mediated by a transient protonated *p*-quinone methide **IV**[19] as an electrophile. It was speculated that the formation of tetrahydropyran **3.49** occurs *via* a concerted fashion by oxyalkylation of the alkene with *p*-quinone methide **IV** (Scheme 3.23B).

A. Reaction of 4-hydroxybenzyl alcohol 3.48 with 3.38a



B. Proposed mechanism for the formation of 3.49



Scheme 3.20 Reaction with 4-hydroxybenzyl alcohol (**3.48**) [a]The reactions were conducted using 0.3 mmol of aryl alkene **3.38** within 23 h.

3.4. Conclusion

Diastereoselective construction of vicinal stereogenic centers was achieved by hydroalkylation of prochiral *endo*-aryl alkenes with activated alcohols such as diphenylmethanol as the source of carbocations under the Bronsted acid catalysis. This process is featured by regioselective electrophilic alkylation of aryl alkenes with external *in-situ* generated carbocations and ensuing 1,5-hydride shift in a single operation.

3.5. References

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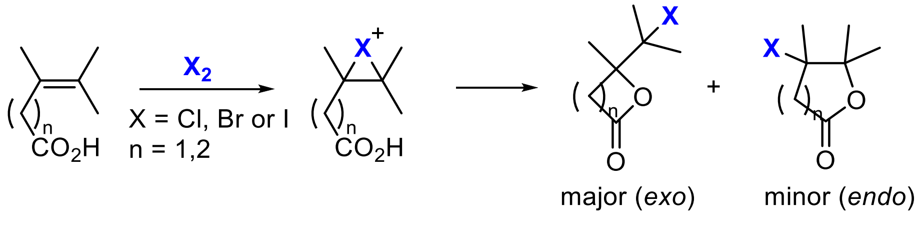
Chapter 4. Diastereoselective Intramolecular Hydride Transfer Triggered by Electrophilic Halogenation of Alkenes: Synthesis of Tetrahydrofurans

4.1 Introduction

Electrophilic halogenation of alkenes in the presence of appropriate internal or external nucleophiles has been utilized as a facile strategy for halo-functionalization of alkenes. This introductory section will describe the recent reports on the functionalization of alkenes upon the addition of electrophilic halogen source. It also highlights recent selected works on the synthesis of tetrahydrofuran motifs.

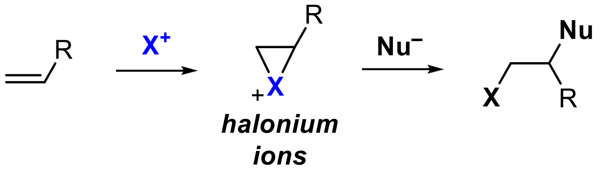
4.1.1 Electrophilic Halofunctionalization of Alkenes

The simple addition of electrophilic halogenation reagents to alkenes is a fundamental process in organic chemistry, leading development of numbers of synthetic methodologies. In the early 1900, Bougault reported the first iodolactonisation using molecular iodine (Scheme 4.1).[1] Since then, a wide variety of electrophilic halogenation reagents, such as *N*-haloamides, halosuccinimides, halonium acetates and hypervalent iodine(III) reagents have been explored and utilized.[2] With a combination with this electrophilic halogenation of alkenes, a variety of nucleophiles based on carbon or heteroatoms have been engaged in subsequent nucleophilic cyclization onto the transient halonium ions for the construction of carbo- and heterocyclic compounds.[3]



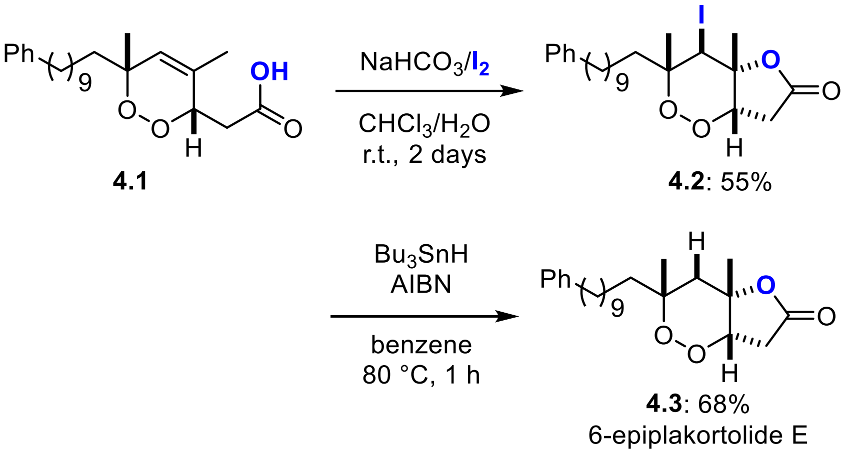
Scheme 4.1 An early report on halolactonization

The generally accepted mechanism of electrophilic halo-functionalization of alkenes begins with the formation of the halonium ion immediately after the treatment of alkene with an electrophilic halogenation source (Scheme 4.2). Such halonium ions were observed as a stable form in liquid SO_2 in a series of NMR studies performed by Olah and co-workers.[4] This reactive halonium ion can be further captured by a variety of carbon and heteroatom-based nucleophiles.



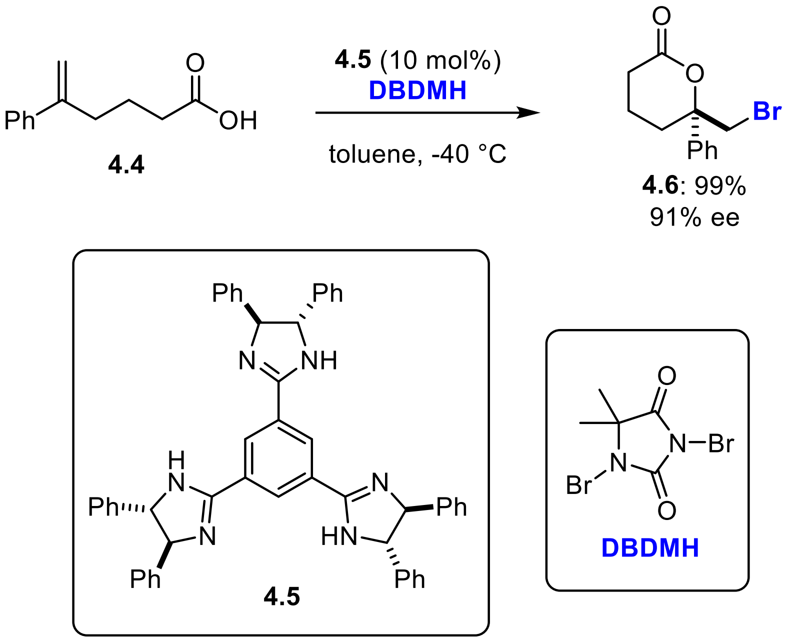
Scheme 4.2 General mechanism of electrophilic halofunctionalization of alkene

Jung and co-workers[5] synthesized 6-epiplakortolide E **4.3**, a potent anti-cancer agent, using an iodolactonisation of a cylic peroxide **4.1** (Scheme 4.3). Treatment of **4.1** with iodine and sodium hydrogen carbonate in a chloroform-water co-solvent system gave cylic peroxylactone **4.2**, that is followed by subsequent radical de-iodination to afford the targeted natural product precursor **4.3**.



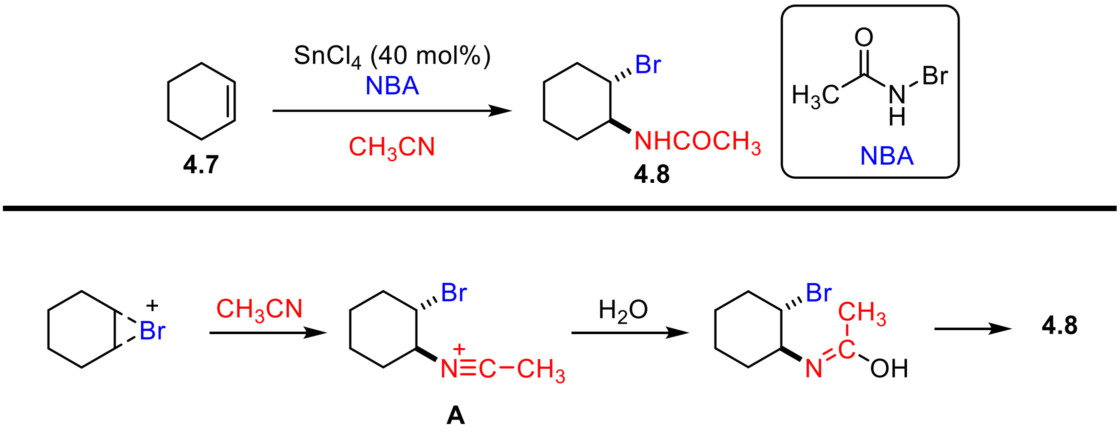
Scheme 4.3 Jung’s synthesis of 6-epiplakortolide E

In 2010, Fujioka and co-workers[6] reported the enantioselective bromolactonization of 5-arylhexenoic acid **4.4** using 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) as an electrophilic brominating source in the presence of C_3-symmetric trisimidazoline catalyst **4.5** (Scheme 4.4).



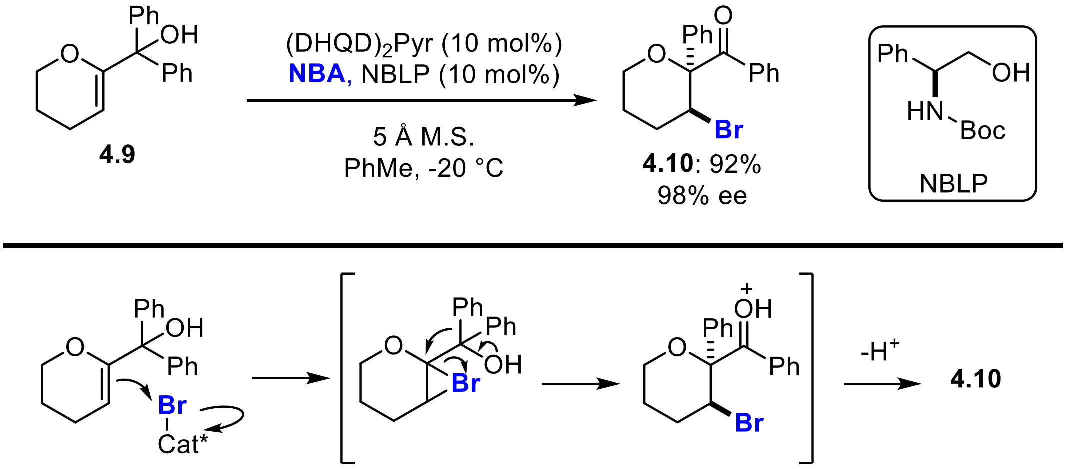
Scheme 4.4 Enantioselective bromolactonization with chiral trisimidazoline

The haloamidation of alkenes in acetonitrile was described in the Corey's report on synthesis of oseltamivir phosphate (Tamiflu) on 2006 (Scheme 4.5).[7] It was reported that the use of a catalytic amount of $SnCl_4$ catalyzes the haloamidation process in the presence of *N*-bromoacetamide (NBA) as the brominating source and acetonitrile as the external nucleophile. The process is promoted via a ring opening of bromonium ion by acetonitrile to generate intermediate **A**, which is hydrolyzed by water to give the bromoamide product **4.8**.



Scheme 4.5 Tin(IV) chloride catalyzed haloamidation of olefin

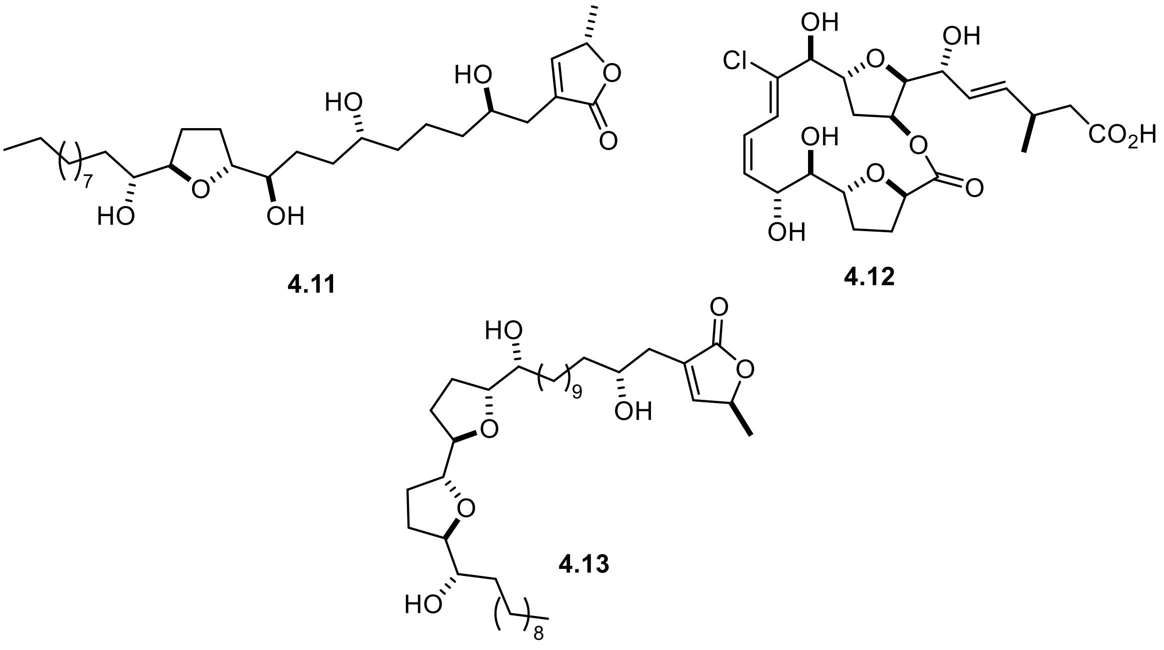
Tu and co-workers also reported the use of *N*-bromoacetamide to induce enantioselective intramolecular bromofunctionalization via semi-pinacol rearrangement of tertiary alcohol **4.9** to bromoketones **4.10** (Scheme 4.6). This transformation is achieved using a combination of cinchona alkaloid based (DHQD)$_2$Pyr and *N*-Boc-L-phenylglycine (NBLP) catalyst to afford highly enantioenriched bromoketones **4.10**. This process involves the formation of bromonium ion intermediate, which induces the following 1,2-phenyl shift to furnish the final product.



Scheme 4.6. Enantioselective semi-pinacol rearrangement

4.1.2 Construction of Tetrahydrofuran motifs

Substituted tetrahydrofurans are found in a wide array of biologically active molecules (Scheme 4.7). One of the examples is glacin A **4.11**, a member of the *annonaceous acetogenins*, exhibiting a diverse array of biological activities including antitumor and antimalarial.[8] Chagonsensine **4.12** was isolated from Red Sea calcareous sponge having a chlorinated 16-membered macrolactone with a 2,3,5-trisubstituted and 2,5-disubstituted tetrahydrofuran rings.[9] Bullatacin **4.13**, containing two consecutive tetrahydrofuran moieties, is a fatty acid lactone isolated from several fruits from *Annonaceae* family.[10]



4.11

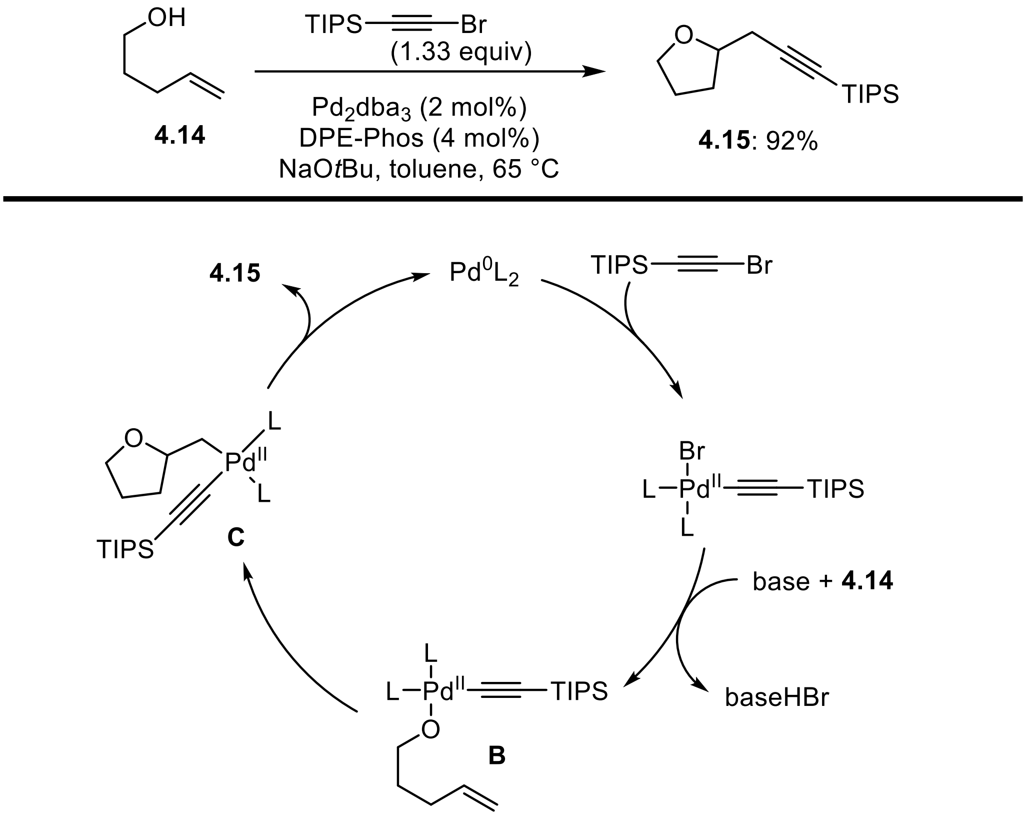
4.12

4.13

Scheme 4.7 Tetrahydrofuran moiety in natural product precursor

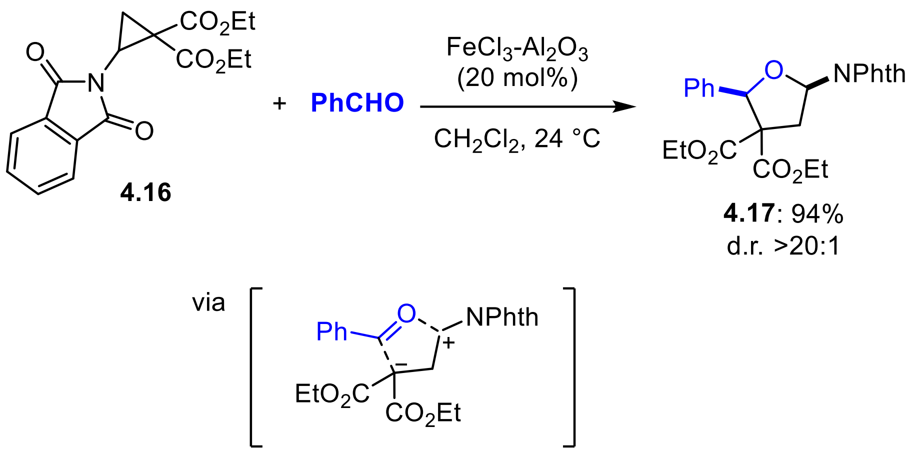
Over the years, a number of studies on the construction of multi-substituted tetrahydrofuran motifs were reported.[11] For example, Waser and co-workers[12] reported Pd(0)-catalyzed intramolecular oxyalkynylation of non-activated olefins **4.14** to provide 2-substituted tetrahydrofuran **4.15** (Scheme 4.8). This process involves oxidative addition of

Pd(0) to the alkynyl bromide before oxypalladation and reductive elimination via intermediate **B** and **C**, respectively, to give tetrahydrofuran product **4.15**.



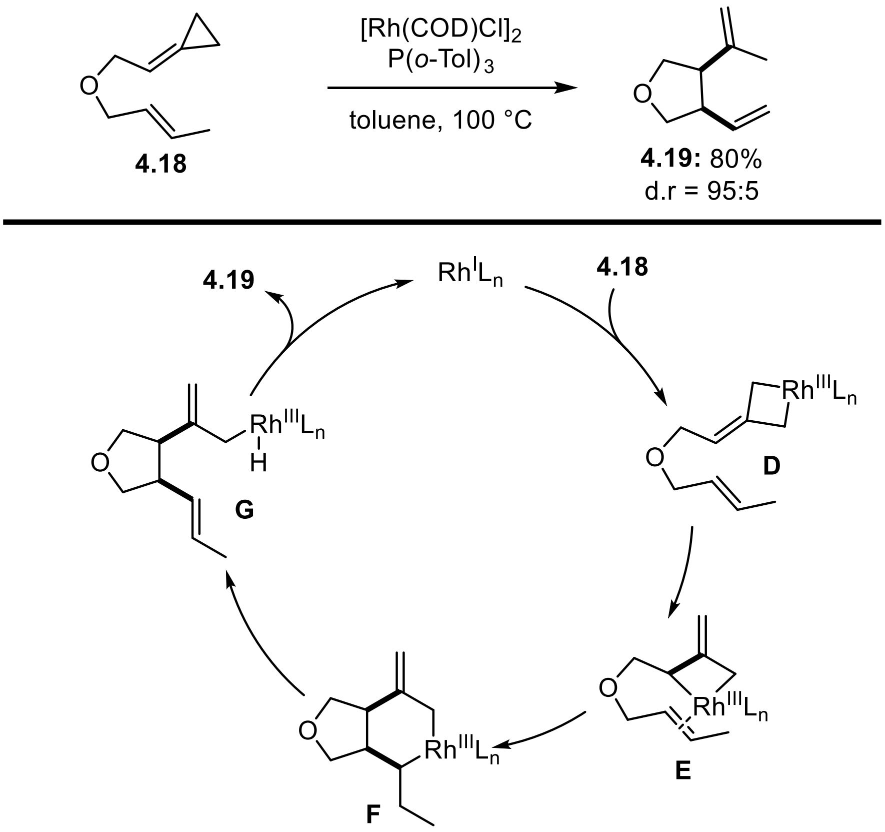
Scheme 4.8 Pd(0)-catalyzed oxyalkynylation of olefin

The same group reported another distinct method to multi-substituted tetrahydrofuran via an [3+2]-annulation of donor-acceptor aminocyclopropanes **4.16** with aldehydes [13] (Scheme 4.9). This reaction is catalysed by iron(III) chloride on alumina to provide 2-aminotetrahydrofurans **4.17** in good yields and excellent 2,5-*cis*-selectivity.



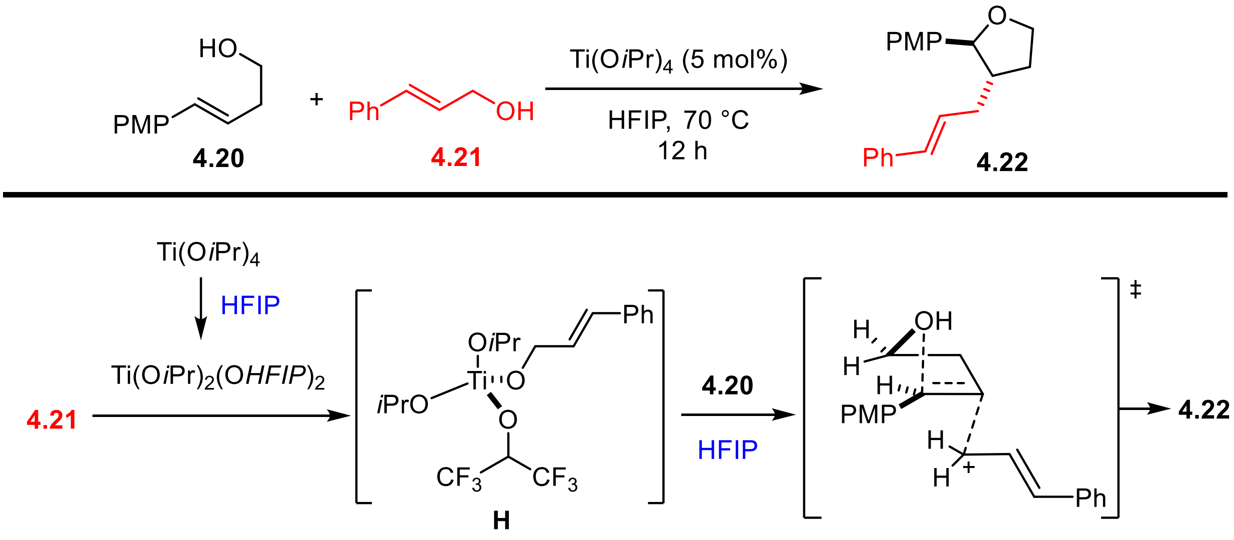
Scheme 4.9 [3+2] Annulation of donor-acceptor aminocyclopropanes with aldehydes

The rhodium-catalyzed ene-cycloisomerization was reported by Evans and co-workers, offering an efficient approach for the construction of *cis*-3,4-disubstituted tetrahydrofuran from alkenylidenecyclopropanes **4.18** (Scheme 4.10).[14] This process is initiated by oxidative addition of rhodium(I) species into the methylenecyclopropyl C-C bond of **4.18** to generate the metallacyclobutene **D**, which then undergoes rearrangement to afford **E**. The following stereoselective carbometallation of the alkene provides the *cis*-fused metallacycle **F**, which then undergoes selective β-hydride elimination at the terminal position to afford the Rh-H intermediate **G**. The reductive elimination finally provides the desired product **4.19**.



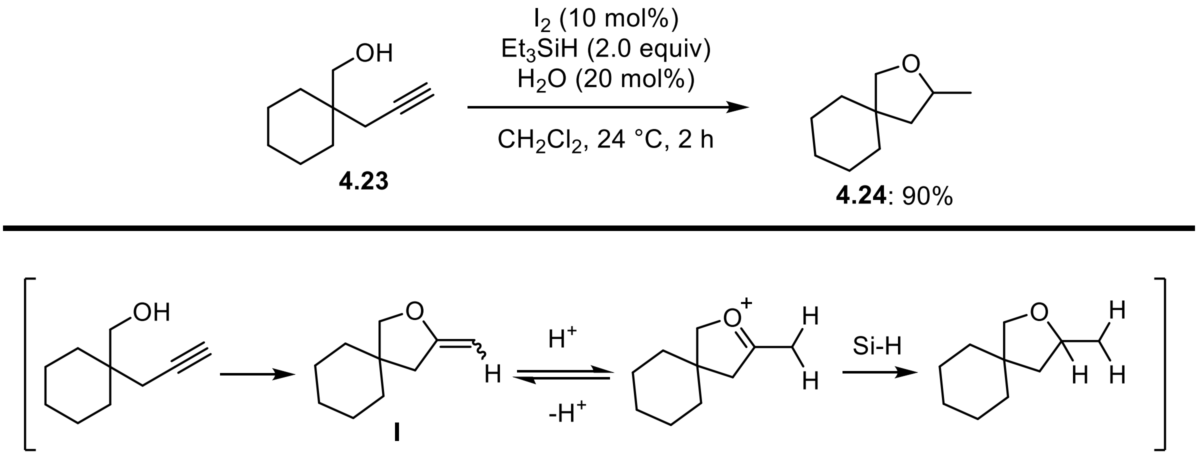
Scheme 4.10 Rhodium-catalyzed ene-cycloisomerization of alkenlidenecyclopropanes

In 2019, the Donohoe's group reported a stereoselective synthesis of *trans*-2,3-disubstituted tetrahydrofurans using allylic alcohols as an alkylating agent (Scheme 4.11).[15] This transformation was enabled by the use of a catalytic amount of Ti(O*i*-Pr)$_4$ in HFIP as a solvent. The process is first triggered by the replacement of two isopropoxy ligands of Ti(O*i*-Pr)$_4$ with two hexafluoroisopropoxy units from HFIP as solvent. Subsequently, allylic alcohol **4.21** replaces one of the hexafluoroisopropoxy unit to form a new species **H**, where the addition of allylic alcohol **4.20** to this active titanium species via an electrophile-triggered cyclization leads to formation of product **4.22** in a diastereoselective manner.



Scheme 4.11 Stereoselective heterocyclization with alcohols as alkylating agents

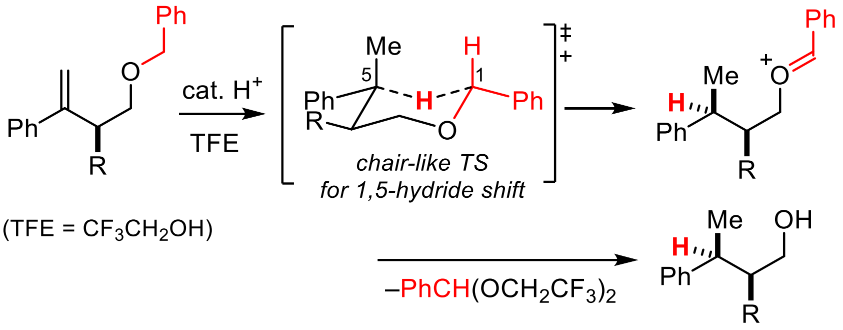
High demand on the transition-metal-free strategy in synthetic chemistry inspired the development of silane-iodine catalysis that mediates intramolecular hydroalkoxylation/reduction of unactivated alkynes to furnish multi-substituted tetrahydrofurans (Scheme 4.12).[16] This process is initiated by the treatment of hydroxy alkyne **4.23** in a catalytic amount of I_2 with a small amount of water, to form *exo*-cyclic enol ether **I**, which is further reduced under stoichiometric amount of Et_3SiH to furnish 2,4-disubstituted tetrahydrofuran **4.24** with high efficiency.



Scheme 4.12 I_2/Et_3SiH catalyzed hydroalkoxylation/reduction of olefin

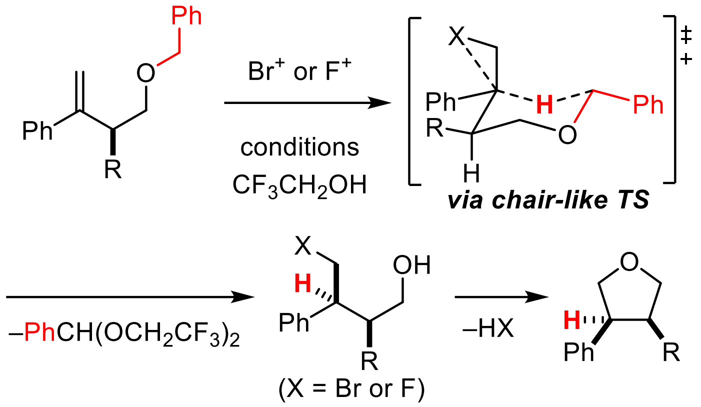
4.2 Working Hypothesis

In Chapter 2, the author has demonstrated an intramolecular 1,5-hydride transfer process from alkyl ethers to a carbocation, which is generated from upon protonation of alkenes under Brønsted acid catalysis (Scheme 4.13). This process proceeds through a 6-membered ring chair-like transition state to construct stereogenic centers with a high level of diastereoselectivity.



Scheme 4.13 Brønsted acid catalysed 1,5-hydride transfer

The halonium intermediates derived from electrophilic halogenation of alkenes undergo ring-opening in the presence of appropriate internal or external nucleophile. However, the use of hydrides (H^-), which potentially enable hydrohalogenation of alkenes, have rarely been reported compared to carbon or heteroatom-based nucleophiles. Inspired by these backgrounds, the author hypothesized a ring opening of halonium ions, generated from electrophilic halogenation of homoallylic alcohol *O*-Bn ethers, with intramolecular 1,5-hydride transfer to enable *anti*-Markovnikov hydrohalogenation. The resulting diastereomerically enriched haloalkyl alcohols would undergo subsequent intramolecular nucleophilic substitution to furnish substituted tetrahydrofurans (Scheme 4.14).

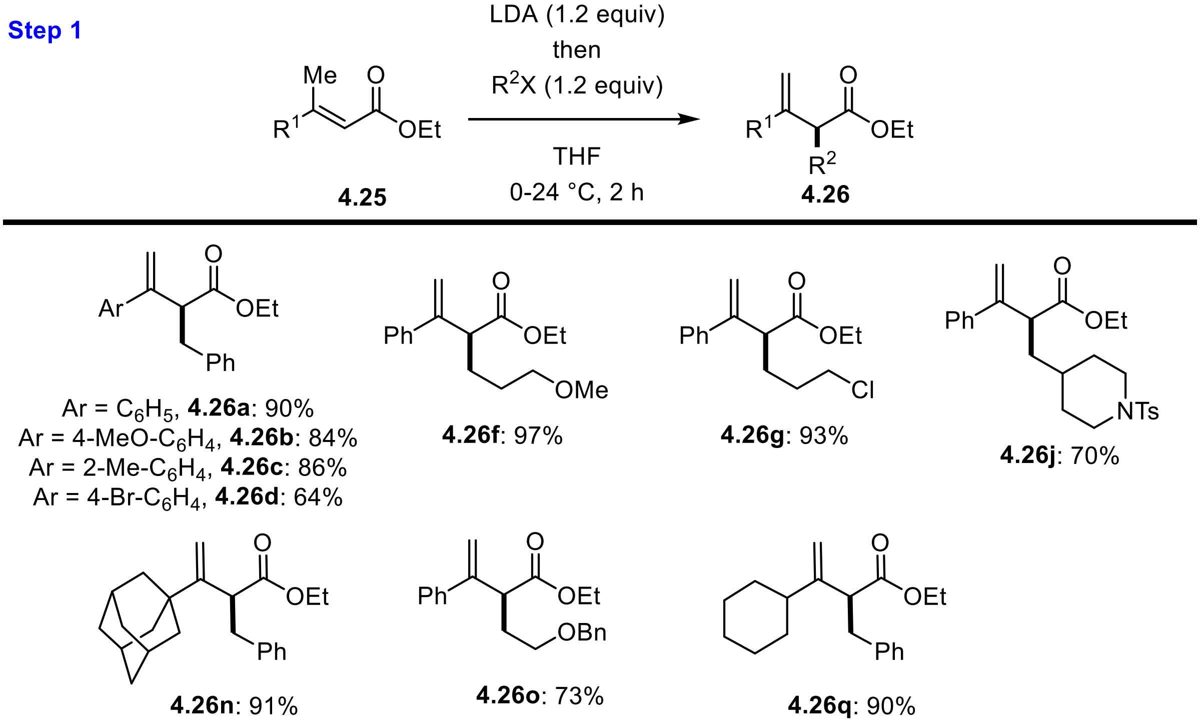


Scheme 4.14 Working Hypothesis

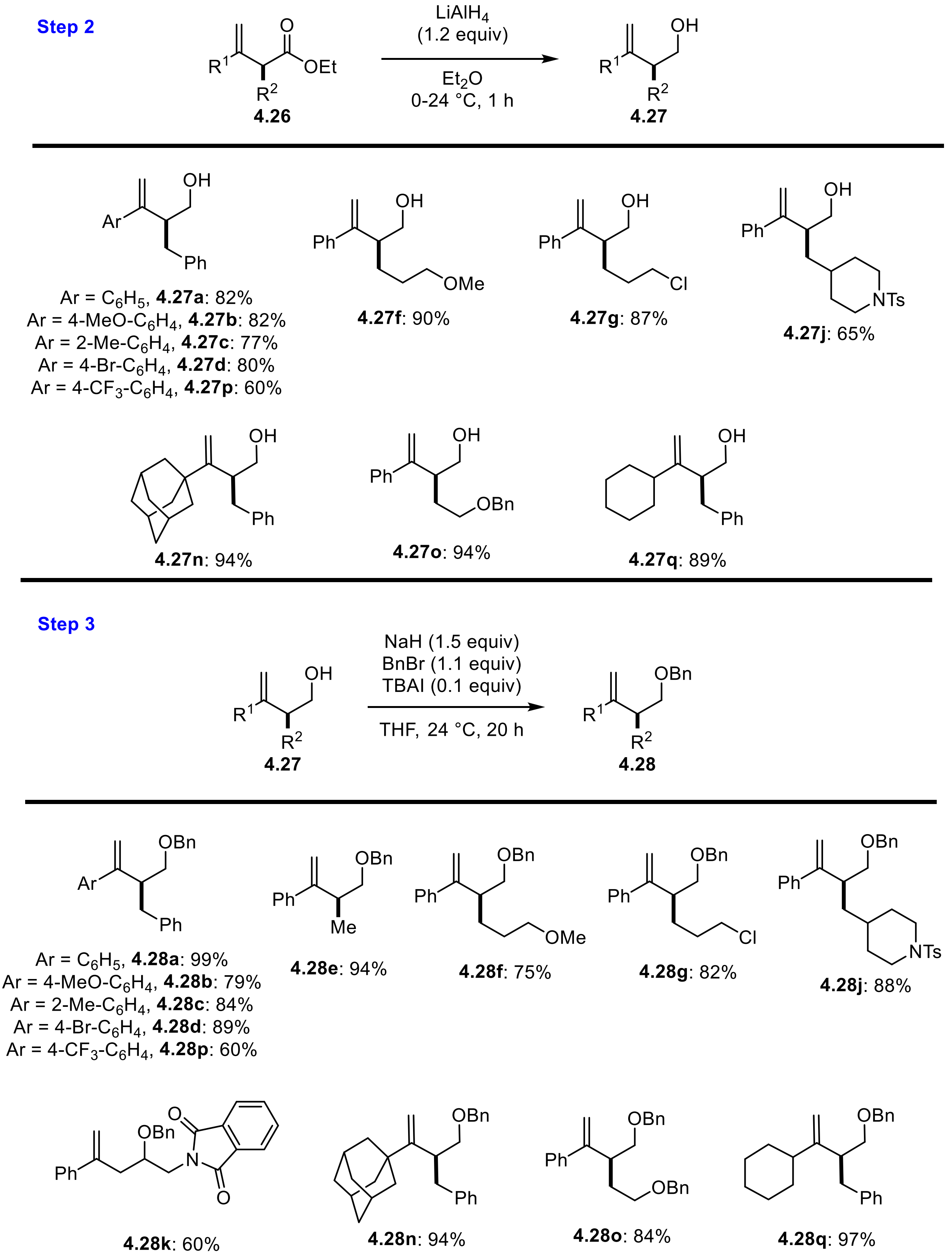
4.3 Results and Discussions

4.3.1 Substrate Synthesis

Homoallylic alcohol *O*-benzyl ethers **4.28a-4.28r** were prepared in 3-step syntheses, namely: 1) α-alkylation of *α,β*-unsaturated esters **4.25**[17] with the corresponding alkyl halides (Scheme 4.15); 2) reduction of esters **4.26** with $LiAlH_4$; and 3) benzyl protection of homoallylic alcohol **4.27** (Scheme 4.16).

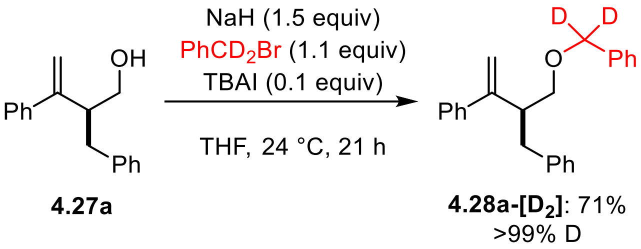


Scheme 4.15 Step 1 - alkylation of *α,β*-unsaturated esters



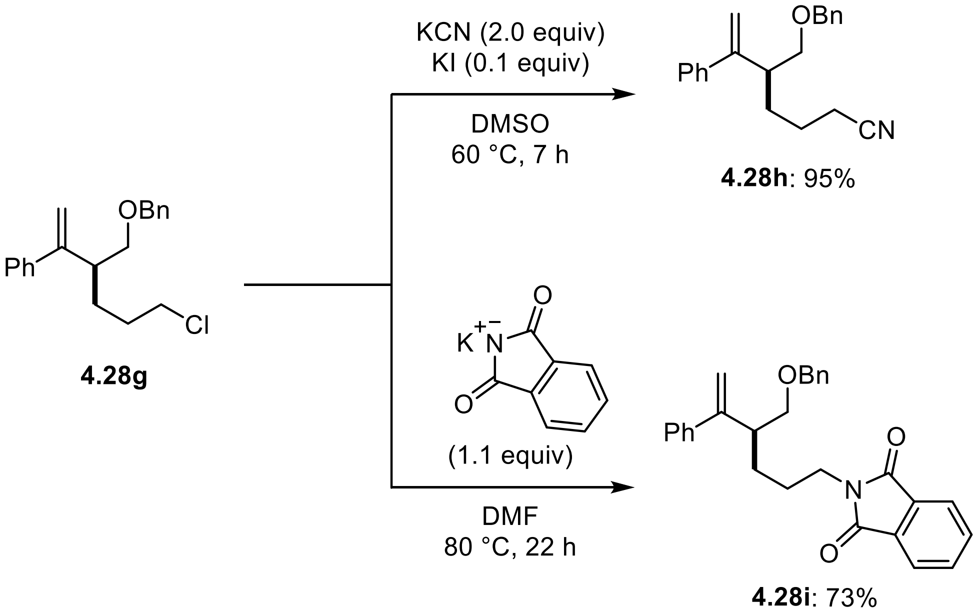
Scheme 4.16 Step 2&3 - reduction of esters to alcohol and benzyl protection of homoallylic alcohols

Deuterated benzyl ether **4.28a-[D2]** was synthesized from the benzylation of **4.27a** with deuterated benzyl bromide (Scheme 4.17).



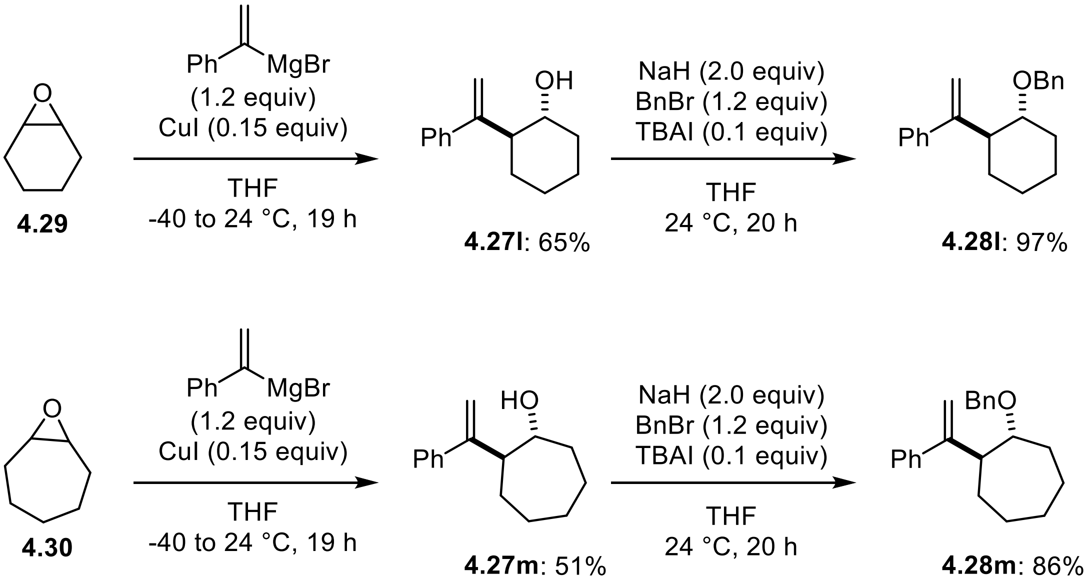
Scheme 4.17 Synthesis of **4.3a-[D2]**

Homoallylic alcohol *O*-benzyl ethers **4.28h** and **4.28i** were prepared via nucleophilic substitution of chloride **4.28g** with potassium cyanide and potassium phtalimide, respectively, in polar aprotic solvents (Scheme 4.18).



Scheme 4.18. Nucleophilic substitution of **4.28g**

Homoallylic alcohol *O*-benzyl ethers **4.28l** and **4.28m** were prepared in 2-step syntheses from cyclohexene oxide and cycloheptene oxide, respectively (Scheme 4.19). These epoxides were treated with (1-phenylvinyl)magnesium bromide in the presence of CuI as a catalyst to give homoallylic alcohol **4.27l** and **4.27m**. Benzyl protection in the presence of NaH and tetrabutylammonium iodide furnished benzyl ethers **4.28l** and **4.28m**.

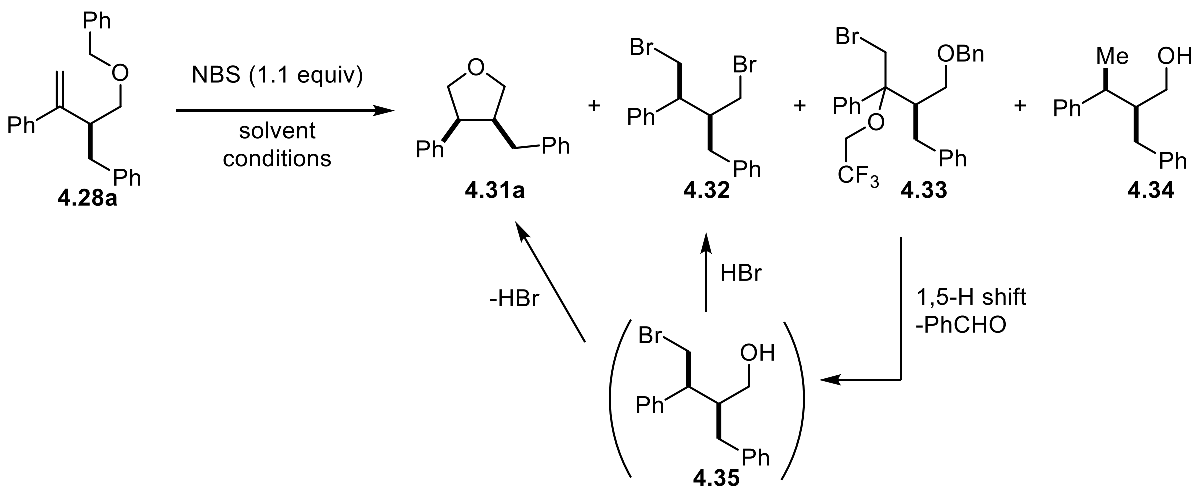


Scheme 4.19. Synthesis of **4.28l** and **4.28m**

4.3.2 Optimization of the reaction conditions

The reactions of **4.28a** with *N*-bromosuccinimide (NBS) were optimized by varying the reaction parameters (Table 4.1). The reaction in 2,2,2-trifluoroethanol (TFE) (0.1 M) at 50 °C led to the full conversion of **4.28a** within 4 h to afford tetrahydrofuran **4.31a** in 51% yield in 91:9 diastereomeric ratio along with acyclic dibromide **4.32** in 31% yield as a single diastereomer (entry 1). The formation of dibromide **4.32** should be mediated by bromination of the hydroxy group of bromoalcohol **4.35** by HBr and intramolecular substitution of **4.35** forms furan **4.31a** with elimination of HBr (**4.35** should be formed by 1,5-H shift from bromoetherificated intermediate **4.33**). Formation of dibromide **4.32** could be prevented by diluting the reaction to 0.05 M (entry 2), while another side product **4.34**, which is formed by protonation of alkene **4.28a**, was formed in 6% yield. It was found that the reaction of **4.28a** at room temperature (24 °C) affords ether **4.33** as a sole product via bromo-etherification within 10 min (entry 3). Treatment of **4.28a** with NBS at 24 °C for 10 min and then at 50 °C for 30 mins afforded tetrahydrofuran **4.31a** and bromoalcohol **4.35** in 37% and 45% yields, respectively (entry 4). Stirring of the reaction mixture for 4 h at 50 °C led to formation of tetrahydrofuran **4.31a** in 74% yield as a sole product in 91:9 diastereomeric ratio (entry 5). The reaction at 80 °C could accelerate the process, while the yield of **4.31a** was slightly decreased (entry 6). Other solvents such as 1,2-dichloroethane (DCE) and nitromethane were detrimental to the present process (entries 7 and 8). Therefore, entry 5 was adopted as the optimized conditions labeled as **Condition A**.

Table 4.1 Optimization Table for bromoetherification with NBS



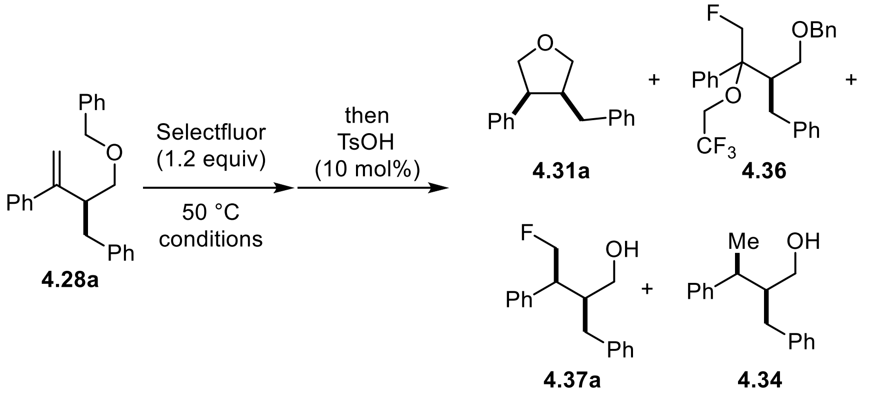
Entry[a]	Solvent (conc.)	Temp (°C)	Time (h)	**4.31a** (%) [d.r.][c]	**4.32** or **4.35** (%) [d.r.][c]	**4.33** (%) [d.r.][d]	**4.34** (%) [d.r.][c]
1	TFE (0.1 M)	50	4	51 [91:9]	**4.32** 31 [>99:1]	0	Trace [ND]
2	TFE (0.05 M)	50	8	71 [91:9]	**4.32** trace	0	6 [>99:1]
3	TFE (0.05 M)	24	0.2	0	0	76 [95:5]	0
4	TFE (0.05 M)	50[b]	0.5	37 [91:9]	**4.35** 45(17)[e,f] [90:10]	0	0
5	TFE (0.05 M)	50[b]	4	74 (74)[e] [91:9]	**4.32** trace	0	0
6	TFE (0.05 M)	80[b]	1	71 [91:9]	**4.32** trace	0	0
7[g]	DCE (0.05 M)	50	24	0	0	0	0
8[g]	$MeNO_2$ (0.05 M)	50	24	4 [ND]	0	0	0

[a]All the reactions were conducted using 0.3 mmol of **4.28a** and ^1H NMR yields of the products were measured using 1,1,2,2-tetrachloroethane as the internal standard. [b]The reaction was stirred at 24 °C for 10 min before heating at 50 °C. [c]The d.r. was determined by ^1H NMR spectroscopy. [d]The d.r. was determined by ^{19}F NMR spectroscopy. [e]Isolated yield. [f]We observed that isolated bromo alcohol **4.35** gradually cyclizes to tetrahydrofuran

4.31a at room temperature. [g]The reactions formed a complex mixture of unidentified compounds.

Next, the author investigated the processes that were initiated by electrophilic fluorination using Selectfluor (Table 4.2). Treatment of **4.28a** with Selectfluor (1.2 equiv) in 2,2,2-trifluoroethanol (0.1 M) at 50 °C for 24 h resulted in formation of fluorinated products **4.36** and **4.37a** in less than 10% combined yields along with alcohol **4.34** in 34% yield as the major product (entry 1). Formation of alcohol **4.34** should be triggered by protonation rather than fluorination under the present reaction conditions (that is followed by 1,5-hydride shift). It was found that the use of nitromethane ($MeNO_2$) as the solvent is a key to promote the desired fluorination as the major pathway. The reaction in $MeNO_2$ gave fluoroalcohol **4.37a** in 44% yield as a single diastereomer (entry 2). Use of the co-solvent system of $MeNO_2-CF_3CH_2OH$ (1:1) resulted in complete conversion of **4.28a** within 2 h to give fluoroetherificated intermediate **4.36** in 52% yield along with fluoroalcohol **4.37a** in 24% yield (entry 3), while prolonging the reaction time to 24 h did not enhance further conversion of **4.36** into **4.37a** (entry 4). Addition of 10 mol% of TsOH was found effective to promote 1,5-hydride shift from intermediate **4.36**. After treatment of **4.28a** with Selectfluor for 2 h, 10 mol% of TsOH was added and the mixture was stirred for 24 h, that afforded a mixture of **4.36**, fluoroalcohol **4.37a** and cyclized tetrahydrofuran **4.31a** in 21%, 30% and 36% yields, respectively (entry 5). Prolonging the reaction time to 48 h successfully enabled complete conversion of **4.37a** and **4.36** to **4.31a**, affording tetrahydrofuran **4.31a** in 82% yield (75% isolated yield) with 96:4 diastereomeric ratio (entry 6). The diastereomeric ratio was slightly reduced during the conversion from **4.37a** (>99:1) to furan **4.31a** (96:4). Fluoroetherificated intermediate **4.36** was obtained as a mixture of two diastereomers and their ratio varies depending on the reaction conditions employed (see entries 1, 3-5). This diastereomeric ratio does not affect the selectivity during the subsequent 1,5-hydride shift step. Entry 6 was therefore adopted as the optimized condition and labelled as **Condition B**.

Table 4.2 Optimization Table for fluoroetherification with Selectfluor



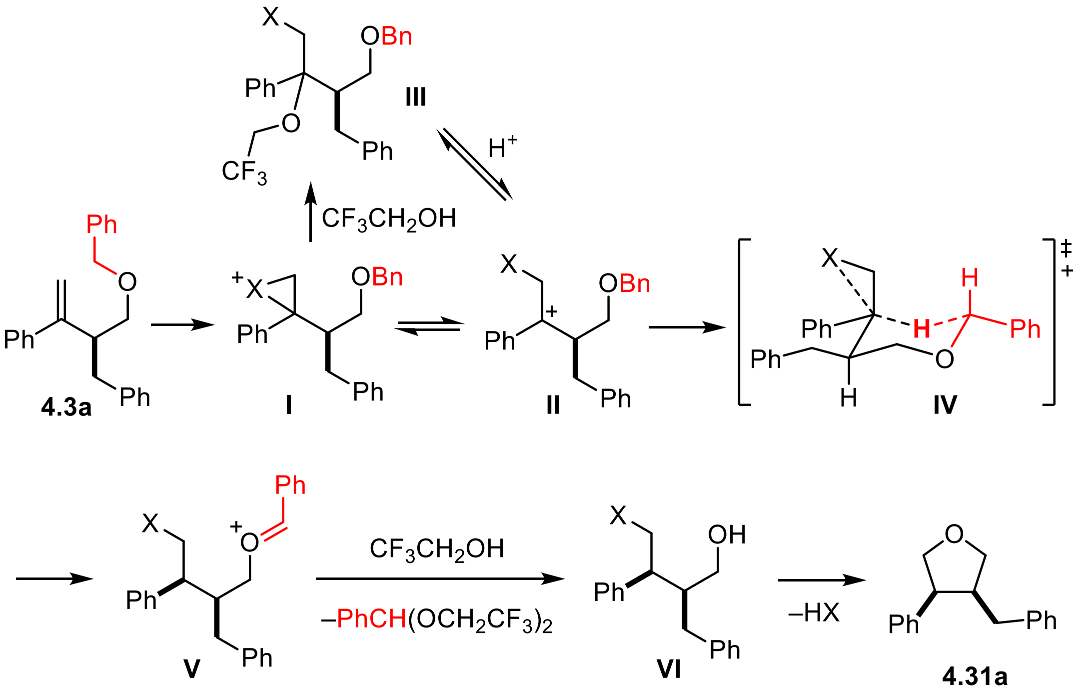
Entry[a]	Solvent (conc.)	Time (h)	Acid	**4.31a** (%)[b] [d.r.][d]	**4.36** (%)[c] [d.r.][e]	**4.37a** (%)[c] [d.r.][e]	**4.34** (%)[b] [d.r.][d]
1	TFE (0.1 M)	24	–	0	2 [36:64]	7 [>99:1]	34 [>99:1]
2	$MeNO_2$ (0.1 M)	24	–	0	0	44 [>99:1]	0
3	$MeNO_2$-TFE (1:1, 0.1 M)	2	–	0	52 [85:15]	24 [>99:1]	0
4	$MeNO_2$-TFE (1:1, 0.1 M)	24	–	0	29 [82:18]	16 [>99:1]	0
5	$MeNO_2$-TFE (1:1, 0.1 M)	2[f] +24	TsOH	36 [95:5]	21 [68:32]	30 [>99:1]	0
6	$MeNO_2$-TFE (1:1, 0.1 M)	2[f] + 48	TsOH	82(76)[g] [96:4]	0	0	0

[a]The reactions were conducted at 0.3 mmol scale. [b]^{1}H NMR yield with 1,1,2,2-tetrachloroethane as internal standard. [c]^{19}F NMR yield with $PhCF_3$ as internal standard. [d]The d.r. was determined by ^{1}H NMR spectroscopy. [e]The d.r was determined by ^{19}F NMR spectroscopy. [f]The reaction mixture was stirred for 2 h before addition of TsOH. [g]Isolated yield in parentheses.

The use of NBS (**Conditions A**) allows for milder reaction conditions and shorter reaction time, however the use of Selectfluor (**Conditions B**) allows higher diastereocontrol of tetrahydrofurans and fluoroalcohols which will be discussed in Scheme 4.26.

4.3.3 Proposed Reaction Mechanism

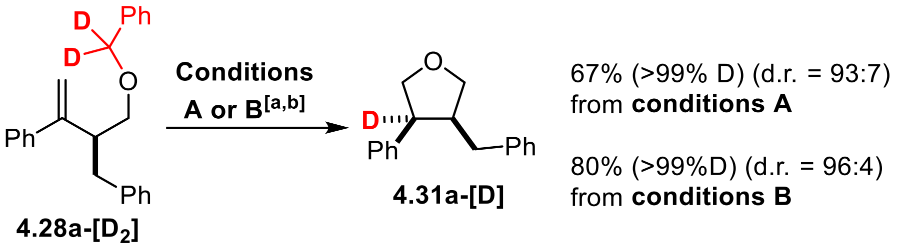
The proposed mechanism of this transformation was initiated by the formation of halonium ion **I**, which was under equilibrium with the tertiary benzylic carbocation **II** via trifluoroethyl ethers **III** (Scheme 4.20). The subsequent 1,5-hydride shift from electron-rich hydride from benzyl ether to the carbocation **II** proceeded via a 6-membered chairlike transition state **IV** where more sterically demanding phenyl and benzyl groups were positioned at the pseudo equatorial positions. Solvolysis of the resulting oxocarbenium ion **V** provided 4-halobutanols **VI** in a diastereoselective manner, which would finally undergo cyclization via intramolecular nucleophilic substitution to form 3,4-*cis*-disubstituted tetrahydrofuran **4.31a.**



Scheme 4.20 Proposed reaction mechanism

The reaction of deuterated **4.28a-[D₂]** resulted in >99% deuterium incorporation at the C3 position of **4.31a-[D]** for both reactions conducted in Selectfluor and NBS (Scheme 4.21).

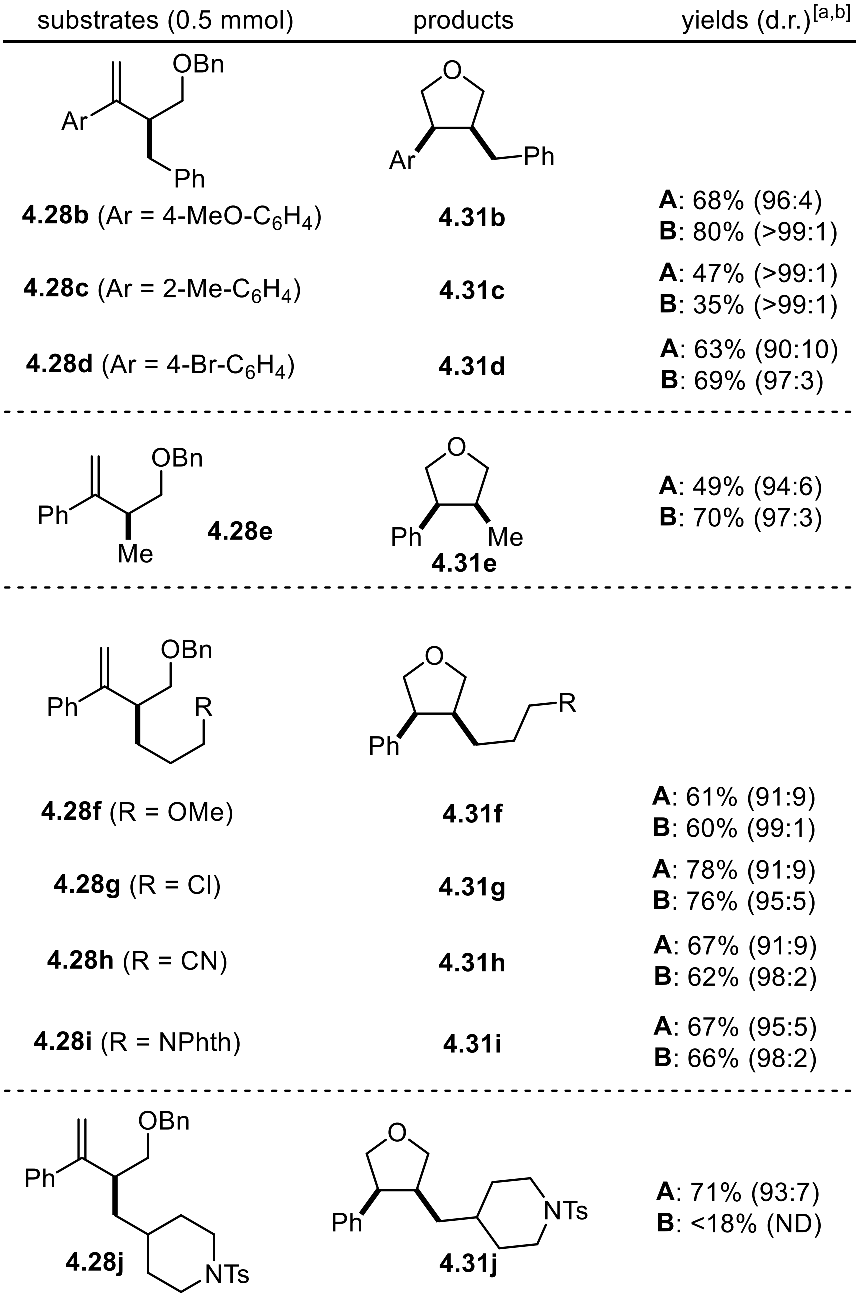
These results unambiguously proved the presence of the 1,5-hydride shift process from the electron-rich benzyl ether moiety.



Scheme 4.21 Deuterium labeling experiments. [a]Reaction conditions A: **4.28a-[D$_2$]** (0.5 mmol), NBS (1.1 equiv), CF_3CH_2OH (6 mL, 0.05 M), r.t., 10 min, then 50 °C, 4 h. [b]Reaction conditions B: **4.28a-[D$_2$]** (0.5 mmol), Selectfluor (1.2 equiv), $MeNO_2$–CF_3CH_2OH (1:1, 5 mL, 0.1 M), 50 °C, 2 h, then TsOH (10 mol%), 50 °C, 48 h.

4.3.4 Scopes and limitations

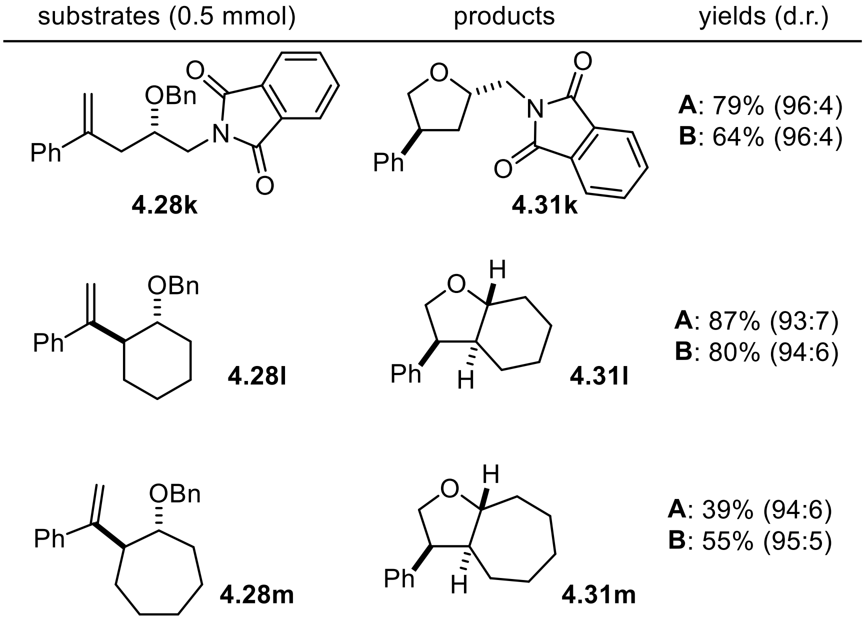
To examine the substrate compatibility, the author investigated the substituent effect of the alkenes **4.28** for the synthesis of 3,4-*cis*-disubstituted tetrahydrofurans **4.31** (Scheme 4.22). As a result, both electron-rich and -deficient aryl groups could be installed (for **4.31b**−**4.31d**), whereas the use of a sterically hindered *ortho*-tolyl group resulted in a sluggish process, providing the corresponding tetrahydrofuran **4.31c** in moderate yields under both reaction conditions A and B. Introduction of a methyl group at the allylic position of the substrate did not influence the diastereoselectivity (for **4.31e**). The method also tolerated the presence of various functional groups such as methyl ether, chloride, cyanide, and phthalimide (for **4.31f**−**4.31i**). Construction of tetrahydrofuran **4.31j** having an *N*-tosylpiperidine moiety was successful under the reaction conditions A with NBS, while the use of Selectfluor (conditions B) gave a complex mixture of unidentified compounds probably due to the oxidation of the piperidine moiety by Selectfluor.



substrates (0.5 mmol)	products	yields (d.r.)[a,b]
4.28b (Ar = 4-MeO-C_6H_4)	**4.31b**	**A**: 68% (96:4) **B**: 80% (>99:1)
4.28c (Ar = 2-Me-C_6H_4)	**4.31c**	**A**: 47% (>99:1) **B**: 35% (>99:1)
4.28d (Ar = 4-Br-C_6H_4)	**4.31d**	**A**: 63% (90:10) **B**: 69% (97:3)
4.28e	**4.31e**	**A**: 49% (94:6) **B**: 70% (97:3)
4.28f (R = OMe)	**4.31f**	**A**: 61% (91:9) **B**: 60% (99:1)
4.28g (R = Cl)	**4.31g**	**A**: 78% (91:9) **B**: 76% (95:5)
4.28h (R = CN)	**4.31h**	**A**: 67% (91:9) **B**: 62% (98:2)
4.28i (R = NPhth)	**4.31i**	**A**: 67% (95:5) **B**: 66% (98:2)
4.28j	**4.31j**	**A**: 71% (93:7) **B**: <18% (ND)

Scheme 4.22 Synthesis of 3,4-*cis*-disubstituted tetrahydrofurans [a]Reaction conditions A: **4.28** (0.3 mmol), NBS (1.1 equiv), CF_3CH_2OH (6 mL, 0.05 M), r.t., 10 min, then 50 °C, 4 h. [b]Reaction conditions B: **4.28** (0.5 mmol), Selectfluor (1.2 equiv), $MeNO_2$–CF_3CH_2OH (1:1, 5 mL, 0.1 M), 50 °C, 2 h, then TsOH (10 mol%), 50 °C, 48 h.

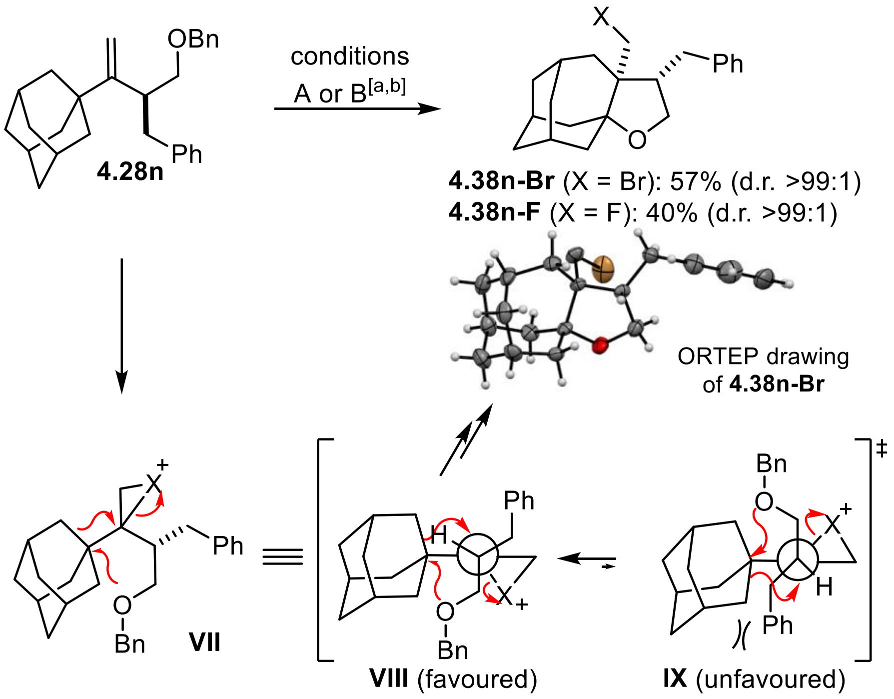
This strategy allows for the construction of 2,4-*trans*-disubstituted tetrahydrofuran **4.31k** from the introduction of substituent at the homoallylic position of the alkene **4.28k**, for which both reaction conditions A and B led to high diastereoselectivities (Scheme 4.23). Similarly, 2,3,4-trisubstituted bicyclic tetrahydrofurans **4.31l** and **4.31m** could be synthesized, albeit with moderate efficiency in the case of **4.31m**.



Scheme 4.23. Synthesis of **4.31k**, **4.31l** and **4.31m** [a]Reaction conditions A: **4.28** (0.3 mmol), NBS (1.1 equiv), CF_3CH_2OH (6 mL, 0.05 M), r.t., 10 min, then 50 °C, 4 h. [b]Reaction conditions B: **4.28** (0.5 mmol), Selectfluor (1.2 equiv), $MeNO_2$−CF_3CH_2OH (1:1, 5 mL, 0.1 M), 50 °C, 2 h, then TsOH (10 mol%), 50 °C, 48 h.

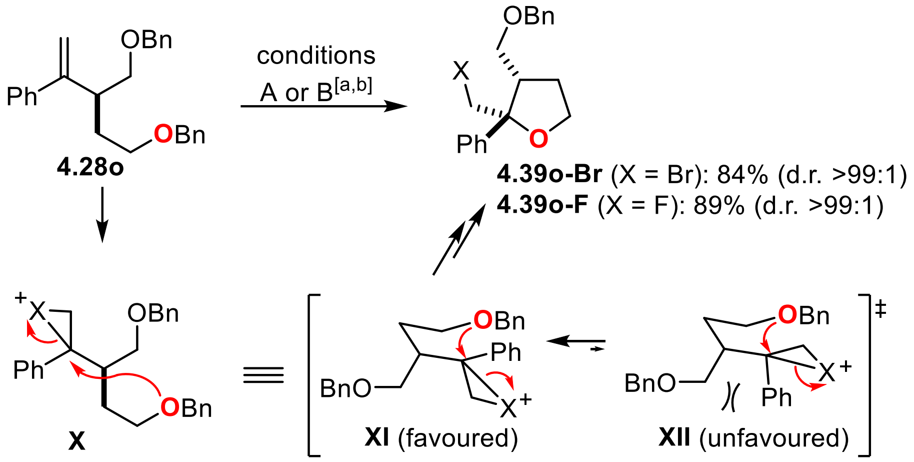
During the substrate scope study, we observed several cases in which the desired 1,5-hydride shift was interrupted. For example, the reactions of adamantyl derivative **4.28n** produced the intriguing polycyclic tetrahydrofurans **4.38n-Br** and **4.38n-F** having a halomethyl tether at the C3 position as a single diastereomer (Scheme 4.24). In this case, a

Wagner−Meerwein type 1,2-carbon shift to the halonium ion intermediates **VII**[18] and concomitant cyclization of the benzyl ether tether could account for the formation of **4.38n**. In this mechanistic scenario, conformation **VIII** would be energetically favored over conformation **IX** having a steric clash between the benzyl tether and adamantyl moiety.



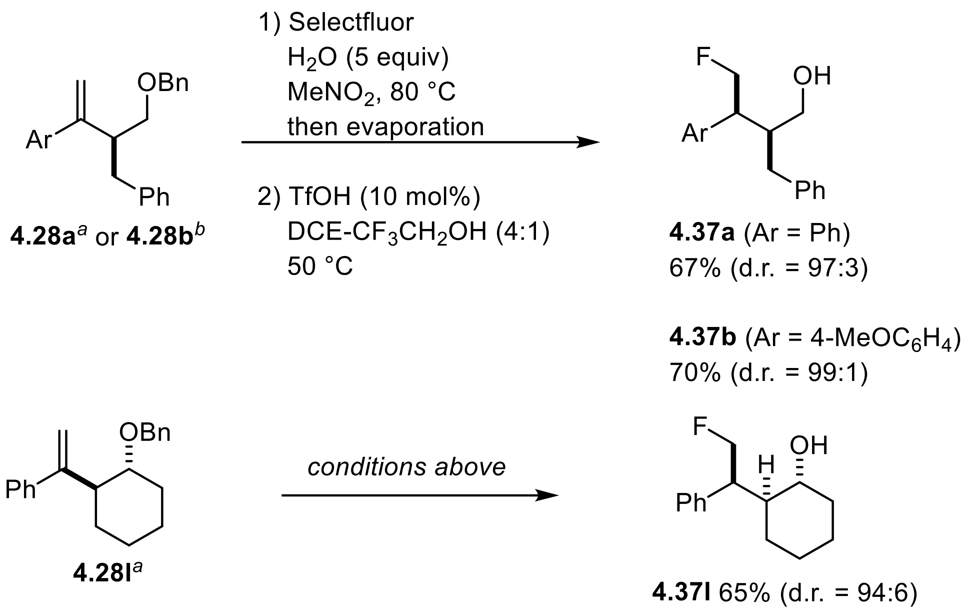
Scheme 4.24. 1,2-Carbon shift over 1,5-hydride shift. [a]Reaction conditions A: **4.28** (0.3 mmol), NBS (1.1 equiv), CF_3CH_2OH (6 mL, 0.05 M), r.t., 10 min, then 50 °C, 4 h. [b]Reaction conditions B: **4.28** (0.5 mmol), Selectfluor (1.2 equiv), $MeNO_2$−CF_3CH_2OH (1:1, 5 mL, 0.1 M), 50 °C, 2 h, then TsOH (10 mol%), 50 °C, 48 h.

Substrate **4.28o** having a benzyloxyethyl tether at the allylic position gave the C2-halomethyl tetrahydrofurans **4.39o-Br** and **4.39o-F** as a single diastereomer (Scheme 4.25). In this case, the nucleophilic attack of the ethereal oxygen to the halonium ion **X** was more favorable than the 1,5-hydride shift.[19] The observed diastereoselectivity could be explained by the involvement of halonium ion **XI**, a conformer that would be more favorable than **XII** due to the presence of the bulkier phenyl group at a pseudo equatorial position.



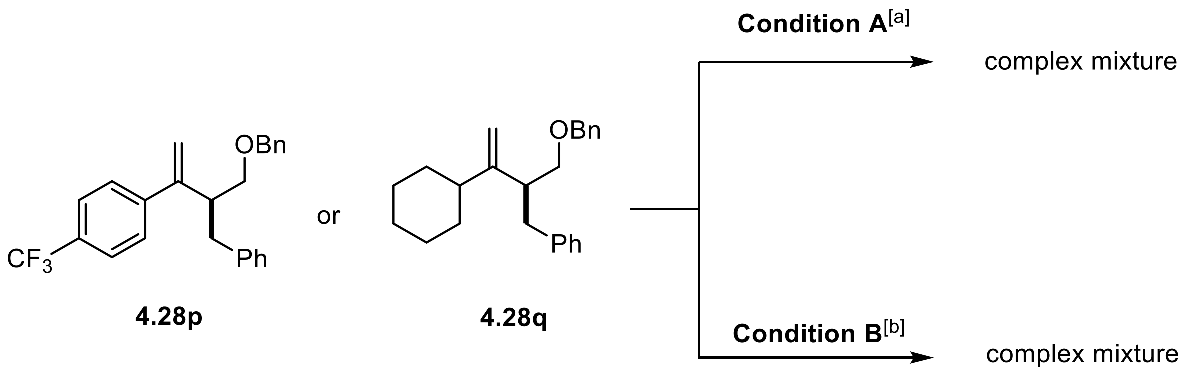
Scheme 4.25. Haloetherification over 1,5-hydride shift. [a]Reaction conditions A: **4.28** (0.3 mmol), NBS (1.1 equiv), CF_3CH_2OH (6 mL, 0.05 M), r.t., 10 min, then 50 °C, 4 h. [b]Reaction conditions B: **4.28** (0.5 mmol), Selectfluor (1.2 equiv), $MeNO_2$−CF_3CH_2OH (1:1, 5 mL, 0.1 M), 50 °C, 2 h, then TsOH (10 mol%), 50 °C, 48 h.

Further modification of the reaction conditions B led to the development of an alternative stepwise protocol for the synthesis of fluoroalcohols as the major products (Scheme 4.26). A fluorohydroxylation step was first implemented by treating alkenes **4.28** with Selectfluor in the presence of water (5 equiv) in $MeNO_2$. The solvent system was then switched to 1,2- dichloroethane (DCE)−trifluoroethanol (4:1), and the resulting crude mixture was treated with trifluoromethanesulfonic acid (TfOH) (10 mol%) at 50 °C for a short period of time in order to prevent the substitution step. Under these conditions, fluoroalcohol **4.37a, 4.37b** and **4.37l** could be obtained in good yield with high diastereoselectivity.



Scheme 4.26. Synthesis of Fluoroalcohols **4.37** [a]Reaction conditions: **4.28a** or **4.28l** (0.55 mmol), Selectfluor (0.5 mmol). Isolated yields were measured based on Selectfluor. [b]Reaction conditions: **4.28b** (0.5 mmol), Selectfluor (0.6 mmol). Isolated yield was measured based on **4.28b**.

Unfortunately, benzyl ether **4.28p** and **4.28q** bearing 4-trifluoromethylphenyl and cyclohexyl moiety respectively were unable to perform the desired transformations in both conditions A and B as they gave unidentified complex mixtures (Scheme 4.27). This could be reasoned by the instability of the corresponding electron-poor benzylic and α-cyclohexyl carbocations generated upon halogenation under the present reaction conditions.



Scheme 4.27. Unsuccessful substrates. [a]Reaction conditions A: **4.28** (0.3 mmol), NBS (1.1 equiv), CF_3CH_2OH (6 mL, 0.05 M), r.t., 10 min, then 50 °C, 4 h. [b]Reaction conditions B: **4.28** (0.5 mmol), Selectfluor (1.2 equiv), $MeNO_2$–CF_3CH_2OH (1:1, 5 mL, 0.1 M), 50 °C, 2 h, then TsOH (10 mol%), 50 °C, 48 h.

4.4. Conclusions

In this chapter, the author demonstrated the synthesis of stereochemically defined tetrahydrofurans by a cascade process involving a diastereoselective 1,5-hydride shift to a halonium ion intermediate as the key step. Overall, this transformation can be regarded as a formal intramolecular *anti*-Markovnikov hydroetherification of an aryl alkene, a reactivity scheme that has been rarely reported in the literature.

4.5 References

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Chapter 5. Experimental Section

5.1 General Information

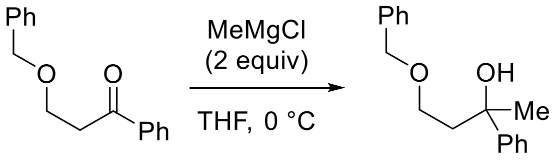
^{1}H NMR spectra (300, 400 and 500 MHz) were recorded on a Bruker Avance 300, 400, 500 and JEOL ECA400 spectrometer using $CDCl_3$ [using TMS (for ^{1}H, $\delta = 0.00$) as internal standard]. ^{13}C NMR spectra (100 or 125 MHz) were recorded on a Bruker Avance 400, 500 or JEOL ECA400 spectrometer in $CDCl_3$ [using $CDCl_3$ (for ^{13}C, $\delta = 77.00$) as internal standard]. ^{19}F NMR spectra (282 or 376 MHz) were recorded on a Bruker Avance 300, 400 or JEOL ECA400 spectrometer in $CDCl_3$. High-resolution mass spectra were obtained with a Waters Q-Tof Premier mass spectrometer. X-ray crystallography analysis was performed on Bruker X8 APEX X-ray diffractionmeter. Gel permeation chromatography (GPC) was performed on LaboACE LC-5060 recycling preparative HPLC. IR spectra were recorded using a Shimadzu IR Prestige-21 FT-IR spectrometer. All the reactions were conducted using flame dried reaction vessels under a N_2 atmosphere. Flash chromatography was performed using Merck silica gel 60 with distilled solvents. Other solvents such as tetrahydrofuran (THF), acetonitrile (MeCN), dichloromethane (CH_2Cl_2), and diethyl ether (Et_2O) were taken from a solvent purification system (PS-400-5, innovative technology Inc.). 2,2,2-Trifluoroethanol and Selectfluor were obtained from Fluorochem Ltd. and Sigma Aldrich, respectively and used as received. *N*-Bromosuccinimide was purchased from Sigma Aldrich and recrystallized from boiling water before use.[1] Other reagents and solvents, unless otherwise noted, were commercially available and used as received.

5.2 Diastereoselective Intramolecular Hydride Transfer under Brønsted Acid Catalysis (Chapter 2)

5.2.1 Alkyl Ethers as Traceless Hydride Donors (Chapter 2, Section 2.3)

5.2.1.1. Synthesis and characterization of the starting materials

5.2.1.1.1. Synthesis of 2.1a-Bn



2.1a-Bn 86%

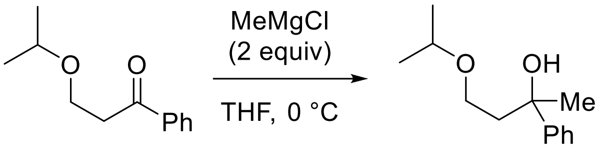
To a solution of 3-benzyloxy-1-phenylpropan-1-one[2] (490 mg, 2.04 mmol) in THF (4 mL) was added methylmagnesium chloride (3.0 M in THF, 1.4 mL) at 0 °C under a N_2 atmosphere. After the reaction mixture was stirred at the same temperature for 15 min, the reaction was quenched with saturated aqueous NH_4Cl solution. Organic materials were extracted thrice with Et_2O and the combine extracts were washed with brine and dried over $MgSO_4$. The volatile materials were removed *in vacuo* and the resulting crude material was purified by flash column chromatography (silica gel, *n*-Hex:EtOAc = 95:5) to yield 4-(benzyloxy)-2-phenylbutan-2-ol (**2.1a-Bn**) in 86% yield (441 mg, 1.72 mmol) as a colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 7.42–7.41 (m, 2H), 7.34–7.20 (m, 8H), 4.38 (d, *J* = 12.0 Hz, 1H), 4.34 (d, *J* = 12.0 Hz, 1H), 4.21 (s, 1 H), 3.58 (ddd, *J* = 10.0, 5.0, 5.0 Hz, 1H), 3.34 (ddd, *J* = 10.0, 10.0, 3.5 Hz, 1H), 2.22 (ddd, *J* = 15.0, 10.0, 5.0 Hz, 1H), 2.06 (ddd, *J* = 15.0, 5.0, 3.5 Hz, 1H), 1.52 (s, 3H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 147.7, 137.5, 128.4, 128.0, 127.8, 127.7, 126.2, 124.9, 75.0, 73.4, 68.0, 42.0, 30.9.

MS (HRMS ESI) Calcd for $C_{17}H_{21}O_2$ $[M+H]^+$ 257.1542, Found: 257.1551.

5.2.1.1.2. Synthesis of 2.1a-iPr



2.1a-*i*Pr 99%

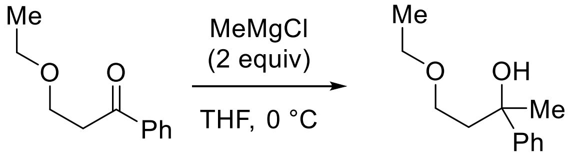
Alcohol **2.1a-*i*Pr** was synthesized using 3-isopropoxy-1-phenylpropan-1-one[3] (430 mg, 2.24 mmol) and methylmagnesium chloride (3.0 M in THF, 1.5 mL) following the procedure described in section 5.2.1.1.1. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 95:5) gave 99% yield (461 mg, 2.21 mmol) of 4-isopropoxy-2-phenylbutan-2-ol (**2.1a-*i*Pr**) as a colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 7.45–7.43 (m, 2H), 7.35–7.32 (m, 2H), 7.24–7.20 (m, 1H), 4.62 (s, 1H), 3.56 (ddd, *J* = 9.5, 4.5, 4.5 Hz, 1H), 3.38 (sept, *J* = 6.0 Hz, 1H), 3.23 (ddd, *J* = 9.5, 9.5, 3.0 Hz, 1H), 2.16 (ddd, *J* = 14.5, 9.5, 4.5 Hz, 1H), 2.02 (ddd, *J* = 14.5, 4.5, 3.0 Hz, 1H), 1.52 (s, 3H), 1.11 (d, *J* = 6.0 Hz, 3H), 1.05 (d, *J* = 6.0 Hz, 3H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 148.0, 128.0, 126.2, 125.0, 75.1, 72.3, 65.8, 42.0, 31.0, 22.0, 21.8.

MS (HRMS ESI) Calcd for $C_{13}H_{20}O_2Na$ $[M+Na]^+$ 231.1361, Found: 231.1353.

5.2.1.1.3. Synthesis of 2.1a-Et



2.1a-Et 77%

Alcohol **2.1a-Et** was synthesized using 3-ethoxy-1-phenylpropan-1-one[2] (180 mg, 1.01 mmol) and methylmagnesium chloride (3.0 M in THF, 0.7 mL) following the procedure described in section 5.2.1.1.1. Purification by flash column chromatography (silica gel, *n*-

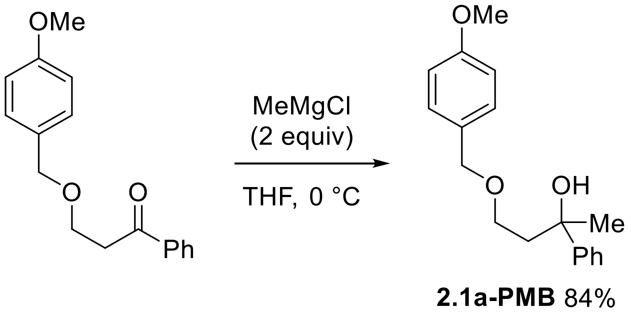
Hex:EtOAc, 95:5) gave 77% yield (151 mg, 0.775 mmol) of 4-ethoxy-2-phenylbutan-2-ol (**2.1a-Et**) as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.45–7.43 (m, 2H), 7.35–7.32 (m, 2H), 7.24–7.20 (m, 1H), 4.40 (s, 1H), 3.54 (ddd, J = 9.2, 4.4, 4.0 Hz, 1H), 3.43–3.24 (m, 3H), 2.17 (ddd, J = 14.8, 9.6, 4.4 Hz, 1H), 2.03 (ddd, J = 14.8, 4.0, 3.6 Hz, 1H), 1.53 (s, 3H), 1.15 (t, J = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 147.9, 128.0, 126.2, 124.8, 75.0, 68.2, 66.6, 41.9, 30.9, 15.0.

MS (HRMS ESI) Calcd for $C_{12}H_{19}O_2$ $[M+H]^+$ 195.1385, Found: 195.1391.

5.2.1.1.4. Synthesis of 2.1a-PMB



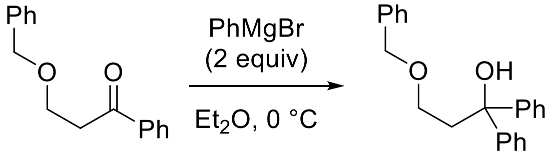
Synthesis of 2.1a-PMB: Alcohol **2.1a-PMB** was synthesized using 3-((4-methoxybenzyl)oxy)-1-phenylpropan-1-one (532 mg, 1.97 mmol) and methylmagnesium chloride (3.0 M in THF, 1.3 mL) following the procedure described in section 5.2.1.1.1. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 90:10) gave 84% yield (472 mg, 1.65 mmol) of 4-((4-methoxybenzyl)oxy)-2-phenylbutan-2-ol (**2.1a-PMB**) as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.42–7.39 (m, 2H), 7.34–7.30 (m, 2H), 7.24–7.20 (m, 1H), 7.20–7.15 (m, 2H), 6.87–6.83 (m, 2H), 4.32 (d, J = 11.2 Hz, 1H), 4.28 (d, J = 11.2 Hz, 1H), 4.26 (s, 1H), 3.80 (s, 3H), 3.57 (ddd, J = 9.6, 4.8, 4.8 Hz, 1H), 3.31 (ddd, J = 9.6, 9.6, 3.6 Hz, 1H), 2.20 (ddd, J = 14.8, 9.6, 4.8 Hz, 1H), 2.05 (ddd, J = 14.8, 4.8, 3.6 Hz, 1H), 1.51 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 159.3, 147.7, 129.6, 129.3, 128.0, 126.2, 124.8, 113.8, 75.0, 73.0, 67.7, 55.2, 41.9, 30.9.

MS (HRMS ESI) Calcd for $C_{18}H_{22}O_3Na$ [M+Na]$^+$ 309.1467, Found: 309.1461.

5.2.1.1.5. Synthesis of 2.1b-Bn



2.1b-Bn 89%

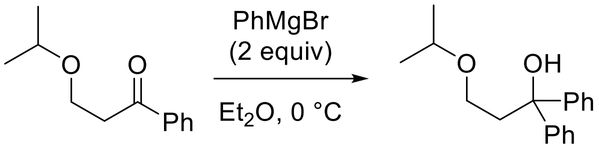
Alcohol **2.1b-Bn** was synthesized using 3-(benzyloxy)-1-phenylpropan-1-one (562 mg, 2.34 mmol) and phenylmagnesium bromide (3.0 M in Et_2O, 1.6 mL) following the procedure described in section 5.2.1.1.1. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 95:5) gave 89% yield (660 mg, 2.07 mmol) of 3-benzyloxy-1,1-diphenylpropan-1-ol (**2.1b-Bn**) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.45–7.43 (m, 4H) 7.33–7.19 (m, 11H), 4.81 (s, 1H), 4.40 (s, 2H), 3.60 (t, J = 5.6 Hz, 2H), 2.62 (t, J = 5.6 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 146.9, 137.3, 128.4, 128.1, 127.8, 127.6, 126.6, 125.9, 78.5, 73.4, 68.1, 40.0.

MS (HRMS ESI) Calcd for $C_{22}H_{22}O_2Na$ [M+Na]$^+$ 341.1517, Found: 341.1530.

5.2.1.1.6. Synthesis of 2.1b-*i*Pr



2.1b-*i*Pr 54%

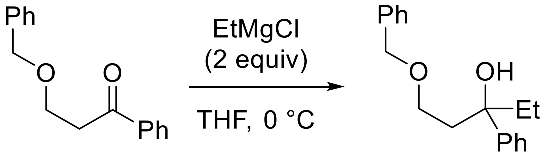
Alcohol **2.1b-*i*Pr** was synthesized using 3-isopropoxy-1-phenylpropan-1-one (385 mg, 2.00 mmol) and phenylmagnesium bromide (3.0 M in Et_2O, 1.4 mL) following the procedure described in section 5.2.1.1.1. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 95:5) gave 54% yield (289 mg, 1.07 mmol) of 3-isopropoxy-1,1-diphenylpropan-1-ol (**2.1b-*i*Pr**) as a colorless oil.

<u>^{1}H NMR (400 MHz, $CDCl_3$):</u> δ(ppm) 7.46–7.44 (m, 4H), 7.32–7.29 (m, 4H), 7.22–7.17 (m, 2H), 5.23 (s, 1H), 3.52 (t, *J* = 5.6 Hz, 2H), 3.39 (sept, *J* = 6.4 Hz, 1H), 2.56 (t, *J* = 5.6 Hz, 2H), 1.08 (d, *J* = 6.4 Hz, 6H),

<u>^{13}C NMR (100 MHz, $CDCl_3$):</u> δ(ppm) 147.1, 128.0, 126.6, 126.0, 78.6, 72.4, 65.8, 40.0, 21.9.

<u>MS (HRMS ESI)</u> Calcd for $C_{18}H_{23}O_2$ $[M+H]^+$ 271.1698, Found: 271.1684.

5.2.1.1.7. Synthesis of 2.1c-Bn



2.1c-Bn 41%

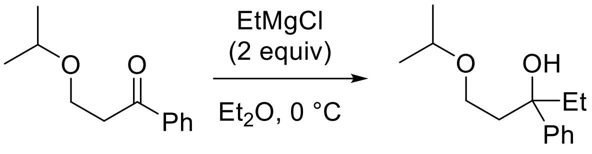
Alcohol **2.1c-Bn** was synthesized using 3-(benzyloxy)-1-phenylpropan-1-one (481 mg, 2.00 mmol) and ethylmagnesium chloride (2.0 M in Et_2O, 2.0 mL) following the procedure described in section 5.2.1.1.1. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 95:5) gave 41% yield (218 mg, 0.805 mmol) of 1-benzyloxy-3-phenylpentan-3-ol (**2.1c-Bn**) as a colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 7.38–7.36 (m, 2H), 7.33–7.20 (m, 8H), 4.35 (d, *J* = 11.5 Hz, 1H), 4.30 (d, *J* = 11.5 Hz, 1H), 4.15 (s, 1H), 3.56 (ddd, *J* = 9.5, 4.5, 4.5 Hz, 1H), 3.32 (ddd, *J* = 9.5, 9.5, 3.5 Hz, 1H), 2.27 (ddd, *J* = 14.5, 9.5, 4.5 Hz, 1H), 2.01 (ddd, *J* = 14.5, 4.5, 3.5 Hz, 1H), 1.86–1.76 (m, 2H), 0.75 (dd, *J* = 7.0, 7.0 Hz, 3H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 146.0, 137.5, 128.4, 127.9, 127.7, 127.6, 126.1, 125.5, 77.4, 73.4, 68.0, 40.6, 36.3, 7.6.

MS (HRMS ESI) Calcd for $C_{18}H_{23}O_2$ [M+H]$^+$ 271.1698, Found: 271.1702.

5.2.1.1.8. Synthesis of 2.1c-*i*Pr



2.1c-*i*Pr 92%

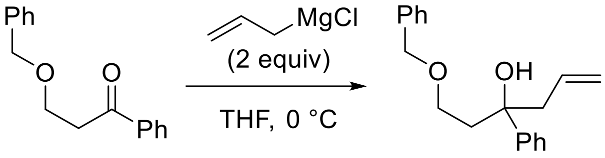
Alcohol **2.1c-*i*Pr** was synthesized using 3-isopropoxy-1-phenylpropan-1-one (559 mg, 2.90 mmol) and ethylmagnesium chloride (2.0 M in Et$_2$O, 3.0 mL) following the procedure described in section 5.2.1.1.1. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 95:5) gave 92% yield (597 mg, 2.69 mmol) of 1-isopropoxy-3-phenylpentan-3-ol (**2.1c-*i*Pr**) as a colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 7.41–7.39 (m, 2H), 7.34–7.31 (m, 2H), 7.23–7.19 (m, 1H), 4.58 (s, 1H), 3.53 (ddd, *J* = 10.0, 4.0, 4.0 Hz, 1H), 3.33 (sept, *J* = 6.0 Hz, 1H), 3.19 (ddd, *J* = 10.0, 9.5, 3.5 Hz, 1H), 2.20 (ddd, *J* = 14.5, 9.5, 4.0 Hz, 1H), 1.96 (ddd, *J* = 14.5, 4.0, 3.5 Hz, 1H), 1.84–1.75 (m, 2H), 1.08 (d, *J* = 6.0 Hz, 3H), 1.02 (d, *J* = 6.0 Hz, 3H), 0.76 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 146.2, 127.8, 126.0, 125.6, 77.5, 72.2, 65.6, 40.6, 36.4, 21.9, 21.7, 7.6.

MS (HRMS ESI) Calcd for $C_{14}H_{22}O_2Na$ $[M+Na]^+$ 245.1517, Found: 245.1525.

5.2.1.1.9. Synthesis of 2.1d-Bn



2.1d-Bn 92%

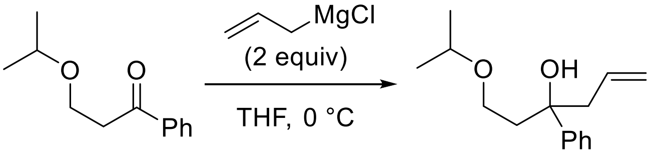
Alcohol **2.1d-Bn** was synthesized using 3-(benzyloxy)-1-phenylpropan-1-one (491 mg, 2.04 mmol) and allylmagnesium chloride (2.0 M in THF, 2.0 mL) following the procedure described in section 5.2.1.1.1. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 95:5) gave 92% yield (529 mg, 1.87 mmol) of 1-benzyloxy-3-phenylhex-5-en-3-ol (**2.1d-Bn**) as a colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 7.39–7.38 (m, 2H), 7.34–7.21 (m, 8H), 5.73–5.63 (m, 1H), 5.03 (d, *J* = 19.0 Hz, 1H), 5.02 (d, *J* = 8.0 Hz, 1H), 4.35 (d, *J* = 12.0 Hz, 1H), 4.31 (d, *J* = 12.0 Hz, 1H), 4.11 (s, 1H), 3.54 (ddd, *J* = 9.0, 4.5, 4.5 Hz, 1H), 3.36 (ddd, *J* = 9.0, 9.0, 3.5 Hz, 1H), 2.59 (dd, *J* = 14.0, 6.5 Hz, 1H), 2.53 (dd, *J* = 14.0, 8.0 Hz, 1H), 2.28 (ddd, *J* = 14.0, 9.0, 4.5 Hz, 1H), 2.04 (ddd, *J* = 14.0, 4.5, 3.5 Hz, 1H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 145.9, 137.5, 133.9, 128.4, 128.0, 127.7, 127.6, 126.3, 125.4, 117.9, 76.6, 73.3, 67.7, 48.2, 40.2.

MS (HRMS ESI) Calcd for $C_{19}H_{23}O_2$ $[M+H]^+$ 283.1698, Found: 283.1709.

5.2.1.1.10. Synthesis of 1d-*i*Pr



2.1d-*i*Pr 92%

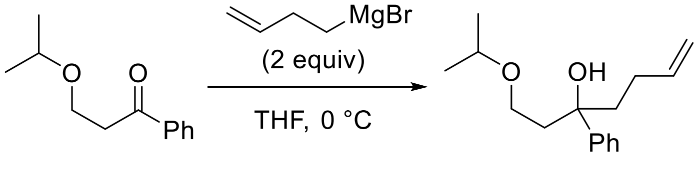
Alcohol **2.1d-*i*Pr** was synthesized using 3-isopropoxy-1-phenylpropan-1-one (360 mg, 1.87 mmol) and allylmagnesium chloride (2.0 M in THF, 1.9 mL) following the procedure described in section 5.2.1.1.1. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 95:5) gave 92% yield (402 mg, 1.72 mmol) of 1-isopropoxy-3-phenylhex-5-en-3-ol (**2.1d-*i*Pr**) as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.42–7.40 (m, 2H), 7.35–7.31 (m, 2H), 7.23–7.19 (m, 1H), 5.71 (dddd, *J* = 17.2, 10.4, 6.4, 6.4 Hz, 1H), 5.05–4.99 (m, 2H), 4.58 (s, 1H), 3.51 (ddd, *J* = 9.6, 4.0, 4.0 Hz, 1H), 3.33 (sept, *J* = 6.4 Hz, 1H), 3.21 (ddd, *J* = 9.6, 9.6, 3.6 Hz, 1H), 2.60–2.49 (m, 2H), 2.23 (ddd, *J* = 14.8, 9.6, 4.0 Hz, 1H), 1.99 (ddd, *J* = 14.8, 4.0, 3.6 Hz, 1H), 1.07 (d, *J* = 6.4 Hz, 3H), 1.02 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 146.0, 134.0, 127.8, 126.2, 125.4, 117.5, 76.7, 72.1, 65.4, 48.3, 40.1, 21.9, 21.7.

MS (HRMS ESI) Calcd for $C_{15}H_{23}O_2$ $[M+H]^+$ 235.1698, Found: 235.1705.

5.2.1.1.11. Synthesis of 2.1e-*i*Pr



2.1e-*i*Pr 31%

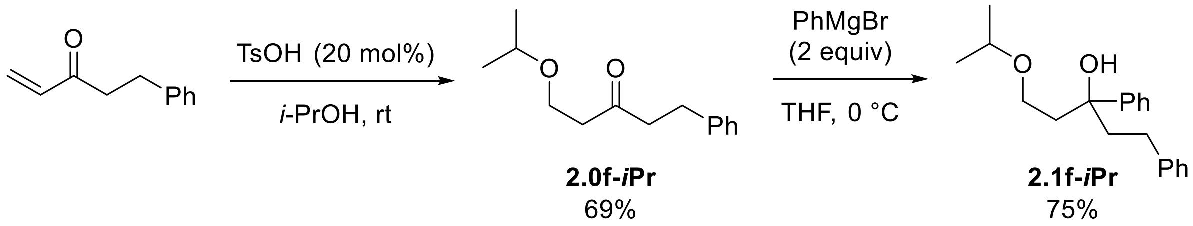
Alcohol **2.1e-*i*Pr** was synthesized using 3-isopropoxy-1-phenylpropan-1-one (577 mg, 3.00 mmol) and freshly prepared butenylmagnesium chloride (0.5 M in THF, 12.0 mL) following the procedure described in section 5.2.1.1.1. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 95:5) gave 31% yield (228 mg, 0.918 mmol) of 1-isopropoxy-3-phenylhept-6-en-3-ol (**2.1e-*i*Pr**) as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.42–7.39 (m, 2H), 7.35–7.32 (m, 2H), 7.24–7.20 (m, 1H), 5.76 (dddd, *J* = 17.2, 10.4, 6.4, 6.4 Hz, 1H), 4.93 (dd, *J* = 17.2, 1.7 Hz, 1H), 4.86 (dd, *J* = 10.4, 1.7 Hz, 1H), 4.67 (s, 1H), 3.53 (ddd, *J* = 9.2, 4.0, 4.0 Hz, 1H), 3.34 (sept, *J* = 6.4 Hz, 1H), 3.18 (ddd, *J* = 9.2, 9.2, 2.8 Hz, 1H), 2.26–2.14 (m, 2H), 2.00–1.74 (m, 4H), 1.07 (d, *J* = 6.4 Hz, 3H), 1.03 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 146.1, 139.2, 128.0, 126.2, 125.6, 113.9, 77.2, 72.3, 65.6, 43.0, 41.0, 27.7, 22.0, 21.8

MS (HRMS ESI) Calcd for $C_{16}H_{25}O_2$ $[M+H]^+$ 249.1855, Found: 249.1856

5.2.1.1.12. Synthesis of 2.1f-*i*Pr



Synthesis of 2.0f-*i*Pr: The synthesis of **2.0f-*i*Pr** was performed following a slightly modified procedure reported by Spencer [4]. To a solution of 5-phenylpent-1-en-3-one[5] (1.445 g, 9.019 mmol) in *i*-PrOH (30 mL) was added TsOH (321 mg, 1.69 mmol, 20 mol%) and the reaction mixture was stirred at room temperature for 28 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution. Organic materials were then extracted thrice with EtOAc and the combined organic layers were washed with brine and dried over $MgSO_4$. After removal of the solvents in vacuo, the resulting crude residue was purified by flash column chromatography (silica gel, *n*-Hex:EtOAc, 95:5) to give 69% yield (1.37 g, 6.22 mmol) of 1-isopropoxy-5-phenylpentan-3-one as a colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 7.28–7.26 (m, 2H), 7.18–7.17 (m, 3H), 3.66 (t, *J* = 6.5 Hz, 2H), 3.55 (sept, *J* = 6.0 Hz, 1H), 2.90 (t, *J* = 7.5 Hz, 2H), 2.78 (t, *J* = 7.5 Hz, 2H), 2.63 (t, *J* = 6.5 Hz, 2H), 1.12 (d, *J* = 6.0 Hz, 6H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 208.6, 141.1, 128.4, 128.3, 126.0, 71.8, 63.1, 44.9, 43.4, 29.5, 22.0.

MS (HRMS ESI) Calcd for $C_{14}H_{21}O_2$ $[M+H]^+$ 221.1542, Found: 221.1543.

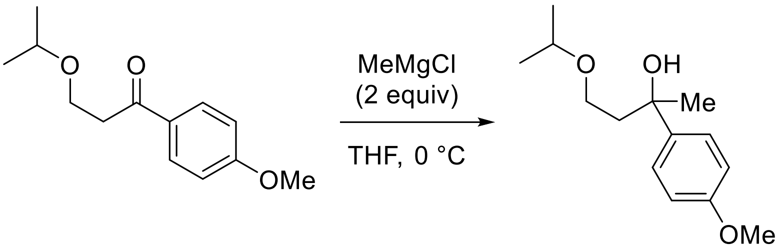
Synthesis of **2.1f-*i*Pr:** Alcohol **2.1f-*i*Pr** was synthesized using **2.0f-*i*Pr** (363 mg, 1.65 mmol) and phenylmagnesium bromide (3.0 M in Et_2O, 1.1 mL) following the procedure described in section 5.2.1.1.1. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 95:5) gave 75% yield (371 mg, 1.24 mmol) of 1-isopropoxy-3,5-diphenylpentan-3-ol (**2.1f-*i*Pr**) as a colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) δ 7.46–7.44 (m, 2H), 7.38–7.35 (m, 2H), 7.26–7.20 (m, 3H), 7.14–7.09 (m, 3H), 4.78 (brs, 1H), 3.54 (ddd, *J* = 9.0, 4.0, 4.0 Hz, 1H), 3.35 (sept, *J* = 6.0 Hz, 1H), 3.19 (ddd, *J* = 9.0, 9.0, 2.5 Hz, 1H), 2.74 (ddd, *J* = 12.0, 9.0, 4.0 Hz, 1H), 2.30–2.22 (m, 2H), 2.13 (ddd, *J* = 12.5, 9.0, 5.0 Hz, 1H), 2.05 (ddd, *J* = 12.5, 9.0, 4.5 Hz, 1H), 1.99 (ddd, *J* = 12.5, 5.0, 3.0 Hz, 1H), 1.09 (d, *J* = 6.0 Hz, 3H), 1.05 (d, *J* = 6.0 Hz, 3H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 146.0, 143.0, 128.3, 128.2, 128.0, 126.2, 125.54, 125.45, 77.3, 72.3, 65.6, 46.0, 41.2, 29.7, 22.0, 21.7.

MS (HRMS ESI) Calcd for $C_{20}H_{27}O_2$ $[M+H]^+$ 299.2011, Found: 299.2007.

5.2.1.1.13. Synthesis of 2.1g-*i*Pr



2.1g-*i*Pr 99%

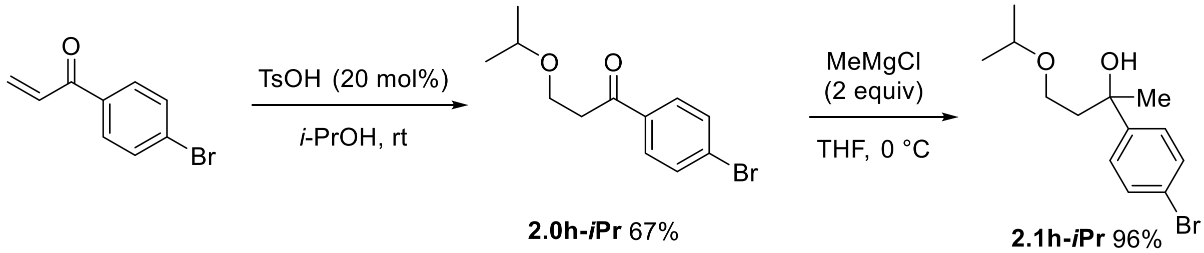
Alcohol **2.1g-*i*Pr** was synthesized using 3-isopropoxy-1-(4-methoxyphenyl)propan-1-one[6] (807 mg, 3.63 mmol) and methylmagnesium chloride (3.0 M in THF, 2.4 mL) following the procedure described in section 5.2.1.1.1. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 91:9) gave 99% yield (853 mg, 3.58 mmol) of 4-isopropoxy-2-(4-methoxyphenyl)butan-2-ol (**2.1g-*i*Pr**) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.35 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 4.58 (s, 1H), 3.81 (s, 3H), 3.56–3.55 (m, 1H), 3.40 (sept, *J* = 6.0 Hz, 1H), 3.37–3.23 (m, 1H), 2.15–2.10 (m, 1H), 2.00–1.97 (m, 1H), 1.50 (s, 3H), 1.10 (d, *J* = 6.0 Hz, 3H), 1.07 (d, *J* = 6.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 158.0, 140.2, 126.1, 113.3, 74.8, 72.3, 65.8, 55.2, 42.1, 31.1, 22.0, 21.8.

MS (HRMS ESI) Calcd for $C_{14}H_{23}O_3$ $[M+H]^+$ 239.1647, Found: 239.1644.

5.2.1.1.14. Synthesis of 1h-*i*Pr



2.0h-*i*Pr 67%

2.1h-*i*Pr 96%

Synthesis of 2.0h-*i*Pr: 2.0h-*i*Pr was synthesized using 1-(4-bromophenyl)prop-2-en-1-one[7] (836 mg, 3.96 mmol) following the procedure described in section 5.2.1.1.12. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 96:4) gave 67% yield (783 mg, 2.89 mmol) of 1-(4-bromophenyl)-3-isopropoxypropan-1-one as a pale-yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.85–7.82 (m, 2H), 7.62–7.59 (m, 2H), 3.84 (t, *J* = 6.4 Hz, 2H), 3.62 (sept, *J* = 6.4 Hz, 1H), 3.19 (t, *J* = 6.4 Hz, 2H), 1.15 (d, *J* = 6.4 Hz, 6H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 197.7, 135.8, 131.9, 129.7, 128.6, 72.0, 63.3, 39.3, 22.0.

MS (HRMS ESI) Calcd for $C_{12}H_{16}O_2Br$ $[M+H]^+$ 271.0334. Found: 271.0338.

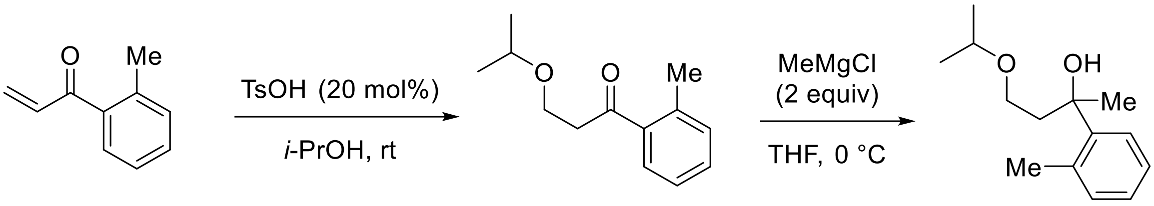
Synthesis of 2.1h-*i*Pr: Alcohol **2.1h-*i*Pr** was synthesized using **2.0h-*i*Pr** (800 mg, 2.87 mmol) and methylmagnesium chloride (3.0 M in THF, 2.0 mL) following the procedure described in section 5.2.1.1.1. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 95:5) gave 96% yield (788 mg, 2.74 mmol) of 2-(4-bromophenyl)-4-isopropoxybutan-2-ol (**2.1h-*i*Pr**) as a pale yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.47–7.44 (m, 2H), 7.34–7.31 (m, 2H), 4.71 (s, 1H), 3.56 (ddd, *J* = 9.6, 4.4, 4.0 Hz, 1H), 3.39 (sept, *J* = 6.4 Hz, 1H), 3.22 (ddd, *J* = 9.6, 9.6, 3.2 Hz, 1H), 2.14 (ddd, *J* = 14.8, 9.6, 4.0 Hz, 1H), 1.98 (ddd, *J* = 14.8, 4.4, 3.2 Hz, 1H), 1.49 (s, 3H), 1.11 (d, *J* = 6.4 Hz, 3H), 1.06 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 147.1, 131.0, 126.9, 120.1, 74.9, 72.4, 65.6, 41.7, 30.9, 22.0, 21.8.

MS (HRMS ESI) Calcd for $C_{13}H_{20}O_2Br$ $[M+H]^+$ 287.0647, Found: 287.0647.

5.2.1.1.15. Synthesis of 2.1i-*i*Pr



2.0i-*i*Pr 58% **2.1i-*i*Pr** 83%

Synthesis of 2.0i-*i*Pr: 2.0i-*i*Pr was synthesized using 1-(*o*-tolyl)prop-2-en-1-one[8] (656 mg, 4.49 mmol) following the procedure described in section 5.2.1.1.12. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 91:9) gave 58% yield (533 mg, 2.58 mmol) of 3-isopropoxy-1-(*o*-tolyl)propan-1-one (**2.0i-*i*Pr**) as a pale yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.67–7.65 (m, 1H), 7.36 (td, *J* = 7.2, 1.2 Hz, 1H), 7.27–7.22 (m, 2H), 3.81 (t, *J* = 6.8 Hz, 2H), 3.59 (sept, *J* = 6.4 Hz, 1H), 3.14 (t, *J* = 6.8 Hz, 2H), 2.50 (s, 3H), 1.14 (d, *J* = 6.4 Hz, 6H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 202.9, 138.04, 137.99, 131.8, 131.2, 128.5, 125.6, 71.8, 63.6, 42.1, 22.0, 21.1.

MS (HRMS ESI) Calcd for $C_{13}H_{19}O_2$ $[M+H]^+$ 207.1385, Found: 207.1387.

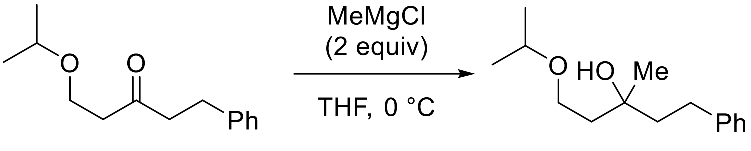
Synthesis of 2.1i-*i*Pr: Alcohol **2.1i-*i*Pr** was synthesized using **2.0i-*i*Pr** (506 mg, 2.45 mmol) and methylmagnesium chloride (3.0 M in THF, 1.7 mL) following the procedure described in section 5.2.1.1.1. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 98:2) gave 83% yield (452 mg, 2.03 mmol) of 2-(4-bromophenyl)-4-isopropoxybutan-2-ol (**2.1i-*i*Pr**) as a pale yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) δ 7.68–7.66 (m, 1H), 7.20–7.10 (m, 3H), 4.56 (s, 1H), 3.59 (ddd, *J* = 9.6, 4.8, 4.4 Hz, 1H), 3.33 (sept, *J* = 6.0 Hz, 1H), 3.23 (ddd, *J* = 9.6, 9.6, 3.2 Hz, 1H), 2.45 (s, 3H), 2.33 (ddd, *J* = 14.8, 4.8, 3.2 Hz, 1H), 2.13 (ddd, *J* = 14.8, 9.6, 4.4 Hz, 1H), 1.57 (s, 3H), 1.09 (d, *J* = 6.0 Hz, 3H), 1.01 (d, *J* = 6.0 Hz, 3H)

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 145.1, 134.0, 132.1, 126.54, 126.51, 125.7, 75.9, 72.2, 65.9, 40.2, 29.2, 22.5, 21.9, 21.7.

MS (HRMS ESI) Calcd for $C_{14}H_{23}O_2$ $[M+H]^+$ 223.1698, Found: 223.1694.

5.2.1.16. Synthesis of 2.1k-*i*Pr



2.1k-*i*Pr 96%

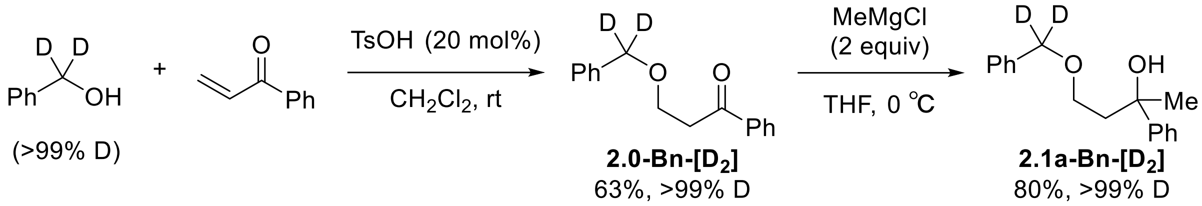
Alcohol **2.1k-*i*Pr** was synthesized using 1-isopropoxy-5-phenylpentan-3-one (1.011 g, 4.59 mmol) and methylmagnesium chloride (3.0 M in THF, 3.0 mL) following the procedure described in section 5.2.1.1.1. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 80:20) gave 96% yield (1.037 g, 4.39 mmol) of 1-isopropoxy-3-methyl-5-phenylpentan-3-ol (**2.1k-*i*Pr**) as a yellow oil.

^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 7.29–7.25 (m, 2H), 7.21–7.16 (m, 3H), 3.74 (s, 1H), 3.73–3.66 (m, 2H), 3.58 (sept, J = 6.0 Hz, 1H), 2.83 (ddd, J = 13.0, 13.0, 5.0 Hz, 1H), 2.58 (ddd, J = 13.0, 13.0, 5.5 Hz, 1H), 1.86–1.71 (m, 4H), 1.27 (s, 3H), 1.18 (d, J = 6.0 Hz, 3H), 1.17 (d, J = 6.0 Hz, 3H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 142.9, 128.31, 128.30, 125.6, 72.22, 72.17, 65.1, 44.4, 39.8, 30.4, 26.4, 22.0 (overlapped).

MS (HRMS ESI) Calcd for $C_{15}H_{24}O_2Na$ $[M+Na]^+$ 259.1674, Found: 259.1676

5.2.1.1.17. Synthesis of 2.1a-Bn-[D$_2$]



Synthesis of 2.0a-Bn-[D$_2$]: The synthesis of **2.0a-Bn-[D$_2$]** was performed following a slightly modified procedure reported by Spencer[9]. To a solution of 1-phenylprop-2-en-1-one[10] (1.30 g, 9.86 mmol) and benzyl alcohol-*d*$_2$[11] (1.59 g, 14.4 mmol) in CH_2Cl_2 (20 mL) was added TsOH (371 mg, 1.95 mmol, 20 mol%) and the reaction mixture was stirred at room temperature for 48 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution. Organic materials were then extracted thrice with EtOAc and the combined organic layers were washed with brine and dried over $MgSO_4$. After removal of the solvents in vacuo, the resulting crude residue was purified by flash column chromatography (silica gel, *n*-Hex:EtOAc, 96:4) to give 63% yield (1.47 g, 6.06 mmol) of 1-phenyl-3-(phenylmethoxy-*d*2)propan-1-one (**2.0a-Bn-[D$_2$]**, 99% D-incorporation) as a colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 7.97–7.95 (m, 2H), 7.57–7.54 (m, 1H), 7.47–7.44 (m, 2H), 7.33–7. 31 (m, 4H), 7.29–7.25 (m, 1H), 3.92 (t, *J* = 6.5 Hz, 2H), 3.29 (t, *J* = 6.5 Hz, 2H).
^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 198.3, 138.0, 137.0, 133.1, 128.5, 128.3, 128.1, 127.7, 127.6, 72.7 (m), 65.5, 38.9.
MS (HRMS ESI) Calcd for $C_{16}H_{15}D_2O_2$ $[M+H]^+$ 243.1354, Found: 243.1364.

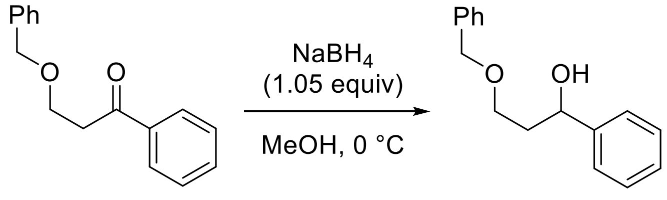
Synthesis of 2.1a-Bn-[D$_2$]: Alcohol **2.1a-Bn-[D$_2$]** was synthesized using (**2.0a-Bn-[D$_2$]** (485 mg, 2.00 mmol) and methylmagnesium chloride (3.0 M in Et_2O, 1.34 mL) following the procedure described in section 5.2.1.1.1. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 95:5) gave 80% yield (412 mg, 1.59 mmol) of 2-phenyl-4-(phenylmethoxy-*d*2)butan-2-ol (**2.1a-Bn-[D$_2$]**, 99% D-incorporation) as a colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 7.43–7.41 (m, 2H), 7.34–7.21 (m, 8H), 4.22 (s, 1H), 3.60 (ddd, *J* = 9.5, 4.5, 4.0 Hz, 1H), 3.35 (ddd, *J* = 9.5, 9.5, 3.5 Hz, 1H), 2.22 (ddd, *J* = 14.5, 9.5, 4.0 Hz, 1H), 2.07 (ddd, *J* = 14.5, 4.5, 3.5 Hz, 1H), 1.53 (s, 3H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 147.7, 137.3, 128.4, 128.0, 127.74, 127.66, 126.2, 124.8, 74.9, 72.7 (m), 42.0, 30.9.

MS (HRMS ESI) Calcd for $C_{17}H_{18}D_2O_2Li$ $[M+Li]^+$ 265.1749, Found: 265.1758.

5.2.1.1.18. Synthesis of 2.1j-Bn



2.1j-Bn 96%

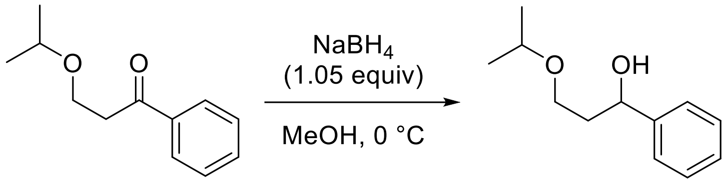
To a solution of 3-(benzyloxy)-1-phenylpropan-1-one (266 mg, 1.11 mmol) in anhydrous MeOH (5.0 mL) was added $NaBH_4$ (44.1 mg, 1.17 mmol) portionwise at 0 °C under a N_2 atmosphere and the reaction mixture was stirred at the same temperature for 2 h. The reaction mixture was then concentrated *in vacuo* and the resulting residue was then dissolved in CH_2Cl_2 and washed with 1M aqueous HCl solution. The organic materials were then extracted thrice with CH_2Cl_2 and the combined extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 90:10) gave 96% yield (256 mg, 1.06 mmol) of 3-benzyloxy-1-phenylpropan-1-ol (**2.1j-Bn**) as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.36–7.22 (m, 10H), 4.98–4.88 (m, 1H), 4.51 (s, 2H), 3.68–3.60 (m, 2H), 3.33 (d, *J* = 2.4 Hz, 1H), 2.09–1.95 (m, 2H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 144.3, 137.8, 128.4, 128.3, 127.75, 127.71, 127.2, 125.7, 73.34, 73.32, 68.6, 38.6.

MS (HRMS ESI) Calcd for $C_{16}H_{19}O_2$ [M+H]$^+$ 243.1385, Found: 243.1387.

5.2.1.1.19. Synthesis of 2.1j-*i*Pr



2.1j-*i*Pr 96%

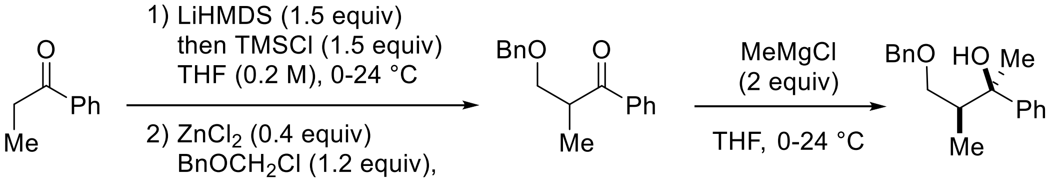
Alcohol **2.1j-*i*Pr** was synthesized using 3-isopropoxy-1-phenylpropan-1-one (245 mg, 1.27 mmol) following the procedure described in section 5.2.1.1.18. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 90:10) gave 96% yield (229 mg, 1.18 mmol) of 3-isopropoxy-1-phenylpropan-1-ol (**2.1j-*i*Pr**) as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.38–7.31 (m, 4H), 7.26–7.22 (m, 1H), 4.93–4.91 (m, 1H) 3.80 (brs, 1H), 3.64–3.55 (m, 3H), 2.01–1.94 (m, 2H), 1.18 (d, J = 6.0 Hz, 3H), 1.17 (d, J = 6.0 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 144.6, 128.4, 127.2, 125.8, 74.3, 72.3, 67.0, 38.8, 22.2, 22.1.

MS (HRMS ESI) Calcd for $C_{12}H_{18}O_2Na$ [M+Na]$^+$ 217.1204, Found: 217.1210.

5.2.1.1.20. Synthesis of 2.4a



2.3a 97% **2.4a** 99%

Synthesis of 2.3a: The synthesis of **2.3a** was performed following a reported procedure.[12] To an ice cold solution of propiophenone (0.70 mL, 5.26 mmol) in THF (10 mL) was slowly added LiHMDS (7.5 mL, 1.0 M in THF) and the reaction mixture was warmed up to 24 °C for 30 min before adding TMSCl (0.95 mL, 7.48 mmol) dropwise. The reaction mixture was then stirred at 24 °C for 5 h. After removal of the solvent under reduced pressure, the resulting crude product was diluted with ether. The mixture was filtered through celite and the celite pad was washed with Et_2O. After the filtrate was concentrated in *vacuo,* the resulting crude material including the thus formed silyl enol ether was used directly for the next step without further purification.

To a solution of the crude silyl enol ether obtained above in CH_2Cl_2 (25 mL) was added BOMCl (0.88 mL, 6.33 mmol) and $ZnCl_2$ (256 mg, 1.88 mmol) at 24 °C. The reaction mixture was stirred at 24 °C for 12 h before being quenched with a saturated aqueous NH_4Cl solution. Organic materials were extracted thrice with CH_2Cl_2, and the combined organic extracts were washed with brine, dry over $MgSO_4$, filtered and concentrated. The resulting crude residue was purified by flash chromatography (silica gel, *n*-Hex:EtOAc, 95:5) to give 97% yield (266 mg, 1.05 mmol) of 3-(benzyloxy)-1,2-diphenylpropan-1-one (**2.3a**) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.99–7.96 (m, 2H), 7.58–7.54 (m, 1H), 7.48–7.44 (m, 2H), 7.32–7.29 (m, 2H), 7.27–7.23 (m, 3H), 4.53 (d, *J* = 12.4 Hz, 1H), 4.48 (d, *J* = 12.4 Hz, 1H), 3.86–3.78 (m, 2H), 3.57–3.53 (m, 1H), 1.22 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 202.6, 138.1, 136.6, 132.9, 128.5, 128.3, 128.2, 127.4 (overlapped), 73.2, 72.5, 41.3, 14.8.

MS (HRMS ESI) Calcd for $C_{17}H_{19}O_2$ $[M+H]^+$ 255.1385, Found: 255.1387.

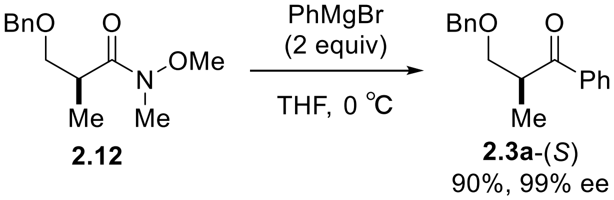
Synthesis of 2.4a: Alcohol **2.4a** was synthesized using **2.3a** (306 mg, 1.20 mmol) and methylmagnesium chloride (3.0 M in THF, 0.8 mL) following the procedure described in section 5.2.1.1.1. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 95:5) gave 99% yield (322 mg, 1.19 mmol) of (2*R**,3*S**)-4-(benzyloxy)-3-methyl-2-phenylbutan-2-ol (**2.4a**) as a single diastereomer (colorless oil).

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.39–7.28 (m, 9H), 7.24–7.19 (m, 1H), 4.50 (s, 2H), 4.22 (s, 1H), 3.70 (dd, *J* = 9.2, 3.6 Hz, 1H), 3.35 (dd, *J* = 9.2, 5.6 Hz, 1H), 2.17–2.09 (m, 1H), 1,57 (s, 3H), 0.85 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100MHz, CDCl$_3$): δ(ppm) 146.6, 137.5, 128.5, 127.9, 127.86, 127.78, 126.2, 125.3, 76.8, 73.7, 73.5, 43.2, 29.0, 13.1.

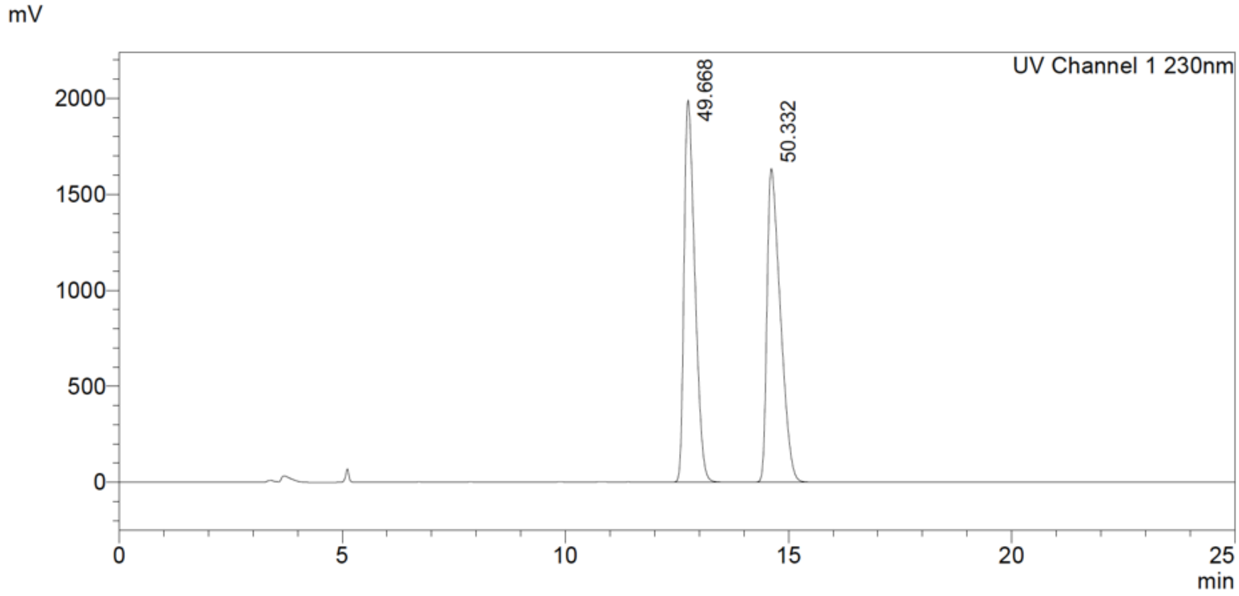
MS (HRMS ESI) Calcd for $C_{18}H_{23}O_2$ $[M+H]^+$ 271.1698, Found: 271.1703.

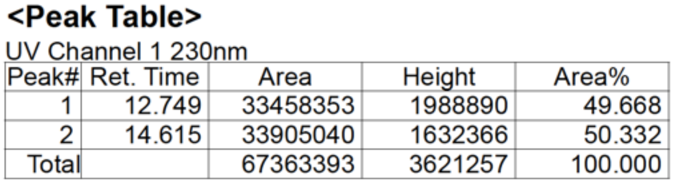
5.2.1.1.21. Synthesis of 2.3a-(*S*)



To solution of (*S*)-3-(benzyloxy)-*N*-methoxy-*N*,2-dimethylpropanamide[13] (619 mg, 2.61 mmol) in THF (5 mL) at 0 °C was added solution of phenylmagnesium bromide (1.0 M in THF, 5.2 mL) dropwise. After stirring at the same temperature for 2 h, the saturated NH_4Cl solution was added and stirred for 10 min at 24 °C. Organic materials were extracted thrice with EtOAc and the combine extracts were washed with brine, and dried over $MgSO_4$. The volatile materials were removed *in vacuo* and the resulting crude material was purified by flash column chromatography (silica gel, *n*-Hex:EtOAc = 95:5) to yield (*S*)-3-(benzyloxy)-1,2-diphenylpropan-1-one (**2.3a**-(*S*)) in 90% yield (595 mg, 2.34 mmol) as a colorless oil. The enantiomeric excess (ee) of **3a'**-(*S*) was measured by HPLC (Daicel Chiralpak IG column), *n*-Hex:*i*-PrOH = 98/2, flow 1.0 mL/min, 230 nm, t_1 = 12.8 min (major), t_2 = 15.2 min (minor); $[\alpha]_D^{25}$ = +12.6° (c = 0.73, $CHCl_3$) for 99% ee.

HPLC chart for racemic **2.3a**

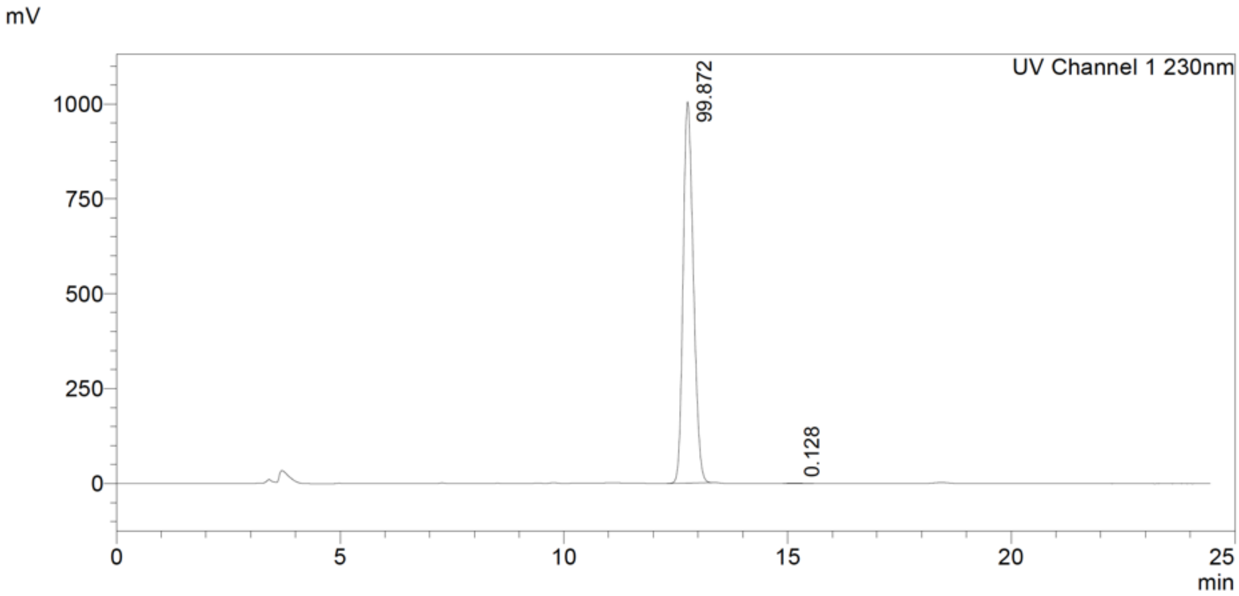



<Peak Table>

UV Channel 1 230nm

Peak#	Ret. Time	Area	Height	Area%
1	12.749	33458353	1988890	49.668
2	14.615	33905040	1632366	50.332
Total		67363393	3621257	100.000

HPLC chart for **2.3a**-(*S*)

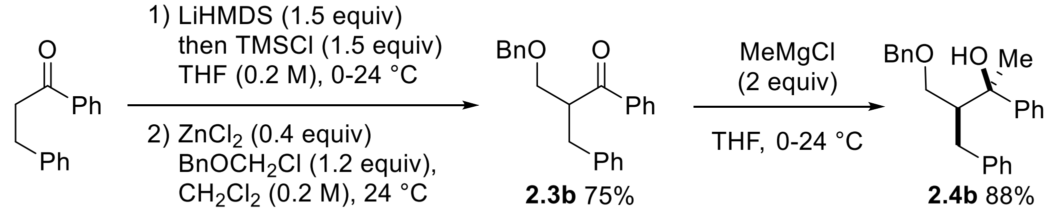


<Peak Table>

UV Channel 1 230nm

Peak#	Ret. Time	Area	Height	Area%
1	12.766	16039229	1004252	99.872
2	15.168	20486	1185	0.128
Total		16059715	1005437	100.000

5.2.1.1.22. Synthesis of 2.4b



Synthesis of 2.3b: Benzyl ether **2.3b** was synthesized using 1,3-diphenylpropan-1-one (419 mg, 1.99 mmol) following the procedure described in section 5.2.1.1.20. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 98:2) gave 75% yield (497 mg, 1.51 mmol) of 2-benzyl-3-(benzyloxy)-1-phenylpropan-1-one (**2.3b**) as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.87–7.85 (m, 2H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.29–7.12 (m, 10H), 4.44 (s, 2H), 4.04 (dddd, *J* = 7.6, 7.6, 6.8, 5.6 Hz, 1H), 3.80 (dd, *J* = 9.2, 7.6 Hz, 1H), 3.62 (dd, *J* = 9.2, 5.6 Hz, 1H), 3.08 (dd, *J* = 13.8, 7.6 Hz, 1H), 2.90 (dd, *J* = 13.8, 6.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 202.2, 139.1, 138.0, 137.4, 132.8, 129.0, 128.44, 128.37, 128.30, 128.26, 127.5, 127.4, 126.3, 73.2, 71.1, 48.9, 35.3.

MS (HRMS ESI) Calcd for $C_{23}H_{22}O_2Na$ [M+Na]$^+$ 353.1517, Found: 353.1515.

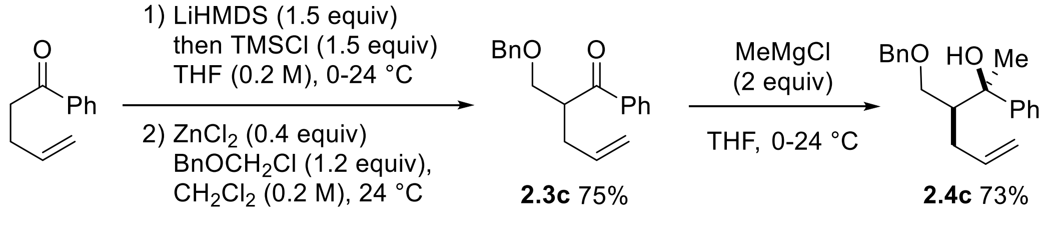
Synthesis of 2.4b: Alcohol **2.4b** was synthesized using **2.3b** (425 mg, 1.29 mmol) and methylmagnesium chloride (3.0 M in THF, 0.9 mL) following the procedure described in section 5.2.1.1.1. Purification by recrystallization from hexane-CH_2Cl_2 gave 88% yield (391 mg, 1.13 mmol) of (2*R**,3*S**)-3-benzyl-4-(benzyloxy)-2-phenylbutan-2-ol (**2.4b**) as a single diastereomer (colorless crystal). The stereochemsitry of **2.4b** could be confirmed by the X-ray crystallographic analysis (CCDC 1823717).

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.50–7.48 (m, 2H), 7.39–7.34 (m, 7H), 7.28–7.22 (m, 1H), 7.20–7.09 (m, 3H), 6.90–6.83 (m, 2H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.21 (s, 1H), 3.83 (dd, *J* = 9.6, 2.0 Hz, 1H), 3.40 (dd, *J* = 9.6, 2.8 Hz, 1H), 2.70 (dd, *J* = 14.0, 12.0 Hz, 1H), 2.48 (dd, *J* = 14.0, 2.8 Hz, 1H), 2.07 (dddd, *J* = 12.0, 2.8, 2.8, 2.0 Hz, 1H), 1.62 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 147.4, 141.3, 137.4, 129.0, 128.5, 128.2, 128.1, 128.0 (overlapped), 126.3, 125.7, 124.8, 76.8, 73.8, 68.4, 50.8, 32.2, 30.0.

MS (HRMS ESI): Calcd for $C_{24}H_{26}O_2Na$ [M+Na]$^+$ 369.1831, Found: 369.1825.

5.2.1.1.23. Synthesis of 2.4c



Synthesis of 2.3c: Benzyl ether **2.3c** was synthesized using 1-phenylpent-4-en-1-one[14] (479 mg, 2.99 mmol) following the procedure described in section 5.2.1.1.20. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 99:1) gave 75% yield (630 mg, 2.25 mmol) of 2-((benzyloxy)methyl)-1-phenylpent-4-en-1-one (**2.3c**) as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.97–7.95 (m, 2H), 7.54–7.52 (m, 1H), 7.46–7.42 (m, 2H), 7.30–7.21 (m, 5H), 5.72 (dddd, *J* = 16.8, 10.0, 7.2, 7.2 Hz, 1H), 5.02 (d, *J* = 16.8, 1H), 4.99 (d, *J* = 10.0, 1H), 4.48 (d, *J* = 12.0 Hz, 1H), 4.45 (d, *J* = 12.0 Hz, 1H), 3.88–3.78 (m, 2H), 3.63 (dd, *J* = 8.8, 5.2 Hz, 1H), 2.52 (ddd, *J* = 14.4, 7.2, 6.8 Hz, 1H), 2.34 (ddd, *J* = 14.4, 7.2, 6.8 Hz, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 201.9, 138.0, 137.3, 134.9, 132.8, 128.4, 128.3, 128.2, 127.4, 127.3, 117.0, 73.1, 70.9, 46.4, 33.5.

MS (HRMS ESI) Calcd for $C_{19}H_{20}O_2Na$ $[M+Na]^+$ 303.1361, Found: 303.1360.

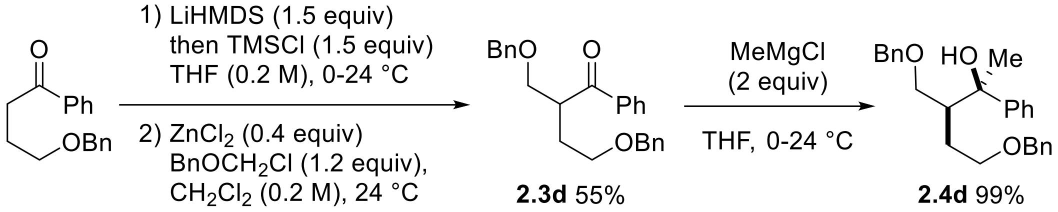
Synthesis of 2.4c: Alcohol **2.4c** was synthesized using **2.3c** (839 mg, 2.99 mmol) and methylmagnesium chloride (3.0 M in THF, 2.0 mL) following the procedure described in section 5.2.1.1.1. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 99:1) gave 73% yield (645 mg, 2.18 mmol) of (2*R**,3*S**)-3-((benzyloxy)methyl)-2-phenylhex-5-en-2-ol (**2.4c**) as a single diastereomer (colorless oil).

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.41–7.37 (m, 2H), 7.36–7.28 (m, 7H), 7.22–7.18 (m, 1H), 5.57 (dddd, *J* = 16.8, 10.4, 9.2, 5.6 Hz, 1H), 4.91–4.84 (m, 2H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.48 (d, *J* = 12.0 Hz, 1H), 4.16 (s, 1H), 3.86 (dd, *J* = 9.6, 2.4 Hz, 1H), 3.58 (dd, *J* = 9.6, 4.0 Hz, 1H), 2.25–2.09 (m, 1H), 1.98–1.89 (m, 2H), 1.58 (s, 3H).

<u>^{13}C NMR (100 MHz, CDCl$_3$):</u> δ(ppm) 147.1, 137.45, 137.43, 128.4, 127.9, 127.85, 127.80, 126.1, 124.9, 116.2, 76.7, 73.7, 69.2, 47.9, 30.9, 29.7.

<u>MS (HRMS ESI)</u> Calcd for $C_{20}H_{24}O_2Na$ [M+Na]$^+$ 319.1674, Found: 319.1682.

5.2.1.1.24. Synthesis of 2.4d



Synthesis of 2.3d: Benzyl ether **2.3d** was synthesized using 4-(benzyloxy)-1-phenylbutan-1-one[15] (1.276 g, 5.016 mmol) following the procedure described in section 5.2.1.1.20. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 95:5) gave 55% yield (1.032 g, 2.76 mmol) of 4-(benzyloxy)-2-((benzyloxy)methyl)-1-phenylbutan-1-one (**2.3d**) as a colorless oil.

<u>^{1}H NMR (400 MHz, CDCl$_3$):</u> δ(ppm) 8.06 (d, *J* = 4.0 Hz, 2H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 2H), 7.34–7.24 (m, 10H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.48 (d, *J* = 12.0 Hz, 1H), 4.42 (d, *J* = 12.0 Hz, 1H), 4.39 (d, *J* = 12.0 Hz, 1H), 4.12–4.08 (m, 1H), 3.84 (dd, *J* = 8.0, 8.0 Hz, 1H), 3.67 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.56–3.53 (m, 1H), 3.49–3.46 (m, 1H), 2.20–2.12 (m, 1H), 1.97–1.90 (m, 1H).

<u>^{13}C NMR (100 MHz, CDCl$_3$):</u> δ(ppm) 202.7, 138.1, 138.0, 137.6, 132.8, 128.36, 128.35, 128.2 (overlapped), 127.5, 127.4, 127.3 (overlapped), 73.1, 72.6, 71.8, 67.8, 43.7, 29.7.

<u>MS (HRMS ESI)</u> Calcd for $C_{25}H_{27}O_3$ [M+H]$^+$ 375.1960, Found: 375.1965

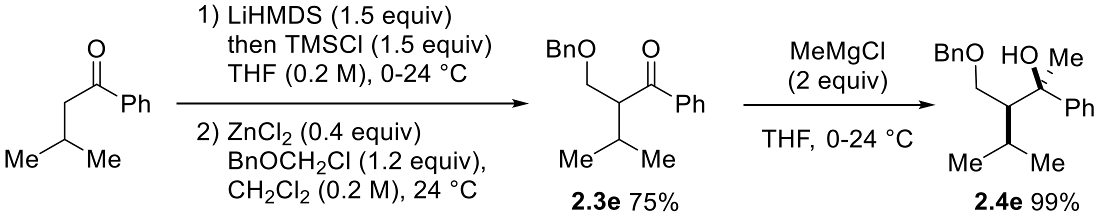
Synthesis of 2.4d: Alcohol **2.4d** was synthesized using **2.3d** (554 mg, 1.48 mmol) and methylmagnesium chloride (3.0 M in THF, 1.0 mL) following the procedure described in section 5.2.1.1.1. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 95:5) gave 99% yield (572 mg, 1.46 mmol) of (2*R**,3*S**)-5-(benzyloxy)-3-((benzyloxy)methyl)-2-phenylpentan-2-ol (**2.4d**) as a single diastereomer (colorless oil).

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.50–7.41 (m, 15H), 4.50 (s, 2H), 4.32–4.26 (m, 3H), 3.89 (dd, *J* = 9.6, 3.6 Hz, 1H), 3.62 (dd, *J* = 9.6, 4.0 Hz, 1H), 3.34–3.29 (m, 2H), 2.15–2.13 (m, 1H), 1.79–1.62 (m, 2H), 1.56 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 147.4, 138.3, 137.5, 128.5, 128.3, 127.90, 127.87, 127.8, 127.54, 127.47, 126.1, 125.9, 76.6, 73.6, 72.4, 69.9, 68.4, 45.1, 29.6, 26.2.

MS (HRMS ESI) Calcd for $C_{26}H_{31}O_3$ [M+H]$^+$ 391.2273, Found: 391.2290

5.2.1.1.25. Synthesis of 2.4e



Synthesis of 2.3e: Benzyl ether **2.3e** was synthesized using 3-methyl-1-phenylbutan-1-one[16] (328 mg, 2.02 mmol) following the procedure described in section 5.2.1.1.20. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 98:2) gave 75% yield (427 mg, 1.51 mmol) of 2-((benzyloxy)methyl)-3-methyl-1-phenylbutan-1-one (**2.3e**) as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.99–7.97 (m, 2H), 7.55–7.53 (m, 1H), 7.48–7.44 (m, 2H), 7.29–7.23 (m, 3H), 7.21–7.19 (m, 2H), 4.48 (d, *J* = 12.0 Hz, 1H), 4.44 (d, *J* = 12.0 Hz, 1H), 3.87 (dd, *J* = 8.8, 8.8 Hz, 1H), 3.73 (dd, *J* = 8.8, 4.4 Hz, 1H), 3.62 (ddd, *J* = 8.8, 6.8, 4.4 Hz, 1H), 2.09 (d of sept, *J* = 6.8, 6.8 Hz, 1H), 0.93 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 203.5, 138.6, 138.2, 132.7, 128.5, 128.3, 128.2, 127.4, 127.3, 73.3, 70.3, 52.9, 29.1, 21.3, 20.0.

MS (HRMS ESI) Calcd for $C_{19}H_{23}O_2$ [M+H]$^+$ 283.1698, Found: 283.1704

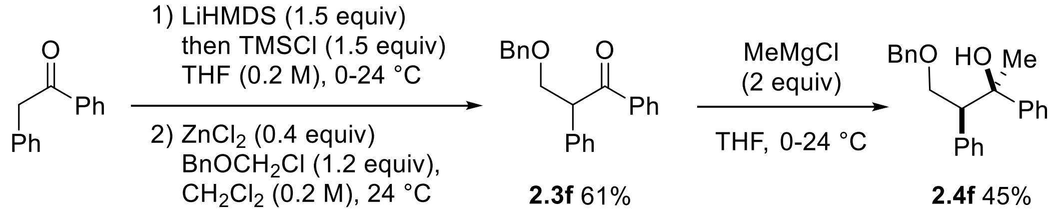
Synthesis of 2.4e: Alcohol **2.4e** was synthesized using **2.3e** (252 mg, 0.893 mmol) and methylmagnesium chloride (3.0 M in THF, 0.6 mL) following the procedure described in section 5.2.1.1.1. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 95:5) gave 99% yield (264 mg, 0.883 mmol) of (2*R**,3*S**)-3-((benzyloxy)methyl)-4-methyl-2-phenylpentan-2-ol (**2.4e**) as a single diastereomer (colorless oil).

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.43–7.41 (m, 2H), 7.37–7.35 (m, 4H), 7.33–7.29 (m, 3H), 7.25– 7.18 (m, 1H), 4.54 (s, 2H), 4.09 (s, 1H), 3.92 (dd, *J* = 10.0, 3.6 Hz, 1H), 3.79 (dd, *J* = 10.0, 3.6 Hz, 1H), 1.80–1.77 (m, 1H), 1.73 (d of sept, *J* = 6.8, 2.4 Hz, 1H), 1.59 (s, 3H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.74 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 147.8, 137.5, 128.5, 127.9, 127.8, 126.0, 125.0 (overlapped), 78.0, 73.8, 68.3, 52.6, 30.6, 26.9, 24.4, 19.3.

MS (HRMS ESI) Calcd for $C_{20}H_{26}O_2Na$ [M+Na]$^+$ 321.1831, Found: 321.1832

5.2.1.1.26. Synthesis of 2.4f



Synthesis of 2.3f: Benzyl ether **2.3f** was synthesized using 1,2-diphenylethan-1-one (212 mg, 1.045 mmol) following the procedure described in section 5.2.1.1.20. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 99:1) gave 61% yield (201 mg, 0.636 mmol) of 3-(benzyloxy)-1,2-diphenylpropan-1-one (**2.3f**) as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.98–7.96 (m, 2H), 7.49–7.45 (m, 1H), 7.39–7.36 (m, 2H), 7.32–7.19 (m, 10H), 4.92 (dd, *J* = 8.8, 5.2 Hz, 1H), 4.58 (d, *J* = 12.0 Hz, 1H), 4.48 (d, *J* = 12.0 Hz, 1H), 4.28 (dd, *J* = 9.2, 8.8 Hz, 1H), 3.73 (dd, *J* = 9.2, 5.2 Hz, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 198.3, 138.2, 136.8, 136.4, 133.0, 129.0, 128.7, 128.5, 128.4, 128.3, 127.6, 127.51, 127.45, 73.4, 72.3, 54.0.

MS (HRMS ESI) Calcd for $C_{22}H_{21}O_2$ [M+H]$^+$ 317.1542, Found: 317.1546.

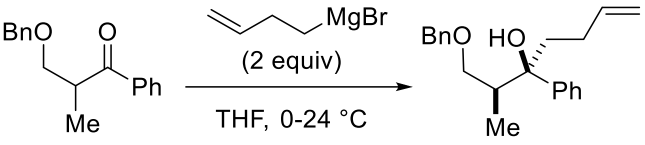
Synthesis of 2.4f: Alcohol **2.4f** was synthesized using **2.3f** (105 mg, 0.331 mmol) and methylmagnesium chloride (3.0 M in THF, 0.22 mL) following the procedure described in section 5.2.1.1.1. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 95:5) gave 45% yield (49 mg, 0.147 mmol) of (2*R**,3*S**)-4-(benzyloxy)-2,3-diphenylbutan-2-ol (**2.4f**) as a single diastereomer (pale yellow oil).

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.38–7.31 (m, 5H), 7.26–7.11 (m, 8H), 6.87 (d, *J* = 7.6 Hz, 2H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.50 (s, 1H), 3.83–3.76 (m, 2H), 3.33 (dd, *J* = 7.2, 5.0 Hz, 1H), 1.57 (s, 3H).

^{13}C NMR (100MHz, CDCl$_3$): δ(ppm) 145.1, 138.9, 137.3, 129.7, 128.5, 127.95, 127.90, 127.6, 127.4, 126.8, 126.5, 126.3, 77.0, 73.7, 72.0, 55.8, 28.7.

MS (HRMS ESI) Calcd for $C_{23}H_{25}O_2$ [M+H]$^+$ 333.1855, Found: 333.1857.

5.2.1.1.27. Synthesis of 2.4g



2.4g 85%

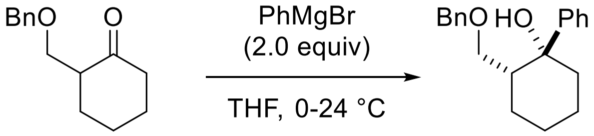
Alcohol **2.4g** was synthesized using 3-(benzyloxy)-2-methyl-1-phenylpropan-1-one (672 mg, 2.64 mmol) and freshly prepared butenylmagnesium bromide (1.5 M in THF, 4.0 mL) following the procedure described in section 5.2.1.1.1. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 98:2) gave 85% yield (700 mg, 2.25 mmol) of (2*S**,3*R**)-1-(benzyloxy)-2-methyl-3-phenylhept-6-en-3-ol (**2.4g**) as a single diastereomer (pale yellow oil).

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.38–7.28 (m, 9H), 7.23–7.19 (m, 1H), 5.77 (dddd, *J* = 16.8, 10.0, 6.4, 6.4 Hz, 1H), 4.92 (d, *J* = 16.8, 1H), 4.87 (d, *J* = 10.0, 1H), 4.48 (s, 2H), 4.27 (s, 1H), 3.71 (dd, *J* = 9.2, 3.6 Hz, 1H), 3.31 (dd, *J* = 9.2, 6.0 Hz, 1H), 2.22–2.10 (m, 2H), 2.02–1.87 (m, 2H), 1.72–1.62 (m, 1H), 0.84 (d, *J* = 7.6 Hz, 3H).

^{13}C NMR (100MHz, CDCl$_3$): δ(ppm) 144.3, 139.3, 137.4, 128.5, 127.9, 127.8, 127.7, 126.1, 125.8, 113.9, 78.9, 73.7, 73.3, 42.6, 40.0, 27.9, 13.0.

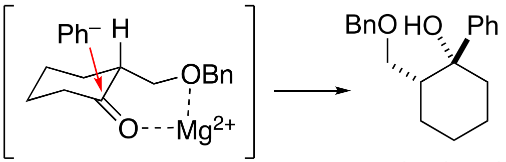
MS (HRMS ESI) Calcd for $C_{21}H_{27}O_2$ [M+H]$^+$ 311.2011, Found: 311.2016.

5.2.1.1.28. Synthesis of 2.4h



2.4h-(1*R**,2*R**)
78%
(as single dr)

Synthesis of 2.4h-(1*R,2*R**):** Alcohol **2.4h**-(1*R**,2*R**) was synthesized using 2-((benzyloxy)methyl)cyclohexan-1-one[17] (547 mg, 2.51 mmol) and phenylmagnesium bromide (3.0 M in Et_2O, 1.6 mL) by following the procedure described in section 5.2.1.1.1. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 98:2) gave 78% yield (577 mg, 1.95 mmol) of (1*R**,2*R**)-2-((benzyloxy)methyl)-1-phenylcyclohexan-1-o-l (**2.4h**-(1*R**,2*R**)) as a single diastereomer (colorless oil). The diastereoselectivity could be explained by a chelation model, in which the carbonyl and benzyloxy moieties are linked with the Mg ion.[18]



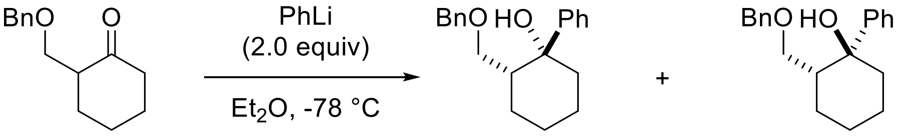
3h-(1*R**,2*R**)

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.46 (d, *J* = 7.6 Hz, 2H), 7.34–7.26 (m, 5H), 7.25–7.20 (m, 3H), 4.29 (d, *J* = 12.8 Hz, 1H), 4.26 (d, *J* = 12.8 Hz, 1H), 4.15 (s, 1H), 3.31 (dd, *J* = 9.2, 3.2 Hz, 1H), 3.25 (dd, *J* = 9.2, 2.4 Hz, 1H), 2.19–2.09 (m, 1H), 1.92–1.78 (m, 3H), 1.76–1.64 (m, 2H), 1.63–1.57 (m, 2H), 1.49–1.35 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 148.8, 137.6, 128.4, 128.0, 127.7, 127.5, 126.1, 124.7, 76.5, 73.5, 73.2, 45.4, 40.7, 26.4, 25.9, 21.9.

MS (HRMS ESI) Calcd for $C_{20}H_{25}O_2$ $[M+H]^+$ 297.1855, Found: 297.1856.

As shown below, the reaction with phenyllithium in Et_2O at -78 °C provided a mixture of diastereomers **2.4h**-(1*R**,2*R**) and **2.4h-**(1*S**,2*R**) in 59% and 27% yields, respectively.



2.4h-(1*R**,2*R**)
59%

2.4h-(1*S**,2*R**)
27%

To a solution of bromobenzene (0.30 mL, 2.85 mmol, 2 equiv) in Et_2O (10.0 mL) was added *tert*-butyllithium (1.3 M in pentane, 4.4 mL, 4 equiv) dropwise at -78 °C. After 1 h, a solution of 2-((benzyloxy)methyl)cyclohexan-1-one (318 mg, 1.46 mmol) in Et_2O (5.0 mL) was added dropwise and the reaction mixture was stirred for another 5 h. The reaction mixture was then quenched with saturated aqueous NH_4Cl solution. Organic materials were extracted thrice with EtOAc and the combined extracts were washed with brine, and dried over $MgSO_4$. After the filtrate was concentrated in *vacuo*, the resulting crude material was purified by flash column chromatography (silica gel, *n*-Hex:EtOAc, 98:2) to give 59% yield (256 mg, 0.864 mmol) of **2.4h**-(1*R**,2*R**) along with 27% yield (116 mg, 0.390 mmol) of **2.4h**-(1*S**,2*R**) (pale yellow oils).

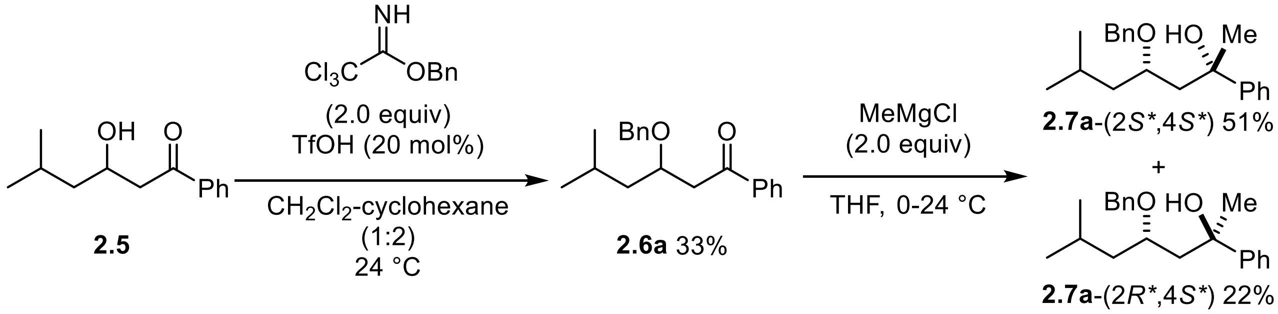
Spectra data of **2.4h**-(1*S**,2*R**):

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.55 (d, *J* = 7.6 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.29–7.21 (m, 4H), 7.15–7.13 (m, 2H), 4.28 (d, *J* = 12.0 Hz, 1H), 4.23 (d, *J* = 12.0 Hz, 1H), 3.36 (dd, *J* = 9.2, 7.6 Hz, 1H), 3.10 (dd, *J* = 9.2, 7.6 Hz, 1H), 3.02 (s, 1H), 2.30–2.23 (m, 1H), 2.10–2.03 (m, 1H), 1.82–1.61 (m, 6H), 1.53–1.46 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 146.9, 138.0, 128.2, 127.9, 127.43, 127.39, 126.8, 126.0, 74.4, 73.0, 71.3, 46.2, 36.5, 24.7, 22.3, 21.7.

MS (HRMS ESI) Calcd for $C_{20}H_{25}O_2$ $[M+H]^+$ 297.1855, Found: 297.1852.

5.2.1.1.29. Synthesis of 2.7a



Synthesis of 2.6a: To a solution of the 3-hydroxy-5-methyl-1-phenylhexan-1-one[19] (1.04 g, 5.04 mmol) and 2,2,2-trichloroacetimidate (1.8 mL, 9.69 mmol) in a mixture of CH_2Cl_2 (16 mL) and cyclohexane (32 mL) was added TfOH (88 μL, 0. 994 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 30 h before it was quenched with saturated aqueous $NaHCO_3$ solution. The organic materials were then extracted with EtOAc and the combined organic layers were washed with brine and dried over $MgSO_4$. After filtration, the volatile materials were removed in *vacuo*. The resulting crude material was purified by flash column chromatography (silica gel, *n*-Hex:EtOAc, 99:1 to 98:2) to give 68% yield (1.01 g, 3.41 mmol) of 3-(benzyloxy)-5-methyl-1-phenylhexan-1-one (**2.6a**) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.98–7.95 (m, 2H), 7.59–7.55 (m, 1H), 7.48–7.44 (m, 2H), 7.31–7.22 (m, 5H), 4.56 (d, *J* = 11.2 Hz, 1H), 4.51 (d, *J* = 11.2 Hz, 1H), 4.23–4.17 (m, 1H), 3.38 (dd, *J* = 16.4, 6.8 Hz, 1H), 3.00 (dd, *J* = 16.4, 5.6 Hz, 1H), 1.88–1.77 (m, 1H), 1.63 (ddd, *J* = 13.6, 8.4, 6.0 Hz, 1H), 1.36 (ddd, *J* = 13.6, 8.4, 4.8 Hz, 1H), 0.923 (d, *J* = 6.8 Hz, 3H), 0.918 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 199.1, 138.4, 137.3, 133.0, 128.5, 128.2, 128.1, 127.8, 127.5, 74.4, 71.8, 44.7, 44.1, 24.6, 23.2, 22.3.

MS (HRMS ESI) Calcd for $C_{20}H_{25}O_2$ $[M+H]^+$ 297.1855. Found: 297.1854.

Synthesis of 2.7a: Alcohol **2.7a** was synthesized using **2.6a** (598 mg, 2.02 mmol) and methylmagnesium chloride (3.0 M in THF, 4.1 mL) following the procedure described in section 2.1.1. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 99:1 as the eluent for the isolation of **2.7a**-(2*R**,4*S**) followed by *n*-Hex:EtOAc, 97:3 as the eluent for the isolation of **2.7a**-(2*S**,4*S**)) gave 22% yield (138 mg, 0.442 mmol) of **2.7a**-(2*R**,4*S**) as colorless oil and 51% yield (319 mg, 1.02 mmol) of **5a**-(2*S**,4*S**) as a white solid.

(2*S**,4*S**)-4-(benzyloxy)-6-methyl-2-phenylheptan-2-ol (**2.7a**-(2*S**,4*S**))

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.48–7.45 (m, 2H), 7.36–7.25 (m, 7H), 7.22–7.17 (m, 1H), 4.61 (d, *J* = 10.8 Hz, 1H), 4.48 (s, 1H), 4.41 (d, *J* = 10.8 Hz, 1H), 3.93–3.87 (m, 1H), 1.99–1.88 (m, 2H), 1.62–1.56 (m, 2H), 1.54 (s, 3H), 1.40–1.32 (m, 1H), 0.89 (d, *J* = 6.4 Hz, 3H), 0.88 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (100MHz, $CDCl_3$): δ(ppm) 149.3, 137.5, 128.5, 128.1, 127.9, 127.8, 126.2, 124.5, 76.1, 73.8, 70.3, 47.5, 42.8, 28.6, 24.7, 23.4, 22.3.

MS (HRMS ESI) Calcd for $C_{21}H_{29}O_2$ $[M+H]^+$ 313.2168, Found: 313.2164.

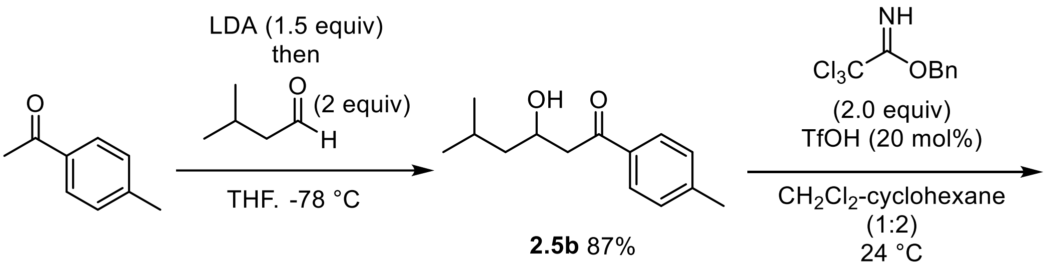
(2*R**,4*S**)-4-(benzyloxy)-6-methyl-2-phenylheptan-2-ol (**2.7a**-(2*R**,4*S**))

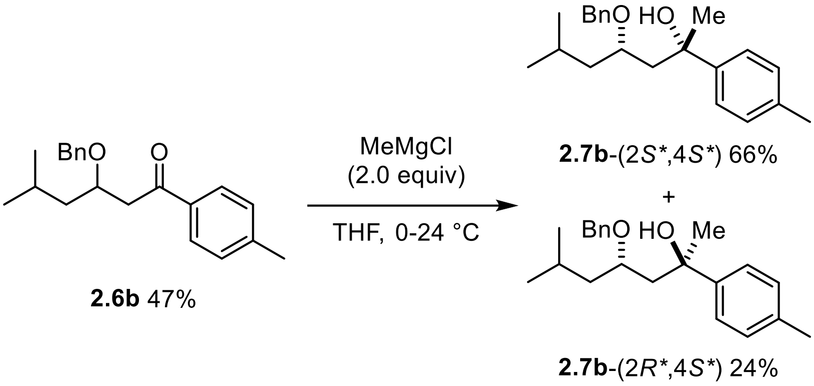
^{1}H NMR (400 MHz, $CDCl_3$): 7.39–7.37 (m, 2H), 7.35–7.28 (m, 5H), 7.27–7.20 (m, 3H), 4.88 (s, 1H), 4.41 (d, *J* = 10.8 Hz, 1H), 3.95 (d, *J* = 10.8 Hz, 1H), 3.29–3.22 (m, 1H), 2.17 (dd, *J* = 15.2, 2.0 Hz, 1H), 2.01 (dd, *J* = 15.2, 10.8 Hz, 1H), 1.65–1.54 (m, 1H), 1.49–1.43 (m, 1H), 1.46 (s, 3H), 1.36 (ddd, *J* = 14.0, 8.8, 5.2 Hz, 1H), 0.89 (d, *J* = 6.4 Hz, 3H), 0.71 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.1, 137.6, 128.5, 128.1, 127.9, 127.8, 126.1, 124.9, 77.2, 74.8, 70.4, 46.6, 42.6, 32.2, 24.8, 23.8, 21.9.

MS (HRMS ESI) Calcd for $C_{21}H_{28}O_2Na$ $[M+Na]^+$ 335.1987, Found: 335.1982.

5.2.1.1.30. Synthesis of 2.7b





Synthesis of 2.5b: To a solution of diisopropylamine (4.5 mL, 32.1 mmol, 1.5 equiv) in THF (60 mL) was added *n*-BuLi (2.0 M in cyclohexane, 16 mL, 1.5 equiv) at -78 °C. The reaction was then stirred for 30 min at -78 °C before 4'-methylacetophenone (2.9 mL, 21.0 mmol) was added. After the mixture was stirred at the same temperature for 30 min, isovaleraldehyde (4.5 mL, 41.9 mmol, 2.0 equiv) was added dropwise. The reaction mixture was then stirred for another 2 h at the same temperature before being quenched with saturated aqueous NH_4Cl solution. The organic materials were then extracted thrice with EtOAc and the combined organic layers were washed with brine and dried over $MgSO_4$. After the filtrate was concentrated in *vacuo*, the resulting crude residue was purified by recrystallization from hexane to give 87% yield (4.042 g, 18.35 mmol) of 3-hydroxy-5-methyl-1-(*p*-tolyl)hexan-1-one (**2.5b**) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.87–7.84 (m, 2H), 7.28–7.26 (m, 2H), 4.32–4.27 (m, 1H), 3.27 (s, 1H), 3.13 (dd, *J* = 18.0, 2.8 Hz, 1H), 3.00 (dd, *J* = 18.0, 9.2 Hz, 1H), 2.42 (s, 3H), 1.91–1.84 (m, 1H), 1.59 (ddd, *J* = 13.2, 9.2, 6.4 Hz, 1H), 1.25 (ddd, *J* = 13.2, 9.2, 4.4 Hz, 1H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 200.7, 144.4, 134.3, 129.3, 128.2, 65.9, 45.6, 45.3, 24.4, 23.3, 22.0, 21.6.

MS (HRMS ESI) Calcd for $C_{14}H_{20}O_2Na$ [M+Na]$^+$ 243.1361, Found: 243.1365

Synthesis of 2.6b: Benzyl ether **2.6b** was synthesized using **2.5b** (660 mg, 3.00 mmol) following the procedure described in section 5.2.1.1.29. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 99:1) gave 47% yield (440 mg, 1.42 mmol) of 3-(benzyloxy)-5-methyl-1-(*p*-tolyl)hexan-1-one as a pale yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.88–7.86 (m, 2H), 7.31–7.25 (m, 7H), 4.56 (d, *J* = 11.2 Hz, 1H), 4.50 (d, *J* = 11.2 Hz, 1H), 4.22–4.16 (m, 1H), 3.35 (dd, *J* = 16.0, 6.4 Hz, 1H), 2.97 (dd, *J* = 16.0, 6.4 Hz, 1H), 2.41 (s, 3H), 1.86–1.75 (m, 1H), 1.66–1.59 (m, 1H), 1.38–1.32 (m, 1H), 0.93–0.91 (m, 6H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 198.8, 143.8, 138.5, 134.9, 129.2, 128.3, 128.2, 127.8, 127.5, 74.5, 71.8, 44.7, 44.1, 24.6, 23.3, 22.2, 21.6.

MS (HRMS ESI) Calcd for $C_{21}H_{27}O_2$ [M+H]$^+$ 311.2011, Found: 311.2015.

Synthesis of 2.7b: Alcohol **2.7b** was synthesized using **2.6b** (383 mg, 1.29 mmol) and methylmagnesium chloride (3.0 M in THF, 0.9 mL) following the procedure described in section 5.2.1.1.1. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 98:2 as the eluent for the isolation of **2.7b**-(2*R**,4*S**) followed by *n*-Hex:EtOAc, 91:9 as the eluent for the isolation of **2.7b**-(2*S**,4*S**)) gave 24% yield (101 mg, 0.311 mmol) of **2.7b**-(2*R**,4*S**) as a pale and 66% yield (279 mg, 0.854 mmol) of **2.7b**-(2*S**,4*S**) as a white solid.

(2*S**,4*S**)-4-(benzyloxy)-6-methyl-2-(*p*-tolyl)heptan-2-ol (**2.7b**-(2*S**,4*S**))

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.36–7.27 (m, 7H), 7.12 (d, *J* = 8.0 Hz, 2H), 4.62 (d, *J* = 11.2 Hz, 1H), 4.424 (d, *J* = 11.2 Hz, 1H), 4.416 (s, 1H), 3.93–3.87 (m, 1H), 2.32 (s, 3H), 1.97–1.87 (m, 2H), 1.65–1.56 (m, 2H), 1.53 (s, 3H), 1.43–1.34 (m, 1H), 0.90 (d, *J* = 6.0 Hz, 3H), 0.89 (d, *J* = 6.0 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 146.5, 137.6, 135.8, 128.7, 128.5, 128.2, 127.9, 124.5, 76.2, 73.8, 70.4, 47.7, 42.9, 28.6, 24.8, 23.5, 22.4, 20.9.

MS (HRMS ESI) Calcd for $C_{22}H_{30}O_2Na$ [M+Na]$^+$ 349.2144, Found: 349.2149

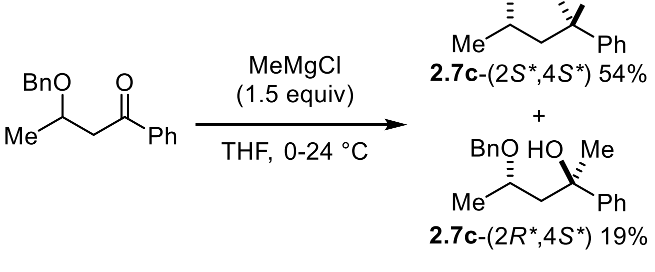
(2*R**,4*S**)-4-(benzyloxy)-6-methyl-2-(*p*-tolyl)heptan-2-ol (**2.7b**-(2*R**,4*S**))

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.35–7.23 (m, 7H), 7.14 (d, *J* = 8.4 Hz, 2H), 4.85 (s, 1H), 4.41 (d, *J* = 10.8 Hz, 1H), 3.97 (d, *J* = 10.8 Hz, 1H), 3.32–3.26 (m, 1H), 2.35 (s, 3H), 2.15 (dd, *J* = 14.8, 2.0 Hz, 1H), 1.99 (dd, *J* = 14.8, 10.8 Hz, 1H), 1.65–1.51 (m, 1H), 1.51–1.42 (m, 1H), 1.44 (s, 3H), 1.41–1.32 (m, 1H), 0.90 (d, *J* = 6.4 Hz, 3H), 0.73 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 145.1, 137.6, 135.5, 128.7, 128.4, 127.9, 127.7, 124.8, 77.3, 74.7, 70.4, 46.5, 42.6, 32.4, 24.7, 23.8, 22.0, 20.9.

MS (HRMS ESI) Calcd for $C_{22}H_{30}O_2Na$ [M+Na]$^+$ 349.2144, Found: 349.2149

5.2.1.1.31. Synthesis of 2.7c



Alcohol **2.7c** was synthesized using 3-(benzyloxy)-1-phenylbutan-1-one[20] (232 mg, 0.908 mmol) and methylmagnesium chloride (3.0 M in THF, 0.63 mL) following the procedure described in section 5.2.1.1.1. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 97:3 as the eluent for the isolation of **2.7c**-(2*R**,4*S**) followed by *n*-Hex:EtOAc, 95:5 as the eluent for the isolation of **2.7c**-(2*S**,4*S**)) gave 19% yield (44.3 mg, 0.164 mmol) of **2.7c**-(2*R**,4*S**) as a colorless oil and 54% yield (132 mg, 0.489 mmol) of **2.7c**-(2*S**,4*S**) as a colorless oil.

(2*S**,4*S**)-4-(benzyloxy)-2-phenylpentan-2-ol (**2.7c**-(2*S**,4*S**))

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.54–7.51 (m, 2H), 7.43–7.32 (m, 7H), 7.27–7.24 (m, 1H), 4.72 (d, *J* = 11.2 Hz, 1H), 4.71 (s, 1H), 4.48 (d, *J* = 11.2 Hz, 1H), 4.14–4.06 (m, 1H), 2.06 (dd, *J* = 14.8, 10.4 Hz, 1H), 1.89 (dd, *J* = 14.8, 2.8 Hz, 1H), 1.60 (s, 3H), 1.27 (d, *J* = 6.0 Hz, 3H).

^{13}C NMR (100MHz, CDCl$_3$): δ(ppm) 149.2, 137.5, 128.5, 128.0, 127.91, 127.85, 126.2, 124.4, 73.7, 73.3, 70.3, 50.0, 28.3, 19.7.

MS (HRMS ESI) Calcd for $C_{18}H_{23}O_2$ $[M+H]^+$ 271.1698, Found: 271.1702.

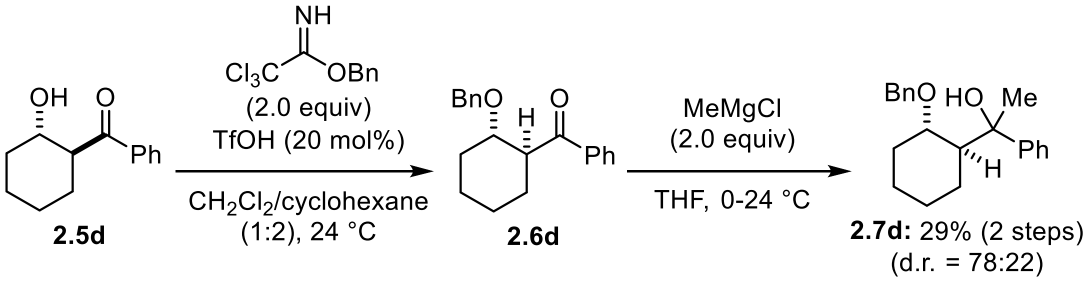
(2*R**,4*S**)-4-(benzyloxy)-2-phenylpentan-2-ol (**2.7c**-(2*R**,4*S**))

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.42–7.22 (m, 10H), 4.97 (s, 1H), 4.45 (d, *J* = 11.2 Hz, 1H), 4.02 (d, *J* = 11.2 Hz, 1H), 3.43–3.35 (m, 1H), 2.16–2.04 (m, 2H), 1.48 (s, 3H), 1.16 (d, *J* = 6.0 Hz, 3H).

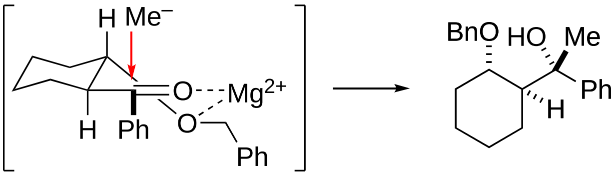
^{13}C NMR (100MHz, CDCl$_3$): δ(ppm) 148.1, 137.6, 128.5, 128.0, 127.9, 127.8, 126.1, 124.9, 74.8, 74.3, 70.4, 49.2, 32.1, 19.5.

MS (HRMS ESI) Calcd for $C_{18}H_{23}O_2$ $[M+H]^+$ 271.1698, Found: 271.1702.

5.2.1.1.32. Synthesis of 2.7d



The synthesis of β-benzyloxy ketone **2.6d** was conducted using ((1*S**,2*S**)-2-hydroxycyclohexyl)(phenyl)methanone[21] (622 mg, 3.04 mmol) and following the procedure described in section 5.2.1.1.29. The resulting crude material was used for the next step without further purification. Alcohol **2.7d** was synthesized using the crude ketone **2.6d** obtained as described above and methylmagnesium chloride (3.0 M in THF, 0.8 mL) ~~by~~ following the procedure described in section 5.2.1.1.1. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 97:3) gave 29% yield over two steps (270 mg, 0.870 mmol) of 1-((1*S**,2*S**)-2-(benzyloxy)cyclohexyl)-1-phenylethan-1-ol (**2.7d**) as an inseparable 78:22 mixture of diastereoisomers (colorless oil). The origin of the diastereoselectivity could be explained by a chelation model as shown below. The structure of the major diastereomer possessing a (*S**)-configuration at the carbinol center might be deduced from this model.



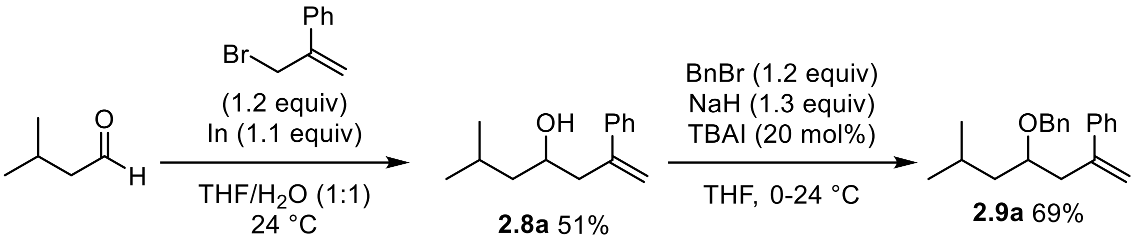
Spectral data of the major isomer are given:

<u>^{1}H NMR (400 MHz, CDCl$_3$):</u> δ(ppm) 7.44–7.21 (m, 10H), 5.99 (s, 1H), 4.57 (d, *J* = 11.2 Hz, 1H), 4.14 (d, *J* = 11.2 Hz, 1H), 2.85 (ddd, *J* = 10.4, 10.4, 4.0 Hz, 1H), 2.17–2.03 (m, 2H), 1.96–1.89 (m, 1H), 1.62–1.75 (m, 2H), 1.51 (s, 3H), 1.25–1.20 (m, 2H), 1.08–0.98 (m, 2H).

<u>^{13}C NMR (100MHz, CDCl$_3$):</u> δ(ppm) 145.9, 137.9, 128.5, 128.0, 127.6, 127.4, 126.24, 126.18, 82.1, 77.6, 69.9, 54.6, 31.0, 28.3, 27.8, 26.0, 24.5.

MS (HRMS ESI) Calcd for $C_{21}H_{27}O_2$ $[M+H]^+$ 311.2011, Found: 311.2021.

5.2.1.1.33. Synthesis of 2.9a



Synthesis of 2.8a: To a solution of (3-bromoprop-1-en-2-yl)benzene[22] (7.10 g, 36.02 mmol, 1.2 equiv) in THF/H_2O (30:30 mL) was added In powder (3.79 g, 33.01 mmol, 1.1 equiv) and isovaleraldehyde (2.58 g, 30.0 mmol) at 24 °C, and the reaction mixture was stirred for 12 h at the same temperature before it was quenched with saturated NH_4Cl aqueous solution. The mixture was then filtered through a Celite pad that was rinsed with Et_2O. The organic layer was separated, and the aqueous layer was washed thrice with Et_2O. The combined organic extracts were washed with brine, dry over $MgSO_4$, filtered and concentrated. The crude material was purified by flash column chromatography (silica gel, *n*-Hex:EtOAc, 95:5) to give 51% yield (3.10 g, 15.18 mmol) of 6-methyl-2-phenylhept-1-en-4-ol (**2.8a**) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.33 (d, *J* = 7.0 Hz, 2H), 7.28–7.18 (m, 3H), 5.34 (s, 1H), 5.09 (s, 1H), 3.68–3.62 (m, 1H), 2.70 (dd, *J* = 14.0, 3.6 Hz, 1H), 2.43 (dd, *J* = 14.0, 8.8 Hz, 1H), 1.76–1.66 (m, 1H), 1.53 (d, *J* = 4.4 Hz, 1H), 1.37 (ddd, *J* = 14.0, 8.4, 5.6 Hz, 1H), 1.22 (ddd, *J* = 14.0, 8.4, 4.4 Hz, 1H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.78 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 145.5, 140.6, 128.4, 127.7, 126.2, 115.2, 67.6, 46.3, 44.3, 24.7, 23.4, 22.1.

MS (HRMS ESI) Calcd for $C_{14}H_{21}O$ $[M+H]^+$ 205.1592, Found: 205.1600.

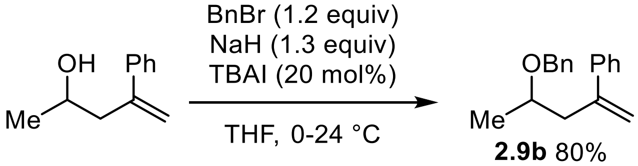
Synthesis of 2.9a: To a solution of **2.8a** (3.09 g, 15.12 mmol) in THF (45 mL) at 0 °C was added NaH (60% dispersion in mineral oil; 25 mg, 18.12 mmol) portion wise and the mixture was stirred for 30 minutes. Benzyl bromide (2.0 mL, 16.6 mmol) and tetrabutylammonoum iodide (TBAI) (1.05 g, 2.84 mmol) were then added and the reaction mixture was stirred at 24 °C for 24 h. The reaction mixture was quenched at 0 °C by slow addition of a pH 9 aqueous ammonium buffer solution. The organic materials were then extracted thrice with EtOAc and the combined organic layers were washed with brine and dried over $MgSO_4$. After the filtrate was concentrated in *vacuo*, the resulting crude material was purified by flash column chromatography (silica gel, *n*-Hex:EtOAc, 98:2) to give 69% yield (3.09 g, 10.50 mmol) of (4-(benzyloxy)-6-methylhept-1-en-2-yl)benzene (**2.9a**) as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.40–7.23 (m, 10H), 5.31 (s, 1H), 5.15 (s, 1H), 4.50 (d, *J* = 11.6 Hz, 1H), 4.37 (d, *J* = 11.6 Hz, 1H), 3.52–3.45 (m, 1H), 2.91 (dd, *J* = 14.0, 6.0 Hz, 1H), 2.60 (dd, *J* = 14.0, 6.8 Hz, 1H), 1.80–1.70 (m, 1H), 1.48 (ddd, *J* = 13.6, 8.4, 5.2 Hz, 1H), 1.28 (ddd, *J* = 13.6, 8.8, 4.8 Hz, 1H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.71 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 145.9, 141.3, 138.7, 128.3, 128.2, 127.9, 127.39, 127.35, 126.2, 114.9, 75.8, 71.2, 43.9, 41.1, 24.4, 23.4, 22.1.

MS (HRMS ESI) Calcd for $C_{21}H_{27}O$ $[M+H]^+$ 295.2062, Found: 295.2053.

5.2.1.1.34. Synthesis of 2.9b



Synthesis of (4-(benzyloxy)pent-1-en-2-yl)benzene (**2.9b**) was conducted using 4-phenylpent-4-en-2-ol[23] (487 mg, 3.00 mmol) and following the procedure described in section

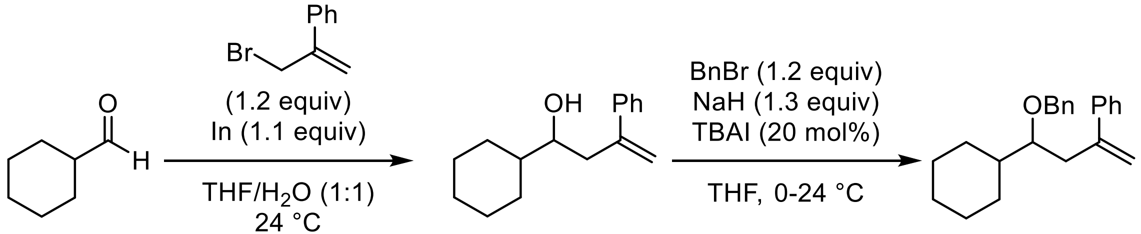
5.2.1.1.33. Purification by flash column chromatography (silica gel, *n*-Hex:Et_2O, 98:2) gave 80% yield (609 mg, 2.41 mmol) of **7b** as a colorless oil.

<u>^{1}H NMR (400 MHz, $CDCl_3$):</u> δ(ppm) 7.38–7.36 (m, 2H), 7.31–7.21 (m, 8H), 5.32 (s, 1H), 5.13 (s, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.41 (d, *J* = 12.0 Hz, 1H), 3.63–3.55 (m, 1H), 2.96 (dd, *J* = 14.0, 6.4 Hz, 1H), 2.55 (dd, *J* = 14.0, 6.8 Hz, 1H), 1.17 (d, *J* = 6.0 Hz, 3H).

<u>^{13}C NMR (100MHz, $CDCl_3$):</u> δ(ppm) 145.6, 141.1, 138.9, 128.3, 128.2, 127.6, 127.34, 127.33, 126.2, 114.8, 73.6, 70.6, 43.0, 19.6.

<u>MS (HRMS ESI)</u> Calcd for $C_{18}H_{21}O$ $[M+H]^+$ 253.1592, Found: 253.1601.

5.2.1.1.35. Synthesis of 2.9c



2.8c 57%

2.9c 98%

Synthesis of 2.8c: Alcohol **2.8c** was synthesized using cyclohexanecarboxaldehyde (1.2 mL, 9.90 mmol) and (3-bromoprop-1-en-2-yl)benzene (2.17 g, 11.0 mmol) and following the procedure described in section **5.2.1.1.33**. Purification by flash column chromatography (silica gel, *n*-Hex:Et_2O, 97:3) gave 57% yield (1.30 g, 5.65 mmol) of 1-cyclohexyl-3-phenylbut-3-en-1-ol (**2.8c**) as a colorless oil.

<u>^{1}H NMR (500 MHz, $CDCl_3$):</u> δ(ppm) 7.40–7.39 (m, 2H), 7.33–7.31 (m, 2H), 7.28–7.24 (m, 1H), 5.41 (s, 1H), 5.16 (s, 1H), 3.40–3.38 (m, 1H), 2.88 (d, *J* = 14.0 Hz, 1H), 2.41 (dd, *J* = 14.0, 10.0 Hz, 1H), 1.86–1.84 (m, 1H), 1.76–1.65 (m, 5H), 1.41–1.36 (m, 1H), 1.30–0.94 (m, 5H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 145.9, 140.4, 128.4, 127.6, 126.2, 115.1, 73.2, 43.3, 40.5, 29.0, 28.0, 26.5, 26.3, 26.1.

MS (HRMS ESI) Calcd for $C_{16}H_{22}OLi$ $[M+Li]^+$ 237.1831, Found: 237.1834.

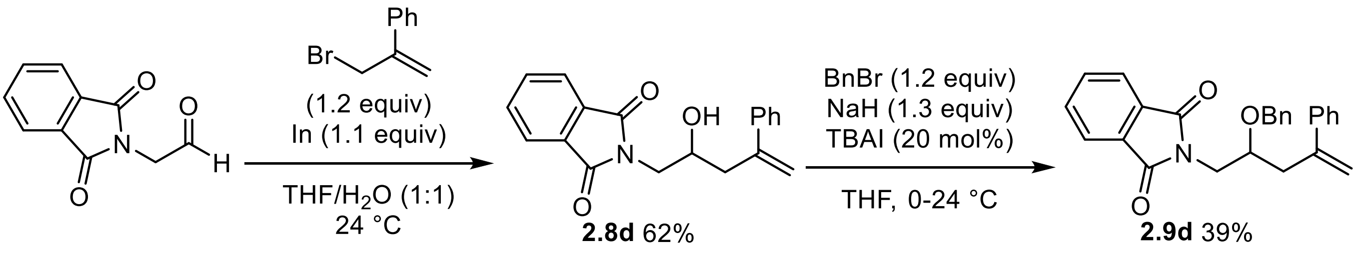
Synthesis of 2.9c: Benzyl ether **2.9c** was synthesized using **2.8c** (703 mg, 3.05 mmol) and following the procedure described in section **5.2.1.1.33**. Purification by flash column chromatography (silica gel, *n*-Hex:Et_2O, 98:2) gave 98% yield (943 mg, 2.94 mmol) of (4-(benzyloxy)-4-cyclohexylbut-1-en-2-yl)benzene (**2.9c**) as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.40–7.38 (m, 2H), 7.33–7.23 (m, 8H), 5.33 (s, 1H), 5.18 (s, 1H), 4.40 (d, *J* = 11.2 Hz, 1H), 4.36 (d, *J* = 11.2 Hz, 1H), 3.26 (ddd, *J* = 8.4, 4.4, 4.4 Hz, 1H), 2.80 (dd, *J* = 14.4, 4.4 Hz, 1H), 2.69 (dd, *J* = 14.4, 8.4 Hz, 1H), 1.80–1.64 (m, 5H), 1.53–1.51 (m, 1H), 1.18–1.09 (m, 5H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 146.3, 141.3, 139.1, 128.3, 128.1, 127.8, 127.31, 127.27, 126.3, 114.9, 82.1, 72.5, 41.9, 37.9, 29.2, 28.1, 26.7, 26.5, 26.4.

MS (HRMS ESI) Calcd for $C_{23}H_{29}O$ $[M+H]^+$ 321.2218, Found: 321.2222.

5.2.1.1.36. Synthesis of 2.9d



Synthesis of 2.8d: Alcohol **2.8d** was synthesized using 2-(1,3-dioxoisoindolin-2-yl)acetaldehyde[24] (3.78 g, 20.0 mmol) and (3-bromoprop-1-en-2-yl)benzene (4.73 g, 24.0 mmol) ~~by~~ following the procedure described in section **5.2.1.1.33.** Purification by flash column chromatography (silica gel, *n*-Hex:Et_2O, 80:20) gave 62% yield (3.82 g, 12.4 mmol) of 2-(2-hydroxy-4-phenylpent-4-en-1-yl)isoindoline-1,3-dione (**2.8d**) as a colorless oil.

<u>^{1}H NMR (400 MHz, $CDCl_3$):</u> δ(ppm) 7.83 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.70 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.42–7.39 (m, 2H), 7.34–7.30 (m, 2H), 7.28–7.24 (m, 1H), 5.41 (s, 1H), 5.21 (s, 1H), 4.02–3.98 (m, 1H), 3.83 (dd, *J* = 14.4, 3.6 Hz, 1H), 3.75 (dd, *J* = 14.4, 8.0 Hz, 1H), 2.81 (dd, *J* = 14.4, 5.2 Hz, 1H), 2.70 (dd, *J* = 14.4, 8.4 Hz, 1H), 2.43 (brs, 1H).

<u>^{13}C NMR (100 MHz, $CDCl_3$):</u> δ(ppm) 168.8, 144.4, 140.4, 134.1, 132.0, 128.5, 127.8, 126.2, 123.4, 115.8, 68.5, 43.9, 41.4.

<u>MS (HRMS ESI)</u> Calcd for $C_{19}H_{18}NO_3$ $[M+H]^+$ 308.1287, Found: 308.1280.

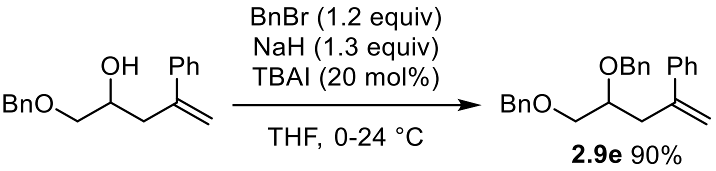
Synthesis of 2.9d: Benzyl ether **2.9d** was synthesized using **2.8d** (2.48 g, 8.06 mmol) and following the procedure described in section **5.2.1.1.33.** Purification by flash column chromatography (silica gel, *n*-Hex:Et_2O, 98:2) gave 39% yield (1.23 g, 3.10 mmol) of 2-(2-(benzyloxy)-4-phenylpent-4-en-1-yl)isoindoline-1,3-dione (**2.9d**) as a pale orange solid.

<u>^{1}H NMR (500 MHz, $CDCl_3$):</u> δ(ppm) 7.77–7.75 (m, 2H), 7.70–7.67 (m, 2H), 7.39–7.37 (m, 2H), 7.33–7.27 (m, 3H), 7.04–7.02 (m, 5H), 5.37 (s, 1H), 5.24 (s, 1H), 4.47 (d, *J* = 11.5 Hz, 1H), 4.35 (d, *J* = 11.5 Hz, 1H), 3.86–3.80 (m, 2H), 3.73–3.70 (m, 1H), 2.88 (dd, *J* = 14.5, 6.5 Hz, 1H), 2.78 (dd, *J* = 14.5, 5.0 Hz, 1H).

<u>^{13}C NMR (125 MHz, $CDCl_3$):</u> δ(ppm) 168.2, 144.7, 140.8, 138.0, 133.7, 132.0, 128.4, 128.0 (overlapped), 127.6, 127.3, 126.2, 123.1, 115.5, 74.7, 71.9, 41.5, 39.6.

<u>MS (HRMS ESI)</u> Calcd for $C_{26}H_{23}NO_3Na$ $[M+Na]^+$ 420.1576, Found: 420.1584.

5.2.1.1.37. Synthesis of 2.9e



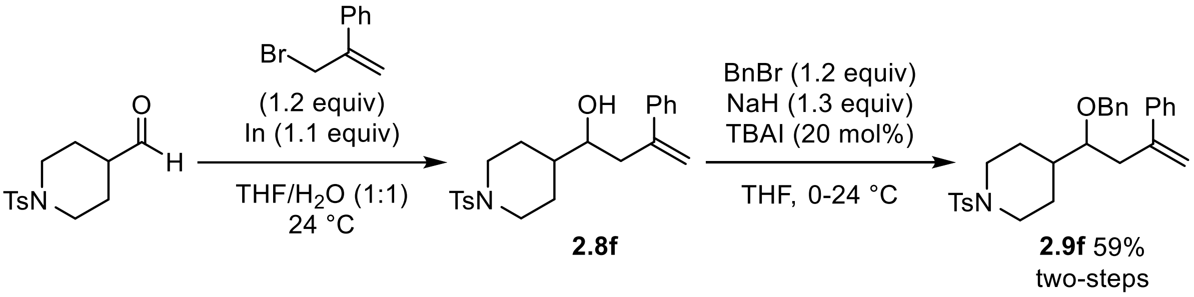
The synthesis of (((4-phenylpent-4-ene-1,2-diyl)bis(oxy))bis(methylene))dibenzene (**2.9e**) was conducted using 1-(benzyloxy)-4-phenylpent-4-en-2-ol[25] (738 mg, 2.75 mmol) following the procedure described in section **5.2.1.1.33.** Purification by flash column chromatography (silica gel, *n*-Hex:Et_2O, 98:2) gave 90% yield (886 mg, 2.47 mmol) of **2.9e** as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.38–7.24 (m, 15H), 5.34 (s, 1H), 5.16 (s, 1H), 4.60 (d, *J* = 11.6 Hz, 1H), 4.51 (s, 2H), 4.49 (d, *J* = 11.6 Hz, 1H), 3.72–3.66 (m, 1H), 3.57–3.51 (m, 2H), 2.84–2.82 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 145.2, 140.8, 138.7, 138.3, 128.32, 128.29, 128.2, 127.8, 127.6, 127.5, 127.4, 126.2 (overlapped), 115.1, 76.8, 73.3, 72.2, 72.1, 38.2.

MS (HRMS ESI) Calcd for $C_{25}H_{27}O_2$ $[M+H]^+$ 359.2011, Found: 359.2007.

5.2.1.1.38. Synthesis of 2.9f



The synthesis of 4-(1-(benzyloxy)-3-phenylbut-3-en-1-yl)-1-tosylpiperidine (**2.9f**) was performed following a 2-step protocol including 1) allylation of 1-tosylpiperidine-4-carbaldehyde[26] (530 mg, 1.98 mmol); 2) *O*-benzylation as described in section **5.2.1.1.33.** Purification by flash column chromatography (silica gel, *n*-Hex:Et_2O, 75:25) gave 59% yield

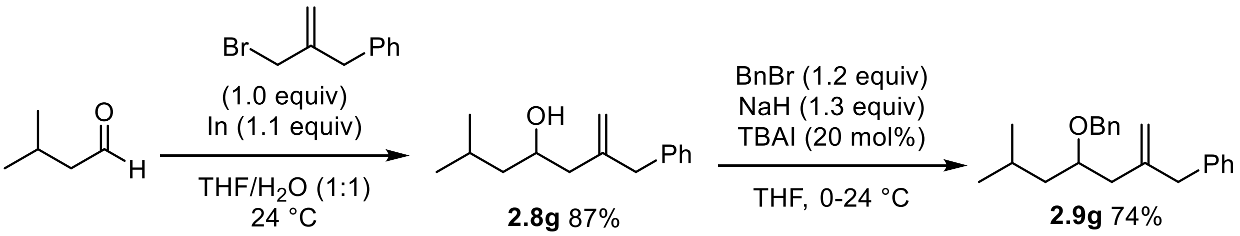
(557 mg, 1.17 mmol) of 4-(1-(benzyloxy)-3-phenylbut-3-en-1-yl)-1-tosylpiperidine (**2.9f**) as a colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 7.62 (d, *J* = 8.5 Hz, 2H), 7.34–7.25 (m, 10H), 7.18 (d, *J* = 6.5 Hz, 2H), 5.31 (s, 1H), 5.14 (s, 1H), 4.42 (d, *J* = 11.5 Hz, 1H), 4.29 (d, *J* = 11.5 Hz, 1H), 3.83–3.78 (m, 2H), 3.25 (ddd, *J* = 12.0, 6.5, 6.0 Hz, 1H), 2.72–2.71 (m, 2H), 2.42 (s, 3H), 2.15–2.12 (m, 2H), 1.79–1.76 (m, 1H), 1.59–1.47 (m, 3H), 1.41–1.38 (m, 1H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 145.5, 143.3, 140.8, 138.4, 133.2, 129.5, 128.4, 128.2, 127.8, 127.7, 127.53, 127.50, 126.2, 115.3, 80.3, 72.5, 46.5, 46.4, 39.3, 37.8, 27.9, 26.3, 21.5.

MS (HRMS ESI) Calcd for $C_{29}H_{34}NO_3S$ $[M+H]^+$ 476.2259, Found: 476.2258.

5.2.1.1.39. Synthesis of 2.9g



Synthesis of 2.8g: Alcohol **2.8g** was synthesized using isovaleraldehyde (0.42 mL, 3.90 mmol) and (2-(bromomethyl)allyl)benzene[27] (831 mg, 3.94 mmol) following the procedure described in section **5.2.1.1.33.** Purification by flash column chromatography (silica gel, *n*-Hex:Et$_2$O, 92:8) gave 87% yield (749 mg, 3.43 mmol) of 2-benzyl-6-methylhept-1-en-4-ol (**2.8g**) as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.31–7.18 (m, 5H), 4.95 (s, 1H), 4.92 (s, 1H), 3.80–3.73 (m, 1H), 3.40 (d, *J* = 14.8 Hz, 1H), 3.35 (d, *J* = 14.8 Hz, 1H), 2.17 (dd, *J* = 14.0, 3.2 Hz, 1H), 2.03 (dd, *J* = 14.0, 9.2 Hz, 1H), 1.80–1.70 (m, 1H), 1.60 (s, 1H), 1.39 (ddd, *J* = 13.6, 8.4, 5.6

Hz, 1H), 1.19 (ddd, *J* = 13.6, 8.4, 4.8 Hz, 1H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 146.0, 139.2, 129.0, 128.4, 126.3, 114.6, 66.9, 46.3, 44.4, 43.0, 24.6, 23.3, 22.1.

MS (HRMS ESI) Calcd for $C_{15}H_{23}O$ $[M+H]^+$ 219.1749, Found: 219.1758.

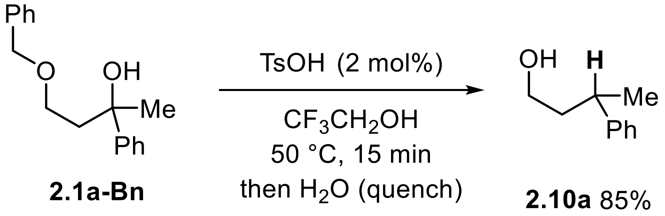
Synthesis of 2.9g: Benzyl ether **2.9g** was synthesized using **2.8g** (749 mg, 3.43 mmol) and following the procedure described in section **5.2.1.1.33.** Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 99:1) gave 74% yield (782 mg, 2.54 mmol) of (((2-benzyl-6-methylhept-1-en-4-yl)oxy)methyl)benzene (**2.9g**) as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.34–7.16 (m, 10H), 4.91 (s, 1H), 4.84 (s, 1H), 4.49 (d, *J* = 11.6 Hz, 1H), 4.38 (d, *J* = 11.6 Hz, 1H), 3.61–3.55 (m, 1H), 3.36 (s, 2H), 2.34 (dd, *J* = 14.0, 6.0 Hz, 1H), 2.11 (dd, *J* = 14.0, 6.4 Hz, 1H), 1.80–1.70 (m, 1H), 1.47 (ddd, *J* = 13.6, 8.4, 5.6 Hz, 1H), 1.25 (ddd, *J* = 13.6, 8.4, 4.4 Hz, 1H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100MHz, CDCl$_3$): δ(ppm) 146.0, 139.5, 138.8, 129.1, 128.31, 128.27, 127.9, 127.4, 126.1, 114.2, 75.6, 70.7, 43.7, 43.3, 40.4, 24.5, 23.4, 22.2.

MS (HRMS ESI) Calcd for $C_{22}H_{29}O$ $[M+H]^+$ 309.2218, Found: 309.2217.

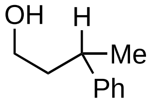
5.2.1.2. General procedure of TsOH-catalyzed 1,5-hydride transfer of benzyl and isopropyl ether



To a solution of 4-(benzyloxy)-2-phenylbutan-2-ol (76.9 mg, 0.300 mmol) in 2,2,2,-trifluoroethanol (2.9 mL) was added a solution of *p*-toluenesulfonic acid monohydrate (TsOH•H_2O) (0.06 M, 0.1 mL, 2 mol%) (prepared from 18.5 mg of TsOH•H_2O and 1.6 mL of 2,2,2-trifluoroethanol) and the reaction mixture was stirred at 50 °C under a N_2 atmosphere for 15 min. The reaction mixture was then cooled down to 24 °C and quenched with addition of a pH 9 aqueous ammonium buffer solution. The organic materials were then extracted thrice with EtOAc and the combine extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (silica gel, *n*-Hex:EtOAc, 91:9) to give 85% yield (38.6 mg, 0.257 mmol) of **2.10a** as a colorless oil.

5.2.1.3 Characterization of the products

3-phenylbutan-1-ol (2.10a)



Prepared from **2.1a-Bn** (76.9 mg, 0.300 mmol) at 50 °C for 15 min. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 91:9) gave 85% yield (38.6 mg, 0.257 mmol) of **2.10a** as a colorless oil.

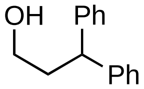
Prepared from **2.1a-*i*Pr** (104.6 mg, 0.502 mmol) at 50 °C for 15 min. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 91:9) gave 78% yield (58.7 mg, 0.391 mmol) of **2.10a** as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.31–7.25 (m, 2H), 7.21–7.17 (m, 3H), 3.60–3.51 (m, 2H), 2.88 (qd, *J* = 7.0, 7.0 Hz, 1H), 1.88–1.83 (m, 2H), 1.28 (d, *J* = 7.0 Hz, 3H), 1.25–1.23 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 146.8, 128.5, 126.9, 126.1, 61.2, 41.0, 36.4, 22.4.

MS (HRMS ESI) Calcd for $C_{10}H_{14}ONa$ $[M+Na]^+$ 173.0942, Found: 173.0937.

3,3-diphenylpropan-1-ol (2.10b)



Prepared from **2.1b-Bn** (159.8 mg, 0.502 mmol) at 50 °C for 10 min. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 91:9) gave 86% yield (90.5 mg, 0.426 mmol) of **2.10b** as a colorless oil.

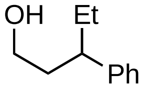
Prepared from **2.1b-*i*Pr** (135.3 mg, 0.500 mmol) at 50 °C for 10 min. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 91:9) gave 83% yield (87.6 mg, 0.413 mmol) of **2.10b** as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.33–7.19 (m, 10H), 4.15 (t, *J* = 8.0 Hz, 1H), 3.60 (t, *J* = 6.8 Hz, 2H), 2.33 (td, *J* = 8.0, 6.8 Hz, 2H), 1.73 (s, 1H).

^{13}C NMR (100MHz, $CDCl_3$): δ(ppm) 144.4, 128.5, 127.8, 126.2, 60.9, 47.2, 38.1.

MS (HRMS ESI) Calcd for $C_{15}H_{17}O$ $[M+H]^+$ 213.1279, Found: 213.1292.

3-phenylpentan-1-ol (2.10c)



Prepared from **2.1c-Bn** (81.4 mg, 0.301 mmol) at 50 °C for 13 h. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 91:9) gave 83% yield (41.0 mg, 0.250 mmol) of **2.10c** as a colorless oil.

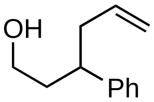
Prepared from **2.1c-*i*Pr** (111.4 mg, 0.501 mmol) at 50 °C for 13 h. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 91:9) gave 84% yield (69.4 mg, 0.423 mmol) of **2.10c** as a colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 7.31–7.28 (m, 2H), 7.21–7.16 (m, 3H), 3.55–3.51 (m, 1H), 3.49–3.34 (m, 1H), 2.62–2.56 (m, 1H), 1.97–1.94 (m, 1H), 1.83–1.79 (m, 1H), 1.72–1.59 (m, 2H), 0.79 (dd, *J* = 7.0, 7.0 Hz, 3H).

^{13}C NMR (100MHz, CDCl$_3$): δ(ppm) 144.9, 128.4, 127.6, 126.1, 61.2, 44.2, 39.2, 29.8, 12.1.

MS (HRMS ESI) Calcd for $C_{11}H_{17}O$ [M+H]$^+$ 165.1279, Found: 165.1285.

3-phenylhex-5-en-1-ol (2.10d)



Prepared from **2.1d-Bn** (142.0 mg, 0.503 mmol) at 50 °C for 10 min. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 92:8) gave 45% yield (43.7 mg, 0.225 mmol) of **2.10d** as colorless oil.

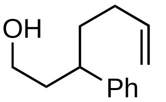
Prepared from **2.1d-*i*Pr** (117.3 mg, 0.501 mmol) at 50 °C for 15 min. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 92:8) gave 36% yield (32.0 mg, 0.182 mmol) of **2.10d** as colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.32–7.26 (m, 2H), 7.22–7.16 (m, 3H), 5.67 (dddd, *J* = 16.8, 10.4, 6.8, 6.8 Hz, 1H), 5.00–4.92 (m, 2H), 3.56–3.52 (m, 1H), 3.48–3.45 (m, 1H), 2.84–2.76 (m, 1H), 2.40–2.37 (m, 2H), 2.04–1.95 (m, 1H), 1.83–1.76 (m, 1H), 1.16 (brs, 1H).

^{13}C NMR (100MHz, CDCl$_3$): δ(ppm) 144.5, 136.7, 128.4, 127.6, 126.3, 116.2, 61.0, 42.3, 41.3, 38.6.

MS (HRMS ESI) Calcd for $C_{12}H_{17}O$ [M+H]$^+$ 177.1279, Found: 177.1286.

3-phenylhept-6-en-1-ol (2.10e)



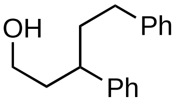
Prepared from **2.1e** (124.3 mg, 0.500 mmol) at 50 °C for 20 min. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 91:9) gave 76% yield (72.2 mg, 0.379 mmol) of **2.10e** as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.31–7.27 (m, 2H), 7.22–7.15 (m, 3H), 5.76 (dddd, *J* = 17.2, 10.4, 6.4, 6.4 Hz, 1H), 4.97–4.91 (m, 2H), 3.55–3.40 (m, 2H), 2.75–2.67 (m, 1H), 1.98–1.88 (m, 3H), 1.84–1.67 (m, 3H), 1.53 (brs, 1H).

^{13}C NMR (100MHz, CDCl$_3$): δ(ppm) 144.6, 138.5, 128.4, 127.6, 126.2, 114.5, 60.9, 41.8, 39.5, 36.0, 31.5.

MS (HRMS ESI) Calcd for $C_{13}H_{19}O$ $[M+H]^+$ 191.1436, Found: 191.1440.

3,5-diphenylpentan-1-ol (2.10f)



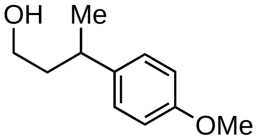
Prepared from **2.1f-*i*Pr** (121.5 mg, 0.407 mmol) at 50 °C for 15 min. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 92:8) gave 90% yield (88.1 mg, 0.367 mmol) of **2.10f** as a colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 7.31–7.30 (m, 2H), 7.26–7.14 (m, 6H), 7.10–7.09 (m, 2H), 3.50 (ddd, *J* = 10.5, 7.0, 5.5 Hz, 1H), 3.43 (ddd, *J* = 10.5, 7.5, 6.5 Hz, 1H), 2.76–2.70 (m, 1H), 2.45 (dd, *J* = 8.0, 8.0 Hz, 2H), 2.01–1.89 (m, 3H), 1.86–1.78 (m, 1H), 1.20 (brs, 1H).

^{13}C NMR (100MHz, CDCl$_3$): δ(ppm) 144.6, 142.3, 128.5, 128.33, 128.26, 127.7, 126.3, 125.7, 61.0, 42.1, 39.7, 38.6, 33.7.

MS (HRMS ESI) Calcd for $C_{17}H_{20}OLi$ $[M+Li]^+$ 247.1674, Found: 247.1669.

3-(4-methoxyphenyl)butan-1-ol (2.10g)



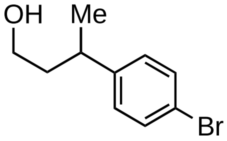
Prepared from **2.1g-*i*Pr** (124.0 mg, 0.520 mmol) at 50 °C for 30 min. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 91:9) gave 65% yield (61.3 mg, 0.340 mmol) of **2.10g** as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.11 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 3.77 (s, 3H), 3.59–3.46 (m, 2H), 2.82 (qdd, *J* = 7.2, 7.2, 7.2 Hz, 1H), 1.86–1.72 (m, 3H), 1.23 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 157.8, 138.9, 127.7, 113.8, 61.0, 55.1, 41.0, 35.5, 22.5.

MS (HRMS ESI) Calcd for $C_{11}H_{17}O_2$ $[M+H]^+$ 181.1229, Found: 181.1232.

3-(4-bromophenyl)butan-1-ol (2.10h)



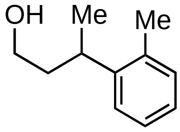
Prepared from **2.1h-*i*Pr** (141.3 mg, 0.492 mmol) at 50 °C for 30 min. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 91:9) gave 87% yield (97.9 mg, 0.427 mmol) of **2.10h** as a yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) δ 7.44–7.36 (m, 2H), 7.10–7.05 (m, 2H), 3.58 (ddd, *J* = 10.8, 6.4, 6.4 Hz, 1H), 3.48 (ddd, *J* = 10.8, 6.8, 6.8 Hz, 1H), 2.87 (qdd, *J* = 7.2, 7.2, 7.2 Hz, 1H), 1.89–1.75 (m, 2H), 1.60 (brs, 1H), 1.25 (d, *J* = 7.2 Hz, 3H). H from OH missing or under the water peak at δ=1.6ppm?

^{13}C NMR (100MHz, $CDCl_3$): δ(ppm) 145.8, 131.5, 128.7, 119.7, 60.9, 40.7, 35.8, 22.2.

MS (HRMS ESI) Calcd for $C_{10}H_{14}OBr$ [M+H]$^+$ 229.0228, Found: 229.0222.

3-(*o*-tolyl)butan-1-ol (2.10i)



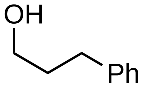
Prepared from **2.1i-*i*Pr** (103.9 mg, 0.499 mmol) at 50 °C for 1.5 h. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 91:9) gave 94% yield (77.2 mg, 0.470 mmol) of **2.10i** as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.23–7.05 (m, 4H), 3.61–3.50 (m, 2H), 3.16 (qdd, *J* = 7.2, 7.2, 7.2 Hz, 1H), 2.34 (s, 3H), 1.92–1.78 (m, 2H), 1.60 (brs, 1H), 1.23 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 145.0, 135.3, 130.2, 126.2, 125.6, 125.2, 61.1, 40.4, 30.9, 21.7, 19.5.

MS (HRMS ESI) Calcd for $C_{11}H_{17}O$ [M+H]$^+$ 165.1279, Found: 165.1275.

3-phenylpropan-1-ol (2.10j)



Prepared from **2.1j-*i*Pr** (58.3 mg, 0.300 mmol) at 80 °C for 1.5 h. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 90:10) gave 85% yield (34.8 mg, 0.255 mmol) of **2.10j** as a colorless oil.

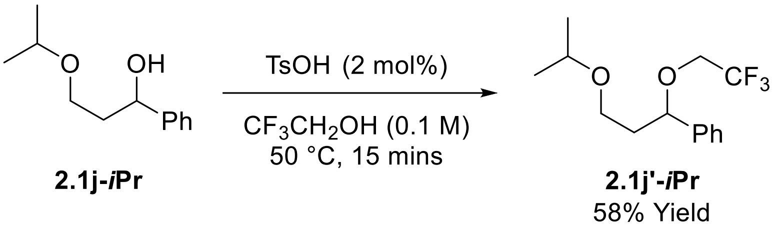
Prepared from **2.1j-Bn** (73.0 mg, 0.301 mmol) at 80 °C for 1.5 h. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 90:10) to give 79% yield (32.3 mg, 0.237 mmol) of **2.10j** as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.31–7.25 (m, 2H), 7.21–7.17 (m, 3H), 3.67 (t, *J* = 6.4 Hz, 2H), 2.71 (t, *J* = 7.6 Hz, 2H), 1.93–1.86 (m, 2H), 1.63 (brs, 1H).

^{13}C NMR (100MHz, CDCl$_3$): δ(ppm) 141.8, 128.38, 128.35, 125.8, 62.2, 34.2, 32.0.

MS (HRMS ESI) Calcd for $C_9H_{12}ONa$ $[M+Na]^+$ 159.0786, Found: 159.0793.

The reaction of **2.1j-*i*Pr** at 50 °C gave trifluoroethylether **2.1j-*i*Pr'**.



Prepared from **2.1j-*i*Pr** (58.8 mg, 0.303 mmol) at 50 °C for 15 min. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 99:1) gave 58% yield (48.4 mg, 0.175 mmol) of (3-isopropoxy-1-(2,2,2-trifluoroethoxy)propyl)benzene (**2.1j-*i*Pr'**) as a colorless oil.

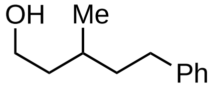
^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.38–7.25 (m, 5H), 4.61–4.58 (m, 1H), 3.71–3.51 (m, 4H), 3.38–3.35 (m, 1H), 2.13–2.06 (m, 1H), 1.90–1.82 (m, 1H), 1.16–1.13 (m, 6H).

^{13}C NMR (100MHz, CDCl$_3$): δ(ppm) 140.7, 128.7, 128.2, 126.8, 124.1 (q, *J* = 279.8 Hz), 80.5, 71.7, 66.7 (q, *J* = 34.3 Hz), 64.0, 38.6, 22.2, 22.1.

^{19}F NMR (282 MHz, CDCl$_3$); δ(ppm) -74.1, (t, *J* = 8.7 Hz).

MS (HRMS ESI) Calcd for $C_{14}H_{20}O_2F_3$ $[M+H]^+$ 277.1415, Found: 277.1420.

3-methyl-5-phenylpentan-1-ol (2.10k)



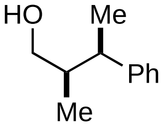
Prepared from **2.1k-*i*Pr** (119.1 mg, 0.5039 mmol) with at 80 °C for 18 h. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 91:9) gave 41% yield (37.0 mg, 0.2076 mmol) of **2.10k** as a colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 7.29–7.25 (m, 2H), 7.19–7.16 (m, 3H), 3.73–3.64 (m, 2H), 2.67 (ddd, *J* = 13.5, 10.0, 5.5 Hz, 1H), 2.58 (ddd, *J* = 13.5, 10.5, 5.5 Hz, 1H), 1.69–1.59 (m, 3H), 1.52–1.41 (m, 2H), 1.25 (s, 1H), 0.97 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (100MHz, CDCl$_3$): δ(ppm) 142.8, 128.31, 128.30, 125.6, 61.1, 39.8, 39.0, 33.3, 29.2, 19.5.

MS (HRMS ESI) Calcd for $C_{12}H_{18}ONa$ $[M+Na]^+$ 201.1255, Found: 201.1259.

(2*R,3*R**)-2-methyl-3-phenylbutan-1-ol (2.11a)**



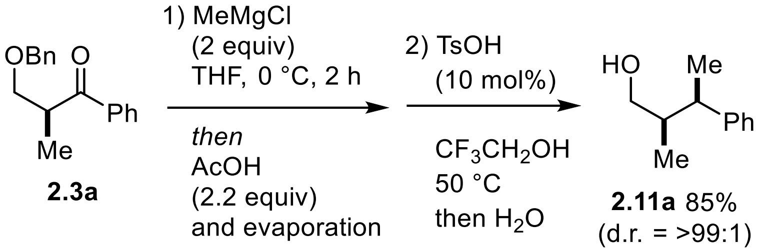
Prepared from **2.4a** (140.4 mg, 0.514 mmol) at 50 °C for 15 min. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 90:10) gave 97% yield of **2.11a** (83.0 mg, 0.505 mmol) as a single diastereomer as a colorless oil. The stereochemsitry of **2.11a** was confirmed by comparison with previously reported data.[28]

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.31–7.25 (m, 2H), 7.20–7.17 (m, 3H), 3.45 (dd, *J* = 10.8, 4.8 Hz, 1H), 3.28 (dd, *J* = 10.8, 6.4 Hz, 1H), 2.68 (dq, *J* = 7.2, 7.2 Hz, 1H), 1.86–1.79 (m, 1H), 1.39 (s, 1H), 1.24 (d, *J* = 7.2 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 146.4, 128.3, 127.3, 126.0, 66.6, 42.1, 41.6, 17.9, 14.1.

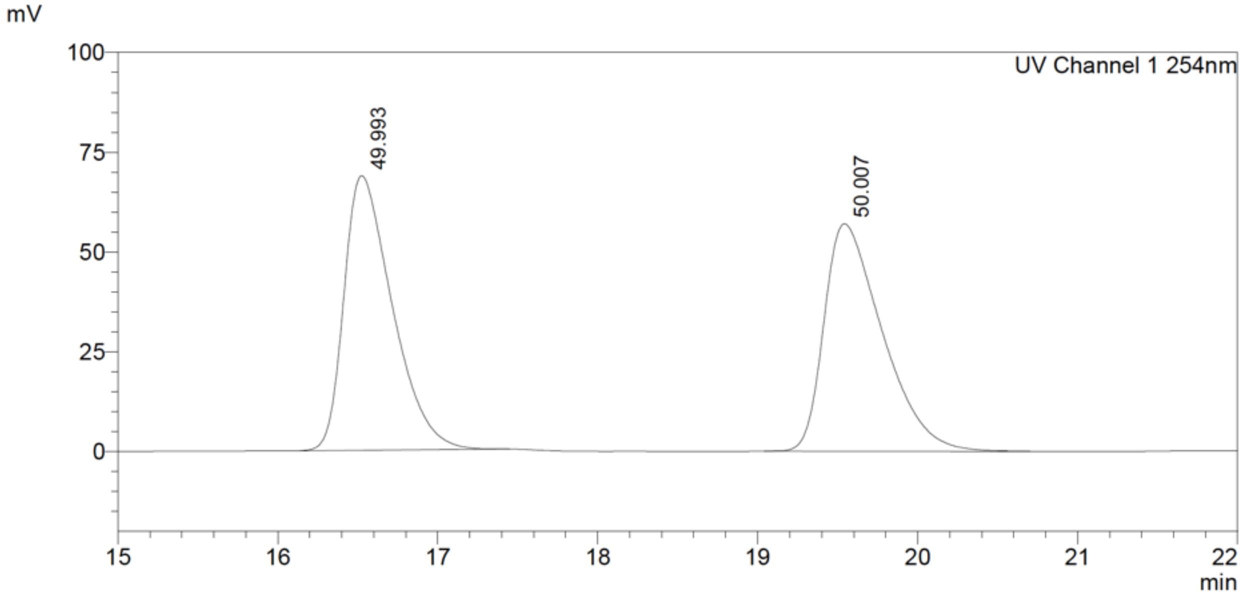
MS (HRMS ESI) Calcd for $C_{11}H_{17}O$ $[M+H]^+$ 165.1279, Found: 165.1283.

One-pot synthesis of 2.11a-(2*R*,3*R*) from ketone 2.3a-(*S*)



To an ice cold solution of (*S*)-3-(benzyloxy)-2-methyl-1-phenylpropan-1-one (128.2 mg, 0.504 mmol) in THF (0.7 mL) was added methylmagnesium chloride solution (3.0 M in THF, 0.3 mL) and the reaction mixture was stirred at the same temperature for 2 h. The reaction was quenched with addition of AcOH (63 μL, 1.10 mmol) and the volatile materials were removed under reduced pressure. The resulting crude residue was subsequently diluted with 2,2,2-trifluoroethanol (4.5 mL) and a solution *p*-toluenesulfonicacid monohydrate in 2,2,2-trifluoroethanol (10 mol%, 0.5 mL, prepared from 20.5 mg of TsOH in 1 mL of trifluoroethanol) was added. The reaction mixture was stirred at 50 °C for 66 h. The reaction mixture was then cooled to room temperature and quenched by addition of a pH 9 aqueous ammonium buffer solution. The organic materials were then extracted thrice with EtOAc and the combine extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (silica gel, *n*-Hex:EtOAc, 90:10) to give 85% yield (70.2 mg, 0.427 mmol) of **2.11a**-(2*R*,3*R*) as a single diastereomer. The enantiomeric excess (ee) of **2.11a**-(2*R*,3*R*) was measured by HPLC (Daicel Chiralpak IG column), *n*-Hex:*i*-PrOH = 98/2, flow 1.0 mL/min, 254 nm, t_1 = 15.0 min (major), t_2 = 18.0 min (minor); $[\alpha]_D^{25}$ = +12.6° (*c* = 0.73, $CHCl_3$) for 99% ee.

HPLC chart for racemic **2.11a**

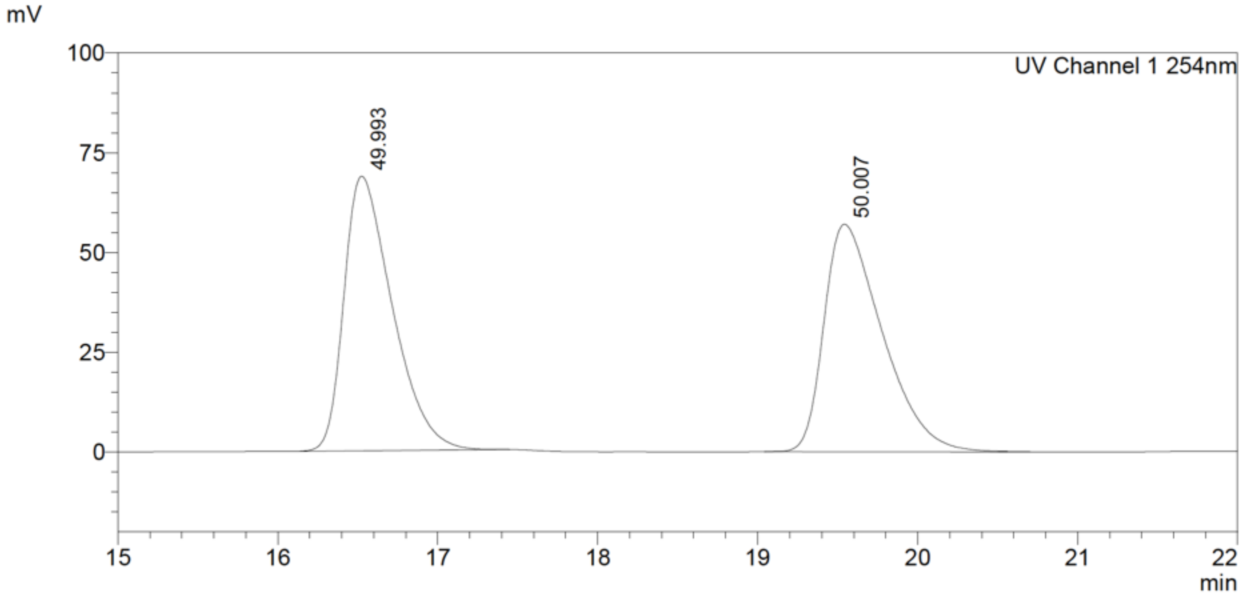


<Peak Table>

UV Channel 1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	16.524	1445479	68820	49.993
2	19.542	1445872	57018	50.007
Total		2891350	125838	100.000

HPLC chart for **2.11a**-(2*R*,3*R*)

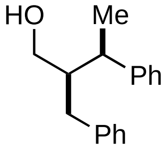


<Peak Table>

UV Channel 1 254nm

Peak#	Ret. Time	Area	Height	Area%
1	16.524	1445479	68820	49.993
2	19.542	1445872	57018	50.007
Total		2891350	125838	100.000

(2*R**,3*R**)-2-benzyl-3-phenylbutan-1-ol (2.11b)



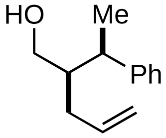
Prepared from **2.4b** (175.2 mg, 0.506 mmol) with 5 mol% of TsOH at 80 °C for 40 h. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 94:6) gave 94% yield of **2.11b** (113.7 mg, 0.473 mmol) as a single diastereomer (colorless oil).

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.33–7.15 (m, 10H), 3.38 (dd, *J* = 11.2, 5.6 Hz, 1H), 3.30 (dd, *J* = 11.2, 4.4 Hz, 1H), 2.96 (qd, *J* = 7.2, 7.2 Hz, 1H), 2.86 (dd, *J* = 13.6, 4.4 Hz, 1H), 2.56 (dd, *J* = 13.6, 10.0 Hz, 1H), 2.02–1.94 (m, 1H), 1.38 (d, *J* = 7.2 Hz, 3H), 1.01 (brs, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 145.9, 140.9, 129.1, 128.44, 128.35, 127.6, 126.2, 125.9, 62.3, 49.2, 40.1, 34.4, 18.4.

MS (HRMS ESI) Calcd for $C_{17}H_{21}O$ $[M+H]^+$ 241.1592, Found: 241.1595.

(*R**)-2-((*R**)-1-phenylethyl)pent-4-en-1-ol (2.11c)



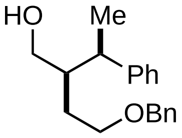
Prepared from 2.4**c** (145.3 mg, 0.490 mmol) at 50 °C for 10 min. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 91:9) gave 89% yield (83.4 mg, 0.438 mmol) of **2.11c** as single diastereomer (colorless oil).

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.30–7.26 (m, 2H), 7.20–7.16 (m, 3H), 5.83 (dddd, *J* = 17.2, 10.4, 8.4, 6.4 Hz, 1H), 5.09 (d, *J* = 17.2 Hz, 1H), 5.04 (d, *J* = 10.4 Hz, 1H), 3.47 (dd, *J* = 11.6, 5.2 Hz, 1H), 3.36 (dd, *J* = 11.6, 5.2 Hz, 1H), 2.82 (qd, *J* = 7.2, 7.2 Hz, 1H), 2.34–2.30 (m, 1H), 2.19-2.13 (m, 1H), 1.80–1.76 (m, 1H), 1.35 (s, 1H), 1.28 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 145.9, 137.0, 128.4, 127.5, 126.1, 116.4, 63.3, 46.7, 39.9, 32.9, 18.6.

MS (HRMS ESI) Calcd for $C_{13}H_{18}ONa$ $[M+Na]^+$ 213.1255, Found: 213.1252.

(*R**)-4-(benzyloxy)-2-((*R**)-1-phenylethyl)butan-1-ol (2.11d)



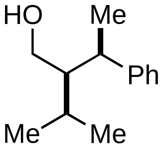
Prepared from **2.4d** (196.1 mg, 0.502 mmol) at 50 °C for 30 mins. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 92:8) gave 67% yield (95.2 mg, 0.335 mmol) of **2.11d** as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.37–7.25 (m, 7H), 7.21–7.17 (m, 3H), 4.50 (s, 2H), 3.62–3.58 (m, 1H), 3.54–3.48 (m, 2H), 3.35 (dd, *J* = 11.6, 6.0 Hz, 1H), 2.85 (qd, *J* = 7.2, 7.2 Hz, 1H), 2.77 (s, 1H), 1.91–1.79 (m, 2H), 1.74–1.66 (m, 1H), 1.25 (d, *J* = 7.2, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 146.0, 137.7, 128.4, 128.3, 127.76, 127.74, 127.5, 126.0, 73.2, 69.0, 64.2, 45.8, 40.7, 29.0, 18.1.

MS (HRMS ESI) Calcd for $C_{19}H_{25}O_2$ $[M+H]^+$ 285.1855, Found: 285.1845.

(2*R**,3*R**)-2-isopropyl-3-phenylbutan-1-ol (2.11e)



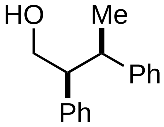
Prepared from **2.4e** (148.7 mg, 0.498 mmol). Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 91:9) gave 85% yield (81.4 mg, 0.423 mmol) of **2.11e** as a single diastereomer (colorless oil).

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.32–7.28 (m, 2H), 7.25–7.17 (m, 3H), 3.50 (dd, *J* = 11.6, 4.8 Hz, 1H), 3.45 (dd, *J* = 11.6, 3.6 Hz, 1H), 2.82 (qd, *J* = 7.2, 7.2 Hz, 1H), 2.07 (sept of d, *J* = 6.8, 3.2 Hz, 1H), 1.56–1.50 (m, 1H), 1.28 (d, *J* = 6.8 Hz, 3H), 1.05 (d, *J* = 7.2 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.77 (brs, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 146.7, 128.6, 127.5, 126.2, 61.7, 52.8, 40.1, 27.2, 22.0, 20.2, 17.4.

MS (HRMS ESI) Calcd for $C_{13}H_{21}O$ $[M+H]^+$ 193.1592, Found: 193.1596.

(2*S,3*R**)-2,3-diphenylbutan-1-ol (2.11f)**



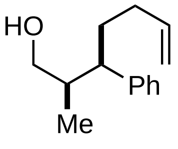
Prepared from **2.4f** (166.2 mg, 0.500 mmol) at 50 °C for 45 mins. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 91:9) gave 88% yield (99.6 mg, 0.440 mmol) of **2.11f** as a single diastereomer (white solid).

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.39–7.23 (m, 10H), 3.61–3.48 (m, 2H), 3.02–2.90 (m, 2H), 1.03 (d, *J* = 6.8 Hz, 3H), 1.00 (s, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 145.5, 141.5, 128.7, 128.61, 128.59, 127.3, 126.9, 126.5, 65.9, 55.6, 42.5, 20.9.

MS (HRMS ESI) Calcd for $C_{16}H_{19}O$ $[M+H]^+$ 227.1436, Found: 227.1434.

(2*R,3*R**)-2-methyl-3-phenylhept-6-en-1-ol (2.11g)**



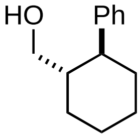
Prepared from **2.4g** (156.3 mg, 0.503 mmol) at 50 °C for 15 mins. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 90:10) gave 69% yield (70.8 mg, 0.346 mmol) of **2.11g** as a 97:3 diastereomeric mixture (colorless oil).

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) δ 7.30–7.25 (m, 2H), 7.21–7.17 (m, 1H), 7.15–7.13 (m, 2H), 5.78–5.71 (m, 1H), 4.92–4.88 (m, 2H), 3.41 (dd, *J* = 10.8, 4.4 Hz, 1H), 3.21 (dd, *J* = 10.8, 6.4 Hz, 1H), 2.48 (ddd, *J* = 11.4, 8.7, 3.2 Hz, 1H), 1.89–1.63 (m, 5H), 1.26 (brs, 1H), 1.05 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 143.8, 138.7, 128.4, 128.2, 126.2, 114.4, 66.6, 47.9, 41.4, 31.70, 31.67, 15.2.

MS (HRMS ESI) Calcd for $C_{14}H_{21}O$ $[M+H]^+$ 205.1592, Found: 205.1584.

((1*S,2*S**)-2-phenylcyclohexyl)methanol (2.11h)**



Prepared from **2.4h**-(1*R**,2*R**) (149.0 mg, 0.503 mmol) at 80 °C for 1 h. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 91:9) gave 95% yield (82.9 mg, 0.479 mmol) of **2.11h** as a single diastereomer (colorless oil).

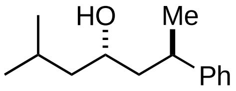
Prepared from **2.4h**-(1*S**,2*R**) (115.5 mg, 0.390 mmol). Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 91:9) gave 94% yield (69.4 mg, 0.365 mmol) of **2.11h** as a single diastereomer (colorless oil).

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.28–7.22 (m, 2H), 7.18–7.15 (m, 3H), 3.32 (dd, *J* = 10.8, 4.4 Hz, 1H), 3.16 (dd, *J* = 10.8, 6.4 Hz, 1H), 2.30 (ddd, *J* = 11.2, 11.2, 3.2 Hz, 1H), 1.97–1.93 (m, 1H), 1.85–1.79 (m, 3H), 1.72–1.63 (m, 1H), 1.47–1.20 (m, 5H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 145.7, 128.4, 127.3, 126.1, 66.2, 47.1, 45.1, 35.4, 29.8, 26.6, 26.0.

MS (HRMS ESI) Calcd for $C_{13}H_{19}O$ [M+H]$^+$ 191.1436, Found: 191.1427.

(4*S,6*R**)-2-methyl-6-phenylheptan-4-ol (2.13a)**



Prepared from **2.7a**-(2*S**,4*S**) (155.9 mg, 0.499 mmol) at 50 °C for 10 mins. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 93:7) gave 91% yield of **2.13a** (93.6 mg, 0.454 mmol) as a 86:14 diastereomeric mixture (based on ^{1}H NMR analysis) (colorless oil).

Prepared from **2.7a**-(2*R**,4*S**) (114.2 mg, 0.362 mmol) at 50 °C for 10 mins. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 93:7) gave 92% yield of **2.13a** (68.6 mg, 0.332 mmol) as a 89:11diastereomeric mixture (based on ^{1}H NMR analysis) (colorless oil).

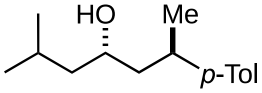
Spectral data of the major isomer:

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.33–7.29 (m, 2H), 7.24–7.18 (m, 3H), 3.72–3.66 (m, 1H), 2.93 (qdd, *J* = 7.2, 7.2, 7.2 Hz, 1H), 1.78–1.62 (m, 3H), 1.38–1.34 (m, 1H), 1.30–1.28 (m, 2H), 1.29 (d, *J* = 7.2 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 147.5, 128.5, 126.8, 126.0, 68.2, 47.0, 46.8, 36.6, 24.5, 23.5, 22.0, 21.9.

MS (HRMS ESI) Calcd for $C_{14}H_{23}O$ [M+H]$^+$ 207.1749, Found: 207.1759.

(4*S,6*R**)-2-methyl-6-(p-tolyl)heptan-4-ol (2.13b)** [29]



Prepared from **2.7b** (164.2 mg, 0.503 mmol) at 50 °C for 20 mins. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 93:7) gave 82% yield of **2.13b** (90.5 mg, 0.411 mmol) as a 88:12 diastereomeric mixture (based on ^{1}H NMR analysis) (colorless oil).

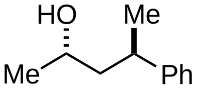
Spectral data of the major isomer:

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.10–7.09 (m, 4H), 3.69–3.63 (m, 1H), 2.85 (qdd, *J* = 7.2, 7.2, 7.2 Hz, 1H), 2.31 (s, 3H), 1.77–1.62 (m, 3H), 1.38–1.33 (m, 2H), 1.27–1.22 (m, 1H), 1.25 (d, *J* = 7.2 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 144.4, 135.5, 129.2, 126.7, 68.3, 47.0, 46.9, 36.3, 24.4, 23.5, 22.02, 21.98, 20.9.

MS (HRMS ESI) Calcd for $C_{15}H_{25}O$ $[M+H]^+$ 221.1905, Found: 221.1905.

(2*S,4*R**)-4-phenylpentan-2-ol (2.13c)**[30]



Prepared from single diastereomer **2.7c**-(2*S**,4*S**) (139.3 mg, 0.516 mmol). Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 91:9) gave 89% yield (75.1 mg, 0.458 mmol) of **2.13c** as a 88:12 diastereomeric mixture (based on ^{1}H NMR analysis) (colorless oil).

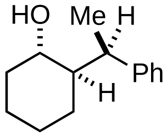
Spectra data of the major isomer:

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.32–7.27 (m, 2H), 7.22–7.17 (m, 3H), 3.80–3.72 (m, 1H), 2.88 (qdd, *J* = 7.6, 7.6, 7.6 Hz, 1H), 1.82 (ddd, *J* = 13.6, 7.6, 7.6 Hz, 1H), 1.64 (ddd, *J* = 13.6, 7.6, 5.6 Hz, 1H), 1.35 (brs, 1H), 1.26 (d, *J* = 7.6 Hz, 3H), 1.18 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 147.2, 128.5, 126.8, 126.1, 66.4, 47.8, 36.9, 23.7, 22.3.

MS (HRMS ESI) Calcd for $C_{11}H_{17}O$ $[M+H]^+$ 165.1279, Found: 165.1281.

(1*S,2*R**)-2-((*R**)-1-phenylethyl)cyclohexan-1-ol (2.13d)**



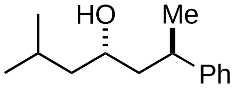
Prepared from **2.7d** (113.4 mg, 0.365 mmol) at 50 °C for 10 mins. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 92:8) gave 83% yield (61.7 mg, 0.302 mmol) of **2.13d** as a single diastereomer (colorless oil). The stereochemsitry of **2.13d** was confirmed by comparison with previously reported one.[31]

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.32–7.28 (m, 2H), 7.25–7.23 (m, 2H), 7.21–7.17 (m, 1H), 3.47 (ddd, *J* = 9.6, 9.6, 4.6 Hz, 1H), 3.33 (qd, *J* = 7.2, 4.2 Hz, 1H), 2.01–1.97 (m, 1H), 1.71–1.68 (m, 1H), 1.60–1.56 (m, 1H), 1.52–1.44 (m, 3H), 1.29–1.22 (m, 2H), 1.24 (d, *J* = 7.2 Hz, 3H), 1.12–1.00 (m, 2H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 146.4, 128.1, 127.8, 125.7, 72.2, 51.4, 38.2, 35.9, 25.4, 24.8, 24.5, 13.7.

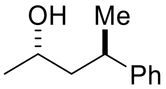
MS (HRMS ESI) Calcd for $C_{14}H_{21}O$ $[M+H]^+$ 205.1592, Found: 205.1598.

(4*S,6*R**)-2-methyl-6-phenylheptan-4-ol (2.14a = 2.13a)** (for Scheme 2.26)



Prepared from **2.9a** (88.0 mg, 0.299 mmol) at 50 °C for 20 mins. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 93:7) gave 81% yield of **2.14a** (= **2.13a**) (50.6 mg, 0.245 mmol) as a 86:14 diastereomeric mixture (based on ^{1}H NMR analysis) (colorless oil).

(2*S,4*R**)-4-phenylpentan-2-ol (2.14b = 2.13c)** (for Scheme 2.26)



Prepared from **2.9b** (126.2 mg, 0.500 mmol) at 50 °C for 5 mins. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 91:9) gave 81% yield of **2.14b** (= **2.13b**) (66.2 mg, 0.403 mmol) as a 86:14 diastereomeric mixture (based on ^{1}H NMR analysis) (colorless oil).

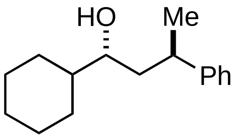
Spectra data of the major isomer:

^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.30–7.27 (m, 2H), 7.21–7.16 (m, 3H), 3.77–3.71 (m, 1H), 2.88–2.81 (m, 1H), 1.84–1.78 (m, 1H), 1.69–1.60 (m, 2H), 1.26 (d, *J* = 6.0 Hz, 3H), 1.18 (d, *J* = 6.0 Hz, 3H).

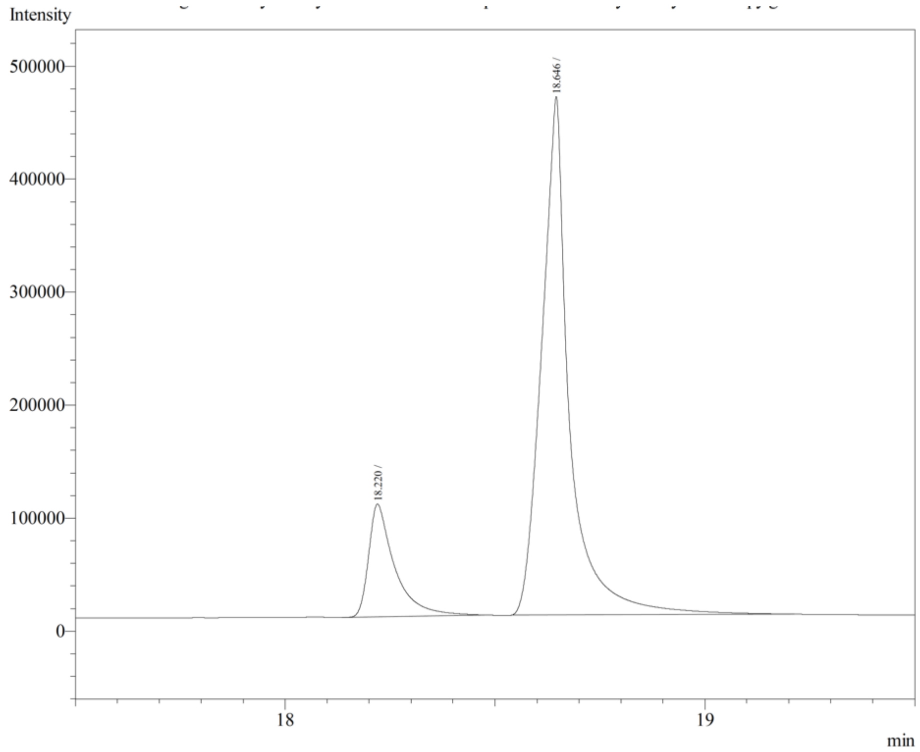
^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 147.2, 128.5, 126.8, 126.1, 66.2, 47.7, 36.8, 23.6, 22.3.

MS (HRMS ESI) Calcd for $C_{11}H_{17}O$ $[M+H]^+$ 165.1279, Found: 165.1281.

1-cyclohexyl-3-phenylbutan-1-ol (2.14c)



Prepared from **2.9c** (111.0 mg, 0.346 mmol) at 50 °C for 10 mins. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 92:8) gave 99% yield of **2.14c** (79.4 mg, 0.342 mmol) as a 83:17 diastereomeric mixture (based on GC analysis) (colorless oil).



Peak Table - Channel 1

Peak#	Ret.Time	Area	Height	Area%
1	18.220	430244	99380	16.7937
2	18.646	2131686	457327	83.2063
Total		2561930	556707	100.0000

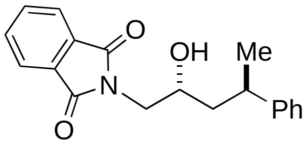
Spectra data of the major isomer:

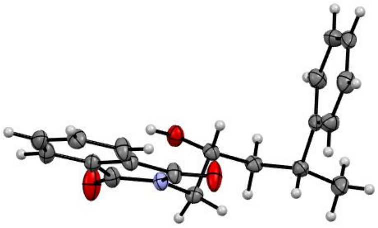
^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.32–7.17 (m, 5H), 3.47 (ddd, *J* = 6.0, 6.0, 6.0 Hz, 1H), 2.93 (qdd, *J* = 7.2, 7.2, 7.2 Hz, 1H), 1.79–1.62 (m, 7H), 1.32–1.03 (m, 7H), 1.26 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 148.0, 128.5, 126.9, 126.0, 74.3, 44.0, 43.1, 36.7, 29.2, 27.5, 26.6, 26.4, 26.2, 21.4.

MS (HRMS ESI) Calcd for $C_{16}H_{25}O$ [M+H]$^+$ 233.1905, Found: 233.1906.

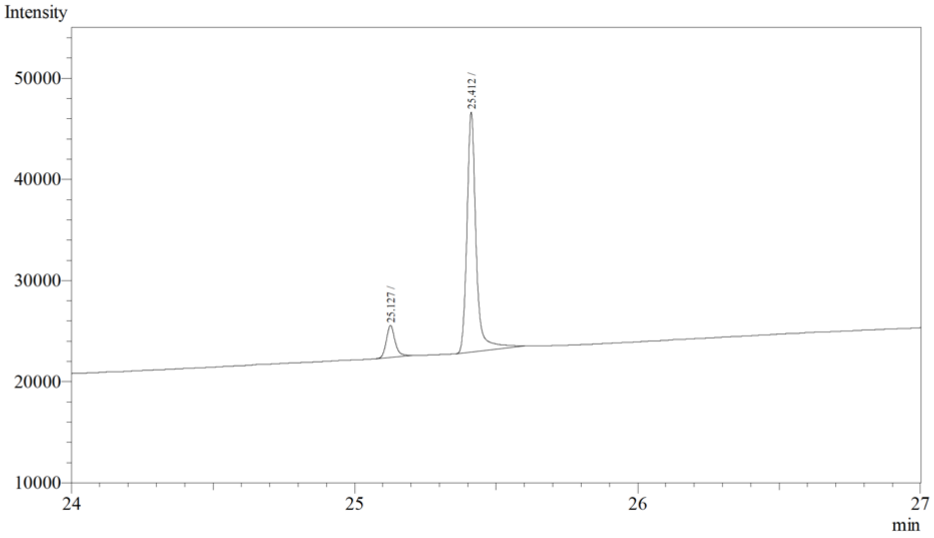
2-(2-hydroxy-4-phenylpentyl)isoindoline-1,3-dione (2.14d)





X-ray of major isomer

Prepared from **2.9d** (191.5 mg, 0.485 mmol) at 50 °C for 2 h. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 80:20) gave 84% yield (125.3 mg, 0.405 mmol) of **2.14d** as a 89:11 diastereomeric mixture (based on GC analysis) (white solid). Recrystallization from a *n*-Hex:EtOAc:*i*PrOH mixture gave a single crystal of the major isomer, the structure of which could be confirmed by the X-ray crystallographic analysis (CCDC 1821569).



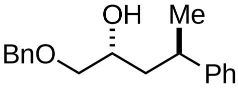
Peak#	Ret.Time	Area	Height	Area%
1	25.127	6861	3147	11.3701
2	25.412	53480	23572	88.6299
Total		60341	26719	100.0000

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.84–7.81 (m, 2H), 7.73–7.69 (m, 2H), 7.30–7.15 (m, 5H), 3.94–3.90 (m, 1H), 3.82–3.67 (m, 2H), 2.99 (qdd, J = 7.2, 7.2, 7.2 Hz, 1H for the major isomer), 2.34 (brs, 1H), 1.83–1.71 (m, 2H), 1.27 (d, *J* = 7.2 Hz, 3H for both the major and minor isomer).

^{13}C NMR (100 MHz, CDCl$_3$): (for the major isomer) δ(ppm) 169.0, 147.0, 134.1, 131.9, 128.5, 126.9, 126.2, 123.4, 68.9, 44.4, 43.3, 36.2, 21.6.

MS (HRMS ESI) Calcd for $C_{19}H_{20}NO_3$ $[M+H]^+$ 310.1443, Found: 310.1447.

1-(benzyloxy)-4-phenylpentan-2-ol (2.14e)



Prepared from **2.9e** (179.0 mg, 0.499 mmol) at 50 °C for 40 mins. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 85:15) gave 80% yield (108.1 mg, 0.400 mmol) of **2.14e** as a 87:13 diastereomeric mixture (based on ^{1}H NMR analysis) (colorless oil).

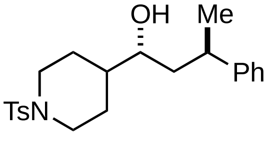
Spectra data of the major isomer:

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.36–7.25 (m, 7H), 7.22–7.15 (m, 3H), 4.51 (s, 2H), 3.85–3.79 (m, 1H), 3.48 (dd, *J* = 9.5, 3.0 Hz, 1H), 3.31 (dd, *J* = 9.5, 7.2 Hz, 1H), 2.90 (qdd, *J* = 6.8, 6.8, 5.2 Hz, 1H), 2.34 (s, 1H), 1.81 (ddd, *J* = 13.9, 8.1, 6.8 Hz, 1H), 1.62 (ddd, *J* = 13.9, 8.4, 5.2 Hz, 1H), 1.25 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 147.3, 137.8, 128.38, 128.36, 127.69, 127.68, 126.7, 126.0, 74.4, 73.2, 68.3, 41.4, 35.8, 21.6.

MS (HRMS ESI) Calcd for $C_{18}H_{23}O_2$ $[M+H]^+$ 271.1698, Found: 271.1692.

3-phenyl-1-(1-tosylpiperidin-4-yl)butan-1-ol (2.14f)



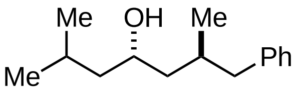
Prepared from **2.9f** (260.1 mg, 0.546 mmol) at 50 °C for 2 h. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 85:15) gave 82% yield (143.6 mg, 0.442 mmol) of **2.14f** as a 85:15 diastereomeric mixture (based on ^{1}H NMR analysis) (colorless oil).

^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 7.63 (d, *J* = 8.0 Hz, 2H), 7.32–7.26 (m, 5H), 7.18 (d, *J* = 8.0 Hz, 2H), 3.84–3.80 (m, 2H), 3.46–3.45 (m, 1H), 2.87 (qdd, *J* = 7.0, 7.0, 7.0 Hz, 1H), 2.42 (s, 3H), 2.17 (m, 2H), 1.66–1.60 (m, 4H), 1.48–1.35 (m, 4H), 1.23 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 147.3, 143.4, 133.1, 129.5, 128.6, 127.6, 126.8, 126.2, 73.1, 46.31, 46.26, 42.9, 41.5, 36.7, 27.6, 26.4, 21.48, 21.46.

MS (HRMS ESI) Calcd for $C_{22}H_{30}NO_3S$ [M+H]$^+$ 388.1946, Found: 388.1951.

2,6-dimethyl-1-phenylheptan-4-ol (2.14g)



Prepared from **2.9g** (137.4 mg, 0.445 mmol) at 50 °C for 19 h. Purification by flash chromatography (silica gel, *n*-Hex:EtOAc, 94:6) gave 26% yield (25.8 mg, 0.117 mmol) of **2.14g** as a 88:12 diastereomeric mixture (based on ^{1}H NMR analysis) (colorless oil).

Spectra data of the major isomer:

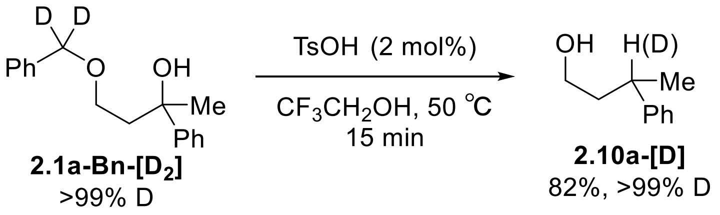
^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.29–7.25 (m, 2H), 7.19–7.14 (m, 3H), 3.81–3.75 (m, 1H), 2.60 (dd, *J* = 13.6, 6.8 Hz, 1H), 2.45 (dd, *J* = 13.6, 8.0 Hz, 1H), 2.06–1.93 (m, 1H), 1.80–1.69 (m, 1H), 1.49–1.41 (m, 1H), 1.39–1.32 (m, 1H), 1.24–1.17 (m, 2H), 0.91 (d, *J* = 6.0 Hz, 9H). (1H from the hydroxy group is not visible.)

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 141.1, 129.2, 128.1, 125.7, 67.6, 47.7, 45.0, 44.4, 31.3, 24.6, 23.3, 22.2, 19.1.

MS (HRMS ESI) Calcd for $C_{15}H_{25}O$ [M+H]$^+$ 221.1905, Found: 221.1912.

5.2.1.4. Deuterium labelling experiments

5.2.1.4.1. TsOH-catalyzed 1,5-hydride transfer of 2.1a-Bn-[D$_2$]



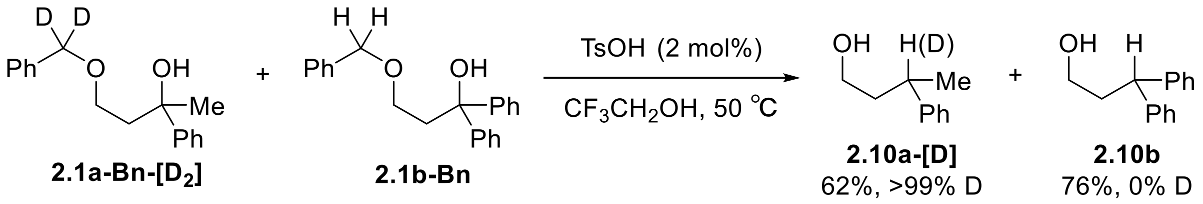
The reaction was performed according to general procedure in section 5.2.1.2 with **2.1a-Bn-[D$_2$]** (77.6 mg, 0.300 mmol) at 50 °C for 15 min. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 91:9) gave 82% yield (37.1 mg, 0.245 mmol) of 3-phenylbutan-3-*d*-1-ol (**2.10a-[D]**) as a colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 7.31–7.28 (m, 2H), 7.21–7.18 (m, 3H) 3.60–3.50 (m, 2H), 1.86–1.83 (m, 2H), 1.27 (s, 4H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 146.8, 128.5, 126.9, 126.1, 61.2, 40.9, 36.0 (t, J = 19.4 Hz), 22.3.

MS (HRMS ESI) Calcd for $C_{10}H_{13}DOLi$ $[M+Li]^+$ 158.1267, Found: 158.1268.

5.2.1.4.2. Crossover experiment with 2.1a-Bn-[D$_2$] and 2.1b-Bn

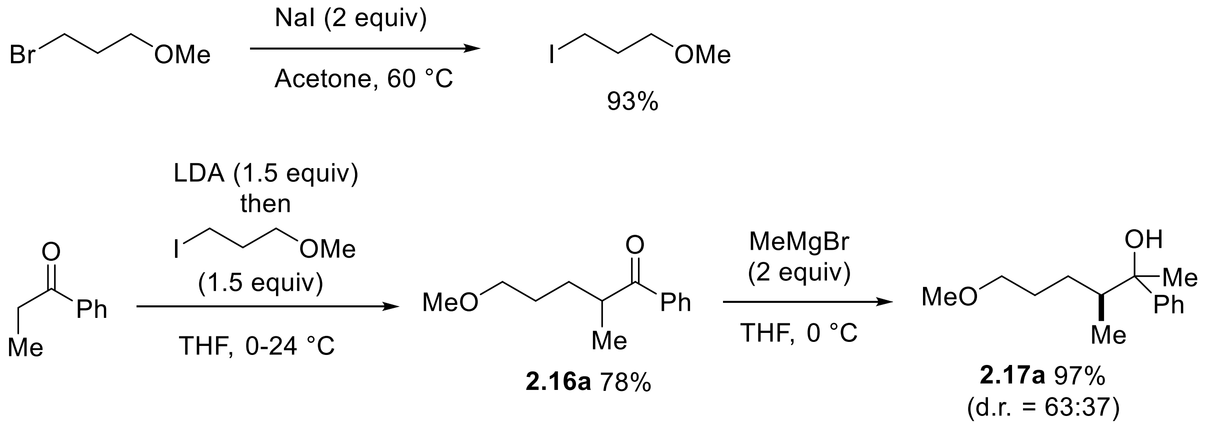


The reaction was performed according to general procedure in section 5.2.1.2 with **2.1a-Bn-[D$_2$]** (77.3 mg, 0.299 mmol) and **2.1b-Bn** (95.6 mg, 0.300 mmol) at 50 °C for 15 mins. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc, 91:9) gave inseparable mixture of **2.10a-[D]** and **2.10b** (83.0 mg) in 62% and 76% respectively, including 7% of benzyl alcohol. The yields were calculated based on ^{1}H NMR analysis.

5.2.2. Distal Alkyl Ethers as Hydride Donors (Chapter 2, Section 2.4)

5.2.2.1. Synthesis and characterization of the starting materials

5.2.2.1.1. Synthesis of (3*S**)-6-methoxy-3-methyl-2-phenylhexan-2-ol (2.17a)



Synthesis of 1-iodo-3-methoxypropane: To a solution of NaI (33.9 g, 226 mmol) in acetone (200 mL) was added 1-bromo-3-methoxypropane (12.0 mL, 107 mmol) and the reaction was stirred for 3 h at 60 °C. After being cooled down to 24 °C, the reaction mixture was diluted with water, and the organic materials were extracted thrice with *n*-pentane. The combined organic layers were washed with brine and dried over $MgSO_4$ before the filtrate was concentrated in *vacuo* to give 1-iodo-3-methoxypropane (19.8 g, 98.9 mmol, 93% yield) as a colorless oil. The material was pure enough to be used for the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) δ 3.44 (t, *J* = 5.6 Hz, 2H), 3.35 (s, 3H), 3.27 (t, *J* = 6.8 Hz, 2H), 2.12 – 1.98 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 72.0, 58.7, 33.3, 3.2.

MS (HRMS ESI): Calcd for $C_4H_{10}OI$ $[M+H]^+$ 200.9776, Found: 200.9778.

Synthesis of 5-methoxy-2-methyl-1-phenylpentan-1-one (2.16a): To a solution of diisopropylamine (0.91 mL, 6.50 mmol) in THF (6 mL) was added *n*-BuLi (2.4 M in hexane, 2.7 mL, 6.48 mmol) at 0 °C, and the reaction mixture was stirred for 30 min at the same temperature. To the resulting LDA solution, propiophenone (0.58 mL, 4.36 mmol) was added at 0 °C, and the mixture was stirred at the same temperature for 2 h before a solution of 1-iodo-3-methoxypropane (1.30 g, 6.50 mmol) in THF (1 mL) was added dropwise. The reaction mixture was then slowly warmed up to 24 °C and stirred continuously for 24 h. The reaction was subsequently quenched with saturated aqueous NH_4Cl solution and the organic materials were extracted thrice with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$ before the combined extracts were concentrated *in vacuo*. The resulting crude residue was purified by flash column chromatography (silica gel, Hex:EtOAc = 97:3) to give **2.16a** in 78% yield (706 mg, 3.42 mmol) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) δ 7.96 (d, *J* = 7.6 Hz, 2H), 7.57 – 7.54 (m, 1H), 7.48 – 7.45 (m, 2H), 3.58 – 3.45 (m, 1H), 3.36 (dd, *J* = 6.0, 6.0 Hz, 2H), 3.29 (s, 3H), 1.94 – 1.82 (m, 1H), 1.67 – 1.45 (m, 3H), 1.21 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 204.1, 136.6, 132.8, 128.5, 128.2, 72.5, 58.4, 40.2, 30.1, 27.3, 17.4.

MS (HRMS ESI): Calcd for $C_{13}H_{18}O_2Na$ $[M+Na]^+$ 229.1204, Found: 229.1206.

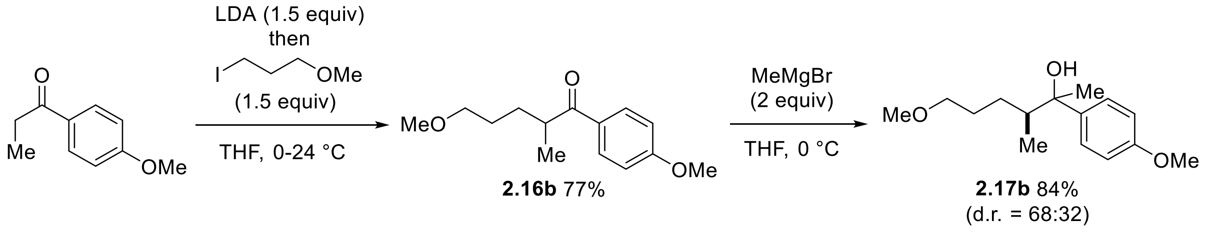
Synthesis of (3*S)-6-methoxy-3-methyl-2-phenylhexan-2-ol (2.17a):** To a solution of **2.16a** (929 mg, 4.50 mmol) in THF (6 mL) was added MeMgBr (3.0 M in Et_2O, 3.0 mL, 9.0 mmol) at 0 °C and the reaction mixture was stirred at the same temperature for 3 h. The reaction was then quenched with saturated NH_4Cl solution and the organic materials were extracted thrice using EtOAc. The combined extracts were washed with brine and dried over $MgSO_4$. The volatile materials were removed under reduced pressure to give the crude material, which was purified by flash column chromatography (silica gel, Hex:EtOAc = 95:5) to give **2.17a** in 97% yield (971 mg, 4.37 mmol) as an estimated 66:34 diastereomeric mixture (based on ^{13}C NMR spectroscopy analysis), and as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.42 – 7.40 (m, 2×0.66H + m, 2×0.34H), 7.33 – 7.30 (m, 2×0.66H, +m, 2×0.34H), 7.24 – 7.20 (m, 1×0.66H, +m, 1×0.34H), 3.33 – 3.23 (m, 2×0.66H, +m, 2×0.34H), 3.28 (s, 3×0.34H), 3.27 (s, 3×0.66H), 1.90 – 1.74 (m, 2×0.66H, +m, 2×0.34H), 1.74 – 1.59 (m, 1×0.66H, +m, 1×0.34H), 1.60 – 1.46 (m, 1×0.66H, +m, 1×0.34H), 1.53 (s, 3×0.34H), 1.50 (s, 3×0.66H), 1.46 – 1.29 (m, 1×0.66H, +m, 1×0.34H), 1.07 – 0.92 (m, 1×0.66H, +m, 1×0.34H), 0.86 (d, *J* = 6.8 Hz, 3×0.66H), 0.83 (d, *J* = 6.8 Hz, 3×0.34H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 148.0, 147.7, 127.9, 127.8, 126.4 (overlapped with 2C), 125.4, 125.2, 77.0, 76.9, 73.0 (overlapped with 2C), 58.42, 58.39, 43.8 (overlapped with 2C), 28.1, 28.0, 27.7, 27.5, 26.6, 26.2, 14.2, 14.1.

MS (HRMS ESI): Calcd for $C_{14}H_{23}O_2$ $[M+H]^+$ 223.1698, Found: 223.1705.

5.2.2.1.2 Synthesis of (3*S**)-6-methoxy-2-(4-methoxyphenyl)-3-methylhexan-2-ol (2.17b)



Synthesis of 5-methoxy-1-(4-methoxyphenyl)-2-methylpentan-1-one (2.16b): Compound **2.16b** was synthesized following the procedure described in section **5.2.2.1.1** and using 1-(4-methoxyphenyl)propan-1-one (257 mL, 1.56 mmol) and 1-iodo-3-methoxypropane (475 mg, 2.37 mmol). Purification by flash column chromatography (silica gel, Hex:EtOAc = 91:9) gave **2.16b** (285 mg, 1.21 mmol) in 77% yield as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.95 (d, *J* = 9.0 Hz, 2H), 6.94 (d, *J* = 9.0 Hz, 2H), 3.86 (s, 3H), 3.46 (ddq, *J* = 7.0, 7.0, 7.0 Hz, 1H), 3.36 (dd, *J* = 6.5, 6.5 Hz, 2H), 3.29 (s, 3H), 1.89 – 1.83 (m, 1H), 1.64 – 1.47 (m, 3H), 1.19 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 202.7, 163.3, 130.5, 129.6, 113.7, 72.6, 58.4, 55.4, 39.8, 30.3, 27.4, 17.5.

MS (HRMS ESI) Calcd for $C_{14}H_{21}O_3$ $[M+H]^+$ 237.1491, Found: 237.1499.

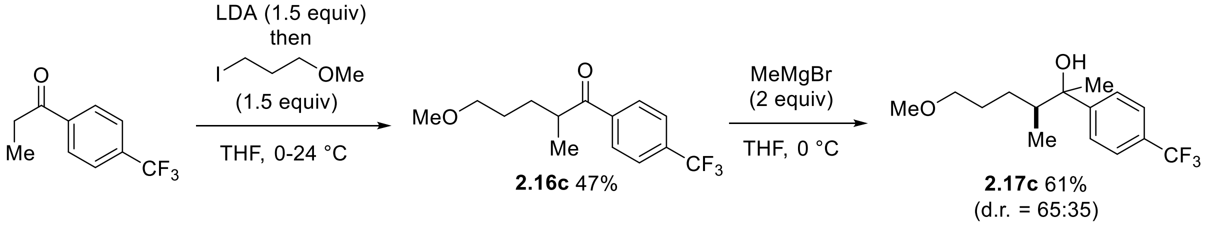
Synthesis of (3*S)-6-methoxy-2-(4-methoxyphenyl)-3-methylhexan-2-ol (2.17b):** Compound **2.17b** was synthesized using **2.16b** (285 mg, 1.21 mmol) and MeMgBr (3.0 M in Et_2O, 0.8 mL, 2.4 mmol) by following the procedure described in section **5.2.2.1.1**. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc = 91:9) gave 84% yield of **2.17b** (257 mg, 1.02 mmol) as an estimated 68:32 diastereomeric mixture (based on ^{13}C NMR spectroscopy analysis) and as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.39 – 7.34 (m, 2×0.68H, +m, 2×0.32H), 6.87 – 6.85 (m, 2×0.68H, +m, 2×0.32H), 3.81 (s, 3×0.68H, +s, 3×0.32H), 3.34 – 3.28 (m, 2×0.68H, +m, 2×0.32H), 3.31 (s, 3×0.32H), 3.29 (s, 3×0.68H), 1.79 – 1.73 (m, 1×0.68H, +m, 1×0.32H), 1.70 – 1.61 (m, 1×0.68H, +m, 1×0.32H), 1.66 (brs, 1×0.68H), 1.64 (brs, 1×0.32H), 1.53 – 1.59 (m, 1×0.68H, +m, 1×0.32H), 1.52 (s, 3×0.32H), 1.49 (s, 3×0.64H), 1.46 – 1.33 (m, 1×0.68H, +m, 1×0.32H), 1.09 – 0.92 (m, 1×0.68H, +m, 1×0.32H), 0.86 (d, *J* = 7.6 Hz, 3×0.32H), 0.84 (d, *J* = 7.2 Hz, 3×0.68H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 158.1 (overlapped with 2C), 140.2, 139.8, 126.6, 126.4, 113.14, 113.10, 76.7, 76.6, 73.03, 73.00, 65.8, 58.4, 55.1, 44.0, 28.1, 28.0, 27.7, 27.6, 26.3, 26.0, 15.2 (overlapped with 2C), 14.2, 14.1.

MS (HRMS ESI) Calcd for $C_{15}H_{25}O_3$ [M+H]$^+$ 253.1804, Found: 253.1804.

5.2.2.1.3. Synthesis of (3*S**)-6-methoxy-3-methyl-2-(4-(trifluoromethyl)phenyl) hexan-2-ol (2.17c)



Synthesis of 5-methoxy-2-methyl-1-(4-(trifluoromethyl)phenyl)pentan-1-one (2.16c): Compound **2.16c** was synthesized using 1-(4-trifluoromethylphenyl)propan-1-one (699 mg, 3.46 mmol) and 1-iodo-3-methoxypropane (1.05 g, 5.25 mmol) by following the procedure described in section **5.2.2.1.1**. Purification by flash column chromatography (silica gel, Hex:EtOAc = 92:8) gave **2.16c** (444 mg, 1.62 mmol) in 47% yield as a colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 8.05 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 8.0 Hz, 2H), 3.50 (ddq, *J* = 7.0, 7.0, 7.0 Hz, 1H), 3.37 – 3.34 (m, 2H), 3.28 (s, 3H), 1.94 – 1.80 (m, 1H), 1.65 – 1.47 (m, 3H), 1.21 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 203.1, 139.3, 134.1 (q, *J* = 32.5 Hz), 128.5, 125.6 (q, *J* = 3.7 Hz), 123.6 (q, *J* = 271.3 Hz), 72.4, 58.4, 40.7, 30.0, 27.3, 17.1.

MS (HRMS ESI): Calcd for $C_{14}H_{18}O_2F_3$ $[M+H]^+$ 275.1259, Found: 275.1268.

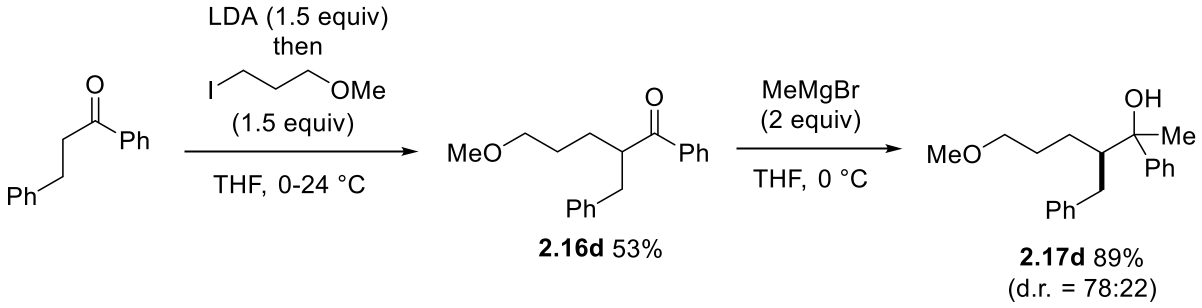
Synthesis of (3*S)-6-methoxy-3-methyl-2-(4-(trifluoromethyl)phenyl)hexan-2-ol (2.17c):** Compound **2.17c** was synthesized using **2.16c** (444 mg, 1.62 mmol) and MeMgBr (3.0 M in Et_2O, 1.1 mL) by following the procedure described in section **5.2.2.1.1**. Purification by flash column chromatography (silica gel, Hex:EtOAc = 90:10) gave 61% yield of **2.17c** (288 mg, 0.993 mmol) as an estimated 65:35 diastereomeric mixture (based on ^{1}H NMR spectroscopy analysis) and as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.58 (d, *J* = 8.5 Hz, 2×0.65H, +d, *J* = 8.5 Hz, 2×0.35H), 7.53 (d, *J* = 8.5 Hz, 2×0.65H, +d, *J* = 8.5 Hz, 2×0.35H), 3.37 – 3.24 (m, 2×0.65H, +m, 2×0.35H), 3.29 (s, 3×0.35H), 3.26 (s, 3×0.65H), 1.94 (brs, 1×0.65H, +brs, 1×0.35H), 1.83 – 1.78 (m, 1×0.65H, +m, 1×0.35H), 1.72 – 1.62 (m, 1×0.65H, +m, 1×0.35H), 1.55 (s, 3×0.35H), 1.52 (s, 3×0.65H), 1.46 – 1.35 (m, 2×0.65H, +m, 2×0.35H), 1.06 – 0.96 (m, 1×0.65H, +m, 1×0.35H), 0.89 (d, *J* = 6.5 Hz, 3×0.65H), 0.81 (d, *J* = 6.5 Hz, 3×0.35H).

^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 152.1, 151.7, 128.7 (q, *J* = 32.0 Hz, overlapped with 2C), 125.8, 125.7, 124.9 – 124.8 (m, overlapped with 2C), 124.3 (q, *J* = 270.1 Hz, overlapped with 2C), 77.0, 76.8, 72.9, 72.8, 58.44, 58.39, 43.7, 43.6, 27.94, 27.88, 27.6, 27.3, 27.0, 26.6, 14.1, 13.8.

MS (HRMS ESI): Calcd for $C_{15}H_{22}O_2F_3$ $[M+H]^+$ 291.1572, Found: 291.1569.

5.2.2.1.4. Synthesis of (3*R**)-3-benzyl-6-methoxy-2-phenylhexan-2-ol (2.17d)



Synthesis of 2-benzyl-5-methoxy-1-phenylpentan-1-one (2.16d): Compound **2.16d** was synthesized using 1,3-diphenylpropan-1-one (845 mg, 4.02 mmol) and 1-iodo-3-methoxypropane (1.36 g, 6.80 mmol) by following the procedure described in section **5.2.2.1.1**. Purification by flash column chromatography (silica gel, n-Hex:EtOAc = 98:2) gave **2.16d** in 53% yield (597 mg, 2.11 mmol) as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) δ 7.89 – 7.82 (m, 2H), 7.53 – 7.45 (m, 1H), 7.41 – 7.37 (m, 2H), 7.26 – 7.18 (m, 2H), 7.18 – 7.09 (m, 3H), 3.79 – 3.72 (m, 1H), 3.29 (dd, *J* = 6.0, 6.0 Hz, 2H), 3.24 (s, 3H), 3.09 (dd, *J* = 13.6, 7.6 Hz, 1H), 2.77 (dd, *J* = 13.6, 6.4 Hz, 1H), 1.91 – 1.78 (m, 1H), 1.69 – 1.45 (m, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 203.6, 139.7, 137.4, 132.8, 128.9, 128.5, 128.3, 128.1, 126.1, 72.5, 58.4, 47.9, 38.3, 28.9, 27.3.

MS (HRMS ESI): Calcd for $C_{19}H_{22}O_2Na$ $[M+Na]^+$ 305.1517, Found: 305.1512.

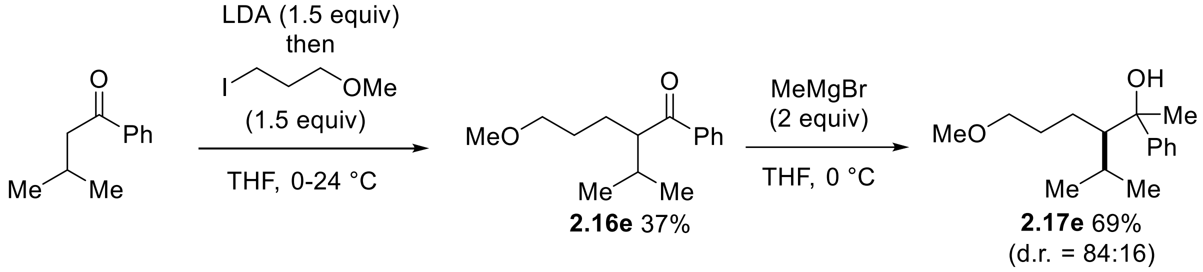
Synthesis of (3*R)-3-benzyl-6-methoxy-2-phenylhexan-2-ol (2.17d):** Compound **2.17d** was synthesized using **2.16d** (317 mg, 1.12 mmol) and MeMgBr (3.0 M in Et_2O, 1.0 mL, 3.0 mmol) by following the procedure described in section **5.2.2.1.1**. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc = 80:20) gave 89% yield of **2.17d** (297 mg, 0.996 mmol) as an estimated 78:22 diastereomeric mixture (based on ^{13}C NMR spectroscopy analysis) and as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.54 – 7.43 (m, 2×0.78H, +m, 2×0.22H), 7.35 (t, *J* = 7.6 Hz, 2×0.78H, +t, *J* = 7.6 Hz, 2×0.22H), 7.26 – 7.20 (m, 3×0.78H, +m, 3×0.22H), 7.15 – 7.12 (m, 1×0.78H, +m, 1×0.22H), 7.09 – 7.08 (m, 2×0.78H, +m, 2×0.22H), 3.17 (s, 3×0.78H), 3.16 (s, 3×0.22H), 3.12 – 3.07 (m, 2×0.78H, +m, 2×0.22H), 2.90 – 2.79 (m, 1×0.78H, +m, 1×0.22H), 2.33 (dd, *J* = 13.6, 9.2 Hz, 1×0.78H, +dd, *J* = 13.6, 9.2 Hz, 1×0.22H), 2.13 – 2.08 (m, 1×0.78H, +m, 1×0.22H), 2.08 (brs, 1×0.78H), 1.91 (brs, 1×0.22H), 1.61 – 1.54 (m, 1×0.78H, +m, 1×0.22H), 1.59 (s, 3×0.78H), 1.58 (s, 3×0.22H), 1.40 – 1.14 (m, 3×0.78H, +m, 3×0.22H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 148.00, 147.95, 141.9 (overlapped with 2C), 128.9, 128.8, 128.1, 128.0, 127.90, 127.88, 126.5, 126.4, 125.54, 125.49, 125.3, 125.2, 77.3, 77.2, 72.75, 72.73, 58.0 (overlapped with 2C), 51.0, 50.9, 37.0, 36.7, 28.41, 28.36, 27.2, 26.7, 26.4, 26.0.

MS (HRMS ESI): Calcd for $C_{20}H_{27}O_2$ $[M+H]^+$ 299.2011, Found: 299.2015.

5.2.2.1.5. Synthesis of (3*R**)-3-isopropyl-6-methoxy-2-phenylhexan-2-ol (2.17e)



Synthesis of 2-isopropyl-5-methoxy-1-phenylpentan-1-one (2.16e): Compound **2.16e** was synthesized using 3-methyl-1-phenylbutan-1-one (655 mg, 4.04 mmol) and 1-iodo-3-methoxypropane (1.21 g, 6.04 mmol) by following the procedure described in section **5.2.2.1.1**.

Purification by flash column chromatography (silica gel, Hex:EtOAc = 96:4) gave **2.16e** in 37% yield (348 mg, 1.48 mmol) as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.94 – 7.92 (m, 2H), 7.55 – 7.51 (m, 1H), 7.46 – 7.42 (m, 2H), 3.32 – 3.25 (m, 3H), 3.24 (s, 3H), 2.07 – 1.96 (m, 1H), 1.85 – 1.78 (m, 1H), 1.65 – 1.59 (m, 1H), 1.53 – 1.36 (m, 2H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 204.4, 138.3, 132.7, 128.6, 128.1, 72.8, 58.4, 52.2, 30.7, 27.8, 25.2, 21.3, 19.3.

MS (HRMS ESI) Calcd for $C_{15}H_{23}O_2$ [M+H]$^+$ 235.1698, Found: 235.1700.

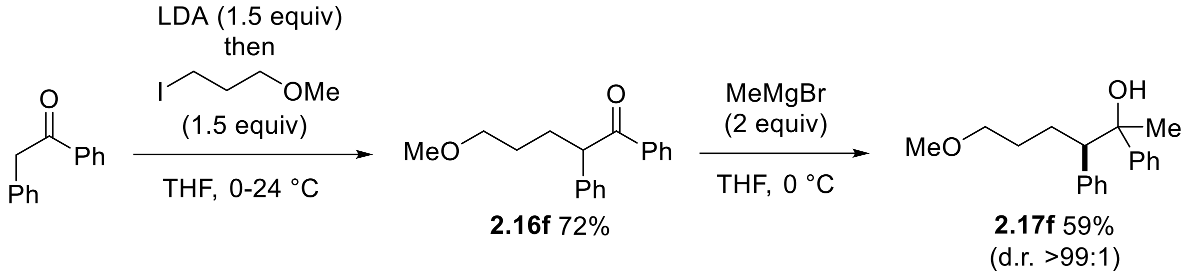
Synthesis of (3*R)-3-isopropyl-6-methoxy-2-phenylhexan-2-ol (2.17e):** Compound **2.17e** was synthesized using **2.16e** (329 mg, 1.40 mmol) and MeMgBr (3.0 M in Et$_2$O, 0.9 mL) following the procedure described in section **5.2.2.1.1**. Purification by flash column chromatography (silica gel, Hex:EtOAc = 91:9) gave **2.17e** in 69% yield (241 mg, 0.964 mmol) as an estimated 92:8 diastereomeric mixture (based on ^{1}H NMR spectroscopy analysis) and as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$) for the major isomer: δ(ppm) 7.43 – 7.40 (m, 2H), 7.35 – 7.27 (m, 2H), 7.24 – 7.19 (m, 1H), 3.34 (dd, *J* = 6.4, 6.4 Hz, 2H), 3.31 (s, 3H), 1.75 – 1.48 (m, 6H), 1.53 (s, 3H), 1.44 – 1.32 (m, 1H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.78 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) for the major isomer: δ(ppm) 146.6, 128.0, 126.3, 125.0, 78.6, 73.1, 58.5, 53.6, 31.8, 29.5, 27.9, 24.2, 21.1, 17.6.

MS (HRMS ESI) Calcd for $C_{16}H_{27}O_2$ [M+H]$^+$ 251.2011, Found: 251.2016.

5.2.2.1.6. Synthesis of (3*R**)-6-methoxy-2,3-diphenylhexan-2-ol (2.17f)



Synthesis of 5-methoxy-1,2-diphenylpentan-1-one (2.16f): Compound **2.16f** was synthesized using 1,2-diphenylethan-1-one (986 mg, 5.02 mmol) and 1-iodo-3-methoxypropane (1.50 g, 7.51 mmol) by following the procedure described in section **5.2.2.1.1**. Purification by flash column chromatography (silica gel, Hex:EtOAc = 96:4) gave **2.16f** in 72% yield (960 mg, 3.58 mmol) as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.96 – 7.94 (m, 2H), 7.49 – 7.44 (m, 1H), 7.39 – 7.35 (m, 2H), 7.31 – 7.26 (m, 4H), 7.20 – 7.16 (m, 1H), 4.57 (dd, *J* = 9.0, 9.0 Hz, 1H), 3.36 (dd, *J* = 8.0, 8.0 Hz, 2H), 3.27 (s, 3H), 2.28 – 2.19 (m, 1H), 1.94 – 1.85 (m, 1H), 1.65 – 1.45 (m, 2H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 199.8, 139.6, 136.9, 132.8, 128.9, 128.6, 128.5, 128.2, 127.0, 72.6, 58.5, 53.4, 30.7, 27.7.

MS (HRMS ESI) Calcd for $C_{18}H_{21}O_2$ [M+H]$^+$ 269.1542, Found: 269.1544.

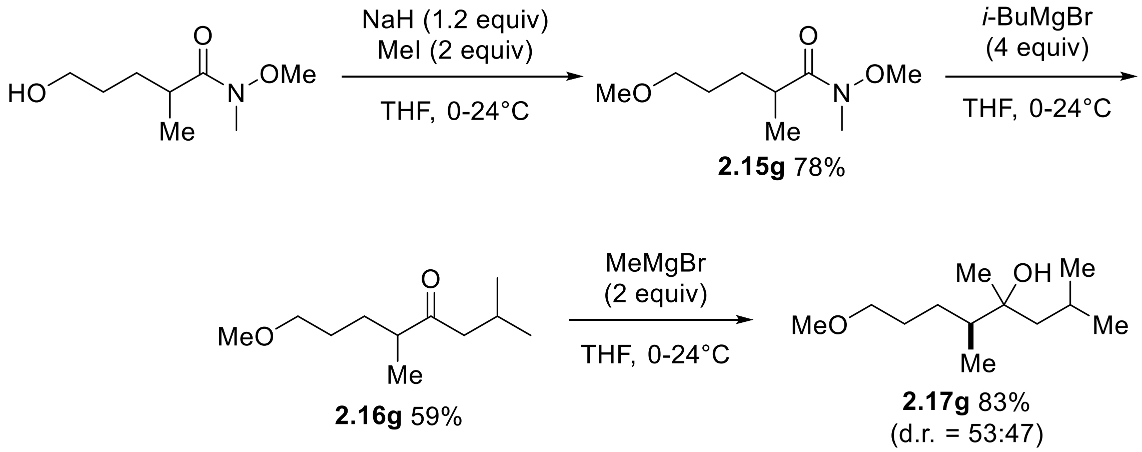
Synthesis of (3*R)-6-methoxy-2,3-diphenylhexan-2-ol (2.17f):** Compound **2.17f** was synthesized using **2.16f** (755 mg, 2.65 mmol) and MeMgBr (3.0 M in Et_2O, 1.8 mL) following the procedure described in section **5.2.2.1.1.** Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc = 91:9) gave **2.17f** in 59% yield (741 mg, 1.56 mmol) as a single diastereomer (based on ^{1}H NMR spectroscopy analysis) and as a white solid. The stereochemistry at C1 was not determined.

^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.33 – 7.31 (m, 2H), 7.28 – 7.26 (m, 2H), 7.23 – 7.16 (m, 4H), 7.05 – 7.03 (m, 2H), 3.22 (dd, *J* = 6.5, 6.5 Hz, 2H), 3.21 (s, 3H), 2.93 (dd, *J* = 11.5, 3.0 Hz, 1H), 1.81 – 1.68 (m, 3H), 1.57 (s, 3H), 1.33 – 1.86 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 146.7, 139.9, 130.0, 127.9, 127.6, 126.7, 126.6, 125.9, 76.4, 72.6, 58.4, 57.7, 28.0, 26.3, 25.6.

MS (HRMS ESI): Calcd for $C_{19}H_{25}O_2$ $[M+H]^+$ 285.1855, Found: 285.1852.

5.2.2.1.7. Synthesis of (5*S**)-8-methoxy-2,4,5-trimethyloctan-4-ol (2.17g)



Synthesis of *N*,5-dimethoxy-*N*,2-dimethylpentanamide (2.15g): To a suspension of NaH (60% dispersion in mineral oil, 235 mg, 5.86 mmol) and MeI (0.56 ml, 9.00 mmol) in THF (10 mL) was slowly added a solution of 5-hydroxy-*N*-methoxy-*N*,2-dimethylpentanamide[32] (794 mg, 4.53 mmol) in THF (9 mL) at 0 °C. The reaction mixture was then slowly warmed up to 24 °C and stirred continuously for 13 h before being quenched with water. The organic materials were then extracted thrice with EtOAc and the combined organic extracts were washed with brine and dried over $MgSO_4$. After the filtrate was concentrated in *vacuo*, the resulting crude residue was purified by flash column chromatography (silica gel, n-Hex: EtOAc= 75:25) to give **2.15g** in 78% yield (666 mg, 3.52 mmol) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 3.69 (s, 3H), 3.41 – 3.33 (m, 2H), 3.32 (s, 3H), 3.19 (s, 3H), 2.89 (s, 1H), 1.76 – 1.67 (m, 1H), 1.63 – 1.51 (m, 2H), 1.51 – 1.38 (m, 1H), 1.12 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 177.7, 72.6, 61.3, 58.4, 34.9, 32.1, 30.2, 27.5, 17.4.

MS (HRMS ESI): Calcd for $C_9H_{20}NO_3$ $[M+H]^+$ 190.1443, Found: 190.1448.

Synthesis of 8-methoxy-2,5-dimethyloctan-4-one (2.16g): To a solution of **2.15g** (664 mg, 3.51 mmol) in THF (5 mL) was added freshly prepared *i*-BuMgBr (0.74 M in THF, 19 mL, 14.0 mmol) at 0 °C, and the reaction mixture was then slowly warmed up to 24 °C and stirred continuously for 24 h before being quenched with a saturated NH_4Cl solution. The organic materials were extracted thrice with EtOAc and the combined extracts were washed with brine and dried over $MgSO_4$. The volatile materials were removed in *vacuo* to afford the crude material, which was purified by flash column chromatography (silica gel, Hex:EtOAc = 90:10) to give **2.16g** in 59% yield (386 mg, 2.07 mmol) and as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 3.35 (dd, *J* = 6.4, 6.4 Hz, 2H), 3.32 (s, 3H), 2.50 (qdd, *J* = 6.8, 6.8, 6.8 Hz, 1H), 2.39 – 2.24 (m, 2H), 2.15 (m, 1H), 1.75 – 1.65 (m, 1H), 1.59 – 1.47 (m, 2H), 1.41 – 1.32 (m, 1H), 1.06 (d, *J* = 7.2 Hz, 3H), 0.91 (d, *J* = 6.4 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 214.1, 72.5, 58.4, 50.1, 46.2, 29.2, 27.3, 24.1, 22.54, 22.49, 16.2.

MS (HRMS ESI): Calcd for $C_{11}H_{23}O_2$ $[M+H]^+$ 187.1698, Found: 187.1700.

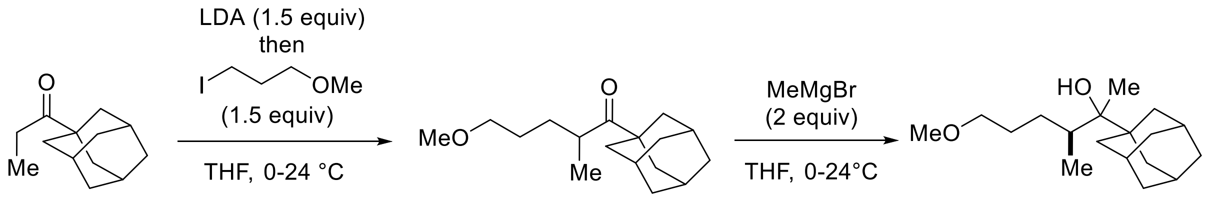
Synthesis of (5*S)-8-methoxy-2,4,5-trimethyloctan-4-ol (2.17g):** Compound **2.17g** was synthesized using **2.16g** (386 mg, 2.07 mmol) and MeMgBr (3.0 M in Et$_2$O, 1.1 mL, 3.3 mmol) by following the procedure described in section **5.2.2.1.1**. Purification by flash column chromatography (silica gel, Hex:EtOAc = 88:12) gave 2.17**g** in 83% yield (346 mg, 1.71 mmol) as an estimated 53:47 diastereomeric mixture (based on ^{1}H NMR analysis) and as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 3.44 – 3.35 (m, 2×0.53H, +m, 2×0.47H), 3.33 (s, 3×0.53H, +s, 3×0.47H), 1.84 – 1.81 (m, 1×0.53H, +m, 1×0.47H), 1.77 – 1.71 (m, 1×0.53H, +m, 1×0.47H), 1.71 – 1.66 (m, 1×0.53H), 1.63 – 1.53 (m, 1×0.53H), 1.52 – 1.43 (m, 2×0.53H, +m, 2×0.47H), 1.43 – 1.39 (m, 0.47H), 1.39 – 1.34 (m, 2×0.53H, +m, 2×0.47H), 1.34 – 1.30 (m, 1×0.47H), 1.11 (d, *J* = 6.8 Hz, 3×0.53H, +d, *J* = 6.8 Hz, 3×0.47H), 1.07 – 0.94 (m, 1×0.53H, +m, 1×0.47H), 1.00 – 0.94 (m, 6×0.53H, +m, 6×0.47H), 0.92 (d, *J* = 6.8 Hz, 3×0.47H), 0.88 (d, *J* = 6.8 Hz, 3×0.53H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 75.6, 75.5, 73.1, 73.0, 58.4 (overlapped with 2C), 48.2, 47.3, 43.5, 43.1, 28.4, 28.3, 28.0, 27.5, 25.0, 24.9, 24.8, 24.7, 24.0, 23.7, 23.6, 23.5, 14.6, 13.8.

MS (HRMS ESI): Calcd for $C_{12}H_{26}O_2Na$ $[M+Na]^+$ 225.1831, Found: 225.1828.

5.2.2.1.8. Synthesis of (3*S**)-2-(adamantan-1-yl)-6-methoxy-3-methylhexan-2-ol (2.17h)



2.16h 55%

2.17h 99%
(d.r. = 55:45)

Synthesis of 1-(adamantan-1-yl)-5-methoxy-2-methylpentan-1-one (2.16h): Compound **2.16h** was synthesized using 1-(adamantan-1-yl)propan-1-one (1.23 g, 6.37 mmol) and 1-iodo-

3-methoxypropane by following the procedure described in section **5.2.2.1.1**. Purification by flash column chromatography (silica gel, Hex:EtOAc = 98:2) gave **2.16h** in 51% yield (856 mg, 3.24 mmol) as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 3.39 – 3.25 (m, 2H), 3.31 (s, 3H), 3.02 (ddq, *J* = 6.8, 6.8, 6.8 Hz, 1H), 2.04 (s, 3H), 1.87 – 1.57 (m, 13H), 1.57 – 1.46 (m, 1H), 1.46 – 1.27 (m, 2H), 1.00 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 219.0, 72.7, 58.4, 46.6, 38.4, 37.8, 36.5, 30.6, 27.8, 27.7, 18.3.

MS (HRMS ESI): Calcd for $C_{17}H_{29}O_2$ $[M+H]^+$ 265.1268, Found: 265.1267.

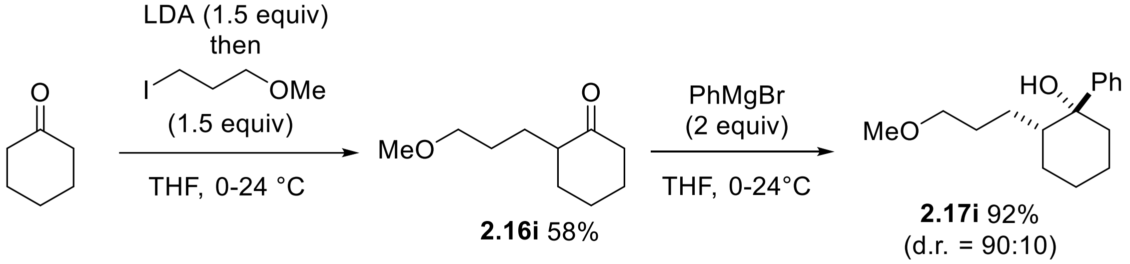
Synthesis of (3*S)-2-(adamantan-1-yl)-6-methoxy-3-methylhexan-2-ol (2.17h):** Compound **2.17h** was synthesized using **2.16h** (758 mg, 2.87 mmol) and MeMgBr (3.0 M in Et_2O, 1.9 mL, 5.70 mmol) by following the procedure described in section **5.2.2.1.1**. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc = 90:10) gave **2.17h** in 99% yield (794 mg, 2.83 mmol) as an estimated 55:45 diastereomeric mixture (based on ^{13}C NMR spectroscopy analysis) and as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 3.43 – 3.29 (m, 2×0.55H, +m, 2×0.45H), 3.33 (s, 3×0.55H, +s, 3×0.45H), 2.00 (s, 3×0.55H, +s, 3×0.45H), 1.87 – 1.55 (m, 15×0.55H, +m, 15×0.45H), 1.54 – 1.44 (m, 1×0.55H, +m, 1×0.45H), 1.23 (s, 1×0.45H), 1.11 (s, 1×0.55H), 1.08 – 0.97 (m, 1×0.55H, +m, 1×0.45H), 0.99 (s, 3×0.55H, +s, 3×0.45H), 0.94 (d, *J* = 6.8 Hz, 3×0.45H), 0.93 (d, *J* = 6.8 Hz, 3×0.55H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 77.7, 77.3, 73.3, 72.9, 58.49, 58.46, 40.7, 40.5, 38.3, 37.13 (overlapped with 2C), 37.09, 36.73, 36.71, 30.7, 29.0, 28.8, 28.70, 28.66, 28.4, 17.8, 17.2, 16.8, 15.3.

MS (HRMS ESI): Calcd for $C_{18}H_{33}O_2$ $[M+H]^+$ 281.2481, Found: 281.2477.

2.9. Synthesis of (2*R**)-2-(3-methoxypropyl)-1-phenylcyclohexan-1-ol (2.17i)



Synthesis of 2-(3-methoxypropyl)cyclohexan-1-one (2.16i): Compound **2.16i** was synthesized using cyclohexanone (0.42 mL, 4.053 mmol) and 1-iodo-3-methoxypropane (1.27 g, 6.33 mmol) by following the procedure described in section **5.2.2.1.1**. Purification by flash column chromatography (silica gel, Hex:EtOAc = 95:5) gave **2.16i** in 58% yield (400 mg, 2.35 mmol) as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 3.37 (ddd, *J* = 6.4, 6.4, 2.8 Hz, 2H), 3.32 (s, 3H), 2.44 – 2.35 (m, 1H), 2.34 – 2.23 (m, 2H), 2.16 – 2.07 (m, 1H), 2.07 – 1.98 (m, 1H), 1.91 – 1.74 (m, 2H), 1.73 – 1.62 (m, 2H), 1.62 – 1.51 (m, 1H), 1.45 – 1.34 (m, 1H), 1.32 – 1.23 (m, 2H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 213.0, 72.7, 58.4, 50.4, 41.9, 33.9, 27.9, 27.2, 26.0, 24.8.

MS (HRMS ESI): Calcd for $C_{10}H_{18}O_2Na$ $[M+Na]^+$ 193.1204, Found: 193.1202.

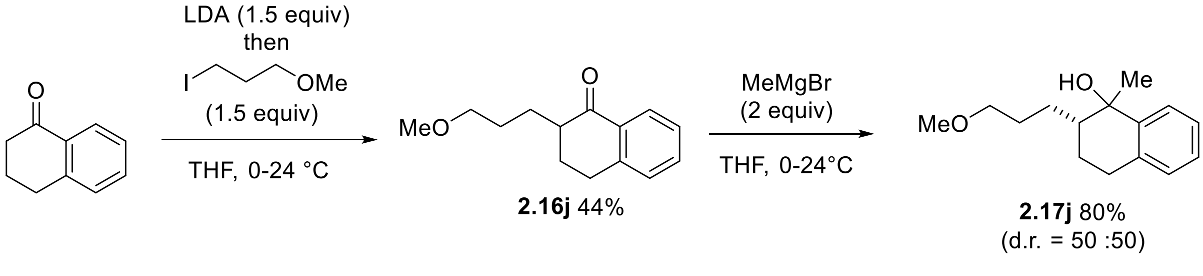
Synthesis (2*R)-2-(3-methoxypropyl)-1-phenylcyclohexan-1-ol (2.17i):** Compound **2.17i** was synthesized using **2.16i** (436 mg, 2.56 mmol) and PhMgBr (3.0 M in Et_2O, 1.7 mL, 5.10 mmol) by following the procedure described in section **5.2.2.1.1**. Purification by flash column chromatography (silica gel, Hex:EtOAc = 80:20) gave **2.17i** in 92% yield (585 mg, 2.36 mmol) as an estimated 90:10 diastereomeric mixture (based on ^{1}H NMR spectroscopy analysis) and as a colorless oil. The stereochemistry at C1 for the major (and minor) isomer was not determined.

^{1}H NMR (400 MHz, $CDCl_3$) for the major isomer: δ(ppm) 7.50 – 7.40 (m, 2H), 7.32 (t, *J* = 8.0 Hz, 2H), 7.23 – 7.19 (m, 1H), 3.19 (s, 3H), 3.19 – 3.08 (m, 2H), 1.89 – 1.80 (m, 2H), 1.80 – 1.64 (m, 5H), 1.65 – 1.50 (m, 2H), 1.45 – 1.32 (m, 2H), 1.31 – 1.20 (m, 1H), 1.15 – 0.95 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) for the major isomer: δ(ppm) 148.4, 128.0, 126.1, 124.6, 76.3, 72.9, 58.3, 44.8, 41.7, 27.4, 27.2, 26.3, 26.0, 22.0.

MS (HRMS ESI): Calcd for $C_{16}H_{24}O_2Na$ $[M+Na]^+$ 271.1674, Found: 271.1678.

5.2.2.1.10. Synthesis of (2*R**)-2-(3-methoxypropyl)-1-methyl-1,2,3,4-tetrahydronaphthalen-1-ol (2.17j)



Synthesis of 2-(3-methoxypropyl)-3,4-dihydronaphthalen-1(2*H*)-one (2.16j): Compound **2.16j** was synthesized using α-tetralone (0.53 mL, 3.98 mmol) and 1-iodo-3-methoxypropane (1.21 g, 6.03 mmol) by following the procedure described in section **5.2.2.1.1**. Purification by flash column chromatography (silica gel, Hex:EtOAc = 90:10) gave **2.16j** in 44% yield (385 mg, 1.76 mmol) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 8.02 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.44 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.28 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 3.48 – 3.36 (m, 2H), 3.33 (s, 3H), 3.03 – 2.96 (m, 2H), 2.55 – 2.44 (m, 1H), 2.21 – 2.28 (m, 1H), 2.05 – 1.86 (m, 2H), 1.78 – 1.51 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 200.0, 143.8, 133.0, 132.5, 128.6, 127.4, 126.5, 72.8, 58.5, 47.3, 28.35, 28.34, 27.1, 26.2.

MS (HRMS ESI): Calcd for $C_{14}H_{18}O_2Li$ $[M+Li]^+$ 225.1467, Found: 225.1477.

Synthesis of (2*R)-2-(3-methoxypropyl)-1-methyl-1,2,3,4-tetrahydronaphthalen-1-ol (2.17j):** Compound **2.17j** was synthesized using **2.16j** (984 mg, 4.51 mmol) and MeMgBr (3.0 M in Et_2O, 3.0 mL, 9.0 mmol) by following the procedure described in section **5.2.2.1.1**. Purification by flash column chromatography (silica gel, Hex:EtOAc = 85:15) gave **2.17j** in 80% yield (840 mg, 3.59 mmol) as an estimated 50:50 diastereomeric mixture (based on ^{1}H NMR spectroscopy analysis) and as a pale yellow oil.

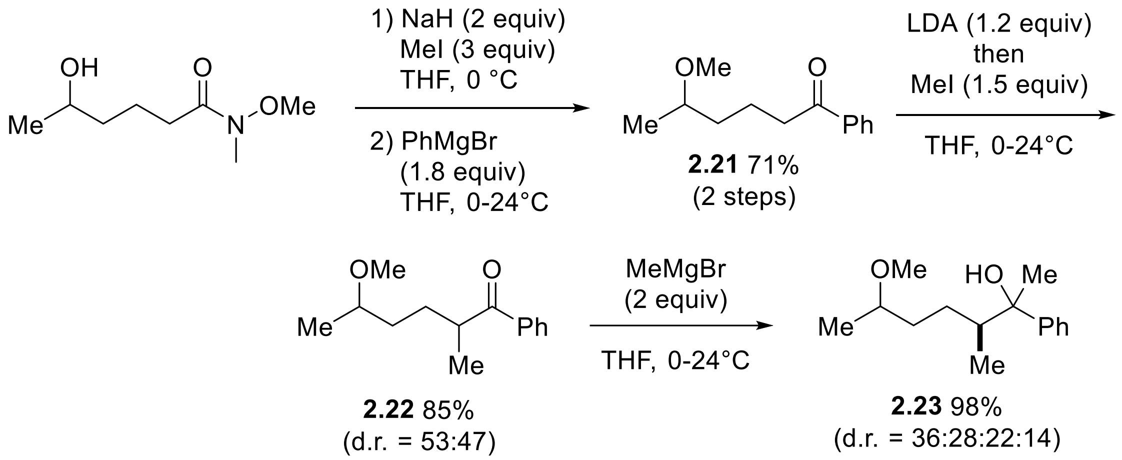
^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.67 – 7.59 (m, 1×0.50H, +m, 1×0.50H), 7.23 – 7.19 (m, 1×0.50H, +m, 1×0.50H), 7.15 (dddd, *J* = 7.2, 7.2, 3.6, 1.6 Hz, 1×0.50H, +dddd, *J* = 7.2, 7.2, 3.6, 1.6 Hz, 1×0.50H), 7.01 – 7.03 (m, 1×0.50H, +m, 1×0.50H), 3.48 – 3.38 (m, 2×0.50H,

+m, 2×0.50H), 3.35 (s, 3×0.50H), 3.33 (s, 3×0.50H), 2.89 – 2.67 (m, 2×0.50H, +m, 2×0.50H), 2.06 – 1.75 (m, 3×0.50H, +m, 3×0.50H), 1.75 – 1.63 (m, 4×0.50H, +m, 4×0.50H), 1.58 (s, 3×0.50H), 1.36 (s, 3×0.50H), 1.32 – 1.14 (m, 1×0.50H, +m, 1×0.50H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 145.0, 142.8, 135.9, 135.5, 128.6, 128.4, 126.84, 126.78, 126.7, 126.35, 126.31, 126.2, 74.0, 73.2, 73.1, 72.7, 58.5 (overlapped with 2C), 46.6, 44.7, 30.4, 29.1, 28.15, 28.12, 27.3, 26.0, 25.6, 25.4, 24.5, 23.7.

MS (HRMS ESI): Calcd for $C_{15}H_{22}O_2Na$ $[M+Na]^+$ 257.1517, Found: 257.1512.

5.2.2.1.11. Synthesis of (3*S**)-6-methoxy-3-methyl-2-phenylheptan-2-ol (2.23)



Synthesis of 5-methoxy-1-phenylhexan-1-one (2.21): Compound **2.21** was synthesized from 5-hydroxy-*N*-methoxy-*N*-methylhexanamide[33] (1.41 g, 8.03 mmol) via a sequence of methylation of the hydroxyl group and subsequent addition of PhMgBr. Methylation was conducted using NaH (60% dispersion in mineral oil, 640 mg, 16.0 mmol) and MeI (1.5 ml, 24.1 mmol) by following the procedure described in section **5.2.2.1.7.** The resulting crude residue was treated with PhMgBr (3.0 M in Et_2O, 4.9 mL, 14.7 mmol) in Et_2O (20 mL) by following the procedure described in section **2.7**. Purification by flash column chromatography (silica gel, Hex:EtOAc = 95:5) gave **2.21** in 71% yield over two steps (1.18 g, 5.73 mmol) as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 8.01 – 7.91 (m, 2H), 7.57 – 7.53 (m, 1H), 7.47 – 7.44 (m, 2H), 3.41 – 3.26 (m, 1H), 3.32 (s, 3H), 2.99 (dd, *J* = 7.2, 7.2 Hz, 2H), 1.91 – 1.70 (m, 2H), 1.65 – 1.44 (m, 2H), 1.15 (d, *J* = 6.0 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 200.2, 137.0, 132.9, 128.5, 128.0, 76.6, 55.9, 38.5, 35.9, 20.3, 18.9.

MS (HRMS ESI): Calcd for $C_{13}H_{19}O_2$ $[M+H]^+$ 207.1385, Found: 207.1389.

Synthesis of 5-methoxy-2-methyl-1-phenylhexan-1-one (2.22): Compound **2.22** was synthesized using **2.21** (757 mg, 3.67 mmol) and MeI (0.35 mL, 5.62 mmol) by following the procedure described in section **5.2.2.1.1**. Purification by flash column chromatography (silica gel, Hex:EtOAc = 95:5) gave **2.22** in 85% yield (687 mg, 3.12 mmol) as an estimated 53:47 diastereomeric mixture (based on ^{13}C NMR spectroscopy analysis) and as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.96 (d, *J* = 7.6 Hz, 2×0.53H, +d, *J* = 7.6 Hz, 2×0.47H), 7.57 – 7.53 (m, 1×0.53H, +m, 1×0.47H), 7.48 – 7.44 (m, 2×0.53H, +m, 2×0.47H), 3.47 (ddq, *J* = 6.8, 6.8, 6.8 Hz, 1×0.53H, +ddq, *J* = 6.8, 6.8, 6.8 Hz, 1×0.47H), 3.37 – 3.15 (m, 1×0.53H, +m, 1×0.47H), 3.29 (s, 3×0.47H), 3.25 (s, 3×0.53H), 2.00 – 1.77 (m, 1×0.53H, +m, 1×0.47H), 1.63 – 1.34 (m, 3×0.53H, +m, 3×0.47H), 1.20 (d, *J* = 6.8 Hz, 3×0.53H, +d, *J* = 6.8 Hz, 3×0.47H), 1.11 (d, *J* = 6.4 Hz, 3×0.53H), 1.10 (d, *J* = 6.0 Hz, 3×0.47H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 204.3, 204.1, 136.63, 136.57, 132.78. 132.77, 128.6 (overlapped with 2C), 128.2 (overlapped with 2C), 76.6 (overlapped with 2C), 55.9, 55.8, 40.5 (overlapped with 2C), 34.1, 33.8, 29.5, 29.2, 18.9, 18.8, 17.5, 17.3.

MS (HRMS ESI) Calcd for $C_{14}H_{21}O_2$ $[M+H]^+$ 222.1542, Found: 222.1548.

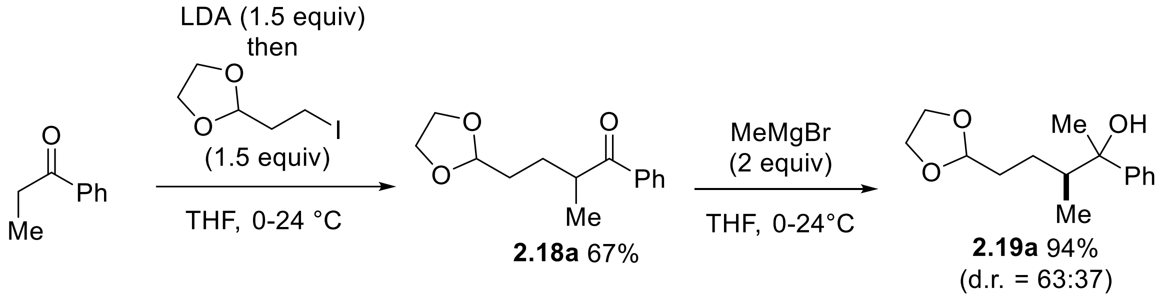
Synthesis of (3*S)-6-methoxy-3-methyl-2-phenylheptan-2-ol (2.23):** Compound **2.23** was synthesized using **2.22** (431 mg, 1.96 mmol) and MeMgBr (3.0 M in Et_2O, 1.3 mL, 0.39 mmol) by following the procedure described in section **5.2.2.1.1**. Purification by flash column chromatography (silica gel, Hex:EtOAc = 75:25) gave **2.23** in 98% yield (452 mg, 1.91 mmol) as an estimated 36:28:22:14 diastereomeric mixture (based on ^{13}C NMR spectroscopy analysis) and as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.46 – 7.38 (m, 2×0.36H, +m, 2×0.28H, +m, 2×0.22H, +m, 2×0.14H), 7.34 – 7.30 (m, 2×0.36H, +m, 2×0.28H, +m, 2×0.22H, +m, 2×0.14H), 7.24 – 7.20 (m, 1×0.36H, +m, 1×0.28H, +m, 1×0.22H, +m, 1×0.14H), 3.27 (s, 3×0.22H), 3.24 (s, 3×0.36H), 3.231 (s, 3×0.14H), 3.227 (s, 3×0.28H), 3.30 – 3.13 (m, 1×0.36H, +m, 1×0.28H, +m, 1×0.22H, +m, 1×0.14H), 1.87 – 1.71 (m, 2×0.36H, +m, 2×0.28H, +m, 2×0.22H, +m, 2×0.14H), 1.65 – 1.47 (m, 4×0.36H, +m, 4×0.28H, +m, 4×0.22H, +m, 4×0.14H), 1.47 – 1.16 (m, 2×0.36H, +m, 2×0.28H, +m, 2×0.22H, +m, 2×0.14H), 1.11 – 0.90 (m, 4×0.36H, +m, 4×0.28H, +m, 4×0.22H, +m, 4×0.14H), 0.87 – 0.81 (m, 3×0.36H, +m, 3×0.28H, +m, 3×0.22H, +m, 3×0.14H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 148.1, 148.0, 147.8, 147.7, 127.86, 127.85, 127.83, 127.81, 126.40 (overlapped with 2C), 126.38 (overlapped with 2C), 125.4, 125.3, 125.2 (overlapped with 2C), 77.09 (overlapped with 2C), 77.05, 77.03, 76.9 (overlapped with 2C), 76.8, 76.7, 65.8 (overlapped with 2C), 65.7 (overlapped with 2C), 44.02, 43.97 (overlapped with 2C), 43.94, 35.0, 34.7, 34.5 (overlapped with 2C), 27.0, 26.9, 26.8, 26.72, 26.67, 26.4, 26.2, 26.1, 19.0 (overlapped with 2C), 18.83, 18.76, 14.25, 14.20, 14.16, 14.09.

MS (HRMS ESI): Calcd for $C_{15}H_{25}O_2$ $[M+ H]^+$ 237.1855, Found: 237.1853.

5.2.2.1.12. Synthesis of (3*S**)-5-(1,3-dioxolan-2-yl)-3-methyl-2-phenylpentan-2-ol (2.19a)



Synthesis of 4-(1,3-dioxolan-2-yl)-2-methyl-1-phenylbutan-1-one (2.18a): Compound **2.18a** was synthesized using propiophenone (1.33 mL, 10.0 mmol) and 2-(2-iodoethyl)-1,3-dioxolane[34] (3.45 g, 15.1 mmol) by following the procedure described in section **5.2.2.1.1**. Purification by flash column chromatography (silica gel, Hex:EtOAc = 90:10) gave **2.18a** in 67% yield (1.58 g, 6.73 mmol) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.96 (d, *J* = 7.6 Hz, 2H), 7.57 – 7.54 (m, 1H), 7.48 – 7.44 (m, 2H), 4.85 (dd, *J* = 4.4, 4.4 Hz, 1H), 4.03 – 3.88 (m, 2H), 3.89 – 3.76 (m, 2H), 3.61 – 3.47 (m, 1H), 2.01 – 1.92 (m, 1H), 1.72 – 1.67 (m, 2H), 1.65 – 1.54 (m, 1H), 1.21 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 204.0, 136.6, 132.8, 128.6, 128.2, 104.3, 64.8 (overlapped with 2C), 40.2, 31.4, 27.6, 17.4.

MS (HRMS ESI): Calcd for $C_{14}H_{18}O_3Na$ [M+Na]$^+$ 257.1154, Found: 257.1157.

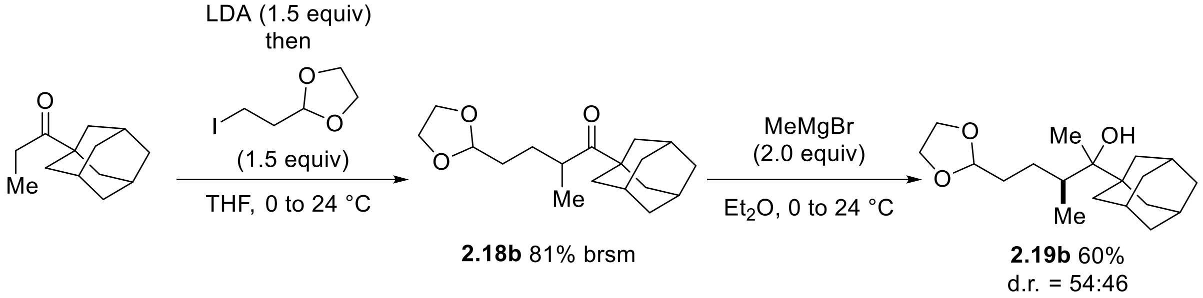
Synthesis of (3*S)-5-(1,3-dioxolan-2-yl)-3-methyl-2-phenylpentan-2-ol (2.19a)**: Compound **2.19a** was synthesized using **2.18a** (588 mg, 2.51 mmol) and MeMgBr (3.0 M in Et_2O, 7.7 mL, 5.10 mmol) by following the procedure described in section **5.2.2.1.1**. Purification by flash column chromatography (silica gel, Hex:EtOAc = 90:10) gave **2.19a** in 94% yield (591 mg, 2.36 mmol) as an estimated 63:37 diastereomeric mixture (based on ^{13}C NMR spectroscopy analysis) and as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.41 – 7.40 (m, 2×0.63H, +m, 2×0.37H), 7.35 – 7.28 (m, 2×0.63H, +m, 2×0.37H), 7.22 – 7.19 (m, 1×0.63H, +m, 1×0.37H), 4.77 – 4.73 (m, 1×0.63H, +m, 1×0.37H), 3.94 – 3.83 (m, 2×0.63H, +m, 2×0.37H), 3.83 – 3.67 (m, 2×0.63H, +m, 2×0.37H), 1.97 – 1.94 (m, 1×0.63H, +m, 1×0.37H), 1.87 – 1.75 (m, 1×0.63H, +m, 1×0.37H), 1.75 – 1.59 (m, 2×0.63H, +m, 2×0.37H), 1.53 – 1.47 (m, 1×0.63H, +m, 1×0.37H), 1.53 (s, 3×0.37H), 1.50 (s, 3×0.63H), 1.16 – 0.98 (m, 1×0.63H, +m, 1×0.37H), 0.83 (d, *J* = 6.0 Hz, 3×0.63H), 0.82 (d, *J* = 6.0 Hz, 3×0.37H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 147.9, 147.5, 127.81, 127.78, 126.4, 126.3, 125.32, 125.28, 104.7 (overlapped with 2C), 76.9, 76.8, 64.8, 64.71, 64.69, 64.6, 43.9, 43.8, 32.3, 32.2, 26.7, 25.9, 25.6, 25.3, 14.1, 14.0.

MS (HRMS ESI): Calcd for $C_{15}H_{23}O_3$ $[M+H]^+$ 251.1647, Found: 251.1640.

5.2.2.1.13. Synthesis of (3*S**)-2-(adamantan-1-yl)-6-methoxy-3-methylhexan-2-ol (2.19b)



Synthesis of 1-(adamantan-1-yl)-4-(1,3-dioxolan-2-yl)-2-methylbutan-1-one (2.18b): Compound **2.18b** was synthesized using 1-(adamantan-1-yl)propan-1-one (771 mg, 4.02 mmol) and 2-(2-iodoethyl)-1,3-dioxolane by following the procedure described in section

5.2.2.1.1. Purification by flash column chromatography (silica gel, Hex:EtOAc = 99:1) gave **2.18b** in 35% yield (412 mg, 1.41 mmol) as a colorless oil and unreacted starting material was recovered in 57% yield (440 mg, 2.29 mmol) (81% yield of **2.18b** based on recovery of the starting material: brsm)

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 4.80 (dd, *J* = 4.8,4.8 Hz, 1H), 4.01 – 3.90 (m, 2H), 3.90 – 3.75 (m, 2H), 3.05 (ddq, *J* = 6.8, 6.8, 6.8 Hz, 1H), 2.04 (s, 3H), 1.89 – 1.63 (m, 13H), 1.63 – 1.47 (m, 2H), 1.47 – 1.30 (m, 1H), 1.01 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 218.8, 104.3, 64.81, 64.80, 46.7, 38.4, 37.8, 36.5, 31.9, 28.3, 27.8, 18.3.

MS (HRMS ESI): Calcd for $C_{18}H_{29}O_3$ $[M+H]^+$ 293.2117, Found: 293.2119.

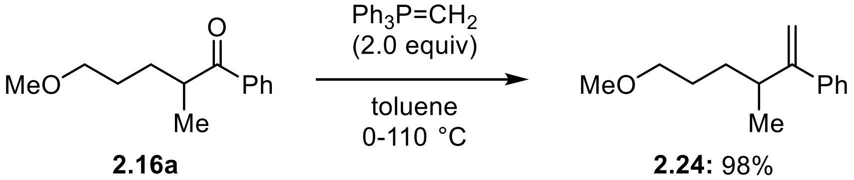
Synthesis of (3*S)-2-(-adamantan-1-yl)-5-(1,3-dioxolan-2-yl)-3-methylpentan-2-ol (2.19b):** Compound **2.19b** was synthesized using **2.18b** (293 mg, 1.00 mmol) and MeMgBr (3.0 M in Et_2O, 0.67 mL, 2.01 mmol) by following the procedure described in section **5.2.2.1.1**. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc = 90:10) gave **2.19b** in 60% yield (186 mg, 0.602 mmol) as an estimated 54:46 diastereomeric mixture (based on ^{1}H NMR spectroscopy analysis) and as a colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 4.86 (dd, *J* = 4.5, 4.5 Hz, 1×0.46H), 4.82 (dd, *J* = 4.5, 4.5 Hz, 1×0.54H), 4.03 – 3.90 (m, 2×0.46H, +m, 2×0.54H), 3.90 – 3.77 (m, 2×0.46H, +m, 2×0.54H), 2.00 (s, 3×0.46H, +s, 3×0.54H), 1.92 – 1.51 (m, 17×0.46H, +m, 17×0.54H), 1.27 (s, 1×0.54H, +s, 1×0.46H), 1.00 (s, 3×0.54H), 0.99 (s, 3×0.46H), 0.94 (d, *J* = 6.5 Hz, 3×0.46H, +d, *J* = 6.5 Hz, 3×0.54H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 105.0, 104.7, 77.7, 77.4, 64.85, 64.81, 64.80, 64.79, 40.7, 40.5, 38.4, 37.3, 37.14, 37.13, 36.73, 36.70, 33.0, 32.7, 28.8, 28.7, 28.5, 26.9, 17.8, 17.2, 16.8, 15.2.

MS (HRMS ESI): Calcd for. $C_{19}H_{33}O_3$ [M+H]$^+$ 309.2430, Found: 309.2436.

5.2.2.1.14. Synthesis of (6-methoxy-3-methylhex-1-en-2-yl)benzene (2.24)



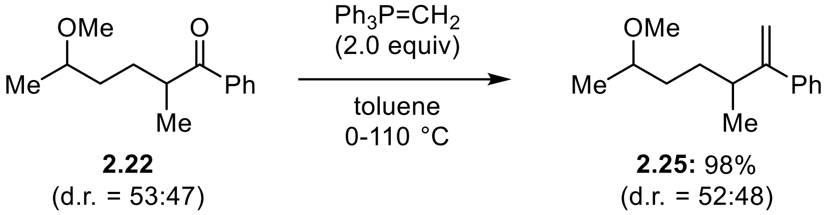
Synthesis of (6-methoxy-3-methylhex-1-en-2-yl)benzene (2.24): To a solution of Ph_3PMeBr (1.43 g, 4.015 mmol) in toluene (5.0 mL) was added NaHMDS (1 M in THF, 4.0 mL, 4.00 mmol) at 0 °C and the mixture was stirred for 1 h before **2.16a** (416 mg, 2.02 mmol) in toluene (1.0 mL) was added. The reaction mixture was stirred for 14 h at 110 °C. After cooling to 24 °C, the mixture was filtered through a pad of silica and eluted with a 95:5 / Hex:EtOAc solvent mixture to give **2.24** in 98% yield (403 mg, 1.97 mmol) as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.36 – 7.28 (m, 4H), 7.28 – 7.22 (m, 1H), 5.18 (d, *J* = 1.2 Hz, 1H), 5.04 – 5.03 (m, 1H), 3.40 – 3.24 (m, 2H), 3.30 (s, 3H), 2.78 – 2.60 (m, 1H), 1.68 – 1.50 (m, 3H), 1.45 – 1.34 (m, 1H), 1.13 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) δ 154.5, 143.0, 128.1, 127.0, 126.6, 111.2, 73.0, 58.5, 37.8, 32.4, 27.3, 20.1.

MS (HRMS ESI): Calcd for $C_{14}H_{21}O$ [M+H]$^+$ 205.1592, Found: 205.1593.

5.2.2.1.15. Synthesis of ((3S*)-6-methoxy-3-methylhept-1-en-2-yl)benzene (2.25)



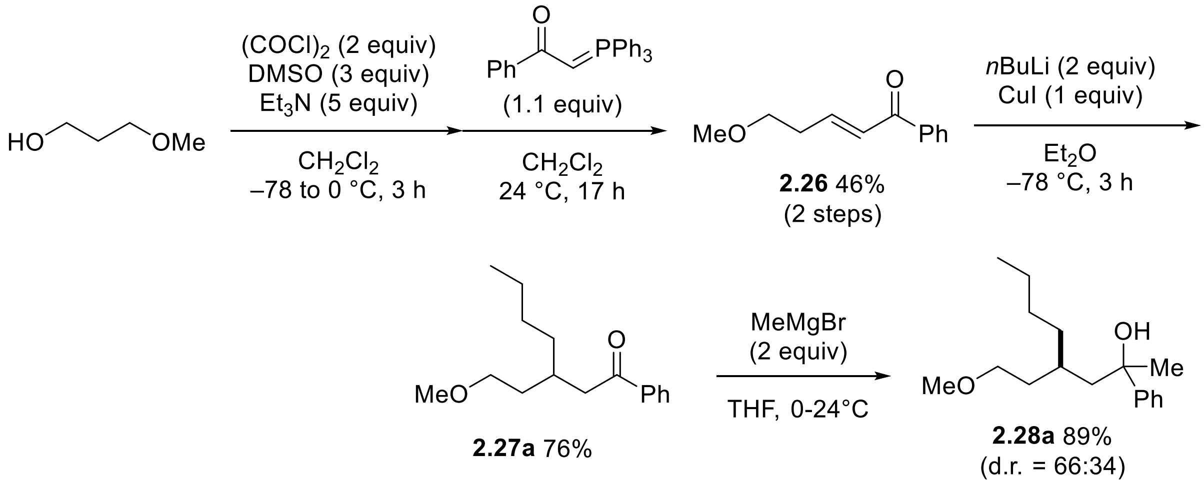
Synthesis of ((3S*)-6-methoxy-3-methylhept-1-en-2-yl)benzene (2.25): Compound **2.25** was synthesized using **2.22** (667 mg, 3.03 mmol), Ph_3PMeBr (1.63 g, 4.56 mmol) and NaHMDS (1 M in THF, 4.5 mL, 4.500 mmol) by following the procedure described in section **5.2.2.1.14**. Purification by flash column chromatography (silica gel, Hex:EtOAc = 95:5) gave **2.25** in 98% yield (649 mg, 2.97 mmol) as an estimated 52:48 diastereomeric mixture (based on ^{13}C NMR spectroscopy analysis) and as a yellow oil.

<u>^{1}H NMR (400 MHz, $CDCl_3$):</u> δ(ppm) 7.36 – 7.28 (m, 4×0.52H, +m, 4×0.48H), 7.28 – 7.21 (m, 1×0.52H, +m, 1×0.48H), 5.19 (s, 1×0.52H, +s, 1×0.48H), 5.04 – 5.03 (m, 1×0.52H, +m, 1×0.48H), 3.33 – 3.16 (m, 1×0.52H, +m, 1×0.48H), 3.28 (s, 3×0.52H), 3.27 (s, 3×0.48H), 2.72 – 2.60 (m, 1×0.52H, +m, 1×0.48H), 1.65 – 1.47 (m, 2×0.52H, +m, 2×0.48H), 1.45 – 1.30 (m, 2×0.52H, +m, 2×0.48H), 1.13 (d, *J* = 6.8 Hz, 3×0.52H, +d, *J* = 6.8 Hz, 3×0.48H), 1.09 (d, *J* = 6.0 Hz, 3×0.48H), 1.07 (d, *J* = 6.0 Hz, 3×0.52H).

<u>^{13}C NMR (100 MHz, $CDCl_3$):</u> δ(ppm) 154.6, 154.5, 142.99, 142.98, 128.1 (overlapped with 2C), 127.0 (overlapped with 2C), 126.6 (overlapped with 2C), 111.2, 111.1, 76.94, 76.89, 55.8 (overlapped with 2C), 38.1, 37.9, 33.9, 33.6, 31.7, 31.5, 20.3, 20.1, 19.0, 18.9.

<u>MS (HRMS ESI):</u> Calcd for $C_{15}H_{23}O$ $[M+H]^+$ 219.1749, Found: 2219.1753.

5.2.2.1.16. Synthesis of (4*R**)-4-(2-methoxyethyl)-2-phenyloctan-2-ol (2.28a)



2.26 46%
(2 steps)

2.27a 76%

2.28a 89%
(d.r. = 66:34)

Synthesis of (*E*)-5-methoxy-1-phenylpent-2-en-1-one (2.26): Oxalyl chloride (2.56 mL, 29.8 mmol) was added into a solution of DMSO (3.20 mL, 45.1 mmol) in CH_2Cl_2 (75 mL) at –78 °C. The reaction mixture was stirred for 30 mins before a solution of the 3-methoxy-1-propanol (1.45 mL, 15.2 mmol) in CH_2Cl_2 (25 mL) was added. After the mixture was stirred for 1.5 h at the same temperature, Et_3N (10.4 mL, 74.6 mmol) was added and the reaction mixture was warmed up to 24 °C and continuously stirred for 2 h. To this mixture was added (phenacylidene)triphenylphosporane (10.9 g, 28.7 mmol) and the reaction mixture was stirred for a further 12 h. The reaction mixture was then concentrated under reduced pressure and the resulting residue was purified by flash column chromatography (silica gel, *n*-Hex:EtOAc = 92:8) to give **2.26** in 46% yield (1.32 g, 6.93 mmol) as a yellow oil.

<u>^{1}H NMR (400 MHz, CDCl$_3$):</u> δ(ppm) 7.93 – 7.91 (m, 2H), 7.57 – 7.52 (m, 1H), 7.47 – 7.44 (m, 2H), 7.08 – 7.97 (m, 1H), 6.92 – 6.96 (m, 1H), 3.56 (t, *J* = 8.0 Hz, 2H), 3.36 (s, 3H), 2.61 – 2.56 (m, 2H).

<u>^{13}C NMR (100 MHz, CDCl$_3$):</u> δ(ppm) 190.6, 146.0, 137.8, 132.6, 128.6, 128.5, 127.4, 70.8, 58.7, 33.2.

<u>MS (HRMS ESI):</u> Calcd for $C_{12}H_{15}O_2$ $[M+H]^+$ 191.1072, Found: 191.1077.

Synthesis of 3-(2-methoxyethyl)-1-phenylheptan-1-one (2.27a): To a suspension of CuI (381 mg, 2.00 mmol) in Et_2O (5 mL) was added BuLi (2.0 M in hexane, 2.0 mL, 4.0 mmol) at 0 °C and the mixture was stirred for 5 min at the same temperature before being cooled down to –78 °C. To the resulting cuprate was added a solution of enone **2.26** (381 mg, 2.00 mmol) in Et_2O (3 mL) and the mixture was stirred at –78 °C for 3 h. The reaction was quenched with a saturated aqueous NH_4Cl solution and the organic materials were extracted thrice with Et_2O. The combine extracts were washed with brine and dried over $MgSO_4$. The volatile materials were removed *in vacuo* and the resulting crude material was purified by flash column chromatography (silica gel, *n*-Hex:EtOAc = 96:4) to give **2.27a** in 76% yield (378 mg, 1.52 mmol) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.96 – 7.93 (m, 2H), 7.55 – 7.51 (m, 1H), 7.46 – 7.42 (m, 2H), 3.45 – 3.34 (m, 2H), 3.25 (s, 3H), 2.98 (dd, *J* = 16.4, 6.4 Hz, 1H), 2.85 (dd, *J* = 16.4, 6.4 Hz, 1H), 2.27 – 2.17 (m, 1H), 1.73 – 1.63 (m, 1H), 1.61 – 1.53 (m, 1H), 1.38 – 1.22 (m, 6H), 0.88 – 0.84 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 200.2, 137.4, 132.7, 128.5, 128.0, 71.0, 58.4, 43.5, 34.2, 34.0, 31.8, 28.8, 22.9, 14.0.

MS (HRMS ESI): Calcd for $C_{16}H_{25}O_2$ $[M+H]^+$ 249.2011, Found: 249.2004.

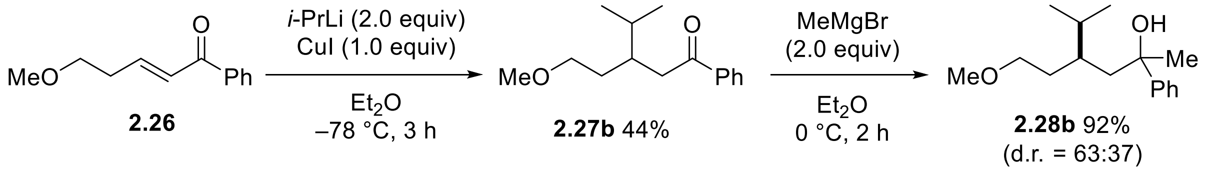
Synthesis of (4*R)-4-(2-methoxyethyl)-2-phenyloctan-2-ol (2.28a):** Compound **2.28a** was synthesized using **2.27a** (378 mg, 1.52 mmol) and MeMgBr (3.0 M in Et_2O, 1.0 mL) following the procedure described in section **5.2.2.1.1**. Purification by flash column chromatography (silica gel, Hex:EtOAc = 95:5) gave **2.28a** in 89% yield (353 mg, 1.33 mmol) as an estimated 70:30 diastereomeric mixture (based on ^{1}H NMR spectroscopy analysis) and as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.46 – 7.42 (m, 2×0.70H, +m, 2×0.30H), 7.33 – 7.29 (m, 2×0.70H, +m, 2×0.30H), 7.22 – 7.18 (m, 1×0.70H, +m, 1×0.30H), 3.53 (s, 1×0.70H), 3.50 – 3.45 (m, 1×0.70H, +m, 1×0.30H), 3.40 – 3.29 (m, 1×0.70H, +m, 1×0.30H), 3.32 (s, 3×0.70H), 3.28 (s, 3×0.30H), 3.02 (s, 1×0.30H), 1.87 (dd, *J* = 14.8, 4.0 Hz, 1×0.70H), 1.79 (dd, *J* = 14.8, 6.4 Hz, 1×0.70H), 1.78 – 1.74 (m, 2×0.30H), 1.68 – 1.58 (m, 2×0.70H), 1.54 (s, 3×0.30H), 1.51 (s, 3×0.70H), 1.53 – 1.18 (m, 2×0.30H), 1.35 – 1.32 (m, 1×0.70H), 1.21 – 1.26 (m, 2×0.70H, +m, 3×0.30H) 1.14 – 0.97 (m, 4×0.70H, +m, 4×0.30H), 0.88 – 0.85 (m, 3×0.30H), 0.77 – 0.74 (m, 3×0.70H).

^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 149.6, 148.1, 127.9, 127.8, 126.2, 126.0, 125.1, 124.6, 74.9, 74.6, 71.2, 71.1, 58.44, 58.41, 48.6, 48.0, 36.3, 36.2, 34.4, 34.3, 32.2, 31.1, 30.7, 29.3, 28.9, 28.6, 22.9, 22.7, 14.1, 13.9.

MS (HRMS ESI) Calcd for $C_{17}H_{29}O_2$ $[M+H]^+$ 265.2168, Found: 265.2175.

5.2.2.1.17. Synthesis of (4*R**)-4-isopropyl-6-methoxy-2-phenylhexan-2-ol (2.28b)



Synthesis of 3-isopropyl-5-methoxy-1-phenylpentan-1-one (2.27b): Compound **2.27b** was synthesized using **2.26** (381 mg, 2.00 mmol) and isopropyllithium (0.7 M in Et_2O, 6.0 mL) following the procedure described in section **5.2.2.1.15**. Purification by flash column chromatography (silica gel, Hex:EtOAc = 96:4) gave **2.27b** in 44% yield (205 mg, 0.875 mmol) as a colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 7.96 – 7.94 (m, 2H), 7.56 – 7.52 (m, 1H), 7.47 – 7.43 (m, 2H), 3.39 (ddd, *J* = 18.0, 9.0, 9.0 Hz, 2H), 3.23 (s, 3H), 2.95 – 2.84 (m, 2H), 2.22 – 2.16 (m, 1H), 1.80 – 1.75 (m, 1H), 1.73 – 1.65 (m, 1H), 1.54 – 1.45 (m, 1H), 0.91 (d, *J* = 8.0 Hz, 6H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 200.3, 137.4, 132.7, 128.5, 128.0, 71.6, 58.3, 40.4, 37.0, 31.1, 30.5, 19.0, 18.9.

MS (HRMS ESI): Calcd for $C_{15}H_{23}O_2$ $[M+H]^+$ 235.1698, Found: 235.1695.

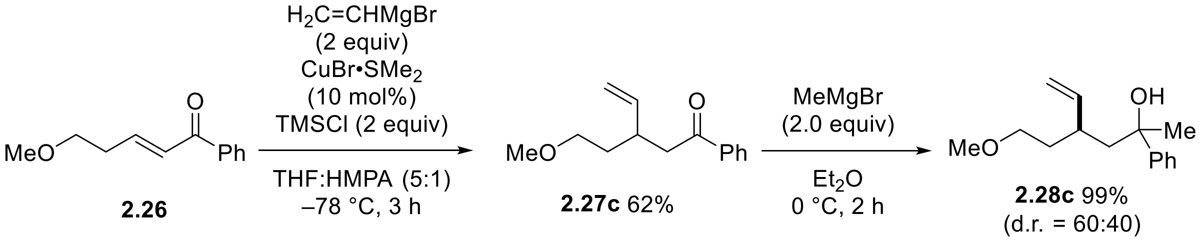
Synthesis of (4*R)-4-isopropyl-6-methoxy-2-phenylhexan-2-ol (2.28b):** Compound **2.28b** was synthesized using **2.27b'** (205 mg, 0.875 mmol) and MeMgBr (2.84 M in Et$_2$O, 0.65 mL) following the procedure described in section **5.2.2.1.1**. Purification by flash column chromatography (silica gel, Hex:EtOAc = 91:9) gave **2.28b** in 92% yield (201 mg, 0.803 mmol) as an estimated 57:43 diastereomeric mixture (based on ^{1}H NMR spectroscopy analysis) and as a colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 7.47 – 7.35 (m, 2×0.43H), 7.42 – 7.40 (m, 2×0.57H), 7.36 – 7.28 (m, 2×0.57H, +m, 2×0.43H), 7.26 – 7.18 (m, 1×0.57H, +m, 1×0.43H), 3.90 (s, 1×0.57H), 3.51 – 3.46 (m, 1×0.57H), 3.43 – 3.39 (m, 1×0.43H), 3.36 (s, 1×0.43H), 3.33 (s, 3×0.57H), 3.31 (s, 3×0.43H), 3.38 – 3.23 (m, 1×0.57H, +m, 1×0.43H), 1.91 (dd, *J* = 14.0, 3.0 Hz, 1×0.57H), 1.85 – 1.74 (m, 1×0.43H), 1.74 – 1.61 (m, 2×0.57H, +m, 2×0.43H), 1.53 (s, 3×0.43H), 1.51 (s, 3×0.57H), 1.61 – 1.47 (m, 3×0.43H), 1.47 – 1.38 (m, 1×0.57H), 1.35 – 1.29 (m, 1×0.57H), 1.27 – 1.18 (1×0.57H), 0.84 (d, *J* = 7.0 Hz, 3×0.43H), 0.82 (d, *J* = 7.0 Hz, 3×0.43H), 0.66 (d, *J* = 7.0 Hz, 3×0.57H), 0.63 (d, *J* = 7.0 Hz, 3×0.57H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 149.9, 148.2, 128.0, 127.8, 126.2, 126.0, 125.2, 124.6, 75.2, 74.4, 72.5, 72.4, 58.5 (overlapped), 46.3, 45.9, 36.4, 36.1, 32.45, 32.42, 32.1, 31.5, 31.4, 29.0, 19.3, 19.0, 18.3, 18.1.

MS (HRMS ESI): Calcd for $C_{16}H_{27}O_2$ $[M+H]^+$ 251.2011, Found: 251.2007.

5.2.2.1.18. Synthesis of (4*R**)-4-(2-methoxyethyl)-2-phenylhex-5-en-2-ol (2.28c)



Synthesis of 3-(2-methoxyethyl)-1-phenylpent-4-en-1-one (2.27c): Conjugate addition of vinyl Grignard reagent was performed by following the procedure reported by Kuwajima.[35] To a solution of vinylmagnesium bromide (1.6 M in THF, 3.0 mL) in THF (3 mL) was added an HMPA solution (0.9 mL) of $CuBr•SMe_2$ (41.8 mg, 0.202 mmol) at –78 °C and the mixture was stirred for 30 min at the same temperature. To the mixture was added a solution of **2.26** (386 mg, 2.03 mmol) and chlorotrimethylsilane (0.5 mL, 3.94 mmol) in THF (1.5 mL) was added dropwise over 30 min at –78 °C. The reaction mixture was stirred for 3 h at the same temperature. It was then quenched with aqueous HCl solution (1 M, 4.0 mL) and stirred for a further 10 min. Organic materials were extracted thrice with Et_2O and the combine extracts were washed with brine and dried over $MgSO_4$. The volatile materials were removed *in vacuo* and the resulting crude material was purified by flash column chromatography (silica gel, Hex:EtOAc = 96:4) to give **2.27c** in 62% yield (272 mg, 1.25 mmol) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.95 – 7.92 (m, 2H), 7.57 – 7.52 (m, 1H), 7.47 – 7.42 (m, 2H), 5.71 (ddd, *J* = 17.5, 9.0, 2.0 Hz, 1H), 5.11 – 4.93 (m, 2H), 3.47 – 3.34 (m, 2H), 3.29 (s, 3H), 3.06 (dd, *J* = 16.0, 6.5 Hz, 1H), 2.99 (dd, *J* = 16.0, 7.0 Hz, 1H), 2.96 – 2.85 (m, 1H), 1.85 – 1.74 (m, 1H), 1.69 – 1.60 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 199.1, 140.9, 137.3, 132.9, 128.6, 128.1, 115.1, 70.6, 58.5, 43.8, 36.8, 34.3.

MS (HRMS ESI) Calcd for $C_{14}H_{19}O_2$ $[M+H]^+$ 219.1385, Found: 219.1389.

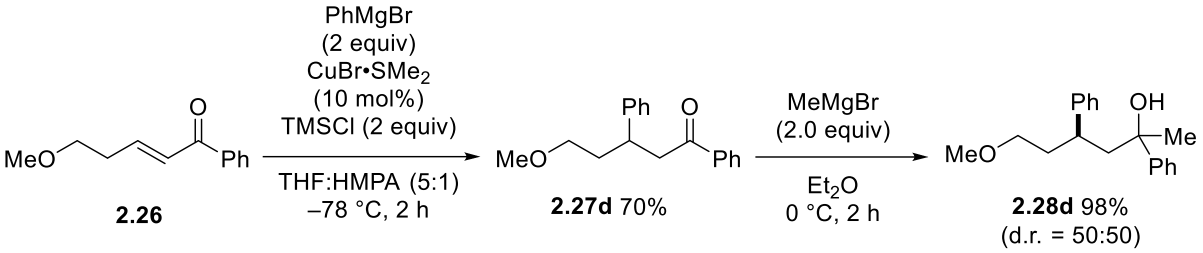
Synthesis of (4*R)-4-(2-methoxyethyl)-2-phenylhex-5-en-2-ol (2.28c):** Compound **2.28c** was synthesized using **2.27c** (272 mg, 1.25 mmol) and MeMgBr (2.84 M in Et_2O, 0.84 mL) by following the procedure described in section **5.2.2.1.1**. Purification by flash column chromatography (silica gel, Hex:EtOAc = 92:8) gave **2.28c** in 99% yield (287 mg, 1.23 mmol) as an estimated 60:40 diastereomeric mixture (based on ^1H NMR spectroscopy analysis) and as a colorless oil.

^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.44 – 7.41 (m, 1×0.60H, +m, 1×0.40H), 7.39 – 7.29 (m, 3×0.60H, +m, 3×0.40H), 7.24 – 7.19 (m, 1×0.60H, +m, 1×0.40H), 5.77 – 5.56 (m, 1×0.60H, +m, 1×0.40H), 5.02 – 4.83 (m, 2×0.60H, +m, 2×0.40H), 3.39 – 3.18 (m, 2×0.60H, +m, 2×0.40H), 3.29 (s, 3×0.60H), 3.22 (s, 3×0.40H), 2.81 (brs, 1×0.40H), 2.69 (brs, 1×0.60H), 2.38 – 2.29 (m, 1×0.60H), 2.16 – 2.04 (m, 1×0.40H, +m, 2×0.40H), 1.93 – 1.86 (m, 2×0.60H), 1.68 – 1.46 (m, 2×0.60H, +m, 2×0.40H), 1.61 (s, 3×0.60H), 1.58 (s, 3×0.40H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 148.5, 148.2, 144.2, 143.7, 128.1, 128.0, 126.4, 126.3, 124.77, 124.75, 116.0, 114.7, 75.8, 74.8, 70.21, 70.17, 58.5, 58.4, 48.9, 48.0, 37.7, 37.1, 35.6, 35.3, 35.1, 30.2.

MS (HRMS ESI): Calcd for $C_{15}H_{23}O_2$ $[M+H]^+$ 235.1698, Found: 235.1706.

5.2.2.1.19. Synthesis of (4*R**)-6-methoxy-2,4-diphenylhexan-2-ol (2.28d)



Synthesis of 5-methoxy-1,3-diphenylpentan-1-one (2.27d): Compound **2.27d** was synthesized using **2.26** (571 mg, 3.00 mmol) and PhMgBr (1.6 M in THF, 3.0 mL) by following the procedure described in section **5.2.2.1.18**. Purification by flash column chromatography (silica gel, Hex:EtOAc = 96:4) gave **2.27d** in 70% yield (560 mg, 2.09 mmol) as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.92 – 7.89 (m, 2H), 7.54 – 7.50 (m, 1H), 7.44 – 7.40 (m, 2H), 7.31 – 7.23 (m, 4H), 7.22 – 7.16 (m, 1H), 3.55 – 3.48 (m, 1H), 3.31 (dd, J = 6.8, 2.0 Hz, 2H), 3.29 – 3.20 (m, 2H), 3.23 (s, 3H), 2.11 – 2.03 (m, 1H), 1.92 – 1.83 (m, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 198.7, 144.2, 137.1, 132.9, 129.5, 128.5 (overlapped with 2C), 128.0, 127.5, 70.6, 58.4, 45.6, 38.0, 36.0.

MS (HRMS ESI): Calcd for $C_{18}H_{21}O_2$ $[M+H]^+$ 269.1542, Found: 269.1537.

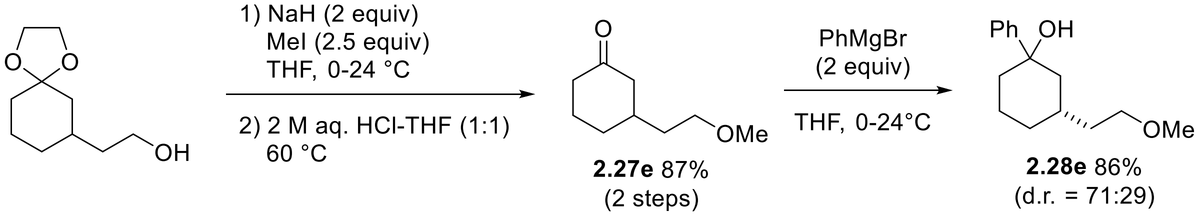
Synthesis of (4*R)-6-methoxy-2,4-diphenylhexan-2-ol (2.28d):** Compound **2.28d** was synthesized using **2.27d** (194 mg, 0.723 mmol) and MeMgBr (2.84 M in Et_2O, 0.55 mL) following the procedure described in section **5.2.2.1.1**. Purification by flash column chromatography (silica gel, Hex:EtOAc = 92:8) gave **2.28d** in 98% yield (202 mg, 0.709 mmol) as a 50:50 diastereomeric ratio (based on ^{1}H NMR spectroscopy analysis) and as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.35 – 7.32 (m, 3×0.50H, +m, 3×0.50H), 7.09 – 7.11 (m, 5×0.50H, +m, 5×0.50H), 7.06 – 7.00 (m, 2×0.50H, +m, 2×0.50H), 3.22 (s, 3×0.50H), 3.16 (s, 3×0.50H), 3.21 – 2.98 (m, 2×0.50H, +m, 2×0.50H), 2.78 – 2.63 (m, 1×0.50H, +m, 1×0.50H), 2.34 – 2.16 (m, 2×0.50H, +m, 2×0.50H), 1.95 – 1.68 (m, 2×0.50H, +m, 2×0.50H), 1.66 (brs, 0.50×1H), 1.58 (brs, 0.50×1H),1.48 (s, 3×0.50H), 1.40 (s, 3×0.50H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 148.1, 148.0, 146.1, 145.0, 128.8, 128.5, 128.1, 128.0, 127.9, 127.6, 126.6, 126.4, 126.3, 126.1, 124.9, 124.8, 75.5, 75.1, 70.5, 70.4, 58.5, 58.4, 50.3, 49.7, 38.6, 38.4, 37.9, 37.8, 31.7, 30.6.

MS (HRMS ESI) Calcd for $C_{19}H_{25}O_2$ $[M+H]^+$ 285.1855, Found: 285.1855.

5.2.2.1.20 Synthesis of (3*S**)-3-(2-methoxyethyl)-1-phenylcyclohexan-1-ol (2.28e)



Synthesis of 3-(2-methoxyethyl)cyclohexan-1-one (2.27e): To a suspension of NaH (60% dispersion in mineral oil, 1.21 g, 30.250 mmol) in THF (15 mL) was slowly added a solution of 2-(1,4-dioxaspiro[4.5]decan-7-yl)ethan-1-ol[36] (2.73 g, 14.6 mmol) in THF (10 mL) at 0 °C and the reaction mixture was stirred at the same temperature for 30 min. To the mixture was added MeI (2.3 ml, 36.9 mmol) and the solution was slowly warmed up to 24 °C and stirred continuously for 3 h before being quenched with water. The organic materials were then extracted thrice with EtOAc and the combined organic layers were washed with brine and dried over $MgSO_4$. After the filtrate was concentrated *in vacuo*, the resulting crude residue was used for the next step without further purification.

To a solution of the above crude residue in THF (20 mL) was added aqueous HCl solution (2 M, 20 mL) and the mixture was stirred for 5 h at 60 °C. The reaction was then quenched with water at 24 °C and the organic materials were extracted thrice with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. After the filtrate was concentrated *in vacuo*, the resulting crude residue was purified by flash column chromatography (silica gel, Pentane:Et_2O = 90:10 to 80:20) to give **2.27e** in 87% yield (2.00 g, 12.8 mmol) over two steps and as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 3.46 – 3.36 (m, 2H), 3.32 (s, 3H), 2.47 – 2.43 (m, 1H), 2.41 – 2.32 (m, 1H), 2.32 – 2.20 (m, 1H), 2.08 – 2.00 (m, 2H), 1.99 – 1.86 (m, 2H), 1.75 – 1.49 (m, 3H), 1.44 – 1.30 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 211.4, 70.0, 58.5, 47.8, 41.3, 36.1, 35.9, 31.2, 25.1.

MS (HRMS ESI): Calcd for $C_9H_{16}O_2Na$ $[M+Na]^+$ 179.1048, Found: 179.1043.

Synthesis of (3*S)-3-(2-methoxyethyl)-1-phenylcyclohexan-1-ol (2.28e):** Compound **2.28e** was synthesized using **2.27e** (648 mg, 4.15 mmol) and PhMgBr (3.0 M in Et_2O, 2.8 mL) by following the procedure described in section **5.2.2.1.1**. Purification by flash column chromatography (silica gel, Hex:EtOAc = 80:20) gave **2.28e** in 86% yield (837 mg, 3.57 mmol) as an estimated 71:29 diastereomeric mixture (based on ^{1}H NMR spectroscopy analysis) and as a colorless oil.

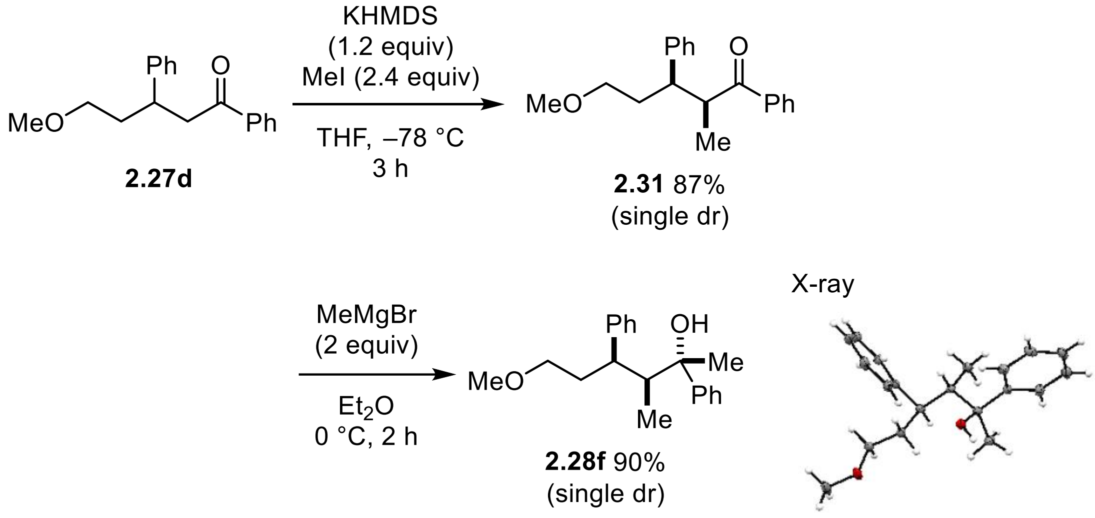
^{1}H NMR (400 MHz, $CDCl_3$): 7.56 – 7.46 (m, 2×0.71H, +m, 2×0.29H), 7.40 – 7.29 (m, 2×0.71H, +m, 2×0.29H), 7.27 – 7.21 (m, 1×0.71H, +m, 1×0.29H), 3.50 – 3.35 (m, 2×0.71H, +m, 2×0.29H), 3.31 (s, 3×0.29H), 3.29 (s, 3×0.71H), 2.43 – 2.35 (m, 1×0.71H), 2.28 – 2.20 (m, 1×0.29H), 1.96 – 1.90 (m, 1×0.71H), 1.89 – 1.60 (m, 6×0.71H, +m, 6×0.29H), 1.60 – 1.36

(m, 3×0.71H, +m, 3×0.29H), 1.33 – 1.19 (m, 1×0.29H), 1.10 (m, 1×0.29H), 1.02 – 0.89 (m, 1×0.71H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 149.6, 145.5, 128.4, 128.1, 127.1, 126.6, 126.0, 124.4, 73.54, 73.52, 70.8, 70.6, 58.48, 58.46, 45.7, 44.1, 38.6, 38.5, 36.8, 36.0, 32.30, 32.28, 32.1, 30.2, 22.3, 21.7.

MS (HRMS ESI): Calcd for $C_{15}H_{22}O_2Na$ $[M+Na]^+$ 257.1517, Found: 257.1516.

5.2.2.1.21. Synthesis of (2*S**,3*S**,4*R**)-6-methoxy-3-methyl-2,4-diphenylhexan-2-ol (2.28f)



Synthesis of (2*S,3*R**)-5-methoxy-2-methyl-1,3-diphenylpentan-1-one (2.31):** To a solution of **2.27d** (560 mg, 2.09 mmol) in THF (5.0 mL) was added KHMDS (1 M in THF, 2.50 mL, 2.50 mmol) at –78 °C and the mixture was stirred for 1 h before MeI (0.30 mL, 4.81 mmol) was added. The reaction mixture was stirred for 4 h at –78 °C and was quenched with a saturated aqueous NH_4Cl solution. The organic materials were then extracted thrice with Et_2O and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (silica gel, Hex:EtOAc = 94:6) to give **2.31** in 87% yield (511 mg, 1.81 mmol) as a single diastereomer (based on ^{1}H NMR spectroscopy analysis) and as a colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 8.03 – 8.01 (m, 2H), 7.60 (m, 1H), 7.51 – 7.48 (m, 2H), 7.34 – 7.31 (m, 2H), 7.26 – 7.22 (m, 3H), 3.76 (ddd, *J* = 16.5, 13.5, 7.0 Hz, 1H), 3.21 – 3.05 (m, 3H), 3.15 (s, 3H), 1.95 – 1.89 (m, 1H), 1.81 – 1.73 (m, 1H), 0.91 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 204.3, 142.2, 137.3, 133.0, 128.7, 128.5, 128.30, 128.28, 126.6, 70.7, 58.3, 46.0, 45.5, 34.6, 17.0.

MS (HRMS ESI): Calcd for $C_{19}H_{23}O_2$ [M+H]$^+$ 283.1698, Found: 283.1689.

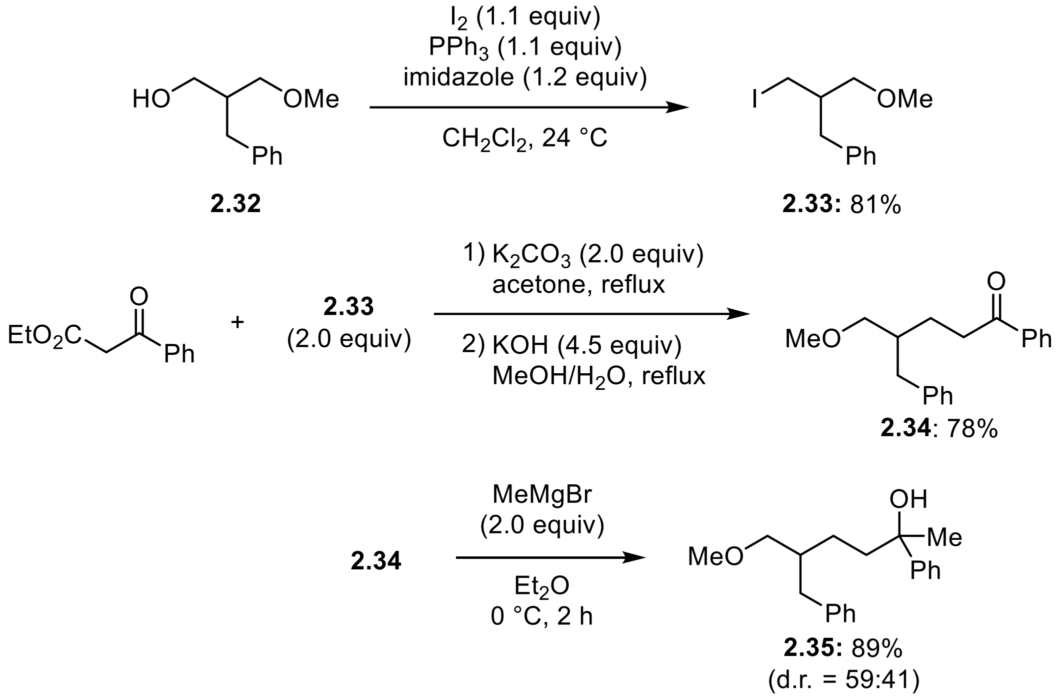
Synthesis of (2*S,3*S**,4*R**)-6-methoxy-3-methyl-2,4-diphenylhexan-2-ol (2.28f):** Compound **2.28f** was synthesized using **2.31** (511 mg, 1.81 mmol) and MeMgBr (2.84 M in Et$_2$O, 1.2 mL) following the procedure described in section **5.2.2.1.1**. Purification by flash column chromatography (silica gel, Hex:EtOAc = 92:8) gave 90% yield of **2.28f** (484 mg, 1.62 mmol) as a single diastereomer (based on ^{1}H NMR spectroscopy analysis) and as a white solid. Compound **10f** was recrystallized from CH_2Cl_2 to afford a colorless crystal. The stereochemistry of **10f** was confirmed by X-ray crystallography analysis (CCDC-1894805).

^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 7.43 – 7.41 (m, 2H), 7.39 – 7.36 (m, 2H), 7.27 – 7.24 (m, 3H), 7.20 – 7.17 (m, 1H), 7.02 – 7.00 (m, 2H), 3.13 (s, 3H), 3.07 – 2.97 (m, 2H), 2.87 (ddd, *J* = 6.5, 6.5, 3.5 Hz, 1H), 2.35 (qd, *J* = 7.5, 3.5 Hz, 1H), 1.92 – 1.84 (m, 2H), 1.51 (s, 1H), 1.34 (s, 3H), 1.10 (d, *J* = 7.5 Hz, 3H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 149.2, 142.3, 129.3, 128.3, 128.1, 126.7, 126.3, 124.9, 78.2, 70.8, 58.3, 46.9, 41.9, 35.6, 29.1, 10.2.

MS (HRMS ESI) Calcd for $C_{20}H_{27}O_2$ $[M+H]^+$ 299.2011, Found: 299.2003.

5.2.2.1.22. Synthesis of 5-benzyl-6-methoxy-2-phenylhexan-2-ol (2.35)



Synthesis of (3-iodo-2-(methoxymethyl)propyl)benzene: To a solution of PPh_3 (4.34 g, 16.5 mmol), I_2 (4.19 g, 16.5 mmol) and imidazole (1.20 mg, 17.7 mmol) in CH_2Cl_2 (40 mL) was added 3-methoxy-2-phenylpropan-1-ol[37] (2.70 g, 15.0 mmol in 5 mL dichloromethane) at 24 °C and the reaction mixture was then stirred for 4 h at 24 °C. The reaction was poured into a saturated aqueous $Na_2S_2O_3$ solution and the organic materials were extracted thrice with CH_2Cl_2. The combined organic layers were washed with brine and dried over $MgSO_4$. After the filtrate was concentrated *in vacuo*, the resulting crude residue was purified by flash chromatography (silica gel, Hex:EtOAc = 90:10) to give (3-iodo-2-(methoxymethyl)propyl)benzene in 81% yield (3.48 g, 12.0 mmol) as a pale yellow oil.

^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 7.31 – 7.20 (m, 5H), 3.37 – 3.32 (m, 2H), 3.35 (s, 3H), 3.26 (dd, *J* = 9.5, 7.0 Hz, 1H), 3.19 (dd, *J* = 9.5, 5.0 Hz, 1H), 2.69 (dd, *J* = 13.5, 6.0 Hz, 1H), 2.61 (dd, *J* = 13.5, 7.5 Hz, 1H), 1.80 – 1.78 (m, 1H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 139.1, 129.1, 128.5, 126.3, 74.6, 58.9, 41.7, 37.3, 11.8.

MS (HRMS ESI): Calcd for $C_{11}H_{15}OINa$ $[M+Na]^+$ 313.0065, Found: 313.0058.

Synthesis of 4-benzyl-5-methoxy-1-phenylpentan-1-one (2.34): To a solution of ethyl benzoylacetate (1.04 mL, 6.01 mmol) and (3-iodo-2-(methoxymethyl)propyl)benzene (3.48 g, 12.0 mmol) in acetone (20 mL) was added K_2CO_3 (1.67 g, 12.1 mmol) and the mixture was stirred at reflux for 48 h. After volatile materials were removed *in vacuo*, the resulting crude mixture was treated with an aqueous KOH solution (1.52 g, 27.1 mmol, in 10 mL of H_2O) and MeOH (10 mL) and the mixture was then stirred at reflux temperature for 12 h. The reaction was quenched with water at 24 °C and the organic materials were extracted thrice with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. After the filtrate was concentrated *in vacuo*, the resulting crude residue was purified by flash column chromatography (silica gel, Hex:EtOAc = 97:3) to give **2.34** in 78% yield (1.32 g, 4.67 mmol) as a colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 7.93 – 7.91 (m, 2H), 7.55 – 7.52 (m, 1H), 7.45 – 7.42 (m, 2H), 7.30 – 7.25 (m, 2H), 7.21 – 7.18 (m, 3H), 3.33 – 3.23 (m, 2H), 3.30 (s, 3H), 3.08 – 2.92 (m, 2H), 2.74 (dd, *J* = 13.6, 7.6 Hz, 1H), 2.63 (dd, *J* = 13.6, 7.6 Hz, 1H), 2.04 – 1.90 (m, 1H), 1.90 – 1.76 (m, 2H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 200.3, 140.4, 137.0, 132.8, 129.2, 128.5, 128.3, 128.0, 125.9, 74.8, 56.8, 40.0, 38.0, 36.4, 26.3.

MS (HRMS ESI): Calcd for $C_{19}H_{23}O_2$ $[M+H]^+$ 283.1698, Found: 283.1698.

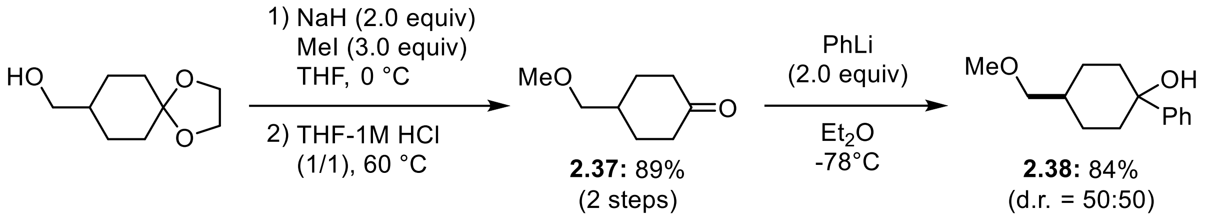
Synthesis of 5-benzyl-6-methoxy-2-phenylhexan-2-ol (2.35): It was synthesized using **2.34** (561 mg, 1.99 mmol) and MeMgBr (2.84 M in Et_2O, 1.3 mL) following the procedure described in section **5.2.2.1.1**. Purification by flash column chromatography (silica gel, Hex:EtOAc = 92:8) gave 89% yield of **2.35** (509 mg, 1.76 mmol) as an estimated 59:41 diasteromeric mixture (based on ^{13}C NMR spectroscopy analysis) and as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.42 – 7.40 (m, 2×0.59H, +m, 2×0.41H), 7.35 – 7.31 (m, 2×0.59H, +m, 2×0.41H), 7.25 – 7.22 (m, 3×0.59H, +m, 3×0.41H), 7.18 – 7.15 (m, 1×0.59H, +m, 1×0.41H), 7.09 – 7.08 (m, 2×0.59H, +m, 2×0.41H), 3.26 (s, 3×0.59H, +s, 3×0.41H), 3.23 – 3.11 (m, 2×0.59H, +m, 2×0.41H), 2.63 – 2.49 (m, 2×0.59H, +m, 2×0.41H), 2.02 (brs, 1×0.59H, +brs, 1×0.41H), 1.93 – 1.79 (m, 3×0.59H, +m, 3×0.41H), 1.53 (m, 3×0.59H, +s, 3×0.41H), 1.40 – 1.22 (m, 2×0.59H, +m, 2×0.41H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 148.0, 147.9, 140.47, 140.45, 129.1 (overlapped with 2C), 128.12, 128.11, 128.0 (overlapped with 2C), 126.4 (overlapped with 2C), 125.7 (overlapped with 2C), 124.8 (overlapped with 2C), 74.6, 74.58, 74.55, 74.53, 58.6 (overlapped with 2C), 41.1, 40.9, 40.5, 40.3, 37.5 (overlapped with 2C), 30.05, 30.02, 25.3, 25.27.

MS (HRMS ESI): Calcd for $C_{20}H_{27}O_2$ $[M+H]^+$ 299.2011, Found: 299.2012.

5.2.2.1.23. Synthesis of 4-(methoxymethyl)-1-phenylcyclohexan-1-ol (2.38)



Synthesis of 4-(methoxymethyl)cyclohexan-1-one (2.37): Compound **2.37** was synthesized by following the procedure described in section **5.2.2.1.20**, using NaH (60% dispersion in mineral oil, 1.01 g, 25.3 mmol), (1,4-dioxaspiro[4.5]decan-8-yl)methanol[36] (1.96 g, 11.4 mmol) and MeI (2.13 ml, 34.2 mmol) for the *O*-methylation and an aqueous HCl solution (1 M, 45 mL) in THF (45 mL) for the acetal cleavage. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc = 80:20) gave **2.37** in 89% yield (1.44 g, 10.2 mmol) over two steps as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 3.36 (s, 3H), 3.29 (d, *J* = 6.4 Hz, 2H), 2.47 – 2.27 (m, 4H), 2.15 – 1.96 (m, 3H), 1.50 – 1.40 (m, 2H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) δ 211.8, 76.7, 58.9, 40.4, 36.4, 29.5.

MS (HRMS ESI): Calcd for $C_8H_{14}O_2Na$ $[M+Na]^+$ 165.0891, Found: 165.0892.

Synthesis of 4-(methoxymethyl)-1-phenylcyclohexan-1-ol (2.38): To a solution of **2.37** (364 mg, 2.57 mmol) in Et_2O (6 mL) was added PhLi (1.8 M in dibutyl ether, 2.9 mL, 5.22 mmol) at -78 °C and the reaction mixture was stirred at the same temperature for 5 h. The reaction was quenched with saturated NH_4Cl solution and the organic materials were extracted thrice using EtOAc. The combined extracts were washed with brine and dried over $MgSO_4$. The volatile materials were removed under reduced pressure to give the crude material, which was purified by flash chromatography (silica gel, Hex:EtOAc = 90:10) to give **2.38** in 84% yield

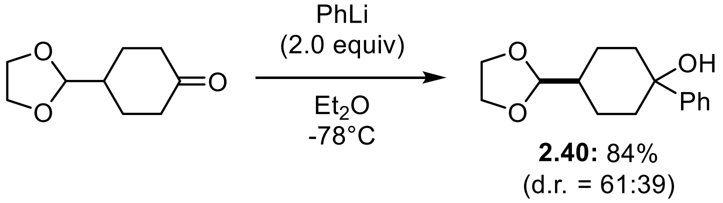
(475 mg, 2.16 mmol) as an estimated 50:50 diastereomeric mixture (based on ^{1}H NMR spectroscopy analysis) and as a white solid.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.54 – 7.50 (m, 2×0.50H, +m, 2×0.50H), 7.39 – 7.33 (m, 2×0.50H, +m, 2×0.50H), 7.31 – 7.21 (m, 1×0.50H, +m, 1×0.50H), 3.36 (s, 3×0.50H), 3.32 (s, 3×0.50H), 3.28 (d, J = 6.0 Hz, 2×0.50H), 3.25 (d, J = 6.4 Hz, 2×0.50H), 2.37 – 2.24 (m, 1×0.50H, +m, 1×0.50H), 1.94 – 1.81 (m, 4×0.50H, +m, 4×0.50H), 1.79 – 1.62 (m, 3×0.50H, +m, 3×0.50H), 1.54 – 1.48 (m, 1×0.50H, +m, 1×0.50H), 1.31 – 1.16 (m, 1×0.50H, +m, 1×0.50H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) δ 149.4, 146.2, 128.4, 128.2, 127.1, 126.7, 125.6, 124.4, 78.4, 76.1, 73.3, 72.9, 58.8, 58.7, 38.2, 37.2, 36.2, 35.2, 25.5, 25.3.

MS (HRMS ESI): Calcd for $C_{14}H_{21}O_2$ $[M+H]^+$ 221.1542, Found: 221.1539.

5.2.2.1.24. Synthesis of 4-(1,3-dioxolan-2-yl)-1-phenylcyclohexan-1-ol (2.40)



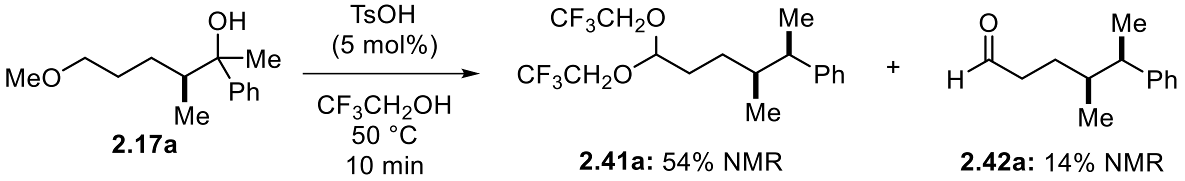
Synthesis of 4-(1,3-dioxolan-2-yl)-1-phenylcyclohexan-1-ol (2.40): Compound **2.40** was synthesized using 4-(1,3-dioxolan-2-yl)cyclohexan-1-one[38] (343 mg, 2.02 mmol) and PhLi (1.8 M in dibutyl ether, 2.2 mL, 3.96 mmol) by following the procedure described in section **5.2.2.1.23**. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc = 85:15) gave **2.40** in 83% yield (417 mg, 1.68 mmol) as an estimated 61:39 diastereomeric mixture (based on ^{13}C NMR spectroscopy analysis) and as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.54 – 7.49 (m, 2×0.61H, +m, 2×0.39H), 7.40 – 7.31 (m, 2×0.61H, +m, 2×0.39H), 7.30 – 7.20 (m, 1×0.61H, +m, 1×0.39H), 4.70 (d, *J* = 4.4 Hz, 1×0.61H), 4.69 (d, *J* = 5.6 Hz, 1×0.39H), 4.05 – 3.86 (m, 4×0.61H), 3.95 – 3.78 (m, 4×0.39H), 2.46 – 2.36 (m, 1×0.61H, +m, 1×0.39H), 1.95 – 1.82 (m, 3×0.61H, +m, 3×0.39H), 1.75 – 1.80 (m, 1×0.61H, +m, 1×0.39H), 1.75 – 1.69 (m, 2×0.61H, +m, 2×0.39H), 1.67 – 1.61 (m, 2×0.61H, +m, 2×0.39H), 1.46 – 1.32 (m, 1×0.61H, +m, 1×0.39H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 149.2 (overlapped with 2C), 128.5, 128.2, 127.2, 126.8, 125.7, 124.2, 107.2, 106.4, 73.2, 72.7, 65.0 (overlapped with 2C), 64.9 (overlapped with 2C), 40.9, 39.3, 38.0, 36.6, 23.8, 22.7.

MS (HRMS ESI): Calcd for $C_{15}H_{20}O_3Na$ $[M+Na]^+$ 271.1310, Found: 271.1306.

5.2.2.2 Isolation and characterization of acetal 2.41a and aldehyde 2.42a



To a solution of **2.17a** (66.3 mg, 0.298 mmol) in 2,2,2,-trifluoroethanol (2.9 mL) was added a solution of *p*-toluenesulfonic acid monohydrate (TsOH•H_2O) (0.149 M, 0.1 mL, 5 mol%) (prepared from 28.3 mg of TsOH•H_2O and 1 mL of 2,2,2-trifluoroethanol) and the reaction mixture was stirred at 50 °C for 10 min. The reaction mixture was cooled to 24 °C and quenched with a pH 10 aqueous ammonium buffer solution. The organic materials were then extracted thrice with EtOAc and the combine extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. ^{1}H NMR spectroscopy analysis of the resulting crude material using 1,1,2,2-tetrachloroethane as an internal standard revealed that it contains ditrifluoroethyl acetal **2.41a** and aldehyde **2.42a** in 54% and 14% yields, respectively. Ditrifluoroethyl acetal **2a** was isolated by preparative TLC (silica gel, Hex:EtOAc = 98:2) in 32% yield (35.9 mg, 0.096 mmol) as an estimated 98:2 diastereomeric mixture (based on ^{1}H NMR spectroscopy analysis) and as a pale yellow oil.

Data for ditrifluoroethyl acetal 2.41a:

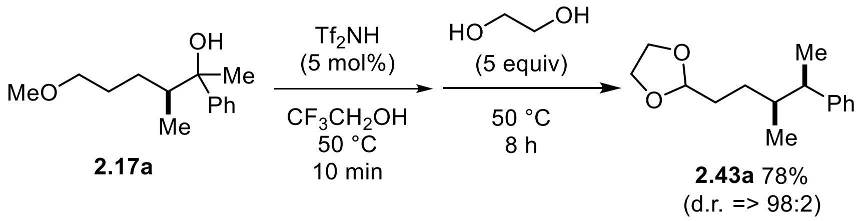
^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.35 – 7.23 (m, 2H), 7.19 – 7.14 (m, 3H), 4.62 (dd, *J* = 6.0, 6.0 Hz, 1H), 3.94 – 3.60 (m, 4H), 2.54 (dq, *J* = 7.2, 7.2 Hz, 1H), 1.71 – 1.62 (m, 2H), 1.55 – 1.45 (m, 1H), 1.38 – 1.29 (m, 1H), 1.22 (d, *J* = 7.2 Hz, 3H), 1.14 – 0.99 (m, 1H), 0.92 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 146.5, 128.2, 127.5, 126.0, 123.8 (q, *J* = 278.9 Hz, overlapped with 2C), 103.4, 62.1 (q, *J* = 35.4 Hz), 61.7 (q, *J* = 35.4 Hz), 44.8, 38.8, 29.7, 29.2, 18.0, 16.4.

^{19}F NMR (376 MHz, CDCl$_3$); δ(ppm) -74.21 (t, *J* = 9.02 Hz, 3F), -74.24 (t, *J* = 9.02 Hz, 3F).

MS (HRMS ESI): Calcd for $C_{17}H_{22}F_6O_2Na$ $[M+Na]^+$ 395.1422, Found: 395.1424.

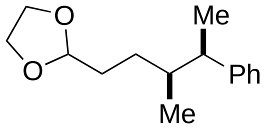
5.2.2.3 General procedure: synthesis of 2.43a



To a solution of **2.17a** (111.5 mg, 0.502 mmol) in 2,2,2,-trifluoroethanol (4.9 mL) was added a solution of trifluoromethanesulfonimide (Tf_2NH) (0.249 M, 0.1 mL, 5 mol%) (the solution was prepared from 27.3 mg of Tf_2NH with 0.39 mL of 2,2,2-trifluoroethanol) and the reaction mixture was stirred at 50 °C for 10 min. Ethylene glycol (0.14 mL, 2.510 mmol) was then added and the mixture was continuously stirred at 50 °C for 9 h. The reaction mixture was cooled to 24 °C and quenched with pH 10 aqueous ammonium buffer solution. The organic materials were then extracted thrice with EtOAc and the combine extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (silica gel, Hex:EtOAc = 98:2) to give **2.43a** in 78% yield (91.7 mg, 0.391 mmol) as an estimated 98:2 diastereomeric mixture (based on ^{1}H NMR spectroscopy analysis) and as a colorless oil.

5.2.2.4. Characterization of the products (Scheme 2.36)

2-((3S*,4R*)-3-methyl-4-phenylpentyl)-1,3-dioxolane (2.43a)

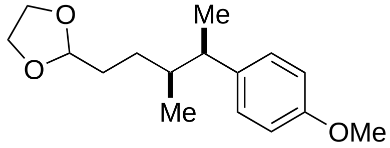


^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.33 – 7.23 (m, 2H), 7.18 – 7.14 (m, 3H), 4.74 (dd, *J* = 4.8, 4.8 Hz, 1H), 3.98 – 3.87 (m, 2H), 3.87 – 3.74 (m, 2H), 2.63 (dq, *J* = 7.2, 7.2 Hz, 1H), 1.77 – 1.64 (m, 2H), 1.62 – 1.50 (m, 1H), 1.50 – 1.38 (m, 1H), 1.21 (d, *J* = 7.2 Hz, 3H), 1.18 – 1.09 (m, 1H), 0.86 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 146.8, 128.1, 127.6, 125.7, 104.9, 64.80, 64.76, 44.5, 39.2, 31.8, 29.1, 16.9, 15.8.

MS (HRMS ESI): Calcd for $C_{15}H_{23}O_2$ [M+H]$^+$ 235.1698, Found: 235.1696.

2-((3S*,4R*)-4-(4-methoxyphenyl)-3-methylpentyl)-1,3-dioxolane (**2.43b**)



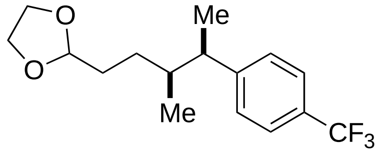
Prepared from **2.17b** (126.3 mg, 0.500 mmol) with 5 mol% of Tf_2NH at 24 °C for 10 min, followed by 5 equiv. of ethylene glycol at 50 °C for 24 h. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc = 98:2) gave **3b** in 68% yield (90.4 mg, 0.342 mmol) as an estimated 98:2 diastereomeric mixture (based on ^{1}H NMR spectroscopy analysis) and as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.13 – 7.02 (m, 2H), 6.88 – 6.76 (m, 2H), 4.75 (dd, *J* = 4.8, 4.8 Hz, 1H), 3.99 – 3.86 (m, 2H), 3.86 – 3.80 (m, 2H), 3.76 (s, 3H), 2.58 (dq, *J* = 6.8, 6.8 Hz, 1H), 1.76 – 1.50 (m, 3H), 1.50 – 1.37 (m, 1H), 1.26 – 1.05 (m, 1H), 1.18 (d, *J* = 7.2 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 157.6, 138.9, 128.4, 113.4, 104.9, 64.8, 64.7, 55.2, 43.6, 39.3, 31.8, 29.0, 17.0, 15.8.

MS (HRMS ESI) Calcd for $C_{16}H_{25}O_2$ $[M+H]^+$ 265.1804, Found: 265.1810.

2-((3S*,4R*)-3-methyl-4-(4-(trifluoromethyl)phenyl)pentyl)-1,3-dioxolane (2.43c)



Prepared from **2.17c** (145.1 mg, 0.500 mmol) with 5 mol% of Tf_2NH at 80 °C for 45 min, followed by 5 equiv. of ethylene glycol at 80 °C for 20 h. Purification by flash column chromatography (silica gel, *n*-Hex: EtOAc = 96:4) gave **2.43c** in 51% yield (76.7 mg, 0.254

mmol) as a single diastereomer (based on ^{1}H NMR spectroscopy analysis) and as a colorless oil.

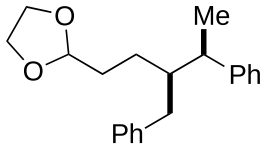
^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.54 – 7.52 (m, 2H), 7.28 – 7.26 (m, 2H), 4.75 (dd, *J* = 4.8, 4.8 Hz, 1H), 3.99 – 3.87 (m, 2H), 3.87 – 3.75 (m, 2H), 2.77 – 2.62 (m, 1H), 1.78 – 1.63 (m, 2H), 1.63 – 1.50 (m, 1H), 1.49 – 1.36 (m, 1H), 1.22 (d, *J* = 7.2 Hz, 3H), 1.18 – 1.08 (m, 1H), 0.87 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 150.9, 128.1 (q, *J* = 32.6 Hz), 127.9, 125.0 (q, *J* = 3.88 Hz), 124.4 (q, *J* = 270.0 Hz), 104.7, 64.82, 64.78, 44.5, 39.0, 31.6, 29.0, 16.8, 15.7.

^{19}F NMR (376 MHz, CDCl$_3$): δ(ppm) -62.1 (s, 3F).

MS (HRMS ESI) Calcd for $C_{16}H_{22}F_3O_2$ [M+H]$^+$ 303.1572, Found: 303.1569.

2-((3R*,4R*)-3-benzyl-4-phenylpentyl)-1,3-dioxolane (2.43d)



Prepared from **2.17d** (149.5 mg, 0.5010 mmol) with 5 mol% of Tf_2NH at 50 °C for 10 min, followed by 5 equiv. of ethylene glycol at 50 °C for 24 h. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc = 98:2) gave **2.43d** in 76% yield (118.2 mg, 0.381 mmol) as a single diastereomer (based on ^{1}H NMR spectroscopy analysis) and as a colorless oil.

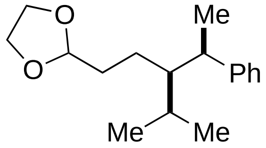
^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.32 – 7.29 (m, 2H), 7.24 – 7.12 (m, 6H), 7.05 – 7.04 (m, 2H), 4.69 (dd, *J* = 4.8, 4.8 Hz, 1H), 3.92 – 3.83 (m, 2H), 3.82 – 3.73 (m, 2H), 2.92 (dq, *J*

= 7.2, 7.2 Hz, 1H), 2.64 (dd, *J* = 13.8, 4.8 Hz, 1H), 2.36 (dd, *J* = 13.8, 8.8 Hz, 1H), 2.00 – 1.88 (m, 2H), 1.71 – 1.55 (m, 2H), 1.50 – 1.37 (m, 1H), 1.28 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 145.8, 141.6, 129.0, 128.15, 128.10, 127.9, 125.9, 125.6, 104.8, 64.7 (overlapped with 2C), 46.5, 40.7, 36.3, 31.4, 25.0, 16.2.

MS (HRMS ESI): Calcd for $C_{21}H_{27}O_2$ [M+H]$^+$ 311.2011, Found: 311.2021.

2-((3R*,4R*)-3-isopropyl-4-phenylpentyl)-1,3-dioxolane (2.43e)



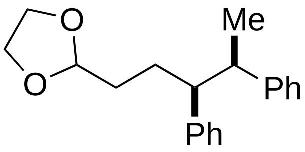
Prepared from **2.17e** (125.3 mg, 0.5008 mmol) with 5 mol% of Tf_2NH at 24 °C for 10 min, followed by 5 equiv. of ethylene glycol (0.14 mL, 2.510 mmol) at 50 °C for 18 h. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc = 98:2) gave **2.43e** in 68% yield (89.6 mg, 0.3415 mmol) as an estimated 97:3 diastereomeric mixture (based on ^{1}H NMR spectroscopy analysis) and as a colorless oil.

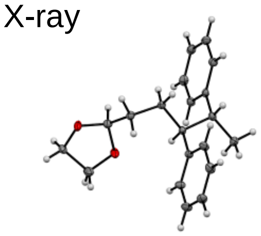
^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.28 – 7.24 (m, 2H), 7.20 – 7.13 (m, 3H), 4.54 (dd, *J* = 5.2, 5.2 Hz, 1H), 3.84 – 3.79 (m, 2H), 3.75 – 3.70 (m, 2H), 2.66 (dq, *J* = 6.8, 6.8 Hz, 1H), 1.99 (tdd, *J* = 14.0, 7.2, 6.8 Hz, 1H), 1.40 – 1.27 (m, 3H), 1.22 (d, *J* = 7.2 Hz, 3H), 1.19 – 1.08 (m, 2H), 0.91 (d, *J* = 6.8 Hz, 3H), 1.85 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 147.2, 128.1, 127.8, 125.8, 104.8, 64.6, 64.5, 49.9, 42.9, 34.2, 28.1, 22.4, 21.9, 19.6, 16.7.

MS (HRMS ESI) Calcd for $C_{17}H_{27}O_2$ [M+H]$^+$ 263.2011, Found: 263.2014.

2-((3S*,4R*)-3,4-diphenylpentyl)-1,3-dioxolane (2.43f)





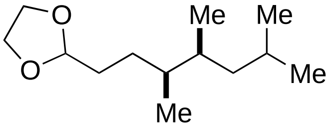
Prepared from **2.17f** (142.6 mg, 0.5014 mmol) with 5 mol% of Tf_2NH at 50 °C for 10 min, followed by 5 equiv. of ethylene glycol at 50 °C for 20 h. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc = 98:2) gave **2.43f** in 50% yield (73.4 mg, 0.2476 mmol) as a single diastereomer (based on ^1H NMR analysis) as a white solid, which was recrystallized from hexane-CH_2Cl_2 to afford colorless crystal. The stereochemistry of **2.43f** could be confirmed by the X-ray crystallography analysis (CCDC-1894803).

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.33 – 7.29 (m, 4H), 7.23 – 7.17 (m, 6H), 4.61 (dd, *J* = 5.2, 5.2 Hz, 1H), 3.83 – 3.75 (m, 2H), 3.74 – 3.67 (m, 2H), 2.91 – 2.83 (m, 1H), 2.71 – 2.65 (m, 1H), 1.60 – 1.48 (m, 2H), 1.33 – 1.28 (m, 2H), 0.99 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 146.4, 143.7, 128.35, 128.32, 128.2, 127.6, 126.2, 126.0, 104.6, 64.7, 64.6, 53.0, 46.4, 32.1, 28.7, 21.0.

MS (HRMS ESI): Calcd for $C_{20}H_{25}O_2$ $[M+H]^+$ 297.1855, Found: 297.1855.

2-((3S*,4S*)-3,4,6-trimethylheptyl)-1,3-dioxolane (2.43g)



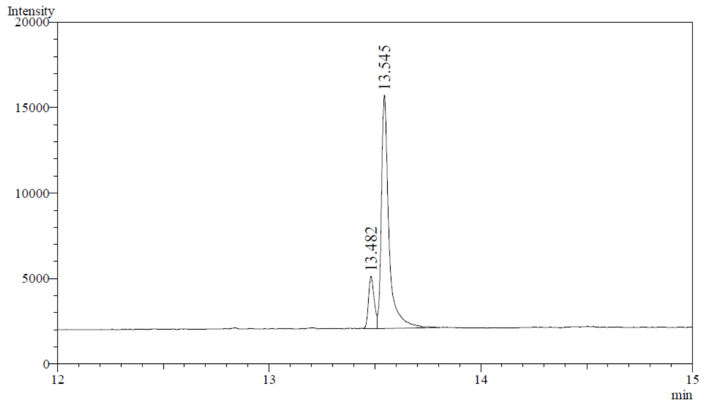
Prepared from **2.17g** (102.4 mg, 0.506 mmol) with 5 mol% of Tf_2NH at 24 °C for 10 min, followed by 5 equiv. of ethylene glycol at 50 °C for 17 h. Purification by flash column chromatography (silica gel, *n*-pentane:Et_2O = 99:1) gave **2.43g** in 72% yield (78.3 mg, 0.365 mmol) as an estimated 85:15 diastereomeric mixture (based on GC spectroscopy analysis) and as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) δ 4.84 (dd, *J* = 4.8, 4.8 Hz, 1×0.85H, +dd, *J* = 4.8, 4.8 Hz, 1×0.15H), 4.03 – 3.91 (m, 2×0.85H, +m, 2×0.15H), 3.91 – 3.78 (m, 2×0.85H, +m, 2×0.15H), 1.77 – 1.47 (m, 3×0.85H, +m, 3×0.15H), 1.47 – 1.33 (m, 2×0.85H, +m, 2×0.15H), 1.32 – 1.17 (m, 1×0.85H, +m, 1×0.15H), 1.14 – 0.96 (m, 2×0.85H, +m, 2×0.15H), 0.92 – 0.80 (m, 7×0.85H, +m, 7×0.15H), 0.80 – 0.70 (m, 6×0.85H, +m, 6×0.15H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 105.02, 104.98, 64.82 (overlapped with 2C), 64.80 (overlapped with 2C), 44.2, 42.1, 37.7, 36.7, 34.7, 33.7, 32.2 (overlapped with 2C), 29.0, 27.1, 25.4, 25.2, 24.0, 23.4, 22.3, 21.8, 16.4, 16.1, 14.3, 14.2.

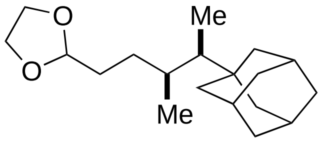
MS (HRMS ESI): Calcd for $C_{13}H_{27}O_2$ $[M+H]^+$ 215.2011, Found: 215.2012.

GC trace:



Peak#	Ret.Time	Area%
1	13.482	14.4212
2	13.545	85.5788
Total		100.0000

2-((3S*,4R*)-4-(adamantan-1-yl)-3-methylpentyl)-1,3-dioxolane (2.43h)



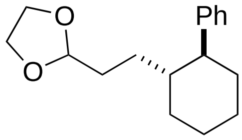
Prepared from **2.17h** (140.2 mg, 0.500 mmol) with 5 mol% of Tf_2NH at 50 °C for 10 min, followed by 5 equiv. of ethylene glycol at 50 °C for 15 h. Purification by flash column chromatography (silica gel, *n*-Hex:Et_2O = 99:1) gave **2.43h** in 73% yield (112.3 mg, 0.364 mmol) as a single diastereomer (colorless oil).

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 4.82 (dd, *J* = 4.8, 4.8 Hz, 1H), 4.02 – 3.92 (m, 2H), 3.91 – 3.78 (m, 2H), 1.94 (m, 3H), 1.85 – 1.73 (m, 1H), 1.73 – 1.43 (m, 14H), 1.33 – 1.20 (m, 2H), 1.05 – 1.00 (m, 1H), 0.78 (d, *J* = 6.8 Hz, 3H), 0.70 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 105.0, 64.84, 64.82, 46.2, 40.3, 37.4, 35.5, 32.4, 32.3, 30.7, 28.9, 16.5, 7.5.

MS (HRMS ESI): Calcd for $C_{19}H_{33}O_2$ $[M+H]^+$ 293.2481, Found: 293.2485.

2-(2-((1*R,2*S**)-2-phenylcyclohexyl)ethyl)-1,3-dioxolane (2.43i)**



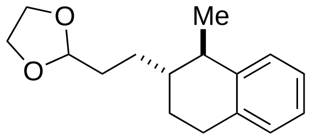
Prepared from **2.17i** (124.6 mg, 0.502 mmol) with 5 mol% of Tf_2NH at 50 °C for 10 min, followed by 5 equiv. of ethylene glycol (0.14 mL, 2.510 mmol) at 50 °C for 9 h. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc = 95:5) gave **2.43i** in 75% yield (98.0 mg, 0.377 mmol) as a single diastereomer and as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.31 – 7.22 (m, 2H), 7.14 – 7.17 (m, 3H), 4.61 (dd, *J* = 4.8, 4.8 Hz, 1H), 3.91 – 3.80 (m, 2H), 3.79 – 3.69 (m, 2H), 2.18 (ddd, *J* = 11.2, 11.2, 2.8 Hz, 1H), 1.96 – 1.93 (m, 1H), 1.81 – 1.78 (m, 3H), 1.68 – 1.56 (m, 1H), 1.57 – 1.50 (m, 1H), 1.50 – 1.21 (m, 5H), 1.11 – 0.89 (m, 2H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 146.5, 128.3, 127.5, 125.8, 105.0, 64.7, 64.6, 50.9, 42.0, 36.1, 32.0, 30.8, 28.6, 26.9, 26.5.

MS (HRMS ESI): Calcd for $C_{17}H_{25}O_2$ $[M+H]^+$ 261.1855, Found: 261.1857.

2-(2-((1*R**,2*R**)-1-methyl-tetrahydronaphthalen-2-yl)ethyl)-1,3-dioxolane (2.43j)



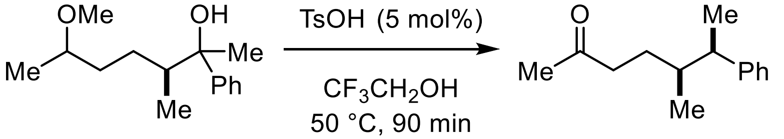
Prepared from **2.17j** (117.1 mg, 0.500 mmol) with 10 mol% of Tf_2NH at 24 °C for 10 min, followed by 5 equiv. of ethylene glycol at 50 °C for 48 h. Purification by flash column chromatography (silica gel, Hex:EtOAc = 98:2) gave **2.43j** in 74% yield (91.9 mg, 0.373 mmol) as a single diastereomer and as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.20 – 6.99 (m, 4H), 4.84 (dd, *J* = 4.8, 4.8 Hz, 1H), 4.03 – 3.90 (m, 2H), 3.90 – 3.78 (m, 2H), 2.83 – 2.58 (m, 3H), 2.05 – 1.92 (m, 1H), 1.86 – 1.64 (m, 2H), 1.64 – 1.47 (m, 3H), 1.45 – 1.36 (m, 1H), 1.29 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 141.4, 136.2, 129.2, 128.8, 125.7, 125.2, 104.8, 64.83, 64.82, 39.8, 38.1, 31.7, 27.6, 26.7, 24.1, 23.5.

MS (HRMS ESI): Calcd for $C_{16}H_{23}O_2$ $[M+H]^+$ 247.1698, Found: 247.1708.

(5*S**,6*R**)-5-methyl-6-phenylheptan-2-one (2.44) (Scheme 2.37)



2.23

2.44 98% (dr = >99:1)

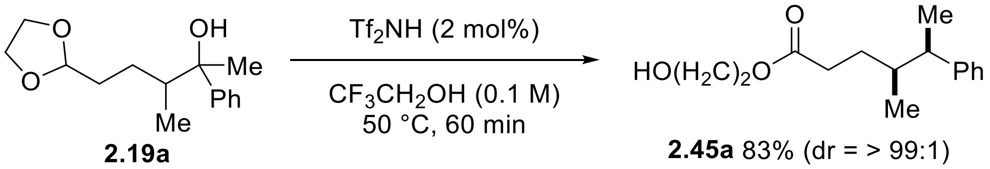
Prepared from **2.23** (118.4 mg, 0.501 mmol) with 5 mol% of TsOH at 50 °C for 1.5 h. Purification by flash column chromatography (silica gel, Hex:EtOAc = 95:5) gave **2.44** in 98% yield (100.0 mg, 0.490 mmol) as a single diastereomer and as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.29 – 7.25 (m, 2H), 7.18 – 7.14 (m, 3H), 2.57 (dq, *J* = 7.6, 7.6 Hz, 1H), 2.41 (ddd, *J* = 16.4, 10.0, 6.0 Hz, 1H), 2.30 (ddd, *J* = 16.4, 9.6, 6.0 Hz, 1H), 2.04 (s, 3H), 1.67 – 1.53 (m, 2H), 1.32 – 1.22 (m, 1H), 1.21 (d, *J* = 7.6 Hz, 3H), 0.87 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 209.2, 146.5, 128.1, 127.5, 125.8, 44.7, 41.7, 38.7, 29.6, 28.9, 17.4, 15.9.

MS (HRMS ESI) Calcd for $C_{14}H_{20}ONa$ $[M+Na]^+$ 227.1412, Found: 227.1414.

2-hydroxyethyl (4*S**,5*R**)-4-methyl-5-phenylhexanoate (2.45a) (Scheme 2.37)



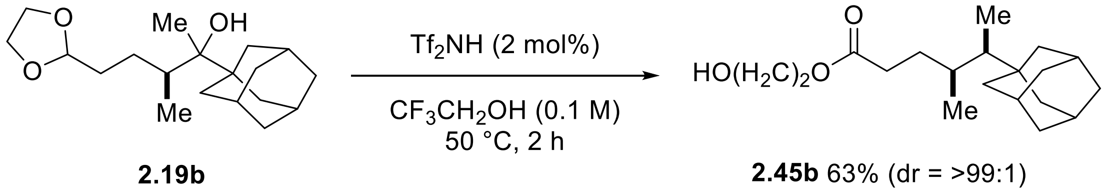
Prepared from **2.19a** (125.0 mg, 0.499 mmol) with 5 mol% of TsOH at 50 °C for 1 h. Purification by flash column chromatography (silica gel, Hex:EtOAc = 80:20) gave **2.45a** in 83% yield (104.2 mg, 0.416 mmol) as a single diastereomer and as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.32 – 7.24 (m, 2H), 7.22 – 7.13 (m, 3H), 4.20 – 4.13 (m, 2H), 3.84 – 3.75 (m, 2H), 2.59 (dq, *J* = 7.2, 7.2 Hz, 1H), 2.37 (ddd, *J* = 15.6, 9.6, 6.0 Hz, 1H), 2.26 (ddd, *J* = 15.6, 9.2, 6.4 Hz, 1H), 1.80 (brs, 1H), 1.73 – 1.64 (m, 2H), 1.41 – 1.27 (m, 1H), 1.22 (d, *J* = 7.2 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 174.2, 146.4, 128.1, 127.5, 125.9, 65.8, 61.1, 44.6, 38.7, 32.1, 29.9, 17.4, 15.9.

MS (HRMS ESI): Calcd for $C_{15}H_{22}O_3Na$ [M+Na]$^+$ 273.1467, Found: 273.1474.

2-hydroxyethyl (4*S**,5*R**)-5-(adamantan-1-yl)-4-methylhexanoate (2.45b) (Scheme 2.37)



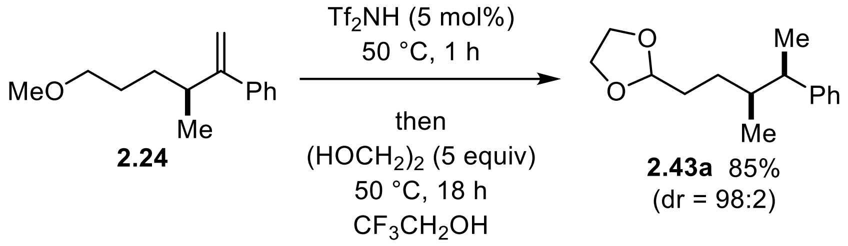
Prepared from **2.19b** (154.5 mg, 0.501 mmol) with 5 mol% of Tf_2NH at 50 °C for 2 h. Purification by flash column chromatography (silica gel, *n*-Hex:Et_2O = 99:1) gave **2.45b** in 63% yield (96.9 mg, 0.314 mmol) as a single diastereomer (colorless oil).

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 4.22 – 4.20 (m, 2H), 3.84 – 3.82 (m, 2H), 2.37 – 2.30 (m, 2H), 2.10 (brs, 1H), 1.95 (s, 3H), 1.82 – 1.74 (m, 1H), 1.70 – 1.39 (m, 14H), 0.99 (dq, *J* = 6.8, 6.8 Hz, 1H), 0.79 (d, *J* = 6.8 Hz, 3H), 0.72 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 174.5, 65.9, 61.3, 46.2, 40.3, 37.3, 35.5, 33.0, 32.7, 30.3, 28.8, 16.3, 7.5.

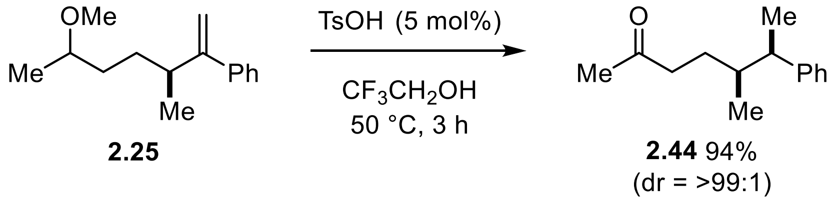
MS (HRMS ESI): Calcd for $C_{19}H_{33}O_3$ [M+H]$^+$ 309.2430, Found: 309.2423.

2-((3*S**,4*R**)-3-methyl-4-phenylpentyl)-1,3-dioxolane (2.43a) (Scheme 2.38)



Prepared from **2.24** (101.5 mg, 0.497 mmol) with 5 mol% of Tf$_2$NH at 50 °C for 1 h, followed by 5 equiv. of ethylene glycol at 50 °C for 18 h. Purification by flash column chromatography (silica gel, Hex:EtOAc = 98:2) gave **2.43a** in 85% yield (99.1 mg, 0.423 mmol) as a 98:2 diastereomeric mixture (based on ^{1}H NMR spectroscopy analysis) and as a colorless oil.

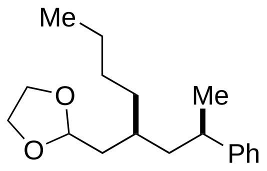
(5*S**,6*R**)-5-methyl-6-phenylheptan-2-one (2.44) (Scheme 2.38)



Prepared from **2.25** (108.7 mg, 0.498 mmol) with 5 mol% of TsOH at 50 °C for 3 h. Purification by flash column chromatography (silica gel, Hex:EtOAc = 95:5) gave **2.44** in 94% yield (95.4 mg, 0.467 mmol) as a single diastereomer and as a colorless oil.

5.2.2.5. Characterization of the products (Scheme 2.39)

2-((S*)-2-((*R**)-2-phenylpropyl)hexyl)-1,3-dioxolane (2.46a)



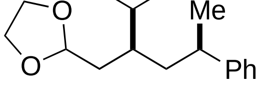
Prepared from **2.28a** (132.5 mg, 0.501 mmol) with 5 mol% of Tf_2NH at 50 °C for 10 min, followed by ethylene glycol (0.14 mL, 2.510 mmol) at 50 °C for 8 h. Purification by flash column chromatography (silica gel, Hex:EtOAc = 98:2) gave **2.46a** in 73% yield (101.1 mg, 0.366 mmol) as an estimated 72:28 diastereomeric mixture (based on ^{1}H NMR spectroscopy analysis) and as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.29 – 7.26 (m, 2×0.72H, +m, 2×0.28H), 7.19 – 7.14 (m, 3×0.72H, +m, 3×0.28H), 4.86 (dd, *J* = 5.2, 5.2 Hz, 1×0.28H), 4.81 (dd, *J* = 5.2, 5.2 Hz, 1×0.72H), 3.98 – 3.89 (m, 2×0.72H, +m, 2×0.28H), 3.87 – 3.75 (m, 2×0.72H, +m, 2×0.28H), 2.79 (dq, *J* = 6.4, 6.4 Hz, 1×0.72H, +dq, *J* = 6.4, 6.4 Hz, 1×0.28H), 1.67 – 1.43 (m, 4×0.72H, +m, 4×0.28H), 1.34 – 1.16 (m, 10×0.72H, +m, 10×0.28H), 0.89 – 0.83 (m, 3×0.72H, +m, 3×0.28H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 147.90, 147.85, 128.3 (overlapped with 2C), 127.0 (overlapped with 2C), 125.77, 125.75, 103.9, 103.8, 64.7, 64.64, 64.62, 64.58, 43.1 (overlapped with 2C), 38.1 (overlapped with 2C), 37.24, 37.18, 33.6, 33.5, 31.7, 31.6, 28.3, 28.2, 23.0, 22.9, 22.6, 22.5, 14.1 (overlapped with 2C).

MS (HRMS ESI): Calcd for $C_{18}H_{29}O_2$ $[M+H]^+$ 277.2168, Found: 277.2169.

2-((2S*,4R*)-2-isopropyl-4-phenylpentyl)-1,3-dioxolane (2.46b)



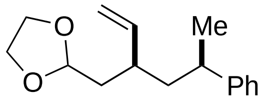
Prepared from **2.28b** (125.4 mg, 0.501 mmol) with 5 mol% of Tf_2NH at 50 °C for 10 min, followed by ethylene glycol (0.14 mL, 2.510 mmol) at 50 °C for 24 h. Purification by flash column chromatography (silica gel, *n*-Hex:EtOAc = 98:2) gave **2.46b** in 70% yield (91.5 mg, 0.349 mmol) as an estimated 72:28 diastereomeric mixture (based on ^{1}H NMR spectroscopy analysis) and as a colorless oil.

<u>^{1}H NMR (400 MHz, CDCl$_3$):</u> δ(ppm) 7.30 – 7.25 (m, 2×0.72H, +m, 2×0.28H), 7.20 – 7.15 (m, 3×0.72H, +m, 3×0.28H), 4.85 (dd, *J* = 5.2, 5.2 Hz, 1×0.28H), 4.78 (dd, *J* = 5.2, 5.2 Hz, 1×0.72H), 3.97 – 3.87 (m, 2×0.72H, +m, 2×0.28H), 3.85 – 3.73 (m, 2×0.72H, +m, 2×0.28H), 2.76 (dq, *J* = 7.2, 7.2 Hz, 1H×0.72H, +dq, *J* = 7.2, 7.2 Hz, 1H×0.28H), 1.84 (ttd, *J* = 6.8, 6.8, 2.8 Hz, 1×0.72H), 1.74 (ttd, *J* = 6.8, 6.8, 2.8 Hz, 1×0.28H), 1.69 – 1.37 (m, 5×0.72H, +m, 5×0.28H), 1.23 (d, *J* = 7.2 Hz, 3×0.28H), 1.22 (d, *J* = 7.2 Hz, 3×0.72H), 0.85 (d, *J* = 7.2 Hz, 3×0.72H), 0.82 (d, *J* = 7.2 Hz, 3×0.28H), 0.79 (d, *J* = 7.2 Hz, 3×0.72H), 0.72 (d, *J* = 7.2 Hz, 3×0.28H).

<u>^{13}C NMR (100 MHz, CDCl$_3$):</u> δ(ppm) 148.1, 147.8, 128.3 (overlapped with 2C), 127.1, 127.0, 125.8, 125.7, 104.3 (overlapped with 2C), 64.7 (overlapped with 2C), 64.6 (overlapped with 2C), 39.9, 39.6, 37.5, 37.3, 37.1, 37.0, 35.1, 34.8, 29.2, 29.1, 22.7, 22.3, 18.9, 18.54, 18.46, 18.3.

<u>MS (HRMS ESI)</u> Calcd for $C_{17}H_{27}O_2$ [M+H]$^+$ 263.2011, Found: 263.2014.

2-((2S*,4R*)-4-phenyl-2-vinylpentyl)-1,3-dioxolane (2.46c)



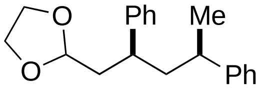
Prepared from **2.28c** (117.2 mg, 0.500 mmol) with 5 mol% of Tf_2NH at 50 °C for 10 min, followed by ethylene glycol (0.14 mL, 2.510 mmol) at 50 °C for 21 h. Purification by flash column chromatography (silica gel, Hex:EtOAc = 98:2) gave **2.46c** in 81% yield (100.2 mg, 0.407 mmol) as an estimated 67:33 diastereomeric mixture (based on ^{1}H NMR spectroscopy analysis) and as a colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.22 – 7.17 (m, 2×0.67H, +m, 2×0.33H), 7.11 – 7.07 (m, 3×0.67H, +m, 3×0.33H), 5.55 – 5.45 (m, 1×0.67H, +m, 1×0.33H), 5.00 – 4.94 (m, 1×0.67H, +m, 1×0.33H), 4.86 (d, *J* = 1.6 Hz, 1×0.67H), 4.78 (d, *J* = 1.6 Hz, 1×0.33H), 4.77 (dd, *J* = 5.2, 5.2 Hz, 1×0.33H), 4.69 (dd, *J* = 5.2, 5.2 Hz, 1×0.67H), 3.89 – 3.65 (m, 4×0.67H, +m, 4×0.33H), 2.77 – 2.62 (m, 1×0.67H, +m, 1×0.33H), 2.32 – 2.23 (m, 1×0.33H), 2.04 – 1.95 (m, 1×0.67H), 1.83 – 1.65 (m, 1×0.67H, +m, 1×0.33H), 1.61 – 1.47 (m, 2×0.67H, +m, 2×0.33H), 1.45 – 1.40 (m, 1×0.67H, +m, 1×0.33H), 1.14 (d, *J* = 6.8 Hz, 3×0.33H), 1.13 (d, *J* = 6.8 Hz, 3×0.67H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 148.2, 147.0, 141.9, 141.7, 128.3 (overlapped with 2C), 127.2, 126.9, 125.83, 125.80, 115.2, 115.1, 103.34, 103.27, 64.73, 64.67, 64.64, 64.62, 44.1, 43.6, 39.45, 39.41, 38.1, 38.0, 37.2, 36.6, 23.5, 20.8.

MS (HRMS ESI): Calcd for $C_{16}H_{23}O_2$ $[M+H]^+$ 247.1698, Found: 247.1691.

2-((2S*,4R*)-2,4-diphenylpentyl)-1,3-dioxolane (2.46d)



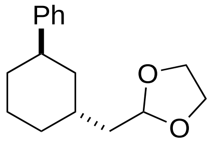
Prepared from **2.28d** (130.8 mg, 0.4600 mmol) with 5 mol% of Tf$_2$NH at 50 °C for 10 min, followed by 5 equiv. of ethylene glycol at 50 °C for 24 h. Purification by flash column chromatography (silica gel, Hex:EtOAc = 98:2) gave **2.46d** in 65% yield (88.7 mg, 0.299 mmol) as an estimated 72:28 diastereomeric mixture (based on ^{1}H NMR spectroscopy analysis) and as a colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 7.36 – 7.12 (m, 7×0.72H, +m, 7×0.28H), 7.10 – 7.07 (m, 3×0.72H, +m, 3×0.28H), 4.54 (dd, *J* = 7.5, 3.5 Hz, 1×0.28H), 4.47 (dd, *J* = 7.0, 3.0 Hz, 1×0.72H), 3.97 – 3.80 (m, 2×0.72H, +m, 2×0.28H), 3.80 – 3.61 (m, 2×0.72H, +m, 2×0.28H), 2.91 (dddd, *J* = 7.0, 7.0, 7.0, 7.0 Hz, 1×0.28H), 2.59 (dddd, *J* = 7.0, 7.0, 7.0, 7.0 Hz, 1×0.72H), 2.51 – 2.37 (m, 1×0.72H, +m, 1×0.28H), 2.09 – 1.77 (m, 4×0.72H, +m, 4×0.28H), 1.22 (d, *J* = 6.5 Hz, 3×0.28H), 1.14 (d, *J* = 6.5 Hz, 3×0.72H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 148.0, 146.8, 144.6, 144.3, 128.5, 128.33, 128.29, 127.9, 127.69, 127.66, 127.3, 126.8, 126.24, 125.15, 125.9, 125.8, 103.1, 103.0, 64.7 (overlapped with 3C), 64.5, 45.9, 45.3, 41.4, 41.3, 39.5, 39.4, 37.3, 36.6, 23.7, 20.6.

MS (HRMS ESI) Calcd for $C_{20}H_{25}O_2$ [M+H]$^+$ 297.1855, Found: 297.1858.

2-(((1*R,3*R**)-3-phenylcyclohexyl)methyl)-1,3-dioxolane (2.46e)**



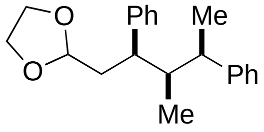
Prepared from **2.28e** (117.7 mg, 0.502 mmol) with 5 mol% of Tf$_2$NH at 80 °C for 10 min, followed by 5 equiv of ethylene glycol (0.14 mL, 2.510 mmol) at 80 °C for 12 h. Purification by flash column chromatography (silica gel, Hex:EtOAc = 98:2) gave **2.46e** in 58% yield (71.7 mg, 0.291 mmol) as a single diastereomer and as a pale yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.30 – 7.26 (m, 2H), 7.22 – 7.21 (m, 2H), 7.19 – 7.11 (m, 1H), 4.91 (dd, *J* = 5.2, 5.2 Hz, 1H), 4.04 – 3.90 (m, 2H), 3.90 – 3.74 (m, 2H), 2.86 – 2.67 (m, 1H), 2.15 – 2.12 (m, 1H), 1.91 – 1.68 (m, 5H), 1.68 – 1.42 (m, 5H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 147.3, 128.2, 126.9, 125.7, 104.2, 64.7 (overlapped with 2C), 38.3, 38.1, 36.3, 33.8, 30.3, 29.6, 21.3.

MS (HRMS ESI): Calcd for $C_{16}H_{23}O_2$ $[M+H]^+$ 247.1698, Found: 247.1701.

2-((2*R**,3*R**,4*R**)-3-methyl-2,4-diphenylpentyl)-1,3-dioxolane (2.46f)



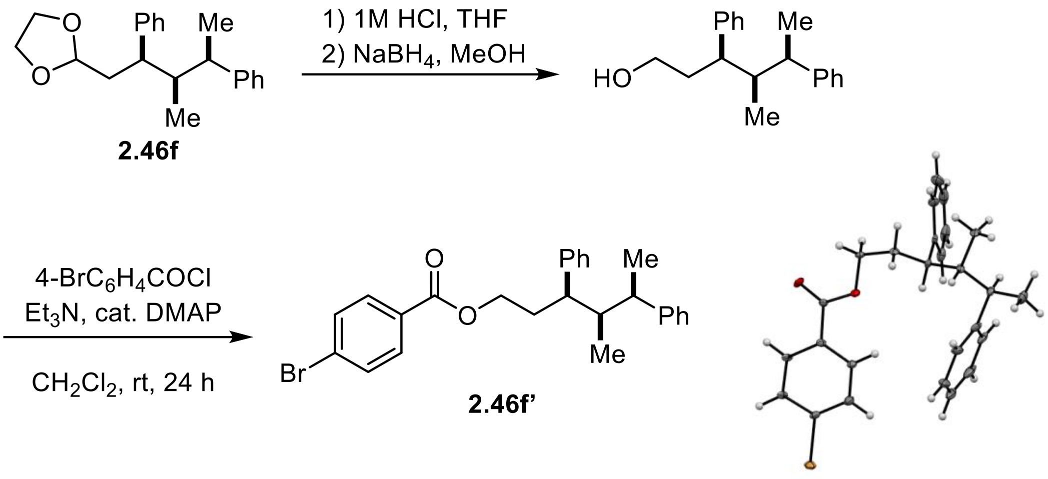
Prepared from **2.28f** (2.368 g, 7.934 mmol) with 5 mol% of Tf_2NH at 24 °C for 10 min, followed by 5 equiv of ethylene glycol (2.22 mL, 39.672 mmol) at 50 °C for 38 h. Purification by flash column chromatography (silica gel, Hex:EtOAc = 98:2) gave **2.46f** in 64% yield (1.571 g, 5.059 mmol) as an estimated 93:7 diastereomeric mixture (based on ^{1}H NMR spectroscopy analysis) and as a pale yellow oil. The stereochemistry of the major isomer was confirmed by X-ray crystallography analysis of the corresponding 4-bromobenzoate derivative as shown below.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.33 – 7.28 (m, 2H), 7.27 – 7.15 (m, 6H), 7.12 – 7.07 (m, 2H), 4.45 (dd, *J* = 6.8, 3.6 Hz, 1H), 3.96 – 3.86 (m, 2H), 3.80 – 3.65 (m, 2H), 2.89 (dq, *J* = 7.2, 7.2 Hz, 1H), 2.81 – 2.75 (m, 1H), 2.16 – 1.99 (m, 3H), 1.15 (d, *J* = 7.2 Hz, 3H), 0.61 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 147.1, 142.9, 128.8, 128.2, 128.0, 127.8, 126.1, 125.7, 103.5, 64.7, 64.6, 44.3, 43.7, 40.8, 38.4, 15.4, 12.1.

MS (HRMS ESI): Calcd for $C_{21}H_{27}O_2$ $[M+H]^+$ 311.2011, Found: 311.2010.

(3*R**,4*R**,5*R**)-4-methyl-3,5-diphenylhexyl 4-bromobenzoate (2.46f')



2.46f

2.46f'

X-ray of **2.46f'**

To a solution of **2.46f** (311.3 mg, 1.003 mmol) in THF (2 mL) was added aqueous HCl solution (1 M, 2 mL) and the mixture was stirred for 15 h at 50 °C. The reaction was then quenched with water at 24 °C and the organic materials were extracted thrice with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. After the filtrate was concentrated *in vacuo*, the resulting crude residue was used for the next step without further purification.

To a solution of the above crude residue in MeOH (5 mL) was slowly added $NaBH_4$ (126.3 mg, 3.339 mmol) and the mixture was stirred for 5 h at 0 °C. The reaction was then quenched with water at 24 °C and the organic materials were extracted thrice with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. After the filtrate was concentrated *in vacuo*, the resulting crude residue was purified by flash column chromatography (silica gel, Hex:EtOAc = 93:7 to 91:9) to give (3*R**,4*R**,5*R**)-4-methyl-3,5-diphenylhexan-1-ol in 80% yield (215.9 mg, 0.804 mmol) over two steps and as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.37 – 7.29 (m, 2H), 7.29 – 7.15 (m, 6H), 7.10 – 7.08 (m, 2H), 3.53 – 3.30 (m, 2H), 2.84 (dq, *J* = 7.2, 7.2 Hz, 1H), 2.65 (ddd, *J* = 10.8, 6.4, 4.4 Hz, 1H), 2.17 – 1.87 (m, 3H), 1.15 (d, *J* = 6.8 Hz, 3H), 1.06 (brs, 1H), 0.67 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 147.3, 142.8, 128.8, 128.3, 128.1, 127.7, 126.2, 125.8, 61.5, 44.8, 43.8, 41.2, 36.9, 16.2, 12.4.

MS (HRMS ESI): Calcd for $C_{19}H_{24}O$ [M+Na]$^+$ 291.1725, Found: 291.1725.

To a solution of (3*R**,4*R**,5*R**)-4-methyl-3,5-diphenylhexan-1-ol (44.0 mg, 0.164 mmol), 4-bromobenzoyl chloride (70.3 mg, 0.320 mmol) and DMAP (3.0 mg, 0.024 mmol) in dichloromethane (3 mL) was slowly added Et_3N (55 μL, 0.392 mmol) and the mixture was stirred for 24 h at 24 °C. The reaction was then quenched with water at 24 °C and the organic materials were extracted thrice with dichloromethane. The combined organic layers were washed with brine and dried over $MgSO_4$. After the filtrate was concentrated *in vacuo*, the resulting crude residue was purified by flash column chromatography (silica gel, Hex:EtOAc = 99:1) to give **2.46f'** in 99% yield (74.0 mg, 0.164 mmol) as white solid. Compound **2.46f'** which was recrystallized from hexane-CH_2Cl_2 to give a colorless crystal suitable for X-ray crystallography analysis (CCDC-1894807).

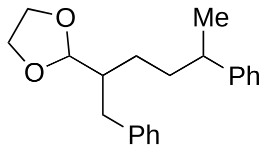
^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.68 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.34 – 7.15 (m, 8H), 7.08 (d, *J* = 7.2 Hz, 2H), 4.15 (ddd, *J* = 11.2, 11.2, 5.6 Hz, 1H), 4.01 – 3.95 (m, 1H), 2.82 – 2.65 (m, 2H), 2.28 – 1.98 (m, 3H), 1.14 (d, *J* = 7.2 Hz, 3H), 0.77 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 165.7, 147.2, 141.7, 131.6, 131.0, 129.2, 129.0, 128.4, 128.1, 127.8, 127.7, 126.4, 125.8, 63.8, 44.4, 43.6, 41.8, 33.2, 17.6, 12.8.

MS (HRMS ESI): Calcd for $C_{26}H_{27}O_2BrNa$ [M+Na]$^+$ 473.1092, Found: 437.1089.

5.2.2.6. Characterization of the products (Scheme 2.41)

2-(1,5-diphenylhexan-2-yl)-1,3-dioxolane (2.47a)



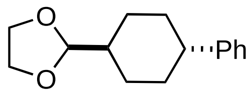
Prepared from **2.35a** (150.5 mg, 0.504 mmol) with 5 mol% of Tf_2NH at 50 °C for 10 min, followed by 5 equiv of ethylene glycol at 50 °C for 21 h. Purification by flash column chromatography (silica gel, Hex:EtOAc = 98:2) gave **2.47a** in 75% yield (117.6 mg, 0.379 mmol) as an estimated 50:50 diastereomeric mixture (based on ^{1}H NMR spectroscopy analysis) and as a colorless oil.

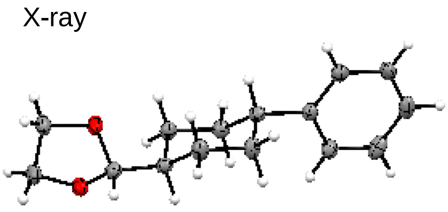
^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.32 – 7.22 (m, 4×0.50H, +m, 4×0.50H), 7.23 – 7.13 (m, 6×0.50H, +m, 6×0.50H), 4.80 (d, *J* = 4.0 Hz, 1×0.50H), 4.77 (d, *J* = 4.0 Hz, 1×0.50H), 4.00 – 3.91 (m, 2×0.50H, +m, 2×0.50H), 3.89 – 3.81 (m, 2×0.50H, +m, 2×0.50H), 2.85 (m, 1×0.50H, +m, 1×0.50H), 2.69 – 2.54 (m, 2×0.50H, +m, 2×0.50H), 2.03 – 1.94 (m, 1×0.50H, +m, 1×0.50H), 1.74 – 1.32 (m, 4×0.50H, +m, 4×0.50H), 1.23 (d, *J* = 6.8 Hz, 3×0.50 H, +d, *J* = 6.8 Hz, 3×0.50 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 147.6 (overlapped with 2C), 140.6, 140.5, 129.2 (overlapped with 2C), 128.2 (overlapped with 2C), 128.12, 128.11, 126.9 (overlapped with 2C), 125.70 (overlapped with 2C), 125.67 (overlapped with 2C), 105.7 (overlapped with 2C), 64.9 (overlapped with 4C), 43.5, 43.3, 40.2, 40.1, 35.9, 35.7, 35.3 (overlapped with 2C), 26.6, 26.5, 22.1 (overlapped with 2C).

MS (HRMS ESI): Calcd for $C_{21}H_{27}O_2$ $[M+H]^+$ 311.2011, Found: 311.2020.

2-((1r*,4r*)-4-phenylcyclohexyl)-1,3-dioxolane (2.47b)





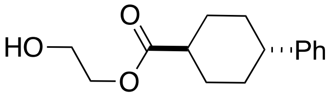
Prepared from **2.38** (110.2 mg, 0.501 mmol) with 5 mol% of Tf_2NH at 80 °C for 1 h, followed by 5 equiv of ethylene glycol at 80 °C for 36 h. Purification by flash column chromatography (silica gel, Hex:EtOAc = 96:4) gave **2.47b** in 64% yield (74.3 mg, 0.320 mmol) as an estimated 96:4 diastereomeric mixture (based on ^1H NMR spectroscopy analysis) as white solid. Compound **2.47b** was recrystallized from hexane-CH_2Cl_2 to give a colorless crystal. The stereochemistry of the major isomer was confirmed by the X-ray crystallography analysis (CCDC-1894808).

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.30 – 7.26 (m, 2H), 7.21 – 7.15 (m, 3H), 4.66 (d, *J* = 5.2 Hz, 1H), 3.99 – 3.92 (m, 2H), 3.91 – 3.83 (m, 2H), 2.48 (tt, *J* = 15.2, 2.8 Hz, 1H), 1.97 – 1.94 (m, 4H), 1.68 – 1.59 (m, 1H), 1.52 – 1.42 (m, 2H), 1.34 – 1.24 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 147.4, 128.3, 126.8, 125.9, 107.5, 65.0 (overlapped with 2C), 44.2, 41.3, 33.4, 27.4.

MS (HRMS ESI): Calcd for $C_{15}H_{21}O_2$ $[M+H]^+$ 233.1542, Found: 233.1545.

2-hydroxyethyl (1R*,4R*)-4-phenylcyclohexane-1-carboxylate (2.47c)



Prepared from **2.40** (123.1 mg, 0.496 mmol) with 10 mol% of Tf_2NH at 80 °C for 1 h. Purification by flash column chromatography (silica gel, Hex:EtOAc = 75:25) gave **2.47c** in

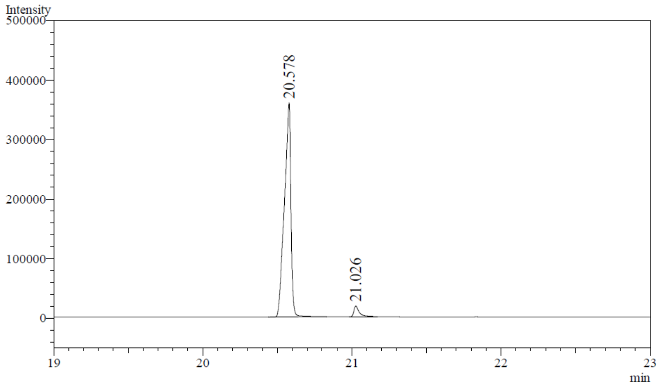
45% yield (54.8 mg, 0.221 mmol) as an estimated 96:4 diastereomeric mixture (based on GC spectroscopy analysis) and as a pale yellow solid.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) δ 7.32 – 7.28 (m, 2H), 7.21 – 7.17 (m, 3H), 4.25 – 4.23 (m, 2H), 3.85 (br, 2H), 2.53 (tt, *J* = 12.0, 3.2 Hz, 1H), 2.42 (tt, *J* = 12.0, 3.6 Hz, 1H), 2.18 – 2.08 (m, 2H), 2.02 – 1.93 (m, 3H), 1.69 – 1.56 (m, 2H), 1.50 (dddd, *J* = 12.8, 12.8, 3.2, 3.2 Hz, 2H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 176.3, 146.7, 128.4, 126.7, 126.1, 65.9, 61.3, 43.5, 42.9, 33.2, 29.3.

MS (HRMS ESI): Calcd for $C_{15}H_{20}O_3Na$ [M+Na]$^+$ 271.1310, Found: 271.1302.

GC trace:

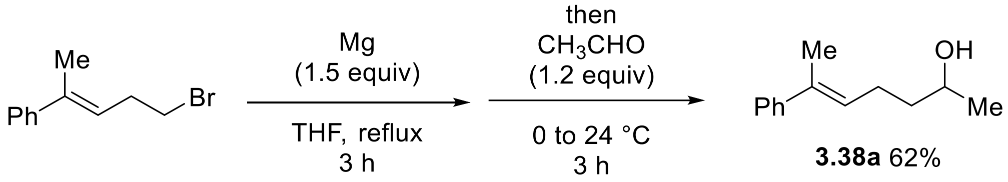


Peak#	Ret.Time	Area%
1	20.578	95.9966
2	21.026	4.0034
Total		100.0000

5.3 Hydroalkylation (Chapter 3)

5.3.1 Synthesis and Characterization of the aryl alkenes

5.3.1.1 Synthesis of (*E*)-6-phenylhept-5-en-2-ol (3.38a)



(*E*)-(5-bromopent-2-en-2-yl)benzene (3.321 g, 14.89 mmol)[39] in dry THF (20 mL) was added dropwise to magnesium turnings (540.3 mg, 22.51 mmol) in a flame-dried round-bottom flask equipped with a reflux condenser at room temperature. The mixture was allowed to stir at 80 °C for 3 h. The resulting Grignard reagent was cannulated dropwise to a solution of acetaldehyde (1.01 mL, 18.07 mmol) in THF (10 mL) at 0 °C. The reaction was allowed to warm to room temperature and stirred for another 3 h. The reaction was then quenched with saturated aqueous NH_4Cl solution and the organic materials were extracted thrice with Et_2O. The combined organic layers were washed with brine and dried over $MgSO_4$ before being concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, hexane:EtOAc = 90:10) to give **3.38a** in 62% yield (1.763 g, 9.27 mmol) as a colorless oil.

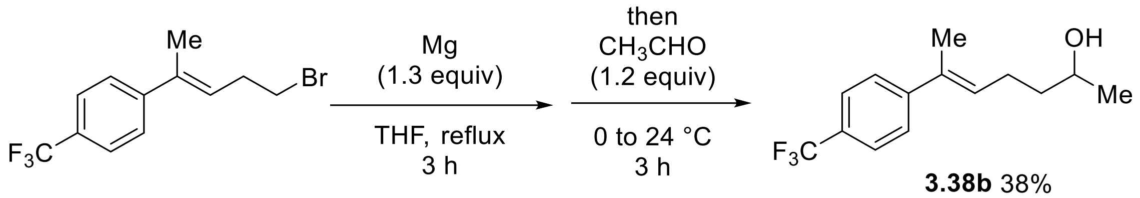
^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.36 (d, *J* = 7.7 Hz, 2H), 7.29 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.20 (t, *J* = 7.7 Hz, 1H), 5.77 (dd, *J* = 7.3, 7.3 Hz, 1H), 3.85 (ddq, *J* = 6.2, 6.2, 6.2 Hz, 1H), 2.31 (dddd, *J* = 14.8, 7.3, 7.3, 7.3 Hz, 1H), 2.26 (dddd, *J* = 14.8, 7.3, 7.3, 7.3 Hz, 1H), 2.04 (s, 3H), 1.66 – 1.57 (m, 2H), 1.22 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 143.8, 135.1, 128.1, 127.7, 126.5, 125.5, 67.7, 38.9, 25.1, 23.5, 15.7

MS (HRMS ESI): Calcd for $C_{13}H_{19}O$ $[M+H]^+$ 191.1436, Found: 191.1430.

IR (neat, cm^{-1}): 3366 [ν (O-H)], 1676 [ν (C=C)].

5.3.1.2. Synthesis of (*E*)-6-(4-(trifluoromethyl)phenyl)hept-5-en-2-ol (3.38b)



3.38b 38%

It was synthesized following the procedure described in section **5.3.1.1** using ethyl (*E*)-1-(5-bromopent-2-en-2-yl)-4-(trifluoromethyl)benzene[40] (8.69 g, 29.64 mmol) and acetaldehyde (1.98 mL, 35.51 mmol). Purification by flash column chromatography (silica gel, hexane:EtOAc = 91:9) gave **3.38b** (2.93 g, 11.35 mmol) in 38% yield as colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.54 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 8.3 Hz, 2H), 5.86 (dd, *J* = 7.2, 7.2 Hz, 1H), 3.86 (ddq, *J* = 6.2, 6.2, 6.2 Hz, 1H), 2.35 (dddd, *J* = 14.7, 7.2, 7.2, 7.2 Hz, 1H), 2.30 (dddd, *J* = 14.7, 7.2, 7.2, 7.2 Hz, 1H), 2.06 (s, 3H), 1.65 – 1.59 (m, 2H), 1.24 (d, *J* = 6.2 Hz, 3H).

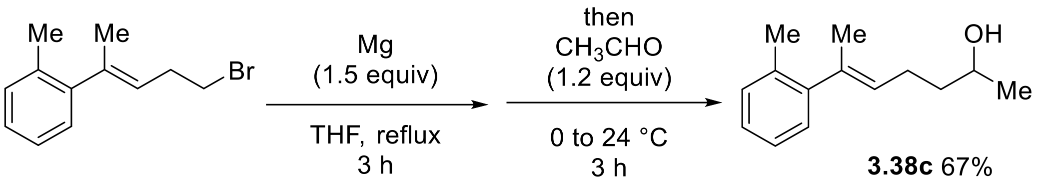
^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 147.3, 134.2, 130.0, 128.6 (q, *J* = 32.0 Hz), 125.8, 125.1 (q, *J* = 4.0 Hz), 124.3 (q, *J* = 271.0 Hz), 67.7, 38.8, 25.2, 23.6, 15.6.

^{19}F NMR (376 MHz, CDCl$_3$): δ(ppm) -62.4 (s, 3F)

MS (HRMS ESI): Calcd for $C_{14}H_{18}OF_3$ [M+H]$^+$ 259.1310, Found: 259.1309.

IR (neat, cm^{-1}): 3375 [ν (O-H)], 1614 [ν (C=C)], 1327 [ν (C-F)].

5.3.1.3. Synthesis of (*E*)-6-(o-tolyl)hept-5-en-2-ol (3.38c)



It was synthesized following the procedure described in section **5.3.1.1** using ethyl (*E*)-1-(5-bromopent-2-en-2-yl)-2-methylbenzene[40] (3.89 g, 16.27 mmol) and acetaldehyde (1.10 mL, 19.73 mmol). Purification by flash column chromatography (silica gel, hexane:EtOAc = 91:9) gave **3.38c** (2.22 g, 10.87 mmol) in 67% yield as a colorless oil.

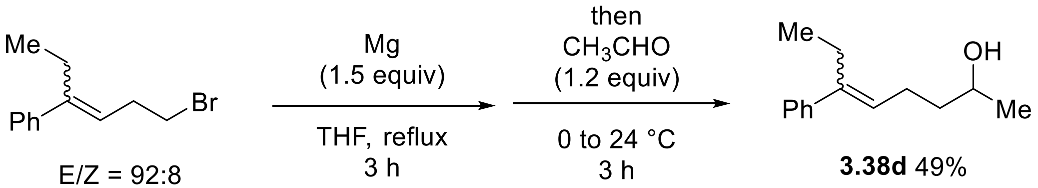
^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.17 – 7.11 (m, 3H), 7.06 – 7.04 (m, 1H), 5.29 (qt, *J* = 1.3, 7.2 Hz, 1H), 3.88 (ddq, *J* = 6.2, 6.2, 6.2 Hz, 1H), 2.26 (s, 3H), 2.33 – 2.22 (m, 2H), 1.93 (d, *J* = 1.3 Hz, 3H), 1.65 – 1.54 (m, 2H), 1.24 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 145.6, 136.6, 134.7, 130.0, 128.8, 128.2, 126.4, 125.5, 67.9, 38.9, 24.7, 23.6, 19.8, 17.9.

MS (HRMS ESI): Calcd for $C_{14}H_{21}O$ $[M+H]^+$ 205.1592, Found: 205.1587.

IR (neat, cm^{-1}): 3350 [ν (O-H)], 1625 [ν (C=C)].

5.3.1.4. Synthesis of (E)-6-phenyloct-5-en-2-ol (3.38d)



It was synthesized following the procedure described in section **5.3.1.1** using ethyl (6-bromohex-3-en-3-yl)benzene[39] (1.85 g, 7.72 mmol, *E*:*Z* = 92:8) and acetaldehyde (0.52 mL, 9.26 mmol). Purification by flash column chromatography (silica gel, hexane:EtOAc = 91:9) gave **3.38d** (765.2 mg, 3.75 mmol) in 49% yield as a colorless oil (*E*:*Z* = 92:8).

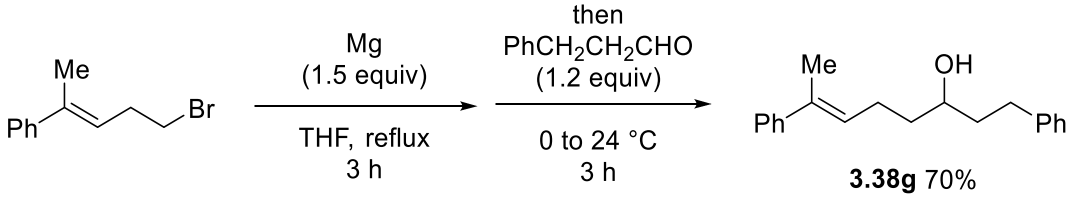
<u>^{1}H NMR (400 MHz, CDCl$_3$):</u> δ(ppm) 7.34 – 7.27 (m, 4H), 7.23 – 7.19 (m, 1H), 5.62 (dd, *J* = 7.5, 7.5 Hz, 1H), 3.86 (ddq, *J* = 6.2, 6.2, 6.2 Hz, 1H), 2.52 (q, *J* = 7.5 Hz, 2H), 2.32 (dddd, *J* = 14.8, 7.5, 7.5, 7.5 Hz, 1H), 2.26 (dddd, *J* = 14.8, 7.5, 7.5, 7.5 Hz, 1H), 1.66 – 1.56 (m, 2H), 1.22 (d, *J* = 6.2 Hz, 3H), 0.98 (t, *J* = 7.5, 3H).

<u>^{13}C NMR (100 MHz, CDCl$_3$):</u> δ(ppm) 142.9, 142.1, 128.1, 127.4, 126.5, 126.2, 67.7, 39.3, 24.8, 23.5, 23.2, 22.9, 13.5

<u>MS (HRMS ESI):</u> Calcd for $C_{14}H_{21}O$ $[M+H]^+$ 205.1592, Found: 205.1588.

<u>IR (neat, cm^{-1}):</u> 3360 [ν (O-H)], 1597 [ν (C=C)].

5.3.1.5. Synthesis of (*E*)-1,7-diphenyloct-6-en-3-ol (3.38g)



It was synthesized following the procedure described in section **5.3.1.1** using ethyl (*E*)-(5-bromopent-2-en-2-yl)benzene[39] (2.237 g, 10.03 mmol) and hydrocinnamaldehyde (1.58 mL, 12.00 mmol). Purification by flash column chromatography (silica gel, hexane:EtOAc = 92:8) gave **3.38g** (1.97 g, 7.04 mmol) in 70% yield as a colorless oil.

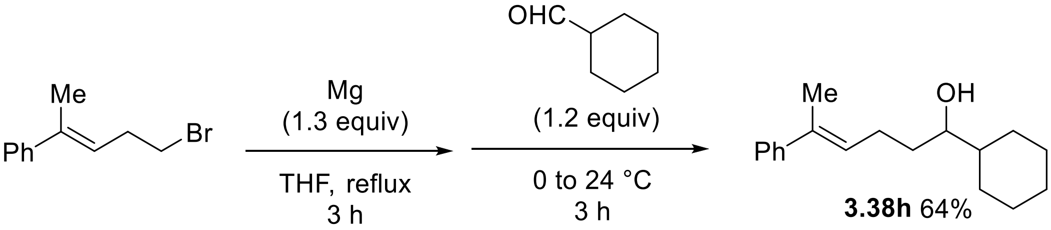
<u>^{1}H NMR (500 MHz, CDCl$_3$):</u> δ(ppm) 7.35 (d, *J* = 7.2 Hz, 2H), 7.32 – 7.27 (m, 4H), 7.23 – 7.17 (m, 4H), 5.77 (dd, *J* = 7.0, 7.0 Hz, 1H), 3.70 (dddd, *J* = 8.2, 8.2, 4.5, 4.5 Hz, 1H), 2.81 (ddd, *J* = 13.9, 6.3, 6.3 Hz, 1H), 2.69 (ddd, *J* = 13.9, 6.3, 6.3 Hz, 1H), 2.35 (dddd, *J* = 14.8, 7.0, 7.0, 7.0 Hz, 1H), 2.29 (dddd, *J* = 14.8, 7.0, 7.0, 7.0 Hz, 1H), 2.04 (s, 3H), 1.87 – 1.74 (m, 2H), 1.70 – 1.60 (m, 2H)

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 143.7, 142.1, 135.3, 128.4, 128.1, 127.7, 126.6, 125.8, 125.6, 71.0, 39.2, 37.2, 32.1, 25.0, 15.8

MS (HRMS ESI): Calcd for $C_{20}H_{24}ONa$ $[M+Na]^+$ 303.1725, Found: 303.1733.

IR (neat, cm^{-1}): 3390 [ν (O-H)], 1601 [ν (C=C)].

5.3.1.6. Synthesis of (*E*)-1-cyclohexyl-5-phenylhex-4-en-1-ol (3.38h)



It was synthesized following the procedure described in section **5.3.1.1** using ethyl (*E*)-(5-bromopent-2-en-2-yl)benzene[39] (1.42 g, 6.37 mmol) and cyclohexylcarboxaldehyde (0.95 mL, 7.64 mmol). Purification by flash column chromatography (silica gel, hexane:EtOAc = 91:9) gave **3.38h** (1.06 g, 4.10 mmol) in 64% yield as a colorless oil.

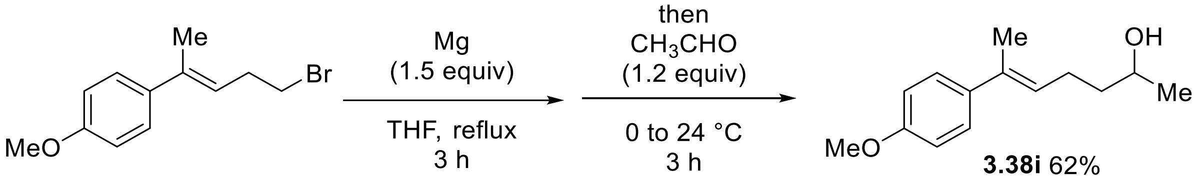
^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 7.37 (d, J = 7.4 Hz, 2H), 7.30 (dd, J = 7.4, 7.4 Hz, 2H), 7.21 (t, J = 7.4 Hz, 1H), 5.79 (dd, *J* = 7.5, 7.5 Hz, 1H), 3.41 (ddd, *J* = 8.8, 5.3, 3.4 Hz, 1H), 2.37 (dddd, *J* = 15.0, 7.5, 7.5, 7.5 Hz, 1H), 2.28 (dddd, *J* = 15.0, 7.5, 7.5, 7.5 Hz, 1H), 2.05 (s, 3H), 1.83 – 1.75 (m, 3H), 1.69 – 1.61 (m, 2H), 1.58 – 1.51 (m, 2H), 1.37 – 1.31 (m, 1H), 1.28 – 0.98 (m, 5H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 143.8, 135.1, 128.11, 128.06, 126.5, 125.6, 75.9, 43.7, 33.9, 29.2, 27.8, 26.5, 26.3, 26.2, 25.3, 15.8.

MS (HRMS ESI): Calcd for $C_{18}H_{26}ONa$ $[M+Na]^+$ 281.1881, Found: 281.1873.

IR (neat, cm^{-1}): 3294 [ν (O-H)], 1729 [ν (C=C)].

5.3.1.7. Synthesis of (*E*)-6-(4-methoxyphenyl)hept-5-en-2-ol (3.38i)



It was synthesized following the procedure described in section **5.3.1.1** using ethyl (*E*)-1-(5-bromopent-2-en-2-yl)-4-methoxybenzene[40] (6.39 g, 25.09 mmol) and acetaldehyde (1.70 mL, 30.49 mmol). Purification by flash column chromatography (silica gel, hexane:EtOAc = 91:9) gave **3.38i** (3.43 g, 15.55 mmol) in 62% yield as a white solid.

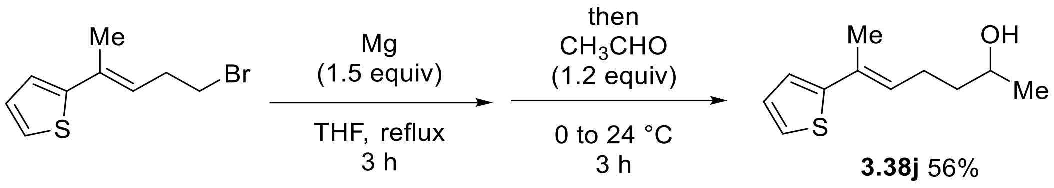
^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 7.31 (d, *J* = 8.9 Hz, 2H), 6.84 (d, *J* = 8.9 Hz, 2H), 5.70 (ddq, *J* = 7.3, 7.3, 1.3 Hz, 1H), 3.86 (ddq, *J* = 6.2, 6.2, 6.2 Hz, 1H), 3.80 (s, 3H), 2.31 (dddd, *J* = 15.1, 7.3, 7.3, 7.3 Hz, 1H), 2.26 (dddd, *J* = 15.1, 7.3, 7.3, 7.3 Hz, 1H), 2.02 (d, *J* = 1.3 Hz, 3H), 1.65 – 1.57 (m, 2H), 1.23 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 158.5, 136.4, 134.5, 126.6, 126.2, 113.5, 67.9, 55.3, 39.1, 25.1, 23.6, 15.8.

MS (HRMS ESI): Calcd for $C_{14}H_{21}O_2$ [M+H]$^+$ 221.1542, Found: 221.1551.

IR (neat, cm^{-1}): 3331 [ν (O-H)], 1607 [ν (C=C)].

5.3.1.8. Synthesis of (*E*)-6-(thiophen-2-yl)hept-5-en-2-ol (3.38j)



It was synthesized following the procedure described in section **5.3.1.1** using ethyl (*E*)-2-(5-bromopent-2-en-2-yl)thiophene[40] (5.31 g, 22.96 mmol) and acetaldehyde (11.50 mL, 26.90 mmol). Purification by flash column chromatography (silica gel, hexane:EtOAc = 91:9) gave **3.38j** (2.54 g, 12.94 mmol4) in 56% yield as a colorless oil.

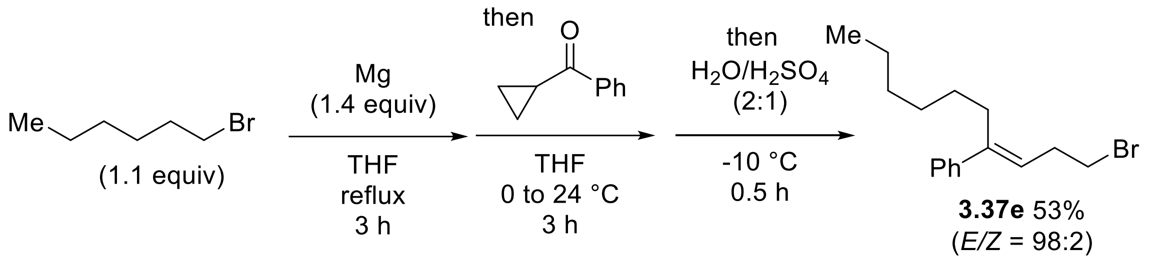
^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.09 (t, *J* = 4.0 Hz, 1H), 6.96 – 6.94 (m, 2H), 5.93 (dd, *J* = 7.4, 7.4 Hz, 1H), 3.85 (ddq, *J* = 6.2, 6.2, 6.2 Hz 1H), 2.30 (dddd, *J* = 14.7, 7.4, 7.4, 7.4 Hz, 1H), 2.28 (dddd, 14.7, 7.4, 7.4, 7.4 Hz, 1H), 2.06 (s, 3H), 1.64 – 1.56 (m, 2H), 1.22 (d, *J* = 6.2 Hz, 3H).

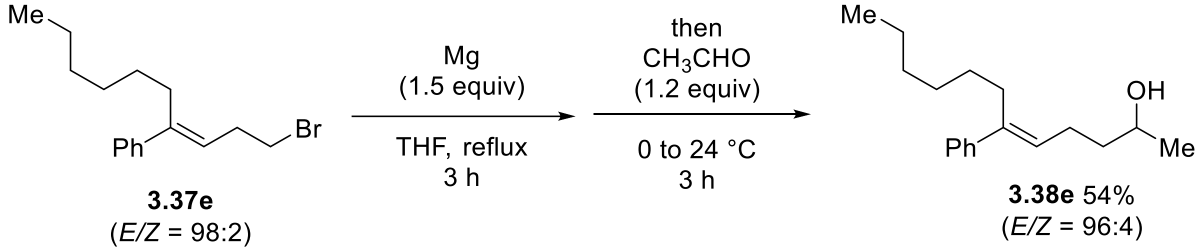
^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 147.9, 129.3, 127.2, 126.6, 122.9, 122.0, 67.7, 38.8, 24.8, 23.6, 15.7

MS (HRMS ESI): Calcd for $C_{11}H_{17}OS$ $[M+H]^+$ 197.1000, Found: 197.0995.

IR (neat, cm^{-1}): 3331 [ν (O-H)], 1607 [ν (C=C)].

5.3.1.9. Synthesis of 6-phenyldodec-5-en-2-ol (3.38e)





(1-bromodec-3-en-4-yl)benzene (**3.37e**) was synthesized adapting the procedure described by Xiaodan.[39] To a solution of freshly prepared hexylmagnesium bromide (0.70 M, 30 mL) was added cyclopropyl phenyl ketone (2.77 mL, 20.05 mmol) at 0 °C. The resulting solution was warmed up to 24 °C and stirred for 3 h. The mixture was then cooled to -10 °C, and then a mixture of H_2O and H_2SO_4 (H_2O:H_2SO_4 = 2:1, v/v, 18 mL) was added dropwise. The resulting mixture was stirred for 30 min and extracted thrice with Et_2O. The combined organic layers were washed with brine and dried over $MgSO_4$ before being concentrated *in vacuo*. Purification by flash column chromatography (silica gel, hexane:EtOAc = 91:9) gave **3.37e** (3.137 g, 10.55 mmol) in 53% yield as a colorless oil (*E*:*Z* = 98:2).

The NMR spectrum of the major *E*-isomer are shown below.

<u>^{1}H NMR (500 MHz, CDCl$_3$):</u> δ(ppm) 7.35 – 7.29 (m, 4H), 7.25 – 7.22 (m, 1H), 5.60 (t, *J* = 7.2 Hz, 1H), 3.44 (t, *J* = 7.2 Hz, 2H), 2.77 (dt, *J* = 7.2, 7.2 Hz, 2H), 2.48 (t, *J* = 7.5 Hz, 2H), 1.35 – 1.21 (m, 8H), 0.85 (t, *J* = 7.0 Hz, 3H).

<u>^{13}C NMR (125 MHz, CDCl$_3$):</u> δ(ppm) 143.4, 142.7, 128.2, 126.9, 126.4, 124.7, 32.5, 32.1, 31.6, 30.1, 29.2, 28.6, 22.6, 14.0.

<u>MS (HRMS ESI):</u> Calcd for $C_{16}H_{24}Br$ $[M+H]^+$ 295.1061, Found: 295.1058.

6-phenyldodec-5-en-2-ol (**3.38e**) was synthesized following the procedure described in section **5.3.1.1** using (1-bromodec-3-en-4-yl)benzene (2.886 g, 9.78 mmol) and acetaldehyde (0.66 mL, 11.84 mmol). Purification by flash column chromatography (silica gel, hexane:EtOAc = 93:7) gave **3.38e** (1.37 g, 5.27 mmol) in 54% yield as a colorless oil (*E*:*Z* = 96:4).

The NMR spectrum of the major *E*-isomer are shown below.

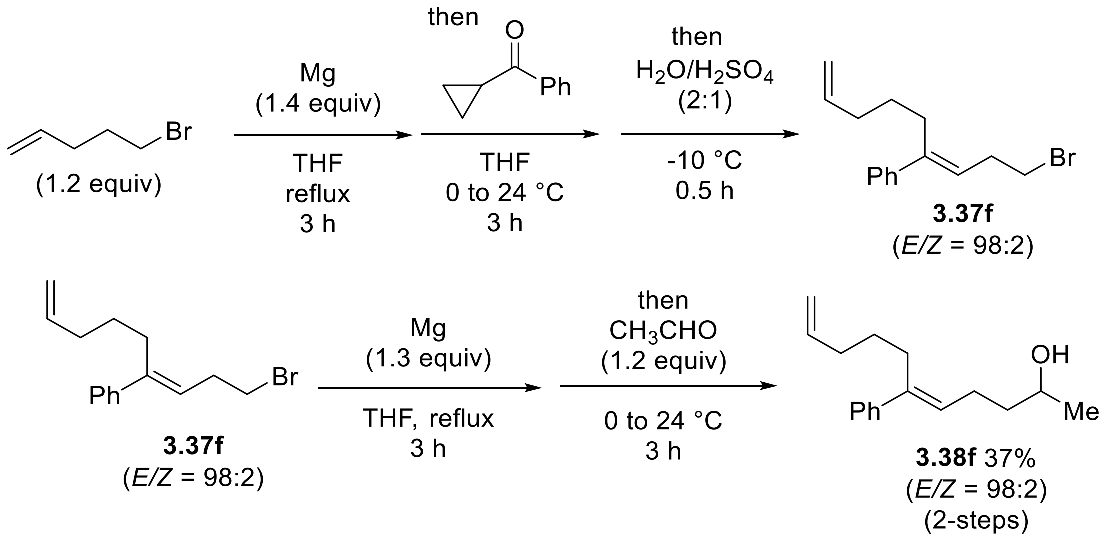
^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.33 – 7.27 (m, 4H), 7.21 (tt, *J* = 7.0, 1.5 Hz, 1H), 5.63 (dd, *J* = 7.3, 7.3 Hz, 1H), 3.87 (ddq, *J* = 6.2, 6.2, 6.2 Hz, 1H), 2.50 (t, *J* = 7.5 Hz, 2H), 2.32 (dddd, *J* = 14.7, 7.3, 7.3, 7.3 Hz, 1H), 2.27 (dddd, *J* = 14.7, 7.3, 7.3, 7.3 Hz, 1H), 1.66 – 1.57 (m, 2H), 1.35 – 1.25 (m, 8H), 1.23 (d, *J* = 6.2 Hz, 3H), 0.85 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 143.3, 140.8, 128.12, 128.06, 126.5, 126.3, 67.8, 39.3, 31.7, 29.8, 29.3, 28.7, 25.0, 23.6, 22.6, 14.0.

MS (HRMS ESI): Calcd for $C_{18}H_{29}O$ $[M+H]^+$ 261.2218, Found: 261.2211.

IR (neat, cm^{-1}): 3360 [ν (O-H)], 1599 [ν (C=C)].

5.3.1.10. Synthesis of 6-phenylundeca-5,10-dien-2-ol (3.38f)



(1-bromonona-3,8-dien-4-yl)benzene (**3.37f**) (*E*:*Z* = 98:2) was synthesized adapting the procedure described by Xiaodan.[39] To a solution of freshly prepared pent-1-enylmagnesium bromide (0.53 M, 80 mL) was added cyclopropyl phenyl ketone (5.60 mL, 40.53 mmol) at 0 °C. The resulting solution was warmed up to 24 °C and stirred for 3 h. The mixture was then cooled to -10 °C, and then a mixture of H_2O and H_2SO_4 (H_2O:H_2SO_4 = 2:1, v/v, 18 mL) was added dropwise. The resulting mixture was stirred for 30 min and extracted thrice with Et_2O. The combined organic layers were washed with brine and dried over $MgSO_4$ before being concentrated *in vacuo*. The crude material was run through a short plug of silica with hexane and then concentrated *in vacuo*. The resulting residue including (1-bromonona-3,8-dien-4-yl)benzene (*E*:*Z* = 98:2) was used for the next step without further purification.

6-Phenylundeca-5,10-dien-2-ol (**3.38f**) was synthesized following the procedure described in section **5.3.1.1** using the above crude residue including **3.37f** (*E*:*Z* = 98:2) and acetaldehyde (2.24 mL, 48.32 mmol). Purification by flash column chromatography (silica gel, hexane:EtOAc = 91:9) gave **3.38f** (3.63 g, 14.84 mmol) in 37% yield over 2-steps with respect to cyclopropyl phenyl ketone as a colorless oil (*E*:*Z* = 98:2).

The NMR spectrum of the major *E*-isomer are shown below.

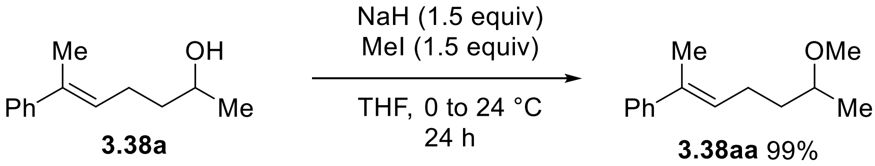
^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.36 – 7.25 (m, 4H), 7.19 (t, *J* = 7.1 Hz, 1H), 5.76 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.64 (dd, *J* = 7.3, 7.3 Hz, 1H), 5.00 – 4.91 (m, 2H), 3.83 (ddq, *J* = 6.2, 6.2, 6.2 Hz, 1H), 2.51 (t, *J* = 7.8, 2H), 2.34 – 2.21 (m, 2H), 2.05 – 2.00 (m, 3H), 1.64 – 1.51 (m, 1H), 1.47 – 1.40 (m, 2H), 1.20 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 143.0, 140.3, 138.5, 128.4, 128.1, 126.4, 126.2, 114.5, 67.5, 39.1, 33.4, 29.0, 27.7, 24.8, 23.4

MS (HRMS ESI): Calcd for $C_{17}H_{25}O$ $[M+H]^+$ 245.1905, Found: 245.1903.

IR (neat, cm^{-1}): 3352 [ν (O-H)], 1639 [ν (C=C)].

5.3.1.11. Synthesis of (*E*)-(6-methoxyhept-2-en-2-yl)benzene (1aa)



To a suspended solution of NaH (60% dispersion in mineral oil; 458.8 mg, 11.5 mmol) in THF (10 mL) was slowly added **3.38a** (1.50 g, 7.33 mmol), which was synthesized following the procedure described in section **5.3.1.1** in THF (5 mL) at 0 °C before methyl iodide (0.7 mL, 11.24 mmol) was then added and the reaction mixture was stirred at 24 °C for 15 h. The reaction mixture was quenched at 0 °C by slow addition of saturated aqueous NH_4Cl solution. The organic materials were then extracted thrice with Et_2O and the combined organic layers were washed with brine and dried over $MgSO_4$. After the filtrate was concentrated *in vacuo*, the resulting crude material was purified by flash column chromatography (silica gel, hexane:EtOAc = 97:3) to give **3.38aa** (1.50 g, 7.33 mmol) in 99% yield as a colorless oil.

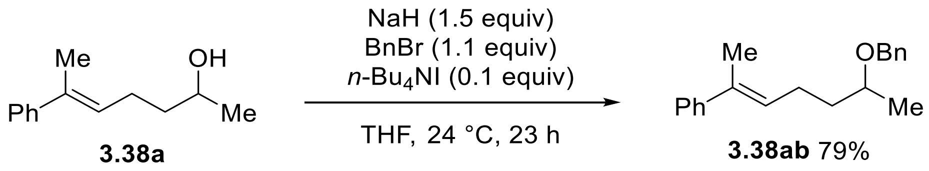
^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 7.37 (d, *J* = 7.6 Hz, 2H), 7.30 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.21 (t, *J* = 7.6 Hz, 1H), 5.76 (t, *J* = 7.3 Hz, 1H), 3.34 – 3.31 (m, 1H), 3.33 (s, 3H), 2.27 (td, *J* = 7.3, 7.3 Hz, 2H), 2.04 (s, 3H), 1.72 – 1.65 (m, 1H), 1.57 – 1.50 (m, 1H), 1.16 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 143.9, 134.9, 128.1, 128.0, 126.5, 125.6, 76.2, 56.0, 36.1, 24.7, 19.0, 15.7.

MS (HRMS ESI): Calcd for $C_{14}H_{21}O$ $[M+H]^+$ 205.1592, Found: 205.1594.

IR (neat, cm^{-1}): 1597 [ν (C=C)], 1092 [ν (C-O)].

5.3.1.12. Synthesis of (*E*)-(6-(benzyloxy)hept-2-en-2-yl)benzene (3.38ab)



To a suspended solution of NaH (60% dispersion in mineral oil; 47.3 mg, 1.18 mmol) in THF (3.0 mL) was slowly added **3.38a** (136.9 g, 0.719 mmol), which was synthesized following the procedure described in section **5.3.1.1** in THF (1.0 mL) at 0 °C and the mixture was stirred for 1 h. Benzyl bromide (0.1 mL, 0.842 mmol) and tetrabutylammonium iodide (TBAI) (23.8 mg, 0.074 mmol) were then added and the reaction mixture was stirred at 24 °C for 22 h. The reaction mixture was quenched at 0 °C by slow addition of saturated aqueous NH_4Cl solution. The organic materials were then extracted thrice with Et_2O and the combined organic layers were washed with brine and dried over $MgSO_4$. After the filtrate was concentrated *in vacuo*, the resulting crude material was purified by flash column chromatography (silica gel, hexane:EtOAc = 99:1) to give **3.38ab** (159.0 mg, 0.567 mmol) in 79% yield as a colorless oil.

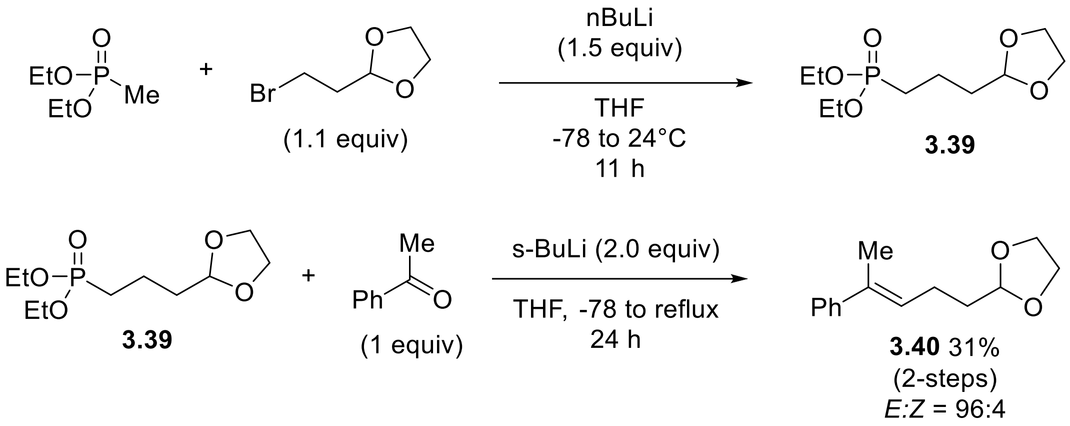
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.36 – 7.23 (m, 9H), 7.21 – 7.17 (m, 1H), 5.75 (t, *J* = 7.2 Hz, 1H), 4.58 (d, *J* = 11.7 Hz, 1H), 4.45 (d, *J* = 11.7, 1H), 3.57 (qt, *J* = 6.1, 6.1 Hz, 1H), 2.29 (td, *J* = 7.2, 7.2 Hz, 2H), 2.02 (s, 3H), 1.80 – 1.71 (m, 1H), 1.63 – 1.54 (m, 1H), 1.22 (d, *J* = 6.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 143.9, 139.1, 134.9, 128.3, 128.11, 128.09, 127.6, 127.3, 126.4, 125.6, 74.3, 70.4, 36.5, 24.8, 19.6, 15.7.

MS (HRMS ESI): Calcd for $C_{20}H_{25}O$ $[M+H]^+$ 281.1905, Found: 281.1904.

IR (neat, cm^{-1}): 1598 [ν (C=C)], 1136 [ν (C-O)].

5.3.1.13. Synthesis of 2-(4-phenylpent-3-en-1-yl)-1,3-dioxolane (3.40)



Preparation of diethyl (3-(1,3-dioxolan-2-yl)propyl)phosphonate (**3.39**): To a solution of diethyl methylphosphonate[41] (3.04 g, 19.98 mmol) in THF (80 mL) at –78 °C, was added *n*-butyllithium (1.57 M in hexane, 19.1 mL) dropwise. The mixture was stirred for 1 h, before 2-(2-bromoethyl)-1,3-dioxolane (2.60 mL, 22.15 mmol) was added. The reaction mixture was then slowly warmed up to 24 °C and stirred for 11 h before it was quenched with saturated aqueous NH$_4$Cl solution. The organic materials were extracted thrice with Et$_2$O. The combined organic layers were washed with brine and dried over MgSO$_4$ before being concentrated *in vacuo*. The crude material including **3.39** was used into the next step without further purification.

Synthesis of 2-(4-phenylpent-3-en-1-yl)-1,3-dioxolane (**3.40**) was done following an adaptation of the procedure described by Rawlinson.[42] To the above residue including diethyl (3-(1,3-dioxolan-2-yl)propyl)phosphonate (**3.39**) in THF (20 mL) at -78 °C, was added *s*-BuLi (1.4 M in cyclohexane, 12.4 ml) dropwise. The solution was allowed to warm to 0 °C then cooled again to -78 °C before addition of acetophenone (2.33 mL, 19.97 mmol) took place. The reaction was then allowed to warm slowly to 24 °C over the period of 2 h, then stirred at 80 °C for another 24 h. The solution was quenched with EtOAc, washed through a short plug of silica with EtOAc and then concentrated in vacuo. Purification by flash column chromatography (silica gel, hexane:EtOAc = 95:5) gave **3.40** (1.35 g, 6.21 mmol) in 31% yield over 2-step with respect to diethyl methylphosphonate as colorless oil.

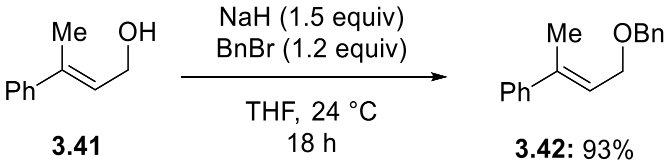
<u>^{1}H NMR (500 MHz, CDCl$_3$):</u> δ(ppm) 7.37 (d, *J* = 7.4 Hz, 2H), 7.29 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.21 (t, *J* = 7.4 1H), 5.78 (t, *J* = 7.2 Hz, 1H), 4.91 (t, *J* = 4.8 Hz, 1H), 3.99 – 3.94 (m, 2H), 3.89 – 3.84 (m, 2H), 2.34 (dt, *J* = 7.4, 7.4 Hz, 2H), 2.04 (s, 3H), 1.83 – 1.79 (m, 2H).

<u>^{13}C NMR (125 MHz, CDCl$_3$):</u> δ(ppm) 143.8, 135.3, 1281, 127.2, 126.5, 125.6, 104.1, 64.9, 33.7, 23.4, 15.7

<u>MS (HRMS ESI):</u> Calcd for $C_{14}H_{19}O_2$ $[M+H]^+$ 219.1385, Found: 219.1377.

<u>IR (neat, cm^{-1}):</u> 1686 [ν (C=C)]. 1140 [ν (C-O)].

5.3.1.14. Synthesis of (*E*)-(4-(benzyloxy)but-2-en-2-yl)benzene (3.42)



To a suspended solution of NaH (60% dispersion in mineral oil; 949.3 mg, 23.73 mmol) in THF (30 mL) was slowly added (*E*)-3-phenylbut-2-en-1-ol (2.36 g, 15.91 mmol) at 0 °C and the mixture was stirred for 1 h. Benzyl bromide (2.30 mL, 19.34 mmol) was then added and the reaction mixture was stirred at 24 °C for 18 h. The reaction mixture was quenched at 0 °C by slow addition of saturated aqueous NH_4Cl solution. The organic materials were then extracted thrice with Et_2O and the combined organic layers were washed with brine and dried over $MgSO_4$. After the filtrate was concentrated *in vacuo*, the resulting crude material was purified by flash column chromatography (silica gel, hexane:EtOAc = 99:1) to give **3.42** (3.33 g, 13.95 mmol) in 93% yield as a colorless oil.

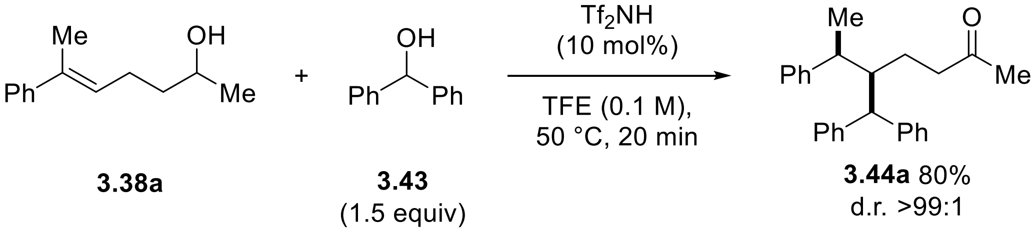
^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm) 7.41 (d, J = 7.2 Hz, 2H), 7.39 – 7.27 (m, 7H), 7.25 (t, = 7.2 Hz, 1H) 5.99 (t, *J* = 6.5 Hz, 1H), 4.57 (s, 2H), 4.23 (d, *J* = 6.5 Hz, 2H), 2.05 (s, 3H)

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 142.9, 138.4, 138.3, 128.4, 128.2, 127.8, 127.6, 127.2, 125.8, 124.3, 72.3, 67.1, 16.2.

MS (HRMS ESI): Calcd for $C_{17}H_{19}O$ $[M+H]^+$ 239.1436, Found: 239.1429.

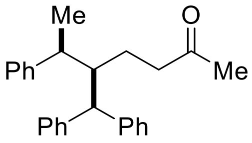
IR (neat, cm^{-1}): 1599 [ν (C=C)]. 1094 [ν (C-O)].

5.3.2. General Procedure of Brønsted acid-catalyzed diastereoselective hydroalkylation of aryl alkenes and Characterization of the products



To a solution of aryl alkene **3.38a** (0.30 mmol) and alcohol **3.43** (0.450 mmol, 1.5 equiv) in 2,2,2,- trifluoroethanol (2.9 mL) was added a solution of trifluoromethanesulfonimide (Tf_2NH) (0.30 M, 0.1 mL, 10 mol%) (the solution was prepared from 36.5 mg of Tf_2NH with 0.43 mL of 2,2,2-trifluoroethanol), and then the reaction mixture was stirred at 50 °C before it was quenched with water. The organic materials were extracted thrice with Et_2O and the combine extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography on silica gel, using the solvent system indicated, to give product **3.44a**.

5.3.2.1 (5*R**,6*S**)-5-benzhydryl-6-phenylheptan-2-one (3.44a)



According to the scheme 5.3.2, (*E*)-6-phenylhept-5-en-2-ol (**3.38a**) (57.0 mg, 0.30 mmol) and diphenylmethanol (**3.43a**) (82.8 mg, 0.450 mmol) gave **3.44a** (85.8 mg, 0.241 mmol) in 80% yield as a colorless oil after purified by flash column chromatography (silica gel, hexane:EtOAc = 95:5) (20 min reaction time). Recrystallization from MeOH:CH_2Cl_2 gave a single crystal, the structure of which could be confirmed by X-ray crystallographic analysis (CCDC-1992396).

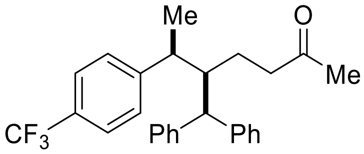
^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.30 – 7.29 (m, 4H), 7.25 – 7.16 (m, 8H), 7.13 – 7.10 (m, 1H), 7.06 (d, *J* = 7.1 Hz, 2H), 3.75 (d, *J* = 10.7 Hz, 1H), 3.03 (qd, *J* = 7.2, 3.8 Hz, 1H), 2.44 – 2.39 (m, 1H), 1.86 – 1.75 (m, 2H), 1.73 (s, 3H), 1.57 – 1.50 (m, 1H), 1.37 – 1.30 (m, 1H), 1.33 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 208.9, 144.2, 143.8, 143.7, 128.7, , 128.6, 128.5, 128.4, 128.3, 127.9, , 126.3, 126.12, 126.10, 55.9. 47.0, 43.0, 40.2, 29.4, 22.8, 19.7.

MS (HRMS ESI): Calcd for $C_{26}H_{29}O$ $[M+H]^+$ 357.2218, Found: 357.2227.

IR (neat, cm^{-1}): 1713 [ν(C=O)].

5.3.2.2 (5*R**,6*S**)-5-benzhydryl-6-(4-(trifluoromethyl)phenyl)heptan-2-one (3.44ba)



According to the scheme 5.3.2, (*E*)-6-(4-(trifluoromethyl)phenyl)hept-5-en-2-ol (**3.38b**) (77.2 mg, 0.299 mmol) and diphenylmethanol (**3.43a**) (83.7 mg, 0.454 mmol) gave **3.44ba** (58.0 mg, 0.137 mmol) in 45% yield as a colorless oil after purified by flash column chromatography (silica gel, hexane:EtOAc = 95:5) (30 min reaction time).

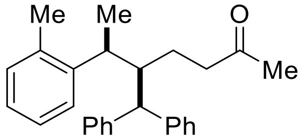
^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.47 (d, *J* = 8.2 Hz, 2H), 7.29 – 7.24 (m, 5H), 7.21 – 7.13(m, 5H), 7.13 (d, *J* = 8.2 Hz, 2H) 3.65 (d, *J* = 11.0 Hz, 1H), 3.14 (qd, *J* = 7.2, 3.4 Hz, 1H), 2.51 – 2.45 (m, 1H), 1.88 – 1.79 (m, 2H), 1.78 (s, 3H), 1.66 – 1.60 (m, 1H), 1.36 (d, *J* = 7.2 Hz, 3H), 1.31 – 1.25 (m, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 208.6, 148.1, 143.7 (overlapped, 2C), 128.8, 128.7, 128.6, 128.53 (q, *J* = 38.0 Hz), 128.50, 128.2, 126.4, 126.3, 124.7 (q, *J* = 4.0 Hz, 1C), 124.4 (q, *J* = 275.0 Hz), 56.1, 46.8, 42.9, 40.1, 29.5, 23.2, 18.7; ^{19}F NMR (376 MHz, CDCl$_3$): δ(ppm) -62.2 (s, 3F).

MS (HRMS ESI): Calcd for $C_{27}H_{28}F_3O$ $[M+H]^+$ 425.2092, Found: 425.2088.

IR (neat, cm^{-1}): 1706 [ν(C=O)], 1240[ν(C-F)].

5.3.2.3 (5*R**,6*S**)-5-benzhydryl-6-(*o*-tolyl)heptan-2-one (3.44ca)



According to the scheme 5.3.2, (*E*)-6-(o-tolyl)hept-5-en-2-ol (**3.38c**) (61.3 mg, 0.300 mmol) and diphenylmethanol (**3.43a**) (83.5 mg, 0.453 mmol) gave **3.44ca** (94.6 mg, 0.255 mmol) in 85% yield as a colorless oil after purified by flash column chromatography (silica gel, hexane:EtOAc = 95:5) (30 min reaction time).

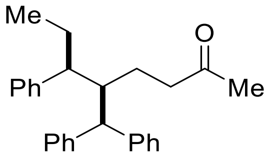
^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 7.33 – 7.27 (m, 4H), 7.24 (d, *J* = 7.0 Hz, 1H)7.21 – 7.18 (m, 3H), 7.13 – 7.09 (m, 4H), 7.04 – 7.03 (m, 2H), 4.10 (d, *J* = 8.0 Hz, 1H), 3.13 (dq, *J* = 7.0, 7.0 Hz, 1H), 2.47 – 2.42 (m, 1H), 1.97 (s, 3H), 1.78 – 1.73 (m, 3H), 1.69 (s, 3H), 1.65 – 1.60 (m, 1H), 1.20 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 208.8, 144.2, 144.1, 142.6, 135.8, 130.4, 129.4, 128.42, 128.41, 128.3, 126.9, 126.4, 126.0, 125.9, 125.7, 54.5, 47.9, 44.0, 37.1, 29.2, 24.4, 20.3, 19.6.

MS (HRMS ESI): Calcd for $C_{27}H_{31}O$ $[M+H]^+$ 371.2375, Found: 371.2375.

IR (neat, cm^{-1}): 1713 [ν(C=O)].

5.3.2.4 (5*R**,6*S**)-5-benzhydryl-6-phenyloctan-2-one (3.44da)



According to the scheme 5.3.2, (*E*)-6-phenyloct-5-en-2-ol (**3.38d**) (61.7 mg, 0.302 mmol) and diphenylmethanol (**3.43a**) (82.8 mg, 0.450 mmol) gave **3.44da** (71.3 mg, 0.192 mmol) in 64% yield as a colorless oil after purified by flash column chromatography (silica gel, hexane:EtOAc = 95:5) (30 min reaction time).

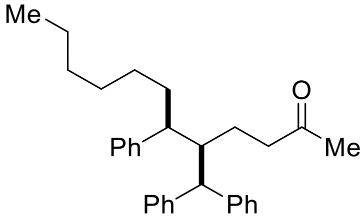
^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 7.35 – 7.31 (m, 4H), 7.25 – 7.17 (m, 8H), 7.12 – 7.09 (m, 1H), 7.01 – 7.00 (m, 2H), 3.62 (d, *J* = 10.9 Hz, 1H), 2.76 (ddd, *J* = 9.2, 6.1, 3.4 Hz, 1H), 2.51 (dddd, *J* = 10.9, 6.6, , 3.45, 3.45 Hz, 1H), 1.95 – 1.76 (m, 4H), 1.74 (s, 3H), 1.52 – 1.46 (m, 1H), 1.32 – 1.26 (m, 1H), 0.78 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 209.0, 144.2, 144.1, 141.8, 129.3, 128.7, 128.6, 128.5, 128.4, 127.8, 126.23, 126.17, 126.15, 56.1, 48.3, 45.0, 43.1, 29.5, 26.7, 22.8, 12.6.

MS (HRMS ESI): Calcd for $C_{27}H_{30}OLi$ $[M+Li]^+$ 377.2457, Found: 377.2454.

IR (neat, cm^{-1}): 1711 [ν(C=O)].

5.3.2.5 (5*R**,6*S**)-5-benzhydryl-6-phenyldodecan-2-one (3.44ea)



According to the scheme 5.3.2, (*E*)-6-phenyldodec-5-en-2-ol (**3.38e**) (77.5 mg, 0.298 mmol) and diphenylmethanol (**3.43a**) (83.1 mg, 0.452 mmol) gave **3.44ea** (78.9 mg, 0.185 mmol) in 62% yield as a colorless oil after purified by flash column chromatography (silica gel, hexane:EtOAc = 95:5) (4 h reaction time).

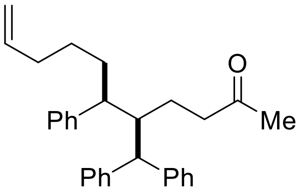
^{1}H NMR (500 MHz, CDCl$_3$): δ 7.35 – 7.31 (m, 4H), 7.24 – 7.17 (m, 8H), 7.11 – 7.08 (m, 1H), 7.01 – 6.99 (m, 2H), 3.60 (d, *J* = 11.1 Hz, 1H), 2.85 (ddd, *J* = 9.1, 5.7, 3.4 Hz, 1H), 2.48 (dddd, *J* = 11.1, 6.6, 3.4, 3.4 Hz, 1H), 1.95 – 1.88 (m, 1H), 1.86 – 1.76 (m, 2H), 1.74 (s, 3H), 1.72 – 1.66 (m, 1H), 1.50 – 1.44 (m, 1H), 1.33 – 1.08 (m, 9H), 0.83 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 209.0, 144.2, 144.1, 142.1, 129.2, 128.7, 128.6, 128.5, 128.4, 127.8, 126.22, 126.17, 126.1, 56.2, 46.2, 45.4, 43.1, 33.9, 31.7, 29.5, 29.3, 27.8, 22.8, 22.6, 14.0.

MS (HRMS ESI): Calcd for $C_{31}H_{39}O$ $[M+H]^+$ 427.3001, Found: 427.3005.

IR (neat, cm^{-1}): 1715 [ν(C=O)].

5.3.2.6 (5*R**,6*S**)-5-benzhydryl-6-phenylundec-10-en-2-one (3.44fa)



According to the scheme 5.3.2, (*E*)-6-phenylundeca-5,10-dien-2-ol (**3.38f**) (73.6 mg, 0.301 mmol) and diphenylmethanol (**3.43a**) (83.5 mg, 0.453 mmol) gave **3.44fa** (68.5 mg, 0.167 mmol) in 56% yield as a colorless oil after purified by flash column chromatography (silica gel, hexane:EtOAc = 96:4) (30 min reaction time).

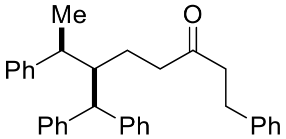
^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 7.35 – 7.31 (m, 4H), 7.25 – 7.17 (m, 8H), 7.12 – 7.09 (m, 1H), 7.01 – 7.00 (m, 2H), 5.71 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 4.94 – 4.88 (m, 2H), 3.60 (d, *J* = 11.1 Hz, 1H), 2.86 (ddd, *J* = 9.2, 5.6, 3.4 Hz, 1H), 2.48 (dddd, *J* = 11.1, 6.6, 3.4, 3.3 Hz, 1H), 1.98 – 1.75 (m, 5H), 1.74 (s, 3H), 1.73 – 1.69 (m, 1H), 1.51 – 1.43 (m, 1H), 1.33 – 1.18 (m, 3H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 209.0, 144.14, 144.07, 141.8, 138.8, 129.2, 128.7, 128.6, 128.5, 128.4, 127.9, 126.3, 126.2 (overlapped, 2C), 114.5, 56.2, 46.1, 45.5, 43.1, 33.7, 33.4, 29.5, 27.1, 22.8.

MS (HRMS ESI): Calcd for $C_{30}H_{35}O$ $[M+H]^+$ 411.2688, Found: 411.2686.

IR (neat, cm^{-1}): 1715 [ν(C=O)], 1633 [ν(C=C)].

5.3.2.7 (6*R**,7*S**)-6-benzhydryl-1,7-diphenyloctan-3-one (3.44ga)



According to the scheme 5.3.2, (*E*)-1,7-diphenyloct-6-en-3-ol (**3.38g**) (84.3 mg, 0.301 mmol) and diphenylmethanol (3.43**a**) (82.8 mg, 0.449 mmol) gave **3.44ga** (106.5 mg, 0.239 mmol) in 79% yield as a colorless oil after purified by flash column chromatography (silica gel, hexane:EtOAc = 95:5) (30 min reaction time).

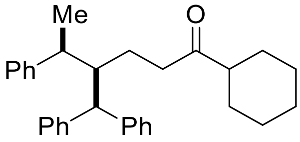
^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 7.30 – 7.21 (m, 8H), 7.19 – 7.16 (m, 7H), 7.11 – 7.04 (m, 5H), 3.73 (d, *J* = 10.7 Hz, 1H), 3.02 (qd, *J* = 7.2, 3.7 Hz, 1H), 2.67 (t, *J* = 7.1, 2H), 2.41 – 2.36 (m, 1H), 2.27 (t, *J* = 7.3, 2H), 1.88 – 1.81 (m, 1H), 1.75 – 1.68 (m, 1H), 1.53 – 1.47 (m, 1H), 1.32 (d, *J* = 7.2 Hz, 3H), 1.31 – 1.26 (m, 1H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 210.0, 144.2, 143.8, 143.6, 141.1, 128.67, 128.66, 128.5 (overlapped, 2C), 128.4, 128.3, 128.2, 127.9, 126.3, 126.13, 126.11, 126.0, 55.9, 47.0, 43.7, 42.1, 40.2, 29.6, 22.8, 19.7.

MS (HRMS ESI): Calcd for $C_{33}H_{35}O$ $[M+H]^+$ 447.2688, Found: 447.2678.

IR (neat, cm^{-1}): 1713 [ν(C=O)].

5.3.2.8 (4*R**,5*S**)-4-benzhydryl-1-cyclohexyl-5-phenylhexan-1-one (3.44ha)



According to the scheme 5.3.2, (*E*)-1-cyclohexyl-5-phenylhex-4-en-1-ol (**3.38h**) (77.5 mg, 0.300 mmol) and diphenylmethanol (**3.43a**) (83.1 mg, 0.451 mmol) gave **3.44ha** (88.9 mg, 0.209 mmol) in 70% yield as a colorless oil after purified by flash column chromatography (silica gel, hexane:EtOAc = 96:4) (30 min reaction time).

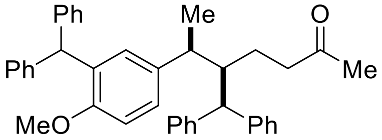
^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 7.304 – 7.295 (m, 4H), 7.25 – 7.15 (m, 8H), 7.13 – 7.09 (m, 1H), 7.06 (d, *J* = 7.1 Hz, 2H), 3.74 (d, *J* = 10.7 Hz, 1H), 3.03 (qd, *J* = 7.2, 3.8 Hz, 1H), 2.43 – 2.38 (m, 1H), 1.89 – 1.72 (m, 3H), 1.65 – 1.63 (m, 2H), 1.58 – 1.52 (m, 2H), 1.51 – 1.43 (m, 2H), 1.33 (d, *J* = 7.2 Hz, 3H), 1.31 – 1.25 (m, 1H), 1.14 – 1.01 (m, 5H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 214.1, 144.3, 143.9, 143.7, 128.72, 128.66, 128.5, 128.4, 128.3, 127.9, 126.2, 126.10, 126.06, 56.0, 50.4, 47.2, 40.3, 40.1, 28.30, 28.25, 25.8, 25.6 (overlapped, 2C), 22.9, 19.7.

MS (HRMS ESI): Calcd for $C_{31}H_{37}O$ $[M+H]^+$ 425.2844, Found: 425.2841.

IR (neat, cm^{-1}): 1712 [ν(C=O)].

5.3.2.9 (5*R**,6*S**)-5-benzhydryl-6-(3-benzhydryl-4-methoxyphenyl)heptan-2-one (3.44ia)



According to the scheme 5.3.2, (*E*)-6-(4-methoxyphenyl)hept-5-en-2-ol (**3.38i**) (66.2 mg, 0.300 mmol) and diphenylmethanol (**3.43a**) (111.3 mg, 0.604 mmol) gave **3.44ia** 109.9 mg, 0.216 mmol) in 72% yield as a white solid after purified by flash column chromatography (silica gel, hexane:EtOAc = 95:5) (30 min reaction time).

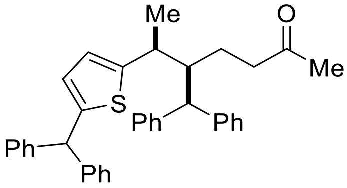
^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 7.36 (t, *J* = 7.6 Hz, 2H), 7.28 – 7.23 (m, 3H), 7.20 – 7.14 (m, 7H), 7.14 – 7.08 (m, 6H), 6.99 – 6.95 (m, 3H), 6.77 (d, *J* = 8.4 Hz, 1H), 6.65 (d, *J* = 2.2 Hz, 1H), 5.97 (s, 1H), 3.69 (s, 3H), 3.54 (d, *J* = 11.3 Hz, 1H), 2.84 (qd, *J* = 7.2, 2.3 Hz, 1H), 2.31 – 2.26 (m, 1H), , 1.74 – 1.68 (m, 1H), 1.71 (s, 3H), 1.65 – 1.58 (m, 1H), 1.43 – 1.36 (m, 1H), 1.22 (d, *J* = 7.2 Hz, 3H), 1.18 – 1.11 (m, 1H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 208.9, 155.5, 144.5, 144.2, 144.0, 143.6, 134.8, 132.0, 131.1, 129.50, 129.45, 128.6, 128.5, 128.4, 128.2, 128.10, 128.07, 126.63, 126.2, 126.1, 126.0, 125.9, 110.3, 55.9, 55.7, 49.3, 46.7, 42.6, 38.8, 29.4, 22.4, 20.0.

MS (HRMS ESI): Calcd for $C_{40}H_{41}O_2$ $[M+H]^+$ 553.3107, Found: 553.3114.

IR (neat, cm^{-1}): 1710 [ν(C=O)], 1030 [ν(C-O)].

5.3.2.10 (5*S**,6*S**)-5-benzhydryl-6-(5-benzhydrylthiophen-2-yl)heptan-2-one (3.44ja)



According to the scheme 5.3.2, (*E*)-6-(thiophen-2-yl)hept-5-en-2-ol (**3.38j**) (59.3 mg, 0.302 mmol) and diphenylmethanol (**3.43a**) (111.2 mg, 0.604 mmol) gave **3.44ja** (95.7 mg, 0.181 mmol) in 60% yield as a colorless oil after purified by flash column chromatography (silica gel, hexane:EtOAc = 95:5) (30 min reaction time).

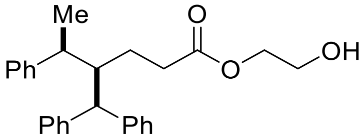
^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.32 – 7.26 (m, 7H), 7.25 – 7.20 (m, 11H), 7.15 - 7.11 (m, 2H), 6.46 (d, *J* = 3.5 Hz, 1H), 6.43 (d, *J* = 3.5 Hz, 1H), 3.85 (d, *J* = 11.1 Hz, 1H), 3.18 (qd, *J* = 7.2, 3.0 Hz, 1H), 2.38 (dtd, *J* = 11.1, 4.9, 3.0 Hz, 1H) , 1.93 – 1.86 (m, 1), 1.80 – 1.73 (m, 1H), 1.78 (s, 3H), 1.69 – 1.64 (m, 1H), 1.44 – 1.37 (m, 1H), 1.33 (d, *J* = 7.2 Hz, 3H),

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 208.7, 146.1, 145.2, 143.84, 143.79, 143.77, 128.8, 128.6, 128.51, 128.48, 128.32, 128.25, 126.6, 126.3, 126.2, 125.7, 124.0, 56.0, 52.3, 46.9, 42.9, 36.6, 29.5, 23.1, 21.2,

MS (HRMS ESI): Calcd for $C_{37}H_{37}OS$ $[M+H]^+$ 529.2565, Found: 529.2562.

IR (neat, cm^{-1}): 1712 [ν(C=O)].

5.3.2.11. 2-Hydroxyethyl (4*R**,5*S**)-4-benzhydryl-5-phenylhexanoate (3.45)



According to the scheme 5.3.2, (*E*)-2-(4-phenylpent-3-en-1-yl)-1,3-dioxolane (**3.40**) (65.3 mg, 0.299 mmol) and diphenylmethanol (**3.43a**) (82.8 mg, 0.449 mmol) gave **3.45** (63.9 mg, 0.159 mmol) in 53% yield as a colorless oil after purified by flash column chromatography (silica gel, hexane:EtOAc = 80:20) (2 h reaction time).

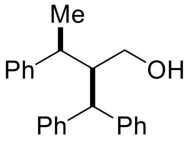
^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.30 – 7.29 (m, 3H), 7.26 – 7.15 (m, 9H), 7.14 – 7.10 (m, 1H), 7.06 (d, *J* = 7.0Hz, 2H), 4.07 – 4.05 (m, 2H), 3.75 (d, *J* = 10.8 Hz, 1H), 3.72 – 3.70 (m, 2H), 3.06 (qd, *J* = 7.2, 3.6 Hz, 1H), 2.48 (dddd, *J* = 10.8, 6.6, 3.6, 3.6 Hz, 1H), 1.92 – 1.83 (m, 1H), 1.77 – 1.69 (m, 1H), 1.63 – 1.55 (m, 1H), 1.45 – 1.37 (m, 1H), 1.34 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 173.8, 144.2, 143.7, 143.6, 128.7, 128.6, 128.5, 128.4, 128.3, 127.9, 126.3, 126.15, 126.13, 65.7, 61.2, 56.0, 47.0, 40.1, 33.4, 24.3, 19.5.

MS (HRMS ESI): Calcd for $C_{27}H_{31}O_3$ $[M+H]^+$ 403.2273, Found: 403.2268.

IR (neat, cm^{-1}): 3435 [ν(O-H)], 1732 [ν(C=O)].

5.3.2.12. (2*R**,3*S**)-2-benzhydryl-3-phenylbutan-1-ol (3.46)



According to the scheme 5.3.2, (*E*)-(4-(benzyloxy)but-2-en-2-yl)benzene (**3.42**) (71.6 mg, 0.300 mmol) and diphenylmethanol (**3.43a**) (83.2 mg, 0.452 mmol) gave **3.46** (25.1 mg, 0.079 mmol) in 26% yield as a colorless oil after purified by flash column chromatography (silica gel, hexane:EtOAc = 91:9) (20 min reaction time).

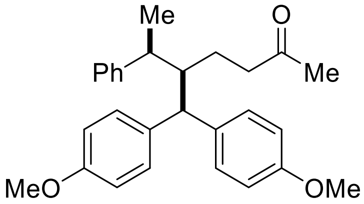
^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.39 (d, *J* = 7.7 Hz, 2H), 7.34 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.30 – 7.18 (m, 8H), 7.15 – 7.09 (m, 3H), 3.92 (d, *J* = 11.5 Hz, 1H), 3.55 (dd, *J* = 12.0, 4.3 Hz, 1H), 3.52 (dd, *J* = 12.0, 4.3 Hz, 1H), 3.07 (qd, *J* = 7.3, 3.9 Hz, 1H), 2.63 (dddd, *J* = 11.5, 4.3, 4.3, 3.9 Hz, 1H), 1.40 (d, *J* = 7.3 Hz, 3H), 0.57 (brs, 1H).

<u>^{13}C NMR (100 MHz, CDCl$_3$):</u> δ(ppm) 143.9, 143.7 (overlapped, 2C), 128.9, 128.7, 128.30, 128.28, 128.2, 128.1, 126.44, 126.41, 126.3, 61.9, 53.5, 50.4, 39.0, 20.4.

<u>MS (HRMS ESI):</u> Calcd for $C_{23}H_{25}O$ $[M+H]^+$ 317.1905, Found: 317.1906.

<u>IR (neat, cm^{-1}):</u> 3370 [ν(O-H)].

5.3.2.13. (5*R**,6*S**)-5-(bis(4-methoxyphenyl)methyl)-6-phenylheptan-2-one (3.44ab)



According to the scheme 5.3.2, (*E*)-6-phenylhept-5-en-2-ol (**3.38a**) (57.0 mg, 0.300 mmol) and bis(4-methoxyphenyl)methanol (**3.43b**) (109.5 mg, 0.448 mmol) gave **3.44ab** (69.7 mg, 0.167 mmol) in 56% yield as a colorless oil after purified by flash column chromatography (silica gel, hexane:EtOAc = 97:3) (30 min reaction time).

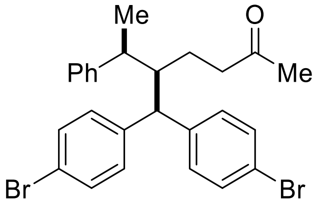
<u>^{1}H NMR (500 MHz, CDCl$_3$):</u> δ(ppm) 7.23 (d, *J* = 7.3 Hz, 2H), 7.19 – 7.16 (m, 3H), 7.10 (d, *J* = 8.7 Hz, 2H), 7.06 (d, *J* = 7.3 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.75 (d, *J* = 8.7 Hz, 2H), 3.78 (s, 3H), 3.73 (s, 3H), 3.67 (d, *J* = 10.5 Hz, 1H), 3.01 (qd, *J* = 7.2, 4.1 Hz, 1H), 2.34 – 2.29 (m, 1H), 1.82 – 1.77 (m, 1H), 1.76 (s, 3H), 1.62 – 1.57 (m, 2H), 1.40 – 1.34 (m, 1H), 1.32 (d, *J* = 7.2 Hz, 3H).

<u>^{13}C NMR (125 MHz, CDCl$_3$):</u> δ(ppm) 209.0, 157.9, 157.7, 143.9, 136.7, 136.3, 129.4, 129.0, 128.4, 127.9, 126.0, 114.0, 113.8, 55.2, 55.1, 53.9, 47.3, 43.1, 40.2, 29.5, 22.9, 19.6.

<u>MS (HRMS ESI):</u> Calcd for $C_{28}H_{33}O_3$ $[M+H]^+$ 417.2430, Found: 417.2432.

IR (neat, cm^{-1}): 1711 [ν(C=O)].

5.3.2.14. (5*R**,6*S**)-5-(bis(4-bromophenyl)methyl)-6-phenylheptan-2-one (3.44ac)



According to the scheme 5.3.2, (*E*)-6-phenylhept-5-en-2-ol (**3.38a**) (57.6 mg, 0.303 mmol) and bis(4-bromophenyl)methanol (**3.43c**) (153.7 mg, 0.449 mmol) gave **3.44ac** (95.8 mg, 0.186 mmol) in 62% yield as a colorless oil after purified by flash column chromatography (silica gel, hexane:EtOAc = 96:4) (30 min reaction time).

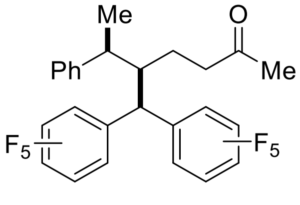
^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.38 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), , 7.25 – 7.18 (m, 3H), 7.09 (d, *J* = 8.3 Hz, 2H), 7.07 (d, *J* = 8.3 Hz, 2H), 7.00 (d, *J* = 6.6 Hz, 2H), 3.69 (d, *J* = 10.6 Hz, 1H), 2.96 (qd, *J* = 7.2, 3.5 Hz, 1H), 2.42 – 2.36 (m, 1H), 1.90 – 1.84 (m, 1H), 1.82 (s, 3H), 1.80 – 1.65 (m, 2H), 1.41 – 1.35 (m, 1H), 1.32 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 208.2, 143.5, 142.7, 142.3, 131.8, 131.7, 130.2, 129.8, 128.2, 128.1, 126.3, 120.4, 120.2, 54.6, 46.9, 42.8, 40.3, 29.6, 23.0, 19.0.

MS (HRMS ESI): Calcd for $C_{26}H_{27}O^{79}Br_2$ $[M+H]^+$ 513.0429, Found: 513.0435.

IR (neat, cm^{-1}): 1713 [ν(C=O)].

5.3.2.15. (5*R**,6*S**)-5-(bis(perfluorophenyl)methyl)-6-phenylheptan-2-one (3.44ad)



According to the scheme 5.3.2, (*E*)-6-phenylhept-5-en-2-ol (**3.38a**) (57.4 mg, 0.302 mmol) and bis(perfluorophenyl))methanol (**3.43d**) (164.3 mg, 0.451 mmol) gave **3.44ad** (82.7 mg, 0.154 mmol) in 51% yield as a colorless oil after purified by flash column chromatography (silica gel, hexane:EtOAc = 95:5) (30 min reaction time).

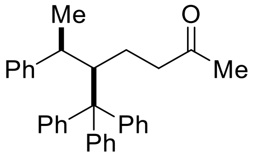
^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.28 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.19 – 7.16 (m, 3H), 6.50 (d, *J* = 10.0 Hz, 1H), 3.50 – 3.47 (m, 1H), 2.68 (dq, *J* = 6.9, 6.9 Hz, 1H), 2.39 – 2.36 (m, 2H), 2.08 (s, 3H), 1.58 – 1.52 (m, 1H~~3H~~), 1.45 – 1.40 (m, 1H), 1.24 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 209.2, 147.2, 144.7 (dm, *J* = 237 Hz, 4C), 141.5 (dm, *J* = 254 Hz, 2C), 137.8 (dm, *J* = 249 Hz, 4C), 128.4, 126.9, 126.0, 114.0 (m, 2C), 61.0, 43.8, 39.9, 37.8, 29.7, 22.2, 22.1; ^{19}F NMR (376 MHz, $CDCl_3$): δ(ppm) -143.1 (d, *J* = 15.0 Hz, 4F), -152.7 (t, *J* = 18.8 Hz, 2F), -160.7 (dd, *J* = 18.8, 15.0 Hz, 4F).

MS (HRMS ESI): Calcd for $C_{26}H_{19}OF_{10}$ $[M+H]^+$ 537.1276, Found: 537.1271.

IR (neat, cm^{-1}): 1717 [ν(C=O)], 1358 [ν (C-F)].

5.3.2.16. (5*R**,6*S**)-6-phenyl-5-tritylheptan-2-one (3.44ae)



According to the scheme 5.3.2, (*E*)-6-phenylhept-5-en-2-ol (**3.38a**) (57.1 mg, 0.300 mmol) and triphenylmethanol (**3.43e**) (117.4 mg, 0.451 mmol) gave **3.44ae** (69.2 mg, 0.160 mmol) in 53% yield as a colorless oil after purified by flash column chromatography (silica gel, hexane:EtOAc = 95:5) (30 min reaction time).

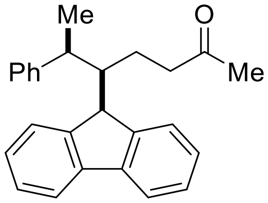
^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 7.31 – 7.23 (m, 17H), 7.18 – 7.16 (m, 3H), 2.92 – 2.90 (m, 1H), 2.67 (dq, *J* = 6.9, 6.9 Hz, 1H), 2.37 – 2.34 (m, 2H), 2.06 (s, 3H), 1.58 – 1.52 (m, 1H), 1.46 – 1.40 (m, 1H), 1.23 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 209.2, 147.3, 146.9, 128.4, 127.98, 127.95, 127.3, 127.0, 126.0, 82.0, 43.8, 39.9, 37.8, 29.8, 22.3, 22.1.

MS (HRMS ESI): Calcd for $C_{32}H_{33}O$ $[M+H]^+$ 433.2531, Found: 433.2534.

IR (neat, cm^{-1}): 1717 [ν(C=O)].

5.3.2.17. (5*R**,6*S**)-5-(9H-fluoren-9-yl)-6-phenylheptan-2-one (3.44af)



According to the scheme 5.3.2, (*E*)-6-phenylhept-5-en-2-ol (**3.38a**) (57.0 mg, 0.300 mmol) and fluoren-9-ol (**3.43f**) (82.3 mg, 0.452 mmol) gave **3.44af** (55.5 mg, 0.157 mmol) in 52% yield as a colorless oil after purified by flash column chromatography (silica gel, hexane:EtOAc = 95:5) (30 min reaction time).

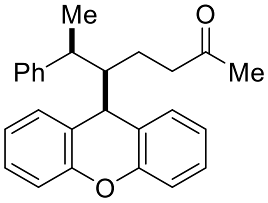
1H NMR (500 MHz, CDCl3): δ(ppm) 7.64 – 7.62 (m, 4H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.32 – 7.25 (m, 4H), 7.19 – 7.15 (m, 3H), 5.56 (d, *J* = 9.5 Hz, 1H), 2.67 (dq, *J* = 6.9, 6.9 Hz, 1H), 2.37 – 2.34 (m, 2H), 2.06 (s, 3H), 1.57 – 1.50 (m, 2H), 1.45 – 1.39 (m, 1H), 1.23 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 209.2, 147.3, 145.7, 140.0, 129.1, 128.4, 127.8, 127.0, 126.0, 125.2, 120.0, 75.2, 43.8, 39.9, 37.8, 29.8, 22.3, 22.1.

MS (HRMS ESI): Calcd for $C_{26}H_{27}O$ $[M+H]^+$ 355.2062, Found: 355.2063.

IR (neat, cm^{-1}): 1714 [ν (C=O)].

5.3.2.18. (5*R**,6*S**)-6-phenyl-5-(9H-xanthen-9-yl)heptan-2-one (3.44ag)



According to the scheme 5.3.2, (*E*)-6-phenylhept-5-en-2-ol (**3.38a**) (57.0 mg, 0.300 mmol) and xanthydrol (**3.43g**) (89.0 mg, 0.449 mmol) gave **3.44ag** (77.8 mg, 0.210 mmol) in 70% yield (ca. 90% purity with inseparable minor impurities) as a colorless oil after purified by flash column chromatography (silica gel, hexane:EtOAc = 94:6) (30 min reaction time).

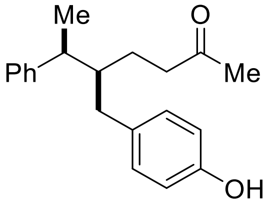
^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 7.60 – 7.59 (m, 2H), 7.37 – 7.33 (m, 2H), 7.28 (t, *J* = 7.7 Hz, 2H), 7.18 – 7.15 (m, 7H), 5.82 (d, *J* = 8.4 Hz, 1H), 2.67 (dq, *J* = 6.9, 6.9 Hz, 1H), 2.37 – 2.35 (m, 2H), 2.07 (s, 3H), 1.58 – 1.52 (m, 2~~3~~H), 1.46 – 1.40 (m, 1H), 1.23 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 209.2, 150.7, 147.2, 129.7, 129.6, 128.4, 127.0, 126.0, 123.5, 122.7, 116.7, 63.7. 43.8, 39.9, 37.8, 29.8, 22.3, 22.1.

MS (HRMS ESI): Calcd for $C_{26}H_{27}O_2$ [M+H]$^+$ 371.2011, Found: 371.2014.

IR (neat, cm^{-1}): 1715 [ν(C=O)].

5.3.2.19. (5*S**,6*S**)-5-(4-hydroxybenzyl)-6-phenylheptan-2-one (3.44ah)



According to the scheme 5.3.2, (*E*)-6-phenylhept-5-en-2-ol (**3.38a**) (57.2 mg, 0.301 mmol) and 4-hydroxybenzyl alcohol (**3.48**) (56.1 mg, 0.452 mmol) gave **3.44ah** (41.8 mg, 0.141 mmol) in 47% yield as a colorless oil after purified by flash column chromatography (silica gel, hexane:EtOAc = 80:20) (23 h reaction time).

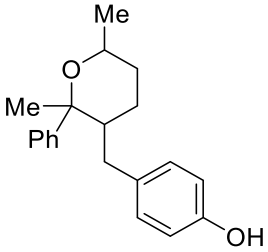
^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 7.31 (t, *J* = 7.6 Hz, 2H), 7.22 – 7.19 (m, 3H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 2H), 5.04 (s, 1H), 2.83 (dq, *J* = 7.1, 7.1 Hz, 1H), 2.64 (dd, *J* = 13.9, 4.4 Hz, 1H), 2.35 – 2.21 (m, 3H), 1.95 (s, 3H), 1.86 – 1.79 (m, 1H), 1.61 – 1.55 (m, 1H), 1.46 – 1.40 (m, 1H), 1.29 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 209.6, 153.7, 145.7, 133.2, 130.0, 128.2, 127.8, 126.0, 115.2, 46.0, 41.5, 41.4, 35.6, 29.6, 25.0, 16.5.

MS (HRMS ESI): Calcd for $C_{20}H_{25}O_2$ $[M+H]^+$ 297.1855, Found: 297.1857.

IR (neat, cm^{-1}): 3352 [ν(O-H)], 1701 [ν(C=O)].

5.3.2.20. 4-((2,6-dimethyl-2-phenyltetrahydro-2H-pyran-3-yl)methyl)phenol (3.49)



3.49 was formed as a side product (29.3 mg, 0.099 mmol, 33% yield) as a colorless oil after purified by flash column chromatography (silica gel, hexane:EtOAc = 92:8) in the formation of **3.44ah** (see *5.3.2.19*).

^{1}H NMR (500 MHz, CDCl$_3$): 7.62 (d, *J* = 7.4 Hz, 2H), 7.36 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.26 (t, *J* = 7.4 Hz, 1H), 6.68 (d, *J* = 8.6 Hz, 2H), 6.62 (d, *J* = 8.6 Hz, 2H), 4.66 (brs, 1H), 3.90 (dqd, *J*

= 12.0, 6.0, 2.3 Hz, 1H), 2.40 (dd, *J* = 12.9, 2.1 Hz, 1H), 1.90 (dd, *J* = 12.9, 11.6 Hz, 1H), 1.78 (dddd, J = 11.6, 11.6, 3.4, 2.1 Hz, 1H), 1.68 – 1.59 (m, 2H), 1.62 (s, 3H), 1.45 – 1.34 (m, 1H), 1.31 – 1.22 (m, 1H), 1.18 (d, *J* = 6.0 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 153.6, 147.2, 133.1, 129.9, 127.9, 127.0, 126.3, 115.0, 78.9, 66.4, 48.8, 36.6, 34.2, 25.1, 22.7, 15.0.

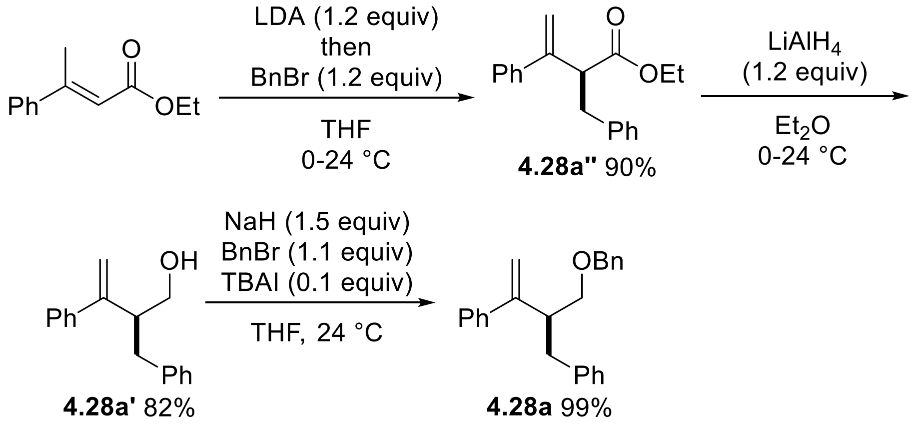
MS (HRMS ESI): Calcd for $C_{20}H_{25}O_2$ $[M+H]^+$ 297.1855, Found: 297.1856.

IR (neat, cm^{-1}): 3410 [ν(O-H)], 1186 [ν(C-O)].

5.4 Diastereoselective Intramolecular Hydride Transfer Triggered by Electrophilic Halogenation (Chapter 4)

5.4.1 Synthesis and characterization of the starting materials

5.4.1.1. Synthesis of (*S**)-(2-((benzyloxy)methyl)but-3-ene-1,3-diyl)dibenzene (4.28a)



Synthesis of ethyl (*S)-2-benzyl-3-phenylbut-3-enoate (4.28a'')**[43]: To a solution of diisopropylamine (3.6 mL, 25.7 mmol) in THF (60 mL) was added *n*-BuLi (1.5 M in hexane, 16.0 mL, 24.0 mmol) at 0 °C, and the reaction mixture was stirred for 30 min at the same temperature. A solution of ethyl (*E*)-3-phenylbut-2-enoate (3.81 g, 20.0 mmol) in THF (8 mL) was added at the same temperature and stirred for 1 h before dropwise addition of benzyl bromide (3.56 mL, 29.974 mmol). The reaction mixture was then slowly warm up to 24 °C and stirred for 2 h. The reaction was then quenched with saturated aqueous NH_4Cl solution and the organic materials were extracted thrice with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$ before being concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, hexane:EtOAc = 99:1) to give **4.28a''** in 90% yield (5.08 g, 18.12 mmol) as pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.42–7.37 (m, 2H), 7.37–7.30 (m, 3H), 7.37–7.25 (m, 2H), 7.21–7.18 (m, 3H), 5.45 (s, 1H), 5.38 (s, 1H), 4.15–4.03 (m, 2H), 3.86 (dd, *J* = 9.2, 5.6 Hz, 1H), 3.26 (dd, *J* = 13.8, 9.2 Hz, 1H), 2.99 (dd, *J* = 13.8, 5.6 Hz, 1H), 1.13 (dd, *J* = 7.2, 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 173.2, 146.6, 141.2, 139.3, 128.9, 128.32, 128.30, 127.7, 126.6, 126.3, 115.0, 60.7, 52.4, 38.2, 14.0.

Synthesis of (*S)-2-benzyl-3-phenylbut-3-en-1-ol (4.28a')** [1]**:** To a suspended solution of $LiAlH_4$ (821.2 mg, 21.64 mmol) in Et_2O (50 mL) was slowly added **4.28a''** (5.080 g, 18.12 mmol) at 0 °C and the reaction mixture was stirred at 24 °C for 1 h. The reaction was then quenched carefully with 15% NaOH solution at 0 °C and the organic materials were extracted thrice using Et_2O. The combined extracts were washed with brine and dried over $MgSO_4$. The volatile materials were removed under reduced pressure to give the crude material, which was purified by flash column chromatography (silica gel, hexane:EtOAc = 95:5) to give **4.28a'** in 82% yield (3.54 g, 14.86 mmol) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.35–7.23 (m, 7H), 7.21–7.12 (m, 3H), 5.40 (d, *J* = 0.8 Hz, 1H), 5.16 (s, 1H), 3.64 (dd, *J* = 10.8, 6.0 Hz, 1H), 3.58 (dd, *J* = 10.8, 4.8 Hz, 1H), 3.13–3.07 (m, 1H), 2.94–2.79 (m, 2H), 1.57 (s, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 149.7, 142.2, 134.0, 129.1, 128.30, 128,27, 127.5, 126.6, 126.1, 114.0, 63.8, 48.1, 37.1.

Synthesis of (*S)-(2-((benzyloxy)methyl)but-3-ene-1,3-diyl)dibenzene (4.28a):** To a suspended solution of NaH (60% dispersion in mineral oil; 880 mg, 22.0 mmol) in THF (40 mL) was slowly added **4.28a'** (3.52 g, 14.78 mmol) in THF (10 mL) at 0 °C and the mixture was stirred for 1 h. Benzyl bromide (2.1 mL, 17.7 mmol) and tetrabutylammonium iodide (TBAI) (522.0 mg, 1.41 mmol) were then added and the reaction mixture was stirred at 24 °C for 20 h. The reaction mixture was quenched at 0 °C by slow addition of saturated aqueous NH_4Cl solution. The organic materials were then extracted thrice with Et_2O and the combined organic layers were washed with brine and dried over $MgSO_4$. After the filtrate was concentrated *in vacuo*, the resulting crude material was purified by flash column chromatography (silica gel, hexane:EtOAc = 99:1) to give **4.28a** (4.80 g, 14.62 mmol) in 99% yield as white solid.

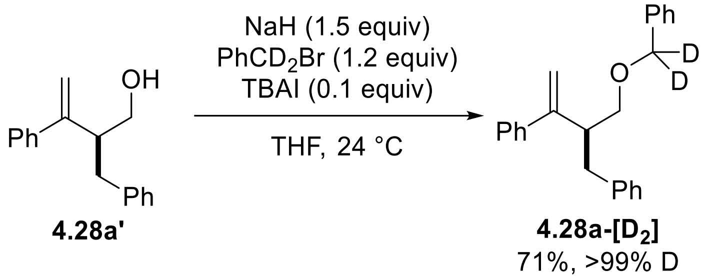
^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.38–7.20 (m, 13H), 7.17–7.14 (m, 2H), 5.30 (s, 1H), 5.10 (s, 1H), 4.47 (s, 2H), 3.52 (dd, *J* = 9.2, 5.6 Hz, 1H), 3.46 (dd, *J* = 9.2, 6.4 Hz, 1H), 3.26–3.11 (m, 1H), 2.97 (dd, *J* = 13.6, 6.8 Hz, 1H), 2.86 (dd, *J* = 13.6, 7.2 Hz, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 149.7, 142.7, 140.2, 138.5, 129.3, 128.3, 128.2, 128.1, 127.6,127.4, 127.2, 126.7, 125.8, 113.8, 73.0, 72.1, 45.9, 37.3.

MS (HRMS ESI): Calcd for $C_{24}H_{25}O$ $[M+H]^+$ 329.1905, Found: 329.1906.

IR (neat, cm^{-1}): 3028 [ν(H–C=C)], 1602 [ν(C=C)], 1171 [ν(C-O)], 1087 [ν(C-O)].

5.4.1.2. Synthesis of (*S**)-(2-((phenylmethoxy-*d*$_2$)methyl)but-3-ene-1,3-diyl)dibenzene (4.28a-[D$_2$])



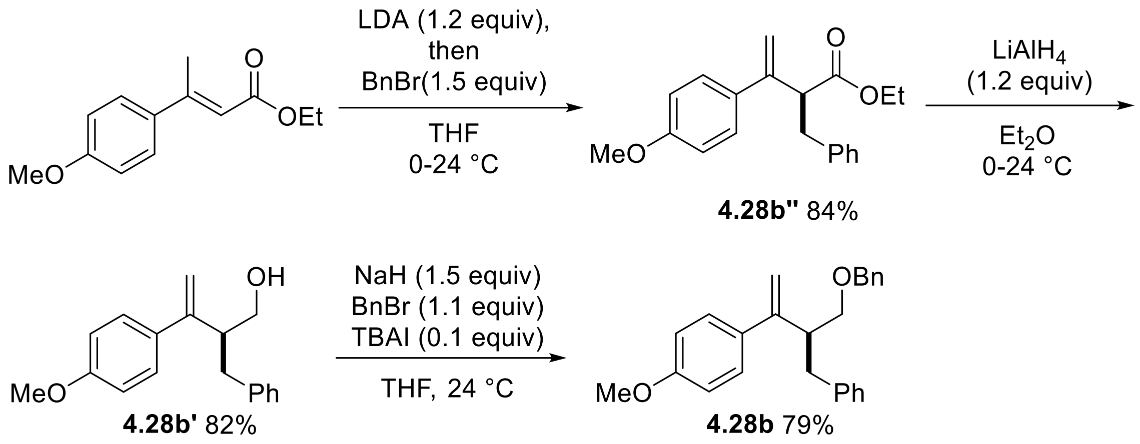
To a suspension of NaH (60% dispersion in mineral oil; 102.3 mg, 2.558 mmol) in THF (4 mL) was slowly added a solution of **4.28a’** (385.2 mg, 1.616 mmol) in THF (1.5 mL) at 0 °C and the mixture was stirred for 1h. Benzyl bromide-α,α-d$_2$ (336.6 mg, 1.942 mmol) and tetrabutylammonium iodide (TBAI) (59.2 mg, 0.184 mmol) were then added and the reaction mixture was stirred at 24 °C for 21 h. The reaction mixture was quenched at 0 °C by slow addition of saturated aqueous NH_4Cl solution. The organic materials were then extracted thrice with Et_2O and the combined organic layers were washed with brine and dried over $MgSO_4$. After the filtrate was concentrated *in vacuo*, the resulting crude material was purified by flash column chromatography (silica gel, hexane:EtOAc = 99:1) to give **4.28a-[D$_2$]** in >99% deuterium incorporation (377.1 mg, 1.141 mmol) in 71% yield as colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.38–7.18 (m, 12H), 7.14–7.16 (m, 3H), 5.30 (s, 1H), 5.10 (s, 1H), 3.51 (dd, *J* = 9.2, 5.6 Hz, 1H), 3.45 (dd, *J* = 9.2, 6.4 Hz, 1H), 3.23–3.13 (m, 1H), 2.97 (dd, *J* = 13.8, 6.8 Hz, 1H), 2.85 (dd, *J* = 13.8, 7.2 Hz, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 149.8, 142.7, 140.2, 138.4, 129.3, 128.3, 128.2, 128.1, 127.6, 127.5, 127.2, 126.7, 125.8, 113.8, 72.3 (tt, $J_{C\text{-}D}$ = 21.5, 21.5 Hz), 72.1, 45.9, 37.4.

MS (HRMS ESI): Calcd for $C_{24}H_{23}D_2O$ $[M+H]^+$ 331.2031, Found: 331.2034.

5.4.1.3. Synthesis of (*S**)-1-(3-benzyl-4-(benzyloxy)but-1-en-2-yl)-4-methoxybenzene (4.28b)



Synthesis of ethyl (*S)-2-benzyl-3-(4-methoxyphenyl)but-3-enoate (1b''):** It was synthesized using ethyl (*E*)-3-(4-methoxyphenyl)but-2-enoate[44] (1.54 g, 7.00 mmol) and benzyl bromide (1.25 mL, 10.51 mmol) by following the procedure described in section 5.4.1.1. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1) gave **4.28b''** (1.82 g, 5.88 mmol) in 84% yield as yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.32–7.31 (m, 2H), 7.28–7.21 (m, 2H), 7.21–7.15 (m, 3H), 6.86–6.85 (m, 2H), 5.36 (s, 1H), 5.26 (s, 1H), 4.10–4.01 (m, 2H), 3.87–3.73 (m, 1H), 3.81 (s, 3H), 3.22 (dd, *J* = 14.0, 9.5 Hz, 1H), 2.95 (dd, *J* = 14.0, 5.5 Hz, 1H), 1.10 (dd, *J* = 7.5, 7.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 173.2, 159.2, 145.9, 139.4, 133.5, 128.9, 128.3, 127.6, 126.3, 113.6, 113.5, 60.6, 55.2, 52.5, 38.1, 14.0.

MS (HRMS ESI): Calcd for $C_{20}H_{23}O_3$ $[M+H]^+$ 311.1647, Found: 311.1650.

Synthesis of (*S)-2-benzyl-3-(4-methoxyphenyl)but-3-en-1-ol (4.28b'):** It was synthesized using **4.28b''** (1.39 g, 4.47 mmol) and $LiAlH_4$ (206.7 mg, 5.45 mmol) by following the procedure described in section 5.4.1.1. Purification by flash column chromatography (silica gel, hexane:EtOAc = 92:8) gave **4.28b’** (984.1 mg, 3.67 mmol) in 82% yield as colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 7.32–7.23 (m, 4H), 7.23–7.15 (m, 3H), 6.86–6.84 (m, 2H), 5.37 (s, 1H), 5.10 (s, 1H), 3.80 (s, 3H), 3.67–3.62 (m, 1H), 3.61–3.57 (m, 1H), 3.11–3.06 (m, 1H), 2.94–2.79 (m, 2H), 1.47–1.45 (m, 1H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 159.1, 148.9, 140.1, 134.5, 129.1, 128.3, 127.7, 126.0, 113.7, 112.7, 63.8, 55.2, 48.1, 37.2.

MS (HRMS ESI): Calcd for $C_{18}H_{21}O_2$ $[M+H]^+$ 269.1542, Found: 269.1534.

Synthesis of (*S)-1-(3-benzyl-4-(benzyloxy)but-1-en-2-yl)-4-methoxybenzene (4.28b):** It was synthesized using **4.28b’** (775.9 mg, 2.891 mmol) and benzyl bromide (0.42 mL, 3.53 mmol) by following the procedure described in section 5.4.1.1. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1) gave **4.28b** (819.0 mg, 2.285 mmol) in 79% yield as colorless oil.

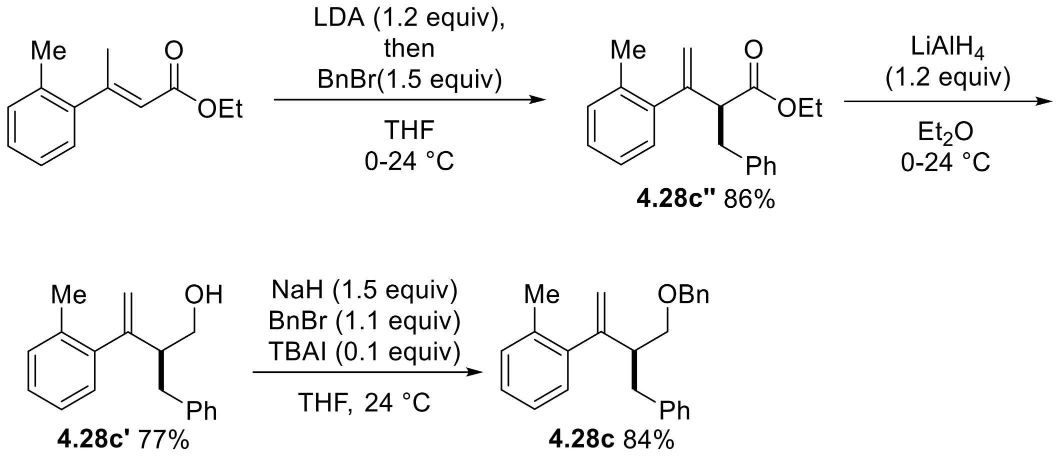
^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.39–7.26 (m, 5H), 7.26–7.18 (m, 4H), 7.17–7.4 (m, 3H), 6.88–6.77 (m, 2H), 5.25 (d, *J* = 1.0 Hz, 1H), 5.02 (s, 1H), 4.47 (s, 2H), 3.79 (s, 3H), 3.52 (dd, *J* = 9.2, 5.6 Hz, 1H), 3.45 (dd, *J* = 9.2, 6.4 Hz, 1H), 3.21–3.09 (m, 1H), 2.96 (dd, *J* = 13.6, 6.8 Hz, 1H), 2.85 (dd, *J* = 13.6, 7.2 Hz, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 158.9, 149.1, 140.3, 138.5, 135.1, 129.3, 128.3, 128.1, 127.8, 127.6, 127.4, 125.8, 113.5, 112.6, 73.0, 72.2, 55.2, 45.9, 37.4.

MS (HRMS ESI): Calcd for $C_{25}H_{27}O_2$ $[M+H]^+$ 359.2011, Found: 359.2000.

IR (neat, cm^{-1}): 3026 [ν(H–C=C)], 1609 [ν(C=C)], 1179[ν(C-O)], 1114 [ν(C-O)].

5.4.1.3. Synthesis of (*S**)-1-(3-benzyl-4-(benzyloxy)but-1-en-2-yl)-2-methylbenzene (4.28c)



Synthesis of ethyl (*S)-2-benzyl-3-(o-tolyl)but-3-enoate (4.28c''):** It was synthesized using ethyl (*E*)-3-(o-tolyl)but-2-enoate[45] (1.42 g, 6.96 mmol) and benzyl bromide (1.25 mL, 10.51 mmol) by following the procedure described in section 2.1. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1) gave **4.28c''** (1.78 g, 6.05 mmol) in 86% yield as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.25–7.23 (m, 2H), 7.20–7.10 (m, 6H), 7.07–7.05 (m, 1H), 5.51 (s, 1H), 5.12 (s, 1H), 4.07–3.94 (m, 2H), 3.58 (dd, *J* = 10.4, 4.4 Hz, 1H), 3.18 (dd, *J* = 14.0, 10.4 Hz, 1H), 2.97 (dd, *J* = 14.0, 4.4 Hz, 1H), 2.28 (s, 3H), 1.07 (dd, *J* = 7.2, 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 172.7, 146.7, 141.8, 139.2, 135.0, 130.2, 128.8, 128.6, 128.3, 127.2, 126.3, 125.4, 116.1, 60.5, 54.2, 37.6, 19.8, 13.9.

MS (HRMS ESI): Calcd for $C_{20}H_{23}O_2$ $[M+H]^+$ 295.1698, Found: 295.1707.

Synthesis of (*S)-2-benzyl-3-(o-tolyl)but-3-en-1-ol (4.28c'):** It was synthesized using **4.28c''** (1.78 g, 6.05 mmol) and $LiAlH_4$ (278.0 mg, 7.325 mmol) by following the procedure described in section 5.4.1.1. Purification by flash column chromatography (silica gel, hexane:EtOAc = 92:8) gave **4.28c'** (1.18 g, 4.66 mmol) in 77% yield as colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.28–7.25 (m, 2H), 7.21–7.15 (m, 5H), 7.15–7.10 (m, 1H), 7.03–7.01 (m, 1H), 5.36 (s, 1H), 5.13 (s, 1H), 3.59–3.53 (m, 1H), 3.53–3.47 (m, 1H), 2.93 (dd, *J* = 13.5, 5.5 Hz, 1H), 2.84 (dd, *J* = 13.5, 9.5 Hz, 1H), 2.79–2.94 (m, 1H), 2.25 (s, 3H), 1.50 (brs, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 150.1, 142.7, 140.2, 135.0, 130.3, 129.1, 128.5, 128.3, 127.1, 126.1, 125.5, 115.2, 62.2, 49.8, 36.2, 19.8.

MS (HRMS ESI): Calcd for $C_{18}H_{21}O$ $[M+H]^+$ 253.1592, Found: 253.1602.

Synthesis of (*S)-1-(3-benzyl-4-(benzyloxy)but-1-en-2-yl)-2-methylbenzene (4.28c):** It was synthesized using **4.28c'** (778.3 mg, 3.084 mmol) and benzyl bromide (0.45 mL, 3.78 mmol) by following the procedure described in section 5.4.1.1. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1) gave **4.28c** (892.4 mg, 2.606 mmol) in 84% yield as colorless oil.

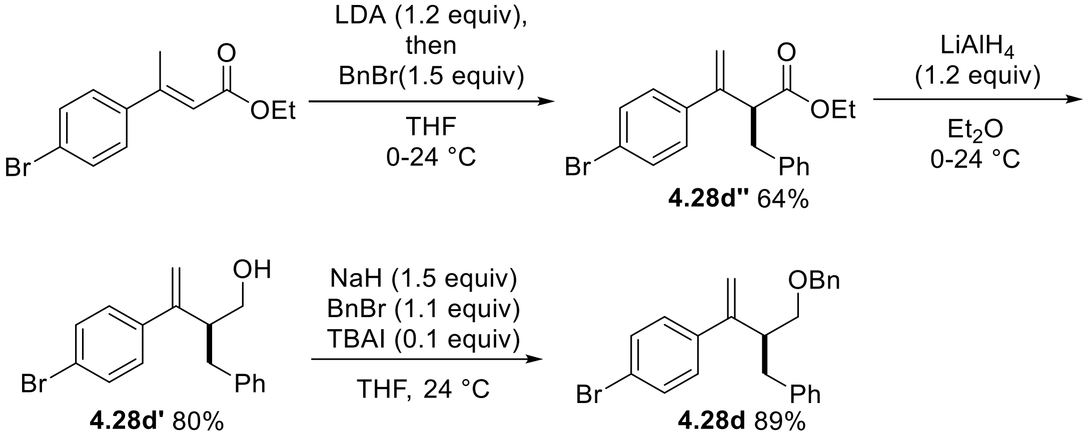
^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.36–7.20 (m, 7H), 7.18–7.12 (m, 5H), 7.09–7.07 (m, 1H), 7.01–6.99 (m, 1H), 5.34 (s, 1H), 5.04 (s, 1H), 4.43 (s, 2H), 3.42 (dd, *J* = 9.5, 5.5 Hz, 1H), 3.36 (dd, *J* = 9.5, 5.0 Hz, 1H), 3.00–2.88 (m, 2H), 2.85–2.83 (m, 1H), 2.21 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 149.8, 143.1, 140.5, 138.5, 135.2, 130.1, 129.3, 128.7, 128.2, 128.1, 127.6, 127.4, 126.7, 125.8, 125.2, 115.0, 72.9, 70.6, 47.6, 36.6, 19.8.

MS (HRMS ESI): Calcd for $C_{25}H_{27}O$ $[M+H]^+$ 343.2062, Found: 343.2070.

IR (neat, cm^{-1}): 3026 [ν(H–C=C)], 1602 [ν(C=C)], 1097 [ν(C–O)], 1066 [ν(C–O)].

5.4.1.4. Synthesis of (*S**)-1-(3-benzyl-4-(benzyloxy)but-1-en-2-yl)-4-bromobenzene (4.28d)



Synthesis of ethyl (*S)-2-benzyl-3-(4-bromophenyl)but-3-enoate (4.28d''):** It was synthesized using ethyl (*E*)-3-(4-bromophenyl)but-2-enoate[46] (1.89 g, 7.02 mmol) and benzyl bromide (1.25 mL, 10.51 mmol) by following the procedure described in section 5.4.1.1. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1) gave **4.28d''** (1.61 g, 4.49 mmol) in 64% yield as yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.46–7.40 (m, 2H), 7.28–7.11 (m, 7H), 5.41 (s, 1H), 5.37 (s, 1H), 4.06 (qd, *J* = 7.2, 1.6 Hz, 2H), 3.76 (dd, *J* = 9.2, 6.0 Hz, 1H), 3.23 (dd, *J* = 14.0, 9.2 Hz, 1H), 2.94 (dd, *J* = 14.0, 6.0 Hz, 1H), 1.10 (dd, *J* = 7.2, 7.2 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 172.9, 145.6, 140.1, 139.0, 131.4, 128.9, 128.3, 128.2, 126.4, 121.7, 115.7, 60.8, 52.3, 38.0, 14.0.

MS (HRMS ESI): Calcd for $C_{19}H_{20}O_2Br$ [M+H]$^+$ 359.0647, Found: 359.0656.

Synthesis of (*S)-2-benzyl-3-(4-bromophenyl)but-3-en-1-ol (4.28d'):** It was synthesized using **4.28d''** (1.61 g, 4.49 mmol) and $LiAlH_4$ (210.8 mg, 5.555 mmol) by following the procedure described in section 5.4.1.1. Purification by flash column chromatography (silica gel, hexane:EtOAc = 92:8) gave **4.28d'** (1.14 g, 3.60 mmol) in 80% yield as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.56–7.36 (m, 2H), 7.28–7.25 (m, 2H), 7.23–7.09 (m, 5H), 5.40 (s, 1H), 5.20 (s, 1H), 3.73–3.52 (m, 2H), 3.13–2.97 (m, 1H), 2.95–2.72 (m, 2H), 1.42 (dd, *J* = 6.0, 6.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 148.7, 141.2, 139.7, 131.4, 129.1, 128.31, 128.29, 126.1, 121.5, 114.5, 64.0, 48.2, 37.2.

MS (HRMS ESI): Calcd for $C_{17}H_{18}OBr$ $[M+H]^+$ 317.0541, Found: 317.0543.

Synthesis of (*S)-1-(3-benzyl-4-(benzyloxy)but-1-en-2-yl)-4-bromobenzene (4.28d):** It was synthesized using **4.28d'** (863.8 mg, 2.723 mmol) and benzyl bromide (0.40 mL, 3.36 mol) by following the procedure described in section 5.4.1.1. Purification by flash column chromatography (silica gel, hexane:EtOAc = 98:2) gave **4.28d** (985.2 mg, 2.426 mmol) in 89% yield as colorless oil.

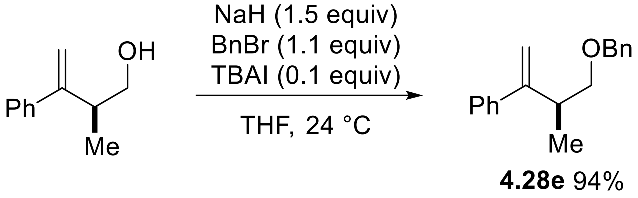
^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.38–7.36 (m, 2H), 7.34–7.24 (m, 5H), 7.23–7.20 (m, 2H), 7.16–7.09 (m, 5H), 5.28 (s, 1H), 5.12 (s, 1H), 4.45 (s, 2H), 3.49 (dd, *J* = 9.5, 6.0 Hz, 1H), 3.44 (dd, *J* = 9.5, 6.0 Hz, 1H), 3.13–3.08 (m, 1H), 2.94 (dd, *J* = 13.5, 7.0 Hz, 1H), 2.80 (dd, *J* = 13.5, 7.0 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 148.9, 141.6, 139.9, 138.3, 131.2, 129.2, 128.4, 128.3, 128.1, 127.54, 127.49, 125.9, 121.1, 114.3, 73.0, 72.1, 45.9, 37.4.

MS (HRMS ESI): Calcd for $C_{24}H_{24}OBr$ $[M+H]^+$ 407.1011, Found: 407.1011.

IR (neat, cm^{-1}): 3027 [ν(H–C=C)], 1602 [ν(C=C)], 1098 [ν(H–C=C)], 1072 [ν(C-O)], 697 [ν(C-Br)].

5.4.1.5. Synthesis of (*S**)-(4-(benzyloxy)-3-methylbut-1-en-2-yl)benzene (4.28e)



4.28e 94%

It was synthesized using 2-methyl-3-phenylbut-3-en-1-ol[47] (712.1 mg, 4.389 mmol) and benzyl bromide (0.58 mL, 4.88 mmol) by following the procedure described in section 5.4.1.1. Purification by flash column chromatography (silica gel, hexane:EtOAc = 98:2) gave **4.28e** (1.04 g, 4.11 mmol) in 94% yield as yellow oil.

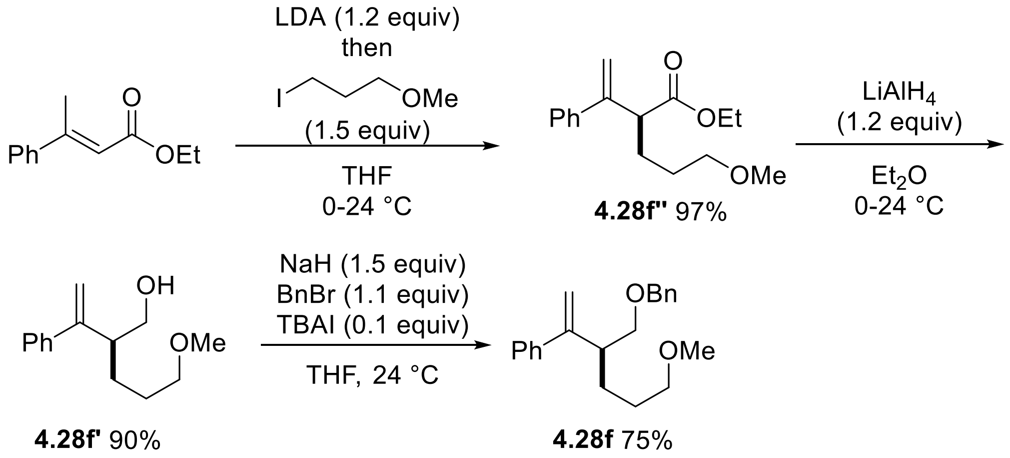
^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.41–7.20 (m, 10H), 5.25 (s, 1H), 5.08 (s, 1H), 4.51 (d, *J* = 12.4 Hz, 1H), 4.46 (d, *J* = 12.4 Hz, 1H), 3.54 (dd, *J* = 9.2, 5.6 Hz, 1H), 3.33 (dd, *J* = 9.2, 8.0 Hz, 1H), 3.10–2.94 (m, 1H), 1.21 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 151.6, 142.4, 138.6, 128.3, 128.2, 127.5, 127.4, 127.2, 126.6, 112.3, 74.7, 73.0, 38.5, 17.5.

MS (HRMS ESI): Calcd for $C_{18}H_{21}O$ $[M+H]^+$ 253.1592, Found: 253.1593.

IR (neat, cm^{-1}): 3028 [ν(H–C=C)], 1601 [ν(C=C)], 1094 [ν(C-O)], 1070 [ν(C-O)].

5.4.1.6. Synthesis of (*S**)-(3-((benzyloxy)methyl)-6-methoxyhex-1-en-2-yl)benzene (4.28f)



Synthesis of ethyl ethyl (*S)-5-methoxy-2-(1-phenylvinyl)pentanoate (4.28f''):** It was synthesized using ethyl (*E*)-3-phenylbut-2-enoate (763.9 mg, 4.016 mmol) and 1-iodo-3-methoxypropane (1.21 g, 6.02 mmol) by following the procedure described in section 5.4.1.1. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1) gave **4.28f''** (1.02 g, 3.88 mmol) in 97% yield as pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.42–7.37 (m, 2H), 7.35–7.24 (m, 3H), 5.39 (s, 1H), 5.27 (s, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.52 (dd, *J* = 8.4, 6.4 Hz, 1H), 3.40–3.32 (m, 2H), 3.30 (s, 3H), 2.01–1.92 (m, 1H), 1.83–1.69 (m, 1H), 1.66–1.52 (m, 2H), 1.19 (dd, *J* = 7.2, 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 173.7, 146.9, 141.3, 128.3, 127.6, 126.5, 114.6, 72.3, 60.6, 58.5, 50.2, 28.8, 27.7, 14.1.

MS (HRMS ESI): Calcd for $C_{16}H_{22}O_3Na$ $[M+Na]^+$ 285.1467, Found: 285.1470.

Synthesis of (*S)-5-methoxy-2-(1-phenylvinyl)pentan-1-ol (4.28f'):** It was synthesized using **4.28f''** (1.23 g, 4.69 mmol) and $LiAlH_4$ (220.0 mg, 5.797 mmol) by following the procedure described in section 5.4.1.1. Purification by flash column chromatography (silica gel, hexane:EtOAc = 85:15) gave **4.28f'** (933.6 mg, 4.241 mmol) in 90% yield as colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.39–7.25 (m, 5H), 5.39 (d, *J* = 0.8 Hz, 1H), 5.13 (s, 1H), 3.69 (dd, *J* = 10.8, 6.8 Hz, 1H), 3.62 (dd, *J* = 10.8, 5.6 Hz, 1H), 3.37–3.34 (m, 2H), 3.31 (s, 3H), 2.87–2.74 (m, 1H), 1.72–1.47 (m, 4H), 1.58 (br s, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 150.0, 142.5, 128.3, 127.4, 126.6, 113.7, 72.8, 65.2, 58.5, 46.7, 27.6, 27.2.

MS (HRMS ESI): Calcd for $C_{14}H_{20}O_2Na$ $[M+Na]^+$ 243.1361, Found: 243.1363.

Synthesis of (*S)-(3-((benzyloxy)methyl)-6-methoxyhex-1-en-2-yl)benzene (4.28f):** It was synthesized using **4.28f'** (900.0 mg, 4.088 mmol) and benzyl bromide (0.59 mL, 4.96 mmol) by following the procedure described in section 5.4.1.1. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1) gave **4.28f** (956.7 mg, 3.082 mmol) in 75% yield as colorless oil.

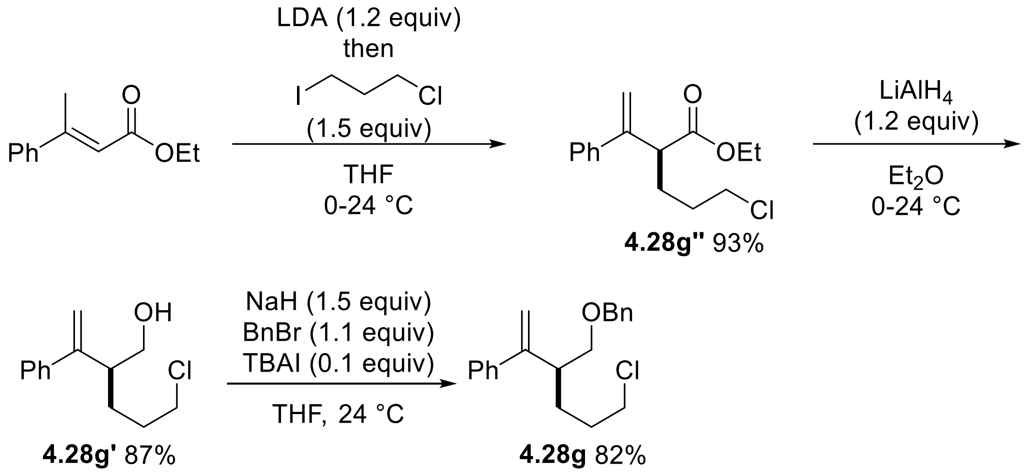
^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.39–7.20 (m, 10H), 5.30 (d, *J* = 0.9 Hz, 1H), 5.09 (s, 1H), 4.49 (s, 2H), 3.54 (dd, *J* = 9.2, 6.0 Hz, 1H), 3.44 (dd, *J* = 9.2, 7.2 Hz, 1H), 3.33 (dd, *J* = 6.0, 6.0 Hz, 2H), 3.29 (s, 3H), 2.97–2.76 (m, 1H), 1.80–1.64 (m, 2H), 1.61–1.47 (m, 2H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 150.2, 142.8, 138.5, 128.3, 128.1, 127.5, 127.4, 127.1, 126.7, 113.3, 73.8, 73.0, 72.9, 58.4, 44.4, 28.1, 27.2.

MS (HRMS ESI): Calcd for $C_{21}H_{26}O_2Na$ $[M+Na]^+$ 333.1831, Found: 333.1825.

IR (neat, cm^{-1}): 3029 [ν(H–C=C)], 1599 [ν(C=C)], 1156 [ν(C-O)], 1113 [ν(C-O)], 1027 [ν(C-O)].

5.4.1.7. Synthesis of (*S**)-(3-((benzyloxy)methyl)-6-chlorohex-1-en-2-yl)benzene (4.28g)



Synthesis of ethyl (*S)-5-chloro-2-(1-phenylvinyl)pentanoate (4.28g''):** It was synthesized using ethyl (*E*)-3-phenylbut-2-enoate (1.14 g, 6.01 mmol) and 1-chloro-3-iodopropane (0.96 mL, 8.94 mmol) by following the procedure described in section 5.4.1.1. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1) gave **4.28g''** (1.493 g, 3.878 mmol) in 93% yield as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.44–7.22 (m, 5H), 5.42 (s, 1H), 5.28 (s, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.60–3.42 (m, 3H), 2.11–1.97 (m, 1H), 1.93–1.72 (m, 3H), 1.20 (dd, *J* = 7.2, 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 173.4, 146.5, 141.1, 128.6, 127.7, 126.5, 114.9, 60.8, 49.8, 44.5, 30.6, 29.3, 14.1.

MS (HRMS ESI): Calcd for $C_{15}H_{20}O_2Cl$ $[M+H]^+$ 267.1152, Found: 267.1154.

Synthesis of (*S)-5-chloro-2-(1-phenylvinyl)pentan-1-ol (4.28g'):** It was synthesized using **4.28g''** (1.49 g, 5.60 mmol) and $LiAlH_4$ (260.0 mg, 6.851 mmol) by following the procedure described in section 5.4.1.1. Purification by flash column chromatography (silica gel, hexane:EtOAc = 90:10) gave **4.28g'** (1.09 g, 4.85 mmol) in 87% yield as colorless oil.

<u>^{1}H NMR (400 MHz, CDCl$_3$):</u> δ(ppm) 7.42–7.26 (m, 5H), 5.41 (s, 1H), 5.14 (s, 1H), 3.73–3.68 (m, 1H), 3.68–3.56 (m, 1H), 3.52 (dd, *J* = 6.4, 6.4 Hz, 2H), 2.85–2.79 (m, 1H), 1.93–1.73 (m, 3H), 1.72–1.61 (m, 1H), 1.47 (br s, 1H).

<u>^{13}C NMR (100 MHz, CDCl$_3$):</u> δ(ppm) 149.5, 142.3, 128.3, 127.5, 126.6, 114.0, 65.2, 46.3, 45.1, 30.2, 28.4.

<u>MS (HRMS ESI):</u> Calcd for $C_{13}H_{18}OCl$ $[M+H]^+$ 225.1046 Found: 225.1050.

Synthesis of (*S)-(3-((benzyloxy)methyl)-6-chlorohex-1-en-2-yl)benzene (4.28g)**: It was synthesized using **4.28g'** (454.1 mg, 2.021 mmol) and benzyl bromide (0.36 mL, 3.03 mmol) by following the procedure described in section 5.4.1.1. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1) gave **4.28g** (521.6 mg, 1.657 mmol) in 82% yield as colorless oil.

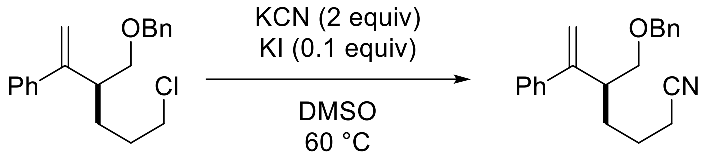
<u>^{1}H NMR (400 MHz, CDCl$_3$):</u> δ(ppm) 7.38–7.24 (m, 10H), 5.32 (s, 1H), 5.09 (s, 1H), 4.50 (s, 2H), 3.56 (dd, *J* = 9.2, 5.6 Hz, 1H), 3.51–3.48 (m, 2H), 3.43 (dd, *J* = 9.2, 7.6 Hz, 1H), 2.94–2.89 (m, 1H), 1.89–1.81 (m, 2H), 1.81–1.71 (m, 1H), 1.71–1.59 (m, 1H).

<u>^{13}C NMR (100 MHz, CDCl$_3$):</u> δ(ppm) 149.7, 142.5, 138.4, 128.3, 128.2, 127.6, 127.5, 127.3, 126.6, 113.5, 73.6, 73.1, 45.2, 44.0, 30.2, 28.9.

<u>MS (HRMS ESI):</u> Calcd for $C_{20}H_{24}OCl$ $[M+H]^+$ 315.1516, Found: 315.1509.

<u>IR (neat, cm^{-1}):</u> 3029 [ν(H–C=C)], 1599 [ν(C=C)], 1099 [ν(C-O)], 1069 [ν(C-O)], 697 [ν(C-Cl)].

5.4.1.8. Synthesis of (*S**)-5-((benzyloxy)methyl)-6-phenylhept-6-enenitrile (4.28h)



4.28g **4.28h** 95%

To a suspended solution of KCN (369.7 mg, 5.677 mmol) and KI (46.7 mg, 0.281 mmol) in DMSO (10 mL) was added **4.28g** (894.1 mg, 2.840 mmol) at 24 °C and the reaction mixture was stirred at 60 °C for 7 h. The reaction was then cooled to 24 °C and quenched with water. The organic materials were then extracted thrice using Et_2O. The combined extracts were washed with brine and dried over $MgSO_4$. The volatile materials were removed under reduced pressure to give the crude material, which was purified by flash chromatography (silica gel, hexane:EtOAc = 95:5) to give **4.28h** in 95% yield (820.3 mg, 2.686 mmol) as colorless oil.

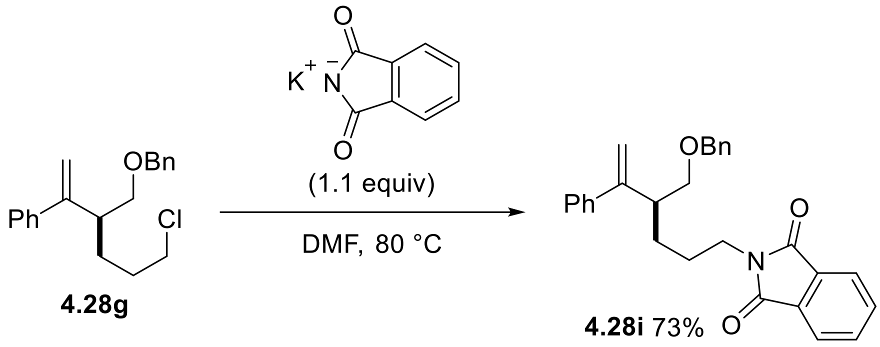
^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.42–7.19 (m, 10H), 5.33 (s, 1H), 5.08 (s, 1H), 4.49 (s, 2H), 3.56 (dd, *J* = 9.2, 5.2 Hz, 1H), 3.42 (dd, *J* = 9.2, 7.6 Hz, 1H), 2.97–2.81 (m, 1H), 2.26 (dd, *J* = 6.4, 6.4 Hz, 2H), 1.90–1.79 (m, 1H), 1.79–1.54 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 149.4, 142.3, 138.2, 128.4, 128.3, 127.6 (overlapped with 2C), 127.4, 126.5, 119.6, 113.7, 73.5, 73.2, 43.9, 30.8, 23.1, 17.3.

MS (HRMS ESI): Calcd for $C_{21}H_{24}ON$ $[M+H]^+$ 306.1858, Found: 306.1855.

IR (neat, cm^{-1}): 3030 [ν(H–C=C)], 2245 [ν(C≡N)], 1600 [ν(C=C)], 1176 [ν(C-O)], 1112 [ν(C-O)].

5.4.1.9. Synthesis of (*S**)-2-(4-((benzyloxy)methyl)-5-phenylhex-5-en-1-yl)isoindoline-1,3-dione (4.28i)



To a suspended solution of potassium phthalimide (613.7 mg, 3.314 mmol) in DMF (15 mL) was added **4.28g** (947.8 mg, 3.010 mmol) at 24 °C and the reaction mixture was stirred at 80 °C for 22 h. The reaction was then cooled to 24 °C and quenched with water. The organic materials were then extracted thrice using EtOAc. The combined extracts were washed with brine and dried over $MgSO_4$. The volatile materials were removed under reduced pressure to give the crude material, which was purified by flash column chromatography (silica gel, hexane:EtOAc = 93:7) to give **4.28i** in 73% yield (934.4 mg, 2.196 mmol) as yellow oil.

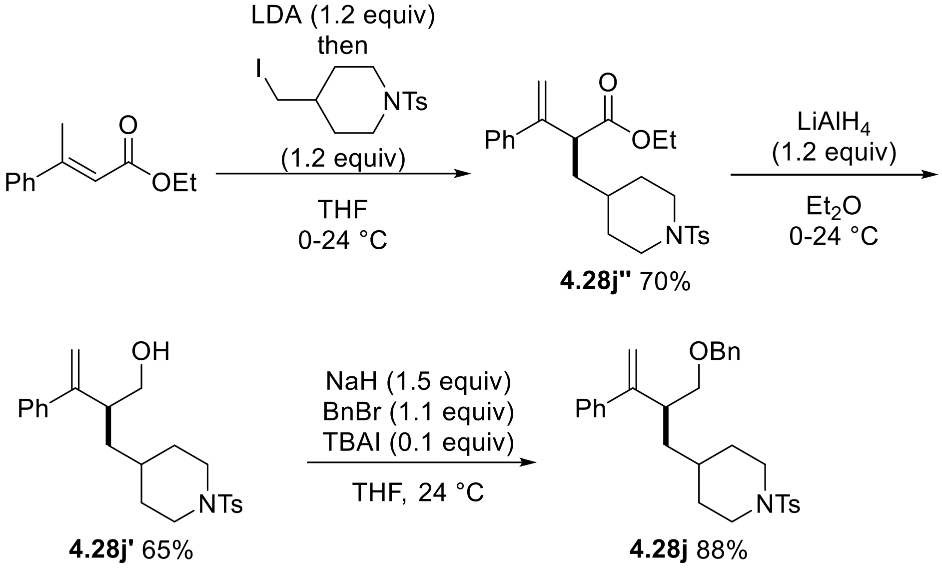
^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.88–7.79 (m, 2H), 7.75–7.65 (m, 2H), 7.38–7.16 (m, 10H), 5.28 (s, 1H), 5.06 (s, 1H), 4.47 (s, 2H), 3.65 (dd, *J* = 6.8, 6.8 Hz, 2H), 3.53 (dd, *J* = 9.2, 6.0 Hz, 1H), 3.41 (dd, *J* = 9.2, 7.2 Hz, 1H), 2.94–2.87 (m, 1H), 1.84–1.62 (m, 3H), 1.62–1.46 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 168.4, 149.8, 142.5, 138.4, 133.8, 132.1, 128.3, 128.1, 127.5, 127.4, 127.2, 126.7, 123.1, 113.6, 73.4, 73.0, 44.2, 38.1, 28.5, 26.1.

MS (HRMS ESI): Calcd for $C_{28}H_{28}NO_3$ $[M+H]^+$ 426.2069, Found: 426.2061.

IR (neat, cm^{-1}): 3029 [ν(H–C=C)], 1707 [ν(C=O)] 1616 [ν(C=C)], 1100 [ν(C-O)], 1070 [ν(C-O)].

5.4.1.10. Synthesis of (*S**)-4-(2-((benzyloxy)methyl)-3-phenylbut-3-en-1-yl)-1-tosylpiperidine (4.28j)



Synthesis of ethyl (*S)-3-phenyl-2-((1-tosylpiperidin-4-yl)methyl)but-3-enoate (4.28j'')**: It was synthesized using ethyl (*E*)-3-phenylbut-2-enoate (951.2 mg, 5.000 mmol) and 4-(iodomethyl)-1-tosylpiperidine[48] (2.24 g, 5.91 mmol) by following the procedure described in section 5.4.1.1. Purification by flash column chromatography (silica gel, Hex:EtOAc = 95:5) gave **4.28j''** (1.55 g, 3.51 mmol) in 70% yield as colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 7.62–7.61 (m, 2H), 7.36–7.27 (m, 7H), 5.36 (s, 1H), 5.21 (s, 1H), 4.17–4.02 (m, 2H), 3.75–3.70 (m, 2H), 3.56 (dd, *J* = 9.0, 6.0 Hz, 1H), 2.43 (s, 3H), 2.20–2.12 (m, 2H), 1.93–1.83 (m, 1H), 1.76–1.73 (m, 1H), 1.65–1.62 (m, 1H), 1.60–1.50 (m, 2H), 1.34–1.19 (m, 2H), 1.16 (dd, *J* = 7.0, 7.0 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 173.5, 146.8, 143.3, 141.0, 133.3, 129.5, 128.4, 127.71, 127.69, 126.4, 114.7, 60.8, 47.5, 46.2 (overlapped with 2C), 38.2, 33.2, 31.5, 31.2, 21.5, 14.0.

MS (HRMS ESI): Calcd for $C_{25}H_{32}O_4NS$ $[M+H]^+$ 442.2052, Found: 442.2055.

Synthesis of (*S)-3-phenyl-2-((1-tosylpiperidin-4-yl)methyl)but-3-en-1-ol (4.28j'):** It was synthesized using **4.28j''** (1.55 g, 3.50 mmol) and $LiAlH_4$ (146.5 mg, 3.850 mmol) by following the procedure described in section 5.4.1.1. Purification by flash column chromatography (silica gel, hexane:EtOAc = 92:8) gave **4.28j'** (889.1 mg, 2.226 mmol) in 65% yield as colorless sticky oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.62–7.60 (m, 2H), 7.35–7.18 (m, 7H), 5.35 (d, *J* = 0.4 Hz, 1H), 5.07 (s, 1H), 3.80–3.66 (m, 2H), 3.60 (dd, *J* = 10.8, 6.8 Hz, 1H), 3.53 (dd, *J* = 10.8, 5.6 Hz, 1H), 2.92–2.77 (m, 1H), 2.42 (s, 3H), 2.25–2.04 (m, 2H), 1.75–1.60 (m, 3H), 1.50–1.39 (m, 2H), 1.38–1.17 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 149.7, 143.3, 142.1, 133.3, 129.5, 128.4, 127.7, 127.6, 126.5, 114.1, 65.6, 46.35, 46.32, 43.9, 37.6, 32.6, 32.1, 31.4, 21.5.

MS (HRMS ESI): Calcd for $C_{23}H_{30}NO_3S$ $[M+H]^+$ 400.1946, Found: 400.1951.

Synthesis of (*S)-4-(2-((benzyloxy)methyl)-3-phenylbut-3-en-1-yl)-1-tosylpiperidine (4.28j):** It was synthesized using **4.28j'** (528.4 mg, 1.323 mmol) and benzyl bromide (0.19 mL, 1.98 mmol) by following the procedure described in section 5.4.1.1. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1) **4.28j** (567.0 mg, 1.158 mmol) in 88% yield as colorless sticky oil.

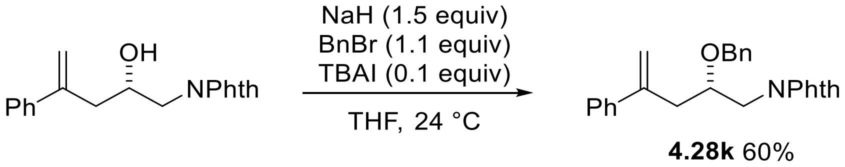
^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.61 (d, *J* = 8.5 Hz, 2H), 7.31–7.25 (m, 12H), 5.26 (s, 1H), 5.03 (s, 1H), 4.45 (s, 2H), 3.75–3.65 (m, 2H), 3.47 (dd, *J* = 9.0, 6.0 Hz, 1H), 3.34 (dd, *J* = 9.0, 7.0 Hz, 1H), 2.94–2.88 (m, 1H), 2.42 (s, 3H), 2.17–2.13 (m, 1H), 2.12–2.03 (m, 1H), 1.67–1.65 (m, 2H), 1.60–1.50 (m, 2H), 1.47–1.42 (m, 1H), 1.36–1.15 (m, 2H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 150.0, 143.3, 142.4, 138.3, 133.2, 129.5, 128.3, 128.2, 127.7, 127.52, 127.49, 127.3, 126.6, 113.6, 74.1, 73.0, 46.40, 46.37, 41.6, 38.2, 32.6, 32.2, 31.3, 21.5.

MS (HRMS ESI): Calcd for $C_{30}H_{36}NO_3S$ $[M+H]^+$ 490.2416, Found: 490.2421.

IR (neat, cm^{-1}): 3030 [ν(H–C=C)], 1597 [ν(C=C)], 1248 [ν(C-N)], 1162 [ν(S=O)], 1092 [ν(C-O)], 1050 [ν(C-O)].

5.4.1.11. Synthesis of (*S**)-2-(2-(benzyloxy)-4-phenylpent-4-en-1-yl)isoindoline-1,3-dione (4.28k)



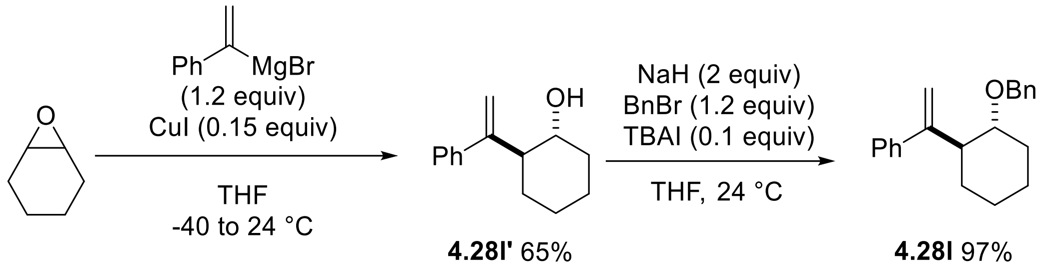
It was synthesized using (*S**)-2-(2-hydroxy-4-phenylpent-4-en-1-yl)isoindoline-1,3-dione[49] (964.7 mg, 2.946 mmol) and benzyl bromide (0.45 mL, 3.78 mmol) by following the procedure described in section 5.4.1.1. Purification by flash column chromatography (silica gel, hexane:EtOAc = 98:2) gave **4.28k**[12] (736.3 mg, 1.789 mmol) in 60% yield as a white solid.

^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 7.77–7.75 (m, 2H), 7.70–7.67 (m, 2H), 7.39–7.37 (m, 2H), 7.33–7.27 (m, 3H), 7.04–7.02 (m, 5H), 5.37 (s, 1H), 5.24 (s, 1H), 4.47 (d, *J* = 11.5 Hz, 1H), 4.35 (d, *J* = 11.5 Hz, 1H), 3.86–3.80 (m, 2H), 3.73–3.70 (m, 1H), 2.88 (dd, *J* = 14.5, 6.5 Hz, 1H), 2.78 (dd, *J* = 14.5, 5.0 Hz, 1H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 168.2, 144.7, 140.8, 138.0, 133.7, 132.0, 128.4, 128.0 (overlapped with 2C), 127.6, 127.3, 126.2, 123.1, 115.5, 74.7, 71.9, 41.5, 39.6.

IR (neat, cm^{-1}): 3032 [ν(H–C=C)], 1707 [ν(C=O)], 1601 [ν(C=C)], 1190 [ν(C-N)], 1137 [ν(C-O)], 1071 [ν(C-O)].

5.4.1.12. Synthesis of (1-((1*S**,2*R**)-2-(benzyloxy)cyclohexyl)vinyl)benzene (4.28l)



Synthesis of (1*R,2*S**)-2-(1-phenylvinyl)cyclohexan-1-ol (4.28l'):** To a suspension of copper(I) iodide (417.7 mg, 2.193 mmol) in THF (10 mL) was added freshly prepared (1-phenylvinyl)magnesium bromide (0.65 M in THF, 27 mL, 17.55 mmol) at -40 °C, and the reaction mixture was stirred for 15 min at the same temperature. A solution of 7-oxabicyclo[4.1.0]heptane (1.48 mL, 14.63 mmol) in THF (2 mL) was then added at the same temperature, and the mixture was slowly warm up to 24 °C for 19 h. The reaction was then quenched with saturated aqueous NH_4Cl solution and the organic materials were extracted thrice with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$ before the combined extracts were concentrated *in vacuo*. The resulting crude residue was filter through a short plug of silica gel (hexane:EtOAc = 95:5). Further purification by distillation (120–125 °C, 2 mbar) gave **4.28l'** (2.10 g, 9.53 mmol) in 65% yield as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.41–7.23 (m, 5H), 5.33 (s, 1H), 5.19 (s, 1H), 3.66 (ddd, *J* = 10.0, 10.0, 4.0 Hz, 1H), 2.50–2.31 (m, 1H), 2.19–2.05 (m, 1H), 2.02 (br s, 1H), 1.90–1.74 (m, 2H), 1.70–1.64 (m, 1H), 1.44–1.28 (m, 2H), 1.28–1.11 (m, 2H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 151.7, 142.6, 128.1, 127.3, 126.8, 112.8, 73.0, 52.2, 34.3, 32.6, 25.9, 24.8.

MS (HRMS ESI): Calcd for $C_{14}H_{19}O$ $[M+H]^+$ 203.1436, Found: 203.1440.

Synthesis of (1-((1*S,2*R**)-2-(benzyloxy)cyclohexyl)vinyl)benzene (4.28l):** It was synthesized using **4.28l'** (2.05 g, 9.29 mmol) and benzyl bromide (1.32 mL, 11.20 mmol) by following the procedure described in section 2.1. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1) gave **4.28l** (2.64 g, 9.03 mmol) in 97% yield as colorless oil.

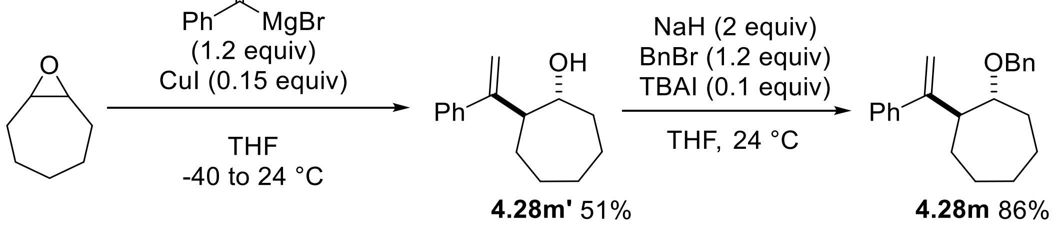
^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.46–7.38 (m, 2H), 7.33–7.27 (m, 2H), 7.27–7.18 (m, 6H), 5.25 (s, 1H), 5.10 (s, 1H), 4.59 (d, *J* = 11.6 Hz, 1H), 4.41 (d, *J* = 11.6 Hz, 1H), 3.40 (ddd, *J* = 10.0, 10.0, 4.0 Hz, 1H), 2.57 (ddd, *J* = 12.6, 10.0, 4.0 Hz, 1H), 2.25–2.22 (m, 1H), 1.95–1.84 (m, 1H), 1.82–1.79 (m, 1H), 1.68–1.65 (m, 1H), 1.40–1.13 (m, 4H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 152.9, 143.7, 139.1, 128.1, 128.0, 127.5, 127.1, 126.9, 126.8, 112.1, 81.4, 70.8, 49.8, 33.5, 31.9, 25.9, 24.8.

MS (HRMS ESI): Calcd for $C_{21}H_{25}O$ $[M+H]^+$ 293.1905, Found: 293.1908.

IR (neat, cm^{-1}): 3028 [ν(H–C=C)], 1598 [ν(C=C)], 1094 [ν(C-O)], 1072 [ν(C-O)].

5.4.1.13. Synthesis of (1*R**,2*S**)-1-(benzyloxy)-2-(1-phenylvinyl)cycloheptane (4.28m)



Synthesis of (1*R,2*S**)-2-(1-phenylvinyl)cycloheptan-1-ol (4.28m'):** It was synthesized using 8-oxabicyclo[5.1.0]octane (662.0 mg, 5.607 mmol), CuI (158.8 mg, 0.834 mmol) and (1-phenylvinyl)magnesium bromide (0.91 M in THF, 7.4 mL, 6.73 mmol) by following the procedure described in section 5.4.1.12. Purification by flash column chromatography (silica gel, Hex:EtOAc = 95:5) gave **4.28m'** (612.9 mg, 2.833 mmol) in 51% yield as pale yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.40–7.38 (m, 2H), 7.36–7.23 (m, 3H), 5.31 (s, 1H), 5.17 (s, 1H), 3.83 (ddd, *J* = 9.0, 9.0, 3.6 Hz, 1H), 2.60–2.55 (m, 1H), 2.09–1.91 (m, 2H), 1.79–1.59 (m, 5H), 1.59–1.32 (m, 4H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 153.6, 142.4, 128.2, 127.4, 126.8, 112.6, 75.5, 54.3, 35.1, 31.2, 27.3, 26.6, 21.9.

MS (HRMS ESI): Calcd for $C_{15}H_{21}O$ $[M+H]^+$ 217.1592, Found: 217.1595.

Synthesis of (1*R,2*S**)-1-(benzyloxy)-2-(1-phenylvinyl)cycloheptane (4.28m):** It was synthesized using **4.28m'** (577.2 mg, 2.668 mmol) and benzyl bromide (0.38 mL, 3.199 mmol) by following the procedure described in section 5.4.1.1. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1) gave **4.28m** (705.3 mg, 2.302 mmol) in 86% yield as colorless oil.

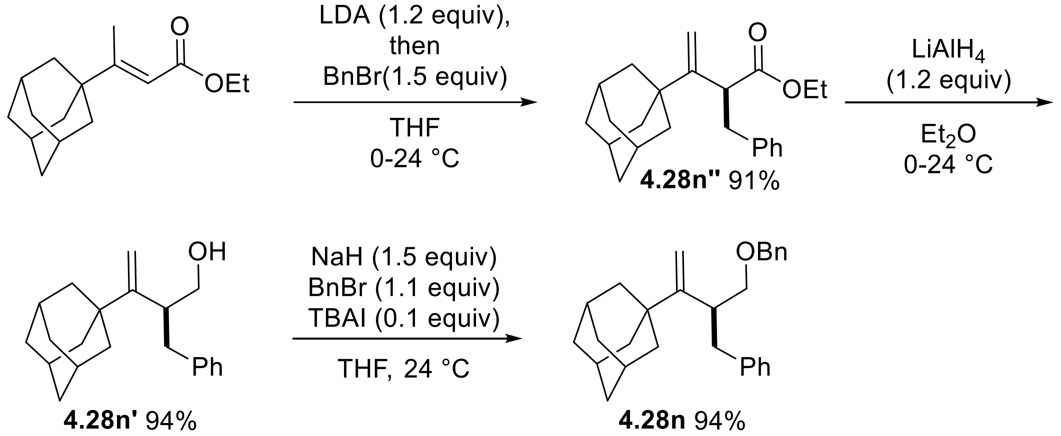
^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.42–7.40 (m, 2H), 7.33–7.15 (m, 8H), 5.18 (s, 1H), 5.06 (s, 1H), 4.50 (d, *J* = 11.2 Hz, 1H), 4.29 (d, *J* = 11.2 Hz, 1H), 3.65 (ddd, *J* = 10.0, 5.6, 4.0 Hz, 1H), 2.80 (dd, *J* = 10.0, 8.8, 2.4 Hz, 1H), 1.92–1.85 (m, 2H), 1.81–1.63 (m, 4H), 1.60–1.37 (m, 4H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 154.8, 143.5, 139.0, 128.1, 128.0, 127.7, 127.2, 127.0, 126.9, 111.5, 84.0, 71.1, 51.9, 31.9, 30.9, 29.1, 27.3, 22.2.

MS (HRMS ESI): Calcd for $C_{22}H_{27}O$ $[M+H]^+$ 307.2062, Found: 307.2061.

IR (neat, cm^{-1}): 3030 [ν(H–C=C)], 1600 [ν(C=C)], 1092 [ν(C-O)], 1067 [ν(C-O)].

5.4.1.14. Synthesis of 1-((*S**)-3-benzyl-4-(benzyloxy)but-1-en-2-yl)adamantane (4.28n)



Synthesis of ethyl (2*S)-3-adamantan-1-yl)-2-benzylbut-3-enoate (4.28n''):** It was synthesized using ethyl (*E*)-3-(adamantan-1-yl)but-2-enoate[50] (1.60 g, 6.45 mmol) and benzyl bromide (0.92 mL, 7.75 mmol) by following the procedure described in section 5.4.1.1. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1) gave **4.28n''** (2.00 g, 5.90 mmol) in 91% yield as colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.40–7.07 (m, 5H), 5.22 (s, 1H), 5.00 (s, 1H), 4.08–3.95 (m, 2H), 3.42 (dd, *J* = 10.8, 4.0 Hz, 1H), 3.17 (dd, *J* = 14.0, 10.8 Hz, 1H), 2.72 (dd, *J* = 14.0, 4.0 Hz, 1H), 2.02 (s, 3H), 1.74–1.63 (m, 12H), 1.11 (dd, *J* = 7.2, 7.2 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 174.1, 156.2, 140.1, 128.9, 128.2, 126.2, 109.5, 60.3, 47.1, 41.0, 40.4, 38.6, 36.8, 28.4, 14.0.

MS (HRMS ESI): Calcd for $C_{23}H_{31}O_2$ $[M+H]^+$ 339.2324, Found: 339.2323.

Synthesis of (2*S)-3-adamantan-1-yl)-2-benzylbut-3-en-1-ol (4.28n'):** It was synthesized using **4.28n''** (1.77 g, 5.24 mmol) and $LiAlH_4$ (244.0 mg, 6.430 mmol) by following the procedure described in section 5.4.1.1. Purification by flash column chromatography (silica gel, hexane:EtOAc = 95:5) gave **4.28n'** (1.46 g, 4.94 mmol) in 94% yield as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.28–7.24 (m, 2H), 7.19–7.15 (m, 3H), 5.03 (s, 1H), 4.91 (s, 1H), 3.60–3.50 (m, 1H), 3.48–3.45 (m, 1H), 2.81–2.65 (m, 3H), 1.98 (s, 3H), 1.71–1.51 (m, 13H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 159.0, 140.6, 129.3, 128.1, 126.0, 107.8, 65.9, 43.1, 40.39, 40.35, 38.2, 36.8, 28.4.

MS (HRMS ESI): Calcd for $C_{21}H_{29}O$ $[M+H]^+$ 297.2218, Found: 297.2220.

Synthesis of 1-((*S)-3-benzyl-4-(benzyloxy)but-1-en-2-yl)adamantane (4.28n):** It was synthesized using **4.28n'** (1.45 g, 4.90 mmol) and benzyl bromide (0.70 mL, 5.89 mmol) by following the procedure described in section 5.4.1.1. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1) gave **4.28n** (1.79 g, 4.63 mmol) in 94% yield as colorless oil.

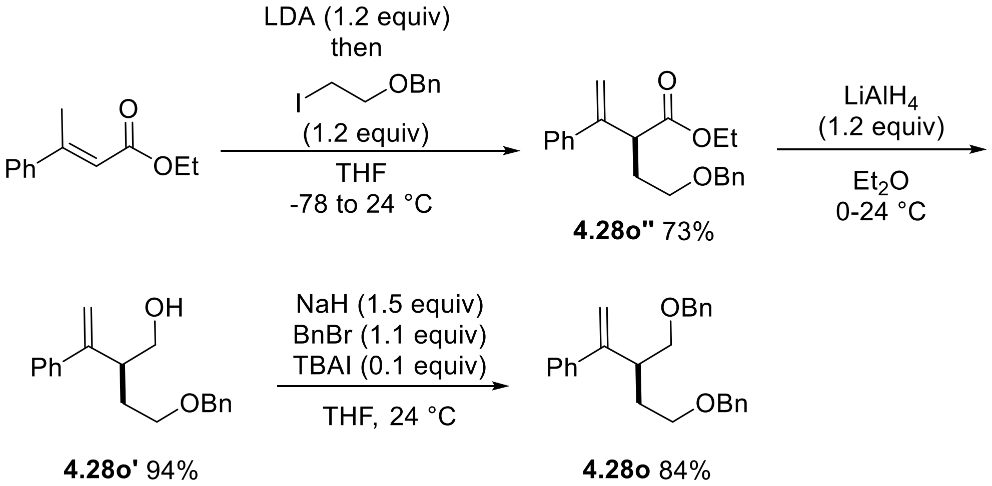
^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.38–7.30 (m, 4H), 7.30–7.24 (m, 1H), 7.21–7.20 (m, 2H), 7.18–7.09 (m, 3H), 4.93 (s, 1H), 4.86 (s, 1H), 4.49 (s, 2H), 3.40 (dd, *J* = 9.2, 4.4 Hz, 1H), 3.29 (dd, *J* = 9.2, 8.0 Hz, 1H), 3.05 (dd, *J* = 12.8, 6.0 Hz, 1H), 2.81–2.72 (m, 1H), 2.66 (dd, *J* = 12.8, 8.0 Hz, 1H), 1.90 (s, 3H), 1.66–1.63 (m, 3H), 1.57–1.54 (m 3H), 1.48–1.38 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 158.4, 141.0, 138.7, 129.7, 128.2, 127.8, 127.5, 127.4, 125.6, 108.0, 75.0, 72.9, 41.3, 40.2, 34.0, 37.9, 36.8, 28.4.

MS (HRMS ESI): Calcd for $C_{28}H_{35}O$ $[M+H]^+$ 387.2688 Found: 387.2692.

IR (neat, cm^{-1}): 3061 [ν(H–C=C)], 1603 [ν(C=C)], 1101 [ν(C-O)], 1073 [ν(C-O)].

5.4.1.15. Synthesis of (*S**)-(((2-(1-phenylvinyl)butane-1,4-diyl)bis(oxy))bis(methylene))dibenzene (4.28o)



Synthesis of ethyl (*S)-2-(2-(benzyloxy)ethyl)-3-phenylbut-3-enoate (4.28o''):** It was synthesized using ethyl (*E*)-3-phenylbut-2-enoate (885.6 mg, 4.655 mmol) and ((2-iodoethoxy)methyl)benzene[51] (1.447 g, 5.520 mmol) by following the procedure described in section 5.4.1.1. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1) gave **4.28o''** (1.11 g, 3.40 mmol) in 73% yield as pale-yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.43–7.40 (m, 2H), 7.36–7.23 (m, 8H), 5.41 (s, 1H), 5.26 (s, 1H), 4.43 (d, *J* = 10.4 Hz, 1H), 4.40 (d, *J* = 10.4 Hz, 1H), 4.16–4.06 (m, 2H), 3.86–3.72 (m, 1H), 3.52–3.48 (m, 2H), 2.34–2.20 (m, 1H), 2.01–1.93 (m, 1H), 1.17 (dd, *J* = 7.2, 7.2 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 173.6, 146.7, 141.2, 138.3, 128.3 (overlapped with 2C), 127.6, 127.5 (overlapped with 2C), 126.5, 114.7, 72.9, 67.8, 60.6, 46.9, 32.1, 14.0.

MS (HRMS ESI): Calcd for $C_{21}H_{25}O_3$ [M+H]$^+$ 325.1804, Found: 325.1812.

Synthesis of (*S)-2-(2-(benzyloxy)ethyl)-3-phenylbut-3-en-1-ol (4.28o'):** It was synthesized using **4.28o''** (1.04 g, 3.21 mmol) and $LiAlH_4$ (150.0 mg, 3.953 mmol) by following the procedure described in section 5.4.1.1. Purification by flash column chromatography (silica gel, hexane:EtOAc = 95:5) gave **4.28o'** (853.5 mg, 3.023 mmol) in 94% yield as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.40–7.23 (m, 10H), 5.36 (s, 1H), 5.10 (s, 1H), 4.48 (s, 2H), 3.74–3.68 (m, 1H), 3.67–3.57 (m, 2H), 3.57–3.48 (m, 1H), 2.99 (dddd, *J* = 6.4, 6.4, 6.4, 6.4 Hz, 1H), 2.30 (dd, *J* = 6.4, 6.4 Hz, 1H), 1.99 – 1.80 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 150.1, 142.4, 138.0, 128.4, 128.3, 127.7, 127.5, 127.4, 126.6, 113.4, 73.1, 68.5, 65.5, 44.2, 31.9.

MS (HRMS ESI): Calcd for $C_{19}H_{23}O_2$ $[M+H]^+$ 283.1698, Found: 283.1704.

Synthesis of (*S)-(((2-(1-phenylvinyl)butane-1,4-diyl)bis(oxy))bis(methylene))dibenzene (4.28o):** It was synthesized using **4.28o'** (853.5 mg, 3.023 mmol) and benzyl bromide (0.43 mL, 3.62 mmol) by following the procedure described in section 5.4.1.1. Purification by flash column chromatography (silica gel, Hex:EtOAc = 99:1) gave **4.28o** (944.4 mg, 2.535 mmol) in 84% yield as colorless oil.

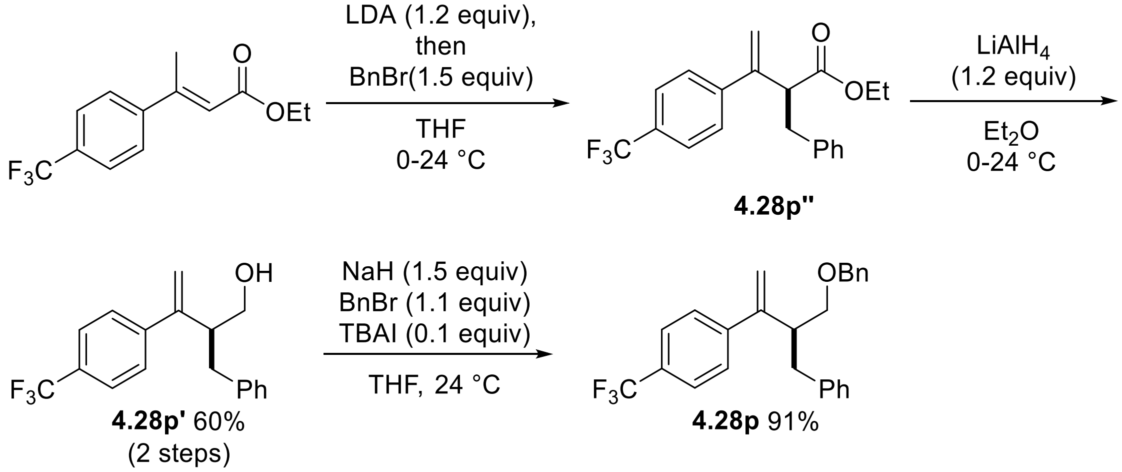
^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.41–7.20 (m, 15H), 5.32 (s, 1H), 5.11 (s, 1H), 4.47 (s, 2H), 4.42 (s, 2H), 3.58–3.50 (m, 3H), 3.45 (dd, *J* = 9.5, 6.8 Hz, 1H), 3.13–3.06 (m, 1H), 2.10–2.02 (m, 1H), 1.90–1.73 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 150.0, 142.7, 138.52, 138.48, 128.3, 128.2, 128.1, 127.6, 127.5, 127.40, 127.38, 127.2, 126.7, 113.4, 73.7, 72.9, 72.8, 68.2, 41.2, 31.8.

MS (HRMS ESI): Calcd for $C_{26}H_{29}O_2$ $[M+H]^+$ 373.2168, Found: 373.2164.

IR (neat, cm^{-1}): 3029 [ν(H–C=C)], 1599 [ν(C=C)], 1093 [ν(C-O)], 1073 [ν(C-O)], 1027 [ν(C-O)].

5.4.1.16. Synthesis of (*S**)-1-(3-benzyl-4-(benzyloxy)but-1-en-2-yl)-4-(trifluoromethyl)benzene (4.28p)



Synthesis of (*S)-2-benzyl-3-(4-(trifluoromethyl)phenyl)but-3-en-1-ol (4.28p'):**

It was synthesized following a 2-step protocol including 1) α-benzylation of ethyl (*E*)-3-(4-(trifluoromethyl)phenyl)but-2-enoate[50] (1.42 g, 5.50 mmol) with benzyl bromide (0.98 mL, 8.25 mmol); 2) Reduction of ester using $LiAlH_4$ (220.1 mg, 5.80 mmol) by following the procedure described in section 2.1. Purification by flash column chromatography (silica gel, hexane:EtOAc = 92:8) gave **4.28p'** (1.014 g, 3.31 mmol) in 60% yield over 2-step as colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.55 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.30–7.22 (m, 2H), 7.22–7.13 (m, 3H), 5.45 (s, 1H), 5.28 (s, 1H), 3.68 (dd, *J* = 10.8, 6.4 Hz, 1H), 3.63 (dd, *J* = 10.8, 5.2 Hz, 1H), 3.17–2.99 (m, 1H), 2.95–2.78 (m, 2H), 1.49 (br s, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 148.9, 146.1, 139.6, 129.6 (q, $J_{C\text{-}F}$ = 32.0 Hz), 129.1, 128.4, 127.0, 126.3, 125.3 (q, $J_{C\text{-}F}$ = 4.0 Hz), 124.2 (q, $J_{C\text{-}F}$ = 270.0 Hz), 115.7, 64.1, 48.3, 37.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ(ppm) -62.43.

MS (HRMS ESI): Calcd for $C_{18}H_{18}OF_3$ $[M+H]^+$ 307.1310, Found: 307.1314.

Synthesis of (*S)-1-(3-benzyl-4-(benzyloxy)but-1-en-2-yl)-4-(trifluoromethyl)benzene (4.28p):** It was synthesized using **4.28p'** (301.5 mg, 0.98 mmol) and benzyl bromide (0.14 mL, 1.18 mmol) by following the procedure described in section 5.4.1.1. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1) gave **4.28p** (356.3 mg, 0.899 mmol) in 91% yield as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.51 (d, *J* = 8.2 Hz, 2H), 7.36–7.22 (m, 9H), 7.20–7.10 (m, 3H), 5.35 (s, 1H), 5.21 (s, 1H), 4.47 (s, 2H), 3.51 (dd, *J* = 9.6, 6.0 Hz, 1H), 3.47 (dd, *J* = 9.6, 6.0 Hz, 1H), 3.20–3.11 (m, 1H), 2.97 (dd, *J* = 13.6, 6.8 Hz, 1H), 2.82 (dd, *J* = 13.6, 7.6 Hz, 1H).

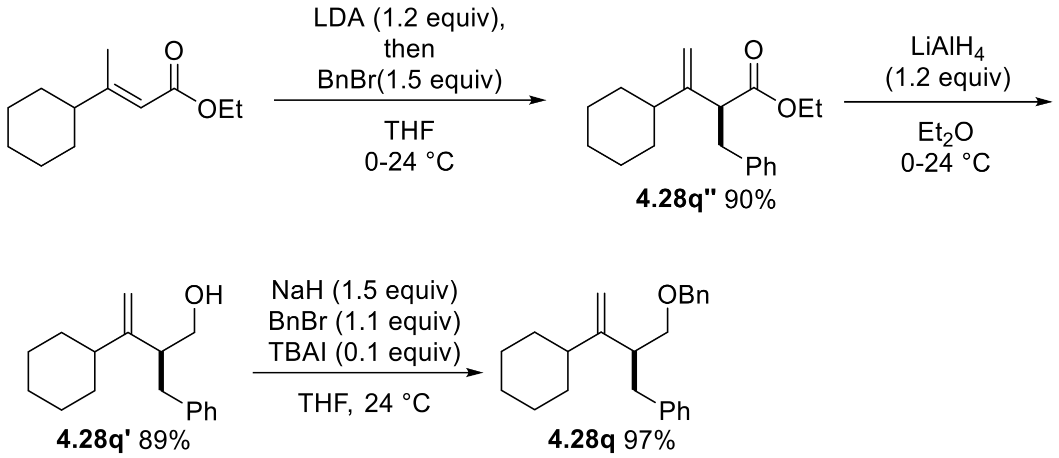
^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 149.1, 146.5, 139.8, 138.3, 129.2 (q, $J_{C\text{-}F}$ = 16.2 Hz), 129.2, 128.3, 128.2, 127.6 (overlapped with 2C), 127.1, 126.0, 125.1 (q, $J_{C\text{-}F}$ = 3.8 Hz), 124.2 (q, $J_{C\text{-}F}$ = 270.3 Hz), 115.5, 73.1, 72.2, 46.1, 37.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ(ppm) -62.42.

MS (HRMS ESI): Calcd for $C_{25}H_{24}OF_3$ $[M+H]^+$ 397.1779, Found: 397.1785.

5.4.1.17. Synthesis of

(*S**)-(((2-benzyl-3-cyclohexylbut-3-en-1-yl)oxy)methyl)benzene (4.28q)



Synthesis of ethyl (*S)-2-benzyl-3-cyclohexylbut-3-enoate (4.28q''):** It was synthesized using ethyl ethyl (*E*)-3-cyclohexylbut-2-enoate[52] (902 mg, 4.595 mmol) and benzyl bromide (0.66 mL, 5.557 mmol) by following the procedure described in section 5.4.1.1. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1) gave **4.28q''** (1.185 g, 4.138 mmol) in 90% yield as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.27–7.24 (m, 2H), 7.22–7.14 (m, 3H), 5.08 (s, 1H), 4.95 (s, 1H), 4.13–3.96 (m, 2H), 3.25 (dd, *J* = 9.6, 5.6 Hz, 1H), 3.15 (dd, *J* = 13.2, 9.6 Hz, 1H), 2.82 (dd, *J* = 13.6, 5.6 Hz, 1H), 1.91–1.60 (m, 6H), 1.33–1.03 (m, 8H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 173.5, 152.6, 139.7, 128.9, 128.2, 126.2, 110.0, 60.4, 52.2, 44.8, 38.7, 32.44, 32.40, 26.7, 26.2, 14.0.

MS (HRMS ESI): Calcd for $C_{19}H_{27}O_2$ $[M+H]^+$ 287.2011, Found: 287.2014.

Synthesis of (*S)-2-benzyl-3-cyclohexylbut-3-en-1-ol (4.28q'):** It was synthesized using **4.28q''** (1.185 g, 4.137 mmol) and $LiAlH_4$ (193.0 mg, 5.086 mmol) by following the procedure described in section 5.4.1.1. Purification by flash column chromatography (silica gel, hexane:EtOAc = 92:8) gave **4.28q'** (902.4 mg, 3.693 mmol) in 89% yield as colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.31–7.21 (m, 2H), 7.19–7.16 (m, 3H), 4.99 (s, 1H), 4.88 (s, 1H), 3.53 (br, 2H), 2.77 (dd, *J* = 13.6, 8.0 Hz, 1H), 2.71 (dd, *J* = 13.6, 6.4 Hz, 1H), 2.55–2.48 (m, 1H), 1.73–1.61 (m, 6H), 1.45 (s, 1H), 1.34–0.95 (m, 5H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 155.6, 140.3, 129.1, 128.2, 125.9, 108.8, 64.1, 48.8, 44.7, 38.0, 32.8, 32.5, 26.8, 26.7, 26.2.

MS (HRMS ESI): Calcd for $C_{17}H_{25}O$ $[M+H]^+$ 245.1905, Found: 245.1898.

Synthesis of (*S)-(((2-benzyl-3-cyclohexylbut-3-en-1-yl)oxy)methyl)benzene (4.28q):** It was synthesized using **4.28q'** (877.6 mg, 3.591 mmol) and benzyl bromide (0.50 mL, 4.210 mmol) by following the procedure described in section 5.4.1.1. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1) gave **4.28q** (1.161 g, 3.472 mmol) in 97% yield as colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.39–7.30 (m, 4H), 7.30–7.18 (m, 3H), 7.16–7.13 (m, 3H), 4.86 (s, 1H), 4.80 (s, 1H), 4.49 (s, 2H), 3.44 (dd, *J* = 9.2, 5.2 Hz, 1H), 3.37 (dd, *J* = 9.2, 7.2 Hz, 1H), 2.97 (dd, *J* = 13.2, 6.0 Hz, 1H), 2.67 (dd, *J* = 13.2, 8.0 Hz, 1H), 2.63–2.50 (m, 1H), 1.78–1.56 (m, 6H), 1.23–0.86 (m, 5H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 155.6, 140.7, 138.6, 129.4, 128.3, 127.9, 127.5, 127.4, 125.7, 108.3, 73.6, 72.9, 46.5, 44.9, 38.4, 32.44, 32.39, 26.8 (overlapped with 2C), 26.3.

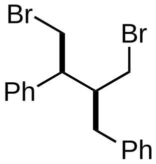
MS (HRMS ESI): Calcd for $C_{24}H_{30}O$ $[M+H]^+$ 335.2375, Found: 335.2379.

5.4.2 Synthesis and characterization of the intermediate and side products

5.4.2.1 Synthesis and characterization of dibromide 4.32 (Table 4.1, entry 1):

It was synthesized using **4.28a** (96.0 mg, 0.293 mmol) and NBS (58.8 mg, 0.330 mmol) in 2,2,2-trifluoroethanol (3 mL) at 50 °C for 4 h. The ^{1}H NMR analysis of the resulting crude mixture using 1,1,2,2-tetrachloroethane as the internal standard revealed that furan **4.31a** and dibromide **4.32** were formed in 51% and 31% yields, respectively. Purification of the crude mixture by flash column chromatography (silica gel, hexane) gave dibromide **4.32** with unidentified products, a part of which was further purified by GPC to obtain pure dibromide **4.32** for characterization.

((*2S*,3S)-4-bromo-2-(bromomethyl)butane-1,3-diyl)dibenzene (4.32)**

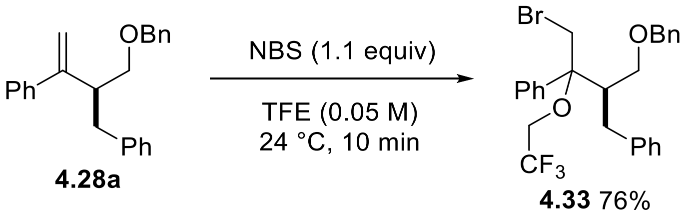


^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.38–7.26 (m, 9H), 7.24–7.21 (m, 1H), 3.87 (dd, *J* = 10.4, 7.2 Hz, 1H), 3.82 (dd, *J* = 10.4, 3.6 Hz, 1H), 3.27 – 3.20 (m, 1H), 3.17 (dd, *J* = 10.4, 3.2 Hz, 1H), 3.06–2.98 (m, 2H), 2.74 (dd, *J* = 13.2, 10.4 Hz, 1H), 2.47–2.36 (m, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 140.3, 139.1, 129.1, 128.62, 128.59, 128.3, 127.5, 126.5, 48.3, 44.3, 37.8, 37.5, 35.2.

MS (HRMS ESI): Calcd for $C_{17}H_{19}O$ [M+H]$^+$ 308.9500, Found: 308.9503.

5.4.2.2 Synthesis and characterization of 4.33 (Table 4.1, entry 3):



It was synthesized by mixing **4.28a** (98.1 mg, 0.299 mmol) and NBS (59.8 mg, 0.330 mmol) in 2,2,2-trifluoroethanol (6 mL) at 24 °C for 10 min. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1) gave **4.33** in 76% yield (115.0 mg, 0.227 mmol) as a 95:5 diastereomeric mixture (based on ^{19}F NMR analysis) as white solid.

<u>^{1}H NMR (400 MHz, CDCl$_3$):</u> δ(ppm) 7.42–7.28 (m, 7H), 7.28–7.20 (m, 5H), 7.19–7.15 (m, 1H), 7.10–7.08 (m, 2H), 4.73 (d, *J* = 12.0 Hz, 1H), 4.42 (d, *J* = 11.6 Hz, 1H), 4.14 (d, *J* = 11.6 Hz, 1H), 4.04 (dq, *J* = 16.8, 8.0 Hz, 1H), 3.86 (d, *J* = 12.0 Hz, 1H), 3.68 (dq, *J* = 16.8, 8.0 Hz, 1H), 3.36–3.22 (m, 2H), 2.99 (dd, *J* = 10.4, 9.2 Hz, 1H), 2.91–2.84 (m, 1H), 1.74 (dd, *J* = 13.6, 11.2 Hz, 1H).

<u>^{13}C NMR (100 MHz, CDCl$_3$):</u> δ(ppm) 140.5, 137.9, 136.5, 129.1, 128.40, 128.36, 128.35, 128.1, 127.7, 127.6, 127.3, 126.0, 124.1 (q, $J_{C\text{-}F}$ = 276.1 Hz), 82.0, 73.0, 68.9, 60.7 (q, $J_{C\text{-}F}$ = 34.2 Hz), 45.0, 37.5, 31.6.

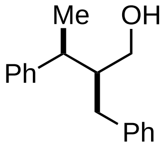
<u>^{19}F NMR (282 MHz, CDCl$_3$):</u> δ -73.43 (dd, *J* = 8.5, 8.5 Hz).

<u>MS (HRMS ESI):</u> Calcd for $C_{26}H_{27}O_2F_3Br$ [M+H]$^+$ 507.1147, Found: 507.1154.

5.4.2.3 Synthesis and characterization of 4.34 (Table 4.1, entry 2):

It was synthesized by mixing **4.28a** (85.0 mg, 0.259 mmol) and NBS (51.2 mg, 0.288 mmol) in 2,2,2-trifluoroethanol (5.2 mL) at 50 °C for 8 h. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1 to 90:10) gave **4.31a** in 72% yield (44.6 mg, 0.187 mmol) as a 91:9 diastereomeric mixture (based on ^{1}H NMR analysis) as colorless oil, along with **4.34** in 3% yield (1.8 mg, 0.08 mmol) as a single diastereomer as colorless oil.

(2*S,3*S**)-2-benzyl-3-phenylbutan-1-ol (4.34)**[49]



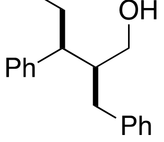
^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.33–7.15 (m, 10H), 3.38 (dd, *J* = 11.2, 5.6 Hz, 1H), 3.30 (dd, *J* = 11.2, 4.4 Hz, 1H), 2.96 (qd, *J* = 7.2, 7.2 Hz, 1H), 2.86 (dd, *J* = 13.6, 4.4 Hz, 1H), 2.56 (dd, *J* = 13.6, 10.0 Hz, 1H), 2.02–1.94 (m, 1H), 1.38 (d, *J* = 7.2 Hz, 3H), 1.01 (br s, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 145.9, 140.9, 129.1, 128.44, 128.35, 127.6, 126.2, 125.9, 62.3, 49.2, 40.1, 34.4, 18.4.

5.4.2.4 Synthesis and characterization of bromo alcohol 4.35 (Table 4.1, entry 4):

It was synthesized using **4.28a** (164.0 mg, 0.499 mmol) and NBS (98.0 mg, 0.551 mmol) in 2,2,2-trifluoroethanol (10 mL) at 24 °C for 10 min, then 50 °C for 30 min. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1) gave **4.31a** in 40% yield (47.4 mg, 0.199 mmol) as a 91:9 diastereomeric mixture (based on ^{1}H NMR analysis) as colorless oil, along with bromoalcohol **4.35** in 17% yield (27.7 mg, 0.089 mmol) as a 90:10 diastereomeric mixture (based on ^{1}H NMR analysis) as colorless oil. The bromoalcohol **4.35** was found to readily undergo cyclization to tetrahydrofuran **4.31a** at room temperature (24 °C) slowly but spontaneously.

(*2S,*3S**)-2-benzyl-4-bromo-3-phenylbutan-1-ol (4.35)**

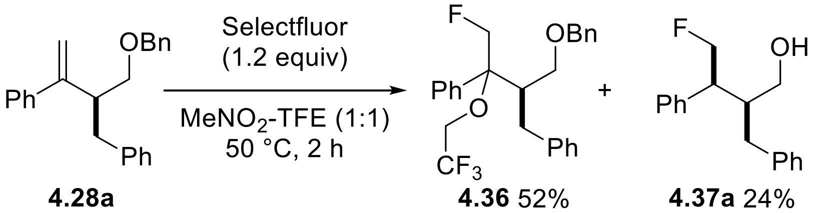


^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.41–7.14 (m, 10H), 3.94 (dd, *J* = 10.4, 5.2 Hz, 1H), 3.83 (dd, *J* = 10.4, 8.4 Hz, 1H), 3.42 (dd, *J* = 11.2, 5.2 Hz, 1H), 3.34 (dd, *J* = 11.2, 4.0 Hz, 1H), 3.20 (ddd, *J* = 7.2, 5.6, 5.6 Hz, 1H), 2.80 (dd, *J* = 13.6, 5.2 Hz, 1H), 2.61 (dd, *J* = 13.6, 9.2 Hz, 1H), 2.43–2.30 (m, 1H), 1.15 (br, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 140.4, 140.0, 129.1, 128.54, 128.52, 128.51, 127.2, 126.2, 61.9, 49.0, 45.5, 37.6, 35.2.

MS (HRMS ESI): Calcd for $C_{17}H_{20}OBr$ $[M+H]^+$ 319.0698, Found: 319.0696.

5.4.2.5 Synthesis and characterization of 4.36 (Table 4.2, entry 3):



It was synthesized by mixing **4.28a** (98.4 mg, 0.300 mmol) and Selectfluor (126.4 mg, 0.357 mmol) in 2,2,2-trifluoroethanol (1.5 mL) and nitromethane (1.5 mL) at 50 °C for 2 h. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1) furnished **4.36** in 52% yield (70.0 mg, 0.157 mmol) as a 85:15 diastereomeric mixture (based on ^{19}F NMR analysis) as colorless oil, along with **4.37a** in 24% yield (19.0 mg, 0.073 mmol) as a 99:1 diastereomeric mixture (based on ^{19}F NMR analysis) as colorless oil.

NMR data of the major isomer of **4.36** are described below:

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.48–7.28 (m, 9H), 7.24–7.05 (m, 4H), 6.92–6.86 (m, 2H), 5.32 (dd, *J* = 31.6, 11.6 Hz, 1H), 5.20 (dd, *J* = 33.2, 11.6 Hz, 1H), 4.43 (d, *J* = 11.6 Hz, 1H), 4.30 (d, *J* = 11.6 Hz, 1H), 4.06–3.96 (m, 1H), 3.77–3.74 (m, 2H), 3.10 (dd, *J* = 10.0, 5.2 Hz, 1H), 2.55 (dd, *J* = 12.8, 2.4 Hz, 1H), 2.36 (dd, *J* = 12.8, 12.8 Hz, 1H), 2.25 – 2.23 (m, 1H).

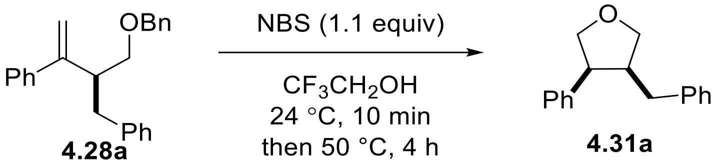
^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 140.3, 138.2, 137.3 (d, $J_{C\text{-}F}$ = 2.0 Hz), 128.9, 128.6, 128.4, 128.1, 127.8, 127.61, 127.58, 126.0, 125.5, 124.1 (q, $J_{C\text{-}F}$ = 276.0 Hz), 85.8 (d, $J_{C\text{-}F}$ =173.2 Hz), 84.5 (d, $J_{C\text{-}F}$ = 15.2 Hz), 73.0, 66.5, 63.6 (qd, $J_{C\text{-}F}$ = 41.2, 7.0 Hz), 51.2 (d, $J_{C\text{-}F}$ = 5.3 Hz), 31.9.

^{19}F NMR (376 MHz, CDCl$_3$): δ -74.42 (dd, J = 8.5, 8.5 Hz, 3F), -223.49 (dd, J = 48.1, 48.1 Hz, 1F).

MS (HRMS ESI): Calcd for $C_{26}H_{27}O_2F_4$ [M+H]$^+$ 447.1947, Found: 447.1948.

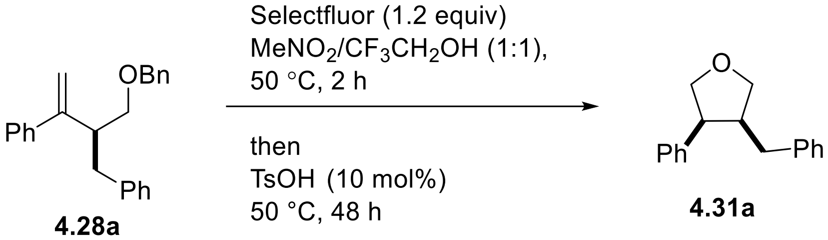
5.4.3 General procedure of Hydrohalogenation

Conditions A



To a solution of (*S**)-(2-((benzyloxy)methyl)but-3-ene-1,3-diyl)dibenzene (**4.28a**) (98.0 mg, 0.298 mmol) in 2,2,2-trifluoroethanol (6 mL) was added NBS (59.3 mg, 0.333 mmol) and the reaction mixture was stirred at 24 °C for 15 min, then at 50 °C for 4 h. The reaction mixture was cooled to 24 °C and quenched with water. The organic materials were then extracted thrice with Et_2O and the combine extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (silica gel, hexane:EtOAc = 99:1) to give **4.31a** in 74% yield (52.7 mg, 0.221 mmol) as a 91:9 diastereomeric mixture (based on ^{1}H NMR analysis) as colorless oil.

Conditions B



To a solution of (*S**)-(2-((benzyloxy)methyl)but-3-ene-1,3-diyl)dibenzene (**4.28a**) (164.0 mg, 0.499 mmol) in 2,2,2-trifluoroethanol (2.3 mL) and nitromethane (2.5 mL) was added Selectfluor (212.4 mg, 0.600 mmol) and the reaction mixture was stirred at 50 °C for 2 h. A solution of *p*-toluenesulfonic acid monohydrate (TsOH•H_2O) (0.250 M, 0.2 mL, 10 mol%) (Prepared from 47.6 mg of TsOH•H_2O and 1 mL of 2,2,2-trifluoroethanol) was added and the reaction mixture was stirred at 50 °C for 48 h. The reaction mixture was cooled to 24 °C and quenched with water. The organic materials were then extracted thrice with Et_2O. The combined extracts were then washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (silica gel, hexane:EtOAc = 99:1) to give **4.31a** in 76% yield (89.9 mg, 0.397 mmol) as a 96:4 diastereomeric mixture (based on ^{1}H NMR analysis) as colorless oil.

5.4.4. Gram-scale procedures for synthesis of 4.31a

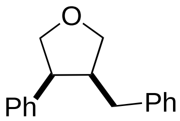
To a solution of (*S**)-(2-((benzyloxy)methyl)but-3-ene-1,3-diyl)dibenzene (**4.28a**) (1.005 g, 3.059 mmol) in 2,2,2-trifluoroethanol (60 mL) was added NBS (599.0 mg, 3.366 mmol) and the reaction mixture was stirred at 24 °C for 15 min. The reaction mixture was stirred at 50 °C for 3 h before it was quenched with water at 24 °C. The organic materials were then extracted thrice with Et_2O and the combined extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (silica gel, hexane:EtOAc = 99:1) to give **4.31a** in 67% yield 485.5 mg, 2.037 mmol) as a 91:9 diastereomeric mixture (based on ^{1}H NMR analysis) as yellow oil.

Conditions B:

To a solution of (*S**)-(2-((benzyloxy)methyl)but-3-ene-1,3-diyl)dibenzene (**4.28a**) (1.019 g, 3.101 mmol) in 2,2,2-trifluoroethanol (15 mL) and nitromethane (15.5 mL) was added Selectfluor (1.387 g, 3.72 mmol) and the reaction mixture was stirred at 50 °C for 2 h. A solution of *p*-toluenesulfonic acid monohydrate (TsOH•H_2O) (0.250 M, 0.5 mL, 10 mol%) (Prepared from 118.6 mg of TsOH•H_2O and 1 mL of 2,2,2-trifluoroethanol) was added and the reaction mixture was stirred at 50 °C for 45h. The reaction mixture was cooled to 24 °C and quenched with water. The organic materials were then extracted thrice with Et_2O and the combine extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (silica gel, hexane:EtOAc = 98:2) to give **4.31a** in 71% yield (520.8 mg, 2.185 mmol) as a 96:4 diastereomeric mixture (based on ^{1}H NMR analysis) as colorless oil.

5.4.5 Characterization of the products

5.4.5.1. (3*S**,4*S**)-3-benzyl-4-phenyltetrahydrofuran (4.31a)



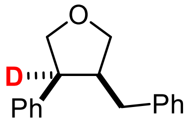
^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.36–7.32 (m, 2H), 7.29–7.19 (m, 5H), 7.17–7.14 (m, 1H), 7.03–7.02 (m, 2H), 4.21 (dd, *J* = 8.4, 6.4 Hz, 1H), 4.15 (dd, *J* = 8.4, 4.0 Hz, 1H), 3.92 (dd, *J* = 8.4, 7.6 Hz, 1H), 3.68 (dd, *J* = 8.4, 8.4 Hz, 1H), 3.47 (ddd, *J* = 10.8, 6.4, 4.0 Hz, 1H), 2.95–2.80 (m, 1H), 2.44 (dd, *J* = 14.0, 5.6 Hz, 1H), 2.12 (dd, *J* = 14.0, 9.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 140.6, 140.3, 128.6, 128.5, 128.33, 128.28, 126.6, 125.9, 73.8, 71.9, 48.3, 45.4, 34.8.

MS (HRMS ESI): Calcd for $C_{17}H_{19}O$ $[M+H]^+$ 239.1436, Found: 239.1441.

IR (neat, cm^{-1}): 1070 [ν(C-O)], 1048 [ν(C-O)].

5.4.5.2. (3*S**,4*S**)-3-benzyl-4-phenyltetrahydrofuran-4-*d* (4.31a-[D])



Conditions A: Prepared from **4.28a-[D$_2$]** (175.5 mg, 0.501 mmol) with NBS (1.1 equiv) at 24 °C for 10 min, followed by stirring at 50 °C for 5 h. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1) gave **4.31a-[D]** in 67% yield (80.7 mg, 0.337 mmol) as a 93:7 diastereomeric mixture (based on ^{1}H NMR analysis) as yellow oil with >99% D incorporation.

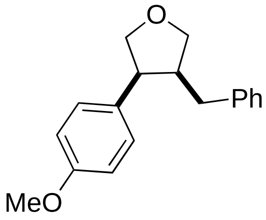
Condition B: Prepared from **4.28a-[D$_2$]** (175.0 mg, 0.500 mmol) with Selectfluor (1.2 equiv) at 50 °C for 2 h, followed by 10 mol% of TsOH•H_2O at 50 °C for 46 h. Purification by flash column chromatography (silica gel, hexane:EtOAc = 98:2) gave **4.31a-[D]** in 80% yield (95.4 mg, 0.400 mmol) as a 97:3 diastereomeric mixture (based on ^{1}H NMR analysis) as colorless oil with >99% D incorporation.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.36–7.32 (m, 2H), 7.29–7.19 (m, 5H), 7.17–7.14 (m, 1H), 7.03–7.01 (m, 2H), 4.20 (d, *J* = 8.4 Hz, 1H), 4.15 (d, *J* = 8.4 Hz, 1H), 3.92 (dd, *J* = 8.4, 8.0 Hz, 1H), 3.68 (dd, J = 8.4, 8.0 Hz, 1H), 2.91–2.83 (m, 1H), 2.44 (dd, J = 14.0, 5.2 Hz, 1H), 2.12 (dd, J = 14.0, 10.0 Hz, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 140.6, 140.3, 128.6, 128.5, 128.34, 128.29, 126.6, 125.9, 73.8, 72.0, 47.9 (t, J_{C-D} = 20.2 Hz), 45.3, 34.9.

MS (HRMS ESI): Calcd for $C_{17}H_{18}DO$ $[M+H]^+$ 240.1499, Found: 240.1500.

5.4.5.3. (3*S**,4*S**)-3-benzyl-4-(4-methoxyphenyl)tetrahydrofuran (4.31b)



Conditions A: Prepared from **4.28b** (179.3 mg, 0.501 mmol) with NBS (1.1 equiv) at 24 °C for 10 min, followed by stirring at 50 °C for 3 h. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1) gave **4.31b** in 68% yield (91.3 mg, 0.340 mmol) as a 96:4 diastereomeric mixture (based on ^{1}H NMR analysis) as yellow oil.

Conditions B: Prepared from **4.28b** (179.7 mg, 0.501 mmol) with Selectfluor (1.2 equiv) at 50 °C for 1 h, followed by 10 mol% of TsOH•H$_2$O at 50 °C for 48 h. Purification by flash column chromatography (silica gel, hexane:EtOAc = 98:2) gave **4.31b** in 80% yield (108.1 mg, 0.403 mmol) as a 99:1 diastereomeric mixture (based on ^{1}H NMR analysis) as colorless oil.

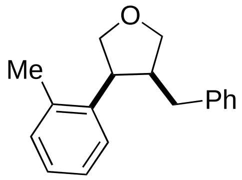
^{1}H NMR (500 MHz, CDCl$_3$): δ(ppm) 7.28–7.20 (m, 2H), 7.19–7.11 (m, 3H), 7.06–7.01 (m, 2H), 6.90–6.84 (m, 2H), 4.18 (dd, J = 8.5, 6.5 Hz, 1H), 4.10 (dd, J = 8.5, 4.0 Hz, 1H), 3.91 (dd, *J* = 8.5, 7.5 Hz, 1H), 3.82 (s, 3H), 3.66 (dd, *J* = 8.5, 8.5 Hz, 1H), 3.43 (ddd, *J* = 6.5, 4.0, 4.0 Hz, 1H), 2.89–2.78 (m, 1H), 2.44 (dd, *J* = 14.0, 5.5 Hz, 1H), 2.13 (dd, *J* = 14.0, 10.0 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 158.3, 140.7, 132.3, 129.5, 128.5, 128.3, 125.9, 113.7, 74.0, 71.8, 55.2, 47.5, 45.4, 34.8.

MS (HRMS ESI): Calcd for $C_{18}H_{21}O_2$ $[M+H]^+$ 269.1542, Found: 269.1541.

IR (neat, cm^{-1}): 1246 [ν(C-O)], 1179 [ν(C-O)].

5.4.5.4. (3*S**,4*S**)-3-benzyl-4-(o-tolyl)tetrahydrofuran (4.31c)



Conditions A: Prepared from **4.28c** (171.2 mg, 0.500 mmol) with NBS (1.1 equiv) at 24 °C for 10 min, followed by stirring at 50 °C for 3 h. Purification by flash column chromatography (silica gel, hexane:EtOAc = 96:4) gave **4.31c** in 47% yield (59.8 mg, 0.237 mmol) as a 99:1 diastereomeric mixture (based on ^{1}H NMR analysis) as colorless oil.

Conditions B: Prepared from **4.28c** (171.3 mg, 0.500 mmol) with Selectfluor (1.2 equiv) at 50 °C for 2 h, followed by 10 mol% of TsOH•H_2O at 50 °C for 48 h. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1) gave **4.31c** in 35% yield (43.9 mg, 0.174 mmol) as a 99:1 diastereomeric mixture (based on ^{1}H NMR analysis) as colorless oil.

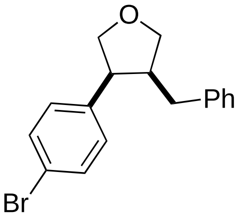
^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.32–7.29 (m, 1H), 7.24–7.19 (m, 3H), 7.18–7.09 (m, 3H), 6.98–6.97 (m, 2H), 4.23–4.14 (m, 2H), 3.93 (dd, *J* = 8.5, 7.5 Hz, 1H), 3.76–3.68 (m, 2H), 2.96–2.91 (m, 1H), 2.37 (dd, *J* = 14.0, 5.0 Hz, 1H), 2.27 (s, 3H), 2.16 (dd, *J* = 14.0, 10.5 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 140.6, 138.3, 136.6, 130.3, 128.6, 128.3, 127.3, 126.4, 126.2, 125.9, 73.4, 72.6, 44.0, 43.7, 35.2, 20.2.

MS (HRMS ESI): Calcd for $C_{18}H_{21}O$ $[M+H]^+$ 253.1592, Found: 253.1599.

IR (neat, cm^{-1}): 1112 [ν(C-O)], 1071 [ν(C-O)].

5.4.5.5. (3*S**,4*S**)-3-benzyl-4-(4-bromophenyl)tetrahydrofuran (4.31d)



Conditions A: Prepared from **4.28d** (204.0 mg, 0.501 mmol) with NBS (1.1 equiv) at 24 °C for 10 min, followed by stirring at 50 °C for 4 h. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1) gave **4.31d** in 63% yield (100.5 mg, 0.317 mmol) as a 90:10 diastereomeric mixture (based on ^{1}H NMR analysis) as yellow oil.

Conditions B: Prepared from **4.28d** (203.5 mg, 0.500 mmol) with Selectfluor (1.2 equiv) at 50 °C for 1 h, followed by 10 mol% of $TsOH•H_2O$ at 50 °C for 48 h. Purification by flash column chromatography (silica gel, hexane:EtOAc = 98:2) gave **4.31d** in 69% yield (109.9 mg, 0.346 mmol) as a 97:3 diastereomeric mixture (based on ^{1}H NMR analysis) as yellow oil.

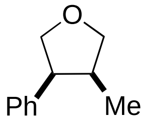
^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.48–7.43 (m, 2H), 7.28–7.21 (m, 2H), 7.20–7.14 (m, 1H), 7.11–7.08 (m, 2H), 7.04–6.99 (m, 2H), 4.17 (dd, *J* = 9.0, 6.0 Hz, 1H), 4.09 (dd, *J* = 9.0, 3.5 Hz, 1H), 3.93 (dd, *J* = 8.5, 7.5 Hz, 1H), 3.64 (dd, *J* = 8.5, 8.5 Hz, 1H), 3.41 (ddd, *J* = 6.0, 3.5, 3.5 Hz, 1H), 2.96–2.85 (m, 1H), 2.41 (dd, *J* = 14.0, 6.0 Hz, 1H), 2.14 (dd, *J* = 14.0, 9.5 Hz, 1H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 140.2, 139.5, 131.4, 130.3, 128.44, 128.36, 126.1, 120.4, 73.9, 71.7, 47.7, 45.1, 34.8.

MS (HRMS ESI): Calcd for $C_{17}H_{18}OBr$ $[M+H]^+$ 317.0541, Found: 317.0546.

IR (neat, cm^{-1}): 1108 [ν(C-O)], 1072 [ν(C-O)], 699 [ν(C-Br)].

5.4.5.6. (3*S**,4*S**)-3-methyl-4-phenyltetrahydrofuran (4.31e)[53]



Conditions A: Prepared from **4.28e** (125.6 mg, 0.498 mmol) with NBS (1.1 equiv) at 24 °C for 10 min, followed by stirring at 50 °C for 11 h. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1) gave **4.31e** in 49% yield (39.4 mg, 0.243 mmol) as a 94:6 diastereomeric mixture (based on ^{1}H NMR analysis) as colorless oil.

Conditions B: Prepared from **4.28e** (125.7 mg, 0.498 mmol) with Selectfluor (1.2 equiv) at 50 °C for 2 h, followed by 10 mol% of TsOH•H$_2$O at 50 °C for 48 h. Purification by flash column chromatography (silica gel, hexane:EtOAc = 98:2) gave **4.31e** in 70% yield (56.3 mg, 0.347 mmol) as a 97:3 diastereomeric mixture (based on ^{1}H NMR analysis) as colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.30–7.29 (m, 2H), 7.25–7.16 (m, 3H), 4.18 (dd, *J* = 8.8, 6.4 Hz, 1H), 4.12 (dd, *J* = 8.8, 4.8 Hz, 1H), 4.06 (dd, *J* = 8.0, 7.2 Hz, 1H), 3.52 (dd, *J* =

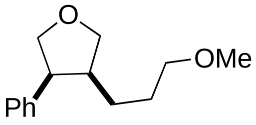
8.0, 7.2 Hz, 1H), 3.41–3.66 (m, 1H), 2.63 (dddt, *J* = 7.2, 7.2, 7.2, 7.2 Hz, 1H), 0.68 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 140.2, 128.4, 128.2, 126.3, 74.0, 73.1, 48.7, 38.0, 13.4.

MS (HRMS ESI): Calcd for $C_{11}H_{15}O$ [M+H]$^+$ 163.1123, Found: 163.1126.

IR (neat, cm^{-1}): 1086 [ν(C-O)], 1049 [ν(C-O)].

5.4.5.7. (3*S**,4*S**)-3-(3-methoxypropyl)-4-phenyltetrahydrofuran (4.31f)



Conditions A: Prepared from **4.28f** (155.3 mg, 0.500 mmol) with NBS (1.1 equiv) at 24 °C for 10 min, followed by stirring at 50 °C for 11 h. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1) gave **4.31f** in 61% yield (66.7 mg, 0.303 mmol) as a 91:9 diastereomeric mixture (based on ^{1}H NMR analysis) as pale yellow oil.

Conditions B: Prepared from **4.28f** (156.0 mg, 0.502 mmol) with Selectfluor (1.2 equiv) at 50 °C for 2 h, followed by 10 mol% of TsOH•H_2O at 50 °C for 48 h. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1) gave **4.31f** in 60% yield (66.4 mg, 0.301 mmol) as a 99:1 diastereomeric mixture (based on ^{1}H NMR analysis) as yellow oil.

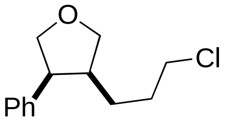
^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.34–7.27 (m, 2H), 7.26–7.17 (m, 3H), 4.17 (dd, *J* = 8.8, 6.4 Hz, 1H), 4.08 (dd, *J* = 8.8, 3.2 Hz, 1H), 4.07 (dd, *J* = 8.4, 8.4 Hz, 1H), 3.58 (dd, *J* = 8.4, 8.4 Hz, 1H), 3.37 (ddd, *J* = 6.4, 3.2, 3.2 Hz, 1H), 3.24 (s, 3H), 3.22 (dd, *J* = 6.8, 6.8 Hz, 2H), 2.57–2.47 (m, 1H), 1.57–1.37 (m, 2H), 1.16–1.08 (m, 1H), 1.01–0.85 (m, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 140.7, 128.4, 128.3, 126.4, 74.3, 72.5, 72.1, 58.4, 48.2, 44.0, 28.6, 25.0.

MS (HRMS ESI): Calcd for $C_{14}H_{21}O_2$ $[M+H]^+$ 221.1542, Found: 221.1544.

IR (neat, cm^{-1}): 1182 [ν(C-O)], 1115 [ν(C-O)], 1086 [ν(C-O)], 1057 [ν(C-O)].

5.4.5.8. (3*S**,4*S**)-3-(3-chloropropyl)-4-phenyltetrahydrofuran (4.31g)



Conditions A: Prepared from **4.28g** (157.1 mg, 0.499 mmol) with NBS (1.1 equiv) at 24 °C for 10 min, followed by stirring at 50 °C for 4 h. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1) gave **4.31g** in 78% yield (88.0 mg, 0.392 mmol) as a 91:9 diastereomeric mixture (based on ^{1}H NMR analysis) as colorless oil.

Conditions B: Prepared from **4.28g** (157.2 mg, 0.499 mmol) with Selectfluor (1.2 equiv) at 50 °C for 2 h, followed by 10 mol% of TsOH•H_2O at 50 °C for 48 h. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1) gave **4.31g** in 76% yield (85.7 mg, 0.381 mmol) as a 95:5 diastereomeric mixture (based on ^{1}H NMR analysis) as colorless oil.

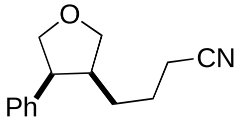
^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.34–7.30 (m, 2H), 7.24–7.20 (m, 3H), 4.18 (dd, *J* = 8.4, 6.0 Hz, 1H), 4.10 (dd, *J* = 8.4, 3.2 Hz, 1H), 4.08 (dd, *J* = 8.4, 8.4 Hz, 1H), 3.58 (dd, *J* = 8.4, 8.4 Hz, 1H), 3.42–3.36 (m, 1H), 3.37 (dd, *J* = 6.8, 6.8 Hz, 2H), 2.57–2.47 (m, 1H), 1.74–1.60 (m, 2H), 1.25–1.16 (m, 1H), 1.07–0.98 (m, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 140.4, 128.4, 128.3, 126.5, 74.2, 71.9, 48.1, 44.6, 43.5, 31.5, 25.9.

MS (HRMS ESI): Calcd for $C_{13}H_{18}OCl$ $[M+H]^+$ 225.1046, Found: 225.1048.

IR (neat, cm^{-1}): 1182 [ν(C-O)], 1085 [ν(C-O)], 703 [ν(C-Cl)].

5.4.5.9. 4-((3*S**,4*S**)-4-phenyltetrahydrofuran-3-yl)butanenitrile (4.31h)



Conditions A: Prepared from **4.28h** (152.7 mg, 0.500 mmol) with NBS (1.1 equiv) at 24 °C for 10 min, followed by stirring at 50 °C for 3 h. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1) gave **4.31h** in 67% yield (71.7 mg, 0.333 mmol) as a 91:9 diastereomeric mixture (based on ^{1}H NMR analysis) as colorless oil.

Conditions B: Prepared from **4.28h** (146.0 mg, 0.478 mmol) with Selectfluor (1.2 equiv) at 50 °C for 2 h, followed by 10 mol% of $TsOH{\bullet}H_2O$ at 50 °C for 46 h. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1) gave **4.31h** in 62% yield (63.4 mg, 0.295 mmol) as a 98:2 diastereomeric mixture (based on ^{1}H NMR analysis) as colorless oil.

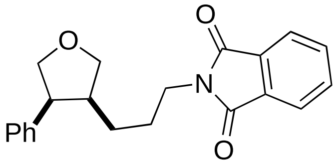
^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.36–7.30 (m, 2H), 7.28–7.23 (m, 1H), 7.22–7.20 (m, 2H), 4.18 (dd, *J* = 8.5, 6.0 Hz, 1H), 4.10 (dd, *J* = 8.5, 3.5 Hz, 1H), 4.08 (dd, *J* = 8.0, 8.0 Hz, 1H), 3.58 (dd, *J* = 8.0, 8.0 Hz, 1H), 3.40 (ddd, *J* = 6.0, 3.5, 3.5 Hz, 1H), 2.57–2.49 (m, 1H), 2.19 (dd, *J* = 7.0, 7.0 Hz, 2H), 1.64–1.47 (m, 2H), 1.25–1.15 (m, 1H), 1.10–0.98 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 140.2, 128.5, 128.3, 126.7, 119.3, 74.2, 71.8, 48.0, 43.5, 27.9, 24.4, 17.2.

MS (HRMS ESI): Calcd for $C_{14}H_{18}ON$ $[M+H]^+$ 216.1388, Found: 216.1398.

IR (neat, cm^{-1}): 2245 [ν(C≡N)], 1085 [ν(C-O)], 1056 [ν(C-O)].

5.4.5.10. 2-(3-((3*S**,4*S**)-4-phenyltetrahydrofuran-3-yl)propyl)isoindoline-1,3-dione (4.31i)



Conditions A: Prepared from **4.28i** (212.9 mg, 0.500 mmol) with NBS (1.1 equiv) at 24 °C for 10 min, followed by stirring at 50 °C for 3 h. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1) gave **4.31i** in 67% yield (111.6 mg, 0.333 mmol) as a 95:5 diastereomeric mixture (based on ^{1}H NMR analysis) as colorless oil.

Conditions B: Prepared from **4.28i** (212.8 mg, 0.500 mmol) with Selectfluor (1.2 equiv) at 50 °C for 2 h, followed by 10 mol% of TsOH•H_2O at 50 °C for 43 h. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1) gave **4.31i** in 66% yield (110.4 mg, 0.329 mmol) as a 98:2 diastereomeric mixture (based on ^{1}H NMR analysis) as colorless oil.

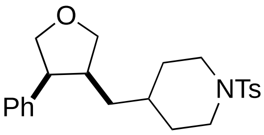
^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.84–7.78 (m, 2H), 7.75–7.67 (m, 2H), 7.24–7.14 (m, 4H), 7.11–7.03 (m, 1H), 4.16 (dd, *J* = 8.5, 6.0 Hz, 1H), 4.07 (dd, *J* = 8.5, 3.0 Hz, 1H), 4.05 (dd, *J* = 8.0, 8.0 Hz, 1H), 3.59–3.46 (m, 3H), 3.37 (ddd, *J* = 6.0, 3.0, 3.0 Hz, 1H), 2.62–2.47 (m, 1H), 1.68–1.49 (m, 2H), 1.09–0.94 (m, 2H).

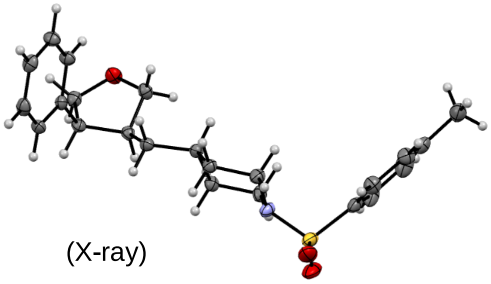
^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 168.2, 140.4, 133.8, 132.0, 128.4, 128.2, 126.3, 123.1, 74.4, 71.9, 47.9, 43.6, 37.7, 27.5, 25.5.

MS (HRMS ESI): Calcd for $C_{21}H_{22}O_3N$ $[M+H]^+$ 336.1600, Found: 336.1591.

IR (neat, cm^{-1}): 1701 [ν(C=O)], 1173 [ν(C-O)], 1157 [ν(C-O)].

5.4.5.11. 4-(((3*S**,4*S**)-4-phenyltetrahydrofuran-3-yl)methyl)-1-tosylpiperidine (4.31j)





(X-ray)

Conditions A: Prepared from **4.28j** (245.2 mg, 0.501 mmol) with NBS (1.1 equiv) at 24 °C for 10 min, followed by stirring at 50 °C for 4 h. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1) gave **4.31j** in 71% yield (114.5 mg, 0.354 mmol) as a 93:7 diastereomeric mixture (based on ^{1}H NMR analysis) as a white solid, which was recrystallized from EtOAc to afford colorless crystal. The stereochemistry of **4.31j** could be confirmed by X-ray crystallography analysis (CCDC-1956712).

Conditions B:

Prepared from **4.28j** (244.8 mg, 0.500 mmol) with Selectfluor (1.2 equiv) at 50 °C for 2 h, followed by 10 mol% of TsOH•H_2O at 50 °C for 45 h to form **4.31j** in 18% yield (based on ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard along) with unidentified complex mixture. The diastereomeric ratio of **4.31j** was not determined.

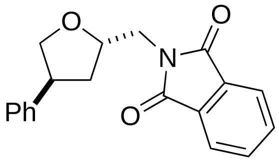
^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.64–7.58 (m, 2H), 7.36–7.27 (m, 4H), 7.25–7.19 (m, 1H), 7.16–7.14 (m, 2H), 4.14 (dd, *J* = 9.0, 6.5 Hz, 1H), 4.06 (dd, *J* = 9.0, 3.5 Hz, 1H), 3.98 (dd, *J* = 8.0, 8.0 Hz, 1H), 3.75–3.67 (m, 2H), 3.48 (dd, *J* = 8.0, 8.0 Hz, 1H), 3.31 (ddd, *J* = 6.5, 3.5, 3.5 Hz, 1H), 2.63–2.50 (m, 1H), 2.43 (s, 3H), 2.17–2.10 (m, 2H), 1.66–1.54 (m, 2H), 1.22–1.09 (m, 2H), 1.06–0.94 (m, 2H), 0.83–0.72 (m, 1H).

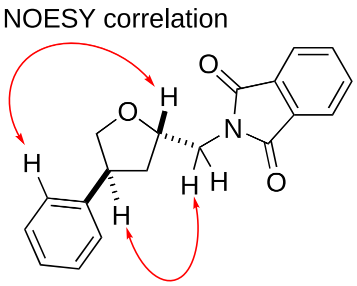
^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 143.3, 140.5, 133.1, 129.5, 128.4, 128.3, 127.7, 126.5, 74.1, 71.8, 48.3, 46.3 (overlapped with 2C), 40.8, 34.9, 33.9, 32.0, 31.1, 21.5.

MS (HRMS ESI): Calcd for $C_{23}H_{30}O_3NS$ $[M+H]^+$ 400.1946, Found: 400.1944.

IR (neat, cm^{-1}): 1245 [ν(C-N)], 1155 [ν(C-O)], 1090 [ν(C-O)], 1071 [ν(S=O)], 1053 [ν(S=O)]

5.4.5.12. 2-(((2*S**,4*S**)-4-phenyltetrahydrofuran-2-yl)methyl)isoindoline-1,3-dione (4.31k)





Condition A:

Prepared from **4.28k** (205.8 mg, 0.500 mmol) with NBS (1.1 equiv) at 24 °C for 20 min and at 80 °C for 7 h. Purification by flash column chromatography (silica gel, hexane:EtOAc = 85:15) gave **4.31k** in 79% yield (121.5 mg, 0.395 mmol) as a 96:4 diastereomeric mixture (based on ^{1}H NMR analysis) as yellow oil.

Condition B: Prepared from **4.28k** (205.3 mg, 0.500 mmol) with Selectfluor (1.2 equiv) at 50 °C for 30 min, followed by 10 mol% of TsOH•H_2O at 80 °C for 53 h. Purification by flash column chromatography (silica gel, hexane:EtOAc = 88:12) gave **4.31k** in 64% yield (98.9 mg, 0.322 mmol) as a 96:4 diastereomeric mixture (based on ^{1}H NMR analysis) as colorless oil.

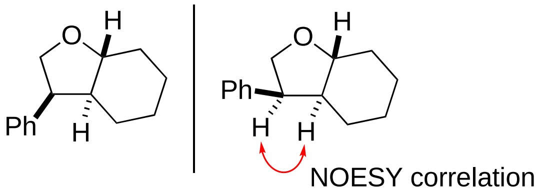
^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.90–7.82 (m, 2H), 7.76–7.67 (m, 2H), 7.32–7.29 (m, 2H), 7.20–7.24 (m, 3H), 4.55 (dddd, *J* = 13.0, 7.5, 7.5, 5.0 Hz, 1H), 4.30 (dd, *J* = 8.5, 7.5 Hz, 1H), 3.91 (dd, *J* = 13.0, 8.5 Hz, 1H), 3.78–3.75 (m, 1H), 3.73 (dd, *J* = 8.5, 5.0 Hz, 1H), 3.56 (dddd, *J* = 7.5, 7.5, 7.5, 7.5 Hz, 1H), 2.25–2.19 (m, 1H), 2.19–2.14 (m, 1H).

^{13}C NMR (125 MHz, CDCl$_3$): δ(ppm) 168.3, 142.1, 133.9, 132.0, 128.6, 127.1, 126.6, 123.3, 76.3, 74.5, 44.1, 41.9, 37.6.

MS (HRMS ESI): Calcd for $C_{19}H_{18}NO_3$ $[M+H]^+$ 308.1287, Found: 308.1292.

IR (neat, cm^{-1}): 1708 [ν(C=O)], 1190 [ν(C-N)], 1134 [ν(C-O)], 1087 [ν(C-O)].

5.4.5.13. (3*R**,3a*R**,7a*S**)-3-phenyloctahydrobenzofuran (4.31l)



Conditions A: Prepared from **4.28l** (163.2 mg, 0.497 mmol) with NBS (1.1 equiv) at 24 °C for 10 min, followed by stirring at 50 °C for 1.5 h. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1) gave **4.31l** in 87% yield (87.6 mg, 0.433 mmol) as a 93:7 diastereomeric mixture (based on ^{1}H NMR analysis) as colorless oil.

Conditions B: Prepared from **4.28l** (146.7 mg, 0.502 mmol) with Selectfluor (1.2 equiv) at 50 °C for 2 h, followed by 10 mol% of TsOH•H$_2$O at 50 °C for 48 h. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1) gave **4.31l** in 80% yield (81.4 mg, 0.402 mmol) as a 94:6 diastereomeric mixture (based on ^{1}H NMR analysis) as colorless oil.

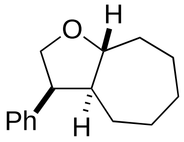
^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.33–7.29 (m, 2H), 7.25–7.20 (m, 3H), 4.31 (dd, *J* = 9.2, 7.2 Hz, 1H), 4.18 (dd, *J* = 9.2, 2.4 Hz, 1H), 3.47 (ddd, *J* = 7.2, 7.2, 2.4 Hz, 1H), 3.37 (ddd, *J* = 10.8, 10.8, 4.0 Hz, 1H), 2.24–2.11 (m, 1H), 1.77–1.55 (m, 4H), 1.40–1.27 (m, 1H), 1.24–0.99 (m, 2H), 0.52–0.42 (m, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 141.4, 128.2, 128.1, 126.2, 79.9, 73.2, 49.8, 47.2, 31.9, 26.3, 25.5, 23.9.

MS (HRMS ESI): Calcd for $C_{14}H_{19}O$ $[M+H]^+$ 2033.1436, Found: 203.1432.

IR (neat, cm^{-1}): 1084 [ν(C-O)], 1061 [ν(C-O)].

5.4.5.14. (3*R**,3a*R**,8a*S**)-3-phenyloctahydro-2H-cyclohepta[b]furan (4.31m)



Condition A: Prepared from **4.28m** (150.1 mg, 0.490 mmol) with NBS (1.1 equiv) at 24 °C for 2.5 h. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1) gave **4.31m** in 39% yield (40.9 mg, 0.189 mmol) as a 94:6 diastereomeric mixture (based on ^{1}H NMR analysis) as colorless oil.

Condition B: Prepared from **4.28m** (152.7 mg, 0.498 mmol) with Selectfluor (1.2 equiv) at 50 °C for 1 h, followed by 10 mol% of TsOH•H_2O at 50 °C for 42 h. Purification by flash column chromatography (silica gel, hexane:EtOAc = 98:2) gave **4.31m** in 55% yield (58.8 mg, 0.272 mmol) as a 95:5 diastereomeric mixture (based on ^{1}H NMR analysis) as yellow oil.

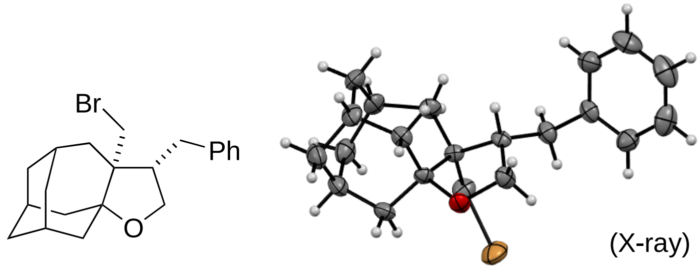
^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.34–7.27 (m, 2H), 7.27–7.17 (m, 3H), 4.27 (dd, *J* = 8.8, 6.0 Hz, 1H), 4.07 (dd, *J* = 8.8, 2.2 Hz, 1H), 3.82 (ddd, *J* = 10.0, 10.0, 4.4 Hz, 1H), 3.41–3.31 (m, 1H), 2.28–2.22 (m, 2H), 1.66–1.60 (m, 1H), 1.58–1.32 (m, 7H), 0.71–0.61 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 141.9, 128.6, 128.1, 126.2, 82.8, 73.8, 50.6, 49.2, 33.9, 27.4, 26.7, 25.7, 24.7.

MS (HRMS ESI): Calcd for $C_{15}H_{21}O$ $[M+H]^+$ 217.1592, Found: 217.1595.

IR (neat, cm^{-1}): 1090 [ν(C-O)], 1067 [ν(C-O)].

5.4.5.15. (3*S**,3a*R**,5*S**,10a*S**)-3-benzyl-3a-(bromomethyl)decahydro-5,9:7,10a-dimethanocyclonona[b]furan (4.38n-Br)



Conditions A: Prepared from **4.28n** (190.0 mg, 0.492 mmol) with NBS (1.1 equiv) at 24 °C for 10 min, followed by stirring at 50 °C for 7 h. Purification by flash column chromatography (silica gel, hexane:EtOAc = 95:5) gave **4.38n-Br** in 57% yield (104.8 mg, 0.279 mmol) as a single diastereomer as white solid which was recrystallized from hexane-CH_2Cl_2 to afford colorless crystal. The stereochemistry of **4.38n-Br** could be confirmed by the X-ray crystallography analysis (CCDC-1956716).

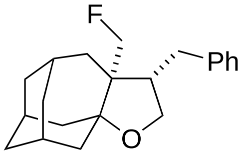
^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.34–7.24 (m, 2H), 7.21–7.18 (m, 3H), 3.85–3.79 (m, 3H), 3.62 (d, *J* = 11.6 Hz, 1H), 2.99–2.90 (m, 2H), 2.89–2.79 (m, 1H), 2.36–2.32 (m, 1H), 2.25–2.21 (m, 1H), 2.15–2.14 (m, 1H), 2.05 (br, 1H), 2.00–1.94 (m, 2H), 1.90–1.73 (m, 4H), 1.69–1.56 (m, 3H), 1.54–1.51 (m, 1H), 1.46–1.43 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 140.8, 128.5, 128.4, 126.1, 86.9, 70.2, 54.1, 51.4, 42.3, 42.2, 42.1, 38.0, 37.4, 37.3, 34.8, 32.2, 30.7, 28.2, 27.7.

MS (HRMS ESI): Calcd for $C_{21}H_{27}OBrNa$ $[M+Na]^+$ 397.1143, Found: 397.1137.

IR (neat, cm^{-1}): 1128 [ν(C-O)], 1088 [ν(C-O)], 655 [ν(C-Br)].

5.4.5.16. (3*S**,3a*R**,5*S**,10a*S**)-3-benzyl-3a-(fluoromethyl)decahydro-5,9:7,10a-dimethanocyclonona[b]furan (4.38n-F)



Conditions B: Prepared from **4.28n** (193.4 mg, 0.500 mmol) with Selectfluor (1.2 equiv) at 50 °C for 2 h, followed by 10 mol% of TsOH•H_2O at 50 °C for 17 h. Purification by flash column chromatography (silica gel, hexane:EtOAc = 96:4) gave **4.38n-F** in 40% yield (62.8 mg, 0.200 mmol) as a single diastereomer as white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.32–7.24 (m, 2H), 7.23–7.14 (m, 3H), 4.72 (dd, *J* = 88.5, 10.0 Hz, 1H), 4.62 (dd, *J* = 88.0, 10.0 Hz, 1H), 3.88 (dd, *J* = 8.5, 8.5 Hz, 1H), 3.66–3.59 (m, 1H), 2.89 (dd, *J* = 13.0, 4.0 Hz, 1H), 2.84–2.77 (m, 1H), 2.70–2.64 (m, 1H), 2.23–2.19 (m, 1H), 2.18–2.08 (m, 2H), 2.06–2.04 (m, 1H), 1.95 (br, 1H), 1.91–1.83 (m, 1H), 1.83–1.74 (m, 4H), 1.68–1.57 (m, 2H), 1.54–1.38 (m, 3H).

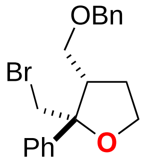
^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 141.0, 128.5, 128.4, 126.1, 86.3 (d, $J_{C\text{-}F}$ = 47.3 Hz), 85.6 (d, $J_{C\text{-}F}$ = 130.6 Hz), 70.8, 52.8, 51.4 (d, $J_{C\text{-}F}$ = 2.8 Hz), 42.1, 42.0, 38.0, 37.4, 36.9 (d, $J_{C\text{-}F}$ = 7.0 Hz), 35.1 (d, $J_{C\text{-}F}$ = 3.6 Hz), 32.3, 30.7, 28.2, 27.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ(ppm) -219.62 (dd, *J* = 49.6, 49.6 Hz).

MS (HRMS ESI): Calcd for $C_{21}H_{28}FO$ $[M+H]^+$ 315.2124, Found: 315.2130.

IR (neat, cm^{-1}): 1183 [ν(C-F)], 1030 [ν(C-O)], 1011 [ν(C-O)].

5.4.5.17. (2*S**,3*R**)-3-((benzyloxy)methyl)-2-(bromomethyl)-2-phenyltetrahydrofuran (4.39o-Br)



Condition A: Prepared from 4.28**o** (111.4 mg, 0.299 mmol) with NBS (1.1 equiv) at 24 °C for 10 min, followed by stirring at 50 °C for 2 h. Purification by flash column chromatography (silica gel, hexane:EtOAc = 95:5) gave **4.39o-Br** in 84% yield (91.0 mg, 0.252 mmol) as a single diastereomer as colorless oil.

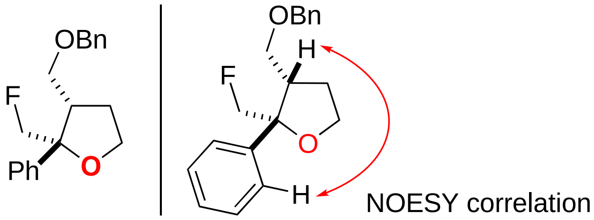
^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.53–7.43 (m, 2H), 7.41–7.29 (m, 7H), 7.29–7.21 (m, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.11 (ddd, *J* = 8.0, 8.0, 5.2 Hz, 1H), 3.94–3.89 (m, 1H), 3.82 (dd, *J* = 9.6, 8.0 Hz, 1H), 3.78 (s, 2H), 3.60 (dd, *J* = 9.6, 6.0 Hz, 1H), 2.89–2.76 (m, 1H), 2.06–1.74 (m, 1H), 1.94–1.85 (m, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 144.6, 137.9, 128.5, 128.1, 127.8, 127.7, 127.1, 125.5, 86.0, 73.4, 69.5, 66.6, 49.5, 39.6, 30.4.

MS (HRMS ESI): Calcd for $C_{19}H_{22}O_2Br$ $[M+H]^+$ 361.0803, Found: 361.0805.

IR (neat, cm^{-1}): 1096 [ν(C-O)], 1060 [ν(C-O)], 1027 [ν(C-O)], 698 [ν(C-Br)].

5.4.5.18. (2*S**,3*R**)-3-((benzyloxy)methyl)-2-(fluoromethyl)-2-phenyltetrahydrofuran (4.39o-F)



Condition B: Prepared from **4.28o** (186.1 mg, 0.500 mmol) with Selectfluor (1.2 equiv) at 50 °C for 2 h, followed by 10 mol% of TsOH•H_2O at 50 °C for 48 h. Purification by flash column chromatography (silica gel, hexane:EtOAc = 99:1) gave **4.39o-F** in 89% yield (133.2 mg, 0.444 mmol) as a single diastereomer as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.58–7.50 (m, 2H), 7.40–7.21 (m, 8H), 4.64 (dd, *J* = 47.6, 9.6 Hz, 1H), 4.61 (d, *J* = 11.6 Hz, 1H), 4.57 (d, *J* = 11.6 Hz, 1H), 4.47 (dd, *J* = 48.0, 9.6 Hz, 1H), 4.13 (ddd, *J* = 8.0, 8.0, 4.0 Hz, 1H), 3.93–3.82 (m, 2H), 3.73–3.64 (m, 1H), 2.90–2.74 (m, 1H), 2.12–1.99 (m, 1H), 1.94–1.79 (m, 1H)..

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 142.87 (d, $J_{C\text{-}F}$ = 5.8 Hz), 138.1, 128.4, 128.2, 127.7, 127.6, 127.3, 125.7, 86.3 (d, $J_{C\text{-}F}$ = 178.2 Hz), 86.2 (d, $J_{C\text{-}F}$ = 17.0 Hz), 73.3, 70.27 (d, $J_{C\text{-}F}$ = 4.1 Hz), 66.8, 48.5, 31.0.

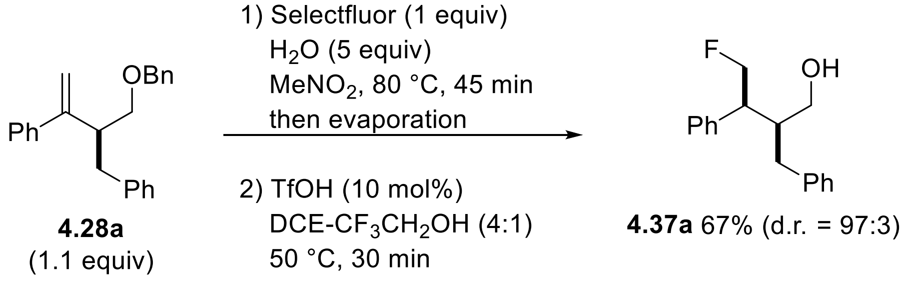
^{19}F NMR (282 MHz, $CDCl_3$): δ -220.94 (dd, *J* = 47.7, 47.4 Hz).

MS (HRMS ESI): Calcd for $C_{19}H_{21}O_2FNa$ $[M+Na]^+$ 323.1423, Found: 323.1424.

IR (neat, cm^{-1}): 1208 [ν(C-F)], 1097 [ν(C-O)], 1066 [ν(C-O)], 1026 [ν(C-O)].

5.4.6. Synthesis of fluoroalcohols:

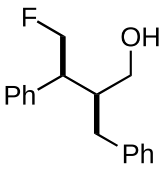
5.4.6.1. A general procedure for synthesis of fluoroalcohol 4.37a in one-pot



To a solution of (*S**)-(2-((benzyloxy)methyl)but-3-ene-1,3-diyl)dibenzene (**4.28a**) (180.7 mg, 0.550 mmol) in $MeNO_2$ (1.67 mL) and water (45 µL, 2.50 mmol) was added Selectfluor (186.5 mg, 0.500 mmol) and the reaction mixture was stirred at 80 °C for 1 h. The reaction mixture was then cooled to 24 °C and then the volatile materials were removed *in vacuo*. The resulting crude residue was re-dissolved in 1,2-dichloroethane-CF_3CH_2OH mixture (5 mL, 4:1) before triflic acid (4.41 µL, 0.050 mmol) was added using micropipette (Eppendorf, 0.5-10 µL) and the reaction mixture was stirred at 50 °C for 40 min. The reaction was quenched at 24 °C with a saturated aqueous solution of sodium bicarbonate. The organic materials were then extracted thrice with Et_2O and the combined extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (silica gel, hexane:EtOAc = 91:9) to give **4.37a** in 67% yield (86.1 mg, 0.333 mmol) based on Selectfluor as a 97:3 diastereomeric mixture (based on ^{19}F NMR analysis) as yellow oil.

5.4.6.2. Characterization of the products

5.4.6.2.1. (2*S**,3*S**)-2-benzyl-4-fluoro-3-phenylbutan-1-ol (4.37a)



<u>^{1}H NMR (400 MHz, $CDCl_3$):</u> δ(ppm) 7.39–7.24 (m, 7H), 7.23–7.19 (m, 3H), 4.90 (ddd, *J* = 28.0, 9.2, 5.6 Hz, 1H), 4.78 (ddd, *J* = 28.0, 9.2, 5.2 Hz, 1H), 3.41 (dd, *J* = 11.2, 4.8 Hz, 1H), 3.30 (dd, *J* = 11.2, 4.0 Hz, 1H), 3.14 (dddd, *J* = 26.0, 7.6, 5.6, 5.2 Hz, 1H), 2.90 (dd, *J* = 13.6, 5.2 Hz, 1H), 2.68 (dd, *J* = 13.6, 9.6 Hz, 1H), 2.34–2.26 (m, 1H), 1.13 (br s, 1H).

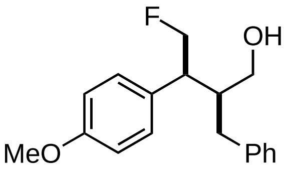
^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 140.25, 140.23 (d, *J* = 3.7 Hz), 129.1, 128.61, 128.56, 128.47, 127.0, 126.1, 85.53 (d, *J* = 169.7 Hz), 61.7, 47.3 (d, *J* = 18.3 Hz), 43.84 (d, *J* = 4.1 Hz), 34.9.

^{19}F NMR (282 MHz, CDCl$_3$): δ(ppm) -220.74 (ddd, *J* = 47.1, 47.1, 25.7 Hz).

MS (HRMS ESI): Calcd for $C_{17}H_{20}OF$ $[M+H]^+$ 259.1498, Found: 259.1496.

IR (neat, cm^{-1}): 3380 [ν(O–H)], 1028 [ν(C-F)], 998 [ν(C-OH)].

5.4.6.2.2. (2*S**,3*S**)-2-benzyl-4-fluoro-3-(4-methoxyphenyl)butan-1-ol (4.37b)



Prepared from **4.28b** (179.3 mg, 0.500 mmol) with Selectfluor (223.8 mg, 0.600 mmol) at 80 °C for 45 min and 10 mol% triflic acid for 15 min. Purification by flash column chromatography (silica gel, hexane:EtOAc = 91:9) gave **4.37b** in 70% yield (101.3 mg, 0.351 mmol) based on **4.37b** as a single diastereomer as yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.34–7.27 (m, 2H), 7.23–7.18 (m, 5H), 6.93–6.84 (m, 2H), 4.87 (ddd, *J* = 24.8, 9.2, 6.0 Hz, 1H), 4.75 (ddd, *J* = 24.4, 9.2, 6.0 Hz, 1H), 3.81 (s, 3H), 3.48–3.38 (m, 1H), 3.34–3.31 (m, 1H), 3.09 (dddd, *J* = 25.8, 7.2, 6.0, 6.0 Hz, 1H), 2.87 (dd, *J* = 13.6, 5.2 Hz, 1H), 2.67 (dd, *J* = 13.6, 9.6 Hz, 1H), 2.33 – 2.22 (m, 1H), 1.07 (br s, 1H).

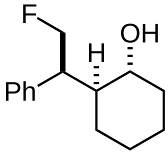
^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 158.6, 140.3, 132.07 (d, $J_{C\text{-}F}$ = 3.9 Hz), 129.5, 129.1, 128.5, 126.1, 114.0, 85.7 (d, $J_{C\text{-}F}$ = 169.6 Hz), 61.8, 55.2, 46.6 (d, $J_{C\text{-}F}$ = 18.1 Hz), 43.9 (d, $J_{C\text{-}F}$ = 3.7 Hz), 35.0.

^{19}F NMR (376 MHz, CDCl$_3$): δ(ppm) -220.48 (ddd, *J* = 47.4, 47.4, 25.6 Hz).

MS (HRMS ESI): Calcd for $C_{18}H_{22}FO_2$ $[M+H]^+$ 289.1604, Found: 289.1598.

IR (neat, cm^{-1}): 3430 [ν(O–H)], 1180 [ν(C-F)], 1030 [ν(C-O)].

5.4.6.2.3. (1*R**,2*S**)-2-((*S**)-2-fluoro-1-phenylethyl)cyclohexan-1-ol (4.37l)



Prepared from **4.28l** (160.7 mg, 0.550 mmol) with Selectfluor (186.5 mg, 0.500 mmol) at 80 °C for 1 h and 10 mol% triflic acid for 50 min. Purification by flash column chromatography (silica gel, hexane:EtOAc = 91:9) gave **4.37l** in 65% yield (71.9 mg, 0.323 mmol) based on Selectfluor as a 94:6 diastereomeric mixture (based on ^{19}F NMR analysis) as colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ(ppm) 7.38–7.15 (m, 5H), 4.98–4.93 (m, 1H), 4.85–4.83 (m, 1H), 3.47–3.24 (m, 2H), 2.04–1.87 (m, 1H), 1.78–1.65 (m, 3H), 1.46 (brs, 1H), 1.34–1.20 (m, 2H), 1.20–0.95 (m, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ(ppm) 140.0 (d, $J_{C\text{-}F}$ = 5.6 Hz), 128.8, 128.3, 126.7, 85.5 (d, $J_{C\text{-}F}$ = 167.4 Hz), 72.0, 48.5 (d, $J_{C\text{-}F}$ = 18.2 Hz), 47.7 (d, $J_{C\text{-}F}$ = 3.8 Hz), 36.3, 28.1, 25.5, 24.5.

^{19}F NMR (376 MHz, CDCl$_3$): δ(ppm) -216.2 (ddd, *J* = 45.9, 45.9, 17.9 Hz).

MS (HRMS ESI): Calcd for $C_{14}H_{20}OF$ $[M+H]^+$ 223.1498, Found: 223.1503.

IR (neat, cm^{-1}): 3381 [ν(O–H)], 1230 [ν(C-F)], 1095 [ν(C-OH)].

5.5. References

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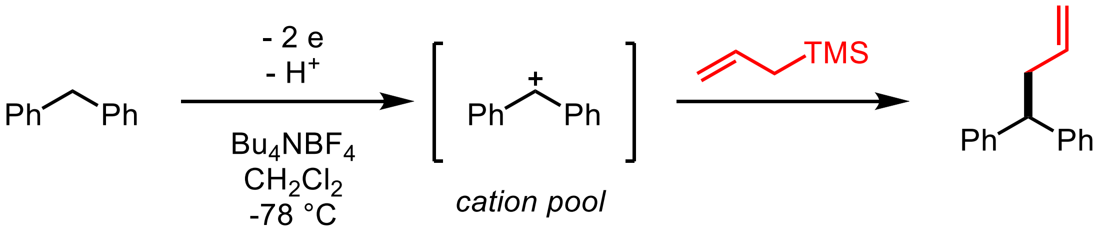
Chapter 6. Conclusion and Perspective

This thesis presented the synthetic applications of diastereoselective 1,5-hydride transfer onto carbocation intermediates formed from alcohols or alkenes upon electrophilic activation under Brønsted acid catalysis. The construction of multiple stereogenic centers was achieved diastereoselectively as the 1,5-hydride shift from electron-rich alkyl ethers to the transient carbocations generated from alcohols or alkenes occurs via the 6-membered chair-like transition state (Chapter 2). Moreover, the use of prochiral *endo*-aryl alkenes and external carbocations which was produced *in-situ* from activated alcohols allowed the *anti*-Markovnikov hydroalkylation of alkenes upon the key 1,5-hydride shift process (Chapter 3). Finally, electrophilic halogenation of aryl alkenes by *N*-bromosuccinimide (NBS) or Selectfluor, was found to trigger 1,5-hydride shift process to deliver *anti*-Markovnikov hydrohalogenation of alkenes, which resulted in the formation of diastereomerically enriched tetrahydrofurans upon the subsequent nucleophilic substitution of the resulting halo alcohols (Chapter 4).

Exploration on asymmetric variants of the 1,5-hydride shift using chiral Brønsted acid catalysis that can leverage rigid 6-membered ring chair-like transition state would be attractive as a future direction. For example, the utilization of chiral phosphoric acid and disulfonimide has been reported by Akiyama[1] and List[2] to undergo various acid-mediated synthesis, including the recent work of Mori and coworkers in enantioselective synthesis of polycyclic compound utilizing 1,5-hydride shift process.[3]

Leveraging on relatively unstable carbocations could also be envisaged by taking advantage of the cation pool methods[4] through electrolysis. For example, oxidative C-H bond dissociation of diarylmethanes was reported using anodic oxidation.[5] This “cation pools” of carbocation which then could be reacted with various nucleophiles, such as allysilanes. The generation of pools of carbocation could be utilized as another external electrophile, which would undergo the general electrophilic activation of our alkene substrates, especially unactivated alkenes and allylic benzyl ethers which are found to be inefficient under Brønsted acid activation method as described in this thesis.



Scheme 6.1. Oxidative generation of diarylcarbenium ion pools

6.1. References

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List of Publications

1. Atsushi Kaga, Dhika Aditya Gandamana, Sayako Tamura, Mesut Demirelli, and Shunsuke Chiba.
   "[3+2] Annulation of Donor–Acceptor Cyclopropanes with Vinyl Azides"
   Synlett **2017**, *28*, 09, 1091.

2. Dhika Aditya Gandamana, Bin Wang, Ciputra Tejo, Benoit Bolte, Fabien Gagosz, and Shunsuke Chiba
   "Use of Alkyl Ethers as Traceless Hydride Donors in Brønsted Acid-Catalyzed Intramolecular Hydrogen Atom Transfer"
   Angew. Chem., Int. Ed. **2018**, *57*, 6181.

3. Bin Wang, Dhika Aditya Gandamana, Fabien Gagosz, and Shunsuke Chiba
   "Diastereoselective Intramolecular Hydride Transfer under Brønsted Acid Catalysis"
   Org. Lett. **2019**, *21*, 2298.

4. Bin Wang, Dhika Aditya Gandamana, David Fabian Leon Rayo, Fabien Gagosz, and Shunsuke Chiba
   "Diastereoselective Intramolecular Hydride Transfer Triggered by Electrophilic Halogenation of Aryl Alkenes"
   Org. Lett. **2019**, *21*, 9179.

5. Dhika Aditya Gandamana, Fabien Gagosz, and Shunsuke Chiba
   "Diastereoselective hydroalkylation of aryl alkenes enabled by Remote hydride transfer"
   Tetrahedron, **2020**, in press.