Exploring New Directions in Homogeneous Catalytic (De)hydrogenation Chemistry

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Abstract

This two-part thesis describes the exploration and development of new routes towards hydrogen transfer chemistry. Initial research focussed on metal-catalysed borrowing hydrogen catalysis, resulting in the development of a one-pot iron-catalysed conversion of allylic alcohols to α-methyl ketones. Overall, this process is referred to as isomerisation-methylation and offers a much greener approach than the one previously known one-pot procedure. The reaction was promoted by a bench-stable iron(cyclopentadienyl) complex and employed methanol as alkylating agent. A good substrate scope was exhibited, providing >25 examples up to 84% isolated yield. Mechanistic experiments provided evidence for plausible reaction intermediates and an iron-hydride species in the catalytic process.

Other miscellaneous borrowing hydrogen processes were given attention, with an aim to discover further useful and interesting transformations catalysed by earth-abundant metal complexes. Firstly, the reactivity of primary allylic alcohols was examined to determine the plausibility for a new route towards δ-methylation using archetypal conditions. Various transformations were observed based on the structural features of the allylic alcohol substrates. Secondly, the regioselective ring-opening of terminal epoxides was examined employing various hydrogen donors. A promising result leading to the selective formation of secondary alcohols has the potential to form the basis of a more comprehensive study. Employing methanol as hydrogen donor resulted in the formation of various β-methoxy alcohols.

Finally, enantioselective hydrogenation of prochiral substrates, promoted by chiral Frustrated Lewis Pairs (FLPs), was investigated. A range of chiral Lewis bases were tested in combination with Lewis acidic boranes for molecular hydrogen activation and subsequent enantioselective hydrogenation. Attempts were also extended to inverse FLP catalysis, with efforts to synthesise weak Lewis acidic boranes and chiral superbases, to catalyse the same transformation. While some key literature reactions were able to be replicated, the strategy to adopt a chiral phosphine was not effective, nor was a revised strategy employing other chiral Lewis bases.

Publications

1) D. E. Latham†, K. Polidano, J. M. J. Williams and L. C. Morrill*. Isomerisation-Methylation of Allylic Alcohols to α-Methyl Ketones. *Org. Lett.*, 2019, **21**, 19, 7914-7918.

2) B. G. Reed-Berendt†, D. E. Latham†, M. B. Dambatta, and L. C. Morrill*. Borrowing Hydrogen for Organic Synthesis. *ACS Cent. Sci.*, 2021, **7**, 4, 570–585.

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*Primary investigator/supervisor

Abbreviations

α	Alpha
β	Beta
γ	Gamma
δ	Delta
µL	Microlitre(s)
ACE	Ace (brand)
App.	Apparent
aq	Aqueous
Ar	Aromatic
atm	Atmosphere(s)
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl
Boc	*N-tert*-Butoxycarbonyl
br	Broad
Bu	Butyl
Bz	Benzoyl
C	Celsius
c	Concentration
Cat.	Catalyst
cm	Centimetre(s)
COD	Cyclooctadiene
Cp	Cyclopentadienyl
CPA	Chiral phosphoric acid
Cy	Cyclohexyl
d	Doublet
D	Deuterium
DFT	Density functional theory
DIBAL-H	Di-iso-butylaluminium hydride
dppe	1,2-Bis(diphenylphosphino)ethane
dr	Diastereomeric ratio
E	Trans (Entgegen = opposite)
EDG	Electron donating group
equiv.	Equivalent(s)

ES	Electrospray
Et	Ethyl
EWG	Electron withdrawing group
g	Gram (s)
h	Hour(s)
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
i or ^{i}	Iso
IPA	Isopropyl alcohol
IR	Infrared
M	Metal complex
M	Molar (i.e. mol dm^{-3})
m	Meta
m	Multiplet
Me	Methyl
Mes	Mesityl
mg	Milligram(s)
MHz	Megahertz
min	Minute(s)
mL	Millilitre(s)
mmol	Millimole(s)
mol	Mole(s)
mol %	Mole percentage
mp	Melting point
n or ^{n}	normal
NMR	Nuclear magnetic resonance
o	Ortho
p	Para
P	Pressure
P	Product
Ph	Phenyl
PNP	Phosphorus-Nitrogen-Phosphorus
ppm	Part(s) per million
Pr	Propyl
q	Quartet
quant.	Quantitative

quint	Quintet
R	Alkyl
R_f	Retardation factor
RSM	Returned starting material
rt	Ambient (room) temperature
s	Singlet
sat.	Saturated
sept	Septet
sex	Sextet
SM	Starting material
T	Temperature
t or ^{t}	Tertiary
t	time
t	Triplet
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Ts	Tosyl
TS	Transition state
Z	Cis (zusammen = together)

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Chapter 1

Introduction to Borrowing Hydrogen Catalysis

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1.1 Hydrogenation Chemistry

Hydrogenation is among the most ubiquitous transformations in chemical synthesis. Often performed in the presence of a catalyst, it is the addition of di-hydrogen across an unsaturated moiety in a molecule. Its application can be found in the vast majority of total syntheses, spanning the reaches of heterogeneous, homogeneous and bio-catalysis.[1,2]

Hydrogenation reactions may be split into two categories - direct hydrogenation with molecular hydrogen (H_2), or transfer hydrogenation; employing an alternative compound as a hydrogen donor source. This chapter will cover metal-catalysed processes. Metal-free/main group processes will be discussed in chapter 5.

1.1.1 Direct Hydrogenation

The importance of catalytic hydrogenation and its astounding influence on the chemical industry has been recognised and honoured by the award of several Nobel prizes to key contributors. Paul Sabatier was awarded the prize in 1912 for discovering the ability for trace metals (e.g. nickel) to facilitate the addition of molecular hydrogen (H_2) to unactivated olefins, as well as carbon dioxide (CO_2) (figure 1a).[3]

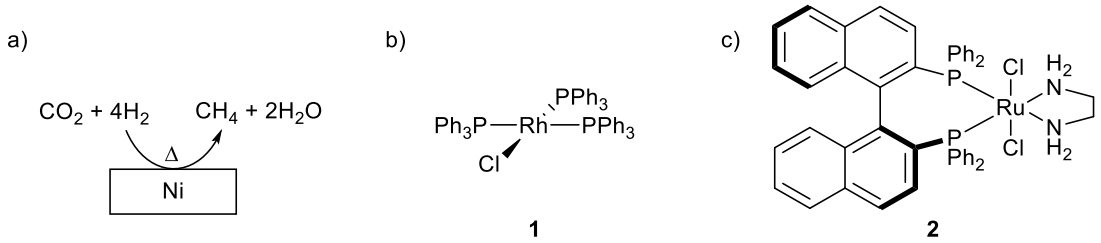
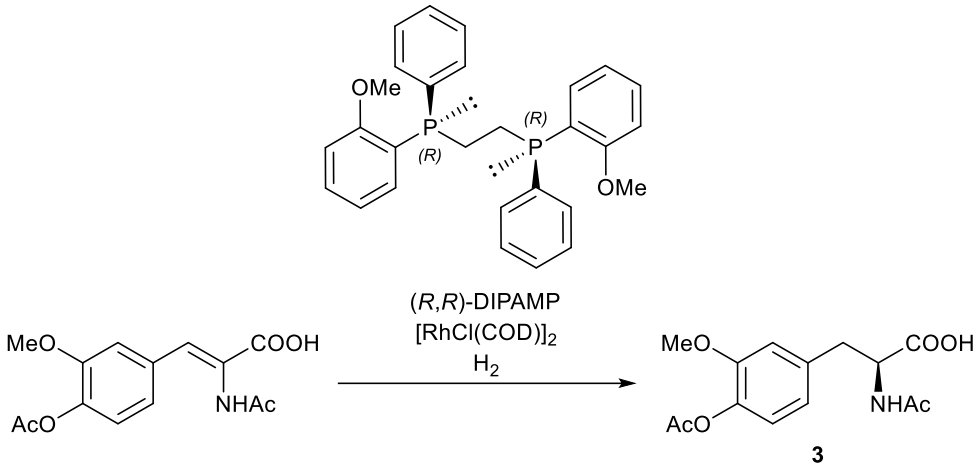


Figure 1: a) Sabatier's reaction – heterogeneous nickel catalysed hydrogenation of CO_2; b) Wilkinson's catalyst; c) Noyori's catalyst.

Geoffrey Wilkinson was awarded the prize in 1973 for developing the famed rhodium complex known as Wilkinson's catalyst (**1**) (figure 1b); a versatile homogenous catalyst for low temperature hydrogenation of olefins.[4] Noyori and Knowles jointly received the prize in 2001 for their contributions to asymmetric hydrogenation.[5]

Noyori notably developed versatile Ru-BINAP catalyst (**2**) (figure 1c), while Knowles applied asymmetric hydrogenation to develop a valuable industrial synthesis of amino acid L–DOPA (**3**) (scheme 1) – a leading drug for the treatment of Parkinson's disease.[6]



Scheme 1: Knowles' reaction – first industrial synthesis of L-DOPA.

The development and application of hydrogenation technologies remains crucial for many industries, including the food, agricultural and pharmaceutical sectors.[7,8] For decades, industrial scale processes have generally favoured employing heterogeneous catalysts over homogeneous catalysts, largely due to the former's ease of separation, practicality and recyclability.[9] For this reason, the application of heterogeneous catalysts for direct hydrogenation processes remains an efficient and economically viable approach. Notable examples include Raney nickel,[10] palladium on charcoal,[11] and Lindlar's catalyst.[12]

Despite its relative underutilisation in industrial processes, homogeneous catalysis still offers many useful advantages such as the possibility of performing reactions under milder conditions, opportunities for higher activity and selectivity, ease of spectroscopic monitoring, and the ability to tune reaction sites (e.g. ligand design).[13] As a result, homogeneous processes for asymmetric hydrogenation have featured within many well-developed drug syntheses at lab and industrial scale.[14] The scope for homogeneous direct hydrogenation spans both precious metal and earth-

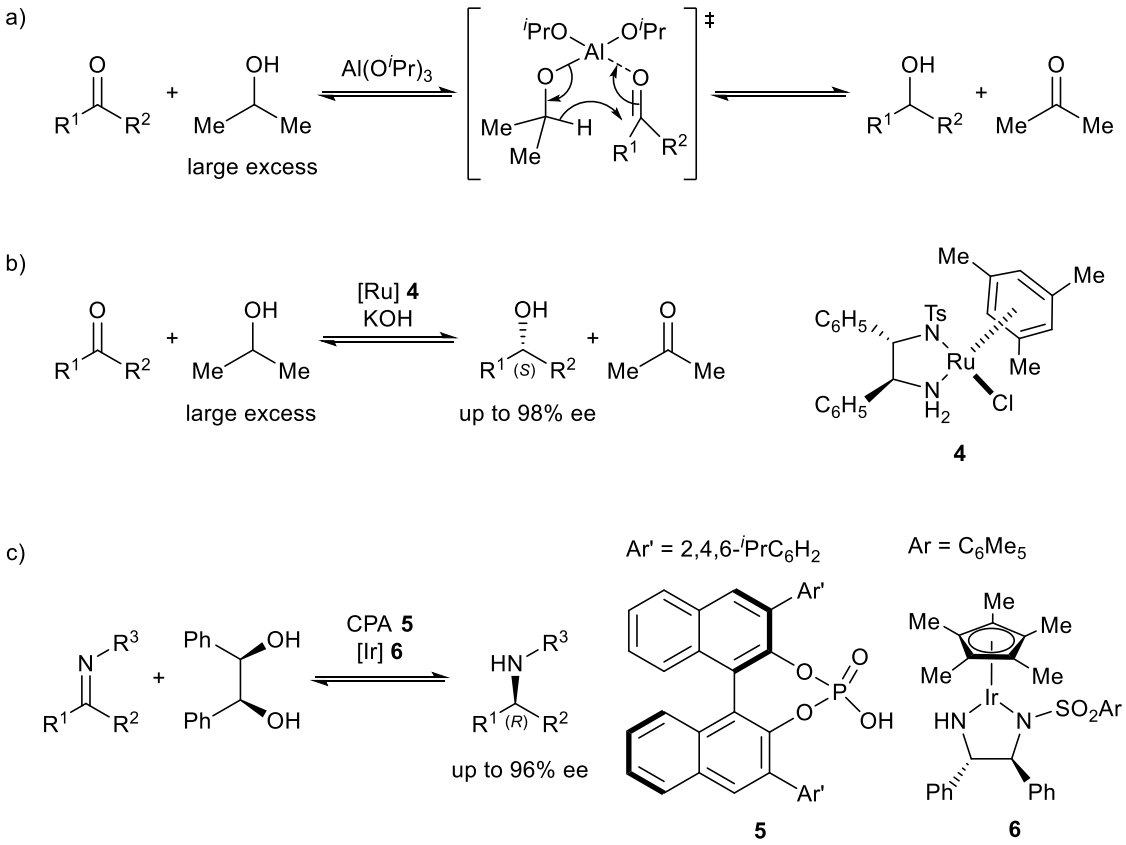
abundant transition-metal catalysis, even extending from the traditional hotplate to the realms of mechanochemistry,[15] and electrochemistry.[16]

1.1.2 Transfer Hydrogenation

The use of molecular hydrogen in direct hydrogenation typically requires special reaction setups and presents several health and safety considerations. On the other hand, transfer hydrogenation (TH) utilises readily available and inexpensive sacrificial compounds as hydrogen donors to accomplish the same desired transformation.[17]

Several homogeneous TH processes, catalysed by either precious metal or earth-abundant metal complexes, have been established for a variety of unsaturated substrates.[18] Within these metal-mediated TH reactions, cheap and environmentally benign alcohols, such as *iso*-propanol, are widely employed as the hydrogen source. Where the reversible nature of this reaction appears to impede conversion, the carbonyl by-product can be removed (e.g. distillation) to force equilibrium in the direction of the desired product.[19] The Meerwein-Ponndorf-Verley (MPV) reduction of ketones, discovered in the 1920s, is a classic example of this approach (scheme 2a).[20]

Influenced by the MPV reduction, in 1995, Noyori and Ikariya successfully developed an efficient method for the asymmetric transfer hydrogenation (ATH) of aryl ketones, catalysed by ruthenium complex **4** bearing a protic amine chelating ligand, and employing *iso*-propanol as solvent and sacrificial hydrogen donor (scheme 2b).[21] The same transformation was later achieved employing formic acid as the hydrogen donor, whereby the irreversible release of carbon dioxide (CO_2) can enhance the conversion.[22] The ATH of imines with alcohol donors is considered more difficult than ketones because of the less polarised C=N bond versus the C=O bond. More recently in 2017, Zhao and co-workers addressed this problem with the inclusion of a chiral phosphoric acid (CPA) **5** to protonate the substrate in an iridium-catalysed process employing catalyst **6** (scheme 2c).[23]



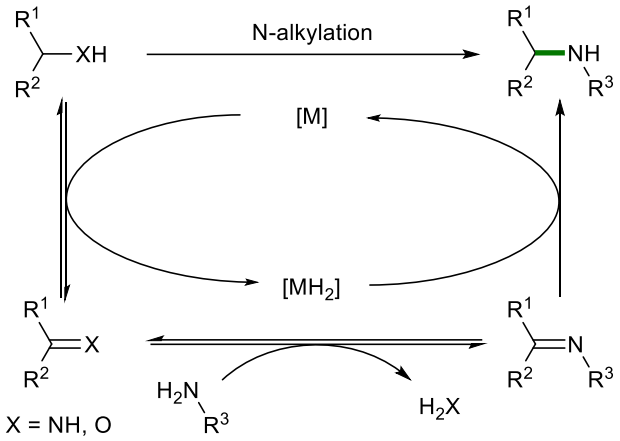
Scheme 2: a) Meerwein-Ponndorf-Verley (MPV) reduction of ketones; b) Asymmetric TH of ketones; c) Asymmetric TH of imines.

1.2 Borrowing Hydrogen

Borrowing hydrogen (BH), also known as hydrogen autotransfer, combines a metal-catalysed transfer hydrogenation cycle with a reaction on the *in-situ* generated intermediate.[24–26] The general pathway for this principle is shown in scheme 3, as illustrated with amine N-alkylation.

The process begins with a metal-mediated dehydrogenation of an alcohol to its corresponding carbonyl intermediate. Alternatively, amines can be employed as the "alkylating agent" to generate the corresponding imine intermediate, however, these processes are less common.[27–29] The reactive intermediate generated *in-situ* can then undergo a variety of transformations, including condensation with an amine. This releases water as the sole by-product of the reaction. The resulting unsaturated species of this concurrent reaction can then be hydrogenated by the metal hydride species formed in the initial dehydrogenation, effectively returning the "borrowed"

hydrogen to produce a new amine. This final step is often deemed irreversible and regenerates the metal catalyst to complete the catalytic cycle.



Scheme 3: The general borrowing hydrogen (BH) cycle as illustrated for N-alkylation.

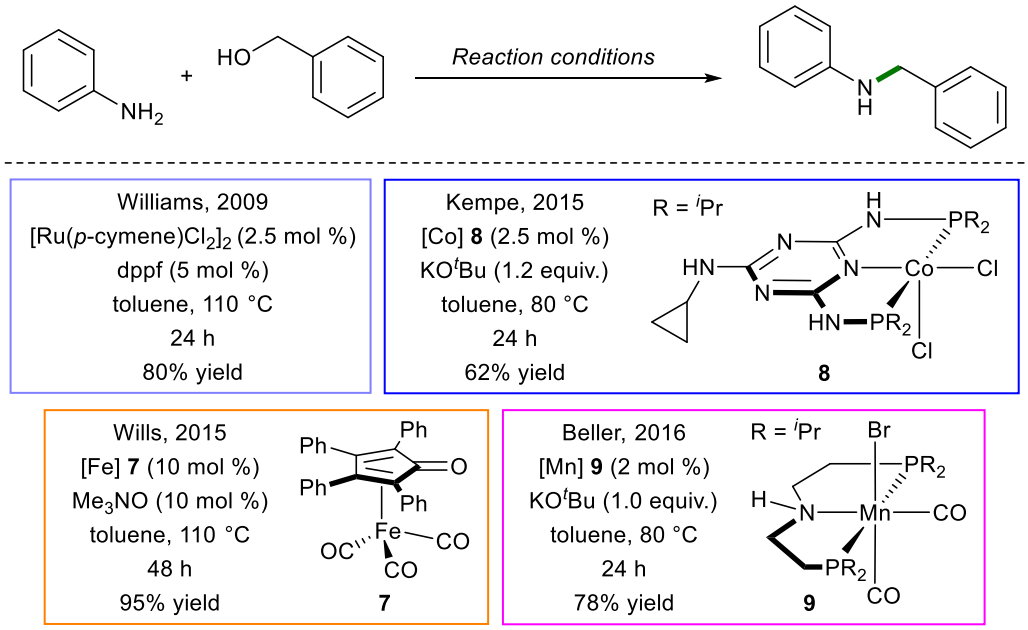
The high atom economy and direct utilisation of commodity alcohols as alkylating agents makes BH an appealing strategy to form new C-N and C-C bonds, when compared to classical alternatives. Favourably, it avoids the utilisation of toxic alkyl halides and negates the need for stoichiometric alcohol activation or reductive processes, such as those needed in the Mitsonobu reaction,[30] and reductive amination.[31] Furthermore, the practicality of the BH principle allows it to be performed in a one-pot fashion. It is also typically selective for monoalkylation. A disadvantage associated with BH chemistry is that it often requires high reaction temperatures (>100 °C) which prohibits the compatibility of some functional groups. Consequently, few enantioselective processes, which typically require milder conditions, have been developed.

Early primitive examples of BH had been demonstrated many decades ago by the likes of Pratta and Frazza, Grigg, and Watanabe.[32–34] The term "borrowing hydrogen" was coined in 2004 by the late Professor Jonathan Williams upon a revival of the methodology. Since these pioneering contributions, many research groups have been inspired to investigate further, including the Morrill group, developing BH processes spanning heterogeneous,[35] homogeneous,[36] and bio-catalysis.[37,38]

This rest of this chapter will focus primarily on homogeneous transition metal processes, which represents the majority of borrowing hydrogen work published this past decade. For a more in-depth account on the significant and recent advances in borrowing hydrogen since 2000 across all disciplines of catalysis, refer to our recent review in *ACS Science*.[24]

1.2.1 N-alkylation

The synthesis of *N*-benzylaniline from aniline and benzyl alcohol is the archetypal C-N bond-forming BH reaction, with a variety of metals having been employed. Selected processes are illustrated in scheme 4. Pre-2014, the BH research area was dominated by the development of various heterogeneous processes, alongside the earliest homogeneous processes, which focused exclusively on the use of precious metals. One such example from Williams and co-workers employed a ruthenium *p*-cymene dichloride dimer.[39] Interestingly, this work was later adapted for solvent-free microwave chemistry, allowing for shorter reaction times.[40] Other precious metals that have been utilised to catalyse this transformation include iridium,[41] palladium,[42] and osmium.[43]

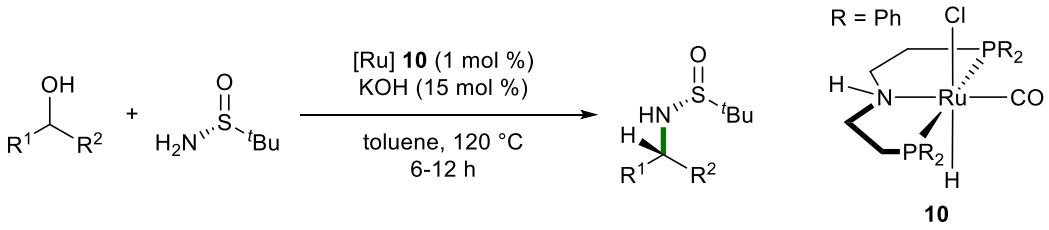


Scheme 4: Selected homogeneous BH processes for the synthesis of *N*-benzylaniline.

A breakthrough was made in 2014 by Feringa and Barta, who were the first to demonstrate the N-alkylation of amines *via* homogeneous BH using an earth-abundant transition-metal catalyst.[44] In this case, the synthesis of *N*-benzylaniline was not explicitly achieved, but an assortment of anilines, benzylamines, primary and secondary aliphatic amines were demonstrated to undergo iron-catalysed coupling with a variety of primary alcohols and diols. This report also marked the first application of cyclopentadienone ligands for iron catalysts in BH chemistry. A similar iron-catalysed process soon followed from Wills and co-workers, which included the synthesis of *N*-benzylamine, employing iron complex **7**.[45]

Many more earth-abundant metal catalysed processes were developed for this transformation in subsequent years. Kempe and co-workers reported a well-defined cobalt complex (**8**) for this transformation,[46] while Beller and co-workers reported a manganese-catalysed reaction using a PNP-pincer precatalyst (**9**).[44] Both reports were conducted under relatively mild reaction conditions – a remarkable feat at the time. Other earth-abundant transition metals that have been utilised for this transformation include copper,[47] nickel,[48] and chromium.[49]

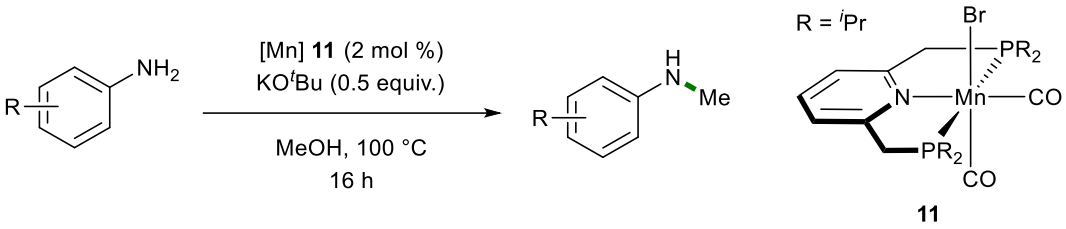
Over the years, in addition to the archetypal C-N bond forming reaction, various scopes of nucleophile and electrophile (or alkylating agent) have been showcased. For example, sulfonamides have been widely reported as nucleophiles,[50,51] as have chiral sulfinamides in a diastereoselective N-alkylation with secondary alcohols with ruthenium complex **10** (scheme 5). Other stereoselective processes employing secondary alcohols as the electrophile are known to have been developed.[52]



Scheme 5: Ruthenium-catalysed diastereoselective N-alkylation of sulfinamides.

Methylation of N-based nucleophiles has been achieved *via* several approaches. A manganese-catalysed process was also developed by Beller and co-workers employing manganese precatalyst **11** (scheme 6). An iron-catalysed process was also developed within the Morrill group employing an iron(0)cyclopentadienone complex.[53]

Finally, allylic alcohols have been employed as electrophiles in a number of chemoselective and stereoselective processes. These are discussed in more detail within chapter 4.



Scheme 6: Manganese-catalysed methylation of anilines.

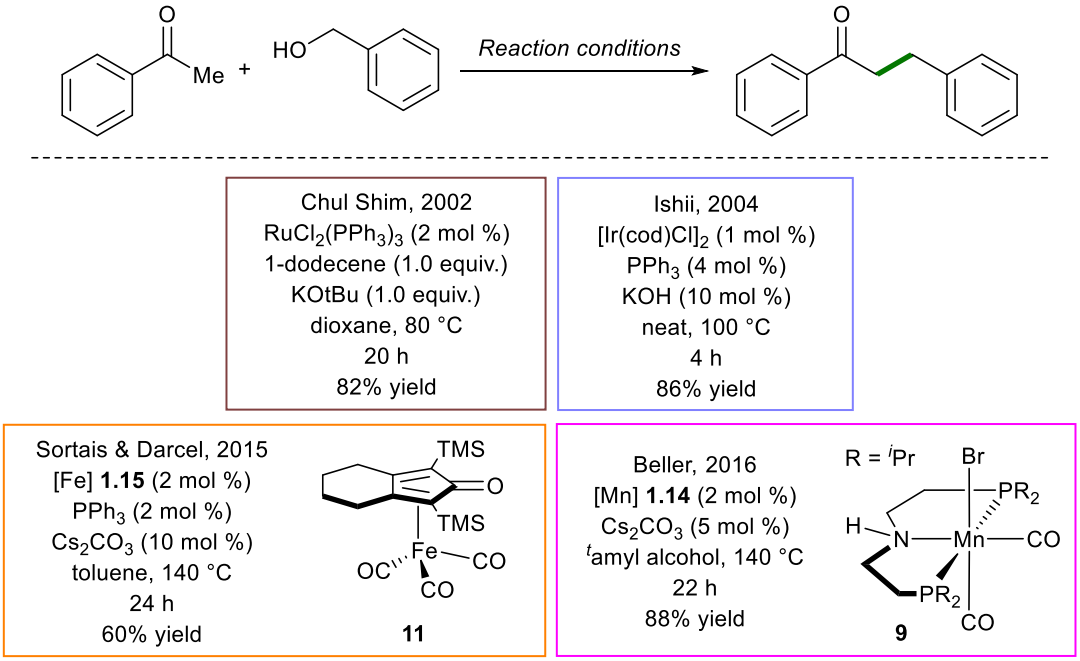
1.2.2 C-alkylation

The synthesis of dihydrochalcone from acetophenone and benzyl alcohol is the archetypal reaction for C-C bond forming developments *via* BH. Selected processes are illustrated in scheme 7.

Much like C-N bond formation, the emergence of metal-catalysed processes followed a similar pattern of development, with early homogeneous works employing precious metal complexes. One such example is an iridium catalysed process from Ishii and co-workers,[54] which was among the first to negate the need for a hydrogen acceptor additive, such as 1-dodecene; previously employed to suppress further reduction of the ketone product to the corresponding alcohol.[55] Other precious metals that have been utilised to catalyse this transformation include ruthenium[55], osmium,[56] rhodium,[57] and rhenium.[58]

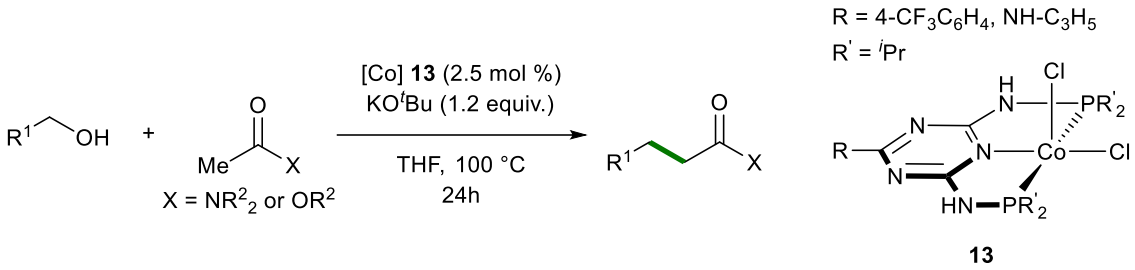
Earth-abundant metal catalysed processes emerged in the late 2010s. Sortais and Darcel reported an iron-catalysed process with iron(0)cyclopentadienone complex

12.[59] Beller and co-workers also pioneered manganese catalysis for C-alkylation, employing the same PNP-pincer precatalyst (**9**) utilised for N-alkylation.[60] Other earth-abundant transition metals that have been utilised for this transformation include cobalt,[61] and nickel.[62]



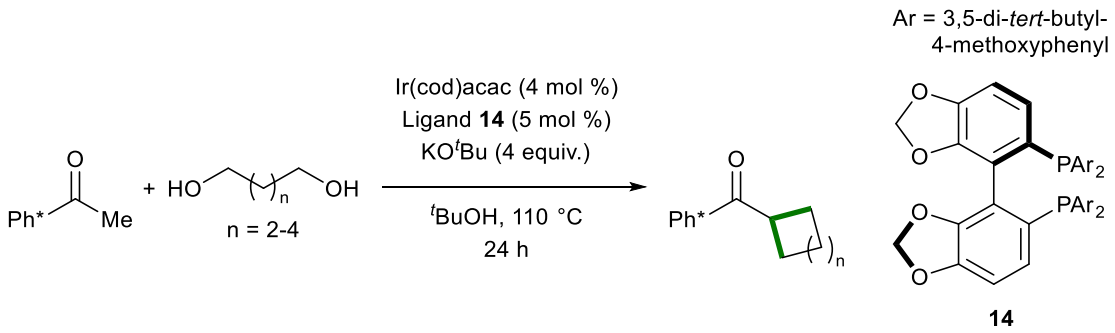
Scheme 7: Selected homogeneous BH processes for the synthesis of dihydrochalcone.

The C-alkylation of various nucleophiles has been achieved employing a range of metal complexes. Kempe and co-workers notably reported homogeneous cobalt complex **13** in the first earth-abundant metal-catalyzed α-alkylation of unactivated esters and amides (scheme 8), a transformation which had earlier proven difficult. [61] On the topic of earth-abundant metal processes, iron-catalysed approaches for C-alkylation of nitriles,[63] indoles,[64] oxindoles[65], and heteroarenes[66] have all been reported. The C-alkylation of sulfones[67] and thioamides[68] have also been reported employing nickel. This is by no means an exhaustive list of examples, with other reported metals having achieved the C-alkylation of the aforementioned nucleophiles.[24]



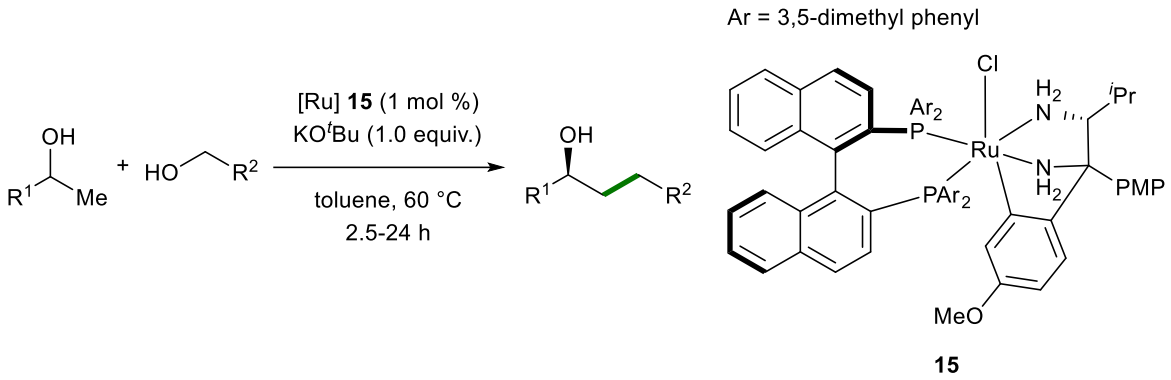
Scheme 8: Manganese-catalysed methylation of anilines.

Early C-alkylation procedures largely utilised benzyl or long chain primary alcohols as alkylating agents. On the other hand, employing secondary alcohols presented the issue of self-condensation that was eventually overcome by Donohoe and co-workers, who installed their carbonyl substrates with a pentamethylphenyl group (Ph*) to sterically shield it from attack by enolates that had formed *in situ*.[69] This effective iridium-catalysed approach was later adapted for cobalt,[70] iron,[71] manganese,[72] and base-free catalysis.[73] It was also adapted for processes employing diols as the alkylating agent (scheme 9).[74]



Scheme 9: Iridium-catalysed alkylation of ketones with secondary alcohols.

Several catalysts for the alkylation of carbonyl compounds are also compatible for the *β*-alkylation of alcohols.[75,76] This methodology has shown early signs of effectiveness in the upgrading of ethanol to *n*-butanol for use as a biofuel.[77,78] More recently, low temperature processes for the *β*-alkylation of alcohols were achieved by Zhao and co-workers, including an enantioselective report employing ruthenium complex **15** (scheme 10).[79] This represents one of very few enantioselective BH reports with respect to C–C bond formation.[80–83]



Scheme 10: Enantioselective ruthenium-catalysed β-alkylation of alcohols.

Both methanol and allylic alcohols have been utilised as alkylating agents in homogeneous BH processes. These are discussed in more detail within chapters 2 and 3, respectively.

1.3 Summary and Outlook

Until recently, the main collective aim for researchers in the area was to translate known precious metal-catalysed transformations into more economical earth-abundant metal-catalysed ones. This goal has largely been achieved, with current targets now set on developing novel and elaborate processes, with a focus on employing mild reaction conditions and low catalyst loadings. To accomplish this may require the design and synthesis of new catalysts, particularly for new stereoselective processes.

Since the publication of our review in early 2021, several interesting stereoselective processes have been developed,[84,85] including a nickel-catalysed diastereo- and enantioselective construction of spirocycles by Kong and co-workers,[88] and a ruthenium-catalysed kinetic resolution of allylic alcohols by Yu and Xing.[89] Another notable report employing allylic alcohols was a manganese-catalysed anti-Markovnikov hydroamination of allyl alcohols, as demonstrated by Maji and co-workers.[87]

The limited cost-effectiveness of homogeneous catalysis at large scale suggests much of BH chemistry is still chiefly limited to the lab. However, its potential use in the pharmaceutical industry has not gone unnoticed, as indicated by a report from AstraZeneca, who evaluated the potential scope of application for BH in its development projects.[86]

Since it has become more challenging to produce novel ideas for BH, a slump in the number of research publications can be expected over the next few years. However, several challenges and opportunities do remain; low temperature and asymmetric processes are arguably still poorly represented with respect to earth-abundant metal catalysis. The aim of the Morrill research group was to broaden the use of earth-abundant metal complexes, namely with iron and manganese, replicating transformations known with precious metal catalysts. We also aimed to build upon existing processes founded in the group and attempt to establish new one-pot transformations using this methodology.

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Chapter 2

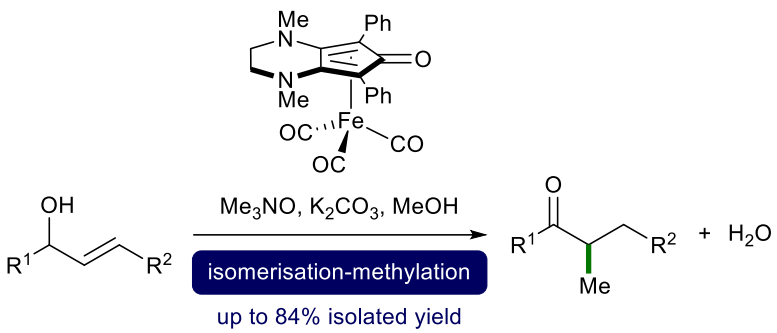
One-Pot Conversion of Allylic Alcohols to α-Methyl Ketones *via* Iron-Catalysed Borrowing Hydrogen

Table of Contents

For related experimental and characterisation data, see chapter 4

2.1 Preface

This chapter discusses the development of a one-pot iron-catalysed conversion of allylic alcohols to α-methyl ketones. Overall, this process is referred to as isomerisation-methylation, which employs a well-defined bench stable (cyclopentadienone)iron carbonyl complex as precatalyst, and methanol as the C1 building block. A variety of allylic alcohols were converted to α-methyl ketones in good yields.



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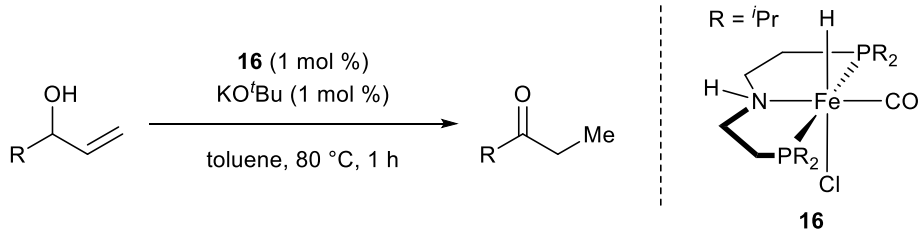
2.2 Introduction

Allylic alcohols are very useful building blocks for organic synthesis due to their widespread availability and diverse reactivity profile.[1] The redox isomerisation of allylic alcohols is of particularly great importance, granting access to synthetically-useful enolisable carbonyl compounds and their inherently substantial reaction scope.[2] Traditionally, this transformation can be achieved using Brønsted base catalysis,[3,4] or transition metal catalysis,[5] with iridium,[6] ruthenium,[7] palladium,[8] and rhodium catalysts,[9] all being reported.

The application of earth-abundant metal catalysts for the isomerisation of allylic alcohols has, much like general borrowing hydrogen catalysis, become increasingly more pertinent.[10] Prior to this investigation, the most recently developed methodology for this transformation came from De Vries and co-workers, as illustrated in scheme 11.[11] In this report, a well-defined PNP pincer-type iron catalyst (**16**) was used to convert a variety of benzylic and *n*-alkyl allylic alcohols into their corresponding carbonyl compounds in excellent yields. Further developments of this transformation continue to be demonstrated involving the utilisation of other earth-abundant metals, including cobalt,[12] and manganese.[13]



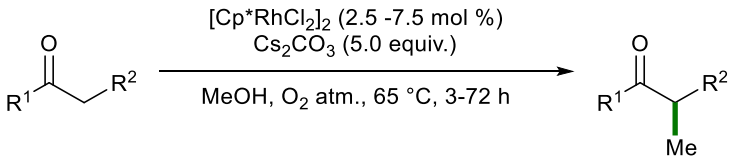
Scheme 11: Iron-catalysed isomerisation of allylic alcohols to ketones.

The methyl group is a prominent feature in many pharmaceutically and biologically active molecules, and can significantly impact the pharmacological properties of a drug.[14,15] Methyl groups also offer improved combustion characteristics for customisable fuel additives.[16] Conventional methylating methods employ toxic and harmful methylating agents such as methyl iodide, diazomethane, or dimethyl sulphate.[17] Another disadvantage of these traditional processes is their poor atom

economy, due to the release of high molecular weight leaving groups, which consequently generate large volumes of toxic waste.

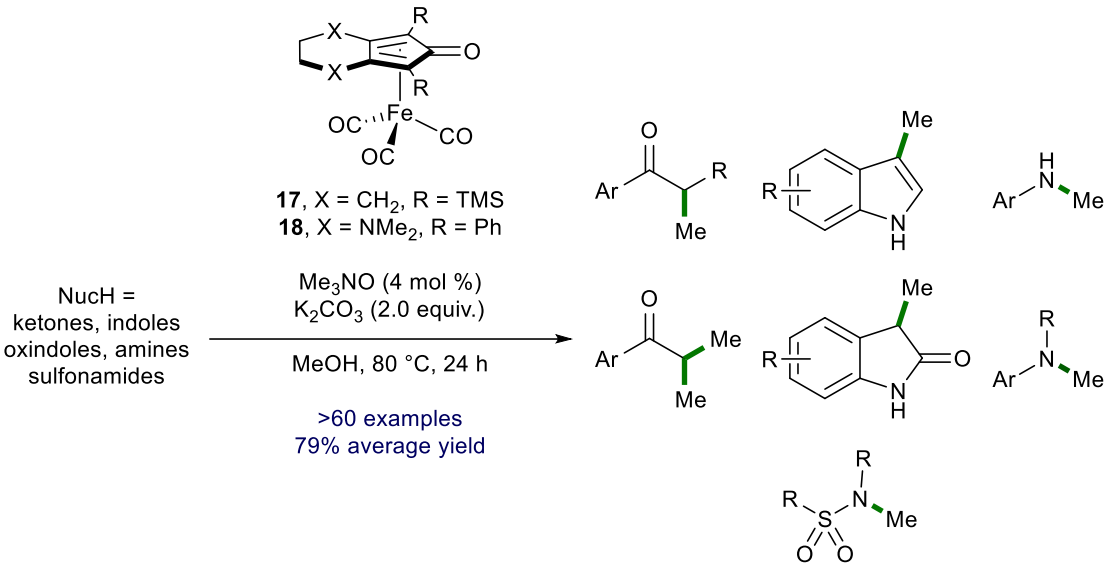
In recent years, methanol has become an increasingly attractive methylating agent due to its vast abundance and biodegradable properties.[18] The utilisation of methanol as the alkylating agent in borrowing hydrogen catalysis offers a highly atom economical means to achieve methylation of various compounds, with water being the sole by-product of the reaction. Such processes have been very challenging to develop, partly due to the relatively high activation energy of methanol dehydrogenation (+84 kJ mol^{-1}),[19] when compared to other longer chain aliphatic alcohols, such as ethanol (+68 kJ mol^{-1}).[20]

The first initial report for methylation using methanol came from Grigg *et al.* in 1981, where they employed a ruthenium catalyst to successfully methylate aryl acetonitriles and aromatic amines.[21] Some decades later in 2014, a significant breakthrough to *α*-methylate ketones was made by Donohoe and co-workers. This rhodium-catalysed process employed methanol as both the methyl source and the solvent (scheme 12).[22] Several *α*-methylation procedures have since been established using both precious metal catalysts,[23] and first row transition metal catalysts.[24,25]



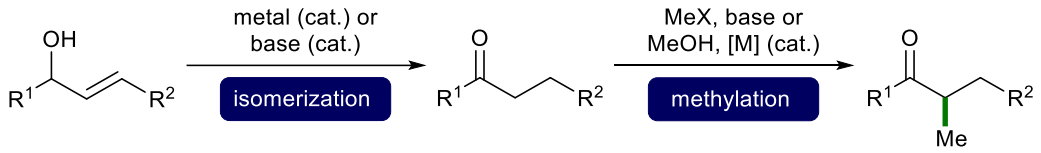
Scheme 12: Ruthenium-catalysed methylation using the borrowing hydrogen approach.

In 2018, prior to this investigation, the Morrill research group made a significant contribution to this field through the methylation of various substrates using iron catalysis.[26] This methodology employed Knölker-type (cyclopentadienone)iron carbonyl complexes **17** and **18** as precatalyst,[27] and exhibited a broad reaction scope. A variety of ketones, indoles, oxindoles, amines, and sulfonamides underwent mono- or di-methylation in excellent isolated yields, as shown in Scheme 13.



Scheme 13: Iron-catalysed methylation using the borrowing hydrogen approach.

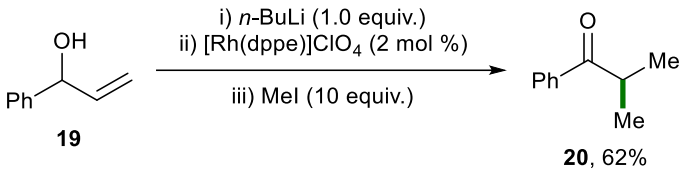
The general method to access *α*-methyl ketones from allylic alcohols is usually a two-step approach; firstly, a base or metal-catalysed isomerisation to the ketone, followed by *α*-methylation, as illustrated in Scheme 14.



Scheme 14: Conventional two-step approach for the conversion of allylic alcohols to *α*-methyl ketones.

The only direct one-step approach was reported by Motherwell and co-workers in 1991 and 1999, as illustrated in Scheme 15.[28,29] In these reports, *n*-BuLi is used to generate an alkoxide from allylic alcohol **19**, followed by rhodium-promoted allylic alkoxide isomerisation, and subsequent alkylation using excess methyl iodide (10 equiv.). Despite the benefits of a one-pot procedure, the disadvantages of this method include the use of a precious metal catalyst, a pyrophoric base, and super-stoichiometric quantities of a toxic methylating agent.

In an effort to address these drawbacks, the aim was to utilise an earth-abundant metal catalyst and MeOH as the C1 building block, to perform the isomerisation–methylation of allylic alcohols to *α*-methyl ketones in a one-pot fashion.



Scheme 15: Conventional two-step approach for the conversion of allylic alcohols to α-methyl ketones.

2.3 Results and Discussion

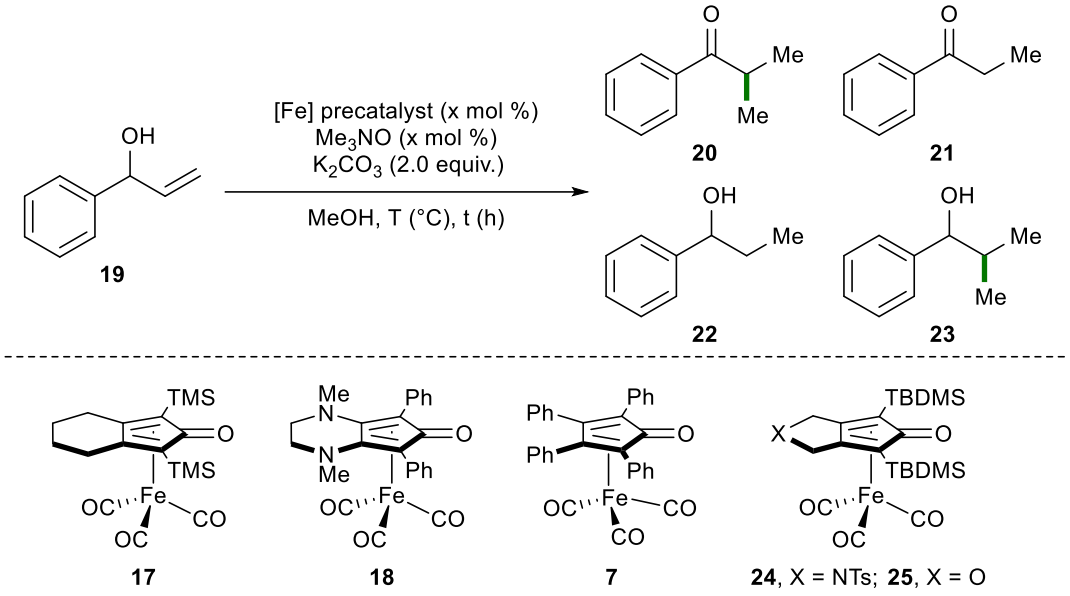
2.3.1 Initial Hit and Precatalyst Synthesis

The initial optimisation was carried out by Kurt Polidano. 1-Phenylprop-2-ene-1-ol (**19**) was selected as the model substrate. All optimisation experiments were carried out in a sealed microwave vial containing a magnetic stirrer bar. A detailed reaction procedure can be found in chapter 4 – experimental.

As previously mentioned, methanol possesses a relatively high activation energy for dehydrogenation when compared to benzyl and other alkyl alcohols. Since the equilibrium between methanol and formaldehyde is shifted towards methanol, an excess quantity of methanol is required to ensure a sufficient concentration of formaldehyde, formed *in-situ*, for subsequent alkylation. Therefore, methanol (MeOH) was utilised as both the solvent and alkylating agent, as was the case in previous methylation studies under a borrowing hydrogen manifold.[22,26] A simultaneous project investigating iron-catalysed β-methylation of alcohols, as conducted by Kurt, also adopted this approach.[30]

To begin, a selection of [Fe] precatalysts (**17, 18, 7, 24, 25**) were tested under similar conditions to Dr Kurt Polidano's previous report on the α-methylation of ketones, as previously illustrated in scheme 13.[26] Despite opening the study with a generous catalyst loading (10 mol %), these reactions were all found to give negligible to low conversion towards the desired isomerisation-methylation product (Pr) **20**, and instead predominantly returned starting material (RSM) **19** in all cases (table 1,

entries 1-5). This implies that the rate determining step for this reaction is involved in the isomerisation process.



Entry[a]	Catalyst (mol %)	Additive (mol %)	T (°C)	**19**[b] RSM (%)	**20**[b] P (%)	**21**[b] (%)	**22**[b] (%)	**23**[b] (%)
1	**17** (5)	Me_3NO (10)	80	100	<2	<2	<2	<2
2	**18** (5)	Me_3NO (10)	80	91	9	<2	<2	<2
3	**7** (5)	Me_3NO (10)	80	90	<2	<2	<2	<2
4	**24** (5)	Me_3NO (10)	80	90	2	<2	<2	<2
5	**25** (5)	Me_3NO (10)	80	88	2	<2	<2	<2
6	**17** (5)	Me_3NO (10)	120	82	11	<2	<2	<2
7	**18** (5)	Me_3NO (10)	120	<2	77	<2	<2	11
8	**24** (5)	Me_3NO (10)	120	83	10	<2	<2	<2
9	**18** (2)	Me_3NO (4)	120	58	32	<2	<2	<2
10	**18** (2)	Me_3NO (4)	130	<2	88	<2	<2	4

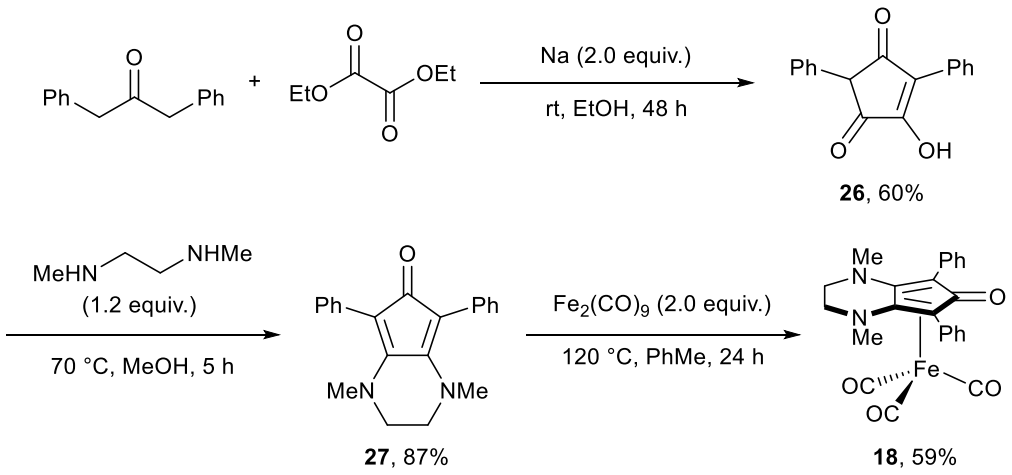
Table 1: Preliminary optimisation for the isomerisation-methylation of **19**.

[a]Reactions performed using 0.5 mmol of allylic alcohol **19** and bench-grade MeOH. [**19**] = 0.5 M. [b]Yield after 24 h as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard.

Three [Fe] precatalysts (**17**, **18**, **24**) were carried forward (**7** and **25** were in short supply at the time) and tested at an elevated temperature of 120 °C (entries 6-8). This temperature was thought to be fair middle ground between applying harsh conditions and the safe handling of MeOH in the reaction setup. Other methylation experiments conducted by Kurt revealed the vial caps were susceptible to popping off at temperatures above 140 °C.

When using [Fe] precatalyst **18**, significant formation of the desired product **20** was observed (77%), together with product **23** (11%), which is formed *via* hydrogenation of **20**. The seemingly superior reactivity of **18** relative to **17** has been demonstrated previously by Renaud and co-workers through the *C*-alkylation of ketones using benzyl alcohol,[31] an improvement on the report by Darcel and co-workers.[32]

An attempt to prevent the over-reduction of **20** was made by lowering the catalyst loading to 2 mol % (entry 9), however, this resulted in loss of conversion to a 32% yield of **20** along with 52% return of **19**. Raising the temperature further to 130 °C gave the optimal result of 88% of **20**, with only 4% of over-reduced product **23** formed. At this stage, the project was passed on to me to continue the optimisation, using a freshly made batch of [Fe] precatalyst **18**. The synthesis of this catalyst involves three steps, as illustrated in Scheme 16.



Scheme 16: Synthesis of [Fe] precatalyst **18**.

Firstly, sodium metal in ethanol generates fresh sodium ethoxide *in-situ* to catalyse the reaction between 1,3-diphenylacetone and diethyl oxalate, furnishing intermediate **26**. Next, the addition of *N*,*N*'-dimethylethylenediamine to compound **26** in a double condensation reaction leads to the formation of cyclopentadienone ligand **27**. Finally, treatment of **27** with $Fe_2(CO)_9$ in dry toluene at reflux for 24 h, followed by alumina chromatography, furnished [Fe] precatalyst **18** in a 59% yield.

2.3.2 Full Optimisation Study

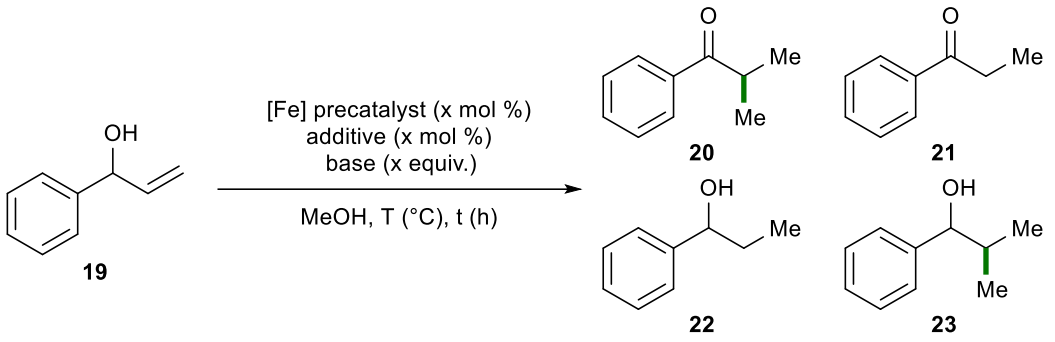
With a fresh supply of [Fe] precatalyst **18** in hand, a full optimisation study was carried out to investigate the effects of systematically varying standard conditions (table 2). The optimised conditions, as determined by Kurt, employed [Fe] precatalyst **18** (2 mol %), trimethyl amine *N*-oxide (Me_3NO) (4 mol %), potassium carbonate (K_2CO_3) (2 equiv.) in MeOH ([**19**] = 0.5 M) at 130 °C for 24 h (entry 1). This set of conditions gave isomerisation-methylation product **20** in 88% NMR yield, isolated in a 76% yield.

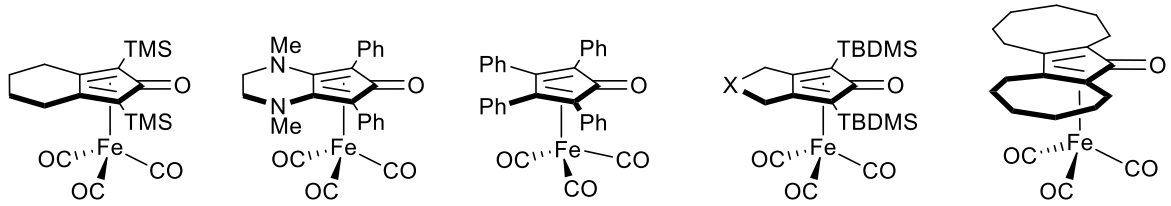
A selection of other structurally related [Fe] precatalysts (**17**, **7**, **24**, **25**, **28**) did not enable significant formation of **20** (entries 2-6), indicating precatalyst **18** was unique in facilitating this transformation. A plausible reason for this is that the nitrogen atoms enhance the cyclopentadienone ligand's ability to shuffle electrons to and from the metal centre, resulting in both more effective hydrogen abstraction and hydride delivery.

The absence of precatalyst, with or without additive (entries 7 and 8), resulted in no formation of product **20**; however, ketone intermediate **21** was observed. This suggests that the isomerisation of a secondary allylic alcohol to a ketone is possible in the presence of alkoxide, formed in equilibrium from K_2CO_3 and MeOH. The absence of additive Me_3NO (entry 9) revealed formation of product **20** in very good yield, suggesting that heat alone is enough to activate precatalyst **18** *via* liberation of carbon monoxide (CO).

Exchanging the additive for triphenylphosphine (PPh_3) resulted in a decrease of the conversion of **19** to **20** (entry 10). From previous reports,[31] and from reports of our own in the Morrill group,[33] PPh_3 is understood to be a beneficial additive for CO decoordination with respect to using other alcohols as alkylating agents, and that the synergistic effect with MeOH is relatively sub-standard compared to its Me_3NO counterpart.

A precatalyst loading of 2 mol % demonstrated to be optimal in ensuring enough conversion of **19** to **20**, while resisting over-reduction of **20** to **23**.





Entry[a]	Catalyst (mol %)	Additive (mol %)	Base (equiv.)	T (°C)	Time (h)	**19**[b] RSM (%)	**20**[b] P (%)	**21**[b] (%)	**22**[b] (%)	**23**[b] (%)
1	**18** (2)	Me_3NO (4)	K_2CO_3 (2.0)	130	24	-	88 (76)	-	-	4
2	**17** (2)	Me_3NO (4)	K_2CO_3 (2.0)	130	24	46	2	7	-	-
3	**7** (2)	Me_3NO (4)	K_2CO_3 (2.0)	130	24	64	3	15	-	-
4	**24** (2)	Me_3NO (4)	K_2CO_3 (2.0)	130	24	59	-	6	-	-
5	**25** (2)	Me_3NO (4)	K_2CO_3 (2.0)	130	24	63	-	14	-	-
6	**28** (2)	Me_3NO (4)	K_2CO_3 (2.0)	130	24	63	3	18	-	-
7	**-**	Me_3NO (4)	K_2CO_3 (2.0)	130	24	56	-	26	-	-
8	**-**	-	K_2CO_3 (2.0)	130	24	58	-	34	-	-
9	**18** (2)	**-**	K_2CO_3 (2.0)	130	24	-	81	4		
10	**18** (2)	**PPh_3** (4)	K_2CO_3 (2.0)	130	24	31	59	<2	-	-
11	**18 (1)**	Me_3NO **(2)**	K_2CO_3 (2.0)	130	24	48	37	8	-	-
12	**18 (3)**	Me_3NO **(6)**	K_2CO_3 (2.0)	130	24	-	83	-	-	10
13	**18 (4)**	Me_3NO **(8)**	K_2CO_3 (2.0)	130	24	-	79	-	-	12
14	**18** (2)	Me_3NO (4)	K_2CO_3 (2.0)	**100**	24	88	6	-	-	3
15	**18** (2)	Me_3NO (4)	K_2CO_3 (2.0)	**110**	24	64	30	-	-	-
16	**18** (2)	Me_3NO (4)	K_2CO_3 (2.0)	**120**	24	58	32	-	-	-
17	**18** (2)	Me_3NO (4)	K_2CO_3 (2.0)	**140**	24	-	85	-	-	3
18	**18** (2)	Me_3NO (4)	**Cs_2CO_3** (2.0)	130	24	-	34	43	-	-
19	**18** (2)	Me_3NO (4)	**NaOH** (2.0)	130	24	-	47	14	<2	10
20	**18** (2)	Me_3NO (4)	**NaO^{t}Am** (2.0)	130	24	-	35	18	-	6
21	**18** (2)	Me_3NO (4)	**KO^{t}Bu** (2.0)	130	24	-	57	8	-	5
22	**18** (2)	Me_3NO (4)	**-**	130	24	74	<2	-	-	-
23	**18** (2)	Me_3NO (4)	K_2CO_3 **(0.1)**	130	24	10	78	-	-	<2
24	**18** (2)	Me_3NO (4)	K_2CO_3 **(1.0)**	130	24	5	83	-	-	3
25	**18** (2)	Me_3NO (4)	K_2CO_3 **(4.0)**	130	24	-	88	-	-	4
26[c]	**18** (2)	Me_3NO (4)	K_2CO_3 (2.0)	130	24	8	73	<2	-	<2
27[d]	**18** (2)	Me_3NO (4)	K_2CO_3 (2.0)	130	24	-	80	-	-	3

Table 2: Full optimisation table for the isomerisation-methylation of **19**.

[a]Reactions performed using 0.5 mmol of allylic alcohol **19** and bench-grade MeOH. [**19**] = 0.5 M. [b]Yield after 24 h as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yield given in parentheses. [c][**19**] = 0.25 M instead of 0.5 M. [d][**19**] = 1.0 M instead of 0.5 M.

Lower conversion is observed with a precatalyst loading of 1 mol % (entry 11), while over-reduced product is observed with increased precatalyst loadings of 3 mol % and 4 mol % (entries 12 and 13).

N.B. the catalyst/additive ratio was kept constant throughout the optimisation study. Lower temperatures between 100-120 °C resulted in lower conversion of **19** to **20** (entries 14-16), while a higher temperature of 140 °C (entry 17) gave relatively similar NMR yields to the optimised reaction at 130 °C.

Employing caesium carbonate (Cs_2CO_3), sodium hydroxide (NaOH), or alkoxide bases (entries 18-21) resulted in lower yields of product **20** at the expense of unwanted formation of side products **21** and **23**. Interestingly, no reaction took place in the absence of base (entry 22), suggesting the isomerisation of allylic alcohol **19** to ketone intermediate **21** could be base-assisted. Doubling the K_2CO_3 loading to 4.0 equiv. (entry 25) gave comparatively similar NMR yields to the optimised conditions, while halving the K_2CO_3 loading to 1.0 equiv. (entry 24) resulted in a slight loss of conversion of **19** to **20**. Gratifyingly, a sub-stoichiometric amount of K_2CO_3 (10 mol %) could be employed without any substantial loss of conversion (entry 23), enabling potential users of this reaction to opt for a higher atom economy process at the expense of conversion.

Altering the reaction concentration had no observed improvement on the yield of **20** (entries 26 and 27). A reaction time of 24 h was determined optimal for carrying out the reaction scope. For time studies, see chapter 2.3.4.1.

2.3.3 Substrate Scope

2.3.3.1 Isomerisation-Methylation of Allylic Alcohols

In general, a diverse selection of 2° allylic alcohols underwent isomerisation-methylation accessing a range of substituted *α*-methyl ketones in moderate to good yields.

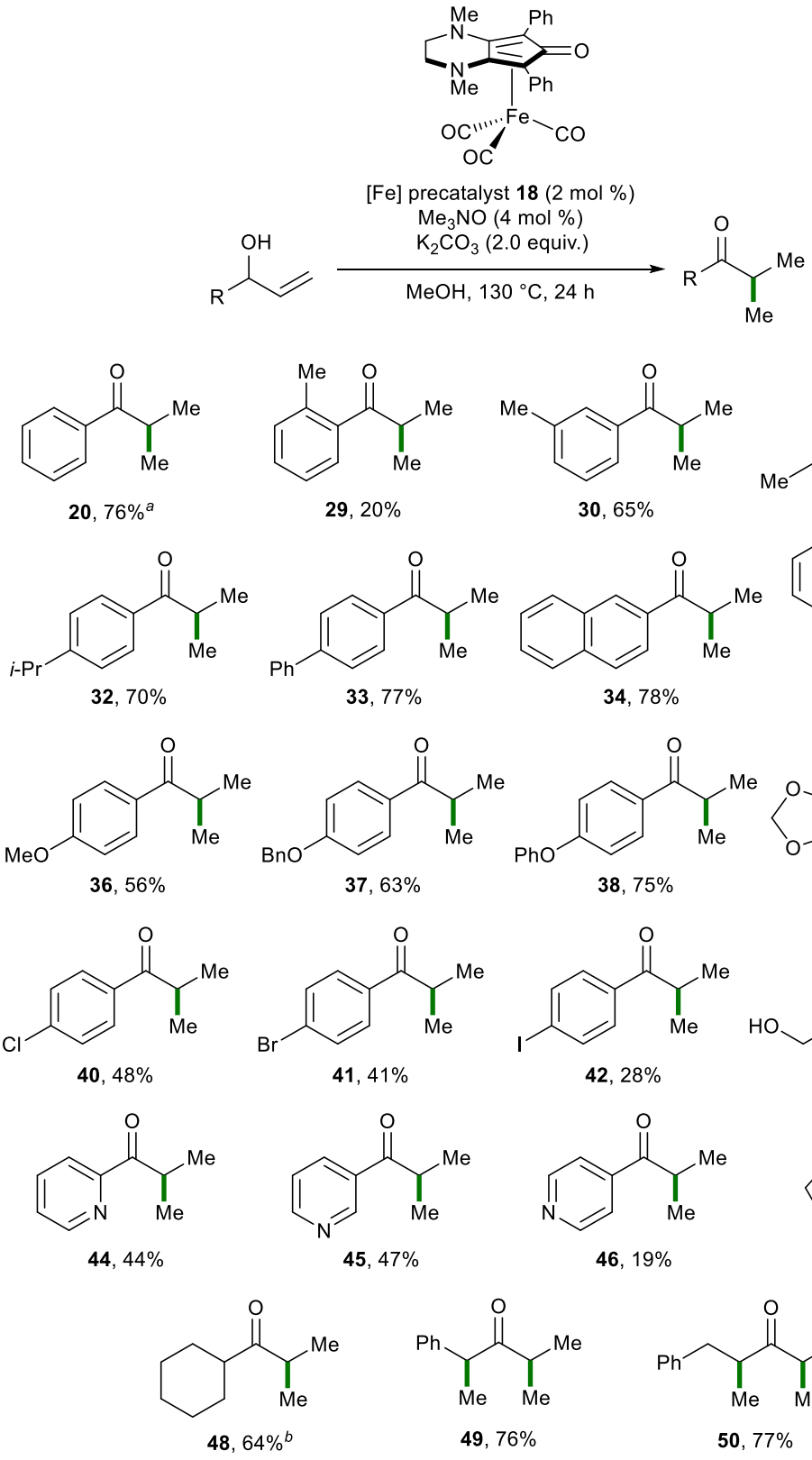


Figure 2: Scope of isomerisation-methylation.

[a]10 mmol scale. [b]Yield after 24 h as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard.

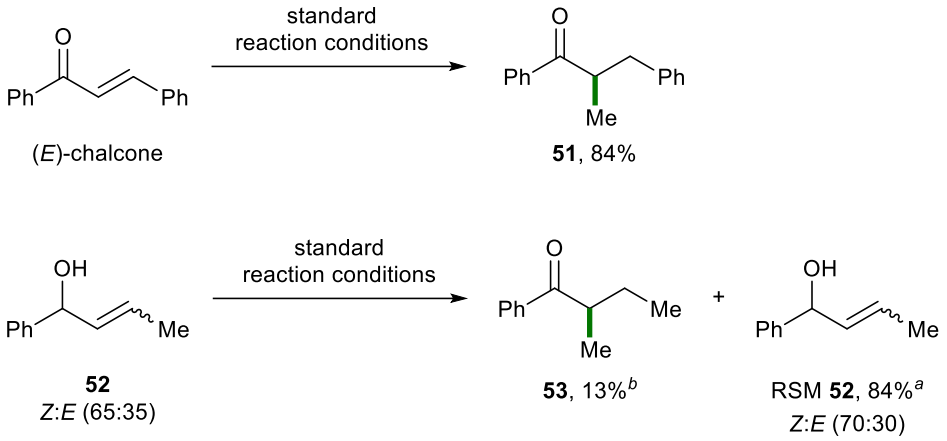
Initially the scalability of this process was demonstrated by performing the transformation on a 10 mmol scale. This reaction was carried out in an ACE pressure tube and delivered product **20** in 76% isolated yield. Within the aryl motif, substitution at the *ortho*, *meta* and *para* positions was explored. Substrates containing 3-Me, 4-Me, 4-*i*Pr, and 4-Ph substituents were tolerated very well (**30**-**33**, 65-77%). Bulky motifs 2-naphthyl and 1-naphthyl were also successful in this transformation (**34**-**35**, 69-78%). The 2-Me substituent was an exception to the tolerability of sterically encumbered motifs (**29**, 20%).
Electron donating groups (OMe, OBn, OPh) were reasonably well-tolerated (**36**-**38**, 56-75%) together with an acetal-protected catechol motif (**39**, 56%). Halide substitution (4-Cl, 4-Br, 4-I) was somewhat tolerated within the allylic alcohol (**40**-**42**, 28-48%), introducing an additional functional handle into the products, allowing for further functionalisation such as cross-coupling.[34]

Interestingly, selective isomerisation–methylation occurs in the presence of a benzyl alcohol functionality (**43**, 73%). Some examples of heterocycle motifs including 2-pyridyl, 3-pyridyl, 4-pyridyl and 2-thiophenyl, were tolerated with varying success (**44**-**47**, 19-47%). Replacing the aryl motif for cyclohexyl (**48**) resulted a 64% NMR yield. This compound was later isolated to 8% to obtain pure NMR spectra for data analysis.

Substrates bearing two enolisable positions were subjected to the optimised reaction conditions. In these cases, di-methylation either side of the carbonyl was observed for benzyl and homobenzyl-containing substrates, in good yield (**49**-**50**, 76-77%). Compound **50** was isolated by Kurt Polidano.

Substitution on the alkene component was also explored. The extent to which 1,2-disubstitution is successful was found to largely depend on the geometric isomer of the starting material (scheme 17). When (*E*)-chalcone was subjected to the standard reaction conditions, a high yield of isomerisation-methylation product (**51**, 84%). For product **53**, the starting material (**52**) was synthesised as a mixture of stereoisomers (*Z*:*E*, 65:35). It can be hypothesised that the low yield of product **53** (13% NMR yield) is due to the higher ratio of *Z to E* isomer in the starting material mixture, and that the

cis conformation is sterically less favourable for metal-catalysed dehydrogenation to proceed. This can be supported by the change in *Z*:*E* ratio for the starting material observed in the crude NMR, where more of the *trans* isomer, despite being in the minority, was consumed in the reaction (figure 3).



Scheme 17: 1,2-Disubstitution at the alkene.

[a]Yield after 24 h as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard.

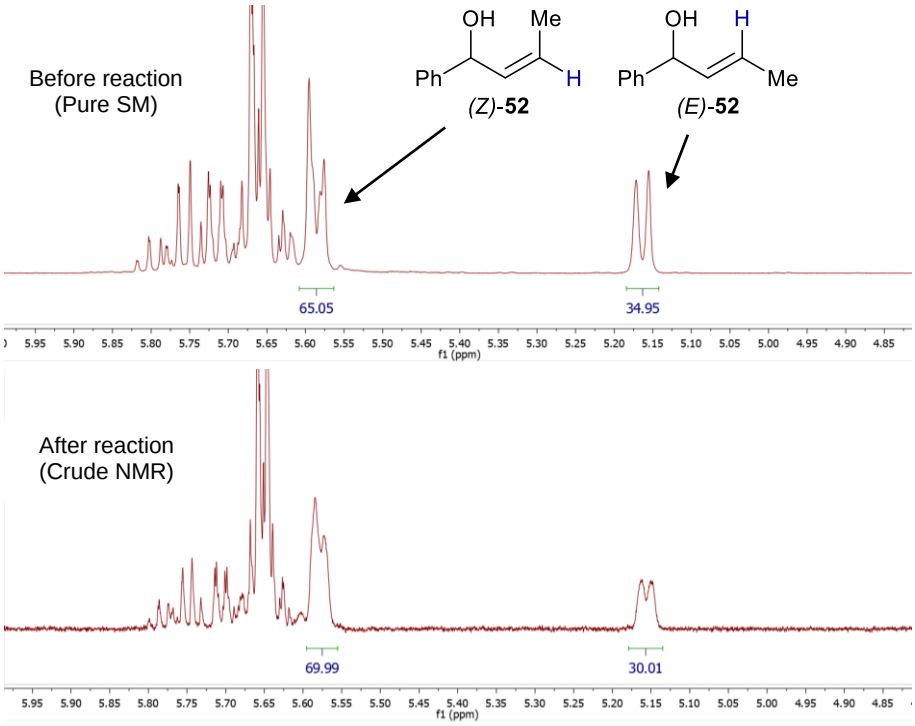
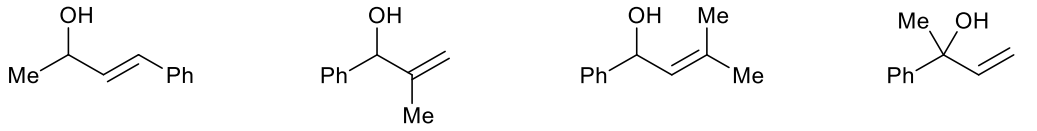


Figure 3: A comparison of the *Z*:*E* ratio of SM 1-phenylbut-2-en-1-ol (**52**) before and after reaction. Ratios were determined using ^{1}H NMR analysis of the pure SM and crude reaction mixture.

Substrates containing a methyl group *β* to the alcohol were expected to undergo dimethylation at the terminal carbon. Dimethylation of methyl ketones was routinely observed within Kurt's publication for the iron-catalysed methylation of methyl ketones.[26] In the case of compound **54** (figure 4), subjection to standard conditions led to the multi-alkylated product **50** in 28% isolated yield. Allylic alcohols containing 1,1-disubstituted (**55**) or trisubstituted alkenes (**56**) were incompatible for this transformation, fully returning starting material. This inactivity can be attributed to the increased steric congestion preventing alcohol dehydrogenation. Compound **57** was included in this study to demonstrate the incompatibility of tertiary allylic alcohols for borrowing hydrogen processes, since they cannot undergo dehydrogenation due to the absence of an *α*-hydrogen.



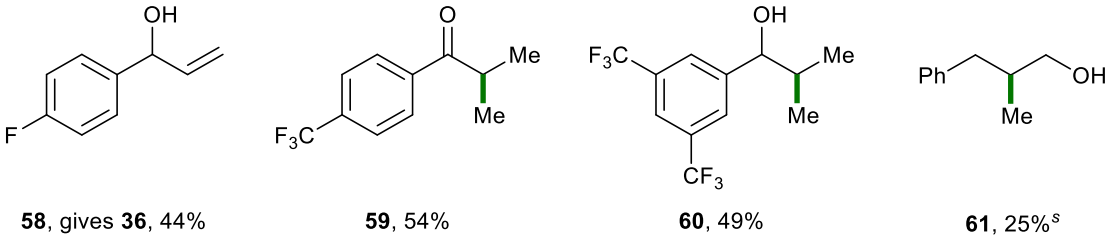
54, gives **50**, 28% **55**, SM returned **56**, SM returned **57**, SM returned

Figure 4: Scope of alkene substitution – continued, and 3° alcohol incompatibility.

[a]Yield after 24 h as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard.

Upon evaluating the effect of electron-withdrawing aryl substituents on the isomerisation–methylation process, 4-F aryl substitution (**58**) led to the formation of 4-OMe aryl ketone **36** (44%) (figure 5). This was presumably formed *via* nucleophilic aromatic substitution of the corresponding 4-F substituted aryl ketone intermediate. An inductively electron withdrawing functionality (4-CF_3) resulted in a moderate yield of desired product (**59**, 54%). Increasing the electron-withdrawing effect further with a 3,5-$(CF_3)_2$ aryl substituted allylic alcohol resulted in the formation of secondary alcohol **60** in 49% isolated yield. The accumulative inductive effect of the two trifluoromethyl groups increased the electrophilicity of the carbonyl such that the intermediate *α*-methyl ketone underwent subsequent transfer hydrogenation. This one-pot transformation represents a formal Markovnikov hydromethylation of the allylic alcohol starting material.

The only primary allylic alcohol to be investigated, cinnamyl alcohol, underwent hydromethylation to form *β*-C(sp^3)-methylated alcohol **61**. The additional hydrogenation of the desired carbonyl product here is effected by the reduced steric hindrance and greater δ^+ charge on the carbon of the aldehyde intermediate, versus a ketone.

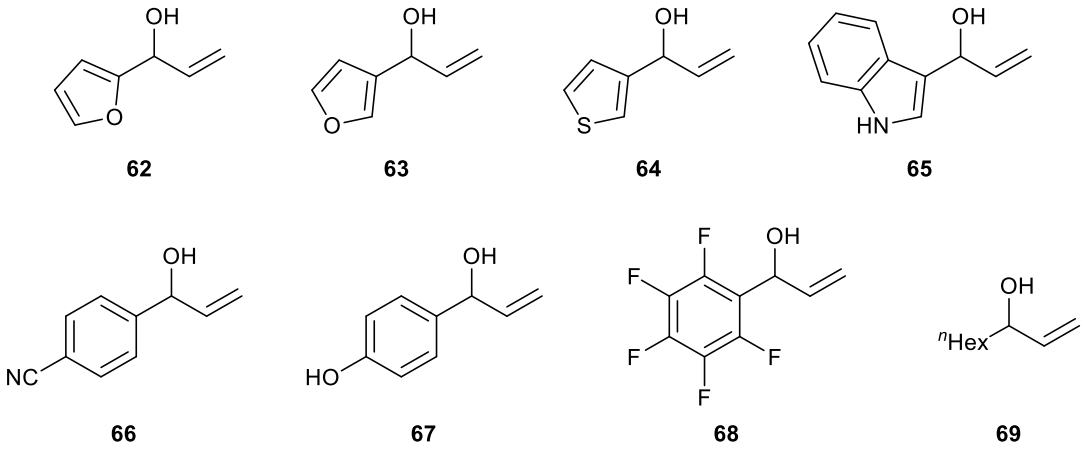


58, gives **36**, 44% **59**, 54% **60**, 49% **61**, 25%^{s}

Figure 5: Scope for isomerisation-methylation – continued.

[a]Yield after 24 h as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard.

Incompatible substrates for this isomerisation-methylation transformation are illustrated in figure 6. Allylic alcohol substrates containing heterocycle motifs 2-furanyl, 3-furanyl, 3-thiophenyl and 3-indolyl (**62-65**) were found to be incompatible in this reaction. In general, many of the heterocycle-containing allylic alcohol starting materials were unstable at room temperature or at 2-8 °C, steadily decomposing after just a few days. It is anticipated that these substrates decompose under the reaction conditions (130 °C) before the reaction has time to occur.



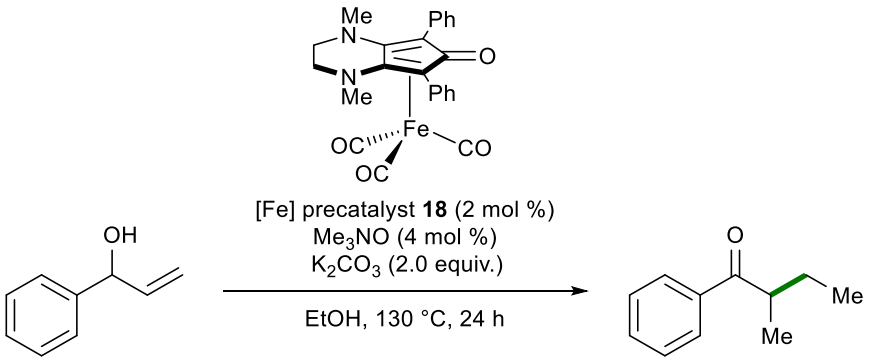
62 **63** **64** **65**

66 **67** **68** **69**

Figure 6: Incompatible and untested substrates for isomerisation-methylation.

The presence of a nitrile functionality within the allylic alcohol (**66**) produced a complex mixture of products, possibly due to competing CN reduction, although no evidence of this was obtained. A phenol functionality (**67**) was also incompatible for this transformation, possibly due to phenol being a catalyst poison. This lack of reactivity has been observed in previous iron-catalysed borrowing hydrogen manifolds.[35] Compounds **68** and **69** were synthesised towards the end of the project, however, both expectedly gave complex mixtures.

Finally, the model reaction was also performed using ethanol as solvent, which gave 46% conversion to *α*-ethylated ketone **70**, determined by ^{1}H NMR and compared with literature reported spectra (see experimental). While the activation barrier for the dehydrogenation of ethanol is lower compared to methanol,[19,20] the hydrogenation of a trisubstituted alkene, in the latter stages of the borrowing hydrogen cycle, is electronically and sterically more challenging than the hydrogenation of a disubstituted alkene. An attempt to increase the yield by raising the temperature to 140 °C, did not improve the efficiency of the reaction (table 3, entry 2).



19 **70**, 46%[a]

Entry[a]	Catalyst (mol %)	Additive (mol %)	Base (equiv.)	T (°C)	Time (h)	**19**[b] RSM (%)	**70**[b] P (%)	**21**[b] (%)	**22**[b] (%)
1	**18** (2)	Me_3NO (4)	K_2CO_3 (2.0)	130	24	-	46	18	20
2	**18** (2)	Me_3NO (4)	K_2CO_3 (2.0)	**140**	24	-	33	18	18

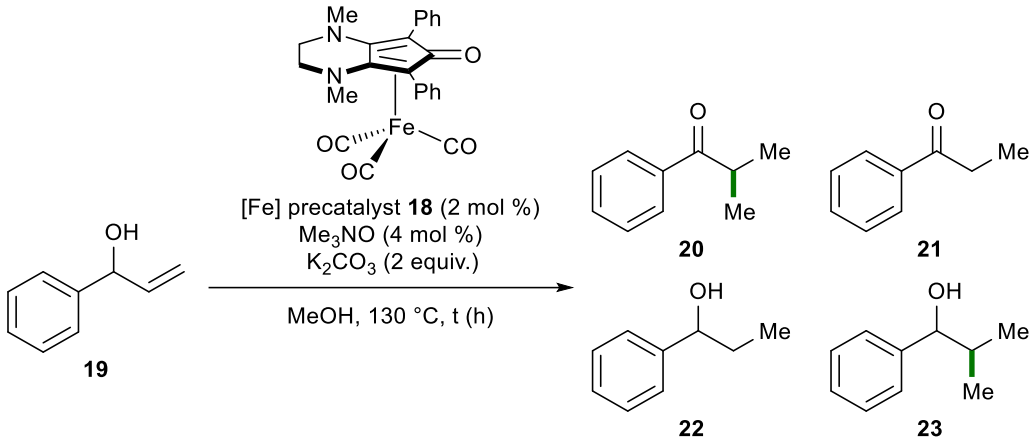
Table 3: Isomerisation-ethylation of **19**.

[a]Reactions performed using 0.5 mmol of allylic alcohol **19** and anhydrous EtOH. [**19**] = 0.5 M. [b]Yield after 24 h as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard.

2.3.4 Mechanistic Investigations

2.3.4.1 Kinetic Studies

In order to gain more insight on the kinetics of this reaction, eight identical setups of the parent reaction using starting material **19** were performed in parallel. These were stopped independently at the specified time points stated in table 4. Reactions underwent the standard mini work up including the addition of mesitylene as the internal standard for subsequent ^{1}H NMR analysis of the crude reaction mixture.



Entry[a]	Catalyst (mol %)	Additive (mol %)	Base (equiv.)	T (°C)	Time (h)	**19**[b] RSM (%)	**20**[b] P (%)	**21**[b] (%)	**22**[b] (%)	**23**[b] (%)
1	**18** (2)	Me_3NO (4)	K_2CO_3 (2.0)	130	**0.25**	90	2	1	-	-
2	**18** (2)	Me_3NO (4)	K_2CO_3 (2.0)	130	**0.5**	90	3	2	-	-
3	**18** (2)	Me_3NO (4)	K_2CO_3 (2.0)	130	**1**	84	7	2	-	-
4	**18** (2)	Me_3NO (4)	K_2CO_3 (2.0)	130	**2**	76	10	2	-	-
5	**18** (2)	Me_3NO (4)	K_2CO_3 (2.0)	130	**4**	28	60	5	-	-
6	**18** (2)	Me_3NO (4)	K_2CO_3 (2.0)	130	**8**	8	83	-	-	-
7	**18** (2)	Me_3NO (4)	K_2CO_3 (2.0)	130	**16**	2	93	-	-	-
8	**18** (2)	Me_3NO (4)	K_2CO_3 (2.0)	130	**24**	0	87	-	-	4

Table 4: Kinetic studies table for the isomerisation-methylation of **19**.

[a]Reactions performed using 0.5 mmol of allylic alcohol **19** and bench-grade MeOH. [**19**] = 0.5 M. [b]Yield after specified time point as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard.

As observed from figure 7, the process takes between 30 minutes and 1 hour until it gradually proceeds. This induction period may be attributed to catalyst activation, or equilibration of the reaction temperature. Initially, the reaction proceeds slowly with only 10% conversion to **20** observed after 2 hours. Beyond 2 hours, the rate of formation of **20** increased, with 60% conversion observed after 4 hours in addition to

5% of ketone intermediate **21**. The observed quantities of **21** remain low throughout the reaction, which suggests that the isomerisation of **19** to **21** contains the rate limiting step, and that the alkylation of **21** proceeds soon after it is formed. Although the transformation reaches its maximum conversion of 93% after 16 hours, all reactions for the substrate scope were carried out for 24 hours to provide less reactive substrates with the opportunity to achieve a high yield. In the case of model substrate **19**, a reaction time of 24 hours resulted in a slight loss of conversion to **21**, due to the formation of corresponding alcohol **23** in a 4% yield (table 4, entry 8).

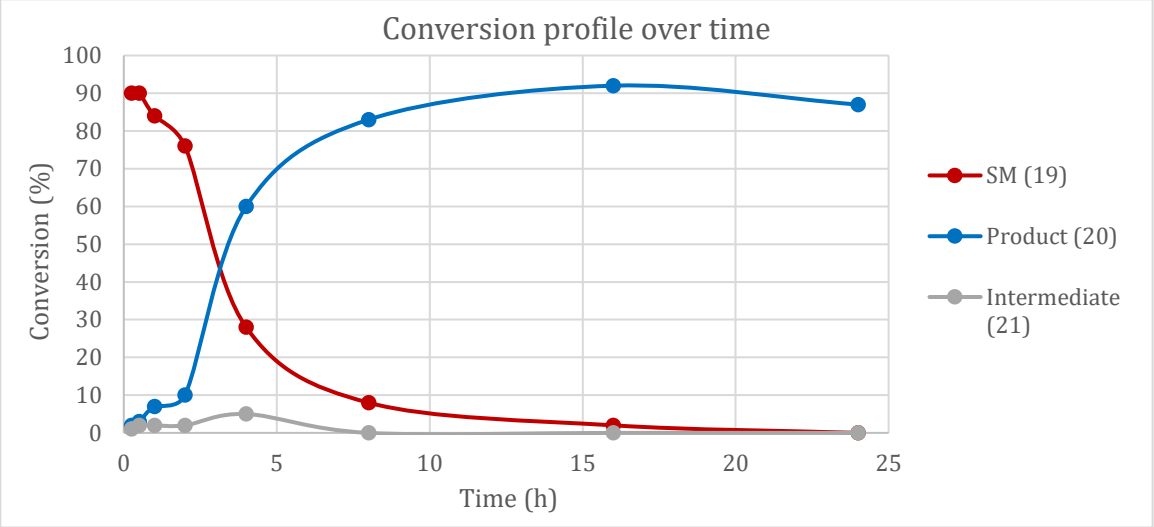
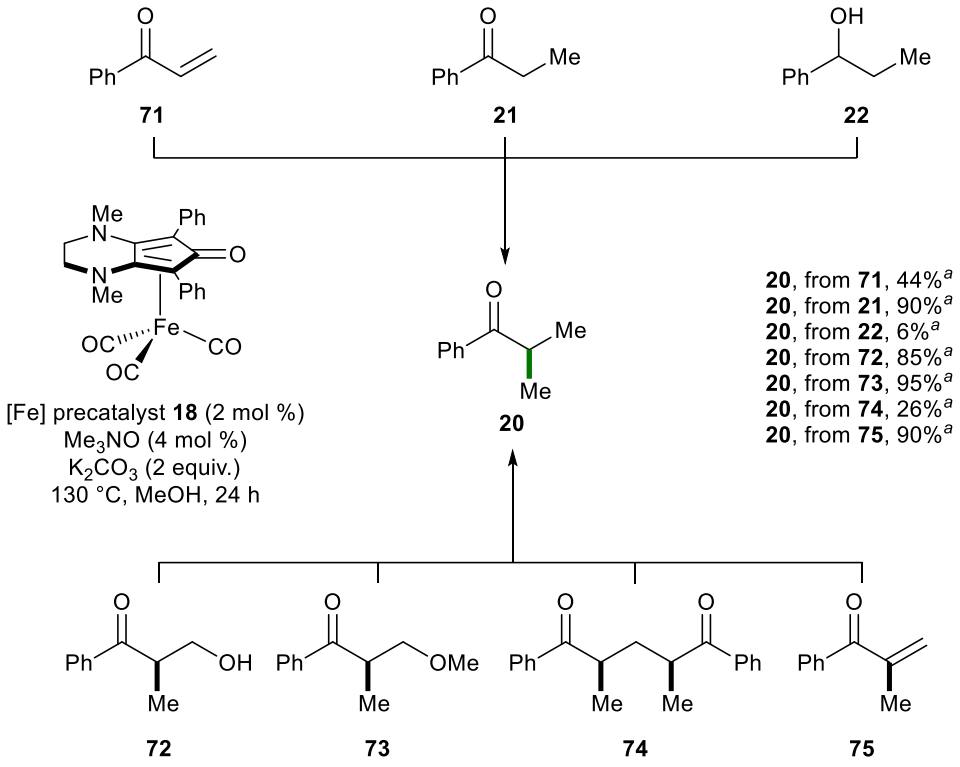


Figure 7: Conversion-time graph for the isomerisation-methylation of **19**.

2.3.4.2 Validation of Plausible Intermediates

Selecting model substrate **19** as a representative isomerisation-methylation example, several plausible intermediates were independently synthesised and subsequently probed using the standard reaction conditions, as shown in scheme 18. Oxidation of **19** would form enone **71**, and subsequent reduction of this would form ketone **21**. The transformation from allylic alcohol **19** to ketone **21** can be described as a redox isomerisation. Secondary alcohol **22** would be generated upon transfer hydrogenation of **21**. Furthermore, *β*-hydroxy ketone **72**, *β*-methoxy ketone **73**, diketone **74**, and enone **75** were also possible intermediates.



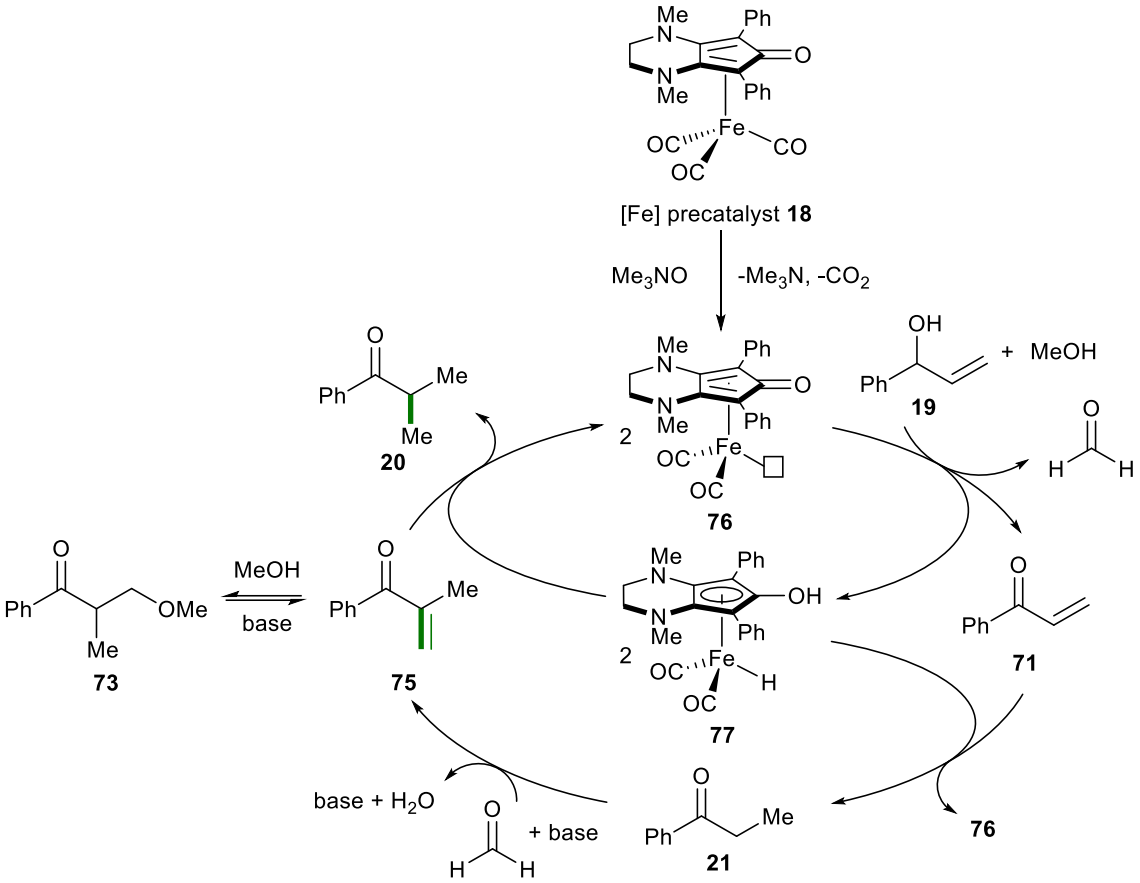
Scheme 18: Validation of plausible intermediates.

[a]Yield after specified time point as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard.

All reactions delivered isomerisation-methylation product **20** with varying levels of conversion and were thus all determined to be plausible reaction intermediates. Enone **71** gave 44% conversion to **20** without any return of starting material or other intermediates, suggesting it is a short-lived species under these standard reaction conditions. It is possible much of **71** may undergo heat-induced dimerisation (cycloaddition) during the induction period of the reaction.[36] Secondary alcohol **22** and diketone **74** only gave 6% and 26% conversion to **20** after 24 hours, respectively, which indicated that these species would retard product formation if they were indeed formed during the reaction.

Based on these mechanistic investigations, and the literature precedent,[37] the following mechanism is postulated for this process. Firstly, isomerisation-methylation proceeds *via* initial Me_3NO-promoted CO decoordination of [Fe] precatalyst **18** to form the active iron complex **76** (scheme 19). This promotes dehydrogenation of both allylic alcohol **19** and methanol to form enone **71** and

formaldehyde, respectively. Hydrogenation of **71** by iron–hydrogen complex **77** gives ketone **21**, which can undergo a subsequent base-catalysed aldol condensation with formaldehyde to produce enone **75**. *β*-methoxy ketone **73** is in equilibrium with enone **75**. Finally, hydrogenation of enone **75** by **77** gives *α*-methyl ketone **20**, completing the catalytic cycle.



Scheme 19: Postulated reaction mechanism for iron-catalysed isomerisation methylation.

2.3.4.3 Employing CD_3OD as Solvent

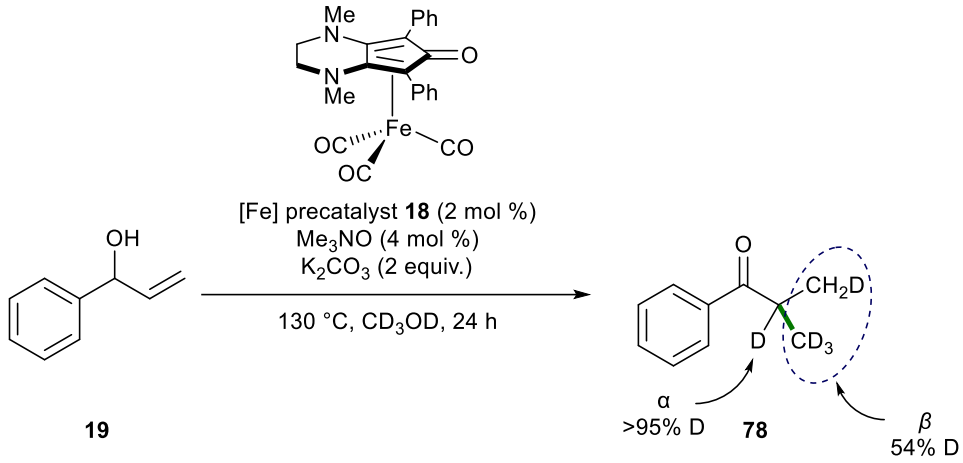
Further mechanistic information was provided by employing CD_3OD as solvent (scheme 20). Significant deuterium incorporation within product **78** was observed at the *α*- and *β*-positions, >95% and 54%, respectively (figure 8). Deuterium incorporation at the *β*-position indicated the involvement of an iron hydride species in the reaction mechanism.

Deuterium incorporation equation:

% D = 100-((peak integral/equivalent protons) *100)

Peak A: 100-((0.05/1)*100) = 95% D

Peak B: 100-((2.78/6)*100) = 54% D



Scheme 20: Hydrogenation of **19** with CD_3OD.

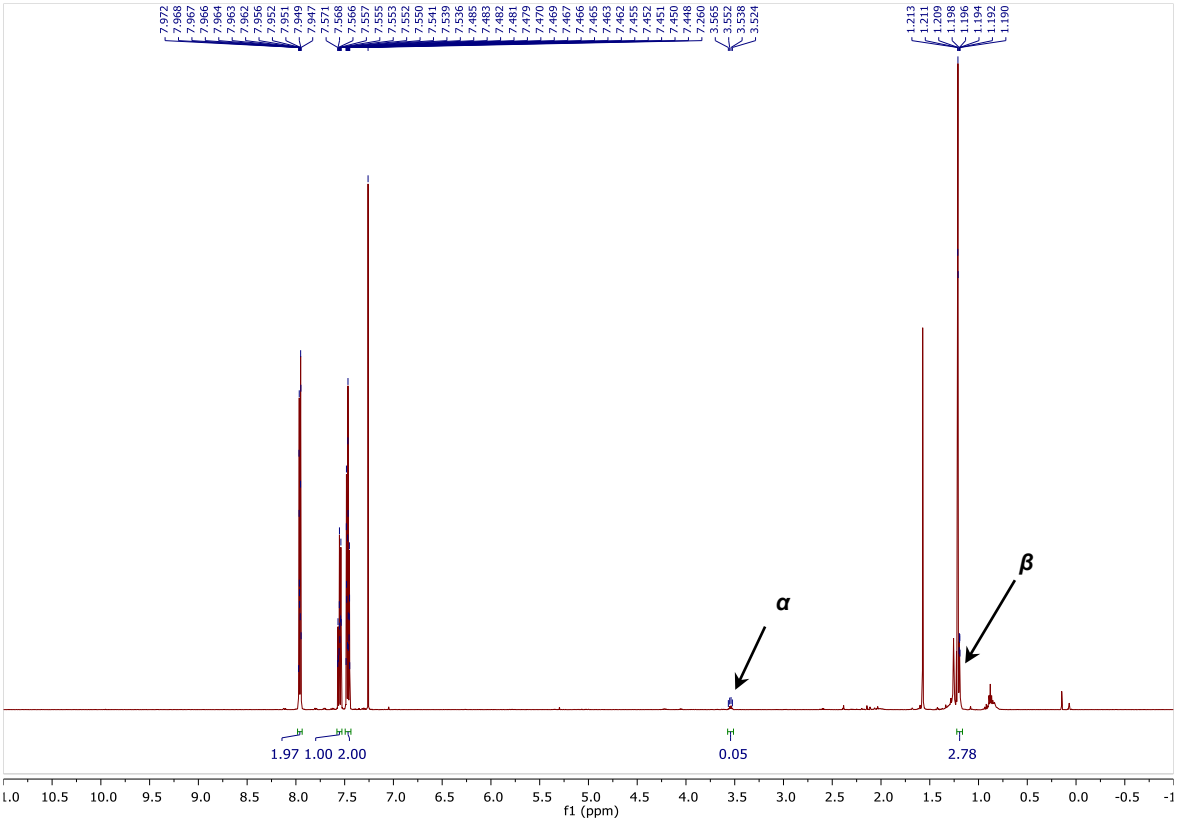
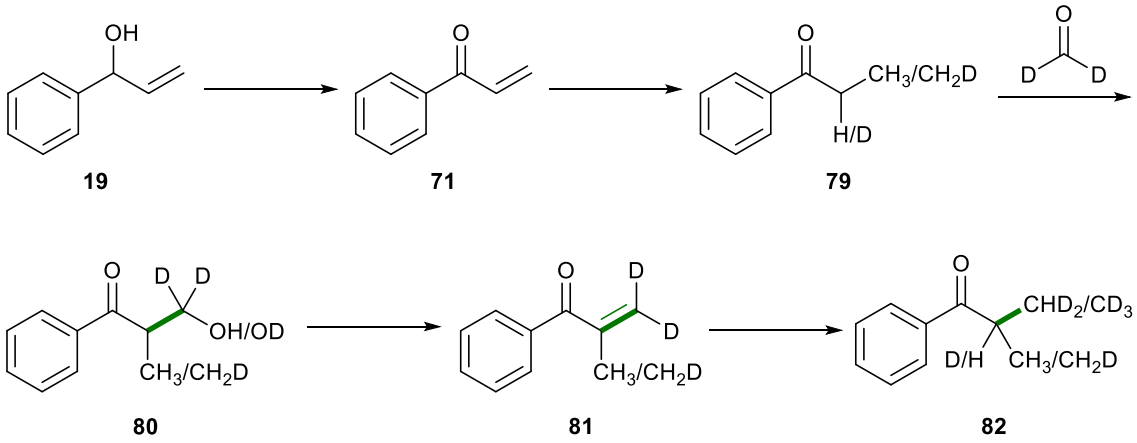


Figure 8: ^1H NMR spectrum of the reaction when employing CD_3OD as solvent.

To fully understand the extent of deuterium incorporation at these positions, we must consider the reaction mechanism stepwise (scheme 21).



Scheme 21: Stepwise formation of **82**.

Initially, allylic alcohol **19** undergoes dehydrogenation to enone **71**, which is hydrogenated to **79** using the same H_2, or alternatively using a source of D_2 from the *in-situ* dehydrogenation of CD_3OD. Base-mediated condensation with formaldehyde-d_2 to **80**, followed by E_1cb elimination, forms intermediate **81** possessing a CD_2 fragment. The final reduction would see H_2 or D_2 add across the alkene component to form **82**.

The deuterium incorporation at the α-position is solely determined by this final step, and thus the maximum possible deuterium incorporation at this position is 100%. A 95% deuterium incorporation at the α-position implies D_2-hydrogenation is more likely to occur because of CD_3OD being in a large excess. Theoretically, the maximum possible deuterium incorporation at the β-position is 66% since two protons (out of six atoms) must remain present in the final product.

2.3.5 Investigating the Pressure inside the Vial

As stated in chapter 2.3.1, all reactions are carried out in a sealed microwave vial, as illustrated in figure 9. MeOH in a closed system at temperatures well above its boiling point would undoubtedly be a safety concern and begs the question: what is the pressure inside the microwave vial at 130 °C? Fortunately, access to a microwave

reactor was gained, meaning the pressure inside the vial could be monitored over time (figure 10). The graph indicates that the pressure inside the vial reaches a maximum of 11 bar, followed by a steady decrease to 9 bar, attributed to reaction equilibration, where it is held until cooling. Interestingly, the conversion of allylic alcohol **19** to product **20** over a 2-hour period was higher when using the microwave (46%, figure 11), versus conventional heating (10%, chapter 2.3.4.1, table 4, entry 4).

Figure 9: General reaction set up of borrowing hydrogen reactions.

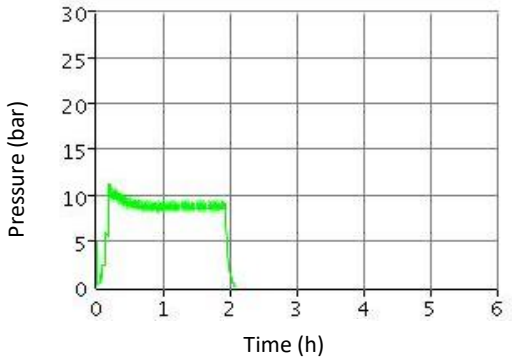


Figure 10: Reaction profile showing pressure over time in the microwave.

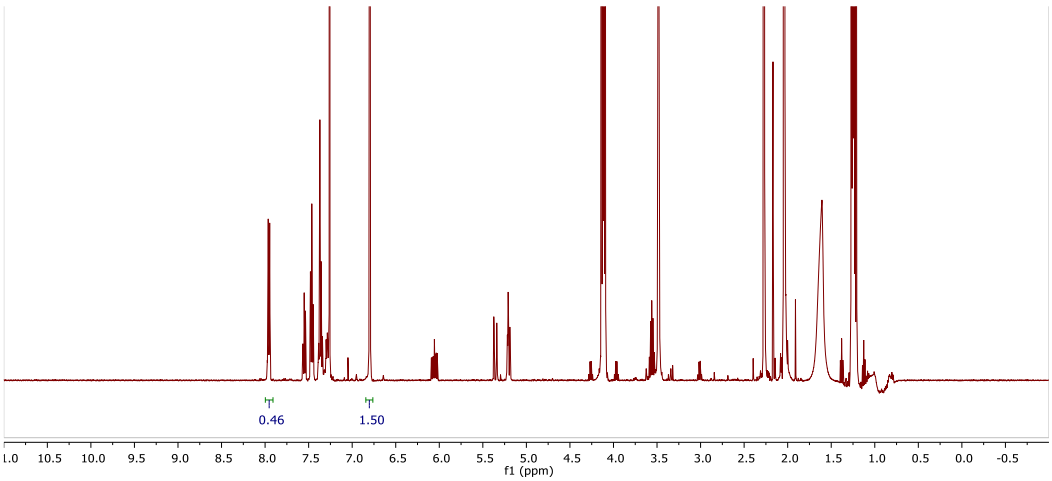


Figure 11: ^{1}H NMR spectrum of crude reaction mixture after 2 h in the microwave, using 1,3,5-trimethylbenzene as the internal standard.

2.4 Conclusion

An operationally simple one-pot transformation for the isomerisation-methylation of allylic alcohols to *α*-methyl ketones has been developed. This process employs a bench-stable iron(cyclopentadienyl) complex to promote the reaction with methanol as the C1 building block. The transformation exhibits a good substrate scope and offers a much greener approach than the one previously known one-pot procedure. Mechanistic experiments provided evidence for plausible reaction intermediates, an iron-hydride species, and methanol as the methylating agent in this catalytic process. Since the publication of this transformation, a similar process describing the palladium catalysed synthesis of *α*-methyl ketones from allylic alcohols and employing methanol has been developed.[38]

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Chapter 3

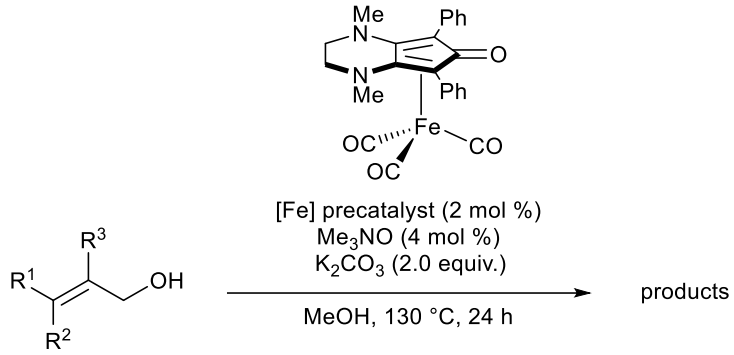
Investigating Miscellaneous Borrowing Hydrogen Processes

Table of Contents

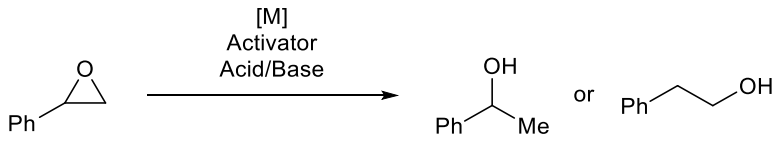
For related experimental and characterisation data, see chapter 4

3.1 Preface

This chapter discusses miscellaneous borrowing hydrogen processes. Firstly, the reactivity of primary allylic alcohols was examined under standard methylation conditions. The position of methyl groups within the structure was found to influence the given transformation. Ultimately, no interesting transformations were uncovered, including δ-methylation of primary allylic alcohols.



Secondly, the regioselective ring-opening of epoxides was examined with earth-abundant metal catalysis and various hydrogen donors. Despite poor mass return across most reactions, a promising result for the selective transfer hydrogenation of a terminal epoxide to a secondary alcohol was found. Employing MeOH as hydrogen donor resulted in the formation of various β-methoxy alcohols.



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Abdul Bari – A supervised part-time PhD student who assisted with the synthesis of allylic alcohols
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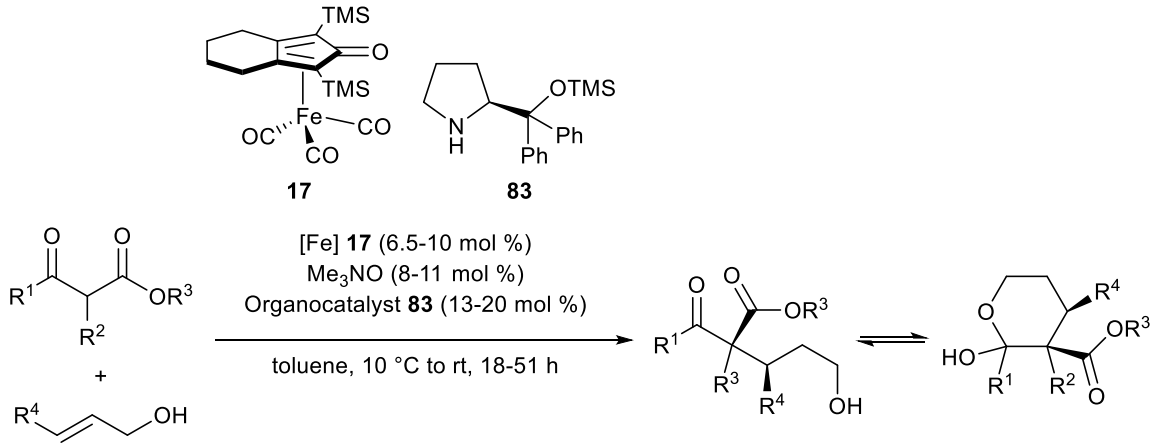
Mubarak Dambatta – a PhD student who assisted with epoxide ring-opening reactions.

3.2 Probing the Reactivity of Allylic Alcohols

3.2.1 Introduction

Within the borrowing hydrogen research area, allylic alcohols are predominantly employed as electrophiles. Despite few publications on the topic, both *α*- and *γ*-functionalization have been demonstrated using nitrogen and carbon-based nucleophiles. In 2013, Quintard and Rodriguez combined an iron-catalyzed borrowing hydrogen cycle with secondary amine organocatalysis to obtain *γ*-functionalised alcohols using mild reaction conditions (scheme 22).[1] This was later extended to a one-pot synthesis of enantioenriched spiro-δ-lactones.[2]

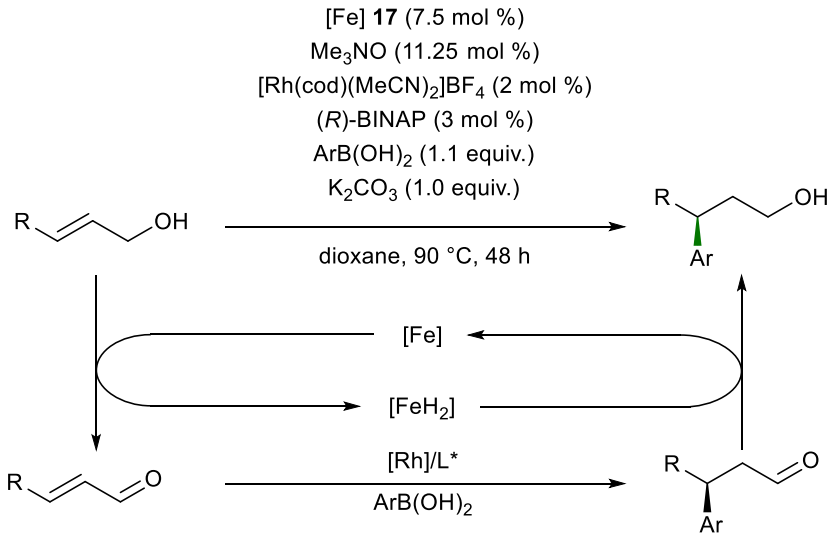


Scheme 22: Dual-catalytic system combining borrowing hydrogen activation and enantioselective organocatalysis.

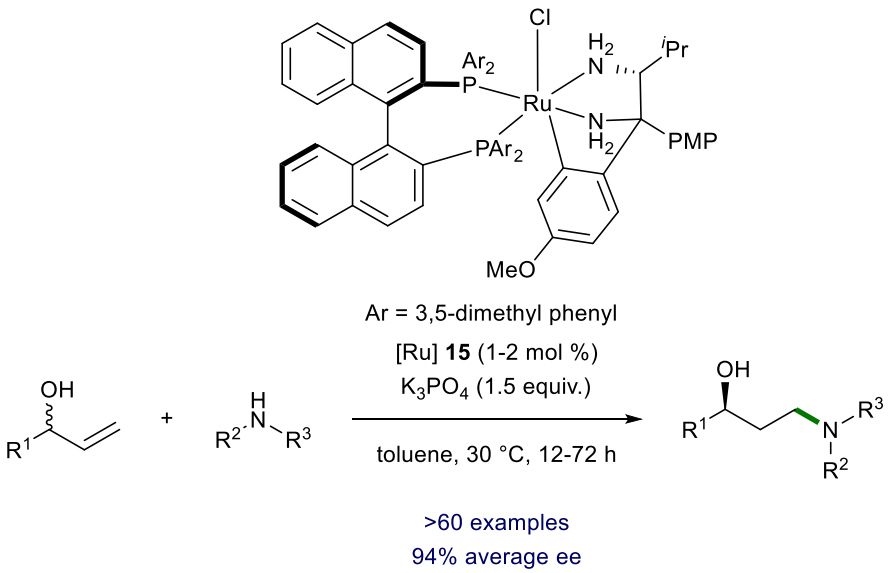
Another noteworthy contribution concerning the *γ*-functionalisation of primary allylic alcohols using carbon-based nucleophiles is a report from Dydio and co-workers in 2019.[3] The authors combined transfer hydrogenation reactions with transition-metal-catalyzed functionalisation to devise one-pot dual-catalytic systems. One such system combined iron-catalysed transfer hydrogenation with rhodium-catalysed hydroarylation to access enantioenriched *γ*-aryl alcohols (scheme 23).

Concerning nitrogen-based nucleophiles, anti-Markovnikov hydroamination of both primary and secondary allylic alcohols has been reported employing ruthenium[4] and iron catalysis.[5] A low temperature, stereoselective variant of this transformation was

developed by Xiao and Wang in 2020 (scheme 24), utilising a chiral ruthenium diamine-diphosphine complex (**15**).[6] Enantiomerically enriched γ-amino alcohols were obtained with a 94% average ee over 60 examples. A similar procedure was reported shortly after by Xing and co-workers.[7] The aforementioned literature represents some of the very few enantioselective processes discovered for borrowing hydrogen chemistry.

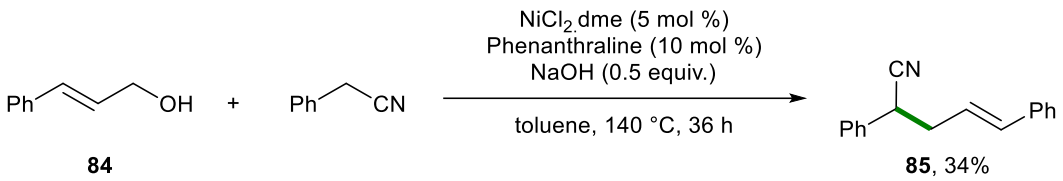


Scheme 23: Dual-catalytic transition-metal system to access enantioenriched γ-aryl alcohols from allylic alcohols.



Scheme 24: Enantioselective hydroamination of racemic secondary allylic alcohols.

In the case of 1,2-addition to allylic alcohols (*α*-functionalisation), Sundararaju and co-workers reported the N-alkylation of amines with primary allylic alcohols.[8] The same authors later applied this strategy to the synthesis of pyrroles.[9] The *α*-functionalisation of allylic alcohols with carbon-based nucleophiles is poorly represented within the literature. Furthermore, allylic alcohol moieties rarely feature within the scope of newly discovered C-C bond-forming borrowing hydrogen processes. Where mentioned, allylic alcohols have been regarded as incompatible under standard reaction conditions. Coincidently, these mentions have only appeared in studies conducted by the Morrill research group; Mn-catalysed alkylation of sulfonamides,[10] and Fe-catalysed alkylation of oxindoles.[11] One study that successfully includes an allylic alcohol moiety as part of the scope is the Ni-catalysed alkylation of nitriles by Banerjee and co-workers (scheme 25).[12] In this example, cinnamyl alcohol (**84**) underwent chemoselective 1,2-addition by benzyl cyanide affording unsaturated product **85** in 34% isolated yield.

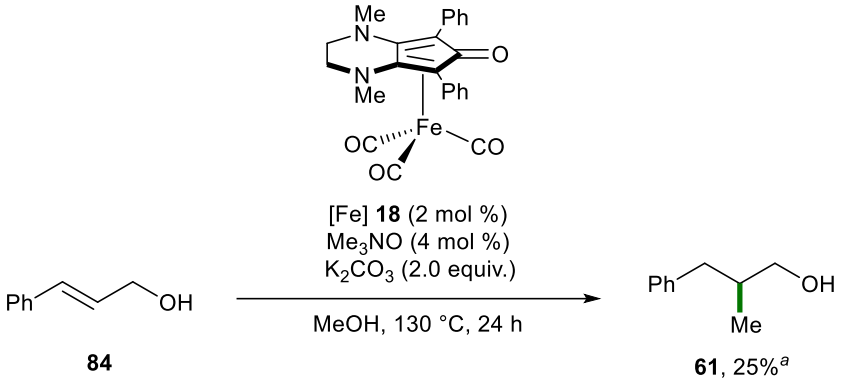


Scheme 25: Ni-catalysed alkylation of cinnamyl alcohol with benzyl cyanide.

There is clear room for improvement surrounding the reactivity of allylic alcohols as alkylating agents. 1,2-addition by various nucleophiles is often overlooked or not optimally achieved, realising the need for a comprehensive study. This chemoselective addition to allylic alcohols is potentially useful to synthetic organic chemists, as it provides an opportunity to perform subsequent functionalisation on the preserved olefin handle.[13]

One example whereby allylic alcohols may be described as "nucleophiles" in borrowing hydrogen is the isomerisation-methylation procedure described in chapter 3.[14] Within this scope, a primary allylic alcohol in cinnamyl alcohol (**84**) underwent hydromethylation to give product **61** in 25% NMR yield (scheme 26). This provoked a question into the general reactivity of allylic alcohols, and whether *δ*-

functionalisation could be accessed, or if other transformations could be influenced by tailoring the allylic alcohol's structure.



Scheme 26: Isomerisation-methylation of cinnamaldehyde.

[a]Yield after 24 h as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard.

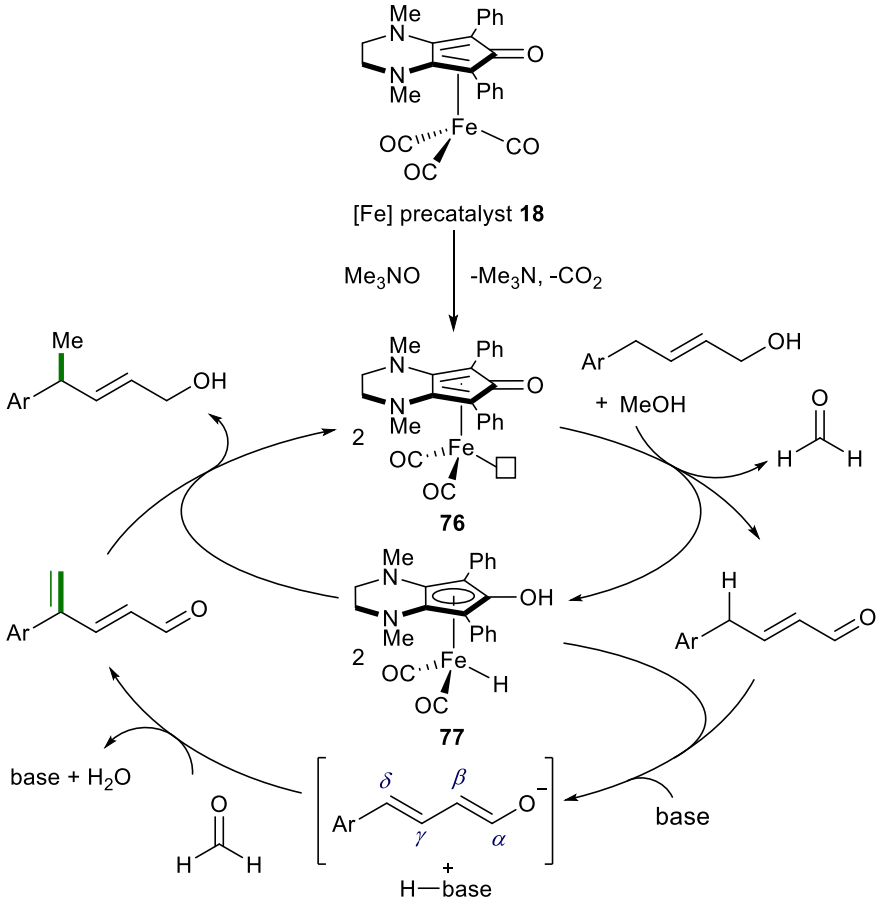
3.2.2 Results and Discussion

This investigation into the reactivity of allylic alcohols as nucleophiles can be considered a continuation of the isomerisation-methylation publication discussed in chapter 2. A collective effort between Lia Mitchell, Abdul Bari and myself was made to synthesise a series of allylic alcohols, each in three steps: 1) ylide formation, 2) Wittig/HWE reaction, 3) ester reduction.

We were interested to learn whether *δ*-methylation *via* a dienolate intermediate was possible for this series of allylic alcohols under the standard methylation conditions from chapter 2. The proposed mechanism for iron-catalysed *δ*-methylation of allylic alcohols is illustrated in scheme 27. Results for the study are displayed in figure 12.

Under the standard conditions, allylic alcohol **86** underwent hydromethylation to product **87** in 25% NMR yield, with methylation occurring exclusively at the *β*-position. It is likely that this transformation follows the isomerisation-methylation mechanism postulated in chapter 2 scheme 19, followed by a final transfer hydrogenation of the aldehyde to a primary alcohol. This hydromethylation

transformation is known, having been observed when cinnamyl alcohol was employed as the substrate (chapter 2.3.3.1, figure 5).



Scheme 27: Proposed mechanism to access *δ*-methylated allylic alcohols *via* iron-catalysed borrowing hydrogen.

Additionally, **86** underwent isomerisation to **88** in 27% NMR yield. A third product (**89**, 28% NMR yield) was identified as its acetylated derivative. This was the result of an oversight in the work up procedure performed by Abdul Bari for this reaction, whereby ethyl acetate was added as a diluent before sufficient cooling of the reaction mixture, and before the addition of a proton source (ammonium chloride) to appropriately quench the reaction. In retrospect, it can be assumed **88** was the major product of this reaction with ~60% having formed prior to work up. No *δ*-methylated products were observed for this reaction.

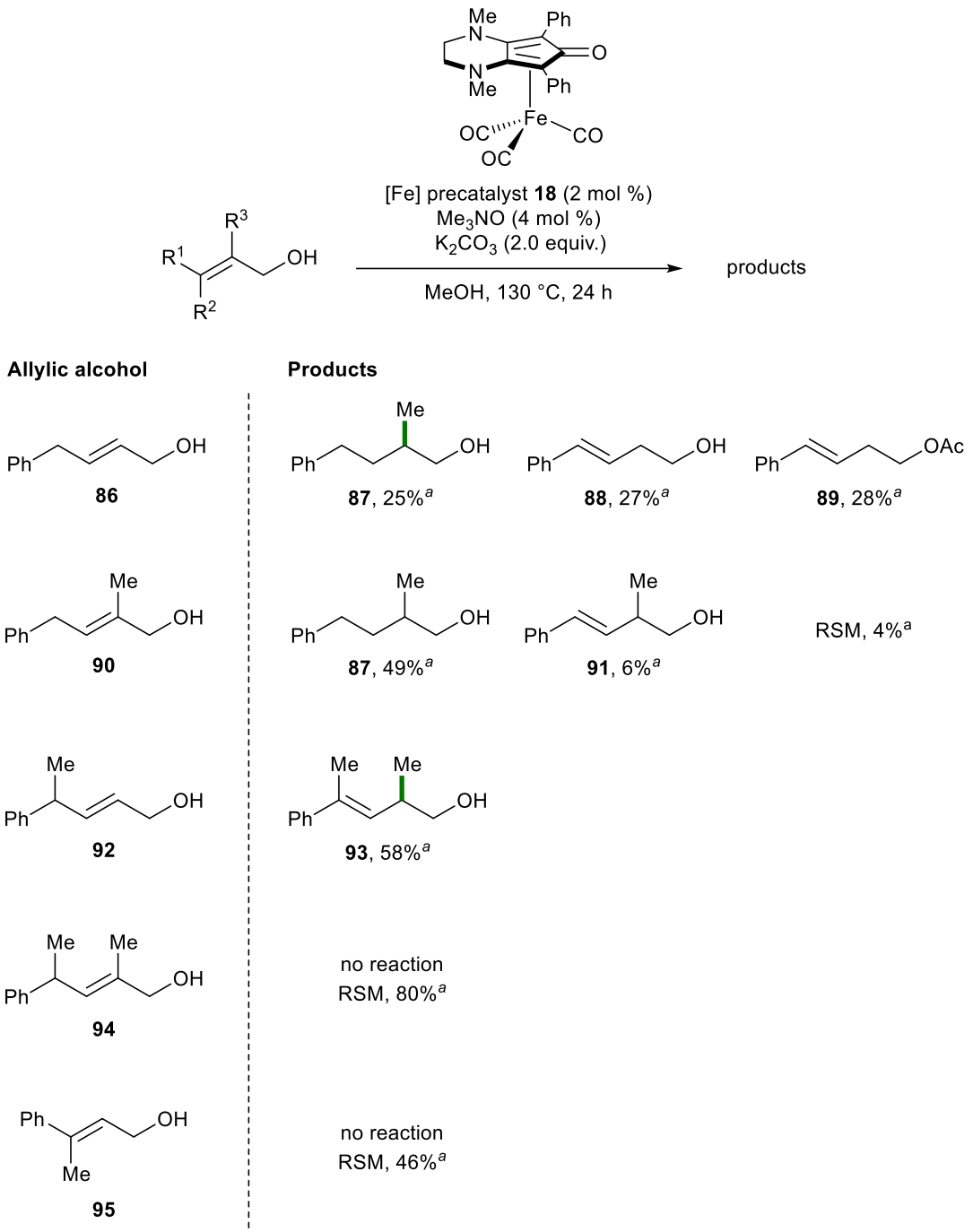


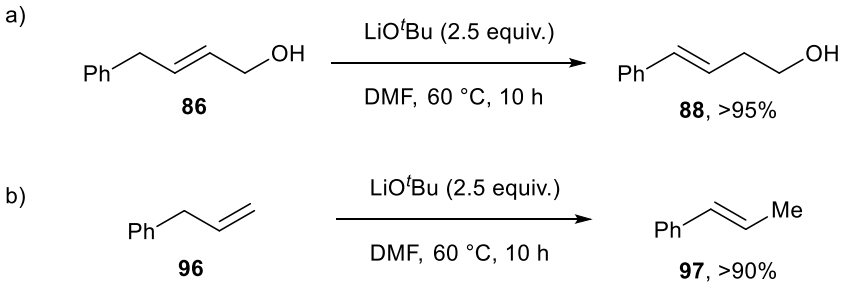
Figure 12: Study investigating the reactivity of allylic alcohols under standard methylation conditions. Reactions performed using 0.5 mmol of allylic alcohol substrate and bench-grade MeOH. [substrate] = 0.5 M. [a]Yield after 24 h as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yields can be found in within experimental chapter 4.

Allylic alcohol **90** was then tested to observe whether "protecting" the *β*-position could encourage methylation at the *δ*-position. Interestingly, **90** underwent transfer hydrogenation to **87** in 49% NMR yield, indicating the pathway towards *δ*-

methylation is unfavourable. Isomerisation product **91** was also observed in 6% NMR yield.

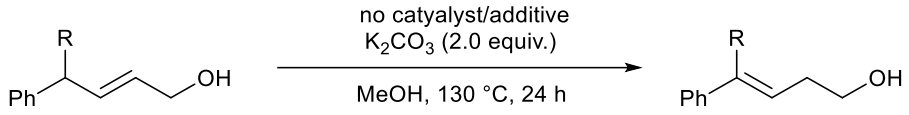
Allylic alcohol **92** underwent isomerisation-methylation to product **93**. *δ*-methylation is not possible in this instance since there is no proton available for E1cB elimination. Therefore, *β*-methylation came as no surprise. In order to reach products **91** and **93** from their respective substrates, we might assume the mechanism proceeds *via* the dienolate to "isomerise" the double bond to the more stable styrene-derivative. However, alkoxide base-promoted isomerisation of allylic alcohols to homo allylic alcohols is known (scheme 28a), as is the isomerisation of allyl benzenes to styrenes (scheme 28b) under the same conditions.[15] As a side note, metal-catalysed isomerisation of allylic alcohols to enols is also known.[16]

Allylic alcohols **94** and **95** did not undergo transfer hydrogenation or isomerisation, returning starting material in both cases.



Scheme 28: Base-promoted isomerisation: a) allylic alcohol to homoallylic alcohol, b) allyl benzene to trans-*β*-methyl styrene.

To gain insight into how the styrene-derived products from the study could have formed, allylic alcohols **86** and **92** were subjected to standard conditions in the absence of catalyst and additive (table 5). The reaction with **86** delivered the isomerised product **88** in 18% yield (entry 1), confirming isomerisation can be base-catalysed without proceeding *via* the dienolate. Interestingly, the reaction with **92** did not produce any of expected tri-substituted alkene **97** (entry 2), presumably due in part to there being fewer available hydrogen atoms for abstraction.



86, R = H; **92**, R = Me

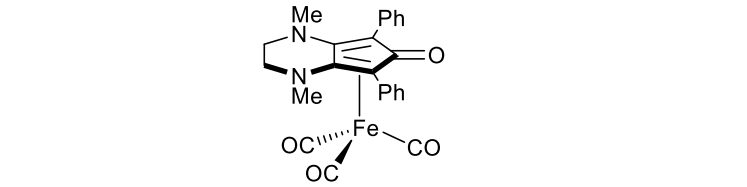
88, R = H; **98**, R = Me

Entry[a]	Substrate	RSM (%)[b]	P (%)[b]	
1	**86**	35	**88**	18
2	**92**	46	**98**	0

Table 5: Study investigating base-catalysed isomerisation of allylic alcohols.

[a]Reactions performed using 0.5 mmol of allylic alcohol substrate and bench-grade MeOH. [substrate] = 0.5 M. [b]Yield after 24 h as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard.

To confirm whether isomerisation occurs in the absence of the alcohol functionality, another small study was performed in collaboration with Abdul Bari investigating the isomerisation of allyl benzene (**96**) to propenyl benzene (**97**). These results are displayed in table 6.



96 **97**

Entry[a]	Catalyst (mol %)	Base	Solvent	**96**[b] RSM (%)	(*E*)-**97**[b] P (%)	(*Z*)-**97**[b] P (%)
1	**18**	K_2CO_3	toluene	100	0	0
2	**18**	-	toluene	100	0	0
3	-	K_2CO_3	toluene	100	0	0
4	**18**	K_2CO_3	BnOH	37	0	0
5	**18**	K_2CO_3	toluene + BnOH (1.0 equiv.)	92	0	0
6	**18**	K_2CO_3	MeOH	9	67	12
7	**18**	-	MeOH	91	0	0
8	-	-	MeOH	88	0	0
9	-	K_2CO_3	MeOH	43	39	7

Table 6: Study investigating base-catalysed isomerisation of allyl benzene.

[a]Reactions performed using 0.5 mmol of **96** and bench-grade MeOH or BnOH. [**96**] = 0.5 M. [b]Yield after 24 h as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard.

It was confirmed that metal or base-catalysed isomerisation under these reaction conditions cannot occur without the presence of an alcohol (entries 1-3). However, reactions employing neat or stoichiometric benzyl alcohol still did not deliver any isomerised product (entries 4 and 5). Employing methanol as solvent delivered product **97** as a mixture of *E* and *Z* isomers, in 67% and 12% NMR yield, respectively (entry 6). Omitting the base led to no product formation (entry 7), as did the omission of both the catalyst and base (entry 8).

Omitting solely the catalyst resulted in the formation of product **97** as a mixture of *E* and *Z* isomers, in 39% and 7% NMR yield, respectively (entry 9). This result confirms isomerisation can be facilitated by methoxide, but that the iron catalyst seemingly promotes this further.

3.2.3 Conclusion

Moving forward, we must assess which observed transformations are known or potentially useful. Firstly, iron-catalysed hydromethylation of primary allylic alcohols has been reported in chapter 2 and is not an interesting enough transformation to warrant its own scope.

Secondly, Brønsted base-catalysed isomerisation of allylic alcohols to homo allylic alcohols is known, therefore a study employing a metal catalyst and base is not interesting.

Finally, iron-catalysed transfer hydrogenation of allylic alcohols is effectively a substrate from the broader concept - transfer hydrogenation of alkenes.[17] More specifically, there have been many reports of metal-catalysed transfer hydrogenation processes of allylic alcohols employing hydrogen donor substitutes instead of molecular hydrogen. Donors include formic acid,[18] hydrazine,[19] boronic acids,[20] water, and iso-propyl alcohol. Asymmetric transfer hydrogenation processes employing earth-abundant metal catalysis with hydrogen donor substitutes have also been reported previously.[21] Furthermore, iron(0) cyclopentadienone catalysts have

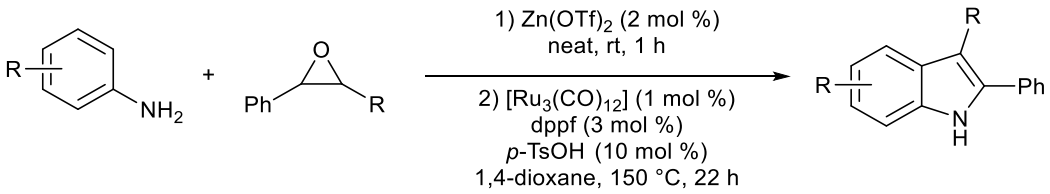
been employed to catalyse a similar transformation - the chemoselective transfer hydrogenation of enones using either molecular hydrogen or a hydrogen donor.[22]

Ultimately, no interesting transformations were uncovered. However, the chemoselective 1,2-addition of allylic alcohols by various nucleophiles does remain an available and interesting project for future research group members to explore.

3.3 Regioselective Ring Opening of Epoxides

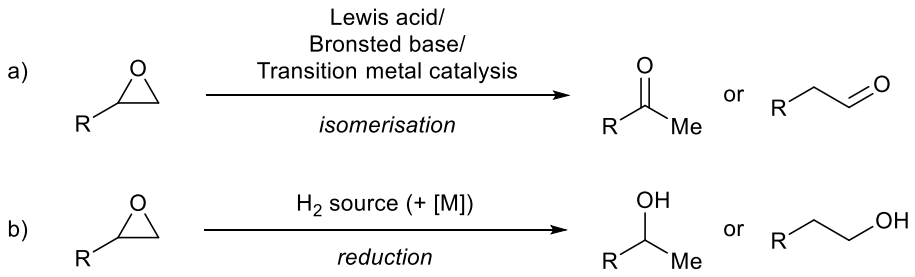
3.3.1 Introduction

Epoxides are very useful synthetic intermediates in organic chemistry due to their inherent reactivity with nucleophiles, and the several methods by which they can be installed.[23] Epoxides have frequently featured as electrophiles in borrowing hydrogen processes aiming to synthesise N-heterocycles.[24,25] One example from Beller and co-workers is the sequential synthesis of substituted indoles from anilines and epoxides (scheme 29).[26] For clarity, the regioselectivity of this reaction proceeds *via* the more stable benzylic carbocation.



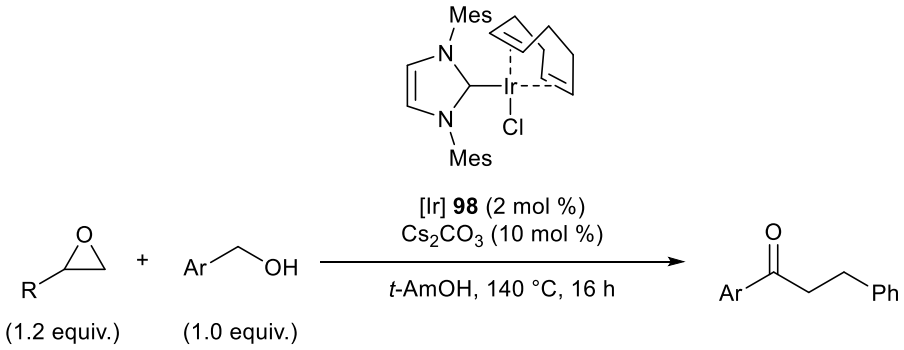
Scheme 29: Ruthenium-catalyzed synthesis of indoles from anilines and epoxides

The isomerisation of epoxides to carbonyl compounds is a particularly useful transformation. Termed the Meinwald rearrangement,[27] this transformation has been achieved employing Lewis acid catalysis,[28] transition metal catalysis,[29] and Brønsted base catalysis,[30] to access methyl ketones and/or aldehydes (scheme 30a).



Scheme 30: a) Meinwald rearrangement of epoxides to ketones and aldehydes. b) Reduction of epoxides to primary and secondary alcohols

Another useful transformation is the reductive opening of epoxides to produce primary and/or secondary alcohols (scheme 30b). Control of regioselectivity for these reactions (Markovnikov *vs.* anti-Markovnikov) is of particular interest. Traditionally, Markovnikov-selective secondary alcohols are accessed using stoichiometric borohydride.[31] More recently, secondary alcohols have been accessed from terminal epoxides *via* homogeneous catalysis-enabled hydrogenation, i.e. transfer hydrogenation.[32,33] Anti-Markovnikov-selective primary alcohols can also be accessed this way.[34] Homogeneous catalysis-enabled hydrosilylation[35] and hydroborylation[36] procedures are also known for accessing primary alcohols. Very recently, Gülcemal and co-workers devised a homogeneous iridium-catalysed borrowing hydrogen process to selectively ring open and alkylate terminal epoxides, as illustrated in scheme 31.[37]



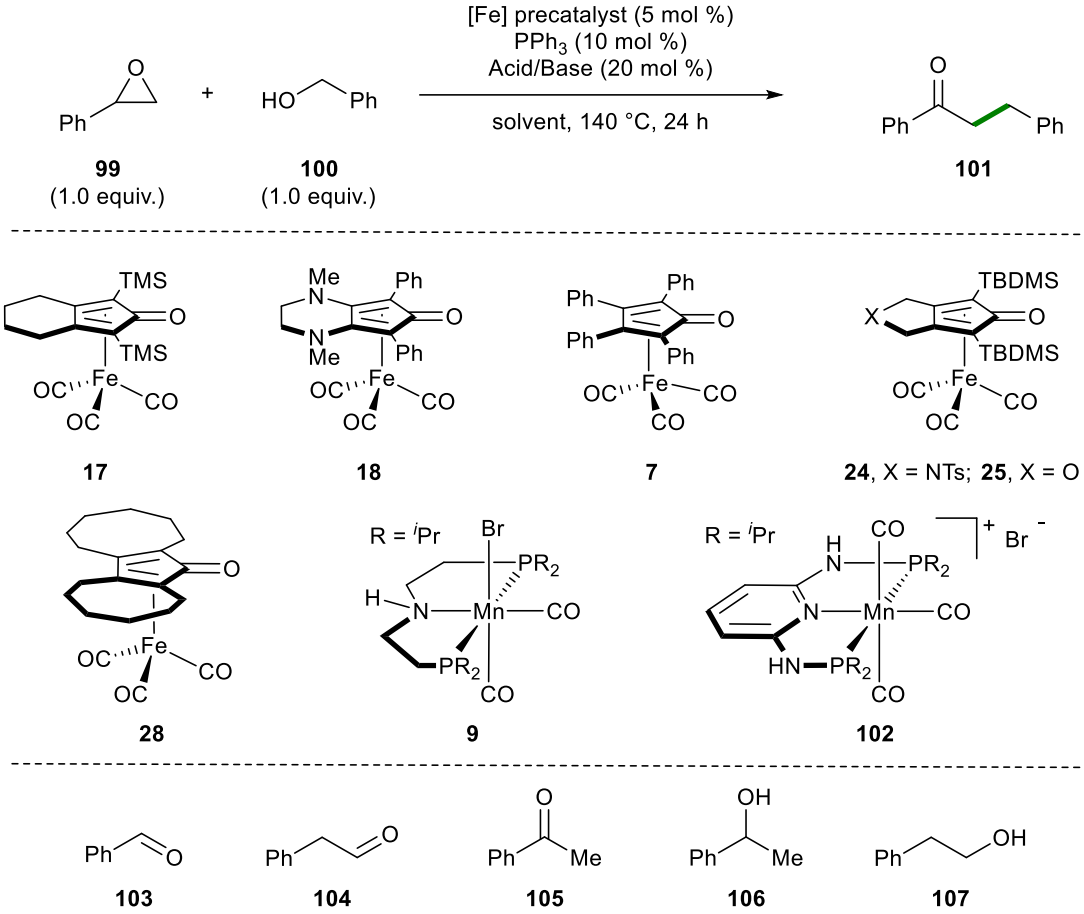
Scheme 31: Selective epoxide opening/alkylation *via* borrowing hydrogen.

3.3.2 Regioselective Ring Opening/Alkylation of Epoxides

At the commencement of this study, no method for regioselective reductive opening of epoxides employing a homogeneous earth-abundant metal catalyst was known, either with molecular H_2 or with an alternative hydrogen donor. The aim was to screen a selection of iron and manganese catalysts for the reductive opening of epoxides, either *via* standard transfer hydrogenation or *via* a borrowing hydrogen process involving subsequent methylation/benzylation. All work in this section was performed in collaboration with Mubarak Dambatta. Firstly, a selection of available iron and manganese complexes were screened for the synthesis of dihydrochalcone (**101**) from styrene oxide (**99**) and benzyl alcohol (**100**). The conditions chosen as a suitable starting point were largely influenced by previous earth-abundant metal borrowing hydrogen reports for the synthesis of dihydrochalcone (**101**) from ketones.[38,39] Unfortunately, none of these reactions led to the formation of dihydrochalcone (**101**) (table 7).

Reactions employing iron precatalysts solely produced primary alcohol **107** in moderately low yields (entries 1-6, 18-30%), with no observed formation of secondary alcohol **106** or return of epoxide starting material **99**. This came as a surprise since it was anticipated that basic conditions would favour formation of secondary alcohols, and that acidic conditions would favour formation of primary alcohols due to carbocation stability. The observation of benzaldehyde (**103**) in the crude mixture infers that dehydrogenation of benzyl alcohol (**100**) is not a limiting factor in achieving the desired transformation. Manganese catalysts performed very poorly, returning approximately half of the epoxide starting material and generating no considerable products (entries 7 and 8).

Remarkably, employing a large excess of hydrogen donor profoundly changed the selectivity of the reaction, producing alcohol **106** as the major product (entries 9 and 10). Employing IPA in excess provided up to 70% NMR yield of **106**. In this case, all the product peaks were partially obscured by other peaks, thus, this is an approximate value. The effect of employing trifluoroacetic acid (TFA) as an additive produced primary alcohol **107** as the major product (entry 11). TFA was previously used by Beller to perform regioselective direct hydrogenation of epoxides using iron catalysis.[40] No additive exclusively resulted in the formation of **107** (entry 12).



Entry[a]	Catalyst	Base/Acid	Solvent	**99**[b] RSM (%)	**100**[b] RSM (%)	**101**[b] P (%)	**103**[b] (%)	**106**[b] (%)	**107**[b] (%)
1	**17**	Cs_2CO_3	toluene	4	22	0	25	0	18
2	**18**	Cs_2CO_3	toluene	0	19	0	45	0	27
3	**7**	Cs_2CO_3	toluene	0	16	0	41	0	28
4	**24**	Cs_2CO_3	toluene	0	22	0	41	0	30
5	**25**	Cs_2CO_3	toluene	0	31	0	26	0	25
6	**28**	Cs_2CO_3	toluene	0	28	0	27	0	27
7	**9**	Cs_2CO_3	toluene	53	41	0	5	0	3
8	**102**	Cs_2CO_3	toluene	50	46	0	15	0	2
9[c]	**24**	Cs_2CO_3	**100**	0	n/a	0	n/a	47	7
10[c]	**24**	Cs_2CO_3	**IPA**	0	n/a	n/a	n/a	70[f]	-
11[c]	**24**	TFA	IPA	0	n/a	n/a	n/a	5	20
12[c]	**24**	-	IPA	0	n/a	n/a	n/a	-	20
13[c]	**24**	Cs_2CO_3	IPA	73	n/a	n/a	n/a	10	-
14[c]	-	-	IPA	98	n/a	n/a	n/a	-	-
15[c,d]	**24**	Cs_2CO_3	IPA	n/a	n/a	n/a	n/a	>95	-
16[c,e]	**24**	Cs_2CO_3	IPA	n/a	n/a	n/a	n/a	-	>95

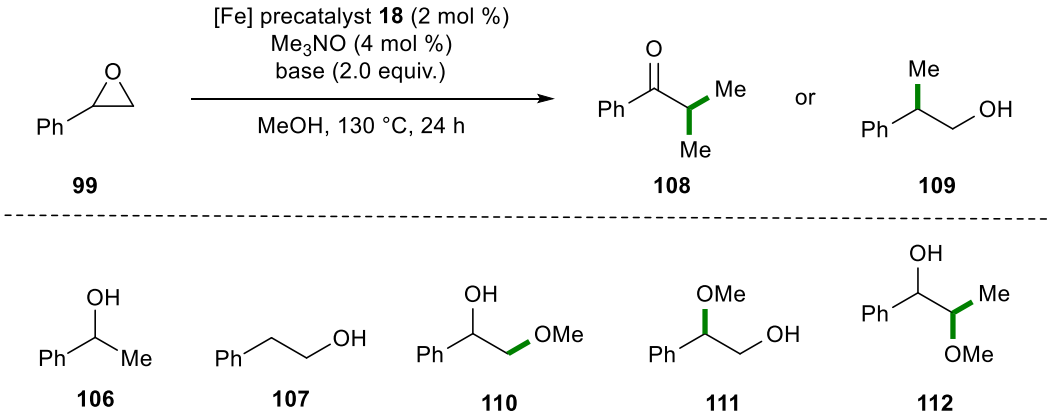
Table 7: Investigation into metal-catalysed regioselective opening/alkylation of epoxides.

[a]Reactions performed using 0.5 mmol of **99**. [**99**] = 0.5 M. [b]Yield after 24 h as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. [c]No benzyl alcohol (**100**) as stoichiometric reagent. [d]SM = **106**. [e]SM = **107**. [f]Approximate value, all products peaks are partly obscured.

In all cases, plausible intermediates acetaldehyde (**104**) and acetophenone (**105**) were not observed in the crude mixtures, causing some concern regarding the lack of mass recovery. The presence of numerous, small, unidentifiable peaks could suggest the formation of other aldol products, since various enolisable intermediates and electrophiles are present within the reaction mixture.

A reaction at 80 °C resulted in low conversion of starting material (entry 13). To eliminate any suspicion regarding the decomposition of starting material or products at higher temperatures, epoxide **99** was heated in IPA for 24 h at 140 °C without the presence of catalyst or base (entry 14) while alcohols **106** and **107** were subjected to the standard reaction conditions (entries 15 and 16). All three reactions returned <95% of their respective starting materials, indicating these do not decompose under these "harsh" conditions.

Another study exploring the use of excess MeOH as hydrogen donor for the regioselective opening of epoxides resulted in the formation of various β-methoxy alcohols (Table 8).



Entry[a]	Base	**99**[b] RSM (%)	**108**[b] P (%)	**109**[b] P (%)	**106**[b] (%)	**107**[b] (%)	**110**[b] (%)	**111**[b] (%)	**112**[b] (%)
1	K_2CO_3	0	0	0	0	0	0	16	22
2	NaOH	0	0	0	0	0	13 (10)	33 (29)	46 (40) 3:1 d.r. (syn:anti)

Table 8: Regioselective ring opening of epoxides employing MeOH.

[a]Reactions performed using 0.5 mmol of **99**. [**99**] = 0.5 M. [b]Yield after 24 h as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yields in parentheses.

110, **111** and **112** were all isolated and characterised using NMR. Higher yields were obtained when employing a stronger base in NaOH (table 8, entry 2), which plausibly leads to higher concentrations of methoxide *in situ*.

3.3.3 Conclusion

The aim of applying borrowing hydrogen methodology to the regioselective ring opening of epoxides (with or without alkylation) was effectively achieved by Gülcemal's iridium catalysed procedure during the onset of the investigation. The result obtained in table 7, entry 10 is a promising result that could form the foundation of a more comprehensive study. This research could still be of interest since there is still no earth-abundant metal process for this transformation that employs a hydrogen donor.

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Chapter 4 – Experimental

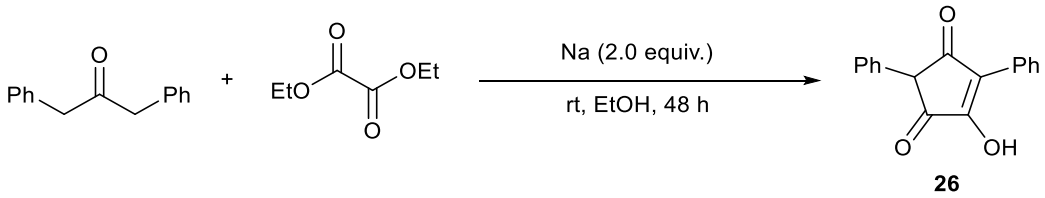
Borrowing Hydrogen

Table of Contents

4.1 Synthesis of Catalysts

Iron precatalysts **17**, **7**, **24**, **25** and **28** were all synthesised by Kurt Polidano.[1] Manganese precatalyst **9** was synthesised by Benjamin Reed-Berendt.[2]

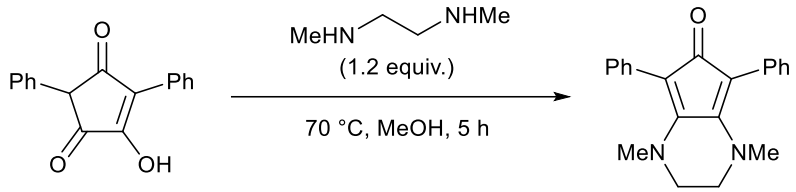
4-Hydroxy-2,5-diphenylcyclopent-4-ene-1,3-dione (26)



26

The title compound was prepared according to a procedure stated in the literature.[3] Under nitrogen, a flame dried Schlenk tube equipped with a magnetic stirrer bar was charged with ethanol (38 mL) and metallic sodium (1.84 g, 80.0 mmol) at 0 °C. After complete dissolution, the solution was charged with 1,3-diphenylacetone (8.41 g, 40.0 mmol) and diethyl oxalate (5.43 mL, 5.85 g, 20.0 mmol). This was left to stir at rt for 48 h. The mixture was cooled to 0 °C and glacial acetic acid was carefully added dropwise until the colour turned yellow/orange. The reaction mixture was then poured into ice/water (200 mL) and the aqueous layer was acidified to pH 1 by careful dropwise addition of concentrated sulfuric acid (96%). The resulting yellow precipitate was filtered. The solid was then dissolved in acetone (100 mL) and transferred to a conical flask. It was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by recrystallisation ($CHCl_3$/hexane) yielded a yellow solid (6.39 g, 60%); mp 168-170 °C (dec) ($CHCl_3$/hexanes), R_f = 0.35 (eluent = 100% EtOAc); **^{1}H NMR (DMSO-*d*6, 500 MHz)** δ_H: 4.46 (1H, s, C*H*), 7.14-7.19 (2H, m, ArC(2',6')*H*), 7.28-7.42 (4H, m, ArC(4,3',4',5')*H*), 7.45-7.50 (2H, m, ArC(3,5)*H*), 8.04-8.08 (2H, m, ArC(2,6)*H*), O*H* not found; **^{13}C NMR (DMSO-*d*6, 126 MHz)** δ_C: 55.9 (*C*H), 127.4 (Ar*C*(4')), 128.0 (Ar*C*), 128.2 (Ar*C*(3,5)), 128.7 (Ar*C*(2',6')), 128.7 (Ar*C*(2,6)), 128.8 (Ar*C*(3',5')), 128.8 (Ar*C*(4)), 129.7 (Ar*C*(1)), 134.5 (Ar*C*(1')), 166.5 (Ar*C*OH), 196.7 (*C*=O), 197.6 (*C*=O). Spectroscopic data in accordance with that stated in the literature.[3]

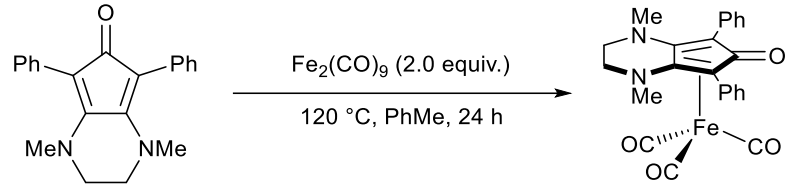
1,4-Dimethyl-5,7-diphenyl-1,2,3,4-tetrahydro-6H-cyclopenta[b]pyrazin-6-one (27)



26 **27**

The title compound was prepared according to a procedure stated in the literature.[3] Under nitrogen, a flame dried round-bottomed flask equipped a magnetic stirrer bar was charged with methanol (20 mL), 4-hydroxy-2,5-diphenylcyclopent-4-ene-1,3-dione (3.0 g, 11.4 mmol), and *N*,*N*'-dimethylethylenediamine (1.48 mL, 1.2 g, 13.6 mmol). The mixture was heated under reflux for 5 h. Following cooling, the mixture was concentrated *in vacuo* to furnish a purple solid as the pure product (3.13 g, 87%); mp 184-186 °C; R_f = 0.50 (eluent = 5% MeOH in CH_2Cl_2); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 2.84 (6H, s, 2×NCH_3), 3.37 (4H, s, N(CH_2)$_2$N), 7.12-7.19 (2H, m, 2×ArC(4)H), 7.23-7.32 (8H, m, 2×ArC(2,3,5,6)H); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 42.3 (2×NCH$_3$), 50.2 (N(CH$_2$)$_2$N), 99.1 (2×CPh), 125.6 (2×ArC(4)), 127.4 (2×ArC(2,6)), 131.2 (2×ArC(3,5)), 133.7 (2×ArC(1)), 151.0 (2×NC=CPh), 195.4 (C=O). Spectroscopic data in accordance with that stated in the literature.[3]

(1,4-Dimethyl-5,7-diphenyl-1,2,3,4-tetrahydro-6H-cyclopenta[b]pyrazin-6-one) iron tricarbonyl complex (28)

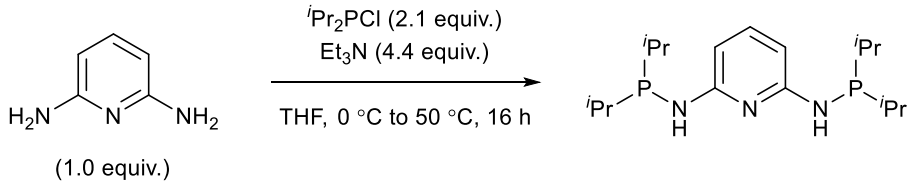


27 **18**

The title compound was prepared according to a procedure stated in the literature.[3] Under nitrogen, a flame dried Schlenk tube equipped with a magnetic stirrer bar and wrapped in aluminium foil was charged with light sensitive diiron nonacarbonyl (1.80g, 5.00 mmol), 1,4-dimethyl-5,7-diphenyl-1,2,3,4-tetrahydro-6H-cyclopenta[b]pyrazin-6-one (800 mg, 2.50 mmol), and degassed toluene (10 mL). The mixture was heated under reflux for 24 h without the presence of light. It was then cooled and concentrated *in vacuo* to form a yellow crude. Purification by flash alumina chromatography surrounded by celite (eluent = 0-1% MeOH in CH_2Cl_2, 50 ×

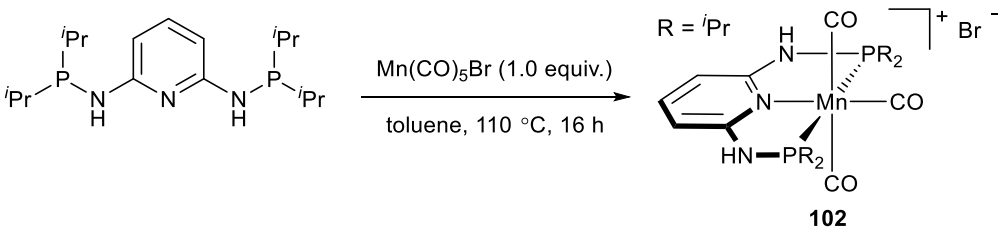
200 mm alumina) followed by precipitation (9:1 pentane/Et_2O) gave an orange-yellow solid (680 mg, 59%), mp 198-200 °C; R_f = 0.46 (eluent = 5% MeOH in CH_2Cl_2); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 2.38 (6H, s, 2×NCH_3), 2.88-2.96 (2H, m, N(CH_AH$_B$)$_2$N), 3.40-3.48 (2H, m, N(CH$_A$$H_B$)$_2$N), 7.30-7.35 (2H, m, 2×ArC(4)H), 7.36-7.41 (4H, m, 2×ArC(3,5)H), 7.51-7.57 (4H, m, 2×ArC(2,6)H); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 41.6 (2×NCH$_3$), 50.1 (2×NCH$_2$), 71.1 (2×C=CNCH$_3$), 114.6 (2×C=CNCH3), 128.0 (2×ArC(4)), 128.4 (2×ArC(3,5)), 131.9 (2×ArC(1)), 132.4 (2×ArC(2,6)), 165.8 (C-(C=O)-C), 210.3 (Fe(CO)3). Spectroscopic data in accordance with that stated in the literature.[3]

N2,N6-Bis(diisopropylphosphaneyl)pyridine-2,6-diamine



The title compound was prepared according to a procedure stated in the literature.[4] A flame-dried 250 mL round bottomed flask equipped with a stirrer bar was charged with 2,6-diaminopyridine (1.09 g, 10.0 mmol, 1.00 equiv.), freshly distilled triethylamine (6.13 mL, 4.45 g, 44.0 mmol, 4.40 equiv.) and dry THF (125 mL). Chlorodiisopropylphosphine (3.34 mL, 3.20 g, 21.0 mmol, 2.10 equiv.) was added dropwise over 10 min at 0 °C. The reaction was allowed to warm to rt, followed by heating at 50 °C for 16 h. The suspension was filtered over a glass filter *via* cannulation, and the remaining solids were washed with THF (50 mL) and discarded. The filtrate was concentrated *in vacuo*, and the resultant crude oil was used directly in the next step.

Manganese Precatalyst (102)



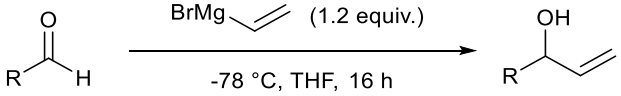
The title compound was prepared according to a procedure stated in the literature.[5] The crude oil obtained in the previous step was diluted in degassed toluene (100 mL),

followed by the addition of $Mn(CO)_5Br$ (2.75 g, 10.0 mmol, 1.00 equiv.). The resulting black solution was heated at reflux for 16 h. The suspension was filtered over a glass filter *via* cannulation, and the solid was washed with THF (2 × 25 mL) and pentane (4 × 25 mL). The filtrate was discarded, while the solid was collected and dried under vacuum to yield manganese precatalyst **102** as a light brown solid (3.33 g, 59% over two steps). **^{1}H NMR (DMSO-d$_6$, 500 MHz)** δ_H: 1.28 (24H, m, 8×CH_3), 2.67-2.87 (4H, m, 4×C*H*), 6.37-6.38 (2H, m, ArC(3,5)*H*), 7.48-7.50 (1H, m, ArC(4)*H*), 9.96 (2H, s, 2×N*H*); **^{31}P NMR (DMSO-d$_6$, 202 MHz)** δ_P: 133.6. Spectroscopic data in accordance with the literature.[5]

4.2 One-Pot Conversion of Allylic Alcohols to α-Methyl Ketones via Iron-Catalysed Borrowing Hydrogen

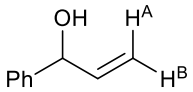
4.2.1 Substrate Synthesis

General Procedure 1: Preparation of Allylic Alcohol Substrates



Under nitrogen, a flame-dried 25 mL round-bottomed flask with a stirrer bar was charged with dry THF and aldehyde (1.00 equiv.), followed by the dropwise addition of vinyl magnesium bromide (1.20-4.00 equiv., 1 M in THF) at -78 °C with stirring. The reaction was warmed to rt and left to stir overnight. The reaction was cooled to 0 °C and quenched with sat. aq. NH_4Cl and H_2O. The organic layer was collected, and the aqueous phase was extracted with EtOAc (× 2). The organics were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*.

1-Phenylprop-2-en-1-ol (19)

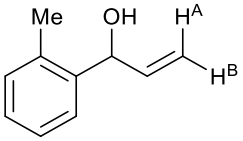


19

The title compound was prepared according to general procedure 1 using benzaldehyde (1.02 mL, 1.06 g, 10.0 mmol), dry THF (10 mL) and vinyl magnesium

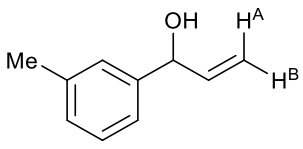
bromide (12.0 mL, 12.0 mmol, 1.20 equiv.). Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 35 × 150 mm silica) gave the title compound as a colourless oil (840 mg, 63%); R_f: 0.19 (10% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.93 (1H, br s, O*H*), 5.20 (1H, app dt, *J* 10.3, 1.2, CH=CH^A*H*^{B}), 5.19-5.24 (1H, m, C*H*OH), 5.36 (1H, app dt, *J* 17.2, 1.3, CH=C*H*^{A}H^B), 6.06 (1H, ddd, *J* 17.1, 10.3, 6.1, (C*H*=CH$_2$), 7.26-7.41 (5H, m, Ar*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 75.5 (*C*HOH), 115.3 (CH=*C*H$_2$), 126.3 (Ar*C*(2,6)), 127.8 (Ar*C*(4)), 128.6 (Ar*C*(3,5)), 140.4 (*C*H=CH$_2$), 142.7 (Ar*C*(1)). Spectroscopic data in accordance with the literature.[6]

1-(*o*-Tolyl)prop-2-en-1-ol



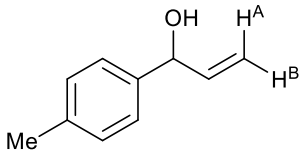
The title compound was prepared according to general procedure 1 using *o*-tolualdehyde (471 µL, 481 mg, 4.00 mmol), dry THF (4 mL) and vinyl magnesium bromide (4.80 mL, 4.80 mmol, 1.20 equiv.). Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 30 × 150 mm silica) gave the title compound as a pale-yellow oil (395 mg, 67%); R_f: 0.25 (eluent = 10% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.85 (1H, d, *J* 3.7, O*H*), 2.37 (3H, s, ArC(2)C*H*$_3$), 5.21 (1H, app dt, *J* 10.3, 1.4, CH=CH^A*H*^{B}), 5.32 (1H, app dt, *J* 16.9, 1.5, CH=C*H*^{A}H^B), 5.39-5.45 (1H, m, C*H*OH), 6.04 (1H, ddd, *J* 17.2, 10.3, 5.7, C*H*=CH$_2$), 7.13-7.26 (3H, m, 3×Ar*H*), 7.45 (1H, dd, *J* 7.5, 1.6, Ar*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 19.3 (ArC(2)C*H*$_3$), 72.2 (*C*HOH), 115.4 (CH=*C*H$_2$), 126.0 (Ar*C*), 126.4 (Ar*C*), 127.8 (Ar*C*), 130.7 (Ar*C*), 135.5 (Ar*C*(2)), 139.5 (*C*H=CH$_2$), 140.6 (Ar*C*(1)). Spectroscopic data in accordance with the literature.[7]

1-(*m*-Tolyl)prop-2-en-1-ol



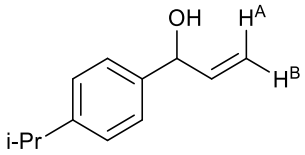
The title compound was prepared according to general procedure 1 using *m*-tolualdehyde (471 μL, 481 mg, 4.00 mmol), dry THF (4 mL) and vinyl magnesium bromide (4.80 mL, 4.80 mmol, 1.20 equiv.). Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 30 × 150 mm silica) gave the title compound as a pale-yellow oil (320 mg, 54%); R_f: 0.29 (eluent = 10% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.92 (1H, br s, CHO*H*), 2.36 (3H, s, ArC(3)C*H*$_3$), 5.15-5.19 (1H, m, C*H*OH), 5.20 (1H, app dt, *J* 10.4, 1.4, CH=CH^A*H*^{B}), 5.32 (1H, app dt, *J* 17.1, 1.4, CH=C*H*^{A}H^B), 6.06 (1H, ddd, *J* 17.2, 10.3, 6.0, C*H*=CH$_2$), 7.08-7.13 (1H, m, Ar*H*), 7.15-7.19 (1H, m, Ar*H*), 7.19-7.21 (1H, m, Ar*H*), 7.23-7.28 (1H, m, Ar*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 21.6 (ArC(3)C*H*$_3$), 75.5 (*C*HOH), 115.1 (CH=*C*H$_2$), 123.5 (Ar*C*), 127.1 (Ar*C*), 128.6 (Ar*C*), 128.7 (Ar*C*), 138.4 (Ar*C*(3)), 140.4 (*C*H=CH$_2$), 142.7 (Ar*C*(1)). Spectroscopic data in accordance with the literature.[8]

1-(*p*-Tolyl)prop-2-en-1-ol



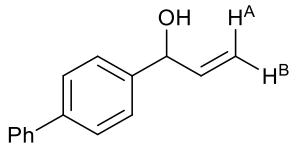
The title compound was prepared according to general procedure 1 using *p*-tolualdehyde (471 μL, 481 mg, 4.00 mmol), dry THF (4 mL) and vinyl magnesium bromide (4.80 mL, 4.80 mmol, 1.20 equiv.). Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 30 × 150 mm silica) gave the title compound as a pale-yellow oil (427 mg, 72%); R_f: 0.16 (eluent = 10% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.90 (1H, br s, O*H*), 2.35 (3H, s, ArC(4)C*H*$_3$), 5.19 (1H, app dt, *J* 10.0, 1.3, CH=CH^A*H*^{B}), 5.17-5.19 (1H, m, C*H*OH), 5.35 (1H, app dt, *J* 16.9, 1.3, CH=C*H*^{A}H^B), 6.05 (1H, ddd, *J* 17.1, 10.2, 6.0, C*H*=CH$_2$), 7.15-7.20 (2H, m, 2×Ar*H*), 7.24-7.29 (2H, m, 2×Ar*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 21.3 (ArC(4)C*H*$_3$), 75.3 (*C*HOH), 115.0 (CH=*C*H$_2$), 126.4 (2×Ar*C*), 129.4 (2×Ar*C*), 137.7 (Ar*C*(4)), 139.8 (Ar*C*(1)), 140.5 (*C*H=CH$_2$). Spectroscopic data in accordance with the literature.[9]

1-(4-Isopropylphenyl)prop-2-en-1-ol



The title compound was prepared according to general procedure 1 using cuminaldehyde (606 µL, 593 mg, 4.00 mmol), dry THF (4 mL) and vinyl magnesium bromide (4.80 mL, 4.80 mmol, 1.20 equiv.). Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 30 × 150 mm silica) gave the title compound as a pale-yellow oil (663 mg, 94%); R_f: 0.29 (eluent = 10% EtOAc in hexanes); **^{1}H NMR (CDCl$_3$, 500 MHz)** δ_H: 1.23-1.27 (6H, d, *J* 7.0, CH(C*H*$_3$)$_2$), 1.87-1.94 (1H, m, CHO*H*), 2.91 (1H, sept, *J* 7.0, C*H*(CH$_3$)$_2$), 5.17-5.21 (1H, m, C*H*OH), 5.20 (1H, app dt, *J* 10.5, 1.0, CH=CH^A*H*^{B}), 5.36 (1H, app dt, *J* 17.0, 1.5, CH=C*H*^{A}H^B), 6.07 (1H, ddd, *J* 17.5, 10.0, 6.0, C*H*=CH$_2$), 7.11 (2H, d, *J* 8.0, Ar*C*(2,6)*H*), 7.31 (2H, d, *J* 8.1, Ar*C*(3,5)*H*); **^{13}C NMR (CDCl$_3$, 126 MHz)** δ_C: 24.1 (CH(*C*H$_3$)$_2$), 34.0 (*C*H(CH$_3$)$_2$), 75.4 (*C*HOH), 115.0 (CH=*C*H$_2$), 126.5 (2×Ar*C*), 126.8 (2×Ar*C*), 140.2 (Ar*C*), 140.4 (Ar*C*), 148.7 (*C*H=CH$_2$). Spectroscopic data in accordance with the literature.[9]

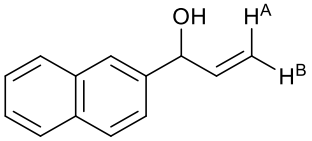
1-([1,1'-Biphenyl]-4-yl)prop-2-en-1-ol



The title compound was prepared according to general procedure 1 using 4-biphenylcarboxaldehyde (1.82 g, 10.0 mmol), dry THF (10 mL) and vinyl magnesium bromide (12.0 mL, 12.0 mmol, 1.20 equiv.). Purification by flash silica chromatography (eluent = 2-5% EtOAc in hexanes, 30 × 170 mm silica) gave the title compound as a white solid (1.68 g, 80%); mp 57-60 °C (lit. 56-59 °C);[10] R_f: 0.17 (eluent = 10% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 488, 613, 689, 743, 762, 822, 853, 918, 984, 1005, 1045, 1105, 1186, 1254, 1402, 1487, 1564, 1597, 1641, 2870, 3032, 3240; **^{1}H NMR (CDCl$_3$, 500 MHz)** δ_H: 2.01 (1H, d, *J* 3.7, CHO*H*), 5.24 (1H, app dt, *J* 10.3, 1.3, CH=CH^A*H*^{B}), 5.25-5.29 (1H, m, C*H*OH), 5.41 (1H, app dt, *J* 17.1, 1.4, CH=C*H*^{A}H^B), 6.10 (1H, ddd, *J* 17.1, 10.3, 6.0, C*H*=CH$_2$), 7.33-7.38 (1H, m, Ar*C*), 7.42-7.48 (4H, m, 4×Ar*C*), 7.57-7.62 (4H, m, 4×Ar*C*); **^{13}C NMR (CDCl$_3$, 126 MHz)** δ_C: 75.3 (*C*HOH), 115.5 (CH=*C*H$_2$), 126.9 (2×Ar*C*), 127.2 (2×Ar*C*), 127.4 (2×Ar*C*), 127.5 (Ar*C*), 128.9 (2×Ar*C*),

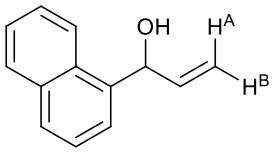
140.2 (*C*H=CH_2), 140.9 (Ar*C*), 140.9 (Ar*C*), 141.7 (Ar*C*); HRMS (**EI**$^+$) calculated for $[C_{15}H_{14}O]^+$ $(M)^+$: m/z 210.1045, found 210.1050, (2.4 ppm).

1-(Naphthalen-2-yl)prop-2-en-1-ol



The title compound was prepared according to general procedure 1 using 2-naphthaldehyde (625 mg, 4.00 mmol), dry THF (4 mL) and vinyl magnesium bromide (4.80 mL, 4.80 mmol, 1.20 equiv.). Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 35 × 150 mm silica) gave the title compound as a yellow oil (649 mg, 88%); R_f: 0.29 (eluent = 10% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 2.05-2.08 (1H, m, CHO*H*), 5.23-5.27 (1H, d, *J* 10.3, CH=CH^A*H*^{B}), 5.36-5.40 (1H, m, C*H*OH), 5.39-5.45 (1H, d, *J* 17.0, CH=C*H*^{A}H^B), 6.13 (1H, ddd, *J* 17.5, 10.5, 6.0, C*H*=CH_2), 7.46-7.51 (3H, m, 3×Ar*H*), 7.81-7.86 (4H, m, 4×Ar*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 75.6 (*C*HOH), 115.6 (CH=*C*H_2), 124.6 (Ar*C*), 125.1 (Ar*C*), 126.1 (Ar*C*), 126.3 (Ar*C*), 127.8 (Ar*C*), 128.1 (Ar*C*), 128.5 (Ar*C*), 133.2 (Ar*C*), 133.5 (Ar*C*), 140.0 (Ar*C*), 140.6 (*C*H=CH_2). Spectroscopic data in accordance with the literature.[9]

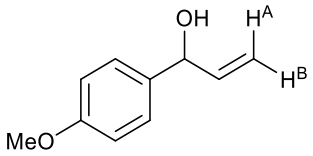
1-(Naphthalen-1-yl)prop-2-en-1-ol



The title compound was prepared according to general procedure 1 using 1-naphthaldehyde (543 µL, 624 mg, 4.00 mmol), dry THF (4 mL) and vinyl magnesium bromide (4.80 mL, 4.80 mmol, 1.20 equiv.). Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 30 × 150 mm silica) gave the title compound as a yellow oil (597 mg, 81%); R_f: 0.30 (eluent = 10% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 2.10 (1H, d, *J* 3.6, CHO*H*), 5.29 (1H, d, *J* 10.4, CH=CH^A*H*^{B}), 5.46 (1H, d, *J* 17.2, CH=C*H*^{A}H^B), 5.92-5.97 (1H, m, C*H*OH), 6.26 (1H, ddd, *J* 17.0, 10.5, 5.5, C*H*=CH_2), 7.45-7.56 (3H, m, 3×Ar*H*), 7.63 (1H, d *J* 7.1, Ar*H*), 7.81 (1H, d *J* 8.2, Ar*H*), 7.88 (1H, d *J* 7.8, Ar*H*), 8.19 (1H, d *J* 8.2, Ar*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)**

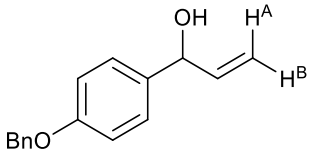
δ_C: 72.5 (*C*HOH), 115.8 (CH=*C*H_2), 123.9 (Ar*C*), 124.1 (Ar*C*), 125.6 (Ar*C*), 125.8 (Ar*C*), 126.3 (Ar*C*), 128.7 (Ar*C*), 129.0 (Ar*C*), 130.9 (Ar*C*), 134.1 (Ar*C*), 138.2 (Ar*C*), 139.8 (*C*H=CH_2). Spectroscopic data in accordance with the literature.[11]

1-(4-Methoxyphenyl)prop-2-en-1-ol



The title compound was prepared according to general procedure 1 using *p*-anisaldehyde (486 µL, 545 mg, 4.00 mmol), dry THF (4 mL) and vinyl magnesium bromide (4.80 mL, 4.80 mmol, 1.20 equiv.). Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 30 × 150 mm silica) gave the title compound as a pale-yellow oil (519 mg, 79%); R_f: 0.10 (eluent = 10% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.89 (1H, br s, CHO*H*), 3.81 (3H, s, OCH_3), 5.15-5.18 (1H, m, C*H*OH), 5.17-5.19 (1H, app dt, *J* 10.5, 1.5, CH=CH^A*H*^{B}), 5.31-5.37 (1H, app dt, *J* 17.0, 1.5, CH=C*H*^{A}H^B), 6.05 (1H, ddd, *J* 17.1, 10.3, 5.9, C*H*=CH_2), 6.89 (2H, d, *J* 8.6, ArC(3,5)*H*), 7.30 (2H, d, *J* 8.4, ArC(2,6)*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 55.4 (O*C*H_3), 75.0 (*C*HOH), 114.1 (Ar*C*(3,5)), 114.9 (CH=*C*H_2), 127.8 (Ar*C*(2,6)), 135.0 (Ar*C*(1)), 140.5 (*C*H=CH_2), 159.4 (Ar*C*(4)). Spectroscopic data in accordance with the literature.[9]

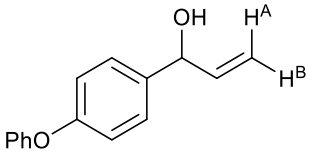
1-(4-(Benzyloxy)phenyl)prop-2-en-1-ol



The title compound was prepared according to general procedure 1 using 4-benzyloxybenzaldehyde (849 mg, 4.00 mmol), dry THF (4 mL) and vinyl magnesium bromide (4.80 mL, 4.80 mmol, 1.20 equiv.). Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 30 × 150 mm silica) gave the title compound as an off-white solid (878 mg, 97%); mp 59-62 °C (lit. 57-59 °C);[11] R_f: 0.07 (eluent = 10% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.86 (1H, d, *J* 3.5, CHO*H*), 5.07 (2H, s, PhCH_2O), 5.14-5.18 (1H, m, C*H*OH), 5.19 (1H, app dt, *J* 10.5, 1.5,

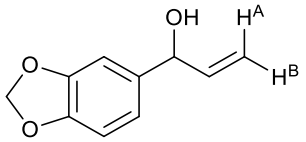
CH=CH^{A}*H*^{B}), 5.34 (1H, app dt, *J* 17.0, 1.5, CH=C*H*^{A}H^{B}), 6.05 (1H, ddd, *J* 16.5, 10.3, 5.9, C*H*=CH$_2$), 6.97 (2H, d, *J* 8.0, 2×Ar'*H*), 7.27-7.35 (3H, m, 3×Ar'*H*), 7.36-7.45 (4H, m, 4×Ar*H*); **^{13}C NMR (CDCl$_3$, 126 MHz)** δ_C: 70.2 (Ph*C*H$_2$O), 75.0 (*C*HOH), 114.8 (Ar*C*), 115.0 (CH=*C*H$_2$), 127.6 (2×Ar*C*), 127.8 (2×Ar*C*), 128.1 (2×Ar*C*), 128.7 (2×Ar*C*)), 135.2 (Ar*C*), 137.1 (Ar*C*), 140.5 (*C*H=CH$_2$), 158.6 (Ar*C*). Spectroscopic data in accordance with the literature.[12]

1-(4-Phenoxyphenyl)prop-2-en-1-ol



The title compound was prepared according to general procedure 1 using 4-phenoxybenzaldehyde (702 μL, 793 mg, 4.00 mmol), dry THF (4 mL) and vinyl magnesium bromide (4.80 mL, 4.80 mmol, 1.20 equiv.). Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 30 × 150 mm silica) gave the title compound as a pale-yellow oil (842 mg, 93%); R_f: 0.14 (eluent = 10% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 691, 748, 851, 870, 924, 988, 1013, 1101, 1165, 1229, 1487, 1504, 1587, 2868, 3038, 3063, 3350; **^{1}H NMR (CDCl$_3$, 500 MHz)** δ_H: 1.93 (1H, br s, CHO*H*), 5.18-5.21 (1H, m, C*H*OH), 5.24 (1H, app dt, *J* 10.2, 1.3, CH=CH^{A}*H*^{B}), 5.37 (1H, app dt, *J* 17.0, 1.4, CH=C*H*^{A}H^{B}), 6.06 (1H, ddd, *J* 17.1, 10.3, 6.0, C*H*=CH$_2$), 6.98-7.03 (4H, m, ArC(2',3',5',6')*H*), 7.08-7.13 (1H, m, ArC(4')*H*), 7.31-7.37 (4H, m, 4×Ar*H*); **^{13}C NMR (CDCl$_3$, 126 MHz)** δ_C: 75.0 (*C*HOH), 115.3 (CH=*C*H$_2$), 119.0 (2×Ar'*C*), 119.0 (2×Ar'*C*), 123.4 (Ar*C*(4')), 128.0 (2×Ar*C*), 129.9 (2×Ar*C*), 137.5 (Ar*C*(1)), 140.3 (*C*H=CH$_2$), 157.0 (Ar*C*(1')), 157.3 (Ar*C*(4)); HRMS (**EI**$^+$) calculated for [C$_{15}$H$_{14}$O$_2$]$^+$ (M)$^+$: m/z 226.0990, found 226.0994, (-1.8 ppm).

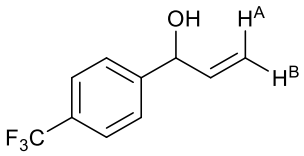
1-(Benzo[d][1,3]dioxol-5-yl)prop-2-en-1-ol



The title compound was prepared according to general procedure 1 using piperonal (601 mg, 4.00 mmol), dry THF (4 mL) and vinyl magnesium bromide (4.80 mL, 4.80

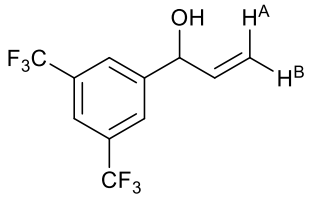
mmol, 1.20 equiv.). Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 30 × 150 mm silica) gave the title compound as a pale-yellow oil (666 mg, 92%); R_f: 0.21 (eluent = 10% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.91 (1H, d, *J* 3.6, CHO*H*), 5.10-5.14 (1H, m, C*H*OH), 5.19 (1H, app dt, 10.3, 1.4, CH=CH^A*H*^{B}), 5.34 (1H, app dt, *J* 17.1, 1.4, CH=C*H*^{A}H^B), 5.95 (2H, s, OC*H*$_2$O), 6.02 (1H, ddd, *J* 17.1, 10.3, 5.9, C*H*=CH$_2$), 6.77-6.80 (1H, m, Ar*H*), 6.83 (1H, ddd, *J* 7.9, 1.7, 0.6, Ar*H*), 6.87-6.89 (1H, m, Ar*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 75.2 (*C*HOH), 101.2 (O*C*H$_2$O), 107.1 (Ar*C*), 108.3 (Ar*C*), 115.1 (CH=*C*H$_2$), 119.9 (Ar*C*), 136.8 (Ar*C*), 140.3 (*C*H=CH$_2$), 147.3 (Ar*C*), 148.0 (Ar*C*). Spectroscopic data in accordance with the literature.[11]

1-(4-Trifluromethylphenyl)prop-2-en-1-ol



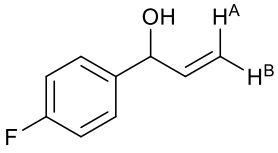
The title compound was prepared according to general procedure 1 using 4-(trifluoromethyl)benzaldehyde (546 µL, 696 mg, 4.00 mmol), dry THF (4 mL) and vinyl magnesium bromide (4.80 mL, 4.80 mmol, 1.20 equiv.). Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 35 × 150 mm silica) gave the title compound as a colourless oil (356 mg, 44%); R_f: 0.17 (eluent = 10% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 2.04 (1H, d, *J* 3.5, CHO*H*), 5.25 (1H, app dt, *J* 10.5, 1.5, CH=CH^A*H*^{B}), 5.26-5.29 (1H, m, C*H*OH), 5.38 (1H, app dt, *J* 17.0, 1.5, CH=C*H*^{A}H^B), 6.01 (1H, ddd, *J* 16.5, 10.5, 6.0, C*H*=CH$_2$), 7.50 (2H, d, *J* 8.0, 2×Ar*H*), 7.62 (2H, d, *J* 8.1, 2×Ar*H*); **^{19}F NMR ($CDCl_3$, 471 MHz)** δ_F: -62.5; **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 75.0 (*C*HOH), 116.3 (CH=*C*H$_2$), 124.3 (q, *J* 272, *C*F$_3$), 125.6 (q, *J* 3.8, Ar*C*(3,5)), 126.7 (Ar*C*(2,6)), 130.0 (q, *J* 32.5, Ar*C*(4)), 139.8 (*C*H=CH$_2$), 146.5 (Ar*C*(1)). Spectroscopic data in accordance with the literature.[13]

1-(3,5-Bis(trifluoromethyl)phenyl)prop-2-en-1-ol



The title compound was prepared according to general procedure 1 using 3,5-bis(trifluoromethyl)benzaldehyde (660 µL, 968 mg, 4.00 mmol), dry THF (4 mL) and vinyl magnesium bromide (4.80 mL, 4.80 mmol, 1.20 equiv.). Purification by flash silica chromatography (eluent = 10% EtOAc in hexanes, 30 × 150 mm silica) gave the title compound as an colourless oil (741 mg, 69%); R_f: 0.22 (eluent = 10% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 422, 602, 665, 681, 708, 827, 847, 901, 962, 1038, 1117, 1163, 1273, 1327, 1379, 1470, 1624, 2893, 2972, 3319, 3385; **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 2.16 (1H, d, *J* 3.5, CHO*H*), 5.32 (1H, app dt, *J* 10.2, 1.0, CH=CH^A*H*^{B}), 5.30-5.35 (1H, m), 5.44 (1H, app dt, *J* 17.1, 1.1, CH=C*H*^{A}H^B), 6.00 (1H, ddd, *J* 17.0, 10.2, 6.7, C*H*=CH_2), 7.79-7.81 (1H, m, ArC(4)*H*), 7.84-7.87 (2H, m, ArC(2,6)*H*); **^{19}F NMR ($CDCl_3$, 471 MHz)** δ_F: -62.9; **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 74.5 (*C*HOH), 117.6 (CH=*C*H_2), 121.5-121.9 (m, Ar*C*(4)), 123.6 (q, *J* 273.0, 2×*C*F3), 126.4-126.8 (m, Ar*C*(2,6)), 131.9 (q, *J* 33.3, Ar*C*(3,5)), 139.1 (CH=CH_2), 145.0 (Ar*C*(1)); HRMS (**EI**$^+$) calculated for $[C_{11}H_8OF_6]^+$ $(M)^+$: m/z 270.0479, found 270.0481, (0.7 ppm).

1-(4-Fluorophenyl)prop-2-en-1-ol (58)

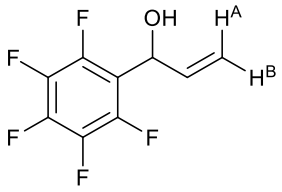


58

The title compound was prepared according to general procedure 1 using 4-fluorobenzaldehyde (429 µL, 496 mg, 4.00 mmol), dry THF (4 mL) and vinyl magnesium bromide (4.80 mL, 4.80 mmol, 1.20 equiv.). Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 30 × 150 mm silica) gave the title compound as a yellow oil (220 mg, 36%); R_f: 0.23 (eluent = 10% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 526, 583, 664, 789, 854, 986, 1020, 1155, 1220, 1413, 1504, 1601, 2882, 3080, 3348; **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.93 (1H, d, *J* 3.4, CHO*H*), 5.17-5.22 (1H, m, C*H*OH), 5.21 (1H, d, *J* 10.0, CH=CH^A*H*^{B}), 5.35 (1H, d, *J* 17.5, CH=C*H*^{A}H^B), 6.03 (1H, ddd, *J* 16.3, 10.3, 6.1, C*H*=CH_2), 7.00-7.08 (2H, m, 2×Ar*H*), 7.31-7.38 (2H, m,

2×Ar*H*); **^{19}F NMR (471 MHz, $CDCl_3$)** δ_F: -114.8; **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 74.9 (*C*HOH), 115.5 (d, *J* 21.4, Ar*C*(3,5)), 115.5 (CH=*C*H_2), 128.2 (d, *J* 8.2, Ar*C*(2,6)), 138.4 (d, *J* 3.2, Ar*C*(1)), 140.2 (*C*H=CH_2), 162.4 (d, *J* 246.3, Ar*C*(4)); HRMS (**EI**$^+$) calculated for $[C_{11}H_{14}OF]^+$ $(M)^+$: m/z 152.0637, found 152.0633, (-2.6 ppm).

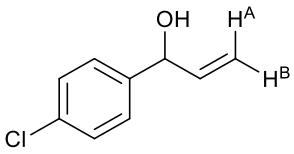
1-(Perfluorophenyl)prop-2-en-1-ol



68

The title compound was prepared according to general procedure 1 using pentafluorobenzaldehyde (1.23 mL, 1.96 g, 10.0 mmol), dry THF (15 mL) and vinyl magnesium bromide (12.0 mL, 12.0 mmol, 1.20 equiv.). Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 30 × 150 mm silica) gave the title compound as a yellow oil (1.71 g, 76%); R_F: 0.20 (eluent = 10% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 2.34 (1H, d, *J* 7.5, CHO*H*), 5.29 (1H, ddt, *J* 10.3, 1.3, 0.7, CH=CH^A*H*^{B}), 5.35 (1H, ddt, *J* 17.1, 1.4, 0.7, CH=C*H*^{A}H^B), 5.54-5.60 (1H, m, C*H*OH), 6.18 (1H, dddt, *J* 17.6, 10.3, 6.0, 1.3, C*H*=CH_2); **^{19}F NMR (471 MHz, $CDCl_3$)** δ_F: -143.4--143.6 (m), -154.7 (t, *J* 20.8), -161.6--161.8 (m); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 66.9 (*C*HOH), 115.6-116.2 (m, Ar*C*), 117.4 (CH=*C*H_2), 136.6 (*C*H=CH_2), 137.7 (dm, *J* 253.1, Ar*C*), 141.0 (dm, *J* 254.3, Ar*C*), 144.9 (dm, *J* 249.0, Ar*C*). Spectroscopic data in accordance with the literature.[14]

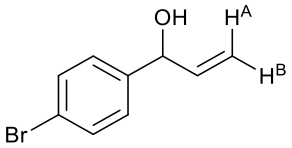
1-(4-Chlorophenyl)prop-2-en-1-ol



The title compound was prepared according to general procedure 1 using 4-chlorobenzaldehyde (562 mg, 4.00 mmol), dry THF (4 mL) and vinyl magnesium bromide (4.80 mL, 4.80 mmol, 1.20 equiv.). Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 35 × 150 mm silica) gave the title

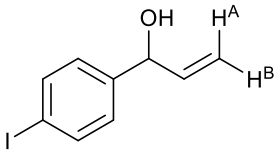
compound as a pale-yellow oil (411 mg, 61%); R_f: 0.17 (eluent = 10% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.96 (1H, br s, CHO*H*), 5.19 (1H, d, *J* 6.1, C*H*OH), 5.21 (1H, app dt, *J* 10.3, 1.3, CH=CH^A*H*^{B}), 5.34 (1H, app dt, *J* 17.1, 1.3, CH=C*H*^{A}H^B), 6.00 (1H, ddd, *J* 17.1, 10.3, 6.1, C*H*=CH$_2$), 7.29-7.35 (4H, m, 4×Ar*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 74.9 (*C*HOH), 115.8 (CH=*C*H$_2$), 127.8 (2×Ar*C*), 128.8 (2×Ar*C*), 133.6 (Ar*C*(4)), 140.0 (*C*H=CH$_2$), 141.1 (Ar*C*(1)). Spectroscopic data in accordance with the literature.[11]

1-(4-Bromophenyl)prop-2-en-1-ol



The title compound was prepared according to general procedure 1 using 4-bromobenzaldehyde (740 mg, 4.00 mmol), dry THF (4 mL) and vinyl magnesium bromide (4.80 mL, 4.80 mmol, 1.20 equiv.). Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 30 × 150 mm silica) gave the title compound as a colourless oil (597 mg, 70%); R_f: 0.25 (eluent = 10% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 517, 556, 627, 719, 795, 816, 841, 924, 986, 1009, 1070, 1400, 1485, 1591, 1638, 2870, 2980, 3080, 3327; **^{1}H NMR ($CDCl_3$, 400 MHz)** δ_H: 1.95 (1H, d, *J* 2.0, CHO*H*), 5.15-5.19 (1H, m, C*H*OH), 5.22 (1H, app dt, *J* 10.4, 1.2, CH=CH^A*H*^{B}), 5.35 (1H, app dt, *J* 17.1, 1.3, CH=C*H*^{A}H^B), 6.00 (1H, ddd, *J* 16.8, 10.0, 6.0, C*H*=CH$_2$), 7.23-7.27 (2H, m, 2×Ar*H*), 7.46-7.50 (2H, m, 2×Ar*H*); **^{13}C NMR ($CDCl_3$, 101 MHz)** δ_C: 74.9 (*C*HOH), 115.8 (CH=*C*H$_2$), 121.7 (Ar*C*(4)), 128.2 (2×Ar*C*), 131.8 (2×Ar*C*), 140.0 (*C*H=CH$_2$), 141.6 (Ar*C*(1)); HRMS (**EI**$^+$) calculated for [C$_9$H$_9$OBr]$^+$ (M)$^+$: m/z 211.9837, found 211.9838, (0.5 ppm).

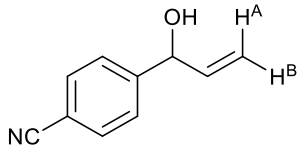
1-(4-Iodophenyl)prop-2-en-1-ol



The title compound was prepared according to general procedure 1 using 4-iodobenzaldehyde (928 mg, 4.00 mmol), dry THF (4 mL) and vinyl magnesium

bromide (4.80 mL, 4.80 mmol, 1.20 equiv.). Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 30 × 150 mm silica) gave the title compound as a creamy-pink solid (766 mg, 74%); mp 38-40 °C; R_f: 0.17 (eluent = 10% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 467, 494, 625, 638, 687, 711, 785, 849, 924, 991, 1003, 1042, 1177, 1250, 1265, 1386, 1413, 1479, 1637, 2887, 2976, 3076, 3183, 3273; **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.97 (1H, br s, CHO*H*), 5.15 (1H, d, *J* 6.1, C*H*OH), 5.21 (1H, app dt, *J* 10.3, 1.3, CH=CH^A*H*^{B}), 5.34 (1H, app dt, *J* 17.1, 1.3, CH=C*H*^{A}H^B), 6.00 (1H, ddd, *J* 17.1, 10.3, 6.1, C*H*=CH_2), 7.09-7.14 (2H, m, 2×Ar*H*), 7.66-7.71 (2H, m, 2×Ar*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 74.6 (*C*HOH), 93.3 (Ar*C*(4)), 115.9 (CH=*C*H_2), 128.4 (2×Ar*C*), 137.7 (2×Ar*C*), 139.9 (*C*H=CH_2), 141.1 (Ar*C*(1)). HRMS (**EI**$^+$) calculated for $[C_9H_9OI]^+$ $(M)^+$: m/z 259.9700, found 259.9699, (0.4 ppm).

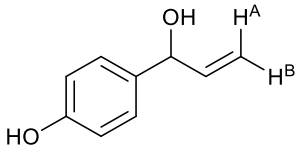
4-(1-Hydroxyallyl)benzonitrile (66)



66

The title compound was prepared according to general procedure 1 using 4-formylbenzonitrile (530 mg, 4.00 mmol), dry THF (4 mL) and vinyl magnesium bromide (4.80 mL, 4.80 mmol, 1.20 equiv.). Purification by flash silica chromatography (eluent = 10-20% EtOAc in hexanes, 30 × 160 mm silica) gave the title compound as a white solid (421 mg, 66%); mp 53-56 °C; R_f: 0.37 (eluent = 30% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 507, 561, 586, 640, 756, 812, 839, 922, 986, 1049, 1119, 1194, 1234, 1315, 1402, 1504, 1609, 2236, 2860, 3443; **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 2.10 (1H, d, *J* 3.1, CHO*H*), 5.23-5.28 (2H, m, C*H*OH and CH=CH^A*H*^{B}), 5.37 (1H, app dt, *J* 17.5, 1.5, CH=C*H*^{A}H^B), 5.97 (1H, ddd, *J* 17.0, 10.5, 6.0, C*H*=CH_2), 7.48-7.52 (2H, m, 2×Ar*H*), 7.62-7.67 (2H, m, 2×Ar*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 74.9 (*C*HOH), 111.5 (Ar*C*(4)), 116.8 (CH=*C*H_2), 118.9 (*C*≡N), 127.0 (2×Ar*C*), 132.5 (2×Ar*C*), 139.4 (*C*H=CH_2), 147.7 (Ar*C*(1)); HRMS (**EI**$^+$) calculated for $[C_{10}H_9NO]^+$ $(M)^+$: m/z 159.0684, found 159.0690, (3.8 ppm).

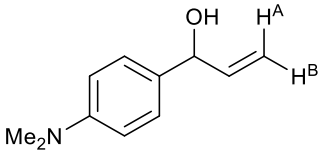
4-(1-Hydroxyallyl)phenol (67)



67

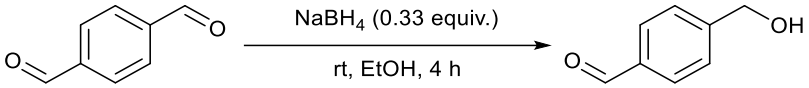
The title compound was prepared according to general procedure 1 using 4-hydroxybenzaldehyde (488 mg, 4.00 mmol, 1 equiv.), dry THF (25 mL) and vinyl magnesium bromide (8.80 mL, 8.80 mmol, 2.2 equiv., 1 M in THF). Purification by flash silica chromatography (eluent = 10-20% EtOAc in hexanes, 30 × 160 mm silica) gave the title compound as a low-melting solid (388 mg, 65%); R_f: 0.10 (eluent = 20% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.87 (1H, d, *J* 3.8, CHO*H*), 4.86 (1H, s, PhO*H*), 5.14-5.20 (1H, m, C*H*OH), 5.19 (1H, app dt, *J* 10.3, 1.4, CH=CH^A*H*^{B}), 5.34 (1H, app dt, *J* 17.2, 1.5, CH=C*H*^{A}H^B), 6.05 (1H, ddd, *J* 17.1, 10.3, 5.8, C*H*=CH_2), 6.78-6.84 (2H, m, 2×Ar*H*), 7.22-7.29 (2H, m, 2×Ar*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 75.6 (*C*HOH), 114.4 (CH=*C*H_2), 116.1 (2×Ar*C*), 129.2 (2×Ar*C*), 135.6 (Ar*C*), 142.3 (*C*H=CH_2), 157.8 (Ar*C*). Spectroscopic data in accordance with the literature.[15]

1-(4-(Dimethylamino)phenyl)prop-2-en-1-ol



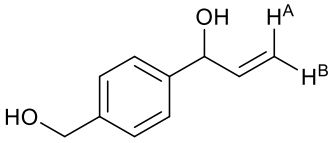
The title compound was prepared according to general procedure 1 using 4-(dimethylamino)benzaldehyde (1.49 g, 10.0 mmol), dry THF (10 mL) and vinyl magnesium bromide (12.0 mL, 12.0 mmol, 1.20 equiv.). Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 35 × 150 mm silica) gave the title compound as a yellow oil (155 mg, 9%); R_f: 0.19 (eluent = 10% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.76-1.80 (1H, m, CHO*H*), 2.95 (6H, s, N(CH_3)$_2$), 5.11-5.15 (1H, m, C*H*OH), 5.17 (1H, app dt, *J* 10.4, 1.5, CH=CH^A*H*^{B}), 5.34 (1H, app dt, *J* 17.1, 1.5, CH=C*H*^{A}H^B), 6.07 (1H, ddd, *J* 17.2, 10.4, 5.7, C*H*=CH_2), 6.69-6.75 (2H, m, 2×Ar*H*), 7.22-7.27 (2H, m, 2×Ar*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 40.8 (N(*C*H_3)$_2$), 75.2 (*C*HOH), 112.7 (2×Ar*C*), 114.4 (CH=*C*H_2), 127.6 (2×Ar*C*), 130.7 (Ar*C*), 140.7 (*C*H=CH_2), 150.5 (Ar*C*). Spectroscopic data in accordance with the literature.[16]

4-(Hydroxymethyl)benzaldehyde



A round-bottomed flask equipped with a magnetic stirrer bar was charged with terephthaldehyde (2.00 g, 14.9 mmol) and EtOH (50 mL). The solution was cooled to 0 °C and was charged with $NaBH_4$ (189 mg, 5.00 mmol). The mixture was left to stir at rt for 4 h. It was then cooled to 0 °C and quenched with sat. aq. NH_4Cl (5 mL) and H_2O (10 mL), then EtOAc (50 mL) was added. The organic layer was collected, and the aqueous phase was extracted with EtOAc (2 × 50 mL). The organics were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash silica chromatography gave the title compound as white solid (1.3 g, 64%); mp 40-42 °C (Lit. 39-40 °C);[17] R_f: 0.14 (eluent = 20% EtOAc in cyclohexane); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 2.08 (1H, br s, CH_2OH), 4.80 (2H, s, CH_2OH), 7.49-7.56 (2H, m, ArC(3,5)*H*), 7.84-7.90 (2H, m, ArC(2,6)*H*)), 9.99 (1H, s, C*H*O); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_H: 64.7 (*C*H_2OH), 127.1 (Ar*C*(3,5)), 130.2 (Ar*C*(2,6)), 135.8 (Ar*C*(1)), 147.9 (Ar*C*(4)), 192.2 (*C*HO). Spectroscopic data in accordance with that stated in the literature.[17]

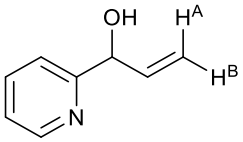
1-(4-(Hydroxymethyl)phenyl)prop-2-en-1-ol



The title compound was prepared according to general procedure 1 using 4-(hydroxymethyl)benzaldehyde (1.26 g, 9.30 mmol, 1.00 equiv.), dry THF (50 mL) and vinyl magnesium bromide (37.0 mL, 37.2 mmol, 4.00 equiv.). Purification by flash silica chromatography (eluent = 20-30% EtOAc in hexanes, 30 × 150 mm silica) gave the title compound as a white solid (840 mg, 55%); mp 80-83 °C; R_f: 0.18 (eluent = 30% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 667, 710, 764, 818, 852, 935, 1013, 1034, 1120, 1261, 1423, 1458, 1510, 2855, 3192, 3291; **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.67 (1H, t, *J* 5.9, CH_2OH), 1.96 (1H, d, *J* 3.8, CHO*H*), 4.69 (2H, d, *J* 5.8, CH_2OH), 5.20 (1H, app dt, *J* 10.3, 1.3, CH=CH^AH^B), 5.20-5.24 (1H, m, C*H*OH), 5.36 (1H, app dt, *J* 17.2, 1.4, CH=CH^AH^B), 6.04 (1H, ddd, 17.2, 10.3, 6.1, C*H*=CH_2), 7.34-7.40 (4H, m, 4×Ar*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 65.2 (*C*H_2OH), 75.3 (*C*HOH), 115.4 (CH=*C*H_2), 126.7

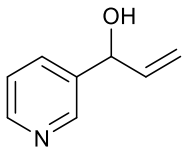
(2×Ar*C*), 127.4 (2×Ar*C*), 140.3 (*C*H=CH_2), 140.5 (Ar*C*), 142.2 (Ar*C*); HRMS (**EI**$^+$) calculated for $[C_{10}H_{12}O_2]^+$ $(M)^+$: m/z 164.0837, found 164.0836, (-0.6 ppm).

1-(Pyridin-2-yl)prop-2-en-1-ol



The title compound was prepared according to general procedure 1 using 2-pyridinecarboxaldehyde (761 µL, 857 mg, 8.00 mmol), dry THF (8 mL) and vinyl magnesium bromide (9.60 mL, 9.60 mmol, 1.20 equiv.). Purification by flash silica chromatography (eluent = 10-20% EtOAc in hexanes, 35 × 150 mm silica) gave the title compound as a dark orange oil (476 mg, 44%); R_f: 0.15 (eluent = 30% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 4.69 (1H, br s, CHO*H*), 5.18 (1H, d, *J* 6.8, C*H*OH), 5.25 (1H, app dt, *J* 10.2, 1.3, CH=CH^A*H*^{B}), 5.46 (1H, app dt, *J* 17.0, 1.3, CH=C*H*^{A}H^B), 5.96 (1H, ddd, *J* 17.0, 10.2, 6.8, C*H*=CH_2), 7.22 (1H, dddd, 7.5, 4.9, 1.2, 0.6, ArC(4)*H*), 7.29 (1H, app dtd, *J* 7.9, 1.1, 0.6, Ar*H*), 7.69 (1H, app dtd, *J* 7.5, 1.5, 0.5, Ar*H*), 8.53-8.57 (1H, m, Ar*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 92.1 (*C*HOH), 116.7 (CH=*C*H_2), 121.0 (Ar*C*), 122.6 (Ar*C*), 137.0 (Ar*C*), 139.6 (*C*H=CH_2), 148.2 (Ar*C*), 160.0 (Ar*C*). Spectroscopic data in accordance with the literature.[18]

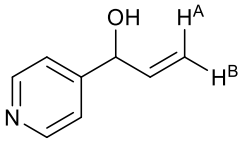
1-(Pyridin-3-yl)prop-2-en-1-ol



The title compound was prepared according to general procedure 1 using 3-pyridinecarboxaldehyde (752 µL, 857 mg, 8.00 mmol), dry THF (8 mL) and vinyl magnesium bromide (9.60 mL, 9.60 mmol, 1.20 equiv.). Purification by flash silica chromatography (eluent = 50% EtOAc in hexanes, 35 × 150 mm silica) gave the title compound as an orange oil (746 mg, 69%); R_f: 0.12 (eluent = 50% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 5.23-5.28 (2H, m, C*H*OH and CH=C*H*H), 5.35-5.42 (1H, m, CH=CH*H*), 5.96-6.08 (1H, m, C*H*=CHH), 7.26-7.31 (1H, m, Ar*H*), 7.70-7.74 (1H, m, Ar*H*), 8.44-8.60 (2H, m, Ar*H*), O*H* not found; **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 73.2

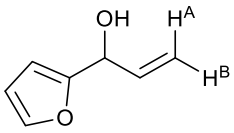
(*C*HOH), 116.2 (CH=*C*H$_2$), 123.6 (Ar*C*), 134.3 (Ar*C*), 138.2 (Ar*C*), 139.7 (*C*H=CH$_2$)), 148.3 (Ar*C*), 149.0 (Ar*C*). Spectroscopic data in accordance with the literature.[19]

1-(Pyridin-4-yl)prop-2-en-1-ol



The title compound was prepared according to general procedure 1 using 4-pyridinecarboxaldehyde (377 μL, 428 mg, 4.00 mmol), dry THF (4 mL) and vinyl magnesium bromide (4.80 mL, 4.80 mmol, 1.20 equiv.). Purification by flash silica chromatography (eluent = 30-60% EtOAc in hexanes, 30 × 150 mm silica) gave the title compound as a dark orange oil (313 mg, 58%); R$_f$: 0.30 (eluent = 50% EtOAc in hexanes); **^{1}H NMR (CDCl$_3$, 500 MHz)** δ_H: 3.63 (1H, br s, CHO*H*), 5.17-5.22 (1H, m, C*H*OH), 5.24 (1H, app dt, *J* 10.2, 1.2, CH=CH^A*H*^{B}), 5.38 (1H, app dt, *J* 17.1, 1,3, CH=C*H*^{A}H^B), 5.97 (1H, ddd, *J* 17.1, 10.2, 6.5, C*H*=CH$_2$), 7.29-7.35 (2H, m, ArC(2,6)*H*), 8.47-8.54 (2H, m, ArC(3,5)*H*); **^{13}C NMR (CDCl$_3$, 126 MHz)** δ_C: 74.1 (*C*HOH), 116.7 (CH=*C*H$_2$), 121.3 (Ar*C*(2,6)), 139.4 (*C*H=CH$_2$), 149.7 (Ar*C*(3,5)), 151.9 (Ar*C*(1)).

1-(Furan-2-yl)prop-2-en-1-ol (62)

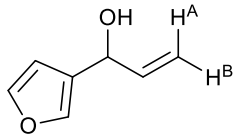


62

The title compound was prepared according to general procedure 1 using 2-furancarboxaldehyde (331 μL, 384 mg, 4.00 mmol), dry THF (4 mL) and vinyl magnesium bromide (4.80 mL, 4.80 mmol, 1.20 equiv.). Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 30 × 150 mm silica) gave the title compound as an orange oil (595 mg, 81%); R$_f$: 0.15 (eluent = 10% EtOAc in hexanes); **^{1}H NMR (CDCl$_3$, 500 MHz)** δ_H: 2.07 (1H, d, *J* 5.1, CHO*H*), 5.20-5.26 (1H, m, C*H*OH), 5.29 (1H, app dt, *J* 10.4, 1.3, CH=CH^A*H*^{B}), 5.46 (1H, app dt, *J* 17.2, 1.5, CH=C*H*^{A}H^B), 6.13 (1H, ddd, *J* 16.5, 10.4, 5.7, C*H*=CH$_2$), 6.24-6.28 (1H, m, Ar*H*), 6.32-6.36 (1H, m, Ar*H*), 7.38-7.43 (1H, m, Ar*H*); **^{13}C NMR (CDCl$_3$, 126 MHz)** δ_C: 68.8 (*C*HOH), 106.8 (Ar*C*),

110.4 (*C*H=CH$_2$), 116.7 (CH=*C*H$_2$), 136.9 (Ar*C*), 142.6 (Ar*C*), 155.1 (Ar*C*(1)). Spectroscopic data in accordance with the literature.[20]

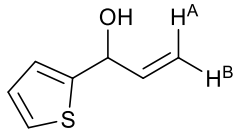
1-(Furan-3-yl)prop-2-en-1-ol (63)



63

The title compound was prepared according to general procedure 1 using 3-furancarboxaldehyde (346 μL, 384 mg, 4.00 mmol), dry THF (4 mL) and vinyl magnesium bromide (4.80 mL, 4.80 mmol, 1.20 equiv.). Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 30 × 150 mm silica) gave the title compound as an orange oil (324 mg, 65%); R_f: 0.15 (eluent = 10% EtOAc in hexanes); **^{1}H NMR (CDCl$_3$, 500 MHz)** δ_H: 1.80-1.90 (1H, m, CHO*H*), 5.14-5.20 (1H, m, C*H*OH), 5.22 (1H, app dt, *J* 10.3, 1.3, CH=CH^A*H*^{B}), 5.36 (1H, app dt, *J* 17.1, 1.4, CH=C*H*^{A}H^B), 6.13 (1H, ddd, *J* 17.1, 10.3, 5.9, C*H*=CH$_2$), 6.38-6.43 (1H, m, Ar*H*), 7.36-7.43 (2H, m, 2×Ar*H*); **^{13}C NMR (CDCl$_3$, 126 MHz)** δ_C: 68.2 (*C*HOH), 109.1 (*C*H=CH$_2$), 116.7 (CH=*C*H$_2$), 127.7 (Ar*C*(1)), 139.4 (Ar*C*), 139.5 (Ar*C*), 143.6 (Ar*C*). Spectroscopic data in accordance with the literature.[21]

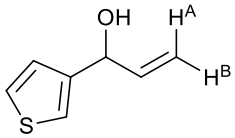
1-(Thiophen-2-yl)prop-2-en-1-ol



The title compound was prepared according to general procedure 1 using 2-thiophenecarboxaldehyde (374 μL, 449 mg, 4.00 mmol), dry THF (4 mL) and vinyl magnesium bromide (4.80 mL, 4.80 mmol, 1.20 equiv.). Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 25 × 150 mm silica) gave the title compound as a pale yellow oil (449 mg, 80%); R_f: 0.15 (eluent = 10% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 692, 768, 800, 831, 852, 928, 953, 986, 1030, 1206, 1229, 1294, 1418, 1435, 1643, 2853, 2920, 3071, 3103, 3368; **^{1}H NMR (CDCl$_3$, 500 MHz)** δ_H: 2.09 (1H, d, *J* 4.4, CHO*H*), 5.26 (1H, dd, *J* 10.5, 1.4, CH=CH^A*H*^{B}), 5.42 (1H, dd, *J* 17.5,

1.4, CH=C*H*^{A}H^{B}), 5.39-5.50 (1H, m, C*H*OH), 6.13 (1H, ddd, *J* 17.5, 10.5, 6.0, C*H*=CH$_2$), 6.96-7.03 (2H, m, 2×Ar*H*), 7.26-7.30 (1H, m, Ar*H*); **^{13}C NMR (CDCl$_3$, 126 MHz)** δ_C: 71.2 (*C*HOH), 115.9 (CH=*C*H$_2$), 124.6 (Ar*C*), 125.5 (Ar*C*), 127.0 (Ar*C*), 139.4 (*C*H=CH$_2$), 146.7 (ArC(1)); HRMS (**EI**$^+$) calculated for [C$_7$H$_8$OS]$^+$ (M)$^+$: m/z 240.0296, found 240.0296, (0.0 ppm).

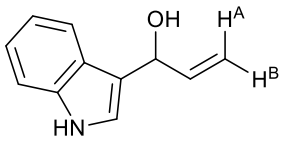
1-(Thiophen-2-yl)prop-2-en-1-ol (64)



64

The title compound was prepared according to general procedure 1 using 3-thiophenecarboxaldehyde (350 µL, 449 mg, 4.00 mmol), dry THF (4 mL) and vinyl magnesium bromide (4.80 mL, 4.80 mmol, 1.20 equiv.). Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 25 × 150 mm silica) gave the title compound as a pale yellow oil (449 mg, 80%); R$_f$: 0.19 (eluent = 10% EtOAc in hexanes); **^{1}H NMR (CDCl$_3$, 500 MHz)** δ_H: 1.92 (1H, br s, CHO*H*), 5.22 (1H, d, *J* 10.3, CH=CH^{A}*H*^{B}), 5.29 (1H, d, *J* 6.1, C*H*OH), 5.36 (1H, d, CH=C*H*^{A}H^{B}), 6.09 (1H, ddd, *J* 16.6, 10.2, 6.1, C*H*=CH$_2$), 7.05-7.10 (1H, m, Ar*H*), 7.20-7.25 (1H, m, Ar*H*), 7.29-7.34 (1H, m, Ar*H*); **^{13}C NMR (CDCl$_3$, 126 MHz)** δ_C: 71.7 (*C*HOH), 115.5 (CH=*C*H$_2$), 121.5 (Ar*C*), 126.3 (Ar*C*), 126.4 (Ar*C*), 139.7 (*C*H=CH$_2$), 144.2 (ArC(1)). Spectroscopic data in accordance with the literature.[21]

1-(1H-Indol-3-yl)prop-2-en-1-ol (65)

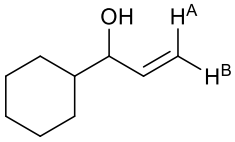


65

The title compound was prepared according to general procedure 1 using indole-3-carboxaldehyde (580 mg, 4.00 mmol), dry THF (20 mL) and vinylmagnesium bromide (8.80 mL, 8.80 mmol, 2.20 equiv.) Purification by flash silica chromatography (eluent = 15-30% EtOAc in hexanes, 30 × 150 mm silica) gave the title compound as a pale

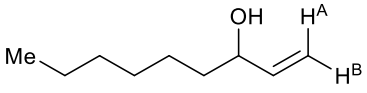
yellow oil (660 mg, 95%); R_f: 0.29 (eluent = 30% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.92 (1H, d, *J* 3.7, CHO*H*), 5.26 (1H, app dt, *J* 10.4, 1.5, CH=CH^A*H*^{B}), 5.48 (1H, app dt, *J* 17.1, 6.1, CH=C*H*^{A}H^B), 5.53-5.59 (1H, m, C*H*OH), 6.28 (1H, ddd, *J* 17.1, 10.3, 5.6, C*H*=CH_2), 7.11-7.18 (2H, m, 2×Ar*H*), 7.20-7.26 (1H, m, Ar*H*), 7.35-7.40 (1H, m, Ar*H*), 7.75-7.79 (1H, m, Ar*H*), 8.13 (1H, br s, N*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 69.2 (*C*HOH), 111.4 (Ar*C*), 115.0 (CH=*C*H_2), 118.3 (Ar*C*), 119.8 (Ar*C*), 120.0 (Ar*C*), 122.0 (Ar*C*), 122.6 (Ar*C*), 125.8 (*C*H=CH_2), 136.7 (Ar*C*), 139.8 (Ar*C*). Spectroscopic data in accordance with the literature.[22]

1-Cyclohexylprop-2-en-1-ol



The title compound was prepared according to general procedure 1 using cyclohexanecarboxaldehyde (1.21 mL, 1.21 g, 10.0 mmol), dry THF (10 mL) and vinyl magnesium bromide (12.0 mL, 12.0 mmol, 1.20 equiv.). Purification by flash silica chromatography (eluent = 5% EtOAc in cyclohexane, 35 × 150 mm silica) gave the title compound as a colourless oil (337 mg, 24%); R_f: 0.20 (eluent = 10% EtOAc in cylcohexane); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 0.93-1.07 (2H, m, Cy*H*), 1.11-1.30 (3H, m, Cy*H*), 1.35-1.45 (1H, m, CHO*H*), 1.60-1.95 (6H, m, Cy*H*), 3.81-3.88 (1H, m, C*H*OH), 5.14 (1H, app dt, *J* 10.5, 1.5, CH=CH^A*H*^{B}), 5.20 (1H, app dt, *J* 17.2, 1.5, CH=C*H*^{A}H^B), 5.86 (1H, ddd, *J* 17.1, 10.4, 6.6, C*H*=CH_2); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 26.2 (Cy*C*), 26.3 (Cy*C*). 26.7 (Cy*C*), 28.5 (Cy*C*), 28.9 (Cy*C*), 43.6 ((CH_2)$_2$*C*H), 77.9 (*C*HOH), 115.6 (CH=*C*H_2), 140.0 (*C*H=CH_2). Spectroscopic data in accordance with the literature.[23]

Non-1-en-3-ol (69)

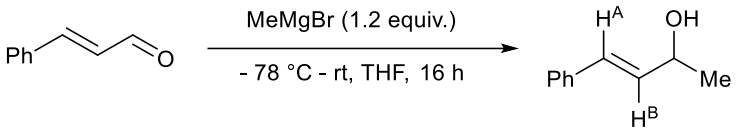


69

The title compound was prepared according to general procedure 1 using heptanal (706 µL, 571 mg, 5.00 mmol), dry THF (5 mL) and vinyl magnesium bromide (6.00 mL, 6.00 mmol, 1.20 equiv.). Purification by flash silica chromatography (eluent = 5-

10% EtOAc in hexanes, 30 × 150 mm silica) gave the title compound as a colourless oil (128 mg, 18%); R_f: 0.26 (eluent = 10% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 0.79-0.84 (3H, m, C*H*$_3$), 1.16-1.30 (8H, $CH_3(CH_2)_4CH_2$), 1.39-1.61 (2H, m, C*H*$_2$CHOH), 2.25-2.31 (1H, m, CHO*H*), 4.00-4.06 (1H, m, C*H*OH), 5.03 (1H, app dt, *J* 10.4, 1.3, CH=CH^A*H*^{B}), 5.15 (1H, app dt, *J* 17.2, 1.4, CH=C*H*^{A}H^B), 5.80 (1H, ddd, *J* 16.7, 10.4, 6.2, C*H*=CH$_2$); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 14.2 (*C*H$_2$), 22.7 (*C*H$_2$). 25.4 (*C*H$_2$), 29.4 (*C*H$_2$), 31.9 (*C*H$_2$), 37.1 (*C*H$_2$), 73.5 (*C*HOH), 114.7 (CH=*C*H$_2$), 141.4 (*C*H=CH$_2$). Spectroscopic data in accordance with the literature.[24]

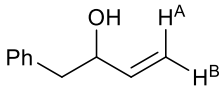
(E)-4-Phenylbut-3-en-2-ol (53)



53

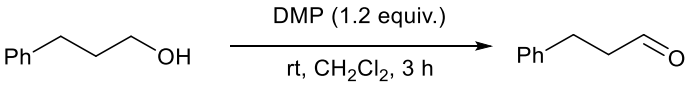
Under nitrogen, a flame-dried 50 mL round-bottomed flask with a stirrer bar was charged with dry THF (10 mL) and cinnamaldehyde (1.26 mL, 1.32 g, 10.0 mmol), followed by the dropwise addition of methyl magnesium bromide (4.00 mL, 12.0 mmol, 1.20 equiv., 3 M in THF) at -78 °C with stirring. The reaction was warmed to rt and left to stir overnight. The reaction was quenched with sat. aq. NH_4Cl (10 mL) and H_2O (10 mL), then EtOAc (10 mL) was added. The organic layer was collected, and the aqueous phase was extracted with EtOAc (2 × 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 15-30% EtOAc in hexanes, 35 × 150 mm silica) gave the title compound as a colourless oil (934 mg, 63%); R_f: 0.15 (eluent = 10% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.38 (3H, d, *J* 6.4, C*H*$_3$), 4.50 (1H, app quint, *J* 6.3, C*H*OH), 6.27 (1H, app dt, *J* 15.9, 6.4, CH^A=C*H*^{B}), 6.57 (1H, d, *J* 15.9, C*H*^{A}=CH^B), 7.21-7.26 (1H, m, Ar*H*), 7.29-7.35 (2H, m, 2×Ar*H*), 7.36-7.41 (2H, m, 2×Ar*H*), O*H* not found; **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 23.6 (C*H*$_3$), 69.1 (*C*HOH), 126.6 (2×Ar*C*), 127.8 (Ar*C*), 128.7 (2×Ar*C*), 129.6 (*C*H), 133.7 (*C*H), 136.8 (Ar*C*(1)). Spectroscopic data in accordance with the literature.[25]

1-Phenylbut-3-en-2-ol



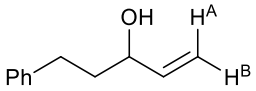
The title compound was prepared according to general procedure 1 using phenylacetaldehyde (445 µL, 481 mg, 4.00 mmol), dry THF (4 mL) and vinyl magnesium bromide (4.80 mL, 4.80 mmol, 1.20 equiv.). Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 30 × 150 mm silica) gave the title compound as a colourless oil (207 mg, 35%); R_f: 0.21 (eluent = 10% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.60-1.66 (1H, m, CHO*H*), 2.70-2.92 (2H, m, PhCH_2), 4.32-4.40 (1H, m, C*H*OH), 5.14 (1H, app dt, *J* 10.5, 1.4, CH=CH^A*H*^{B}), 5.26 (1H, app dt, *J* 17.2, 1.4, CH=C*H*^{A}H^B), 5.94 (1H, ddd, *J* 17.2, 10.5, 5.8, *CH*=CH_2), 7.21-7.27 (3H, m, Ar(2,4,6)*H*), 7.29-7.35 (2H, m, Ar(3,5)*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 44.0 (Ph*C*H_2), 73.8 (*C*HOH), 115.1 (CH=*C*H_2), 126.7 (Ar*C*(4)), 128.6 (Ar*C*(2,6)), 129.7 (Ar*C*(3,5)), 137.8 (Ar*C*(1)), 140.3 (*C*H=CH_2). Spectroscopic data in accordance with the literature.[26]

Hydrocinnamaldehyde



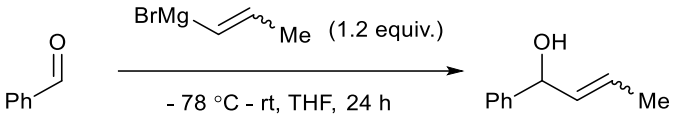
A round-bottomed flask equipped with a magnetic stirrer bar was charged with 3-phenyl-1-propanol (680 µL, 681 mg, 5.00 mmol, 1 equiv.) and CH_2Cl_2 (25 mL). The solution was cooled to 0 °C and charged with Dess-Martin Periodinane (2.54 g, 6.00 mmol, 1.20 equiv.). The suspension was allowed to stir at rt for 3 h. Sat aq. $NaHCO_3$ (15 mL) and CH_2Cl_2 (25 mL) were added to the mixture and the suspension was filtered. The filtrate was washed with sat aq. $NaHCO_3$ (50 mL). The organic layer was collected, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 5% EtOAc in hexanes, 30 × 70 mm silica) gave the title compound as a colourless oil (527 mg, 79 %); R_f = 0.27 (eluent = 5% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 2.76-2.82 (2H, m, PhCH_2), 2.97 (2H, td, *J* 7.6, 1.4, CH_2(C=O)), 7.17-7.24 (3H, m, ArC(2,4,6)*H*), 7.27-7.33 (2H, m, ArC(3,5)*H*), 9.83 (1H, t, *J* 1.4, H(*C*=O)); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 28.3 (Ph*C*H_2), 45.4 (PhCH_2*C*H_2), 126.5 (Ar*C*(4)), 128.4 (Ar*C*(2,6)), 128.8 (Ar*C*(3,5)), 140.5 (Ar*C*(1)), 201.7 (*C*=O). Spectroscopic data in accordance with the literature.[27]

5-Phenylpent-1-en-3-ol



The title compound was prepared according to general procedure 1 using 3-phenylpropanal (521 μL, 531 mg, 4.00 mmol), dry THF (4 mL) and vinyl magnesium bromide (4.80 mL, 4.80 mmol, 1.20 equiv.). Purification by flash silica chromatography (eluent = 7% EtOAc in hexanes, 30 × 150 mm silica) gave the title compound as a colourless oil (431 mg, 66%); R_f: 0.20 (eluent = 10% EtOAc in hexanes); **^{1}H NMR (CDCl$_3$, 500 MHz)** δ_H; 1.53 (1H, br s, CHO*H*), 1.80-1.93 (2H, m, PhCH$_2$C*H*$_2$), 2.65-2.80 (2H, m, PhC*H*$_2$CH$_2$), 4.12-4.16 (1H, m, C*H*OH), 5.14 (1H, app dt, *J* 10.4, 1.3, CH=CH^A*H*^{B}), 5.25 (1H, app dt, *J* 17.2, 1.4, CH=C*H*^{A}H^B), 5.91 (1H, ddd, *J* 17.2, 10.4, 6.2, *CH*=CH$_2$), 7.17-7.23 (3H, m, ArC(2,4,6)*H*), 7.26-7.31 (2H, m, ArC(3,5)*H*); **^{13}C NMR (CDCl$_3$, 126 MHz)** δ_C: 31.8 (PhCH$_2$*C*H$_2$), 38.7 (Ph*C*H$_2$CH$_2$), 72.6 (*C*HOH), 115.1 (CH=*C*H$_2$), 126.0 (ArC(4)), 128.5 (ArC(2,6)), 128.6 (ArC(3,5)), 141.1 (*C*H=CH$_2$), 142.0 (Ar*C*(1)). Spectroscopic data in accordance with the literature.[28]

1-Phenylbut-2-en-1-ol



Under nitrogen, a flame-dried 100 mL round-bottomed flask with a stirrer bar was charged with dry THF (20 mL) and benzaldehyde (1.02 mL, 1.06 g, 10.0 mmol, 1 equiv.) followed by the dropwise addition of 1-propenylmagnesium bromide (12.0 mL, 12.0 mmol, 1.20 equiv., 1 M in THF) at -78 °C with stirring. The reaction was warmed to rt and left to stir overnight. The reaction was quenched with sat. aq. NH_4Cl (10 mL) and H_2O (10 mL), then EtOAc (10 mL) was added. The organic layer was collected, and the aqueous phase was extracted with EtOAc (2 × 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 35 × 150 mm silica) gave the title compound as a pale-yellow oil (1.13 g, 77%, E/Z 29:71); R_f: 0.19 (eluent = 10% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 696, 721, 743, 843, 908,

980, 1028, 1450, 1493, 2859, 2918, 3026, 3061, 3354; HRMS (**EI**$^+$) calculated for $[C_{10}H_{10}]^+$ $(M\text{-}H_2O)^+$: m/z 130.0783, found 130.0777, (-4.6 ppm).

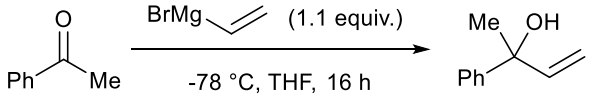
Selected ^{1}H NMR data for the major stereoisomer (*Z*):

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 1.78-1.81 (3H, m, C*H*$_3$), 1.85 (1H, d, *J* 2.8, CHO*H*), 5.56-5.62 (1H, m, C*H*OH), 5.62-5.82 (2H, m, C*H*=C*H*), 7.25-7.30 (1H, m, Ar*H*), 7.32-7.43 (4H, m, 4×Ar*H*). **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 13.5 (*C*H$_3$), 69.6 (*C*HOH), 126.0 (2×Ar*C*), 126.6 (Ar*C*), 127.6 (2×Ar*C*), 128.7 (CH=*C*CH$_3$), 133.0 (*C*H=CCH$_3$), 143.8 (Ar*C*). Spectroscopic data in accordance with the literature.[29]

Selected ^{1}H NMR data for the minor stereoisomer (*E*):

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 1.71-1.74 (3H, m, C*H*$_3$), 1.88 (1H, d, *J* 3.1, CHO*H*), 5.14-5.19 (1H, m, C*H*OH), 5.62-5.82 (2H, m, C*H*=C*H*), 7.25-7.30 (1H, m, Ar*H*), 7.32-7.43 (4H, m, 4×Ar*H*). **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 17.9 (*C*H$_3$), 75.4 (CHOH), 126.2 (2×Ar*C*), 127.6 (Ar*C*), 127.6 (2×Ar*C*), 128.6 (CH=*C*CH$_3$), 133.7 (*C*H=CCH$_3$), 143.5 (Ar*C*). Spectroscopic data in accordance with the literature.[30]

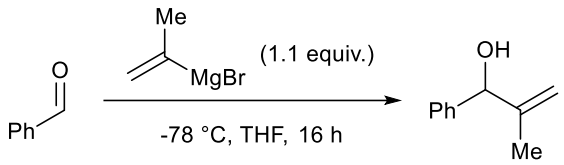
2-Phenylbut-3-en-2-ol (57)



57

The title compound was prepared according to general procedure 1 using acetophenone (467 µL, 481 mg, 4.00 mmol, 1.00 equiv.) dry THF (20 mL) and vinyl magnesium bromide (4.80 mL, 4.80 mmol, 1.20 equiv.) Purification by flash silica chromatography (eluent = 2-5% EtOAc in cyclohexane, 25 × 150 mm silica) gave the title compound as a pale-yellow oil (256 mg, 43%); R_f: 0.21 (eluent = 10% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.66 (3H, s, C*H*$_3$), 1.89 (1H, br s, O*H*), 5.15 (1H, d, *J* 10.6, CH=CH^A*H*^{B}), 5.30 (1H, d, *J* 17.3, CH=C*H*^{A}H^B), 6.18 (1H, dd, *J* 17.3, 10.6, C*H*=CH$_2$), 7.23-7.29 (1H, m, Ar*H*), 7.31-7.38 (2H, m, Ar*H*), 7.45-7.51 (2H, m, Ar*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 29.5 (*C*H$_3$), 74.9 (*C*OHCH$_3$), 112.5 (CH=*C*H$_2$), 125.3 (2×Ar*C*), 127.1 (Ar*C*), 128.4 (2×Ar*C*), 145.0 (*C*H=CH$_3$), 146.05 (Ar*C*). Spectroscopic data in accordance with the literature.[31]

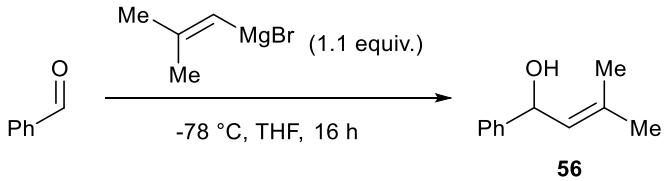
2-Methyl-1-phenylprop-2-en-1-ol (55)



55

Under nitrogen, a flame-dried 25 mL round-bottomed flask with a stirrer bar was charged with dry THF (4 mL) and benzaldehyde (407 µL, 424 mg, 4.00 mmol, 1 equiv.) followed by the dropwise addition of prop-1-en-2-ylmagnesium bromide (8.80 mL, 4.40 mmol, 1.10 equiv., 0.5 M in THF) at -78 °C with stirring. The reaction was warmed to rt and left to stir overnight. The reaction was quenched with sat. aq. NH_4Cl (2 mL) and H_2O (2 mL), then EtOAc (10 mL) was added. The organic layer was collected, and the aqueous phase was extracted with EtOAc (2 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 5-10% EtOAc in cyclohexane, 25 × 150 mm silica) gave the title compound as a pale-yellow oil (497 mg, 84%); R_f: 0.23 (eluent = 10% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.16 (3H, s, C*H*$_3$), 1.89-2.01 (1H, m, CHO*H*), 4.96 (1H, s, C*H*OH), 5.14 (1H, br s, CH=C*H*H), 5.21 (1H, br s, CH=CH*H*), 7.26-7.31 (1H, m, Ar*H*), 7.32-7.41 (4H, m, 4×Ar*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 18.4 (*C*H$_3$), 76.9 (*C*HOH), 111.3 (C(CH$_3$)=*C*H$_2$), 126.8 (2×Ar*C*), 127.8 (Ar*C*), 128.5 (2×Ar*C*), 142.1 (*C*(CH$_3$)=CH$_2$), 147.0 (Ar*C*). Spectroscopic data in accordance with the literature.[32]

3-Methyl-1-phenylbut-2-en-1-ol (56)



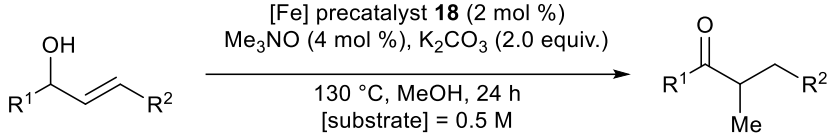
56

Under nitrogen, a flame-dried 25 mL round-bottomed flask with a stirrer bar was charged with dry THF (4 mL) and benzaldehyde (407 µL, 424 mg, 4.0 mmol, 1 equiv.) followed by the dropwise addition of (2-methylprop-1-en-1-yl)magnesium bromide (8.80 mL, 4.40 mmol, 1.10 equiv., 0.5 M in THF) at -78 °C with stirring. The reaction

was warmed to rt and left to stir overnight. The reaction was quenched with sat. aq. NH_4Cl (2 mL) and H_2O (2 mL) then EtOAc (10 mL) was added. The organic layer was collected, and the aqueous phase was extracted with EtOAc (2 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 5-10% Et_2O in pentane, 35 × 150 mm silica) gave the title compound as a pale-yellow oil (402 mg, 62%); R_f: 0.15 (eluent = 10% Et_2O in pentane); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.77 (3H, s, C*H*$_3$), 1.80 (1H, d, *J* 3.2, CHO*H*), 1.83 (3H, s, C*H*$_3$), 5.41-5.45 (1H, m, C*H*=C(CH$_3$)$_2$), 5.48 (1H, dd, *J* 8.9, 3.1, C*H*OH), 7.26-7.30 (1H, m, Ar*H*), 7.33-7.42 (4H, m, 4×Ar*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 18.5 (*C*H$_3$), 26.0 (*C*H$_3$), 70.9 (*C*HOH), 126.0 (2×Ar*C*), 127.4 (*C*H=C(CH$_3$)$_2$), 127.8 (Ar*C*), 128.6 (2×Ar*C*), 135.5 (*C*H=C(CH$_3$)$_2$), 144.4 (Ar*C*). Spectroscopic data in accordance with the literature.[33]

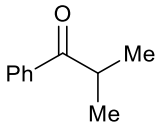
4.2.2 Reaction Scope

General Procedure 2: Isomerisation-methylation of Allylic Alcohols



An oven-dried 10 mL microwave vial equipped with a stirrer bar was charged with [Fe] precatalyst **18** (4.6 mg, 0.01 mmol, 2 mol %), K_2CO_3 (138 mg, 1.00 mmol, 2.00 equiv.), $Me_3NO.2H_2O$ (2.2 mg, 0.02 mmol, 4 mol %) and allylic alcohol (0.5 mmol, 1.00 equiv.). The vial was charged with MeOH (1 mL) before being sealed with a cap. The mixture was left to react at 130 °C for 24 h. The reaction was cooled, diluted with EtOAc (1 mL), and quenched with H_2O (1 mL), before being transferred to a separatory funnel filled with brine (25 mL). The organic layer was collected, and the aqueous phase extracted with EtOAc (2 × 10 mL). The organics were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo.

2-Methyl-1-phenylpropan-1-one (20)



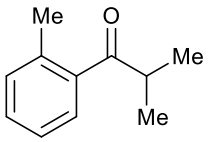
20

The title compound was prepared according to general procedure 2 using 1-phenylprop-2-en-1-ol (**19**) (67 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 20 × 150 mm silica) gave the title compound as a pale-yellow oil (56 mg, 76%); R_f: 0.56 (eluent = 10% EtOAc in hexanes); νmax / cm-1 (film) 644, 696, 789, 868, 926, 978, 1005, 1086, 1159, 1223, 1283, 1350, 1387, 1447, 1466, 1466, 1574, 1593, 1684, 2870, 2934, 2972; **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.22 (6H, d, *J* 6.8, CH(C*H*$_3$)$_2$), 3.56 (1H, hept, *J* 6.9, C*H*(CH$_3$)$_2$), 7.43-7.50 (2H, m, ArC(3,5)*H*), 7.52-7.58 (1H, m, ArC(4)*H*), 7.93-7.99 (2H, m, ArC(2,6)*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 19.3 (CH(*C*H$_3$)$_2$), 35.5 (*C*H(CH$_3$)$_2$), 128.5 (Ar*C*(3,5)), 128.7 (Ar*C*(2,6)), 132.9 (Ar*C*(4)), 136.4 (Ar*C*(1)), 204.7 (*C*=O); HRMS (**EI$^+$**) calculated for $[C_{11}H_{14}O]^+$ $(M)^+$: m/z 148.0888, found 148.0890, (1.4 ppm).

10 mmol Scale

An ACE pressure tube rated at 150 PSI was charged with K_2CO_3 (2.76 g, 20.0 mmol), $Me_3NO.2H_2O$ (45 mg, 0.4 mmol) and [Fe] precatalyst **18** (91 mg, 0.2 mmol). The vessel was charged with MeOH (20 mL) and 1-phenylprop-2-en-1-ol (**19**) (1.34 g, 10.0 mmol). It was sealed with the appropriate screw top cap, placed in an oil bath behind a blast shield, and the mixture was left to react at 130 °C for 24 hours. It was then cooled and charged with sat aq. NH_4Cl (10 mL), EtOAc (50 mL) and H_2O (20 mL). The mixture was transferred to a separatory funnel filled with brine (50 mL). The organic layer was collected, and the aqueous phase extracted with EtOAc (2 × 50 mL). The organics were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 20 × 150 mm silica) gave a colourless oil (1.15 g, 78%). Spectroscopic data in accordance with that reported previously.

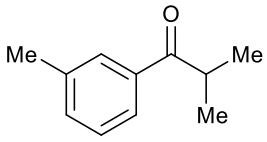
2-Methyl-1-(*o*-tolyl)propan-1-one (29)



29

The title compound was prepared according to general procedure 2 using 1-(*o*-tolyl)prop-2-en-1-ol (74 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 3% Et_2O in hexanes, 25 × 150 mm silica) gave the title compound as a pale-yellow oil (16 mg, 20%); R_f: 0.29 (eluent = 3% Et_2O in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.17 (6H, d, *J* 6.9, CH(CH_3)$_2$), 2.42 (3H, s, PhCH_3), 3.34 (1H, hept, *J* 6.9, C*H*(CH_3)$_2$), 7.20-7.27 (2H, m, 2×Ar*H*), 7.31-7.37 (1H, m, Ar*H*), 7.48-7.53 (1H, m, Ar*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 18.7 (CH(*C*H$_3$)$_2$), 20.9 (Ph*C*H$_3$), 38.9 (*C*H(CH$_3$)$_2$), 128.7 (Ar*C*), 127.5 (Ar*C*), 130.7 (Ar*C*), 131.7 (Ar*C*), 137.6 (Ar*C*), 138.8 (Ar*C*), 209.4 (*C*=O). Spectroscopic data in accordance with the literature.[34]

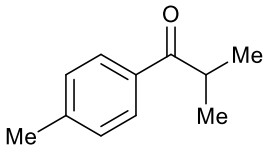
2-Methyl-1-(*m*-tolyl)propan-1-one (30)



30

The title compound was prepared according to general procedure 2 using 1-(*m*-tolyl)prop-2-en-1-ol (74 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 3% Et_2O in hexanes, 25 × 150 mm silica) gave the title compound as a pale-yellow oil (53 mg, 65%); R_f: 0.21 (eluent = 3% Et_2O in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.21 (6H, d, *J* 6.8, CH(CH_3)$_2$), 2.42 (3H, s, PhCH_3), 3.56 (1H, hept, *J* 6.9, C*H*(CH$_3$)$_2$), 7.31-7.39 (2H, m, 2×Ar*H*), 7.71-7.79 (2H, m, 2×Ar*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 19.3 (CH(*C*H$_3$)$_2$), 21.5 (Ph*C*H$_3$), 35.5 (*C*H(CH$_3$)$_2$), 125.6 (Ar*C*), 128.6 (Ar*C*), 129.0 (Ar*C*), 133.7 (Ar*C*), 136.4 (Ar*C*), 138.5 (Ar*C*), 204.9 (*C*=O). Spectroscopic data in accordance with the literature.[35]

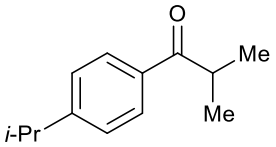
2-Methyl-1-(*p*-tolyl)propan-1-one (31)



31

The title compound was prepared according to general procedure 2 using 1-(*p*-tolyl)prop-2-en-1-ol (74 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 3% Et_2O in pentane, 25 × 150 mm silica) gave the title compound as a pale-yellow oil (58 mg, 71%); R_f: 0.12 (eluent = 5% Et_2O in pentane); ν_{max} / cm^{-1} (film) 476, 592, 748, 822, 980, 1159, 1209, 1229, 1283, 1381, 1408, 1472, 1566, 1605, 1680, 2864, 2928, 2972; **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.20 (6H, d, *J* 6.8, CH(C*H*$_3$)$_2$), 2.40 (3H, s, PhC*H*$_3$), 3.53 (1H, hept, *J* 6.7, C*H*(CH$_3$)$_2$), 7.25 (2H, d, *J* 7.9, ArC(3,5)*H*), 7.85 (2H, d, *J* 8.0, ArC(2,6)*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 19.4 (CH(*C*H$_3$)$_2$), 21.7 (Ph*C*H$_3$), 35.4 (*C*H(CH$_3$)$_2$), 128.6 (2×ArC), 129.4 (2×Ar*C*), 133.8 (Ar*C*), 143.7 (Ar*C*), 204.3 (*C*=O); HRMS (**EI**$^+$) calculated for $[C_{11}H_{14}O]^+$ $(M)^+$: m/z 162.1045, found 162.1043, (-1.2 ppm).

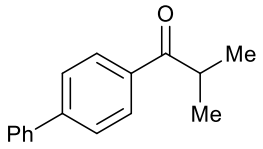
1-(4-Isopropylphenyl)-2-methylpropan-1-one (32)



32

The title compound was prepared according to general procedure 2 using 1-(4-isopropylphenyl)prop-2-en-1-ol (88 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 2% Et_2O in hexanes, 35 × 150 mm silica) gave the title compound as a pale-yellow oil (66 mg, 70%); R_f: 0.36 (3% Et_2O in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.21 (6H, d, *J* 6.8, COCH(C*H*$_3$)$_2$), 1.27 (6H, d, *J* 6.9, PhCH(C*H*$_3$)$_2$), 2.97 (1H, hept, *J* 6.9, PhC*H*(CH$_3$)$_2$), 3.55 (1H, hept, *J* 6.8, COC*H*(CH$_3$)$_2$), 7.29-7.33 (2H, m, ArC(3,5)*H*), 7.88-7.92 (2H, m, ArC(2,6)*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 19.4 (COCH(*C*H$_3$)$_2$), 23.8 (PhCH(*C*H$_3$)$_2$), 34.4 (Ph*C*H(CH$_3$)$_2$), 35.4 (CO*C*H(CH$_3$)$_2$), 126.8 (2×Ar*C*), 128.7 (2×Ar*C*), 134.2 (Ar*C*), 154.4 (Ar*C*), 204.3 (*C*=O). Spectroscopic data in accordance with the literature.[35]

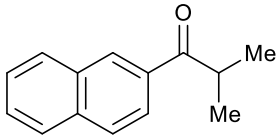
1-([1,1'-Biphenyl]-4-yl)-2-methylpropan-1-one (33)



33

The title compound was prepared according to general procedure 2 using 1-([1,1'-biphenyl]-4-yl)prop-2-en-1-ol (105 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 1-2% Et_2O in pentane, 25 × 150 mm silica) gave the title compound as a yellow crystalline solid (86 mg, 77%); mp 57-60 °C; R_f: 0.27 (eluent = 3% Et_2O in pentane); ν_{max} / cm^{-1} (film) 692, 741, 853, 980, 1159, 1209, 1231, 1344, 1383, 1404, 1462, 1599, 1670, 2872, 2931, 2972; **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.25 (6H, d, *J* 6.8, CH(CH_3)$_2$), 3.60 (1H, hept, *J* 6.8, C*H*(CH_3)$_2$), 7.37-7.43 (1H, m, Ar'*H*), 7.44-7.51 (2H, m, 2×Ar'*H*), 7.63 (2H, d, *J* 7.0, 2×Ar'*H*), 7.69 (2H, d, *J* 8.0, 2×Ar*H*), 8.04 (2H, d, *J* 8.0, 2×Ar*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 19.4 (CH(*C*H_3)$_2$), 35.6 (*C*H(CH_3)$_2$), 127.4 (2×Ar*C*), 127.4 (2×Ar*C*), 128.3 (Ar*C*), 129.1 (2×Ar*C*), 129.1 (2×Ar*C*), 135.0 (Ar*C*), 140.1 (Ar*C*), 145.6 (Ar*C*), 204.2 (*C*=O); HRMS (**EI**$^+$) calculated for $[C_{16}H_{16}O]^+$ $(M)^+$: m/z 224.1201, found 224.1203, (0.9 ppm).

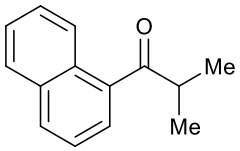
2-Methyl-1-(naphthalen-2-yl)propan-1-one (34)



34

The title compound was prepared according to general procedure 2 using 1-(naphthalen-2-yl)prop-2-en-1-ol (92.1 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 3% Et_2O in hexanes, 25 × 150 mm silica) gave the title compound as a pale-yellow oil (62 mg, 78%); R_f: 0.21 (eluent = 3% Et_2O in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.29 (6H, d, *J* 6.8, CH(CH_3)$_2$), 3.74 (1H, hept, *J* 6.9, C*H*(CH_3)$_2$), 7.52-7.63 (2H, m, 2×Ar*H*), 7.88 (1H, d, *J* 8.1, Ar*H*), 7.91 (1H, d, *J* 8.6, Ar*H*), 7.97 (1H, d, *J* 8.1, Ar*H*), 8.03 (1H, dd, *J* 8.6, 1.7, Ar*H*), 8.48 (1H, s, Ar*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 19.5 (CH(*C*H_3)$_2$), 35.6 (*C*H(CH_3)$_2$), 124.5 (Ar*C*), 126.8 (Ar*C*), 127.9 (Ar*C*), 128.5 (Ar*C*), 128.6 (Ar*C*), 129.7 (Ar*C*), 129.8 (Ar*C*), 132.8 (Ar*C*), 133.7 (Ar*C*), 135.6 (Ar*C*), 204.6 (*C*=O). Spectroscopic data in accordance with the literature.[36]

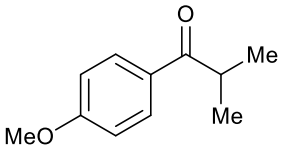
2-Methyl-1-(naphthalen-1-yl)propan-1-one (35)



35

The title compound was prepared according to general procedure 2 using 1-(naphthalen-1-yl)prop-2-en-1-ol (92 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 3% Et_2O in hexanes, 25 × 150 mm silica) gave the title compound as a yellow oil (68 mg, 69%); R_f: 0.21 (eluent = 3% Et_2O in hexanes); ν_{max} / cm^{-1} (film) 447, 507, 565, 629, 773, 797, 943, 1059, 1084, 1159, 1182, 2133, 1339, 1381, 1464, 1508, 1566, 1593, 1680, 2870, 2930, 2968, 3051; **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.25 (6H, d, *J* 6.9, (CH(C*H*$_3$)$_2$), 3.52 (1H, hept, *J* 6.9, (C*H*(CH$_3$)$_2$)), 7.47-7.51 (1H, m, Ar*H*), 7.51-7.59 (2H, m, 2×Ar*H*), 7.74 (1H, dd, *J* 7.2, 1.2, Ar*H*), 7.85-7.90 (1H, m, Ar*H*), 7.94-7.98 (1H, m, Ar*H*), 8.27-8.32 (1H, m, Ar*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 18.9 (CH(*C*H$_3$)$_2$), 39.8 (*C*H(CH$_3$)$_2$), 124.5 (Ar*C*), 125.8 (Ar*C*), 126.0 (Ar*C*), 126.5 (Ar*C*), 127.7 (Ar*C*), 128.5 (Ar*C*), 130.6 (Ar*C*), 131.8 (Ar*C*), 134.1 (Ar*C*), 137.1 (Ar*C*), 209.2 (C=O); HRMS (**EI$^+$**) calculated for $[C_{14}H_{14}O]^+$ $(M)^+$: m/z 198.1045, found 198.1049, (2.0 ppm).

1-(4-Methoxyphenyl)-2-methylpropan-1-one (36)



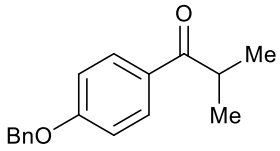
36

The title compound was prepared according to general procedure 2 using 1-(4-methoxyphenyl)prop-2-en-1-ol (82 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 5% Et_2O in hexanes, 25 × 150 mm silica) gave the title compound as a pale-yellow oil (89.1 mg, 56%); R_f: 0.24 (5% Et_2O in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.21 (6H, d, *J* 6.8, CH(C*H*$_3$)$_2$), 3.52 (1H, hept, *J* 6.8, C*H*(CH$_3$)$_2$), 3.87 (3H, s, OC*H*$_3$), 6.94 (2H, d, *J* 8.8, ArC(3,5)*H*), 7.95 (2H, d, *J* 8.9, ArC(2,6)*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 19.5 (CH(*C*H$_3$)$_2$), 35.1 (*C*H(CH$_3$)$_2$), 55.6

(O*C*H$_3$), 113.9 (Ar*C*), 129.3 (2×Ar*C*), 130.7 (2×Ar*C*), 163.4 (ArC), 203.2 (*C*=O)). Spectroscopic data in accordance with the literature.[37]

The title compound was also prepared according to general procedure 2 using **1-(4-Fluorophenyl)prop-2-en-1-ol (58)** (76 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes) gave the title compound as a pale-yellow oil (27 mg, 44%).

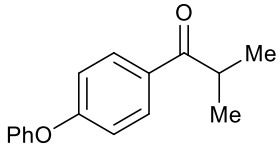
1-(4-(Benzyloxy)phenyl)-2-methylpropan-1-one (37)



37

The title compound was prepared according to general procedure 2 using 1-(4-(benzyloxy)phenyl)prop-2-en-1-ol (120 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 3% Et$_2$O in hexanes, 25 × 150 mm silica) gave the title compound as an off-white solid (76 mg, 63%); mp 50-53 °C; R_f: 0.07 (eluent = 3% Et$_2$O in hexanes); ν_{max} / cm^{-1} (film) 515, 638, 698, 754, 844, 934, 972, 1001, 1117, 1157, 1180, 1226, 1250, 1312, 1348, 1377, 1418, 1454, 1464, 1504, 570, 1597, 1664, 2872, 2938, 2978, 3061; **^{1}H NMR (CDCl$_3$, 500 MHz)** δ_H: 1.21 (6H, d, *J* 6.8, CH(C*H*$_3$)$_2$), 3.52 (1H, hept, *J* 6.7, C*H*(CH$_3$)$_2$), 5.14 (2H, s, PhC*H*$_2$), 7.02 (2H, d, *J* 8.3, ArC(3,5)*H*), 7.31-7.46 (5H, m, 2×Ar'*H*), 7.95 (2H, d, *J* 8.4, ArC(2,6)*H*); **^{13}C NMR (CDCl$_3$, 126 MHz)** δ_C: 19.5 (CH(*C*H$_3$)$_2$), 35.1 (*C*H(CH$_3$)$_2$), 70.3 (Ph*C*H$_2$), 114.7 (2×Ar*C*), 127.6 (2×Ar*C*), 128.4 (Ar*C*), 128.8 (2×Ar*C*), 129.5 (Ar*C*), 130.7 (2×Ar*C*), 136.4 (Ar*C*), 162.6 (ArC), 203.2 (*C*=O); HRMS (**EI$^+$**) calculated for [C$_{17}$H$_{18}$O$_2$]$^+$ (M)$^+$: m/z 254.1307, found 254.1301, (-2.4 ppm).

2-Methyl-1-(4-phenoxyphenyl)propan-1-one (38)

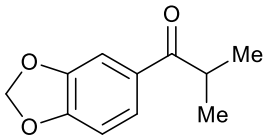


38

The title compound was prepared according to general procedure 2 using 1-(4-phenoxyphenyl)prop-2-en-1-ol (113 mg, 0.5 mmol). Purification by flash silica

chromatography (eluent = 1% Et_2O in pentane, 25 × 150 mm silica) gave the title compound as a pale-yellow oil (90 mg, 75%); R_f: 0.26 (3% Et_2O in pentane); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.21 (6H, d, *J* 6.8, CH(C*H*$_3$)$_2$), 3.52 (1H, hept, *J* 7.0, C*H*(CH$_3$)$_2$), 6.98-7.03 (2H, m, 2×Ar*H*), 7.05-7.10 (2H, m, 2×Ar*H*), 7.17-7.22 (1H, m, ArC(4')*H*), 7.37-7.42 (2H, m, 2×Ar*H*), 7.93-7.97 (2H, m, ArC(2,6)*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 19.4 (CH(*C*H$_3$)$_2$), 35.3 (*C*H(CH$_3$)$_2$), 117.5 (2×Ar*C*), 120.3 (2×Ar*C*), 124.7 (Ar*C*), 130.2 (2×Ar*C*), 130.7 (2×Ar*C*), 130.9 (Ar*C*), 155.7 (Ar*C*), 161.9 (Ar*C*), 203.2 (*C*=O). Spectroscopic data in accordance with the literature.[38]

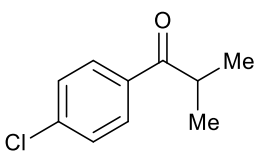
1-(Benzo[d][1,3]dioxol-5-yl)-2-methylpropan-1-one (39)



39

The title compound was prepared according to general procedure 2 using 1-(benzo[d][1,3]dioxol-5-yl)prop-2-en-1-ol (89 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 1-3% Et_2O in pentane, 25 × 150 mm silica) gave the title compound as a pale-yellow oil (54 mg, 56%); R_f: 0.18 (3% Et_2O in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.20 (6H, d, *J* 6.8, CH(C*H*$_3$)$_2$), 3.46 (1H, hept, *J* 6.8, C*H*(CH$_3$)$_2$), 6.04 (2H, s, CH$_2$), 6.85 (1H, d, *J* 8.2, ArC(5)*H*), 7.44 (1H, d, *J* 1.8, ArC(2)*H*), 7.56 (1H, dd, *J* 8.2, 1.7, ArC(6)*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 19.5 (CH(*C*H$_3$)$_2$), 35.2 (*C*H(CH$_3$)$_2$), 101.9 (*C*H$_2$), 108.0 (Ar*C*), 108.4 (Ar*C*), 124.5 (Ar*C*), 131.1 (Ar*C*), 148.4 (Ar*C*), 151.6 (Ar*C*), 202.7 (C=O). Spectroscopic data in accordance with the literature.[38]

1-(4-Chlorophenyl)-2-methylpropan-1-one (40)

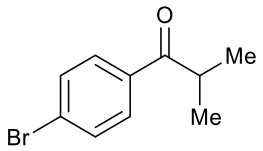


40

The title compound was prepared according to general procedure 2 using 1-(4-chlorophenyl)prop-2-en-1-ol (84 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 0.5-2% Et_2O in hexanes, 25 × 150 mm silica) gave the title

compound as a pale-yellow oil (44 mg, 48%); R_f: 0.21 (3% Et_2O in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.21 (6H, d, *J* 6.8, CH(CH_3)$_2$), 3.50 (1H, hept, *J* 6.8, C*H*(CH$_3$)$_2$), 7.41-7.46 (2H, m, 2×Ar*H*), 7.87-7.92 (2H, m, 2×Ar*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 19.2 (CH(*C*H$_3$)$_2$), 35.6 (*C*H(CH$_3$)$_2$), 129.1 (2×Ar*C*), 129. 9 (2×Ar*C*), 134.6 (Ar*C*), 139.3 (Ar*C*), 203.4 (*C*=O). Spectroscopic data in accordance with the literature.[39]

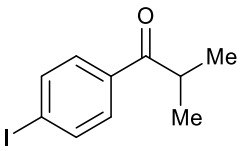
1-(4-Bromophenyl)-2-methylpropan-1-one (41)



41

The title compound was prepared according to general procedure 2 using 1-(4-bromophenyl)prop-2-en-1-ol (107 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 1-2% Et_2O in hexanes, 25 × 180 mm silica) gave the title compound as an orange oil (47 mg, 41%); R_f: 0.15 (3% Et_2O in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.21 (6H, d, *J* 6.8, CH(CH_3)$_2$), 3.49 (1H, hept, *J* 6.8, C*H*(CH$_3$)$_2$), 7.61 (2H, d, *J* 8.4, 2×Ar*H*), 7.82 (2H, d, *J* 8.5, 2×Ar*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 19.2 (CH(*C*H$_3$)$_2$), 35.6 (*C*H(CH$_3$)$_2$), 128.0 (Ar*C*), 130.0 (2×Ar*C*), 132.0 (2×Ar*C*), 135.0 (Ar*C*), 203.5 (*C*=O). Spectroscopic data in accordance with the literature.[40]

1-(4-Iodophenyl)-2-methylpropan-1-one (42)

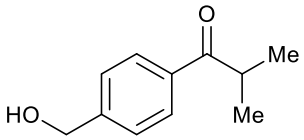


42

The title compound was prepared according to general procedure 2 using 1-(4-iodophenyl)prop-2-en-1-ol (130 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 0.5-1% Et_2O in hexanes, 25 × 200 mm silica) gave the title compound as a pale yellow liquid (39 mg, 28%); R_f: 0.60 (3% Et_2O in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.21 (6H, d, *J* 6.8, CH(CH_3)$_2$), 3.48 (1H, hept, *J* 7.5, C*H*(CH$_3$)$_2$), 7.66 (2H, d, *J* 8.2, 2×Ar*H*), 7.83 (2H, d, *J* 8.2, 2×Ar*H*); **^{13}C NMR ($CDCl_3$, 126**

MHz) δ_C: 19.1 (CH(*C*H$_3$)$_2$), 35.4 (*C*H(CH$_3$)$_2$), 100.6 (Ar*C*), 129.8 (2×Ar*C*), 135.4 (Ar*C*), 137.9 (2×Ar*C*), 203.7 (*C*=O). Spectroscopic data in accordance with the literature.[35]

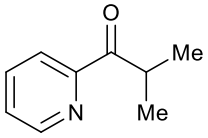
1-(4-(Hydroxymethyl)phenyl)-2-methylpropan-1-one (43)



43

The title compound was prepared according to general procedure 2 using 4-(hydroxymethyl)benzaldehyde (82 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 50% Et$_2$O in pentane, 25 × 150 mm silica) gave the title compound as a colourless oil (65 mg, 73%); R_f: 0.43 (eluent = 50% Et$_2$O in pentane); ν_{max} / cm^{-1} (film) 743, 833, 982, 1045, 1161, 1225, 1356, 1383, 1418, 1466, 1570, 1612, 1670, 2866, 2930, 2968, 3419; **^{1}H NMR (CDCl$_3$, 500 MHz)** δ_H: 1.21 (6H, d, *J* 6.8, CH(C*H*$_3$)$_2$), 1.88 (1H, br s, CH$_2$O*H*), 3.55 (1H, hept, *J* 6.8, C*H*(CH$_3$)$_2$), 4.77 (2H, d, *J* 4.7, C*H*$_2$OH), 7.46 (2H, d, *J* 8.0, 2×Ar*H*), 7.95 (2H, d, *J* 8.2, 2×Ar*H*); **^{13}C NMR (CDCl$_3$, 126 MHz)** δ_C: 19.3 (CH(*C*H$_3$)$_2$), 35.5 (*C*H(CH$_3$)$_2$), 64.8 (*C*H$_2$OH), 126.9 (2×Ar*C*), 128.8 (2×Ar*C*), 135.6 (Ar*C*), 145.9 (Ar*C*), 204.3 (*C*=O); HRMS (**EI**$^+$) calculated for [C$_{11}$H$_{14}$O$_2$]$^+$ (M)$^+$: m/z 178.0994, found 178.0989, (-2.8 ppm).

2-Methyl-1-(pyridin-2-yl)propan-1-one (44)

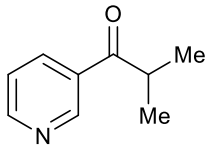


44

The title compound was prepared according to general procedure 2 using 1-(pyridin-2-yl)prop-2-en-1-ol (72 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 20% Et$_2$O in hexanes, 25 × 150 mm silica) gave the title compound as a pale pink oil (33 mg, 44%); R_f: 0.30 (eluent = 20% Et$_2$O in hexanes); **^{1}H NMR (CDCl$_3$, 500 MHz)** δ_H: 1.21 (6H, d, *J* 6.9, CH(C*H*$_3$)$_2$), 4.11 (1H, hept, *J* 6.9, C*H*(CH$_3$)$_2$), 7.45 (1H, ddd, *J* 7.6, 4.8, 1.3, ArC(6)*H*), 7.83 (1H, app td, *J* 7.7, 1.8, Ar*H*), 8.04 (1H, app td, *J* 7.9, 1.1, Ar*H*), 8.68 (1H, ddd, *J* 4.7, 1.7, 0.9, ArC(3)*H*); **^{13}C NMR (CDCl$_3$, 126 MHz)** δ_C: 18.8

(CH(*C*H$_3$)$_2$), 34.4 (*C*H(CH$_3$)$_2$), 122.6 (Ar*C*), 127.0 (Ar*C*), 137.0 (Ar*C*), 149.0 (Ar*C*), 153.0 (Ar*C*), 205.9 (*C*=O). Spectroscopic data in accordance with the literature.[41]

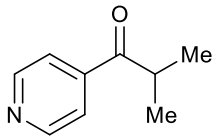
2-Methyl-1-(pyridin-3-yl)propan-1-one (45)



45

The title compound was prepared according to general procedure 2 using 1-(pyridin-3-yl)prop-2-en-1-ol (72 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 50% Et$_2$O in hexanes, 25 × 150 mm silica) gave the title compound as a dark orange oil (35 mg, 47%); R$_f$: 0.29 (eluent = 50% Et$_2$O in hexanes); **^{1}H NMR (CDCl$_3$, 500 MHz)** δ_H: 1.24 (6H, d, *J* 6.8, CH(C*H*$_3$)$_2$), 3.52 (1H, hept, *J* 7.0, C*H*(CH$_3$)$_2$), 7.40-7.45 (1H, m, Ar*H*), 8.20-8.25 (1H, m, Ar*H*), 8.75-8.79 (1H, m, Ar*H*), 9.15-9.18 (1H, m, Ar(2)*H*); **^{13}C NMR (CDCl$_3$, 126 MHz)** δ_C: 19.0 (CH(*C*H$_3$)$_2$), 36.1 (*C*H(CH$_3$)$_2$), 123.8 (Ar*C*), 131.5 (Ar*C*), 135.9 (Ar*C*), 149.9 (Ar*C*), 153.4 (Ar*C*), 203.3 (*C*=O). Spectroscopic data in accordance with the literature.[41]

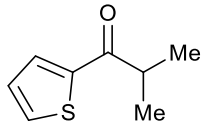
2-Methyl-1-(pyridin-4-yl)propan-1-one (46)



46

The title compound was prepared according to general procedure 2 using 1-(pyridin-4-yl)prop-2-en-1-ol (72 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 100% Et$_2$O, 25 × 150 mm silica) gave the title compound as an orange oil (14 mg, 19%); R$_f$: 0.41 (eluent = 100% Et$_2$O); **^{1}H NMR (CDCl$_3$, 500 MHz)** δ_H: 1.22 (6H, d, *J* 6.9, CH(C*H*$_3$)$_2$), 3.48 (1H, hept, *J* 6.9, C*H*(CH$_3$)$_2$), 7.69-7.75 (2H, m, Ar*H*), 8.76-8.86 (2H, m, Ar*H*); **^{13}C NMR (CDCl$_3$, 126 MHz)** δ_C: 18.8 (CH(*C*H$_3$)$_2$), 36.1 (*C*H(CH$_3$)$_2$), 121.5 (2×Ar*C*), 142.5 (Ar*C*(1)), 151.0 (2×Ar*C*), 203.9 (*C*=O). Spectroscopic data in accordance with the literature.[42]

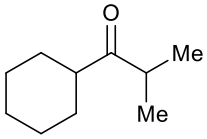
2-Methyl-1-(thiophen-2-yl)propan-1-one (47)



47

The title compound was prepared according to general procedure 2 using 1-(thiophen-2-yl)prop-2-en-1-ol (70 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 0.5-1% Et_2O in hexanes, 25 × 150 mm silica) gave the title compound as a yellow oil (24 mg, 32%); R_f: 0.17 (eluent = 3% Et_2O in hexanes); ν_{max} / cm^{-1} (film) 718, 833, 935, 968, 1055, 1088, 1165, 1223, 1234, 1356, 1383, 1413, 1466, 1518, 1655, 1874, 2932, 2970; **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.25 (6H, d, *J* 6.9, CH(C*H*$_3$)$_2$), 3.39 (1H, hept, *J* 6.8, C*H*(CH$_3$)$_2$), 7.13 (1H, dd, *J* 5.0, 3.8, Ar*H*), 7.63 (1H, dd, *J* 5.0, 1.1, Ar*H*), 7.73 (1H, dd, *J* 3.8, 1.1, Ar*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 19.6 (CH(*C*H$_3$)$_2$), 37.4 (*C*H(CH$_3$)$_2$), 128.2 (Ar*C*), 131.7 (Ar*C*), 133.5 (Ar*C*), 143.8 (Ar*C*), 197.6 (*C*=O); HRMS (**EI$^+$**) calculated for $[C_8H_{10}OS]^+$ $(M)^+$: m/z 154.0452, found 154.0454, (1.3 ppm).

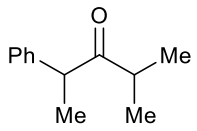
1-Cyclohexyl-2-methylpropan-1-one (48)



48

The title compound was prepared according to general procedure 1 using 1-cyclohexylprop-2-en-1-ol (70 mg, 0.5 mmol) giving a 64% NMR yield. Purification by flash silica chromatography (eluent = 2% EtOAc in hexanes) gave the title compound as a colourless oil (6 mg, 8%); R_f = 0.60 (eluent = 20% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.06 (6H, d, *J* 7.0, CH(C*H*$_3$)$_2$), 1.15-1.40 (9H, m, 9×Cy*H*), 1.63-1.71 (1H, m, Cy*H*), 2.46-2.55 (1H, m, (CH$_2$)$_2$C*H*(C=O)), 2.75 (1H, hept, 7.0, C*H*(CH$_3$)$_2$); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 18.6 (CH(*C*H$_3$)$_2$), 25.9 (2×*C*H$_2$), 26.0 (*C*H$_2$), 28.8 (2×*C*H$_2$), 39.1 (*C*H(CH$_3$)$_2$), 49.2 (*C*H(CH$_2$)$_2$), 218.0 (*C*=O). Spectroscopic data in accordance with that stated in the literature.[43]

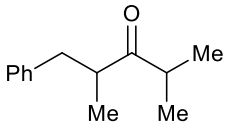
2-Methyl-4-phenylpentan-3-one (49)



49

The title compound was prepared according to general procedure 2 using 1-phenylbut-3-en-2-ol (105 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 1% EtOAc in hexanes, 25 × 150 mm silica) gave the title compound as a pale-yellow oil (67 mg, 76%); R_f: 0.36 (5% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 509, 694, 719, 752, 794, 1015, 1059, 1092, 1125, 1379, 1449, 1466, 1487, 1601, 1707, 2870, 2930, 2968, 3028; **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 0.91 (3H, d, *J* 6.7, CH(C*H*$_3$)(CH$_3$)), 1.07 (3H, d, *J* 7.0, CH(CH$_3$)(C*H*$_3$)), 1.38 (3H, d, *J* 6.9, PhCHC*H*$_3$), 2.68 (1H, app hept, *J* 6.9, C*H*(CH$_3$)$_2$), 3.92 (1H, q, *J* 6.9, PhC*H*CH$_3$), 7.20-7.26 (3H, m, 3×Ar*H*), 7.29-7.34 (2H, m, 2×Ar*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 18.3 (*C*H$_3$), 18.4 (*C*H$_3$), 19.4 (*C*H$_3$), 39.3 (*C*H(CH$_3$)$_2$), 51.3 (Ph*C*HCH$_3$), 127.2 (Ar*C*), 128.1 (2×Ar*C*), 129.0 (2×Ar*C*), 140.9 (Ar*C*), 214.8 (*C*=O); HRMS (**EI**$^+$) calculated for $[C_{12}H_{17}O]^+$ $(M)^+$: m/z 177.1279, found 177.1280, (0.6 ppm).

2,4-Dimethyl-1-phenylpentan-3-one (50)



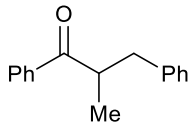
50

The title compound was prepared according to general procedure 2 using 5-phenylpent-1-en-3-ol (81 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 0.5-1% EtOAc in hexanes) gave the title compound as a pale yellow oil (73 mg, 77%); R_f = 0.31 (eluent = 5% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 700, 745, 1013, 1379, 1456, 1491, 1711, 2874, 2934, 2972, 3024; **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 0.88 (3H, d, *J* 7.0, CH(C*H*$_3$)(CH$_3$)), 1.01 (3H, d, *J* 7.0, CH(CH$_3$)(C*H*$_3$)), 1.08 (3H, d, *J* 6.5, CHC*H*$_3$), 2.46-2.62 (2H, m, C*H*CH$_3$ and C*H*(CH$_3$)$_2$), 2.91-3.05 (2H, m, PhC*H*$_2$), 7.11-7.15 (2H, m, ArC(2,6)*H*), 7.16-7.20 (1H, m, ArC(4)*H*), 7.23-7.29 (2H, m, ArC(3,5)*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 17.3 (CH(CH$_3$)(*C*H$_3$)), 17.9 (CH(*C*H$_3$)(CH$_3$)), 18.1 (CH*C*H$_3$), 39.7 (Ph*C*H$_2$), 40.5 (*C*H(CH$_3$)$_2$), 46.7 (*C*HCH$_3$), 126.3 (Ar*C*), 128.5 (2×Ar*C*), 129.1

(2×Ar*C*), 140.1 (Ar*C*), 217.8 (*C*=O); HRMS (**AP**$^+$) calculated for $[C_{13}H_{17}]^+$ ((M-H_2O)+H)$^+$: m/z 173.1330, found 173.1331, (0.6 ppm).

The title compound was also prepared according to general procedure 2 using **(*E*)-4-phenylbut-3-en-2-ol (53)** (74 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 0.5-1% EtOAc in hexanes) gave the title compound as a pale yellow oil (27 mg, 28%).

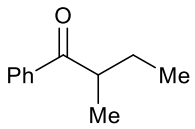
2-Methyl-1,3-diphenylpropan-1-one (51)



51

The title compound was prepared according to general procedure 2 using (*E*)-chalcone (105 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 3% Et_2O in pentane, 25 × 100 mm silica) gave the title compound as a pale-yellow oil (94 mg, 84%); R_f: 0.30 (3% Et_2O in pentane); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.21 (3H, d, *J* 6.9, CHC*H*$_3$), 2.70 (1H, dd, *J* 13.7, 7.9, C*H*H), 3.18 (1H, dd, *J* 13.7, 6.3, CH*H*), 3.76 (1H, dqd *J* 7.9, 6.9, 6.5, C*H*CH$_3$), 7.16-7.23 (3H, m, 3×Ar'*H*), 7.25-7.30 (2H, m, 2×Ar'*H*), 7.42-7.48 (2H, m, ArC(3,5)*H*), 7.52-7.57 (1H, m, ArC(4)*H*), 7.85-8.05 (2H, m, ArC(2,6)*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 17.5 (CH*C*H$_3$), 39.5 (*C*H$_2$), 42.9 (*C*HCH$_3$), 126.3 (Ar*C*(4')), 128.4 (2×Ar*C*), 128.5 (2×Ar*C*), 128.8 (2×Ar*C*), 129.2 (2×ArC), 133.1 (Ar*C*(4)), 136.6 (Ar*C*), 140.1 (Ar*C*), 203.9 (*C*=O). Spectroscopic data in accordance with the literature.[44]

2-Methyl-1-phenylbutan-1-one (53)

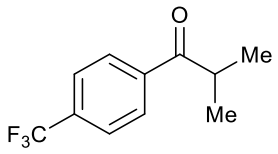


53

The title compound was prepared according to general procedure 2 using 1-phenylbut-2-en-1-ol (**52**) (68 µL, 68 mg, 0.5 mmol). The crude ^{1}H NMR showed 13% conversion to **53**. Purification by flash silica chromatography (eluent = 1-2% Et_2O in pentane, 25 × 150 mm silica) gave the title compound as a pale-yellow oil (4.9 mg,

6%); R_f: 0.25 (3% Et_2O in pentane); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 0.92 (3H, t, *J* 7.4, CH_2CH_3), 1.20 (3H, d, *J* 6.9, $CHCH_3$), 1.44-1.55 (1H, m, C*H*H), 1.79-1.89 (1H, m, CH*H*), 3.40 (1H, app sext, *J* 6.8, C*H*CH_3), 7.44-7.49 (2H, m, ArC(3,5)*H*), 7.53-7.58 (1H, m, ArC(4)*H*), 7.93-7.98 (2H, m, ArC(2,6)*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 11.9 (CH_2CH_3), 16.9 ($CHCH_3$), 26.8 (CH_2CH_3), 42.3 ($CHCH_3$), 128.4 (2×Ar*C*), 128.7 (2×Ar*C*), 132.9 (Ar*C*), 137.0 (Ar*C*), 204.6 (*C*=O). Spectroscopic data in accordance with the literature.[34]

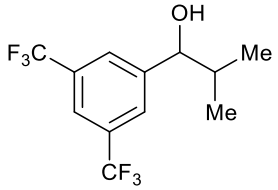
1-(4-(Trifluoromethyl)phenyl)-2-methylpropan-1-one (59)



59

The title compound was prepared according to general procedure 2 using 1-(4-trifluromethylphenyl)prop-2-en-1-ol (82 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 3% Et_2O in hexanes, 25 × 120 mm silica) gave the title compound as a pale-yellow oil (59 mg, 54%); R_f: 0.30 (eluent = 5% Et_2O in hexanes); ν_{max} / cm^{-1} (film) 590, 691, 721, 764, 849, 978, 1063, 1126, 1165, 1221, 1317, 1412, 1468, 1512, 1578, 1690, 2874, 2934, 2974; **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.23 (6H, d, *J* 6.8, $CH(CH_3)_2$), 3.54 (1H, hept, *J* 6.7, C*H*$(CH_3)_2$), 7.73 (2H, d, *J* 8.2, 2×Ar*H*), 8.05 (2H, d, *J* 8.1, 2×Ar*H*); **^{19}F NMR ($CDCl_3$, 471 MHz)** δ_F: -63.1; **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 19.0 ($CH(CH_3)_2$), 36.0 ($CH(CH_3)_2$), 123.8 (q, *J* 273, CF_3), 125.8 (q, *J* 3.7, Ar*C*(3,5)), 128.7 Ar*C*(2,6), 134.2 (q, *J* 32.8, Ar*C*(4)), 139.1 (Ar*C*(1)), 203.6 (*C*=O); HRMS (**EI**$^+$) calculated for $[C_{11}H_{11}OF_3]^+$ $(M)^+$: m/z 216.0762, found 216.0762, (0.0 ppm).

1-(3,5-Bis(trifluoromethyl)phenyl)-2-methylpropan-1-ol (60)

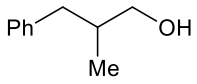


60

The title compound was prepared according to general procedure 2 using 1-(3,5-bis(trifluoromethyl)phenyl)prop-2-en-1-ol (135 mg, 0.5 mmol). Purification by flash

silica chromatography (eluent = 5-10% Et_2O in pentane, 25 × 150 mm silica) gave the title compound as a off-white solid (70 mg, 49%); mp 43-47 °C; R_f: 0.21 (eluent = 10% Et_2O in pentane); ν_{max} / cm^{-1} (film) 665, 679, 708, 827, 845, 901, 961, 1034, 1103, 1119, 1161, 1275, 1329, 1375, 1393, 1468, 2891, 2984, 3314, 3385; **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 0.92 (6H, dd, *J* 28.4, 6.8, CH(C*H*$_3$)$_2$), 1.93-2.04 (2H, m, CHO*H* and C*H*(CH$_3$)$_2$), 4.59 (1H, dd, *J* 5.9, 3.5, C*H*OH), 7.77-7.81 (3H, m, 3×Ar*H*); **^{19}F NMR ($CDCl_3$, 471 MHz)** δ_F: -62.8; **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 17.3 (CH(*C*H$_3$)(CH$_3$)), 19.0 (CH(CH$_3$)(*C*H$_3$)), 35.5 (*C*H(CH$_3$)$_2$), 78.5 (*C*HOH), 121.2-121.6 (m, Ar*C*(4)), 123.5 (q, *J* 273, 2×*C*F$_3$), 126.8 (Ar*C*(2,6)), 131.5 (q, *J* 33.3, Ar*C*(3,5)), 146.2 (Ar*C*(1)); HRMS (**EI$^+$**) calculated for $[C_{12}H_{12}OF_6]^+$ $(M)^+$: m/z 286.0792, found 286.0788, (-1.4 ppm).

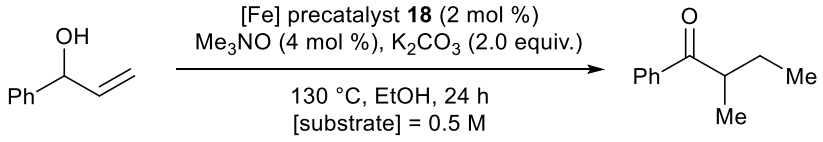
2-Methyl-3-phenylpropan-1-ol (61)



61

The title compound was prepared according to general procedure 2 using 3-phenyl-1-propanol (68 µL, 68 mg, 0.5 mmol). The crude ^{1}H NMR showed 25% conversion to **61**. Purification by flash silica chromatography (eluent = 1-2% Et_2O in pentane, 25 × 150 mm silica) gave the title compound as a pale-yellow oil (16 mg, 21%); R_f: 0.25 (3% Et_2O in pentane); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 0.93 (3H, d, *J* 6.8, C*H*$_3$), 1.39 (1H, br s, O*H*), 1.90-2.01 (1H, m, C*H*), 2.43 (1H, dd, *J* 13.5, 8.1, PhC*H*H), 2.76 (1H, dd, *J* 13.5, 6.3, PhCH*H*), 3.45-3.58 (2H, m, C*H*$_2$OH), 7.15-7.23 (2H, m, 2xAr*H*), 7.26-7.32 (2H, m, 2xAr*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 16.6 (*C*H$_3$), 37.9 (*C*H), 39.8 (Ph*C*H$_2$), 67.8 (*C*H$_2$OH), 126.0 (Ar*C*(4)), 128.4 (2xAr*C*), 129.3 (2xAr*C*), 140.8 (Ar*C*(1)). Spectroscopic data in accordance with the literature.[45]

2-Methyl-1-phenylbutan-1-one (70)



19 **70**

A 10 mL microwave vial equipped with a stirrer bar was charged with K_2CO_3 (138 mg, 1 mmol), 1-phenylprop-2-en-1-ol (67 mg, 0.5 mmol), $Me_3NO.2H_2O$ (2.2 mg, 0.02

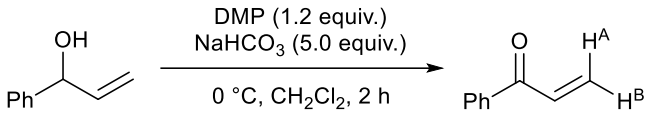
mmol, 4 mol %) and [Fe] precatalyst **2** (4.6 mg, 0.01 mmol, 2 mol %). The vial was charged with EtOH (1 mL) before being sealed with a cap. The mixture was left to react at 130 °C for 24 h. The reaction cooled, treated with mesitylene (70 μL, 60 mg, 0.5 mmol) was diluted with EtOAc (1 mL) and quenched with H_2O (1 mL). The organic layer was sampled and analysed using ^1H NMR giving a 46% yield of the respective product as compared with the data reported in the literature.[45]

4.2.3 Mechanistic Investigations

4.2.3.1 Synthesis of Plausible Reaction Intermediates

Compounds **72, 73 and 74** were synthesized by Kurt Polidano, according to procedures stated in the literature.[41]

1-Phenylprop-2-en-1-one (71)

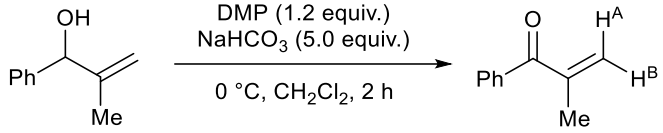


19 **71**

A 50 mL round-bottomed flask equipped with a magnetic stirrer bar was charged with 1-phenylprop-2-en-1-ol (**19**) (537 mg, 4.0 mmol, 1.00 equiv.), $NaHCO_3$ (1.68 g, 20.0 mmol, 5.00 equiv.) and CH_2Cl_2 (20 mL). The mixture was cooled in an ice bath and Dess-Martin Periodinane (2.00 g, 4.80 mmol, 1.20 equiv.) was added portion wise. This was left to react at rt for 16 h. The mixture was quenched with 10 wt% $Na_2S_2O_3$ (25 mL), and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL). The organics were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 2% EtOAc in hexanes, 25 × 150 mm silica) gave the title compound as a yellow oil (168 mg, 32%); R_f: 0.46 (eluent = 10% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 5.94 (1H, dd, *J* 10.6, 1.7, CH=CH^A*H*^{B}), 6.44 (1H, dd, *J* 17.1, 1.7, CH=C*H*^{A}H^B), 7.16 (1H, dd, *J* 17.1, 10.6, C*H*=CH$_2$), 7.46-7.52 (2H, m, ArC(3,5)*H*), 7.55-7.61 (1H, m, ArC(4)*H*), 7.93-7.97 (2H, m, ArC(2,6)*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C:

128.8 (2×Ar*C*), 128.8 (2×Ar*C*), 130.3 (CH=*C*H$_2$), 132.5 (ArC(4)), 133.1 (*C*H=CH$_2$), 137.4 (Ar*C*(1)), 191.2 (*C*=O); Spectroscopic data in accordance with the literature.[46]

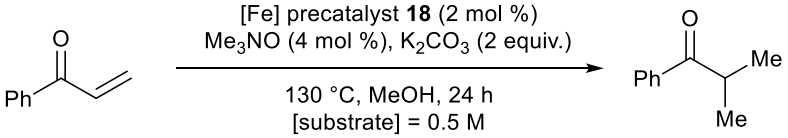
1-Phenylprop-2-en-1-one (75)



19 **75**

A 50 mL round-bottomed flask equipped with a magnetic stirrer bar was charged with 2-methyl-1-phenylprop-2-en-1-ol (**19**) (593 mg, 4.00 mmol, 1.00 equiv.), $NaHCO_3$ (1.68 g, 20.0 mmol, 5.00 equiv.) and CH_2Cl_2 (20 mL). The mixture was cooled in an ice bath and Dess-Martin Periodinane (2.0 g, 4.8 mmol, 1.2 equiv.) was added portion wise. This was left to react at rt for 16 h. The mixture was quenched with 10 wt% $Na_2S_2O_3$ (25 mL), and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL). The organics were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 2% EtOAc in hexanes, 25 × 200 mm silica) gave the title compound as a yellow oil (263 mg, 45%); R_f: 0.46 (eluent = 10% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 2.08 (3H, dd, *J* 1.5, 0.9, C*H*$_3$), 5.62-5.63 (1H, m, CCH$_3$=C*H*H), 5.90-5.93 (1H, m, CCH$_3$=CH*H*), 7.40-7.46 (2H, m, ArC(3,5)*H*), 7.50-7.55 (1H, m, ArC(4)*H*), 7.71-7.75 (2H, m, ArC(2,6)*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 18.8 (*C*H$_3$), 127.2 (*C*H$_2$), 128.3 (2×Ar*C*), 129.5 (2×Ar*C*), 132.1 (Ar*C*(4)), 137.9 (Ar*C*(1)), 143.9 (*C*CH$_3$), 198.5 (*C*=O). Spectroscopic data in accordance with the literature.[47]

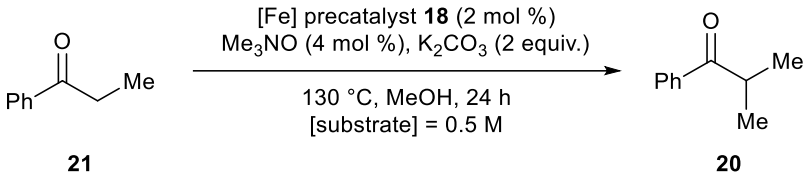
4.2.3.2 Validation of Plausible Reaction Intermediates



71 **20**

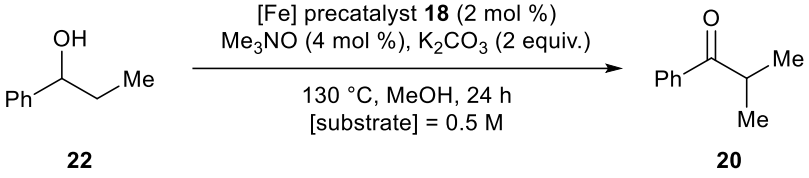
An oven-dried 10 mL microwave vial equipped with a stirrer bar was charged with [Fe] precatalyst **18** (4.6 mg, 0.01 mmol, 2 mol %), K_2CO_3 (138 mg, 1.00 mmol, 2.00 equiv.), and $Me_3NO.2H_2O$ (2.2 mg, 0.02 mmol, 4 mol %). The vial was charged with MeOH (1 mL) and **71** (66 mg, 0.5 mmol) before being sealed with a cap. The mixture was left to react at 130 °C for 24 h. It was then cooled, followed by the addition of

mesitylene (70 µL, 60 mg, 0.50 mmol), EtOAc (1 mL) and H_2O (1 mL). The mixture was stirred for 5 min, the cap was removed, and the mixture was subsequently left to settle for a further 5 min. The top layer was sampled and analysed using ^1H NMR. This revealed 43% of **20**.



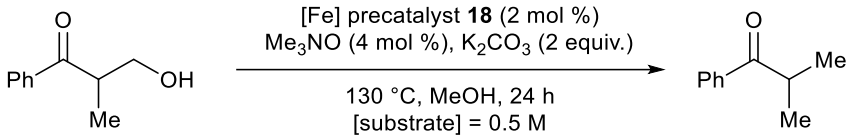
21 **20**

An oven-dried 10 mL microwave vial equipped with a stirrer bar was charged with [Fe] precatalyst **18** (4.6 mg, 0.01 mmol, 2 mol %), K_2CO_3 (138 mg, 1.0 mmol, 2.00 equiv.), and $Me_3NO.2H_2O$ (2.2 mg, 0.02 mmol, 4 mol %). The vial was charged with MeOH (1 mL) and **21** (67 mg, 0.5 mmol) before being sealed with a cap. The mixture was left to react at 130 °C for 24 h. It was then cooled, followed by the addition of mesitylene (70 µL, 60 mg, 0.50 mmol), EtOAc (1 mL) and H_2O (1 mL). The mixture was stirred for 5 min, the cap was removed, and the mixture was subsequently left to settle for a further 5 min. The top layer was sampled and analysed using ^1H NMR. This revealed 90% of **20**.



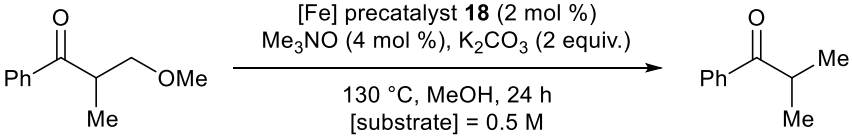
22 **20**

An oven-dried 10 mL microwave vial equipped with a stirrer bar was charged with [Fe] precatalyst **18** (4.6 mg, 0.01 mmol, 2 mol %), K_2CO_3 (138 mg, 1.0 mmol, 2.00 equiv.), and $Me_3NO.2H_2O$ (2.2 mg, 0.02 mmol, 4 mol %). The vial was charged with MeOH (1 mL) and **22** (68 mg, 0.5 mmol) before being sealed with a cap. The mixture was left to react at 130 °C for 24 h. It was then cooled, followed by the addition of mesitylene (70 µL, 60 mg, 0.50 mmol), EtOAc (1 mL) and H_2O (1 mL). The mixture was stirred for 5 min, the cap was removed, and the mixture was subsequently left to settle for a further 5 min. The top layer was sampled and analysed using ^1H NMR. This revealed 6% of **20**.



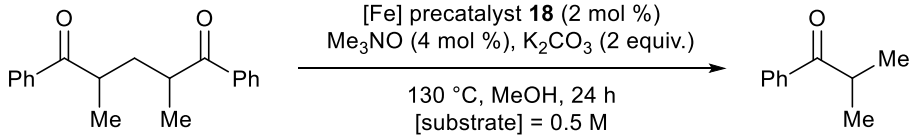
72 **20**

An oven-dried 10 mL microwave vial equipped with a stirrer bar was charged with [Fe] precatalyst **18**(4.6 mg, 0.01 mmol, 2 mol %), K_2CO_3 (138 mg, 1.0 mmol, 2.00 equiv.), and $Me_3NO.2H_2O$ (2.2 mg, 0.02 mmol, 4 mol %). The vial was charged with MeOH (1 mL) and **72** (82 mg, 0.5 mmol) before being sealed with a cap. The mixture was left to react at 130 °C for 24 h. It was then cooled, followed by the addition of mesitylene (70 μL, 60 mg, 0.50 mmol), EtOAc (1 mL) and H_2O (1 mL). The mixture was stirred for 5 min, the cap was removed, and the mixture was subsequently left to settle for a further 5 min. The top layer was sampled and analysed using ^1H NMR. This revealed 85% of **20**.



73 **20**

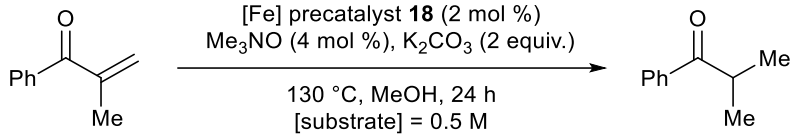
An oven-dried 10 mL microwave vial equipped with a stirrer bar was charged with [Fe] precatalyst **18** (4.6 mg, 0.01 mmol, 2 mol %), K_2CO_3 (138 mg, 1.0 mmol, 2.00 equiv.), and $Me_3NO.2H_2O$ (2.2 mg, 0.02 mmol, 4 mol %). The vial was charged with MeOH (1 mL) and **73** (89 mg, 0.5 mmol) before being sealed with a cap. The mixture was left to react at 130 °C for 24 h. It was then cooled, followed by the addition of mesitylene (70 μL, 60 mg, 0.50 mmol), EtOAc (1 mL) and H_2O (1 mL). The mixture was stirred for 5 min, the cap was removed, and the mixture was subsequently left to settle for a further 5 min. The top layer was sampled and analysed using ^1H NMR. This revealed 95% of **20**.



74 **20**

An oven-dried 10 mL microwave vial equipped with a stirrer bar was charged with [Fe] precatalyst **18** (4.6 mg, 0.01 mmol, 2 mol %), K_2CO_3 (138 mg, 1.0 mmol, 2.00

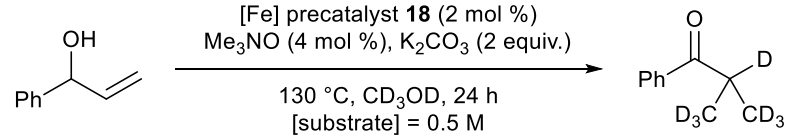
equiv.), and $Me_3NO.2H_2O$ (2.2 mg, 0.02 mmol, 4 mol %). The vial was charged with MeOH (1 mL) and **74** (190 mg, 0.5 mmol) before being sealed with a cap. The mixture was left to react at 130 °C for 24 h. It was then cooled, followed by the addition of mesitylene (70 µL, 60 mg, 0.50 mmol), EtOAc (1 mL) and H_2O (1 mL). The mixture was stirred for 5 min, the cap was removed, and the mixture was subsequently left to settle for a further 5 min. The top layer was sampled and analysed using ^1H NMR. This revealed 26% of **20**.



75 **20**

An oven-dried 10 mL microwave vial equipped with a stirrer bar was charged with [Fe] precatalyst **18** (4.6 mg, 0.01 mmol, 2 mol %), K_2CO_3 (138 mg, 1.0 mmol, 2.00 equiv.), and $Me_3NO.2H_2O$ (2.2 mg, 0.02 mmol, 4 mol %). The vial was charged with MeOH (1 mL) and **75** (74 mg, 0.5 mmol) before being sealed with a cap. The mixture was left to react at 130 °C for 24 h. It was then cooled, followed by the addition of mesitylene (70 µL, 60 mg, 0.50 mmol), EtOAc (1 mL) and H_2O (1 mL). The mixture was stirred for 5 min, the cap was removed, and the mixture was subsequently left to settle for a further 5 min. The top layer was sampled and analysed using ^1H NMR. This revealed 90% of **20**.

4.2.3.3 Employing CD_3OD as Solvent



19 **78**

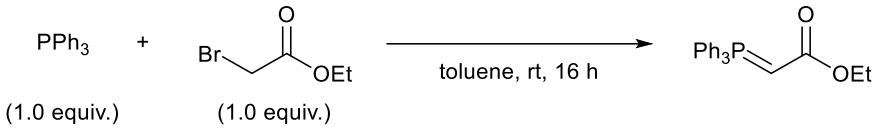
A 10 mL microwave vial equipped with a magnetic stirrer bar was charged with K_2CO_3 (138 mg, 1.00 mmol), $Me_3NO.2H_2O$ (2.2 mg, 0.02 mmol, 4 mol %), [Fe] precatalyst **18** (4.6 mg, 0.01 mmol, 2 mol %), CD_3OD (1 mL) and 1-phenylprop-2-en-1-ol (**19**) (67 mg, 0.5 mmol). The vial was sealed with a cap and was left to stir at 130 °C for 24 h. It was then cooled, treated with sat. aq. NH_4Cl (0.5 mL) and H_2O (0.5 mL), washed with EtOAc (15 mL) and transferred to a separatory funnel filled with brine

(15 mL). The organic layer was collected, and the aqueous phase washed with EtOAc (2 × 15 mL). The organics were combined, dried over MgSO4, filtered, and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 20% Et_2O in *n*-pentane, 20 × 220 mm silica) gave the title compound as a colourless oil (23 mg, 30%).

4.3 Investigating Miscellaneous Borrowing Hydrogen Processes

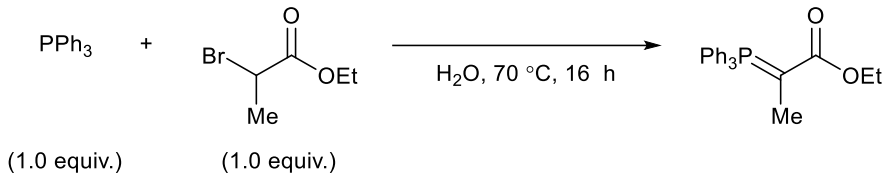
4.3.1 Synthesis of Ylides

Ethyl 2-(triphenyl-l5-phosphaneylidene)acetate



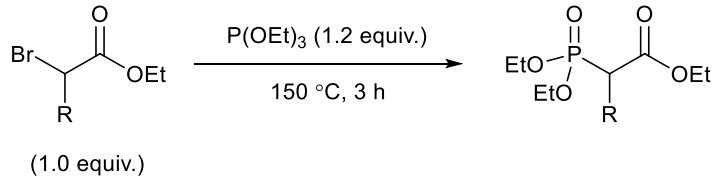
The title compound was prepared according to a procedure stated in the literature.[48] Under nitrogen, a flame-dried 500 mL round-bottomed flask with a stirrer bar was charged triphenylphosphine (15.7 g, 60.0 mmol, 1.00 equiv.) and dry toluene (200 mL), followed by the dropwise addition of ethyl bromoacetate (6.65 mL, 10.0 g, 60.0 mmol, 1.00 equiv.). The resulting mixture was stirred at rt overnight. The separated solid was filtered through a Buchner funnel and washed with petroleum ether (25 mL). The solid was then stirred in toluene (200 mL) and 3.5 M NaOH solution (225 mL) until two distinct layers became clear. The organic layer was collected, dried over Na_2SO_4, and concentrated *in vacuo* to yield the title compound as a white solid (15.8 g, 76%); mp 201-203 °C (lit. 202-205 °C);[49] **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 0.76-1.37 (3H, m, C*H*$_3$), 2.60-3.00 (1H, br s, C*H*), 3.85-4.07 (2H, m, C*H*$_2$), 7.40-7.48 (2H, m, 2×Ar*H*), 7.50-7.57 (1H, m, Ar*H*), 7.61-7.67 (2H, m, 2×Ar*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 14.9 (*C*H$_3$), 30.2 (d, *J* 126.0, *C*H), 57.9 (*C*H$_2$), 128.1 (d, *J* 92.7, 3×Ar*C*(1)), 128.8 (d, *J* 10.0, 6×Ar*C*), 132.0 (d, *J* 2.8, 3×Ar*C*(4)), 133.1 (d, *J* 10.0, 6×Ar*C*), 171.4 (d, *J* 12.8, *C*=O). Spectroscopic data in accordance with the literature.[49]

Ethyl 2-(triphenyl-l5-phosphaneylidene)propanoate



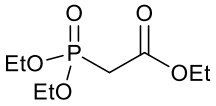
The title compound was prepared according to a procedure stated in the literature.[50] Under nitrogen, a flame-dried 500 mL round-bottomed flask with a stirrer bar was charged triphenylphosphine (15.7 g, 60.0 mmol, 1.00 equiv.) and H_2O (200 mL), followed by the dropwise addition of ethyl 2-bromopropionate (7.79 mL, 10.9 g, 60.0 mmol, 1.00 equiv.). The resulting mixture was stirred at 70 °C overnight. The mixture was then cooled to 0 °C. 2 M NaOH solution (60 mL) was added dropwise, with CH_2Cl_2 added as needed to dissolve the solid ylide product. The organic layer was collected, and the aqueous layer was washed with CH_2Cl_2 (2 × 25 mL). The combined organics were washed with brine (25 mL), dried over Na_2SO_4, and concentrated. The addition of hexanes resulted in precipitation. The solid was filtered under vacuum and dried to yield the title compound as a yellow solid (19.7 g, 91%); mp 151-153 °C (lit. 155-157);[49] **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 0.24-0.81 (3H, m, CH_2CH_3), 1.61 (3H, d, *J* 14.0, CCH_3), 3.50-4.01 (2H, m, CH_2), 7.26-7.73 (15H, m, 15×Ar*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 12.3-13.3 (m, CCH_3), 14.3 (CH_2CH_3), 57.6 (CH_2), 128.4 (d, *J* 12.1, 6×Ar*C*), 131.2-131.8 (m, Ar*C*), 132.0 (m, 3×Ar*C*), 132.1 (d, *J* 9.8 3×Ar*C*), 133.6 (d, *J* 9.6, 6×Ar*C*), 167.8 (*C*=O). Spectroscopic data in accordance with the literature.[49]

General Procedure 3: Preparation of Phosphonate Esters



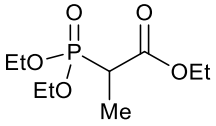
Phosphonate esters were prepared according to a procedure stated in the literature.[51] Under nitrogen, a flame dried flask equipped with stirrer bar was charged with bromoacetate (1.00 equiv.) and triethyl phosphite (1.20 equiv.). The neat mixture was refluxed at 150 °C for 3 h, or until all the bromoacetate had reacted, as monitored by TLC. Unreacted triethyl phosphite was removed under reduced pressure to give the pure product.

Ethyl 2-(diethoxyphosphoryl)acetate



The title compound was prepared according to a general procedure 3 using ethyl bromoacetate (3.33 mL, 5.01 g, 30.0 mmol, 1.00 equiv.) and triethyl phosphite (4.12 mL, 3.99 g, 36.0 mmol, 1.20 equiv.). The title compound was obtained as a colourless oil (4.92 g, 73%); **^{1}H NMR (CDCl$_3$, 500 MHz)** δ_H: 1.22-1.40 (9H, m, 3×C*H*$_3$), 2.89-3.00 (2H, m, PC*H*$_2$), 4.08-4.27 (6H, m, 3×C*H*$_2$); **^{31}P NMR (CDCl$_3$, 202 MHz)** δ_P: 19.8; **^{13}C NMR (CDCl$_3$, 126 MHz)** δ_C: 14.2 (OCH$_2$*C*H$_3$), 16.4 (d, *J* 6.2, P(CH$_2$*C*H$_3$)$_2$), 34.5 (d, *J* 134.0, P*C*H$_2$), 61.7 (O*C*H$_2$CH$_3$), 62.8 (d, *J* 6.3, P(*C*H$_2$CH$_3$)$_2$), 165.9 (*C*=O). Spectroscopic data in accordance with the literature.[52]

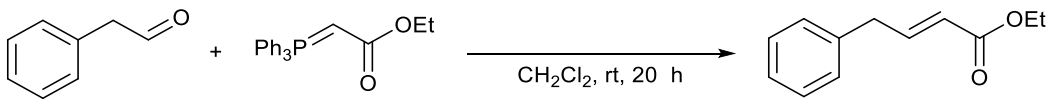
Ethyl 2-(diethoxyphosphoryl)propanoate



The title compound was prepared according to a general procedure 3 using ethyl 2-bromopropionate (2.51 mL, 3.62 g, 20.0 mmol, 1.00 equiv.) and triethyl phosphite (2.74 mL, 2.66 g, 24.0 mmol, 1.20 equiv.). The title compound was obtained as a colourless oil (2.20 g, 46%); **^{1}H NMR (CDCl$_3$, 500 MHz)** δ_H: 1.28 (3H, t, *J* 7.1, OCH$_2$C*H*$_3$), 1.32 (6H, dq, *J* 3.6, 0.6, P(CH$_2$C*H*$_3$)$_2$), 1.43 (3H, dd, *J* 18.0, 7.3, PCHC*H*$_3$), 3.02 (1H, dq, *J* 23.4, 7.3, PC*H*CH$_3$), 4.09-4.26 (6H, m, OC*H*$_2$CH$_3$ and P(C*H*$_2$CH$_3$)$_2$); **^{31}P NMR (CDCl$_3$, 202 MHz)** δ_P: 23.8. Spectroscopic data in accordance with the literature.[53]

4.3.2 Synthesis of *α,β*-Unsaturated Esters

Ethyl (E)-4-phenylbut-2-enoate

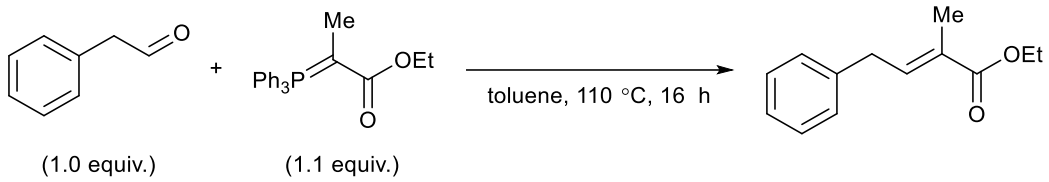


(1.0 equiv.) (1.2 equiv.)

Under nitrogen, a flame dried flask equipped with stirrer bar was charged with phenylacetaldehyde (1.11 mL, 1.20 g, 10.0 mmol, 1.00 mmol), ylide ethyl 2-(triphenyl-l5-phosphaneylidene)acetate (4.18 g, 12.0 mmol, 1.20 equiv.) and dry

CH_2Cl_2 (100 mL). The reaction mixture was stirred at rt overnight. The solvent was removed *in vacuo* and the resulting residue was washed with petroleum ether (5 × 20 mL) to precipitate the by-product triphenylphosphine oxide, which was subsequently filtered under vacuum. The filtrate was concentrated *in vacuo* to deliver a crude residue. Purification *via* flash silica column chromatography (eluent = 2-5% EtOAc in hexanes, 35 × 150 mm silica) gave the title compound as a pale-yellow oil (1.52 g, 80%); R_f: 0.6 (eluent = 5% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.28 (3H, t, *J* 7.3, OCH_2CH_3), 3.52 (2H, dd, *J* 6.8, 1.2, $PhCH_2CH{=}CH$), 4.18 (2H, q, *J* 7.3, OCH_2CH_3), 5.78-5.85 (1H, m, $PhCH_2CH{=}CH$), 7.06-7.14 (1H, m, $PhCH_2CH{=}CH$), 7.16-7.21 (2H, m, 2×Ar*H*), 7.22-7.27 (1H, m, Ar*H*), 7.29-7.35 (2H, m, 2×Ar*H*); **^{13}C NMR ($CDCl_3$, 126 MHz**) δ_C: 14.4 (OCH_2CH_3), 38.6 ($PhCH_2$), 60.4 (OCH_2CH_3), 122.5 (Ar*C*), 126.8 (Ar*C*), 128.8 (2×Ar*C*), 128.9 (2×Ar*C*), 137.8 (C*H*), 147.4 (C*H*), 166.6 (*C*=O). Spectroscopic data in accordance with the literature.[54]

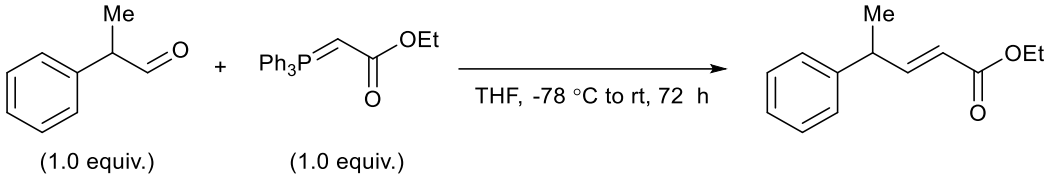
2-Methyl-4-phenyl-but-2-enoate



The title compound was synthesised in collaboration with Lia Mitchell. Under nitrogen, a flame dried flask equipped with stirrer bar was charged with phenylacetaldehyde (0.69 mL, 0.75 g, 6.23 mmol, 1.00 equiv.), ylide ethyl 2-(triphenyl-l5-phosphaneylidene)propanoate (2.50 g, 6.89 mmol, 1.10 equiv.) and dry toluene (40 mL). The reaction mixture was heated at reflux overnight. The mixture was cooled, and the solvent was removed *in vacuo*. The resulting residue was washed with petroleum ether (5 × 15 mL) to precipitate the by-product triphenylphosphine oxide, which was subsequently filtered under vacuum. The filtrate was concentrated *in vacuo* to deliver a crude residue. Purification *via* flash silica column chromatography (eluent = 1-2% EtOAc in hexanes, 35 × 150 mm silica) gave the title compound as a pale-yellow oil (940 mg, 73%); R_f: 0.5 (eluent = 1% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 300 MHz)** δ_H: 1.28 (3H, t, *J* 7.1, OCH_2CH_3), 1.94-1.98 (3H, m), 3.53 (2H, d, *J* 7.6, $PhCH_2CH$), 4.19 (2H, q, *J* 7.1, OCH_2CH_3), 6.92 (1H, m, C*H*), 7.14-7.36 (5H, m, 5×Ar*H*); **^{13}C NMR ($CDCl_3$, 75 MHz**) δ_C: 12.7 (CH_3), 14.4 (OCH_2CH_3), 35.0 ($PhCH_2$),

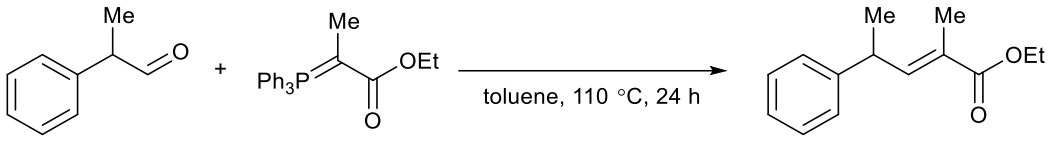
60.7 (O*C*H$_2$CH$_3$), 126.5 (Ar*C*(4)), 128.6 (Ar*C*), 128.7 (2×Ar*C*), 128.8 (2×Ar*C*), 139.0 (CH$_3$*C*CO), 140.1 (C*H*), 168.8 (*C*=O). Spectroscopic data in accordance with the literature.[55]

(E)-Ethyl 4-phenyl-2-pentenoate



The title compound was synthesised in collaboration with Lia Mitchell. Under nitrogen, a 100 mL flame dried round-bottomed flask equipped with stirrer bar was charged with ylide ethyl 2-(triphenyl-l5-phosphaneylidene)acetate (2.64 g, 7.60 mmol, 1.00 equiv.) and dry THF (40 mL), followed by the dropwise addition of 2-phenylpropionaldehyde (1.01 mL, 1.02 g, 7.60 mmol, 1.00 equiv.) at -78 °C. The reaction mixture was stirred at -78 °C for 1 h, followed by stirring at rt for 72 h. The reaction was quenched with NH$_4$Cl solution (30 mL), transferred to a separatory funnel, and extracted with EtOAc (3 × 15 mL). The organic layers were washed with brine (20 mL), dried over MgSO$_4$, filtered, and concentrated *in vacuo*. The resulting residue was washed with ice-cold petroleum ether (5 × 15 mL) to precipitate the by-product triphenylphosphine oxide, which was subsequently filtered under vacuum. The filtrate was concentrated *in vacuo* to deliver a crude residue. Purification *via* flash silica column chromatography (eluent = 2% EtOAc in hexanes, 35 × 170 mm silica) gave the title compound as a colourless oil (840 mg, 54%); R_f: 0.33 (eluent = 2% EtOAc in hexanes); **^{1}H NMR (CDCl$_3$, 300 MHz)** δ_H: 1.28 (3H, t, *J* 7.1, OCH$_2$C*H*$_3$), 1.48 (3H, d, *J* 7.1, CHC*H*$_3$), 3.55-3.69 (1H, m, C*H*CH$_3$), 4.18 (2H, q, *J* 7.2, OC*H*$_2$CH$_3$), 5.80 (1H, dd, *J* 15.7, 1.6, CH=C*H*CO$_2$Et), 7.16 (1H, dd, *J* 15.7, 6.6, C*H*=CHCO$_2$Et), 7.16-7.28 (3H, m, 3×Ar*H*), 7.28-7.37 (2H, m, 2×Ar*H*); **^{13}C NMR (CDCl$_3$, 75 MHz)** δ_C: 14.4 (OCH$_2$*C*H$_3$), 20.4 (CH*C*H$_3$), 42.2 (*C*HCH$_3$), 60.5 (O*C*H$_2$CH$_3$), 120.3 (*C*H), 126.9 (Ar*C*(4)), 127.5 (2×Ar*C*), 128.8 (2×Ar*C*), 143.5 (Ar*C*(1)), 152.7 (*C*H), 166.9 (*C*=O). Spectroscopic data in accordance with the literature.[56]

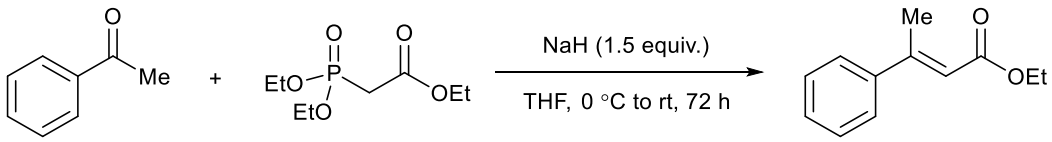
Ethyl (E)-2-methyl-4-phenylpent-2-enoate



(1.0 equiv.) (1.1 equiv.)

Under nitrogen, a flame dried 100 mL round-bottomed flask equipped with stirrer bar was charged with ylide ethyl 2-(triphenyl-l5-phosphaneylidene)propanoate (3.20 g, 8.82 mmol, 1.10 equiv.) and dry toluene (35 mL), followed by the addition of 2-phenylpropionaldehyde (1.08 mL, 1.08 g, 8.03 mmol, 1.00 equiv.). The reaction mixture was heated at reflux for 24 h. The reaction was cooled to rt, quenched with NH_4Cl solution (30 mL), transferred to a separatory funnel, and extracted with EtOAc (3 × 15 mL). The organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting residue was washed with ice-cold petroleum ether (5 × 15 mL) to precipitate the by-product triphenylphosphine oxide, which was subsequently filtered under vacuum. The filtrate was concentrated *in vacuo* to deliver a crude residue. Purification *via* flash silica column chromatography (eluent = 5% EtOAc in hexanes, 40 × 170 mm silica) gave the title compound as a pale yellow oil (933 mg, 55%); R_f: 0.62 (eluent = 10% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.29 (3H, t, *J* 7.1, OCH_2CH_3), 1.40 (3H, d, *J* 6.9, $CHCH_3$), 1.91 (3H, d, *J* 1.5, CCH_3), 3.79 (1H, dq, *J* 9.9, 7.0, $CHCH_3$), 4.18 (2H, dq, *J* 7.1, 1.5, OCH_2CH_3), 6.86 (1H, dq, *J* 9.9, 1.5, $CH{=}CCH_3$), 7.16 (1H, dd, *J* 15.7, 6.6, $CH{=}CHCO_2Et$), 7.18-7.26 (3H, m, 3×Ar*H*), 7.27-7.34 (2H, m, 2×Ar*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 12.6 (CCH_3), 14.3 (OCH_2CH_3), 21.3 ($CHCH_3$), 38.7 ($CHCH_3$), 60.6 (OCH_2CH_3), 126.4 (Ar*C*(4)), 126.7 (CCH_3), 127.0 (2×Ar*C*), 128.7 (2×Ar*C*), 144.6 (Ar*C*(1)), 145.9 (*C*H), 168.3 (*C*=O). HRMS (**EI**$^+$) calculated for $[C_{14}H_{18}O]^+$ $(M)^+$: m/z 218.310, found 218.310, (-0.2 ppm). Spectroscopic data in accordance with the literature.[57]

Ethyl (E)-3-phenylbut-2-enoate

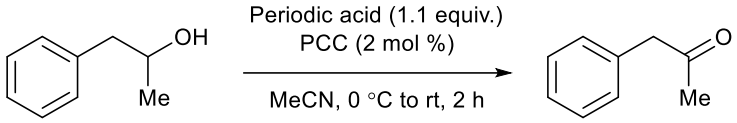


(1.0 equiv.) (1.5 equiv.)

Under nitrogen, a flame dried 100 mL round-bottomed flask equipped with stirrer bar was charged with phosphonate ester ethyl 2-(diethoxyphosphoryl)acetate (3.00

g, 13.4 mmol, 1.50 equiv.) and dry THF (30 mL), followed by the portion-wise addition of NaH (536 mg, 13.4 mmol, 1.50 equiv., 60% dispersion in mineral oil) at 0 °C. The mixture was stirred at 0 °C for 30 min before dropwise addition of acetophenone (1.04 mL, 1.07 g, 8.93 mmol, 1.00 equiv.). The reaction mixture was stirred at rt for 72 h. The reaction mixture was transferred to a separatory funnel filled with brine (50 mL) and extracted with EtOAc (3 × 15 mL). The organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification *via* flash silica column chromatography (eluent = 5% EtOAc in hexanes, 40 × 150 mm silica) gave the title compound as a pale-yellow oil (985 mg, 58%); R_f: 0.66 (eluent = 10% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.32 (3H, t, *J* 7.1, OCH_2CH_3), 2.58 (3H, d, *J* 1.3, CCH_3), 4.22 (2H, q, *J* 7.1, OCH_2CH_3), 6.14 (1H, q, *J* 1.3, $CH{=}CCH_3$), 7.33-7.41 (3H, m, 3×Ar*H*), 7.44-7.51 (2H, m, 2×Ar*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 14.6 (OCH_2CH_3), 18.1 (CCH_3), 60.0 (OCH_2CH_3), 117.3 (C*H*), 126.7 (2×Ar*C*), 127.0 (2×Ar*C*), 128.7 (Ar*C*(4)), 142.4 (Ar*C*(1)), 155.6 (CCH_3), 167.0 (*C*=O). Spectroscopic data in accordance with the literature.[58]

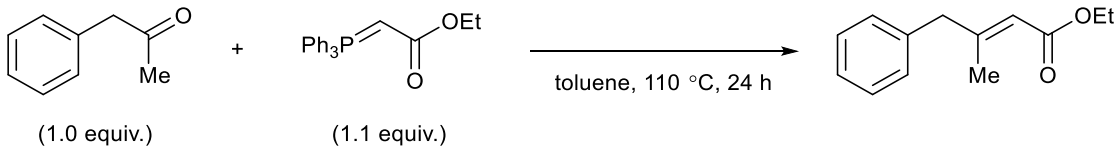
1-Phenylpropan-2-one



The title compound was prepared according to a procedure stated in the literature.[59] Under nitrogen, a flame dried 250 mL round-bottomed flask equipped with stirrer bar was charged with periodic acid (3.76 g, 16.5 mmol, 1.10 equiv.) and dry acetonitrile (25 mL), followed by vigorous stirring for 15 min. The flask was cooled to 0 °C, and 1-phenyl-2-propanol (2.10 mL, 2.04 g, 15.0 mmol, 1.00 equiv.) was added. A solution of pyridinium chlorochromate (65 mg, 0.3 mmol, 2 mol %) in MeCN (10 mL) was then added dropwise at 0 °C over a 5 min period. The reaction mixture was transferred to a separatory funnel filled with brine (50 mL) and extracted with EtOAc (3 × 20 mL). The organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification *via* flash silica column chromatography (eluent = 3-10% EtOAc in hexanes, 40 × 170 mm silica) gave the title compound as a colourless oil (1.49 g, 74%); R_f: 0.50 (eluent = 10% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 2.15-2.16 (3H, m, CH_3), 3.70 (2H, s, CH_2), 7.19-7.23 (2H, m, 2×Ar*H*), 7.25-7.30 (1H, m, Ar*H*)

7.31-7.37 (2H, m, 2×Ar*H*); **^{13}C NMR (CDCl$_3$, 126 MHz)** δ_C: 29.4 (*C*H$_3$), 51.2 (*C*H$_2$), 126.2 (Ar*C*(4)), 128.9 (2×Ar*C*), 129.5 (2×Ar*C*), 134.4 (Ar*C*(1)), 206.6 (*C*=O). Spectroscopic data in accordance with the literature.[60]

Ethyl (E)-3-methyl-4-phenylbut-2-enoate

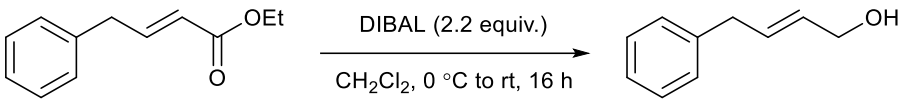


(1.0 equiv.) (1.1 equiv.)

Under nitrogen, a flame dried 100 mL round-bottomed flask equipped with stirrer bar was charged with ylide ethyl 2-(triphenyl-l5-phosphaneylidene)acetate (2.00 g, 5.74 mmol, 1.10 equiv.) and dry toluene (35 mL), followed by the addition of 1-phenylpropan-2-one (700 mL, 700 mg, 5.21 mmol, 1.00 equiv.). The reaction mixture was refluxed for 72 h. The reaction mixture was heated at reflux for 24 h. The reaction was cooled to rt, quenched with NH$_4$Cl solution (30 mL), transferred to a separatory funnel, and extracted with EtOAc (3 × 15 mL). The organic layers were washed with brine (20 mL), dried over MgSO$_4$, filtered, and concentrated *in vacuo*. The resulting residue was washed with ice-cold petroleum ether (5 × 15 mL) to precipitate the by-product triphenylphosphine oxide, which was subsequently filtered under vacuum. The filtrate was concentrated *in vacuo* to deliver a crude residue. Purification *via* flash silica column chromatography (eluent = 5% EtOAc in hexanes, 30 × 170 mm silica) gave the title compound as a pale-yellow oil (20 mg, 3%); R$_f$: 0.82 (eluent = 10% EtOAc in hexanes); **^{1}H NMR (CDCl$_3$, 500 MHz)** δ_H: 1.26 (3H, t, *J* 7.1, OCH$_2$C*H*$_3$), 2.12 (3H, d, *J* 1.3, CC*H*$_3$), 3.40-3.43 (1H, m, PhC*H*$_2$), 4.14 (2H, q, *J* 7.1, OC*H*$_2$CH$_3$), 5.66-5.70 (1H, m, C=C*H*), 7.13-7.18 (2H, m, 2×Ar*H*), 7.20-7.32 (3H, m, 3×Ar*H*); **^{13}C NMR (CDCl$_3$, 126 MHz)** δ_C: 14.4 (OCH$_2$*C*H$_3$), 18.8 (C*C*H$_3$), 47.2 (Ph*C*H$_2$), 59.7 (O*C*H$_2$CH$_3$), 117.4 (C*H*), 126.8 (Ar*C*(4)), 128.7 (2×Ar*C*), 129.3 (2×Ar*C*), 137.9 (Ar*C*(1)), 158.4 (*C*CH$_3$), 166.8 (*C*=O). Spectroscopic data in accordance with the literature.[61]

4.3.3 Synthesis of Allylic Alcohols

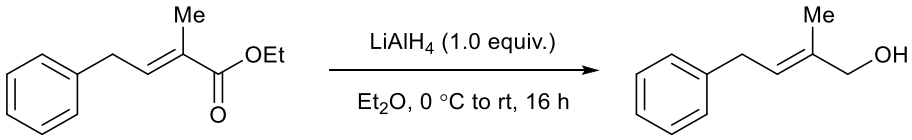
(E)-4-Phenylbut-2-en-1-ol (86)



86

The title compound was synthesised in collaboration with Abdul Bari, according to a procedure in the literature.[62] Under nitrogen, a flame-dried 100 mL round-bottomed flask was charged with *α,β*-unsaturated ester ethyl (*E*)-4-phenylbut-2-enoate (1.00 g, 5.26 mmol, 1.0 equiv.) and dry CH_2Cl_2 (30 mL), followed by the dropwise addition of DIBAL (6.31 mL, 6.31 mmol, 2.20 equiv., 1.0 M in hexane) at 78 °C, over a 30 min period. The mixture was then warmed to rt and stirred overnight. The organic layer was collected, and the aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were washed with $NaHCO_3$ (25 mL) and brine (25 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification *via* flash silica column chromatography (eluent = 10-20% EtOAc in hexanes, 25 × 150 mm), yielded the title compound as a pale-yellow oil (195 mg, 25%); R_F: 0.3 (eluent = 20% EtOAc in hexanes). **^{1}H NMR ($CDCl_3$, 300 MHz)** δ_H: 1.76 (1H, br s, O*H*), 3.39 (2H, d, *J* 6.7, PhCH_2), 4.13 (1H, dq, *J* 5.8, 1.1, CH_2OH), 5.71 (1H, dtt, *J* 15.3, 5.8, 1.5, C*H*), 5.87 (1H, dtt, *J* 15.3, 6.7, 1.4, C*H*), 7.14-7.23 (3H, m, 3×Ar*H*), 7.27-7.33 (2H, m, 2×Ar*H*); **^{13}C NMR ($CDCl_3$, 75 MHz)** δ_C: 38.8 (Ph*C*H_2), 63.6 (*C*H_2OH), 63.9 (*C*H_2OH), 126.3, 128.6 (2×Ar*C*), 128.7 (2×Ar*C*), 130.4, 131.7, 140.1. Spectroscopic data in accordance with the literature.[62]

(E)-2-Methyl-4-phenylbut-2-en-1-ol (90)

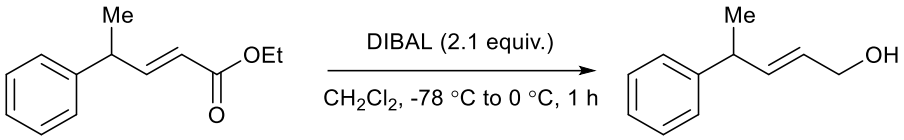


90

The title compound was synthesised in collaboration with Lia Mitchell. Under nitrogen, a flame dried 100 mL round-bottomed flask equipped with stirrer bar was charged with *α,β*-unsaturated ester (*E*)-ethyl 4-phenyl-2-pentenoate (940 mg, 4.6 mmol, 1.00 equiv.) and dry Et_2O (25 mL), followed by the dropwise addition of $LiAlH_4$ (4.60 mL, 4.60 mmol, 1.00 equiv., 1 M in THF) at 0 °C. The reaction mixture was warmed to rt and stirred overnight. The mixture was cooled to 0 °C, and quenched with H_2O (20 mL) and NaOH solution (10 mL, 2 M), followed by stirring for 30 min. The precipitate was filtered and washed with Et_2O (2 × 15 mL). The filtrate was

transferred to a separatory funnel. The organic layer was collected, and the aqueous phase washed with more Et_2O (2 × 15 mL). The organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification *via* flash silica column chromatography (eluent = 20% EtOAc in hexanes, 35 × 150 mm silica) gave the title compound as a colourless oil (660 mg, 89%); R_f: 0.41 (eluent = 20% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 300 MHz)** δ_H: 1.29 (1H, t, *J* 6.2, CH_2OH), 1.79 (3H, s, CH_3), 3.41 (2H, d, *J* 7.4, $PhCH_2$), 4.06 (2H, d, *J* 5.9, CH_2OH), 5.58-5.68 (1H, m, CH), 7.15-7.24 (3H, m, 3×ArH), 7.25-7.34 (2H, m, 2×ArH); **^{13}C NMR ($CDCl_3$, 75 MHz)** δ_C: 14.2 (CH_3), 33.9 ($PhCH_2$), 68.8 (CH_2OH), 124.7, 125.9, 128.3, 128.5, 136.3, 139.7. Spectroscopic data in accordance with the literature.[55]

(E)-4-Phenylpent-2-en-1-ol (92)

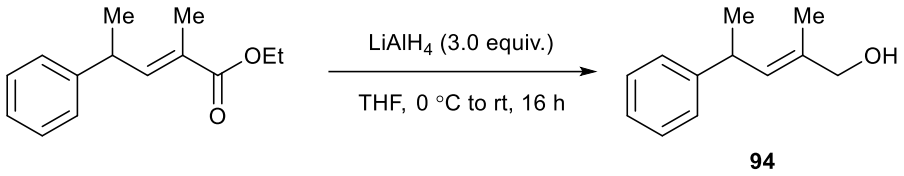


92

The title compound was synthesised in collaboration with Lia Mitchell according to a procedure in the literature.[63] Under nitrogen, a flame-dried 100 mL round-bottomed flask was charged with *α,β*-unsaturated ester (*E*)-ethyl 4-phenyl-2-pentenoate (420 mg, 2.06 mmol, 1.0 equiv.) and dry CH_2Cl_2 (25ml), followed by the dropwise addition of DIBAL (4.30 mL, 4.30 mmol, 2.10 equiv., 1.0 M in hexane) at 78 °C, over a 10 min period. The mixture was then stirred at 0 °C for 1 h, after which MeOH (5 mL) was added to quench the reaction. The mixture was warmed to rt and stirring continued for a further 30 min. To the resulting cloudy mixture was added saturated potassium sodium tartrate solution (15 mL). The mixture was stirred vigorously for a 12 h. The mixture was transferred to a separatory funnel. The organic layer was collected, and the aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were washed with $NaHCO_3$ (25 mL) and brine (25 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification *via* flash silica column chromatography (eluent = 10% EtOAc in hexanes, 20 × 170 mm), yielded the title compound as a light brown oil (230 mg, 67%); R_f: 0.25 (eluent = 10% EtOAc in hexanes). **^{1}H NMR ($CDCl_3$, 300 MHz)** δ_H: 1.38 (1H, d, *J* 7.0, $CHCH_3$), 3.49 (1H, quint, *J* 7.0, PhCH), 4.09-4.18 (2H, m, CH_2OH), 5.67 (1H, dtd, *J* 15.4, 5.8, 1.3, CH), 5.67 (1H, ddt,

J 15.4, 6.6, 1.3, C*H*), 7.15-7.24 (3H, m, 3×Ar*H*), 7.27-7.36 (2H, m, 2×Ar*H*); **^{13}C NMR ($CDCl_3$, 75 MHz)** δ_C: 21.3 (*C*H_3), 42.1 (Ph*C*H), 63.9 (*C*H_2OH), 126.4, 127.3, 127.9, 128.6, 137.7, 144.0. Spectroscopic data in accordance with the literature.[63]

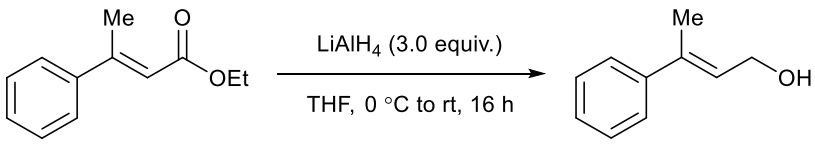
(E)-2-Methyl-4-phenylpent-2-en-1-ol (94)



94

Under nitrogen, a flame dried 100 mL round-bottomed flask equipped with stirrer bar was charged with *α,β*-unsaturated ester ethyl (*E*)-2-methyl-4-phenylpent-2-enoate (800 mg, 3.67 mmol, 1.00 equiv.) and dry THF (20 mL), followed by the dropwise addition of $LiAlH_4$ (11.0 mL, 11.0 mmol, 3.00 equiv., 1 M in THF) at 0 °C, and stirring for 1 h. H_2O (5 mL) and NaOH solution (5 mL, 2 M) were added, and the mixture was stirred at rt overnight. The precipitate was filtered and washed with EtOAc (2 × 15 mL). The filtrate was transferred to a separatory funnel. The organic layer was collected, and the aqueous phase washed with more EtOAc (2 × 15 mL). The organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification *via* flash silica column chromatography (eluent = 10% EtOAc in hexanes, 30 × 170 mm silica) gave the title compound as a colourless oil (388 mg, 60%); R_f: 0.21 (eluent = 10% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.34 (3H, d, *J* 7.0, CHC*H*$_3$), 1.74 (3H, d, *J* 1.4, CC*H*$_3$), 3.71 (1H, dq, *J* 9.4, 7.0, PhC*H*), 4.01 (2H, s, CH_2O*H*), 5.57 (1H, dquint, *J* 9.4, 1.4, C*H*), 7.16-7.21 (1H, m, Ar*H*), 7.22-7.26 (2H, m, 2×Ar*H*), 7.27-7.32 (2H, m, 2×Ar*H*), O*H* absent; **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 14.0 (CH*C*H$_3$), 22.3 (C*C*H$_3$), 37.9 (*C*HCH$_3$), 68.9 (*C*H_2OH), 126.1, 127.0, 128.6, 131.3, 133.8, 139.7. Spectroscopic data in accordance with the literature.[64]

(E)-3-Phenylbut-2-en-1-ol (95)



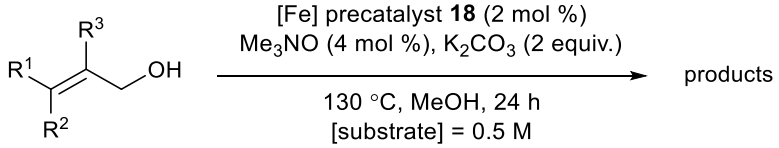
95

The title compound was synthesised in collaboration with Abdul Bari. Under nitrogen, a flame dried 100 mL round-bottomed flask equipped with stirrer bar was charged

with *α*,*β*-unsaturated ester ethyl (*E*)-3-phenylbut-2-enoate (190 mg, 1.00 mmol, 1.00 equiv.) and dry THF (20 mL), followed by the dropwise addition of $LiAlH_4$ (3.00 mL, 3.00 mmol, 3.00 equiv., 1 M in THF) at 0 °C, and stirring for 1 h. H_2O (5 mL) and NaOH solution (5 mL, 2 M) were added, and the mixture was stirred at rt overnight. The precipitate was filtered and washed with EtOAc (2 × 15 mL). The filtrate was transferred to a separatory funnel. The organic layer was collected, and the aqueous phase washed with more EtOAc (2 × 15 mL). The organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification *via* flash silica column chromatography (eluent = 10% EtOAc in hexanes, 30 × 170 mm silica) gave the title compound as a colourless oil (92 mg, 62%); R_f: 0.16 (eluent = 10% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 300 MHz)** δ_H: 2.07-2.11 (3H, m, C*H*$_3$), 4.34-4.44 (2H, m, C*H*$_2$OH), 5.98 (1H, tq, *J* 6.7, 1.3, CH_3C=C*H*), 7.22-7.37 (3H, m, 3×Ar*H*), 7.38-7.46 (2H, m, 2×Ar*H*); **^{13}C NMR ($CDCl_3$, 75 MHz)** δ_C: 16.2 (C*C*H$_3$), 60.1 (*C*H$_2$OH), 125.9, 126.6, 127.4, 128.4, 138.1, 143.0. Spectroscopic data in accordance with the literature.[65]

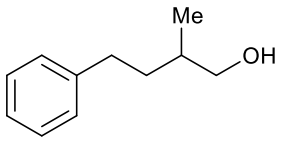
4.3.4 Identified Products

General Procedure 4: Reactions with 1° Allylic Alcohols



An oven-dried 10 mL microwave vial equipped with a stirrer bar was charged with [Fe] precatalyst **18** (4.6 mg, 0.01 mmol, 2 mol %), K_2CO_3 (138 mg, 1.00 mmol, 2.00 equiv.), $Me_3NO.2H_2O$ (2.2 mg, 0.02 mmol, 4 mol %) and allylic alcohol (0.50 mmol, 1.00 equiv.). The vial was charged with MeOH (1 mL) before being sealed with a cap. The mixture was left to react at 130 °C for 24 h. The reaction was cooled, diluted with EtOAc (1 mL), and quenched with H_2O (1 mL), before being transferred to a separatory funnel filled with brine (25 mL). The organic layer was collected, and the aqueous phase washed with EtOAc (2 × 10 mL). The organics were combined, dried over $MgSO_4$, filtered and concentrated in vacuo.

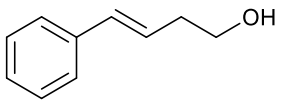
2-Methyl-4-phenylbutan-1-ol (87)



87

The title compound was prepared according to general procedure 4 using **86** or **90** as allylic alcohol. The crude NMR values were found to be 25% and 49%, respectively (chapter 4, figure 12). Purification *via* flash silica column chromatography (eluent = 10-20% EtOAc in hexanes, 20 × 170 mm silica) gave the title compound as a colourless oil. R_f: 0.19 (eluent = 10% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 0.99 (3H, d, J 6.7, C*H*$_3$), 1.42 (1H, br s, O*H*), 1.45 (1H, dddd, *J* 13.5, 10.1, 8.1, 5.6, PhCH$_2$CH*H*), 1.62-1.73 (1H, m, C*H*CH$_3$), 1.77 (1H, dddd, *J* 13.2, 10.2, 6.4, 5.2, PhCH$_2$C*H*H), 2.60 (1H, ddd, *J* 13.7, 10.1, 6.3, PhC*H*H), 2.71 (1H, ddd, *J* 13.6, 10.2, 5.6, PhCH*H*), 3.47 (1H, dd, *J* 10.5, 6.4, C*H*HOH), 3.54 (1H, dd, *J* 10.5, 5.8, CH*H*OH), 7.15-7.73 (3H, m, 3×Ar*H*), 7.26-7.31 (2H, m, 2×Ar*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 16.6 (*C*H$_3$), 33.4 (Ph*C*H$_2$), 35.1 (PhCH$_2$*C*H$_2$), 35.5 (*C*HCH$_3$), 68.4 (*C*H$_2$OH), 125.8 (Ar*C*(4)), 128.5 (2×Ar*C*), 128.5 (2×Ar*C*), 142.7 (Ar*C*(1)). Spectroscopic data in accordance with the literature.[66]

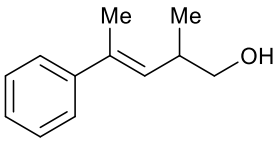
(E)-4-Phenylbut-3-en-1-ol (88)



88

The title compound was prepared according to general procedure 4 using **86** as allylic alcohol. The crude NMR value was found to be 27% (chapter 4, figure 12). Purification *via* flash silica column chromatography (eluent = 10-20% EtOAc in hexanes, 20 × 170 mm silica) gave the title compound as a colourless oil; R_f: 0.12 (eluent = 10% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 400 MHz)** δ_H: 2.46-2.53 (2H, dtd, *J* 7.6, 6.7, 1.4, C*H*$_2$CH$_2$OH), 3.76 (2H, t, *J* 6.3, C*H*$_2$OH), 6.21 (1H, dt, *J* 15.9, 7.1, PhCHC*H*), 6.47-6.54 (1H, m, PhC*H*CH), 7.17-7.39 (5H, m, 5×Ar*H*), O*H* not found; **^{13}C NMR ($CDCl_3$, 101 MHz)** δ_C: 36.6 (*C*H$_2$CH$_2$OH), 63.6 (CH$_2$*C*H$_2$OH), 62.2 (*C*H$_2$OH), 126.2 (2×Ar*C*), 126.5, 127.4, 128.7 (2×Ar*C*), 128.7 (2×Ar*C*), 133.0, 137.4. Spectroscopic data in accordance with the literature.[67]

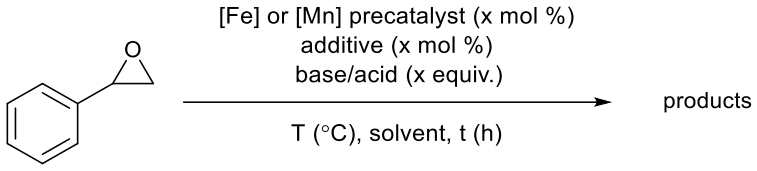
(E)-2-methyl-4-phenylpent-3-en-1-ol (91)



91

The title compound was prepared according to general procedure 4 using **90** as allylic alcohol. The crude NMR value was found to be 58% (chapter 4, figure 12). Purification *via* flash silica column chromatography (eluent = 10-20% EtOAc in hexanes, 20 × 170 mm silica) gave the title compound as a colourless oil; R_f: 0.23 (eluent = 10% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.05 (3H, d, J 6.7, CHC*H*$_3$), 1.21-1.25 (1H, m, O*H*), 2.10 (3H, d, *J* 1.4, CC*H*$_3$), 2.77-2.88 (1H, m, C*H*CH$_3$), 3.49 (1H, dd, *J* 10.5, 7.8, CH*H*OH), 3.58 (1H, dd, *J* 10.5, 6.0, CH*H*OH), 5.55 (1H, dq, *J* 9.5, 1.4, C=C*H*), 7.16-7.42 (5H, m, 5×Ar*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 16.3 (*C*H$_3$), 16.6 (*C*H$_3$), 36.3 (*C*HCH$_3$), 67.9 (*C*H$_2$OH), 125.7 (2×Ar*C*), 126.9 (Ar*C*(4)), 128.2 (2×Ar*C*), 130.6 (*C*H), 136.9 (C), 143.5 (*C*).

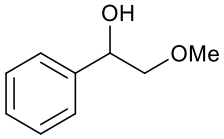
General Procedure 5: Reactions with Epoxides



99

An oven-dried 10 mL microwave vial equipped with a stirrer bar was charged with metal precatalyst, additive, acid/base (if applicable), alkylating agent (if applicable), and epoxide **99** (60.1 mg, 0.5 mmol, 1.0 equiv.). The vial was charged with solvent (1 mL) before being sealed with a cap. The mixture was left to react at 130 °C for 24 h. The reaction was cooled, diluted with EtOAc (1 mL), and quenched with H_2O (1 mL), before being transferred to a separatory funnel filled with brine (25 mL). The organic layer was collected, and the aqueous phase washed with EtOAc (2 × 10 mL). The organics were combined, dried over $MgSO_4$, filtered and concentrated in vacuo.

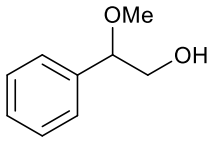
2-Methoxy-1-phenylethan-1-ol (110)



110

The title compound was prepared according to general procedure 5. Further information on reaction components and conditions to access the title compound can be found in chapter 4, table 8. Purification *via* flash silica column chromatography (eluent = 10-20% EtOAc in hexanes, 20 × 170 mm silica) gave the title compound as a colourless oil (8 mg, 10%); R_f: 0.12 (eluent = 10% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 2.76 (1H, d, *J* 2.3, CHO*H*), 3.44 (3H, s, OCH_3), 3.41-3.47 (1H, m, CH*H*), 3.55 (1H, dd, 9.8, 3.2, C*H*H), 4.90 (1H, dd, 9.0, 3.0, C*H*OH), 7.28-7.41 (5H, m, 5×Ar*H*). Spectroscopic data in accordance with the literature.[68]

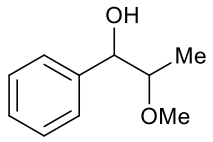
2-Methoxy-2-phenylethan-1-ol (111)



111

The title compound was prepared according to general procedure 5. Further information on reaction components and conditions to access the title compound can be found in chapter 4, table 8. Purification *via* flash silica column chromatography (eluent = 10-20% EtOAc in hexanes, 20 × 170 mm silica) gave the title compound as a colourless oil (22 mg, 29%); R_f: 0.15 (eluent = 10% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 2.23-2.32 (1H, m, CHO*H*), 3.31 (3H, s, OCH_3), 3.58-3.71 (2H, m, CH_2), 4.31 (1H, dd, *J* 8.5, 3.8, C*H*OH), 7.27-7.41 (5H, m, 5×Ar*H*). Spectroscopic data in accordance with the literature.[69]

2-Methoxy-1-phenylpropan-1-ol (112)



112

The title compound was prepared according to general procedure 5. Further information on reaction components and conditions to access the title compound can be found in chapter 4, table 8. Purification *via* flash silica column chromatography (eluent = 10-20% EtOAc in hexanes, 20 × 170 mm silica) gave the title compound as a colourless oil (30 mg, 40%); R_f: 0.14 (eluent = 10% EtOAc in hexanes);

Major diastereoisomer:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 0.98 (3H, d, *J* 6.3, CH_3), 2.49 (1H, d, *J* 2.9, O*H*), 3.42 (3H, s, OCH_3), 3.54 (1H, qd, *J* 6.3, 3.6, C*H*CH_3), 4.91 (1H, t, *J* 3.2, C*H*OH), 7.24-7.39 (5H, m, 5×Ar*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 12.8 (*C*H_3), 56.8 (O*C*H_3), 74.6 (*C*HOH), 80.9 (*C*HOCH_3), 126.4 (2×Ar*C*), 127.4 (Ar*C*(4)), 128.3 (2×Ar*C*), 140.6 (Ar*C*(1)).

Minor diastereoisomer:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 0.98 (3H, d, *J* 6.3, CH_3), 3.24 (1H, d, *J* 1.8, O*H*), 3.42 (3H, s, OCH_3), 3.54 (1H, qd, *J* 8.0, 3.6, C*H*CH_3), 4.39 (1H, dd, *J* 8.0, 1.6, C*H*OH), 7.24-7.39 (5H, m, 5×Ar*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 14.8 (*C*H_3), 56.8 (O*C*H_3), 78.5 (*C*HOH), 81.9 (*C*HOCH_3), 127.4 (2×Ar*C*), 128.1 (Ar*C*(4)), 128.5 (2×Ar*C*), 140.6 (Ar*C*(1)).

Spectroscopic data in accordance with the literature.[70]

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Chapter 5

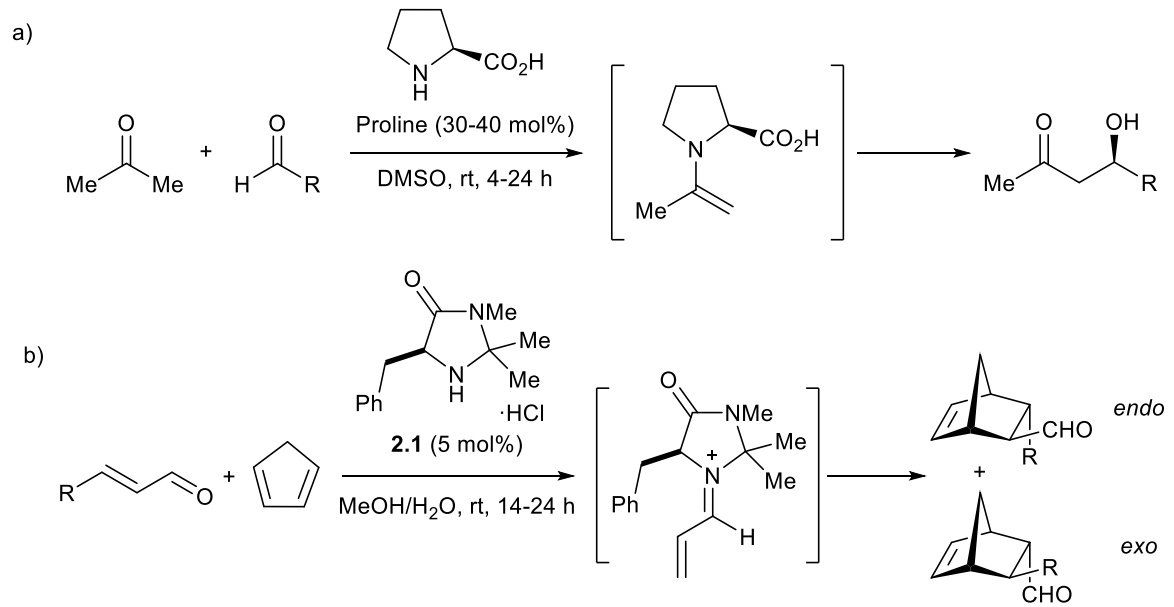
Introduction to Frustrated Lewis Pairs

Table of Contents

5.1 Metal free Catalysis

The application of transition metal catalysts in organic chemistry is associated with several drawbacks such as toxicity, cost, the synthetic requirements to obtain non-commercial ligands, and the threshold obligations in pharmaceutical products. Furthermore, transition metal-catalysis reactions often require oxygen- or moisture-free conditions. These considerations make transition metal-catalysis particularly restrictive when considering them for large-scale applications. Thus, the practicality of transition metal-free chemistry makes it a highly desirable alternative.

The development of organocatalysis was a remarkable feat in chemistry, with Nobel prizes deservedly awarded to Professors Benjamin List and David MacMillan in 2021 for their contributions to asymmetric organocatalysis. In 2000, these researchers independently developed two different strategies. List reported amino acid proline as an effective catalyst for the aldol reaction between acetone and a variety of aldehydes (scheme 32a).[1] Meanwhile, MacMillan reported an enantioselective amine-catalysed Diels–Alder reaction *via* an iminium activation mode (scheme 32b).[2]



Scheme 32: Early asymmetric organocatalytic processes as developed by Nobel laureates Benjamin List (a) and David MacMillan (b).

This research demonstrated that small organic compounds could do the same job as metals or enzymes, triggering a surplus of publications in branching areas, particularly asymmetric processes spanning Brønsted acid,[3] Brønsted base,[4] and Lewis Acid/base catalysis.[5]

5.1.1 Metal Free-Catalysed Hydrogenation

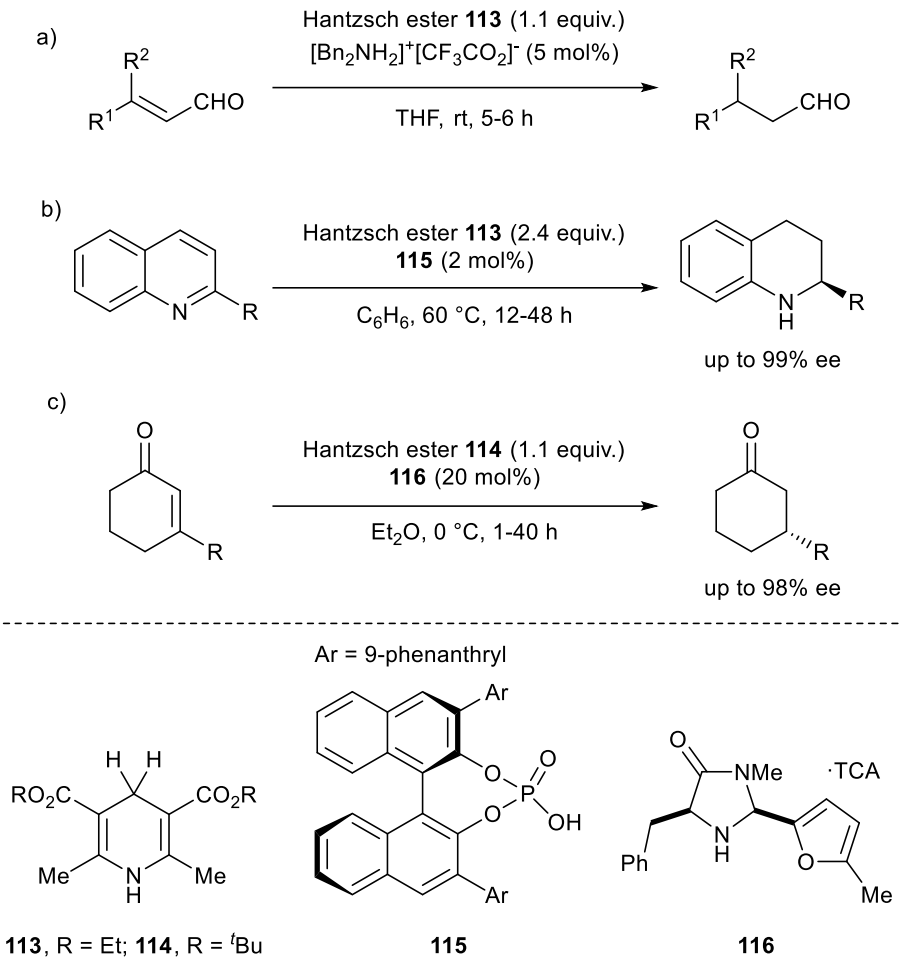
Before 2000, metal-free hydrogenation processes were all but unknown.[6] The earliest known report of a (non-biocatalytic) metal-free catalysed hydrogenation was the use of potassium *tert*-butoxide in the reduction of benzophenone in the 1960s, however, any immediate development was seemingly shunned due to the extremely harsh reaction conditions that were required (210 °C, 135 bar H_2), and the rather pitiful substrate scope.[7,8]

The emergence of organocatalysis in the early 2000s saw the development of several metal-free hydrogenation processes, albeit employing hydrogen donors or surrogates. Direct hydrogenation with molecular hydrogen (H_2) remained exclusive to transition metal-catalysis (as described in chapter 1.1.1).

Hantzsch esters were popularised as hydrogen donors in works by List, Reuping and MacMillan. In 2004, List demonstrated the transfer hydrogenation of α,β-unsaturated aldehydes *via* an enamine intermediate by employing Hantzsch ester **113** (scheme 33a).[9] The same Hantzsch ester was employed by Reuping in 2006, in a Brønsted acid-catalysed asymmetric transfer hydrogenation of 2-substituted quinolines in the presence of chiral phosphoric acid **115** (scheme 33b).[10] Simultaneously, MacMillan employed slightly modified Hantzsch ester **114** in an asymmetric transfer hydrogenation of cyclic enones, which, characteristic of his research output, proceeded *via* iminium activation employing amine catalyst **116** (scheme 33c).[11]

More recently, cyclohexa-1,4-dienes have been utilised by Chatterjee and Oestrich as alternative hydrogen donors to Hantzsch esters for the transfer hydrogenation of alkenes and imines.[12,13] This significant development is a product of organocatalysis,

and has branched into its own unique concept known as Frustrated Lewis Pair catalysis.



Scheme 33: Early metal-free hydrogenation processes employing Hantzsch esters, as developed by List (a), Reuping (b), and MacMillan (c).

5.2 Frustrated Lewis Pairs

When a Lewis base and a Lewis acid combine, the lone pair of electrons on the Lewis base are donated into the empty p-orbital of the Lewis acid, forming a stabilised classical Lewis adduct. A Frustrated Lewis Pair (FLP) is a compound or mixture of two compounds containing a Lewis acid and a Lewis base component, however, they do not combine to form an adduct due to steric hindrance (figure 13). This observation was first noticed by Brown *et al.* in 1942,[14] whereby adduct formation was observed between lutidine and boron trifluoride (BF_3) but did not with trimethylborane (BMe_3) (scheme 34a). In 1966, Tochtermann described trityl anion

and triphenylborane (BPh_3) as the German term "antagonistisches Paar", observing addition to butadiene, rather than "quenched" adduct formation (scheme 34b).[15]

The term "Frustrated Lewis Pair" was coined by Professor Douglas Stephan, who in 2006 reported the first transition metal-free heterolytic splitting of H_2 employing phosphinoborane **117**; which was red in colour.[16] The isolated, colourless, zwitterionic phosphonium borate salt (**118**), which contained both protic and hydridic fragments, liberated H_2 when heated above 100 °C (scheme 34c).

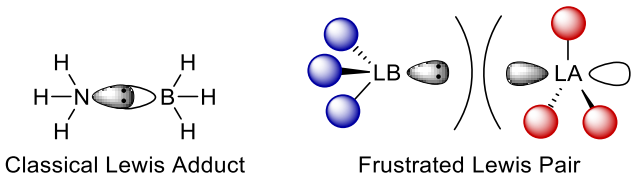
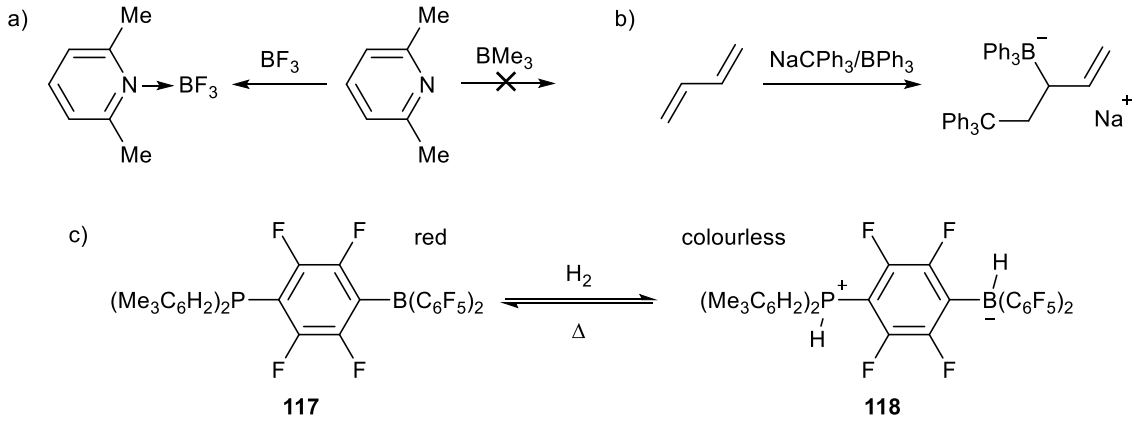


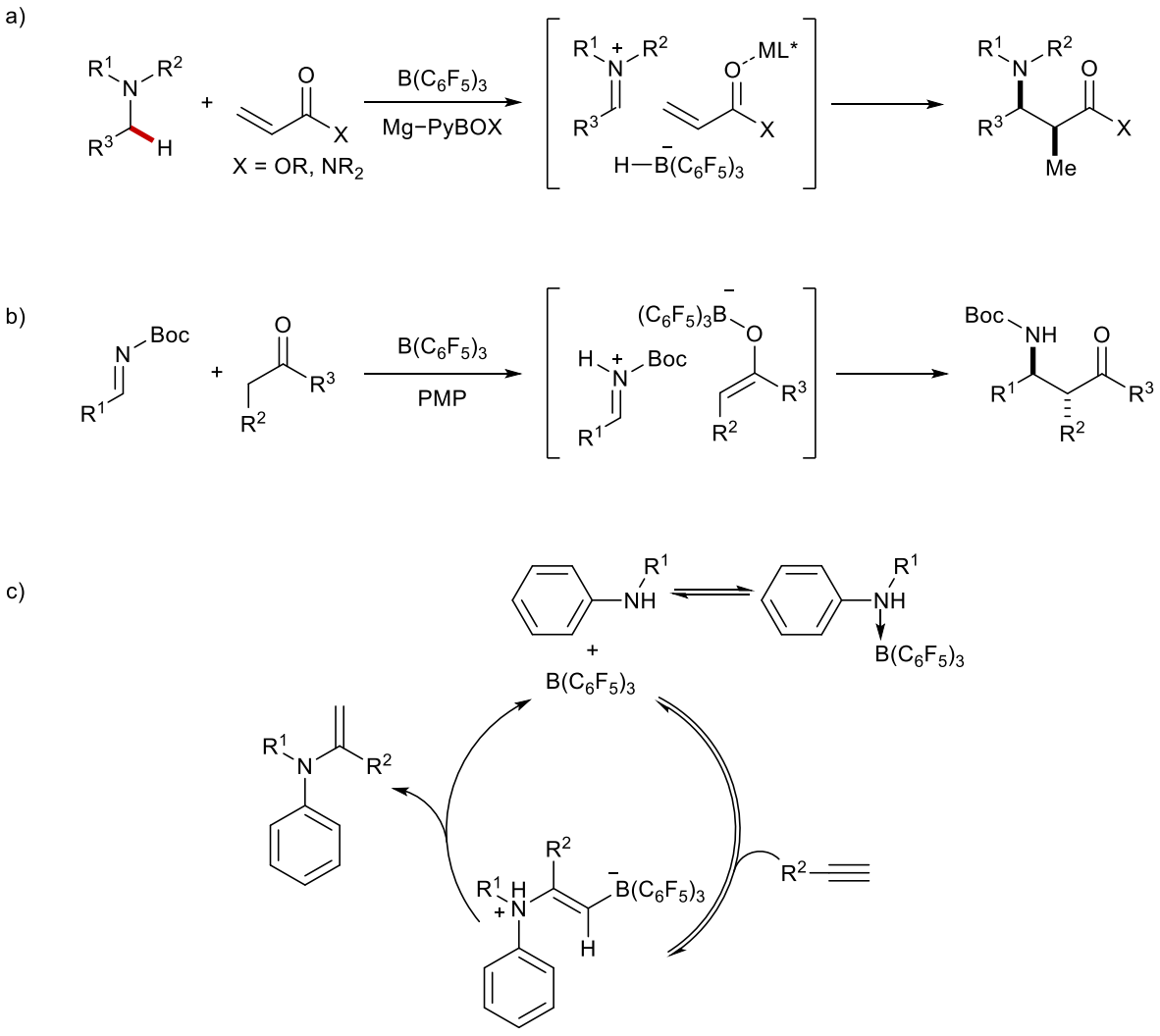
Figure 13: Illustrative representations of a classical Lewis adduct (ammonia-borane) and an FLP.



Scheme 34: a) Brown *et. al* - no adduct formation observed between lutidine and BMe_3; b) Tochtermann – addition of trityl anion and BPh_3 to butadiene; c) Stephan – reversible heterolytic splitting of H_2.

The reversible activation of H_2 by Stephan was an extraordinary discovery considering the strength of the H-H bond (432 kJ mol^{-1}),[17] and encouraged further investigations with other Lewis acid/base pairs.[18,19] For example, amines, phosphines and carbenes have all been utilised as Lewis bases in various FLP-catalysed procedures, often partnered with strongly Lewis acidic fluorinated boranes,[20] such as tris(pentafluorophenyl)borane ($B(C_6F_5)_3$ or BCF).

The diversification of FLPs eventually led to the activation of other small molecules including SO_2, CO_2, CO and NO_2, providing an avenue for the development of capture processes.[21,22] Ashley and O'Hare employed BCF and tetramethylpiperidine to capture and subsequently reduce CO_2 to methanol,[23] while Fontaine developed a phosphinoborane-catalysed hydroboration of CO_2 to afford methoxyboranes; another source of methanol.[24] Aluminium and boron-based Lewis acids have been widely utilised in FLP-catalysed polymerisation processes.[25] Other FLP-catalysed processes include C-H borylation of heteroarenes[26] and alkynes,[27] and hydrosilylation of ketones and alkenes,[28] including enantioselective reports.[29]



Scheme 35: a) Wasa - FLP-catalysed C-H functionalisation; b) Wasa - FLP-catalysed Mannich-type reactions; c) Stephan – proposed cycle for FLP-catalysed hydroamination of terminal alkynes.

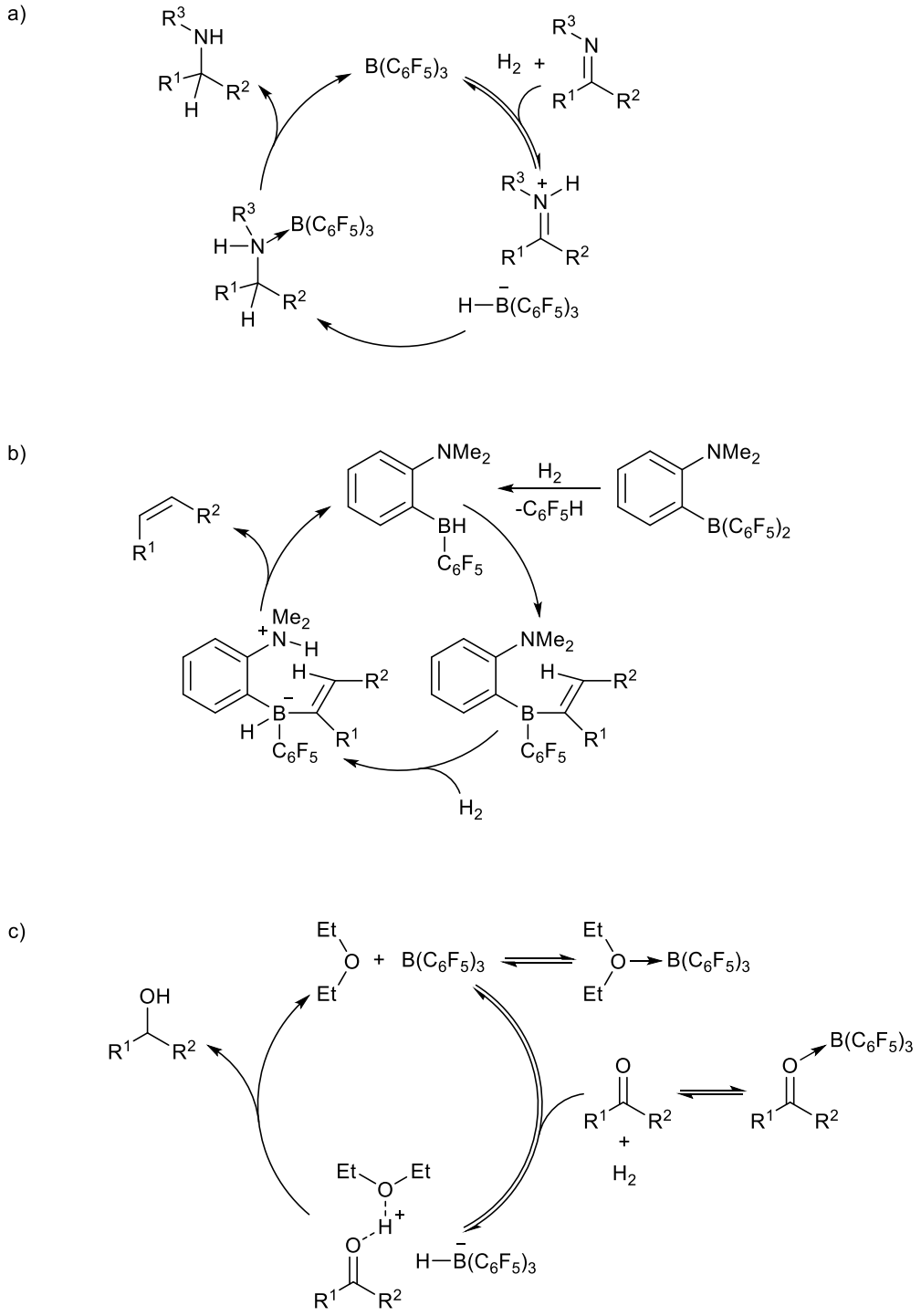
Wasa and co-workers have made significant contributions to the field, demonstrating FLP-catalysed C-H functionalisation of amines *via* hydride abstraction (scheme 35a),[30] and FLP-catalysed Mannich-type reactions *via* iminium activation (scheme 35b).[31] Among many other notable contributions, Stephan and co-workers developed FLP-catalysed hydroamination of terminal alkynes (scheme 35c).[32]

Not surprisingly, following Stephan's initial discovery of H_2 activation, no FLP-catalysed process has been investigated more than hydrogenation.[33] As previously hinted, processes employing hydrogen surrogates are known with cyclohexadienes,[12,13] and ammonia-borane.[34] Hydrosilylation is also known using similar FLP approaches.[35] Despite the safety considerations surrounding its storage and application, H_2 is an extremely atom economical commodity, making it an appealing resource for industrial processes. From here onwards, only direct hydrogenation processes will be discussed.

5.2.1 Frustrated Lewis Pair-Catalysed Hydrogenation

The generation of both a hydridic and protic hydrogen source from FLP-catalysed H_2 activation meant they could be exploited in the reduction of various unsaturated compounds.[36] Imines were the first substrates to successfully be hydrogenated in this way.[37,38] The basic nature of imines allows for its participation in hydrogen activation, in conjunction with a compatible Lewis acid,[39] negating the need for additional amine/phosphine additives. The mechanism is widely perceived to follow protonation of the imine, followed by hydride delivery (scheme 36a).

The scope of hydrogenation has since been extended to enamines,[38] silyl enol ethers,[40] nitriles,[41] amides,[42] N-heterocycles,[43] arenes,[43] and alkenes[44]. In 2013, Repo and co-workers used an intramolecular FLP to catalyse the stereoselective partial hydrogenation of alkynes to *cis*-alkenes (scheme 36b).[45] This represents a metal-free alternative to Lindlar's catalyst for alkyne reduction.[46] The hydrogenation of various Michael acceptors such as aza-Morita-Baylis-Hillman adducts[47], nitroolefins and acrylates,[48] has been demonstrated. More recently in 2021, Ashley and co-workers achieved the first FLP-catalysed direct hydrogenation of esters.[49]



Scheme 36: Catalytic cycles for FLP-catalysed hydrogenation of: a) imines; b) alkenes; and c) ketones.

The reduction of carbonyl compounds was initially challenging due to the lower basicity of oxygen compared to nitrogen. Early attempts to reduce ketones with BCF led to the irreversible formation of borinic esters ($RCH_2OB(C_6F_5)_2$) and pentafluorobenzene (C_6F_5H).[50] The groups of Stephan and Ashley independently

solved this issue by incorporating an abundance of ethereal solvent; diethyl ether and dioxane, respectively.[51,52] The ether functions as the Lewis base for participation in hydrogen activation, and the Brønsted acid that forms is acidic enough to promote direct formation of the alcohol (scheme 36c). This approach was only applicable to non-donor functionalized ketones, *i.e.* containing additional O, N and S atoms.

5.2.1.1 Enantioselective Hydrogenation

Over the years, several FLP-catalysed asymmetric processes have been successfully designed. However, they employ predominantly chiral acidic boranes.[53] This is a result of mechanistic considerations, since it was perceived for many years that the most effective way to induce chirality was *via* face-selective hydride delivery with a chiral Lewis acid – particularly since imines were the most studied.[54] The first example of chiral induction was by Klankermayer *et al.* in 2008, who reported an *α*-pinene derived chiral borane (**119**) for the asymmetric hydrogenation of imines, delivering the amine product in 13% ee.[55] In 2010, this selectivity was significantly improved to 83% ee, whereby a camphor derived borane (**120**) was employed by the same group.[56]

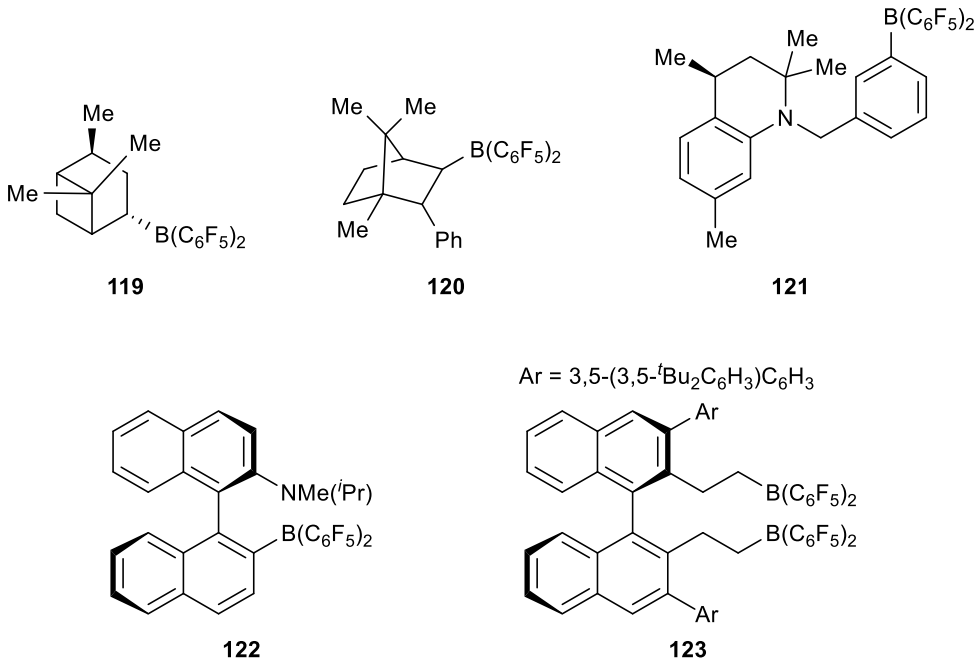
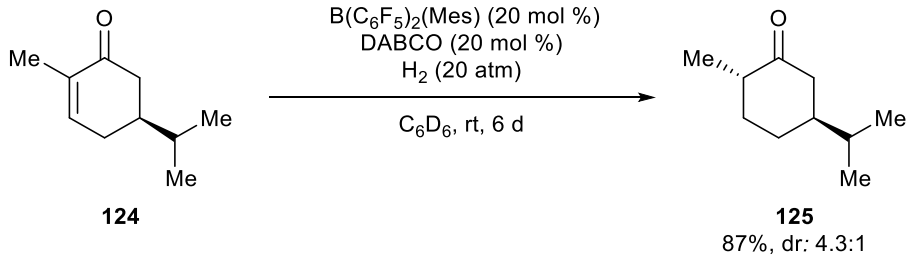


Figure 14: Chiral catalysts employed in asymmetric FLP-catalysed hydrogenation.

In 2011, Repo and co-workers reported an intramolecular FLP (**121**) for the same transformation.[57] In this work, conversion was enhanced by decreasing the basicity of the amine moiety, shifting the equilibrium for proton transfer in the direction of the product. Selectivity was also enhanced using bulkier amine moieties to increase steric hindrance around the active boron centre. Repo also developed a BINAP-derived aminoborane (**122**) for the asymmetric reduction of imines and enamines.[58]

Another key contributor to the field of asymmetric FLP-catalysed hydrogenation is Haifeng Du and co-workers. They popularized the use of chiral bis-boranes (**123**) as Lewis acids for the number of asymmetric processes including the reduction of imines,[59] and silyl enol ethers.[60] These boranes were generated *in-situ* from chiral dienes and Piers borane ($HBC_6F_5)_2$).

Lastly, a noteworthy report from Soos and co-workers reported the substrate-induced diastereoselective hydrogenation of carvone (**124**) to afford dihydrocarvone (**125**) (scheme 37).[61] The authors proposed that the chemoselectivity was attributed to the steric bulk around the C=O bond.



124 **125**
87%, dr: 4.3:1

Scheme 37: Chiral catalysts employed in asymmetric FLP-catalysed hydrogenation.

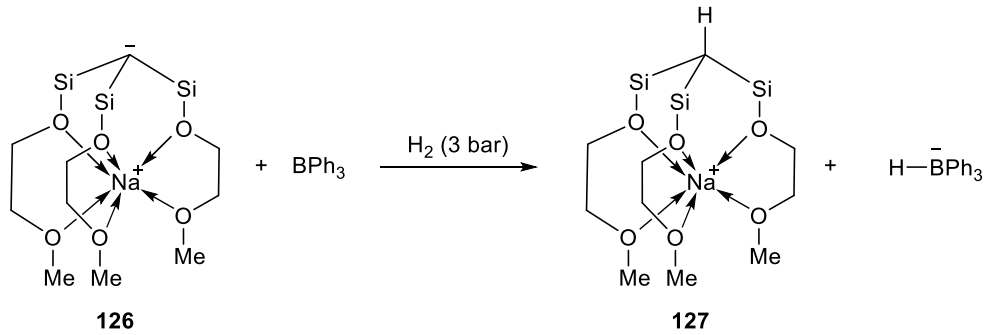
Very few enantioselective direct hydrogenation processes employ chiral Lewis bases. This concept forms much of the discussion in chapter 6.

5.2.2 Inverse Frustrated Lewis Pairs

Lewis acids for FLP catalysis are almost entirely limited to highly acidic and often fluorinated compounds such as $B(C_6F_5)_3$, $RB(C_6F_5)_2$, and $Al(C_6F_5)_3$. Slightly reducing the Lewis acidity of boranes can lead to an inactive FLP with common bases. The

feasibility of utilising weak Lewis acids for H_2 activation was subtly supported by DFT studies by Papai and co-workers. When partnered with a compatible base with sufficiently high Bronsted basicity, the FLP reaches "reactant-state destabilization", synergistically lowering the activation energy required for the heterolysis of H_2.[63]

In 2013, Krempner and co-workers presented the first "inverse" FLP approach to activate H_2. This was achieved by employing a highly basic, bulky, zwitterionic carbanion with weakly to moderately acidic boranes such as BEt_3, BPh_3 and $HBMes_2$ (scheme 38).[62] Despite the pyrophoric nature of **126**, the concept of inverse FLP catalysis was successfully validated, giving rise for potential to harness other strong, perhaps chiral, bases in conjunction with structurally simple and inexpensive boranes.[66]

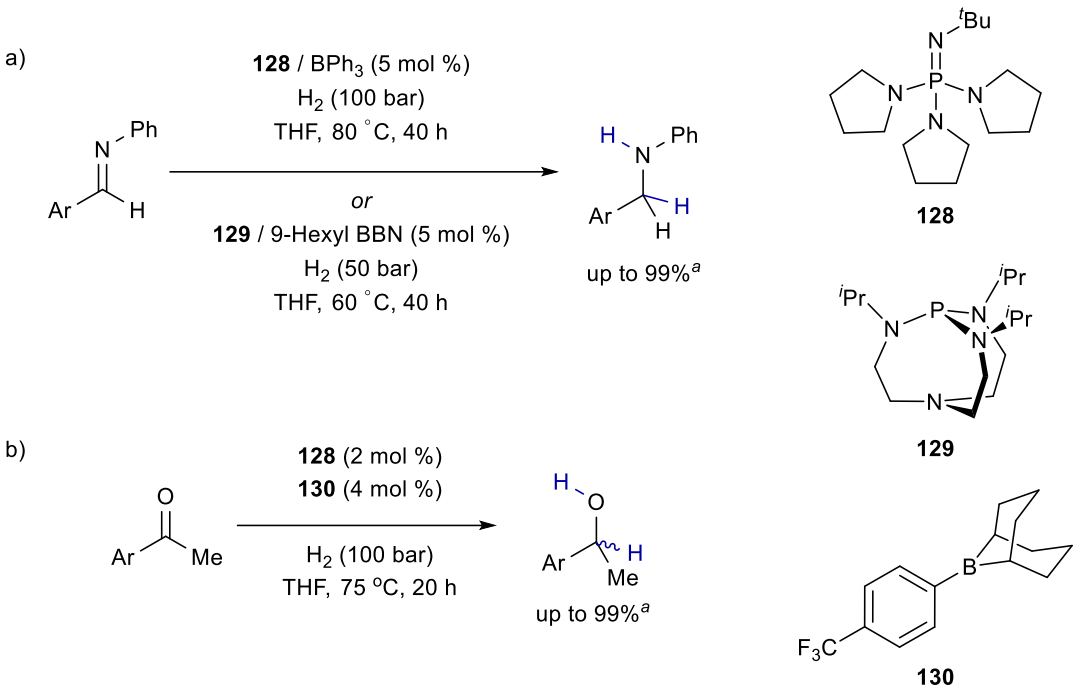


126 **127**

Scheme 38: Inverse FLP-catalysed H_2 activation.

In 2016, the same group devised the first inverse FLP-catalysed hydrogenation of aldimines (scheme 39a).[64] Two compatible FLPs were successfully implemented; phosphazene **128** and BPh_3, and phosphoramide **129** and 9-hexyl BBN, both achieving NMR yields up to 99%.

Inverse FLP-catalysed hydrogenation of ketones was later developed by Krempner and co-workers in 2018 (scheme 39b). They employed phosphazene **128** and 9-BBN derived compound **130**, tolerating ester, amine and amide functionalities up to 99% NMR yield.[65]



Scheme 39: Inverse FLP-catalysed hydrogenation of a) imines; and b) ketones.

[a]NMR yield.

5.3 Summary and Outlook

The discovery of FLP-mediated H_2 activation has resulted in a multitude of studies that advantageously negate the use of transition metals. Since FLP-catalysed hydrogenations are primarily based on fluorinated, often moisture-sensitive, highly Lewis-acidic boranes that require multistep syntheses, there remains interest in using simpler boranes for this transformation. For example, electron rich and aliphatic ketones are often poorly tolerated moieties, requiring the need for more robust and perhaps more intricate asymmetric processes. There is yet to be a well-established asymmetric hydrogenation employing chiral phosphines, and there is certainly potential for an inverse FLP-catalysed hydrogenation process employing chiral superbases.

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Chapter 6

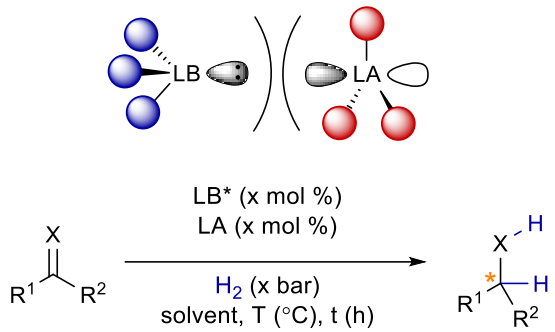
Enantioselective Hydrogenation employing Frustrated Lewis Pair Catalysis

Table of Contents

For related experimental and characterisation data, see chapter 7

6.1 Preface

This chapter discusses investigations into enantioselective hydrogenation promoted by chiral Frustrated Lewis Pairs (FLPs). A range of chiral Lewis bases were tested in combination with strongly Lewis acidic boranes for molecular hydrogen (H_2) activation and subsequent enantioselective hydrogenation of prochiral substrates. Attempts were also extended to Inverse FLP catalysis, with efforts to synthesise weak Lewis acidic boranes and chiral superbases, to catalyse the same transformation.



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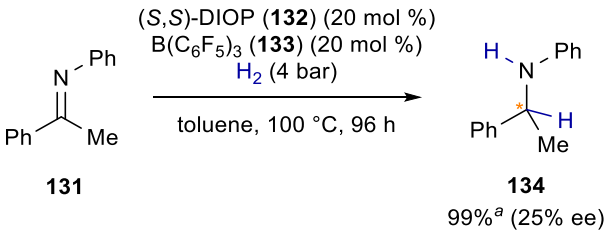
Ioan Bale – A supervised MChem who assisted with chiral superbase syntheses

Dr Imtiaz Khan – A former postdoctoral researcher who synthesised a Lewis acidic borane

6.2 Introduction

As mentioned in chapter 5.2.1.1 the most common approach for achieving FLP-catalysed enantioselective hydrogenation is to utilise a chiral Lewis acid in combination with an achiral Lewis base. Chiral Lewis bases are ubiquitous in asymmetric catalysis, commonly utilised as chiral ligands, or the catalyst itself.[1] They are also generally very stable compounds, and therefore offer a viable alternative to employing moisture sensitive, synthetically laborious chiral Lewis acidic boranes in FLP catalysis. However, the application of chiral Lewis bases with achiral Lewis acids in this field is relatively inferior, with very few examples presented in the literature.

Prior to this investigation, the only known example representing enantioselective hydrogenation of any prochiral substrate using a chiral Lewis base was a preliminary report from Stephan and co-workers in 2011.[2] This rudimentary result described the enantioselective hydrogenation of a ketimine employing an axially-chiral diphosphine, (*S*,*S*)-DIOP (**132**), achieving a 99% NMR yield and 25% ee (scheme 40).



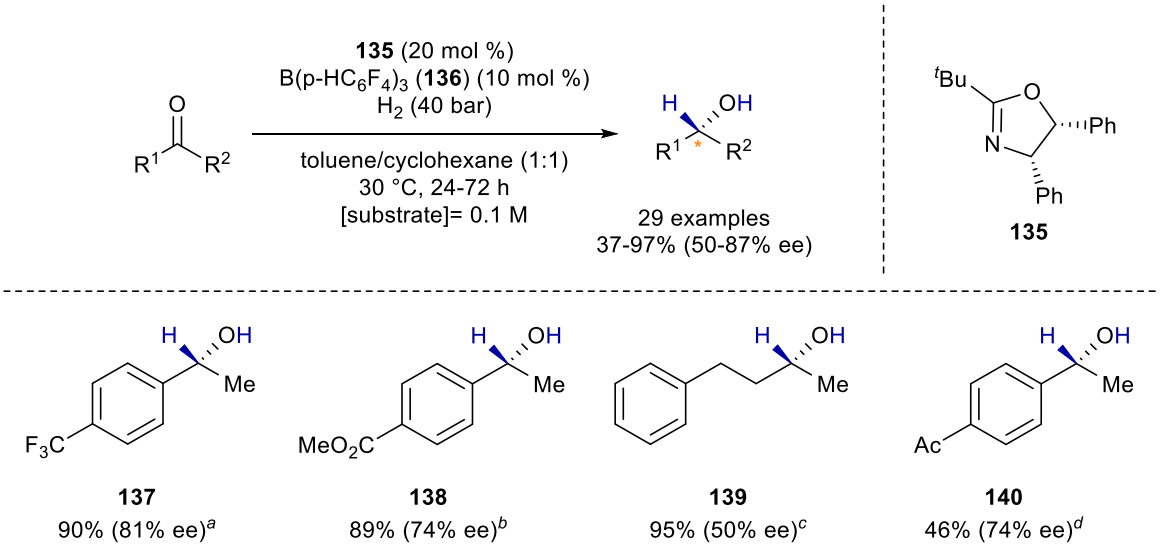
131 **134**

99%[a] (25% ee)

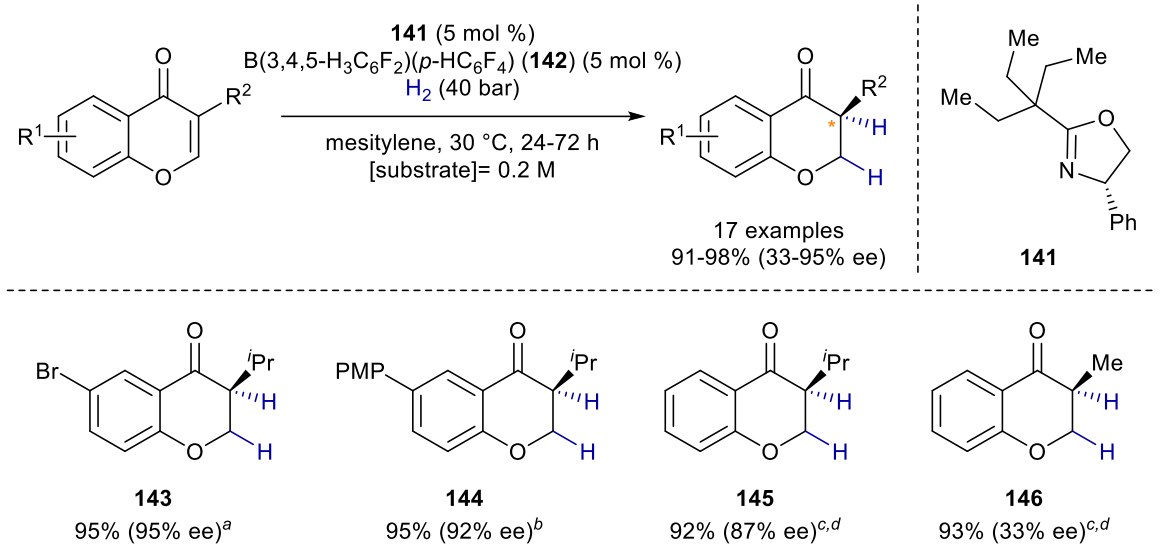
Scheme 40: First report of enantioselective hydrogenation of imines employing a chiral Lewis base. [a]Yield determined by ^{1}H NMR analysis of the crude reaction mixture.

To this day, no follow-up report for FLP-catalysed enantioselective hydrogenation of ketimines, employing a chiral Lewis base, has been disclosed. During the early stages of this investigation, a significant breakthrough was made by Du and co-workers concerning other prochiral substrates.[3] They successfully performed enantioselective hydrogenation on a variety of ketones and activated alkenes, employing modified chiral oxazolines as the Lewis base in combination with a strong Lewis acid. This work is illustrated in schemes 41-43, including representative examples for each substrate class.

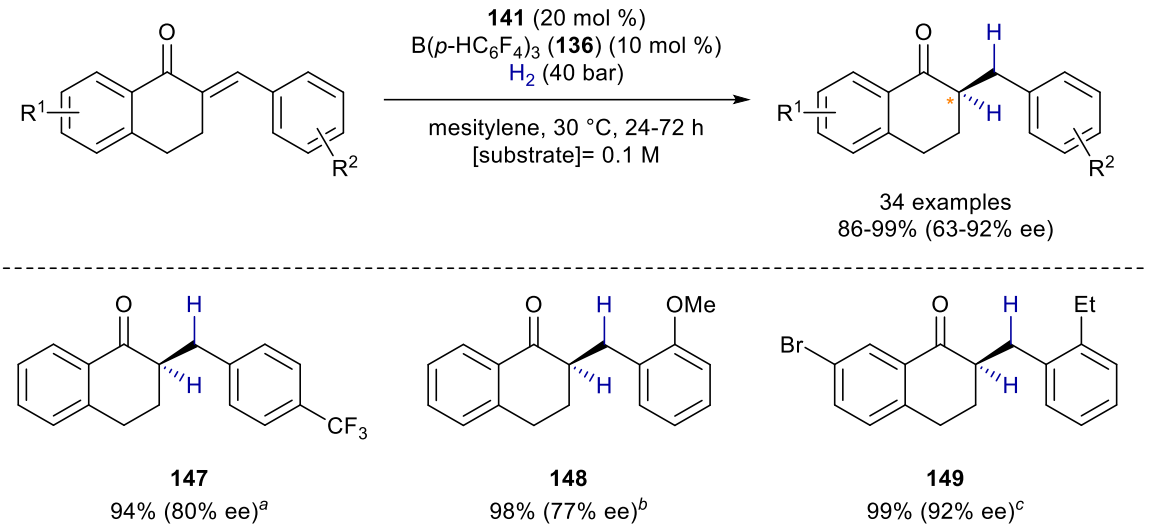
Within their ketone scope (scheme 41), the transformation was limited to electron deficient aryl ketones, and many substrates required longer reaction times and/or an increase in temperature. While the latter is also true for 3-substituted chromones and α-tetralone-derived enones, these activated alkene scopes were tolerant of both electron poor and electron donating substituents (scheme 42-43).



Scheme 41: Du and co-workers - FLP-catalysed enantioselective hydrogenation of ketones.
[a]24 h; [b]48 h; [c]40 °C, 72 h; [d]72 h, **135** (40 mol %) and **136** (20 mol %).



Scheme 42: Du and co-workers - FLP-catalysed enantioselective hydrogenation of chromones.
[a]24 h; [b]48 h; [c]72 h; [d]40 °C.



Scheme 43: Du and co-workers - FLP-catalysed enantioselective hydrogenation of *α*-tetralone-derived enones.

[a]24 h; [b]48 h; [c]72 h.

Despite the emergence of this report, the research plan persisted, since initial plans were to investigate commercially available, point-chiral phosphines as Lewis bases for FLP-catalysed asymmetric hydrogenation of various prochiral substrates.

6.3 Results and Discussion

6.3.1 Initial Studies employing Chiral Phosphines

The aim was to identify an FLP combination that could, firstly, activate H_2, and secondly, facilitate enantioselective hydrogenation of prochiral substrates. An assortment of commercially available chiral phosphines, illustrated in figure 15, were selected for this investigation. These primarily consisted of point-chiral phosphines, as it is anticipated the need for chiral information to be positioned as close to the phosphorus centre as possible to effect enantioselective hydrogen transfer. Proposed mechanisms are discussed in detail for each substrate class within the forthcoming chapters.

As discussed in chapter 5.2.1, it is important to match the Lewis base with a compatible Lewis acid to enable H_2 activation. A selection of achiral boranes of variable Lewis acidity (figure 16) were tested alongside the aforementioned

phosphines to ascertain whether they are able to activate H_2. $B(C_6F_5)_3$ (**133**) and $B(3,5\text{-}H_2C_6F_3)_3$ (**156**) were synthesised in house (see chapter 7 for experimental) or obtained commercially if available. $B(3,4,5\text{-}H_3C_6F_2)$ (**142**) was synthesised in house by a former postdoctoral researcher – Dr Imtiaz Khan. BPh_3 (**158**) was obtained commercially. All Lewis acids were purified in-house *via* sublimation prior to use.

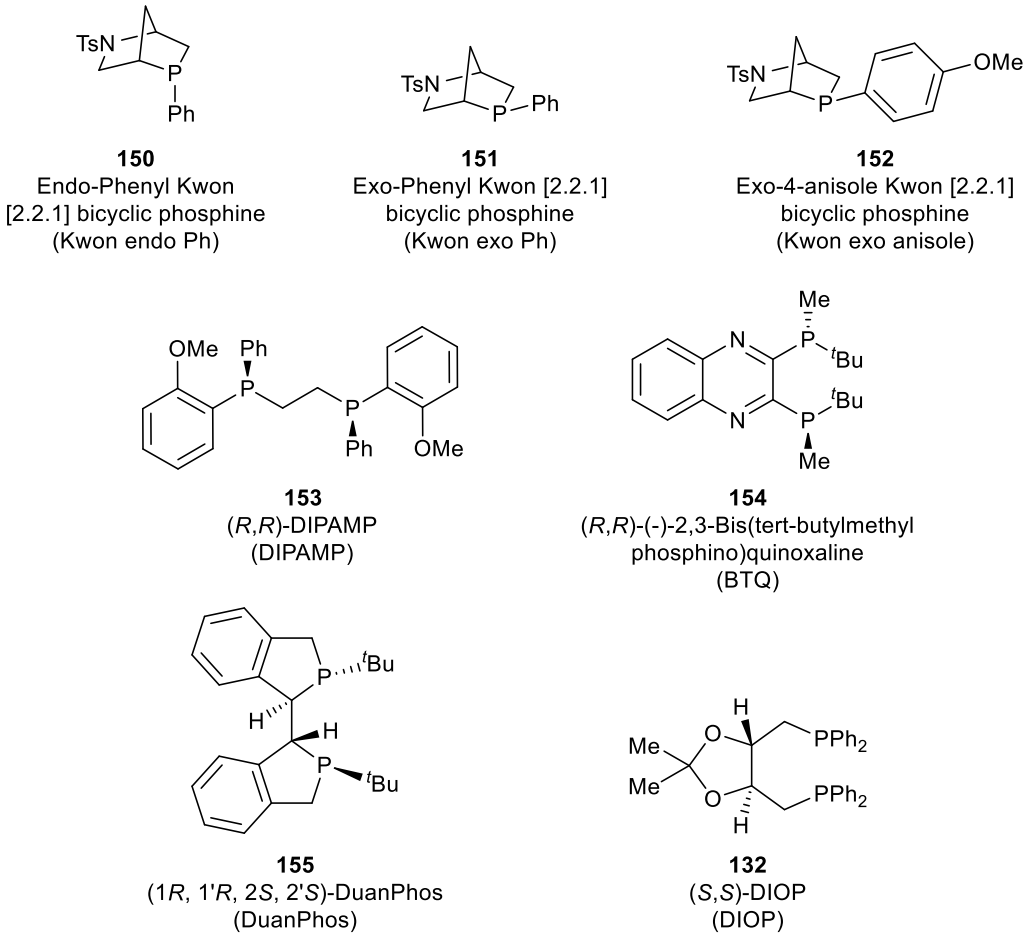


Figure 15: A selection of chiral phosphines employed for initial studies.

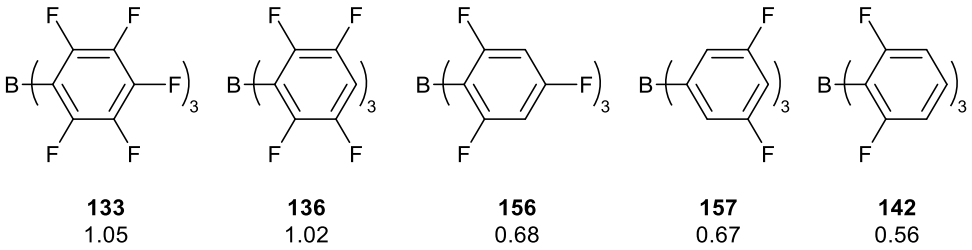
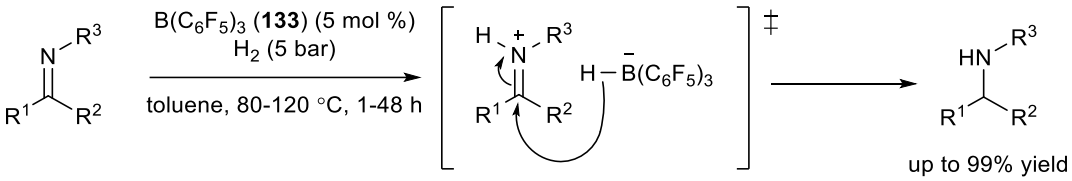


Figure 16: Lewis acidic boranes employed for initial studies and their relative Lewis acidities.[4,5]

6.3.1.1 Imines

It is well-documented that imines can be hydrogenated with H_2 solely in the presence of a Lewis acid catalyst. The imine itself partakes in FLP-catalysed H_2 activation as the Lewis base component due to the available lone pair on nitrogen. This was demonstrated in reports by Stephan and co-workers,[6] with the proposed mechanism illustrated in scheme 44.

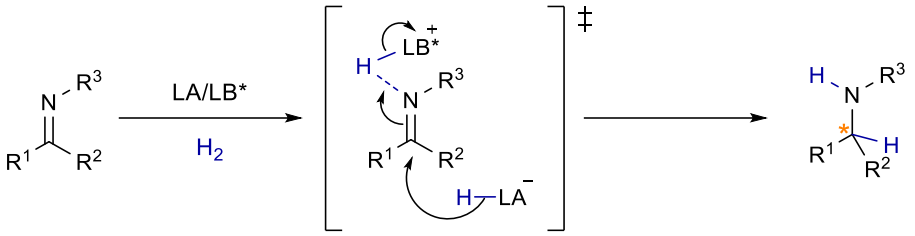


Scheme 44: Lewis acid-catalysed hydrogenation of imines.

Evidently, from the proposed mechanism, there are palpable challenges to overcome in the investigation; namely that the chiral Lewis base must outcompete the substrate for H_2 activation. Should the substrate prevail, and the chiral conjugate acid not form as a result, racemic products are effectively guaranteed. Similarly, if proton transfer from the chiral conjugate acid to the imine occurs first, the chiral Lewis base will be released from the reaction site, and its chirality will have negligible impact on the asymmetric induction. More obviously, if hydride delivery occurs readily, there is nothing to govern stereoselectivity, resulting in racemic products. Given the electrophilic nature of imines, the Lewis acid must be carefully selected to avoid premature hydride delivery. A strong Lewis acid is a less potent source of hydride, while the opposite is true for weak Lewis acids.

From the concerns described above, it is therefore imperative that the mechanism should proceed in a concerted fashion for this transformation to be successful. It is anticipated that hydrogen bonding of the chiral conjugate acid with the substrate, as illustrated in scheme 45, is essential for the chiral FLP to induce any enantioselectivity. Collectively, the mentioned considerations make the enantioselective hydrogenation of imines, employing a chiral Lewis base, an extremely difficult prospect. Overall, a delicate balance of interactions must be

managed between the Lewis acid, Lewis base, and the substrate, to achieve both sufficient H_2 activation and enantioselectivity.



Scheme 45: Proposed concerted mechanism for FLP-catalysed enantioselective hydrogenation of imines, employing a chiral Lewis base and achiral Lewis acid.

The investigation began by confirming the legitimacy of the result obtained by Stephan and co-workers in 2011 employing (*S*,*S*)-DIOP (**132**) as the chiral Lewis base (scheme 40). Attempts were made to replicate the reaction *via* the reported procedure and a modified procedure with a Young's NMR tube. The direct replication led to only 15% mass recovery, all being racemic product. A repeat confirmed the reliability of this result (table 9, entries 1-2). The crude NMR, stacked with starting material **131** and product **134**, are shown in figure 17. Performing the reaction in a Young's NMR tube resulted in full mass recovery, however, conversion of starting material was incredibly poor (entry 3), possibly due to lack of mixing and a much lower surface area between the mixture and H_2 atmosphere. The volume of H_2 in the Young's NMR tube was also considerably lower. Suspecting decomposition of the product at high temperatures, the reaction was performed at 80 °C. Full mass recovery was observed, however, the yield of **134** was not improved.

Entry[a]	Variation from standard conditions	**131**[b] RSM (%)	**134**[b] P (%)	ee (%)
1	None	0	15 (lit. 99)	0 (lit. 25)
2	None (repeat)	0	13	0
3	Reaction performed in Young's NMR tube	96	4	0
4	80 °C instead of 100 °C	85	15	0

Table 9: Attempted replication of reaction as performed by Stephan and coworkers.

[a]Standard conditions: imine **131** (0.5 mmol, 1.0 equiv.), LA **133** (5 mol %), H_2 (4 bar), degassed toluene (2 mL), 100 °C, 96 h. [**131**] = 0.25 M. [b]Yield of amine **134** as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard.

Regardless of these yields, the products were isolated and analysed using HPLC to reveal zero enantiomeric excess in all cases.

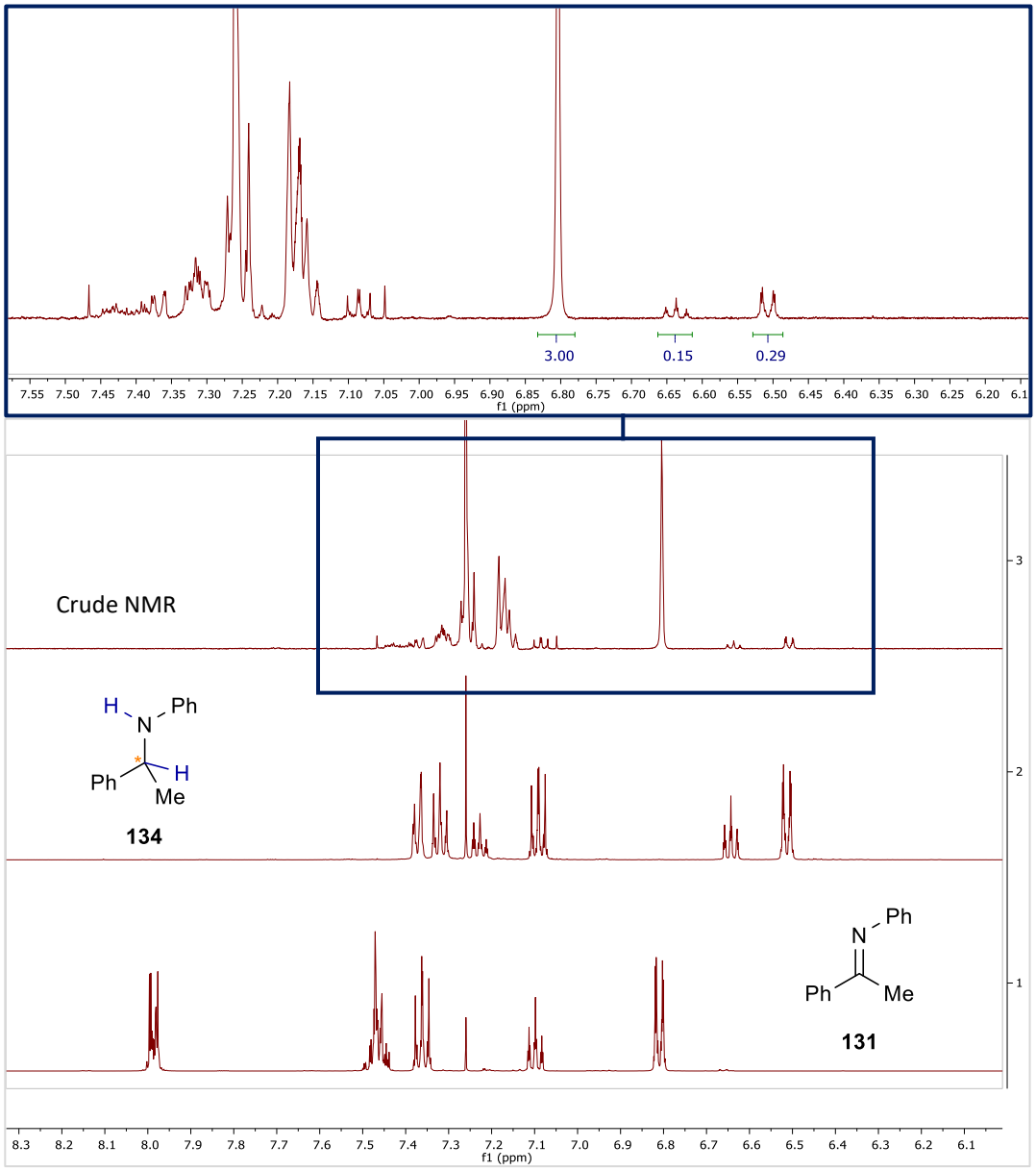
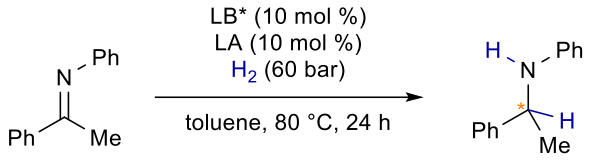


Figure 17: Stacked NMR spectra for **131**, **134** and crude NMR for replication of Stephan's reaction (table 9, entry 1).

The unsuccessful attempt to reproduce this result, despite using fresh reagents and thorough practical techniques, seeded considerable doubt concerning its legitimacy. The commercial sample of (*S*,*S*)-DIOP (**132**) was pure by NMR analysis and also optically active; $[\alpha]_D^{20}$ +26.7 (c 0.3, CH_2Cl_2) {lit.[7] $[\alpha]_D^{20}$ +27.7 (c 0.015, CH_2Cl_2}. Despite suspicions, the decision was made to persist with the investigation. Conditions of 80

°C and 60 bar H_2 were selected, as these were thought to be robust in ensuring sufficient H_2 activation and high consumption of starting material when employing various FLP combinations.

First, using (*E*)-N,1-diphenylethan-1-imine **131** as the substrate, background reactions were carried out to observe whether H_2 activation took place between the imine substrate and Lewis acid. Background reactions were observed using fluorinated Lewis acids **133**, **156** and **157** (table 10, entries 1-3). No background reaction took place when BPh_3 (**158**) was employed as the Lewis acid (entry 4).



131 **134**

Entry[a]	Lewis acid LA		Chiral Lewis base LB*		**131**[b] RSM (%)	**134**[b] P (%)	ee[c] (%)
1	**133**	$B(C_6F_5)_3$	-		0	90 (88)	0
2	**156**	$B(3,5\text{-}H_2C_6F_3)_3$	-		0	91 (81)	0
3	**157**	$B(3,4,5\text{-}H_3C_6F_2)_3$	-		0	93 (84)	0
4	**158**	BPh_3	-		69	0	n/a
5	**133**	$B(C_6F_5)_3$	**150**	Kwon endo Ph	0	94 (89)	0
6	**133**	$B(C_6F_5)_3$	**151**	Kwon exo Ph	0	96 (94)	0
7	**133**	$B(C_6F_5)_3$	**152**	Kwon exo Anisole	0	96 (95)	0
8	**133**	$B(C_6F_5)_3$	**153**	DIPAMP	0	95 (18)	0
9	**133**	$B(C_6F_5)_3$	**154**	BTQ	0	92 (29)	0
10	**133**	$B(C_6F_5)_3$	**155**	DuanPhos	0	96 (95)	0
11	**133**	$B(C_6F_5)_3$	**132**	DIOP	0	98 (92)	0
12	**157**	$B(3,4,5\text{-}H_3C_6F_2)_3$	**150**	Kwon endo Ph	0	99 (95)	0
13	**157**	$B(3,4,5\text{-}H_3C_6F_2)_3$	**151**	Kwon exo Ph	0	99 (91)	0
14	**157**	$B(3,4,5\text{-}H_3C_6F_2)_3$	**152**	Kwon exo Anisole	0	99 (87)	0
15	**157**	$B(3,4,5\text{-}H_3C_6F_2)_3$	**153**	DIPAMP	0	93 (82)	0
16	**157**	$B(3,4,5\text{-}H_3C_6F_2)_3$	**154**	BTQ	0	99 (85)	0
17	**157**	$B(3,4,5\text{-}H_3C_6F_2)_3$	**155**	DuanPhos	0	94 (84)	0
18	**157**	$B(3,4,5\text{-}H_3C_6F_2)_3$	**132**	DIOP	0	99 (98)	0

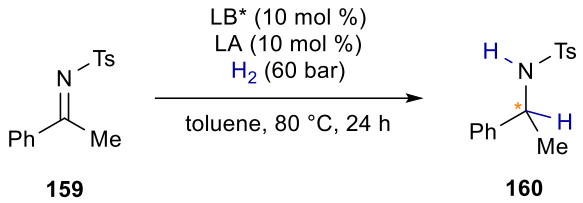
Table 10: Reaction data for FLP-catalysed hydrogenation of *N*-phenyl ketimine **131**.

[a]Reactions performed according to General procedure 1 (experimental chapter 7) using 0.2 mmol of ketimine **131** and degassed toluene. [**131**] = 0.25 M. [b]Yield after 24 h as determined by ^1H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yield given in parentheses. [c]Enantiomeric excess determined by HPLC analysis.

Despite this set of somewhat expected results, it is anticipated the addition of a chiral Lewis base may outcompete the substrate for H_2 activation and induce

enantioselectivity within the product. These subsequent reactions provided excellent NMR yields for product **134**, however, zero enantiomeric excess was observed in all cases (entries 5-18). We cannot determine the method by which H_2 activation arises, nor can we assume the mechanism of overall hydrogen transfer at this stage.

In an effort to thwart its participation in H_2 activation, the imine was thereafter modified by replacing the phenyl group with a more electron withdrawing tosyl group, consequently reducing the basicity of the nitrogen lone pair. Results revealed that the background reaction no longer occurred using Lewis acids **156** and **157** (table 11, entries 2 and 3). The background reaction was also marginally impeded when employing Lewis acid **133**, returning 6% starting material (entry 1). Furthermore, the addition of chiral Lewis bases hampered product formation (entries 5-10), though with one exception (**155**, entry 9).



159 **160**

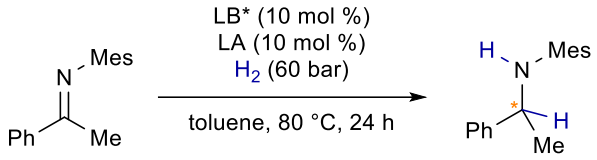
Entry[a]	Lewis acid LA		Chiral Lewis base LB*		**159**[b] RSM (%)	**160**[b] P (%)	ee[c] (%)
1	**133**	$B(C_6F_5)_3$	-		6	83 (75)	0
2	**156**	$B(3,5\text{-}H_2C_6F_3)_3$	-		99	0	n/a
3	**157**	$B(3,4,5\text{-}H_3C_6F_2)_3$	-		92	0	n/a
4	**158**	BPh_3	-		93	0	n/a
5	**133**	$B(C_6F_5)_3$	**151**	Kwon exo Ph	0	35 (25)	0
6	**133**	$B(C_6F_5)_3$	**152**	Kwon exo Anisole	0	20 (17)	0
7	**133**	$B(C_6F_5)_3$	**153**	DIPAMP	0	21 (17)	0
8	**133**	$B(C_6F_5)_3$	**154**	BTQ	0	40 (32)	0
9	**133**	$B(C_6F_5)_3$	**155**	DuanPhos	0	87 (74)	0
10	**133**	$B(C_6F_5)_3$	**132**	DIOP	0	23 (22)	0
11	**156**	$B(3,5\text{-}H_2C_6F_3)_3$	**155**	DuanPhos	99	0	n/a
12	**156**	$B(3,5\text{-}H_2C_6F_3)_3$	**132**	DIOP	99	0	n/a
13	**157**	$B(3,4,5\text{-}H_3C_6F_2)_3$	**155**	DuanPhos	99	0	n/a
14	**157**	$B(3,4,5\text{-}H_3C_6F_2)_3$	**132**	DIOP	99	0	n/a

Table 11: Reaction data for FLP-catalysed hydrogenation of **159**.

[a]Reactions performed according to General procedure 1 (experimental chapter 7) using 0.2 mmol of ketimine **159** and degassed toluene. [**159**] = 0.25 M. [b]Yield after 24 h as determined by ^1H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yield given in parentheses. [c]Enantiomeric excess determined by HPLC analysis. N.b **150** was omitted from the study, as it was deemed similar to **151**.

Chiral Lewis bases **155** and **132** were also tested in combination with Lewis acids **156** and **157**, however, no H_2 activation was observed (entries 11-14). The lack of ee, in all cases of product formation, suggests that hydrogenation only occurs when the substrate partakes in H_2 activation. The introduction of a chiral Lewis base partially inhibits **159**/**133** H_2 activation but does not seem to partake itself.

Another approach to suppress substrate/Lewis acid H_2 activation was to install a bulky mesityl group on the nitrogen atom. Unfortunately, this was ineffective (table 12), producing similarly high NMR yields relative to *N*-phenyl substrate **131** (table 10).



161 **162**

Entry[a]	Lewis acid LA		Chiral Lewis base LB*	**161**[b] RSM (%)	**162**[b] P (%)	ee[c] (%)
1	**133**	$B(C_6F_5)_3$	-	0	93	0
2	**156**	$B(3,5\text{-}H_2C_6F_3)_3$	-	0	97	n/a
3	**157**	$B(3,4,5\text{-}H_3C_6F_2)_3$	-	10	90	n/a
4	**158**	BPh_3	-	99	0	n/a

Table 12: Reaction data for FLP-catalysed hydrogenation of **161**.

[a]Reactions performed according to General procedure 1 (experimental chapter 7) using 0.2 mmol of ketimine **161** and degassed toluene. [**161**] = 0.25 M. [b]Yield after 24 h as determined by ^1H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yield given in parentheses. [c]Enantiomeric excess determined by HPLC analysis.

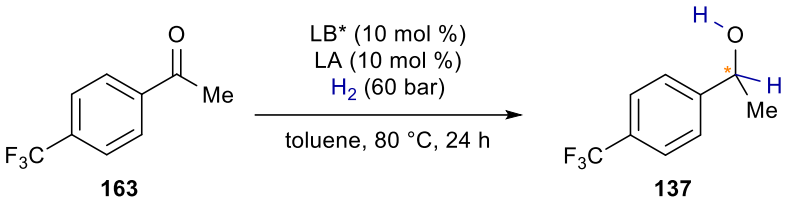
The enantioselective hydrogenation of imines will be revisited as part of a new strategy in chapter 6.3.2.1.

6.3.1.2 Ketones

Ketones are considered less basic than imines, thus the possibility of substrate/Lewis acid H_2 activation is supposedly diminished. The same hydrogenation strategy was applied to an electron withdrawing aryl ketone (**163**) that was easily identifiable by

^{1}H NMR. Background reactions were probed employing each Lewis acid (table 13, entries 1-4), and these showed no conversion of starting material – a promising start. The addition of chiral Lewis bases led to the formation of alcohol **137**, however, HPLC analysis revealed these products were all racemic (entries 5-11).

From these results, we can assume H_2 activation occurs between the Lewis acid and chiral Lewis base, and that the ketone substrate is not involved in this step. The formation of racemic products can be explained under two plausible hypotheses: 1) hydride is delivered readily to the ketone substrate without the need for protonation; 2) An equilibrium exists whereby the chiral conjugate acid readily transfers its proton to the ketone, releasing the chiral Lewis base from the reaction site.



163 **137**

Entry[a]	Lewis acid LA		Chiral Lewis base LB*		**163**[b] RSM (%)	**137**[b] P (%)	ee[c] (%)
1	**133**	$B(C_6F_5)_3$	-		99	0	n/a
2	**156**	$B(3,5\text{-}H_2C_6F_3)_3$	-		99	0	n/a
3	**157**	$B(3,4,5\text{-}H_3C_6F_2)_3$	-		99	0	n/a
4	**158**	BPh_3	-		99	0	n/a
5	**133**	$B(C_6F_5)_3$	**150**	Kwon endo Ph	84	16 (9)	0
6	**133**	$B(C_6F_5)_3$	**151**	Kwon exo Ph	86	9	n/a
7	**133**	$B(C_6F_5)_3$	**152**	Kwon exo Anisole	91	7	n/a
8	**133**	$B(C_6F_5)_3$	**153**	DIPAMP	80	17 (10)	0
9	**133**	$B(C_6F_5)_3$	**154**	BTQ	28	60 (51)	0
10	**133**	$B(C_6F_5)_3$	**155**	DuanPhos	8	82 (72)	0
11	**133**	$B(C_6F_5)_3$	**132**	DIOP	71	28 (23)	0

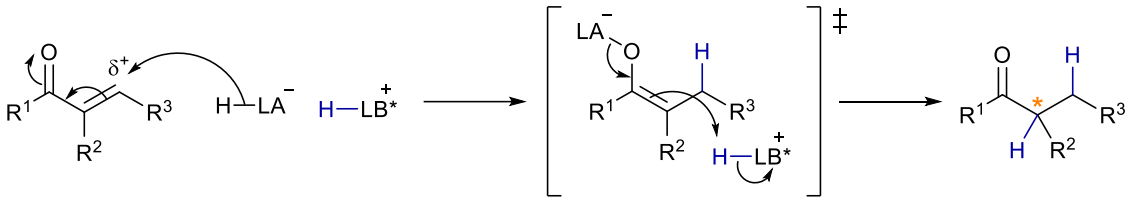
Table 13: Reaction data for FLP-catalysed hydrogenation of **163**.

[a]Reactions performed according to General procedure 1 (experimental chapter 7) using 0.2 mmol of ketone **163** and degassed toluene. [**163**] = 0.25 M. [b]Yield after 24 h as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yield given in parentheses. [c]Enantiomeric excess determined by HPLC analysis. N.b NMR yields for entries 6 and 7 were too low to attempt isolation.

The enantioselective hydrogenation of ketones will be revisited as part of a new strategy in section 6.3.2.2.

6.3.1.3 Alkenes

The enantioselective hydrogenation of alkenes proceeds *via* an alternative mechanism to that of ketones and imines. These alkenes must be "activated" by a dipole to be reactive in nature. One class of substrate that offers such reactivity is enones. Following H_2 activation with the FLP, the achiral conjugate base performs conjugate addition of hydride to the enone.[8] Subsequent protonation of the resulting enolate-type intermediate with the chiral conjugate acid is the stereoselective step of this reaction and provides the ketone product with an α-stereocentre (scheme 46).



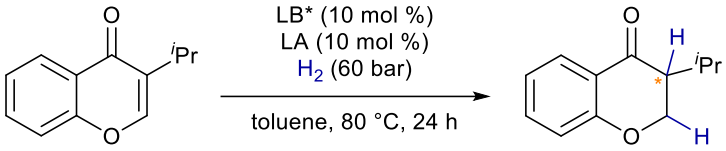
Scheme 46: Proposed concerted mechanism for FLP-catalysed enantioselective hydrogenation of enones, employing a chiral Lewis base and achiral Lewis acid.

Two classes of enone were investigated in the published work from Du and co-workers.[3] These compounds were also examined within the study. Both chromones and tetralone-derived chalcones are privileged scaffolds in drug discovery.[9,10] Chromones are specifically known for their anti-oxidant and anti-inflammatory properties.[11]

To access chiral products from chromones *via* the proposed mechanism in scheme 46, 3-substituted chromone **164** was selected as the substrate - which was synthesised in-house (see experimental chapter 7). No H_2 activation was observed in the absence of chiral Lewis base (table 14, entries 1-4). The two chiral Lewis bases that provided the highest levels of H_2 activation with ketones were then tested in combination with **133**. To clarify, **133** was chosen because it did not activate H_2 with the substrate, and more importantly offers the weakest form of hydride in the series. Disappointingly, the products were racemic (entries 5 and 6).

A similar strategy was taken for an α-tetralone chalcone, a scaffold class previously investigated for inhibitory effect against reactive oxygen species in the body.[12]

Compound **5.36** was selected as the substrate for this study. Within this study, substrate/LA H_2 activation was observed when **133** was employed as the Lewis acid (table 5.7, entry 1).

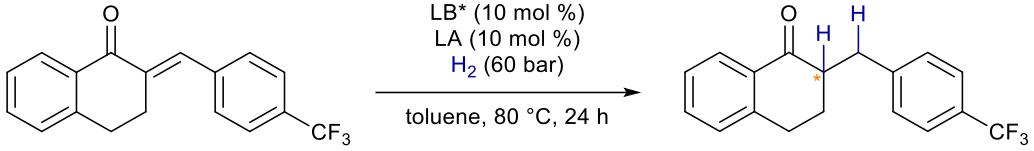


164 **145**

Entry[a]	Lewis acid LA		Chiral Lewis base LB*		**164**[b] RSM (%)	**145**[b] P (%)	ee[c] (%)
1	**133**	$B(C_6F_5)_3$	-		99	0	n/a
2	**156**	$B(3,5\text{-}H_2C_6F_3)_3$	-		99	0	n/a
3	**157**	$B(3,4,5\text{-}H_3C_6F_2)_3$	-		99	0	n/a
4	**158**	BPh_3	-		99	0	n/a
5	**133**	$B(C_6F_5)_3$	**154**	BTQ	0	93 (89)	0
6	**133**	$B(C_6F_5)_3$	**155**	DuanPhos	0	95 (88)	0

Table 14: Reaction data for FLP-catalysed hydrogenation of **164**.

[a]Reactions performed according to General procedure 1 (experimental chapter 7) using 0.2 mmol of ketone **164** and degassed toluene. [**164**] = 0.25 M. [b]Yield after 24 h as determined by ^1H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yield given in parentheses. [c]Enantiomeric excess determined by HPLC analysis.



165 **147**

Entry[a]	Lewis acid LA		Chiral Lewis base LB*		**165**[b] RSM (%)	**147**[b] P (%)	ee[c] (%)
1	**133**	$B(C_6F_5)_3$	-		14	72 (51)	n/a
2	**156**	$B(3,5\text{-}H_2C_6F_3)_3$	-		99	0	n/a
3	**157**	$B(3,4,5\text{-}H_3C_6F_2)_3$	-		99	0	n/a
4	**158**	BPh_3	-		99	0	n/a
5	**133**	$B(C_6F_5)_3$	**151**	Kwon exo Ph	25	9	0
6	**133**	$B(C_6F_5)_3$	**152**	Kwon exo Anisole	28	7	0
7	**133**	$B(C_6F_5)_3$	**154**	BTQ	11	86 (84)	0
8	**133**	$B(C_6F_5)_3$	**155**	DuanPhos	0	90 (87)	0

Table 15: Reaction data for FLP-catalysed hydrogenation of **165**.

[a]Reactions performed according to General procedure 1 (experimental chapter 7) using 0.2 mmol of enone **165** and degassed toluene. [**165**] = 0.25 M. [b]Yield after 24 h as determined by ^1H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yield given in parentheses. [c]Enantiomeric excess determined by HPLC analysis. N.b NMR yields for entries 6 and 7 were too low to attempt isolation.

Continuing with **133** as the Lewis acid, the addition of chiral Lewis bases had a varied effect on the conversion to product. Lower conversion to product was observed when employing bases **151** and **152** (entries 5 and 6), suggesting they impede substrate/LA H_2 activation, but are themselves poor at activating H_2 with **133**. This is consistent with results found in the studies investigating *N*-tosyl imines and ketones. Higher conversion was observed when employing bases **154** and **155** (entries 7 and 8), suggesting they either do not impede substrate/LA H_2 activation, or are themselves efficient at activating H_2 with **133**. The latter hypothesis is consistent with results observed in the study investigating *N*-tosyl imines. Despite this, all products were racemic. From the data gathered, we can assume one of two hypotheses: 1) an equilibrium exists whereby the chiral conjugate acid readily transfers its proton to the ketone, releasing the chiral Lewis base from the reaction site; 2) epimerization of the product is transpiring in what may be overly harsh reaction conditions.

The enantioselective hydrogenation of activated alkenes will be revisited as part of a new strategy in section 6.3.2.3.

6.3.2 Revised Strategy: New Conditions and Various Lewis Bases

With no enantiomeric excesses observed thus far, the strategy was revised, opting for milder reaction conditions, and a wider class and pkaH range of chiral Lewis base. These bases (figure 18) included a tertiary diamine (**166**), an imidazothiazole (**167**), a phosphate (**168**), as well as retaining axially chiral phosphine DIOP (**132**) and point-chiral phosphine DuanPhos (**155**).

The approach was to screen for any background reaction in the absence of chiral Lewis base, to select the most acidic Lewis acid that did not perform a background reaction, and to test it in combination with various Lewis bases. **132**, **155**, **166** and **167** were obtained commercially. **168** was obtained from the corresponding phosphoric acid, which itself was obtained commercially. We also wanted to replicate some results found by Du and co-workers using chiral oxazoline **135**, while also

observing its performance with each substrate in this system. Oxazoline **135** was synthesised by following a straight-forward two-step procedure, as illustrated in scheme 47.

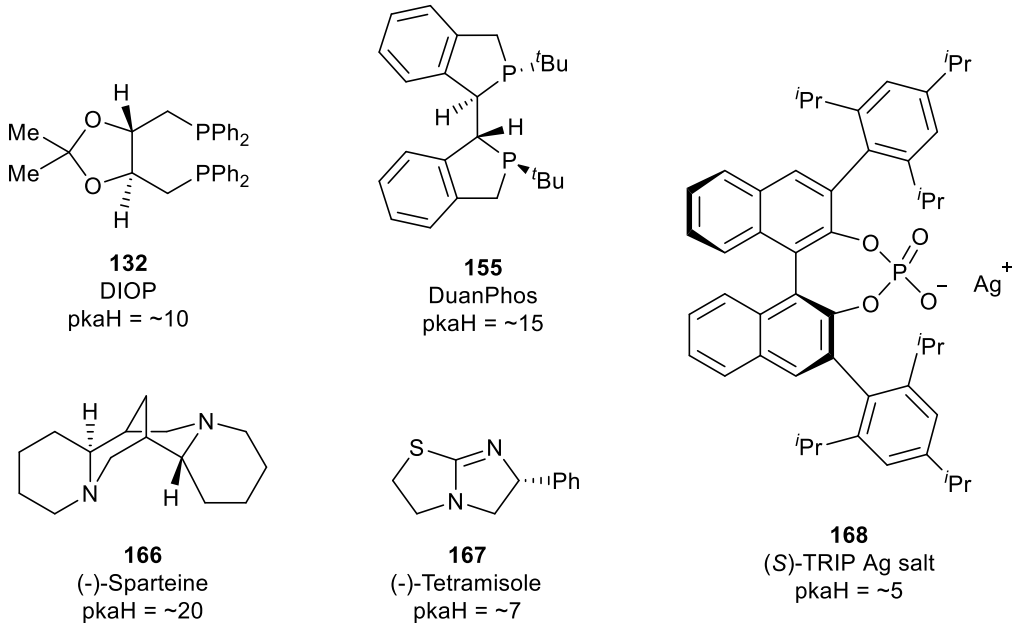
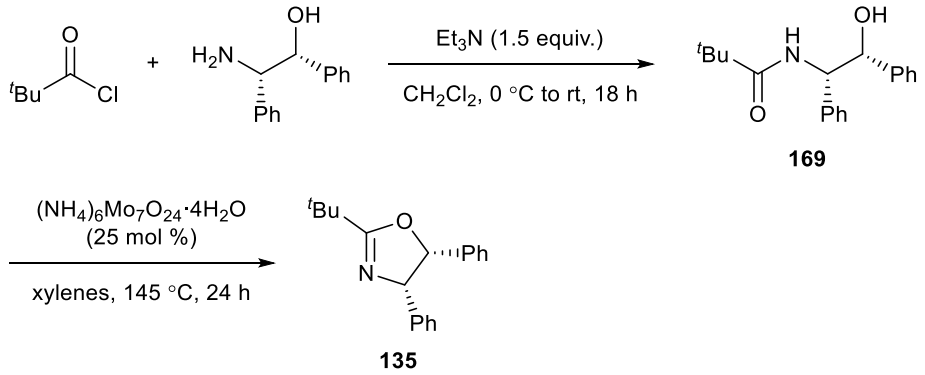


Figure 18: A selection of chiral Lewis bases to be employed in revised study, with approximate pkaH values.[13]



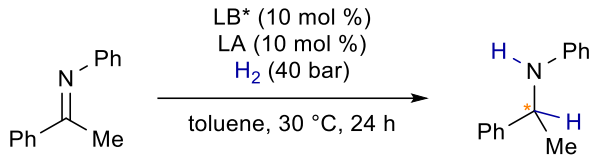
Scheme 47: Synthesis of oxazoline **135**.

6.3.2.1 Imines

As a reminder from chapter 6.3.1.1, imines were found to participate in H_2 activation acting as the Lewis base component of the FLP, and overall produced racemic products, except when using the weakest Lewis acid, BPh_3 (**158**). This is still the case under mild conditions (table 5.8, entries 1-4), albeit a lower conversion of starting

material was observed when using the strongest Lewis acid $B(C_6F_5)_3$ (**133**) (entry 1). Subsequent repeats confirmed the reliability of this result. Employing **133** results in a weaker hydride relative to the other Lewis acids. Given the strong electrophilic nature of imines, it is anticipated this lull in conversion is rather due to poorer H_2 activation ability. This is an example of the fine margins existing for H_2 activation, with any slight change in component or conditions posing a risk to activation capability.

The addition of chiral Lewis bases with BPh_3 (**158**) led to no formation of product (entries 5-10), suggesting BPh_3 is too weakly acidic to participate in H_2 activation in combination with the selected Lewis bases under mild reaction conditions, including Du's oxazoline **135**. A further reaction was performed attempting to closely mimic Du's reaction conditions (20 mol % LB* and 10 mol % strong Lewis acid $B(C_6F_5)_3$ (**133**) but with an imine substrate (entry 11). In this instance, conversion to product **134** was observed (35% NMR yield, 30% isolated), however, this was racemic. From this, it can be deduced that imines are incompatible substrates for enantioselective hydrogenation when employing chiral Lewis bases.



131 **134**

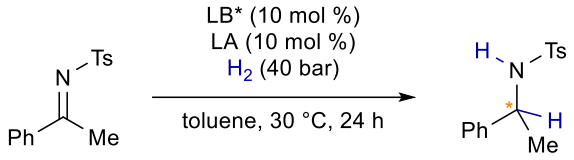
Entry[a]	Lewis acid LA		Chiral Lewis base LB*		**131**[b] RSM (%)	**134**[b] P (%)	ee[c] (%)
1	**133**	$B(C_6F_5)_3$	-		65	24	n/a
2	**156**	$B(3,5\text{-}H_2C_6F_3)_3$	-		0	94	n/a
3	**157**	$B(3,4,5\text{-}H_3C_6F_2)_3$	-		4	93	n/a
4	**158**	BPh_3	-		99	0	n/a
5	**158**	BPh_3	**132**	DIOP	78	0	n/a
6	**158**	BPh_3	**155**	DuanPhos	77	0	n/a
7	**158**	BPh_3	**166**	(-)-Sparteine	75	0	n/a
8	**158**	BPh_3	**167**	(-)-Tetramisole	75	0	n/a
9	**158**	BPh_3	**168**	(*S*)-TRIP salt	68	0	n/a
10	**158**	BPh_3	**135**	Du oxazoline	89	0	n/a
11[d]	**133**	$B(C_6F_5)_3$	**135**	Du oxazoline	41	35 (30)	0

Table 16: Reaction data for FLP-catalysed hydrogenation of **131**.

[a]Reactions performed according to General procedure 1 (experimental chapter 7) using 0.2 mmol of imine **131** and degassed toluene. [**131**] = 0.25 M. [b]Yield after 24 h as determined by ^1H NMR analysis of the crude reaction

mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yield given in parentheses. [c]Enantiomeric excess determined by HPLC analysis. [d]20 mol % LB*.

A study for *N*-tosyl imine **159** was also conducted. Milder conditions seemed to hinder the background reaction with **133** to 31% (table 5.9, entry 1) compared to 85% under harsher conditions (table 11, entry 1). Having selected **158** as Lewis acid, the inclusion of chiral Lewis bases did not lead to any formation of product (entries 2-10). Surprisingly, an attempt to mimic Du reaction conditions with this substrate (entry 11) prevented the background reaction from occurring, with only 78% starting material being observed in the crude ^{1}H NMR.



159 **160**

Entry[a]	Lewis acid LA		Chiral Lewis base LB*		**159**[b] RSM (%)	**160**[b] P (%)	ee[c] (%)
1	**133**	$B(C_6F_5)_3$	-		64	31	n/a
2	**156**	$B(3,5\text{-}H_2C_6F_3)_3$	-		99	0	n/a
3	**157**	$B(3,4,5\text{-}H_3C_6F_2)_3$	-		99	0	n/a
4	**158**	BPh_3	-		99	0	n/a
5	**156**	$B(3,5\text{-}H_2C_6F_3)_3$	**132**	DIOP	95	0	n/a
6	**156**	$B(3,5\text{-}H_2C_6F_3)_3$	**155**	DuanPhos	94	0	n/a
7	**156**	$B(3,5\text{-}H_2C_6F_3)_3$	**166**	(-)-Sparteine	94	0	n/a
8	**156**	$B(3,5\text{-}H_2C_6F_3)_3$	**167**	(-)-Tetramisole	96	0	n/a
9	**156**	$B(3,5\text{-}H_2C_6F_3)_3$	**168**	(*S*)-TRIP salt	97	0	n/a
10	**156**	$B(3,5\text{-}H_2C_6F_3)_3$	**135**	Du oxazoline	96	0	n/a
11[d]	**133**	$B(C_6F_5)_3$	**135**	Du oxazoline	78	0	n/a

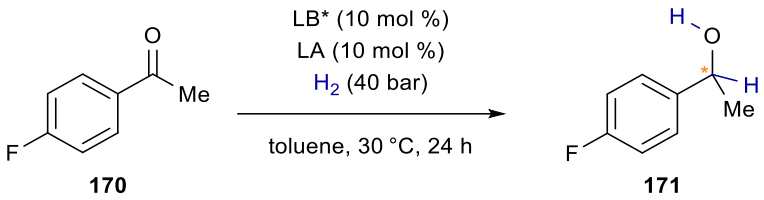
Table 17: Reaction data for FLP-catalysed hydrogenation of **159**.

[a]Reactions performed according to General procedure 1 (experimental chapter 7) using 0.2 mmol of imine **159** and degassed toluene. [**159**] = 0.25 M. [b]Yield after 24 h as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yield given in parentheses. [c]Enantiomeric excess determined by HPLC analysis. [d]20 mol % LB*.

6.3.2.2 Ketones

As a reminder, background reactions did not occur with ketones under harsher conditions. H_2 activation occurred with the addition of chiral Lewis bases; however, the resulting products were racemic (table 13). Under milder conditions, no product

formation was observed (table 18, entries 5-9). Increasing the base loading to 20 mol % also resulted in no product formation (entries 10-14). One exception whereby oxazoline **135** was employed as chiral Lewis base produced **171** in 6% NMR yield. The literature report for this substrate was 72%, although it required a reaction time of 72 h, and was performed in a toluene/cyclohexane solvent system. This product was not isolated. A further study with ketones can be found in chapter 6.3.3.



170 **171**

Entry[a]	Lewis acid LA		Chiral Lewis base LB*		**170**[b] RSM (%)	**171**[b] P (%)	ee[c] (%)
1	**133**	$B(C_6F_5)_3$	-		99	0	n/a
2	**156**	$B(3,5\text{-}H_2C_6F_3)_3$	-		99	0	n/a
3	**157**	$B(3,4,5\text{-}H_3C_6F_2)_3$	-		99	0	n/a
4	**158**	BPh_3	-		99	0	n/a
5	**133**	$B(C_6F_5)_3$	**132**	DIOP	95	0	n/a
6	**133**	$B(C_6F_5)_3$	**155**	DuanPhos	94	0	n/a
7	**133**	$B(C_6F_5)_3$	**166**	(-)-Sparteine	94	0	n/a
8	**133**	$B(C_6F_5)_3$	**167**	(-)-Tetramisole	96	0	n/a
9	**133**	$B(C_6F_5)_3$	**168**	(*S*)-TRIP salt	97	0	n/a
10[d]	**133**	$B(C_6F_5)_3$	**132**	DIOP	99	0	n/a
11[d]	**133**	$B(C_6F_5)_3$	**155**	DuanPhos	96	0	n/a
12[d]	**133**	$B(C_6F_5)_3$	**166**	(-)-Sparteine	97	0	n/a
13[d]	**133**	$B(C_6F_5)_3$	**167**	(-)-Tetramisole	99	0	n/a
14[d]	**133**	$B(C_6F_5)_3$	**168**	(*S*)-TRIP salt	99	0	n/a
15[d]	**133**	$B(C_6F_5)_3$	**135**	Du oxazoline	91	6	n/a

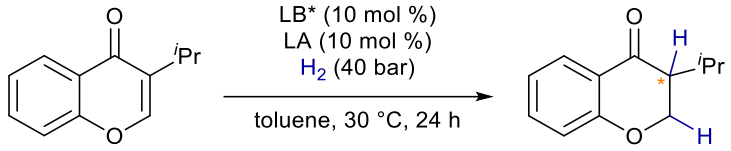
Table 18: Reaction data for FLP-catalysed hydrogenation of **170**.

[a]Reactions performed according to General procedure 1 (experimental chapter 7) using 0.2 mmol of ketone **170** and degassed toluene. [**170**] = 0.25 M. [b]Yield after 24 h as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yield given in parentheses. [c]Enantiomeric excess determined by HPLC analysis. [d]20 mol % LB*.

6.3.2.3 Alkenes

As a reminder, for chromone substrate **164**, no background reaction occurred with any Lewis acid under harsher conditions (table 14), and the addition of chiral Lewis bases resulted in the formation of racemic product **145**. Under milder conditions, no background reaction was observed with any Lewis acid (table 19, entries 1-4), and no

product formation was observed upon the addition of chiral Lewis base (entries 5-9). Interestingly, not even the FLP combination of **133** and oxazoline **135** resulted in the formation of product. We know that this combination can activate H_2 under these reaction conditions from Du's report with ketones. It is hypothesised that H_2 activation does occur, but that the chromone is not electrophilic enough to undergo hydride attack. This would explain why Du and co-workers employed a weaker Lewis acid B(3,4,5-$H_3C_6F_2$)$_2$(*p*-HC_6F_4) (**142**) with chromone substrates, to form a stronger hydride source. Attempts to synthesise this borane for use in this study were unsuccessful. A comprehensive study into the enantioselective hydrogenation of chromones was very recently disclosed by Du and coworkers, revealing how subtle changes in the Lewis acidity of the borane can impact hydrogen conversion.[14]



164 **145**

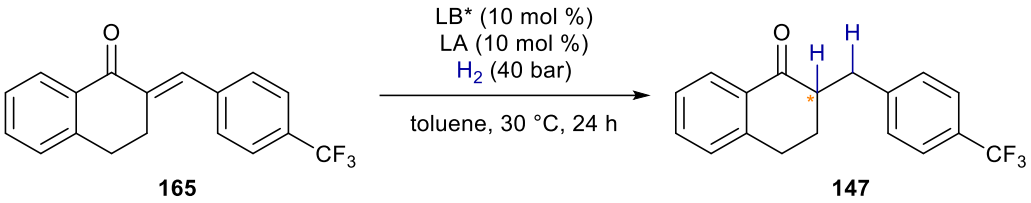
Entry[a]	Lewis acid LA		Chiral Lewis base LB*		**164**[b] RSM (%)	**145**[b] P (%)	ee[c] (%)
1	**133**	$B(C_6F_5)_3$	-		99	0	n/a
2	**156**	$B(3,5\text{-}H_2C_6F_3)_3$	-		89	0	n/a
3	**157**	$B(3,4,5\text{-}H_3C_6F_2)_3$	-		90	0	n/a
4	**158**	BPh_3	-		91	0	n/a
5	**133**	$B(C_6F_5)_3$	**132**	DIOP	97	0	n/a
6	**133**	$B(C_6F_5)_3$	**155**	DuanPhos	96	0	n/a
7	**133**	$B(C_6F_5)_3$	**166**	(-)-Sparteine	95	0	n/a
8	**133**	$B(C_6F_5)_3$	**167**	(-)-Tetramisole	96	0	n/a
9	**133**	$B(C_6F_5)_3$	**168**	(*S*)-TRIP salt	94	0	n/a
10[d]	**133**	$B(C_6F_5)_3$	**135**	Du oxazoline	90	0	n/a

Table 19: Reaction data for FLP-catalysed hydrogenation of **164**.

[a]Reactions performed according to General procedure 1 (experimental chapter 7) using 0.2 mmol of chromone **164** and degassed toluene. [**164**] = 0.25 M. [b]Yield after 24 h as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yield given in parentheses. [c]Enantiomeric excess determined by HPLC analysis. [d]20 mol % LB*.

For the investigation with the enone substrate **164**, the accuracy of the NMR yields was affected by poor solubility in toluene at rt. Following a visual investigation, the solubility of **164** did not improve when immersed in an alternative solvent system (mesitylene, toluene/cyclohexane (1:1), CH_2Cl_2, xylenes, trifluorotoluene). A

background reaction was observed when employing **133** (table 20, entry 1). This background reaction was inhibited upon the addition of Lewis bases, with two exceptions (entries 6 and 9). Since H_2 activation was previously observed between **133** and these Lewis bases under mild reaction conditions (tables 18 and 19), it is suspected that the substrate is involved in H_2 activation. Expectedly, these products turned out to be racemic.



165 **147**

Entry[a]	Lewis acid LA		Chiral Lewis base LB*		**165**[b] RSM (%)	**147**[b] P (%)	ee[c] (%)
1	**133**	$B(C_6F_5)_3$	-		48	45	n/a
2	**156**	$B(3,5\text{-}H_2C_6F_3)_3$	-		41	4	n/a
3	**157**	$B(3,4,5\text{-}H_3C_6F_2)_3$	-		56	5	n/a
4	**158**	BPh_3	-		40	4	n/a
5	**133**	$B(C_6F_5)_3$	**132**	DIOP	85	0	n/a
6	**133**	$B(C_6F_5)_3$	**155**	DuanPhos	45	23 (20)	0
7	**133**	$B(C_6F_5)_3$	**166**	(-)-Sparteine	33	0	n/a
8	**133**	$B(C_6F_5)_3$	**167**	(-)-Tetramisole	82	0	n/a
9	**133**	$B(C_6F_5)_3$	**168**	(*S*)-TRIP salt	46	19 (15)	0

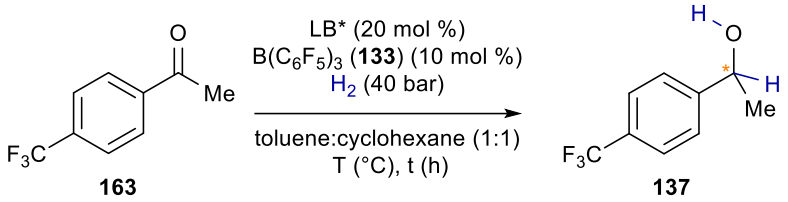
Table 20: Reaction data for FLP-catalysed hydrogenation of **165**.

[a]Reactions performed according to General procedure 1 (experimental chapter 7) using 0.2 mmol of enone **5.36** and degassed toluene. [**165**] = 0.25 M. [b]Yield after 24 h as determined by ^1H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yield given in parentheses. [c]Enantiomeric excess determined by HPLC analysis. [d]20 mol % LB*.

6.3.3 Final Studies

With no encouraging results in hand, a decision was made to quash the project by conducting a strategic set of experiments. Aryl ketone **163** was selected as the substrate for this final investigation, as this substrate was the one used in Du and co-workers' optimisation study. From the same optimisation, two sets of reaction conditions were investigated by Du and co-workers employing **133** as Lewis acid. The study began by checking for background reactions under both set of conditions. At 30 °C for 48 h, no background reaction occurred (table 21, entry 1). At 60 °C for 18 h, a

small background reaction occurred, producing a 12% NMR yield of alcohol **137**, indicating that **163**/**133** H_2 activation is promoted at elevated temperatures.



Entry[a]	Chiral Lewis base LB*		T (°C)	t (h)	**163**[b] RSM (%)	**137**[b] P (%)	ee[c] (%)
1	-		30	48	99	0	n/a
2	-		60	18	84	12 (10)	0
3	**135**	Du oxazoline	30	48	72	27 (24) lit. (50)	70 lit. 78
4	**132**	DIOP	30	48	99	0	n/a
5	**155**	DuanPhos	30	48	99	0	n/a
6	**166**	(-)-Sparteine	30	48	96	0	n/a
7	**167**	(-)-Tetramisole	30	48	99	0	n/a
8	**168**	(*S*)-TRIP salt	30	48	97	0	n/a
9	**135**	Du oxazoline	60	18	27	74 (66) lit. (98)	66 lit. 72
10	**132**	DIOP	60	18	82	14 (10)	0
11	**155**	DuanPhos	60	18	60	40 (32)	0
12	**166**	(-)-Sparteine	60	18	99	0	n/a
13	**167**	(-)-Tetramisole	60	18	96	0	n/a
14	**168**	(*S*)-TRIP salt	60	18	95	0	n/a
15[d]	**135**	Du oxazoline	60	18	17	17 (12)	58
16[e]	**135**	Du oxazoline	60	18	51	49 (41)	62

Table 21: Reaction data for FLP-catalysed hydrogenation of **163**.

[a]Reactions performed according to General procedure 1 (experimental chapter 7) using 0.2 mmol of ketone **163** and degassed toluene. [**163**] = 0.25 M. [b]Yield after 24 h as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yield given in parentheses. [c]Enantiomeric excess determined by HPLC analysis. [d]10 mol % of **135**. [e]toluene only as solvent.

Repeats of the reported literature employing oxazoline **135** confirmed the legitimacy of Du and co-workers' findings (entries 3 and 9). These results matched the established trend of obtaining a higher yield but lower ee for the reaction performed at higher temperature (60 °C) *versus* at lower temperature (30 °C). The crude NMR for the reaction performed at higher temperature (entry 9) is displayed in Figure 19. Despite the obtained yields being comparably lower than those in the literature, the measured enantiomeric excesses were reasonably close to the reported values. Observing ee for the first time erased any doubt in the equipment or practical and

analytical techniques being applied throughout the project. HPLC chromatograms for racemate **±137** and isolated product **137** from entry 3 are displayed in Figure 21.

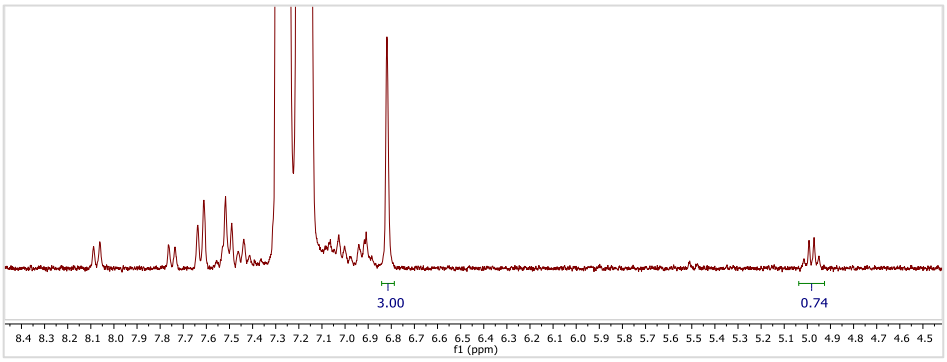


Figure 19: Crude ^{1}H NMR for literature reaction employing oxazoline **5.5** (Table 5.13, entry 3)

Figure 20: HPLC apparatus used to measure enantiomeric excess of products

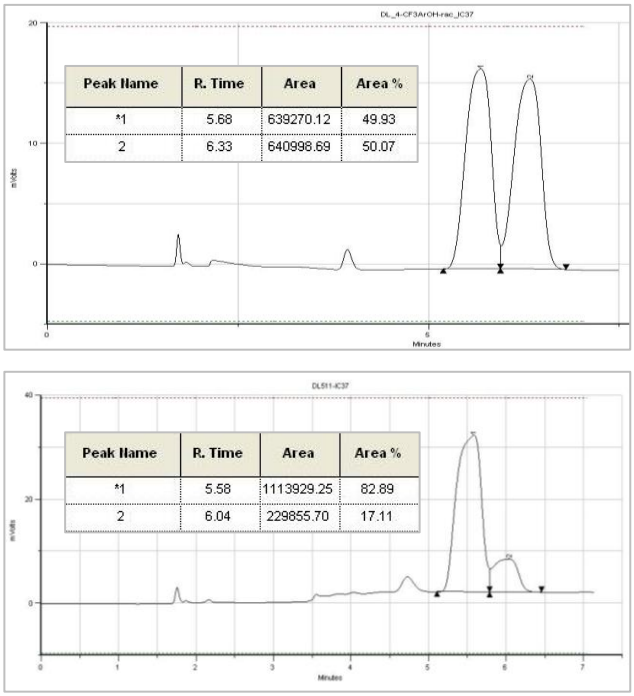


Figure 21: HPLC data for alcohol **137**. Top = racemate, bottom = isolated product from table 21, entry 3. Chiralpak IC (Gilson method 37) = 99:1 Hexane:IPA, 2.0 mL/min, 211 nm, 5.68 and 6.33 min.

Substituting other Lewis bases in for the Du oxazoline at 30 °C resulted in no desired product (entries 4-8). This suggests that out of all the Lewis pair combinations tested, borane **133** and oxazoline **135** were exclusively compatible for H_2 activation under milder conditions. The same set of reactions were conducted at the higher temperature of 60 °C (entries 10-14). Conversion to alcohol **137** was observed when employing DIOP (**132**, entry 10) and DuanPhos (**155**, entry 11), however, these products turned out to be racemic. Should the Lewis bases be partaking in H_2 activation, it is evident that the chiral FLP is not able to induce enantioselectivity *via* hydrogen bonding of the chiral conjugate acid with the substrate.

6.3.4 Inverse FLP

As described in chapter 5.2.2, inverse FLP, contrary to normal FLP, utilises a weak Lewis acid and a strong Lewis base for hydrogen activation. Although being a very underexplored area, it was envisaged this inverse FLP strategy could be employed for enantioselective hydrogenation of prochiral substrates. The following sections describe the synthetic progress made for selected organosuperbases and weak Lewis acids. Experimental procedures and characterisation for compounds synthesised by me can be found in chapter 7.

6.3.4.1 Catalyst Syntheses

As described in chapter 5.2.2, Krempner and co-workers demonstrated the hydrogenation of *N*-benzylidenaniline employing two different inverse FLP combinations; phosphazene **128**/BPh_3 (**158**) and aminophosphine **129**/9-Hexyl BBN.[15] The hydrogenation of aryl ketones was also achieved by Krempner and co-workers employing phosphazene **128** and 9-(4'-trifluoromethyl)phenyl-BBN (**130**).[16]

Krempner's base (**128**) was synthesised in-house and purified using Kugelrohr distillation apparatus. The purity of each fraction was analysed by ^{31}P NMR, as illustrated in figure 23. Verkade's base (**129**) was obtained commercially. Both 9-BBN-derived Lewis acids proved very difficult to synthesise and purify.

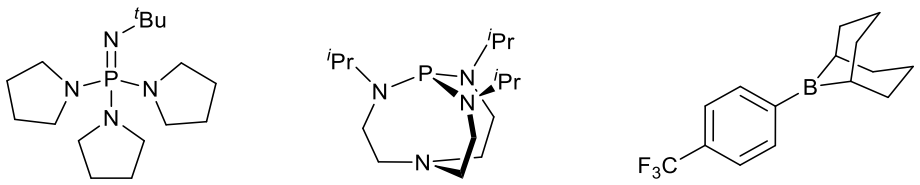


Figure 22: A selection of organosuperbases and weakly Lewis-acidic boranes previously employed for inverse FLP hydrogenation of aldimines or ketones.

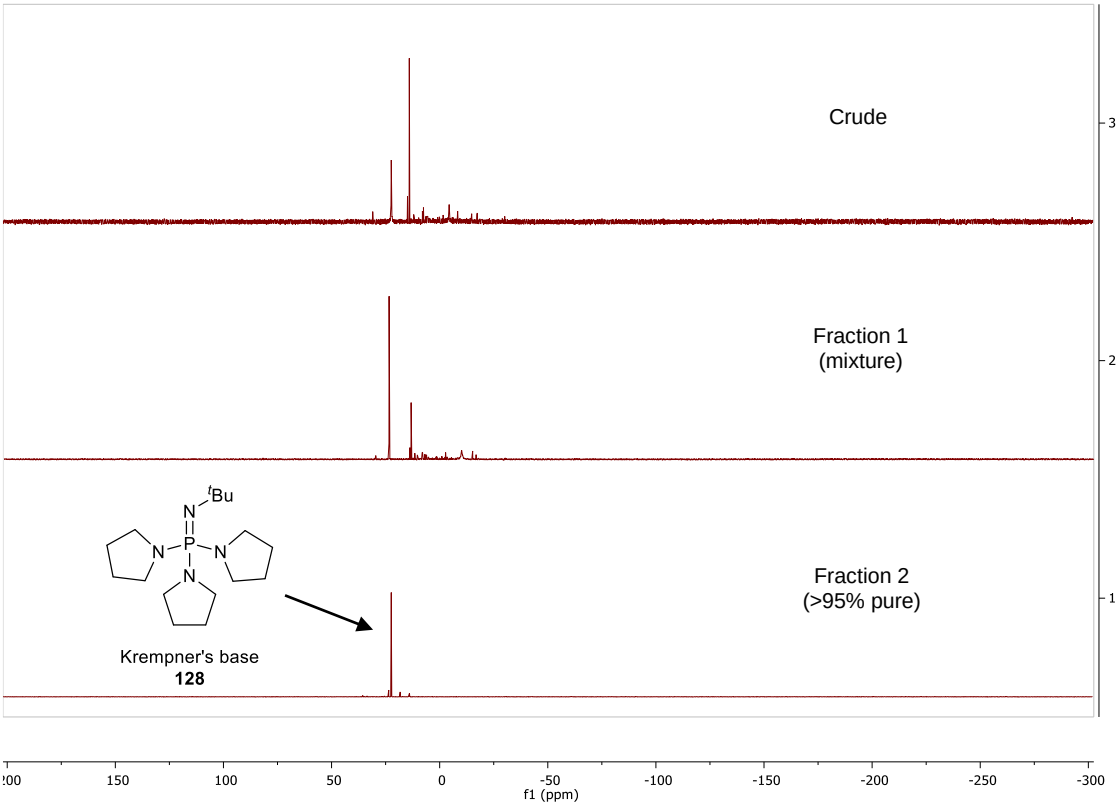


Figure 23: Stacked ^{31}P NMR spectra ($CDCl_3$) of crude mixture and fractions collected using Kugelrohr distillation for the synthesis of Krempner's base **128**.

The preparation of 9-Hexyl BBN was attempted *via* hydroboration of 1-hexene with 9-BBN, followed by purification using Kugelrohr distillation apparatus. The purity of each fraction was analysed by ^{11}B NMR, as illustrated in figure 24. 9-BBN (ca. 28 ppm) and 9-OH-BBN (ca. 58 ppm) were identified in accordance with literature reports.[17,18] 9-Hexyl BBN was identified at ca. 80 ppm. Other peaks remain unidentified. Unfortunately, a pure sample of 9-Hexyl BBN was not obtained, despite further distillation attempts.

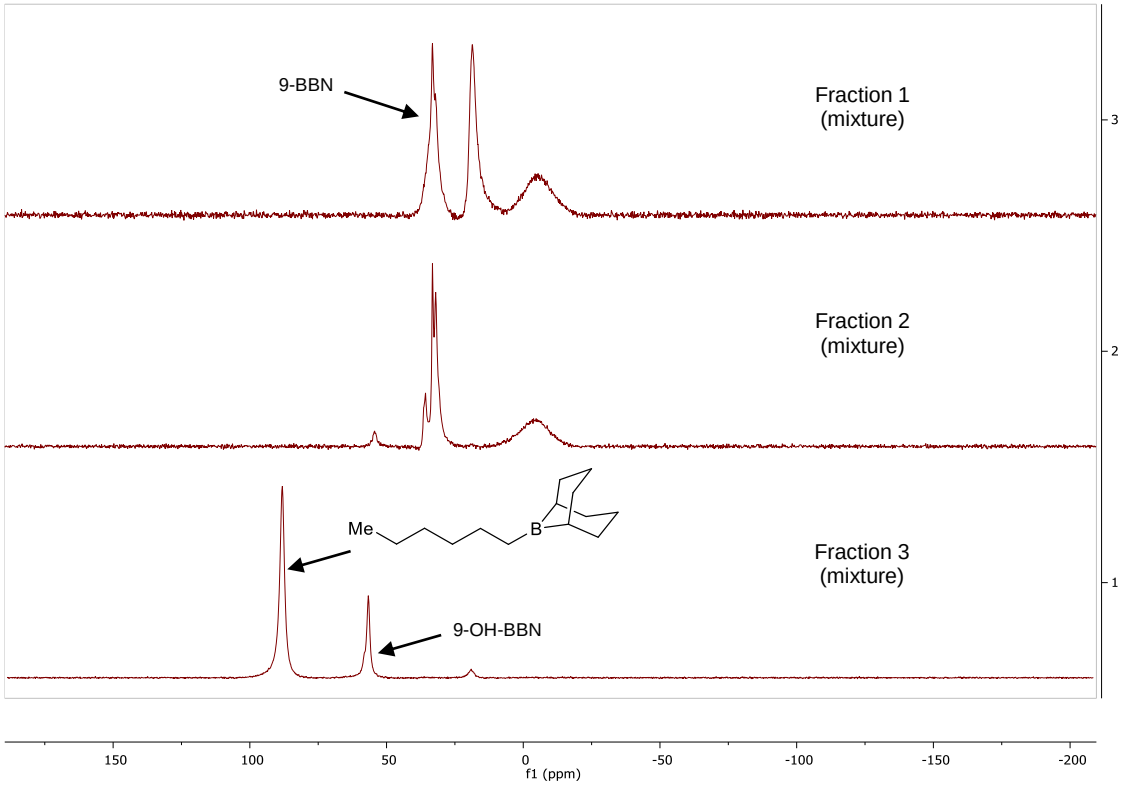


Figure 24: Stacked ^{11}B NMR spectra ($CDCl_3$) of crude mixture and fractions collected using Kugelrohr distillation for the synthesis of 9-hexyl-BBN.

The preparation of 9-(4'-trifluoromethyl)phenyl-BBN (**130**) was attempted *via* nucleophilic addition of an in-situ-generated aryl Grignard to 9-OMe-BBN, followed by purification using Kugelrohr distillation apparatus. The purity of each fraction was analysed by ^{11}B NMR, as illustrated in figure 25. 9-OMe-BBN was identified at ca. 57 ppm in accordance with the literature.[19] **130** was identified at ca. 80 ppm in accordance with the literature.[15] Unfortunately, a pure sample of **130** was not obtained, despite further distillation attempts.

Three chiral organosuperbases were selected as synthetic targets for prospective enantioselective studies; cyclopropenimine **172**, guanidine **173**, and phospahazene **174** (Figure 26). Under my supervision, two MChem students, Ioan Bale and Jake Painter, were tasked with synthesising these chiral superbases. Limited progress was made due to lab time constraints and failed reactions. Cyclopropenimine **172** was developed and employed by Lambert and co-workers for enantioselective Brønsted

base catalysed Michael addition of glycine-derived compounds with α,β-unsaturated carbonyl compounds, such as acrylates.[20]

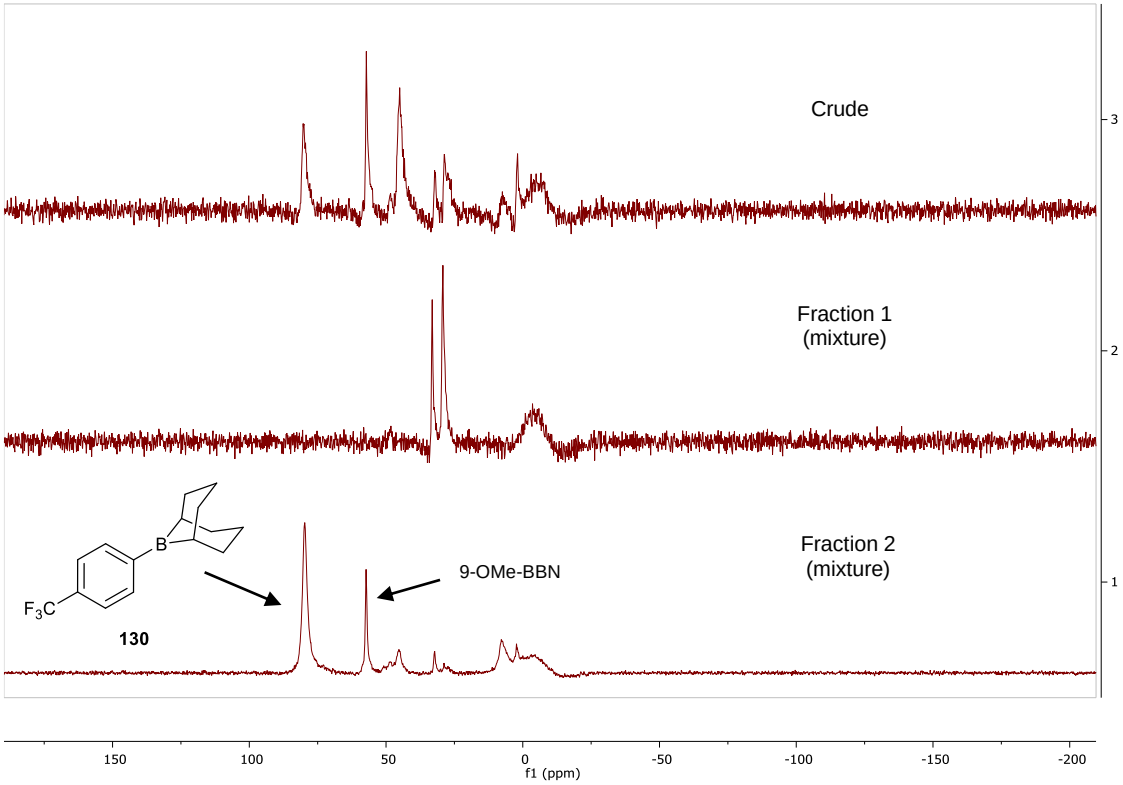


Figure 25: Stacked ^{11}B NMR spectra ($CDCl_3$) of crude mixture and fractions collected using Kugelrohr distillation for the synthesis of 9-(p-$CF_3C_6H_5$)-BBN (**130**).

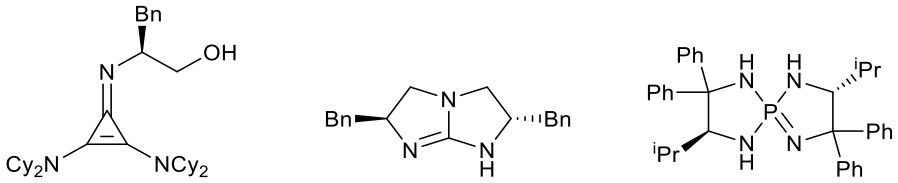
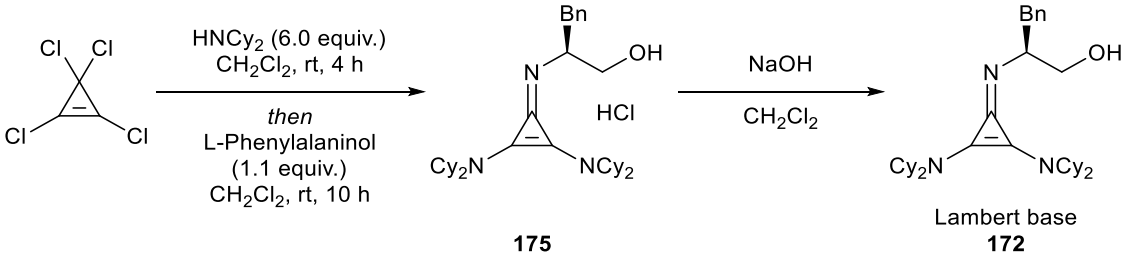


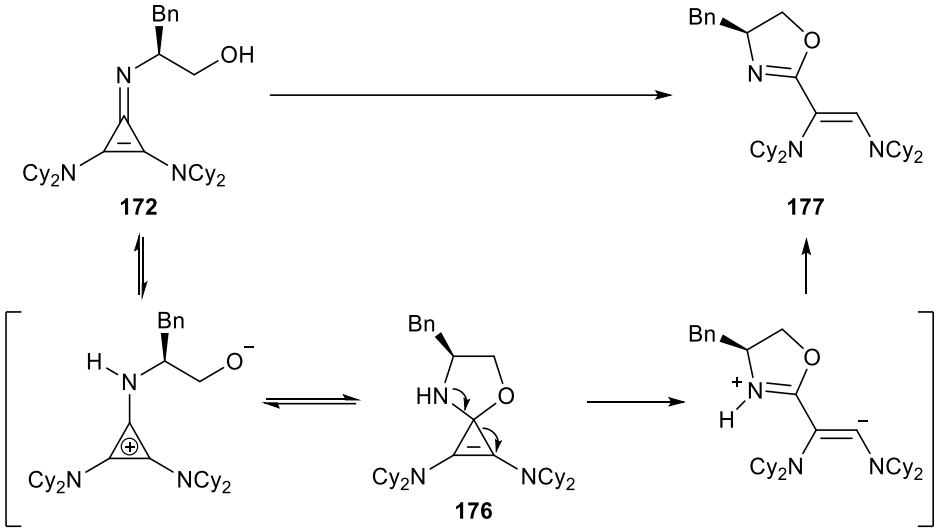
Figure 26: Chiral organosuperbases selected as synthetic targets

The synthetic pathway to obtain Lambert's base (**172**) is illustrated in scheme 48. Intermediate hydrochloride salt **175** was synthesised by a former postdoc – Dr Shyam Basak. This was stored in ambient conditions as the salt, since **172** undergoes decomposition to 4,5-dihydrooxazole derivative **177**. This decomposition reaction is thought to proceed *via* an intramolecular deprotonation of the hydroxyl group, generating the alkoxy cyclopropenimine. Cyclisation to oxazolidine **176**, followed by

ring opening to form the vinyl anion, and intramolecular proton transfer delivers **5.52** (scheme 49). Hydrochloride salt **175** was converted to Lambert base **172** immediately before use in reactions, though was stable in the freezer for up to two days.

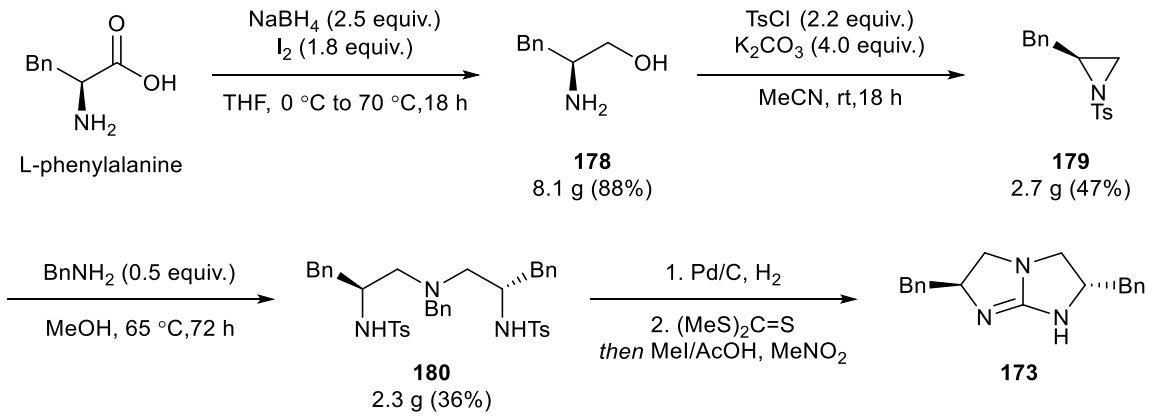


Scheme 48: Chiral organosuperbases selected as synthetic targets

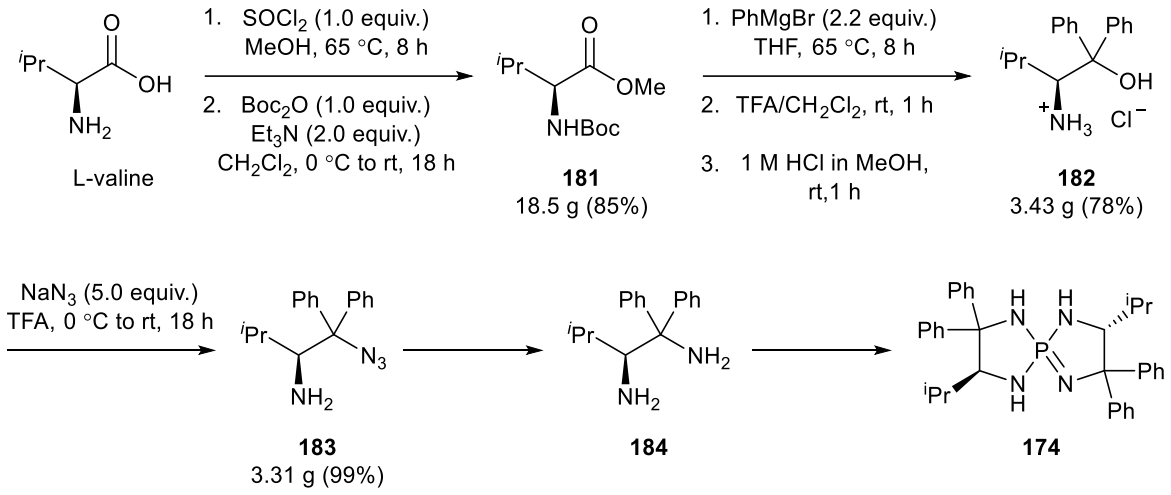


Scheme 49: Decomposition pathway of Lambert base

Efforts to synthesise Tan's base (**173**) were made by Jake Painter starting from L-phenylalanine (**178**), as illustrated in scheme 50.[21] Triamine intermediate **180** was obtained, however, efforts to deprotect and cyclise were unsuccessful. Efforts to synthesise Ooi's base (**174**) were made by Ioan Bale and Jake Painter starting from L-valine, as illustrated in scheme 51.[22] Azide intermediate **183** was obtained, however, efforts to reduce this to the diamine *via* a Staudinger reaction or *via* Pd/C were unsuccessful.



Scheme 50: Synthetic route to obtain Tan's base (**173**)

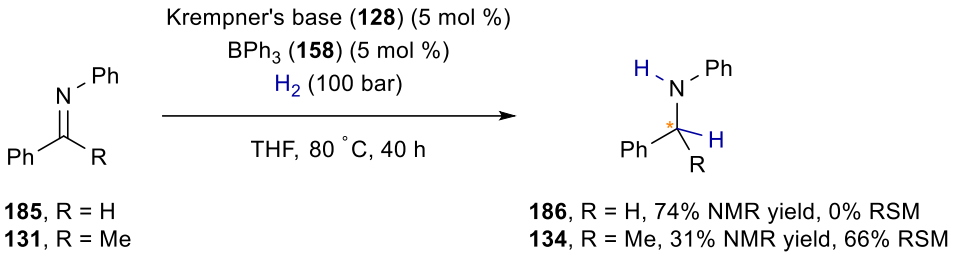


Scheme 51: Synthetic route to obtain Ooi's base (**174**)

6.3.4.2 Reactions

With Krempner's base (**128**), Verkade's base (**129**), BPh3 (**158**) and an impure sample of 9-Hexyl BBN in hand, the replication of Krempner and co-workers' original inverse FLP hydrogenation reaction of N-phenyl aldimine **185** (chapter 5, scheme 39a) was attempted.[16] Initially, these reactions were conducted at a much lower reaction concentration ([substrate] = 0.5 M) compared to the literature ([substrate] = 4.4 M) with the aim to conserve starting material. These resulted in little to no reactivity. Conducting these reactions at the stated concentration and reaction scale resulted in much better conversion. This was the case for the reaction employing

128/158, however, the reaction employing **129**/9-Hexyl BBN gave only 13% NMR yield which is attributed to the impure Lewis acid.



185, R = H
131, R = Me

186, R = H, 74% NMR yield, 0% RSM
134, R = Me, 31% NMR yield, 66% RSM

Scheme 52: Reaction data for inverse FLP-catalysed hydrogenation of imines employing **128/158**. [a]Reactions performed according to General procedure 1 (experimental chapter 7) using 6.6 mmol of imine and degassed THF. [imine] = 4.4 M. [b]Yield after 40 h as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard.

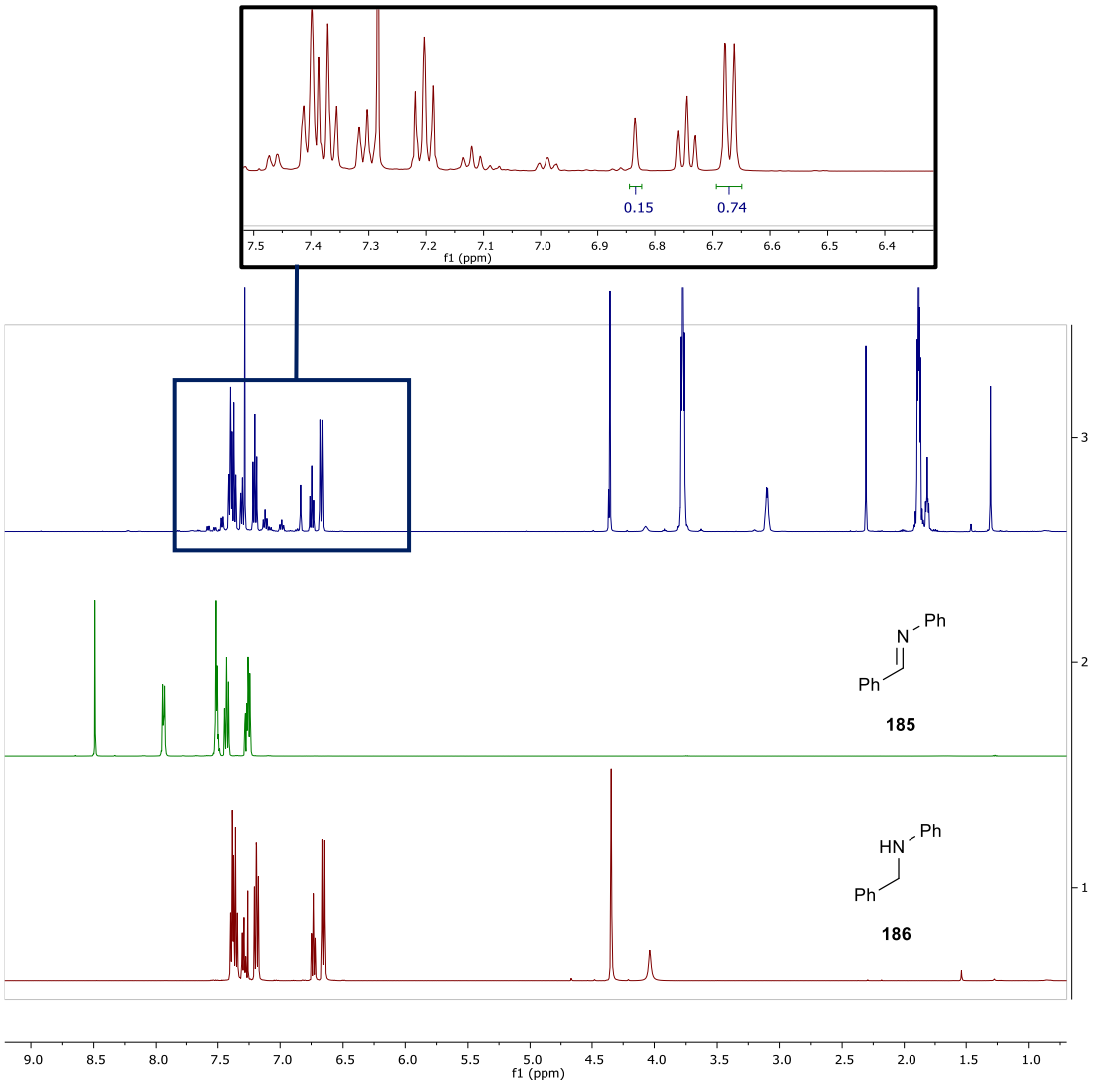


Figure 27: Stacked NMR spectra for crude NMR, **185** and **186** - replication of Krempner's reaction (scheme 52)

Evidently, reaction concentration is perhaps more important than initially anticipated for these general FLP-catalysed hydrogenations. Aldimine **185** was successfully converted to amine **186** in 74% NMR yield (figure 27) with 0% RSM. N.B. 0.1 equivalents of internal standard was used due to the enhanced scale of the reaction.

The same "inverse" FLP conditions were applied to ketimine **131**, producing 31% of secondary amine **134** and 66% RSM (figure 28). To the best of my knowledge, this is the first inverse FLP-catalysed hydrogenation of a prochiral imine, alluding to the prospect that enantioselective hydrogenation of ketimines with chiral superbases can be achieved.

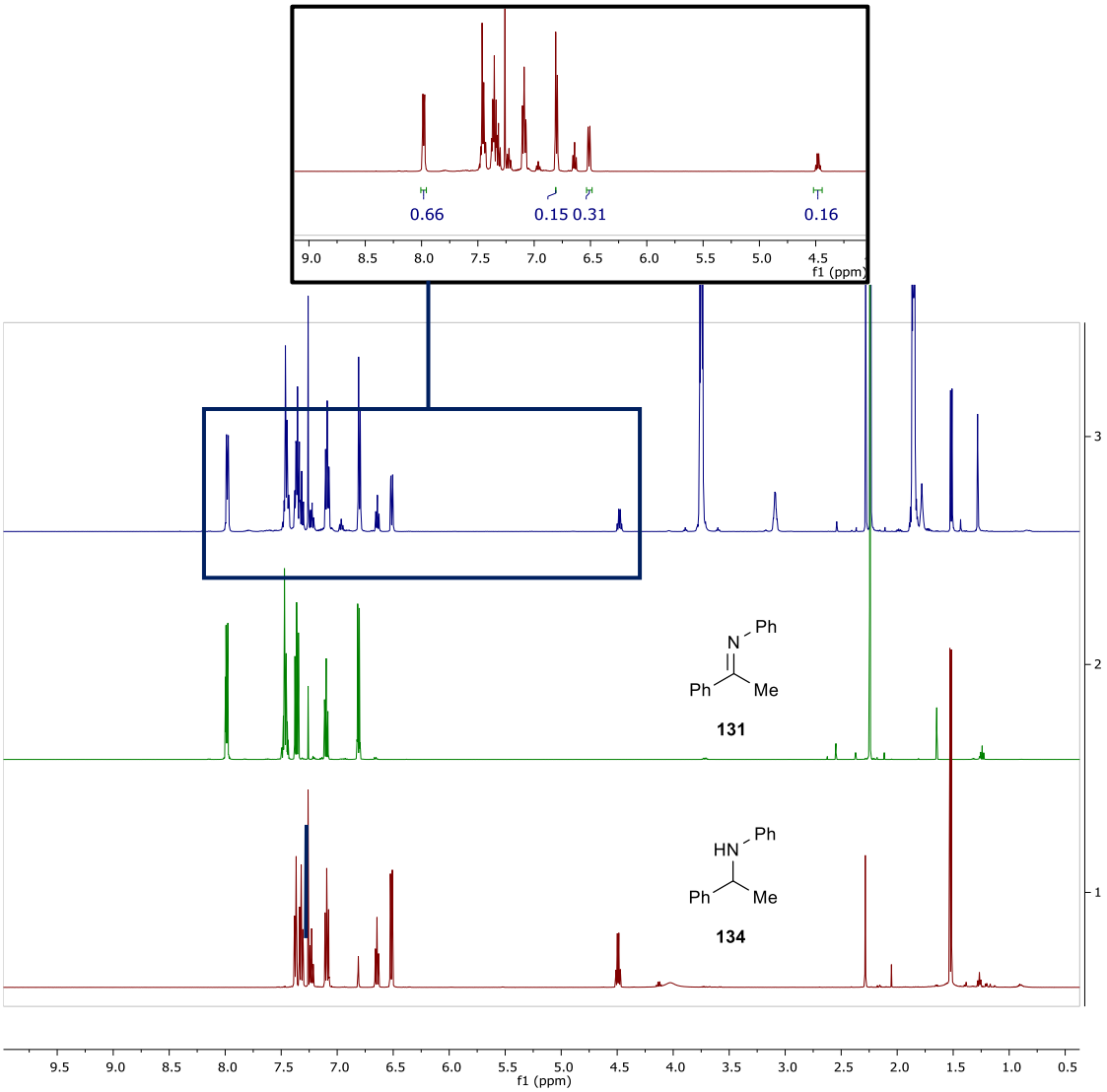
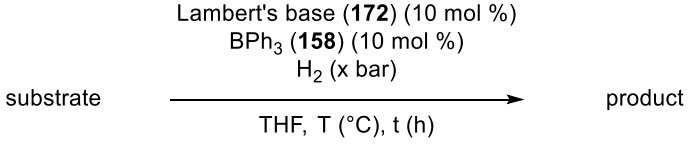


Figure 28: Stacked NMR spectra for crude NMR, **131** and **134** – application of Krempner's conditions to ketimine substrate (scheme 52).

Unfortunately, preliminary results employing Lambert's base (**172**) with BPh_3 (**158**) under similar reaction conditions did not lead to any reduced products. Milder conditions were also attempted; however, no desired products were observed (table 22).



Entry[a]	Substrate	T (°C)	P (bar)	RSM (%)	P (%)
1	**131** NPh ketimine	80	100	71	0
2	**131** NPh ketimine	30	40	73	0

3	**159**	NTs ketimine	80	100	76	0
4	**159**	NTs ketimine	30	40	99	0
5	**164**	Chromone	80	100	96	0
6	**164**	Chromone	30	40	83	0
7	**163**	Ketone	80	100	95	0
8	**163**	Ketone	30	40	98	0

Table 22: Reaction data for FLP-catalysed hydrogenation employing Lambert's base.

[a]Reactions performed according to General procedure 1 (experimental chapter 7) using 0.5 mmol of substrate and degassed THF. [substrate] = 6.6 M. [b]Yield after 24 h as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard.

6.4 Conclusion

Efforts to discover a novel Frustrated Lewis Pair consisting of an achiral Lewis acid and a chiral Lewis base, for the enantioselective hydrogenation of prochiral substrates, has proven difficult and fallen short of success. While some literature reactions were able to be replicated, the strategy to adopt a chiral phosphine was not effective. Nor was the revised strategy to employ other chiral Lewis bases. Discovering synergistic components and suitable conditions for this transformation had indeed proved more difficult than anticipated.

For inverse FLP catalysis, there remains an opportunity to find suitable FLPs for enantioselective hydrogenation. This will require a tremendous synthetic effort to acquire the chiral superbases, including the candidates that were initially proposed. Protection of the alcohol of Lambert's base may require protection since it is possible this may be coordinating to and poisoning the borane catalyst.

6.5 References

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Chapter 7 – Experimental

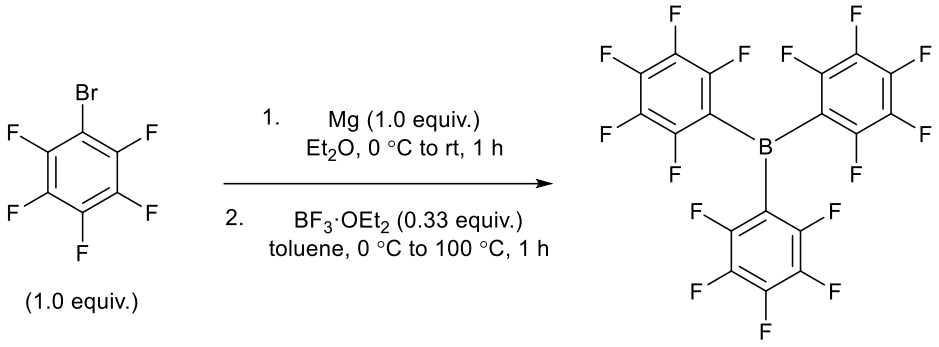
Enantioselective Hydrogenation employing Frustrated Lewis Pair Catalysis

Table of Contents

7.1 Synthesis of Lewis Acids

Tris(2,6-difluorophenyl)borane (**157**) was prepared by Imtiaz Khan, as described in the literature.[1]

Tris(pentafluorophenyl)borane (BCF) (133)

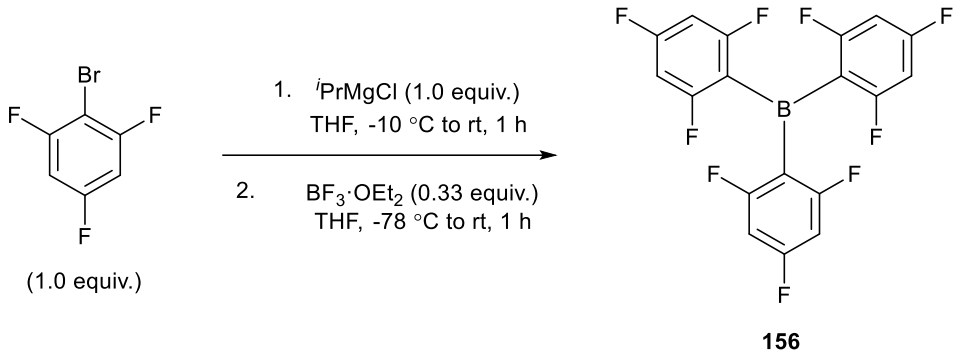


133

The title compound was prepared according to a webpage procedure.[2] All steps, including the extraction process, were carried out under inert conditions. A flame-dried 500 mL round bottomed flask equipped with a stirrer bar was charged with anhydrous diethyl ether (210 mL) and magnesium turnings (3.06 g, 126 mmol, 1.0 equiv.). C_6F_5Br (15.7 mL, 31.1 g, 126 mmol, 1.0 equiv.) was added dropwise at 0 °C until the solution developed a grey turbid appearance. The solution was stirred for an additional hour to ensure complete reaction. The resulting solution was dark brown in appearance. Next, a flame-dried 1 L round-bottomed flask equipped with stirrer bar was charged with $BF_3.Et_2O$ (5.18 mL, 5.96 g, 42 mmol, 0.33 equiv.) and dry toluene (84 mL). This solution was cooled to 0 °C. The Grignard solution was transferred to the cooled 1 L flask *via* a cannula, with vigorous stirring. The resulting solution was warmed to rt, followed by the removal of ~210 mL of solvent (Et_2O) under reduced pressure, with gentle heating if necessary. The flask was fitted with a reflux condenser and heated at 100 °C for 1 h, using a water bath. All volatiles were then removed under vacuum to obtain a brown cake. The product was isolated by extracting this cake with warm (45 °C) hexanes (4 × 50 mL) and cooling the combined organics in the freezer for 2 h. The resulting white crystals were filtered, dried, sublimed at 130 °C, washed with pentane, and dried to deliver pure BCF as a white solid (4.1 g, 19%). **^{11}B NMR ($CDCl_3$, 160 MHz)** δ_B: 58.7; **^{19}F NMR (471 MHz $CDCl_3$)**

δ_F: -128.0, -143.8, -161; **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 112.8-113.6 (Ar*C*(1)), 136.4-137.0 (Ar*C*), 138.4-139.0 (Ar*C*), 143.9-144.5 (Ar*C*), 146.0-146.6 (Ar*C*), 147.2-147.7 (Ar*C*), 149.2-149.7 (Ar*C*). Spectroscopic data in accordance with the literature.[3]

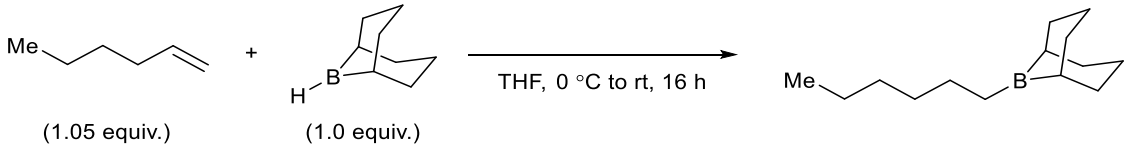
Tris(2,4,6-trifluorophenyl)borane (156)



156

The title compound was prepared according to a procedure stated in the literature.[4] All steps, including the extraction process, were carried out under inert conditions. A flame-dried 250 mL round bottomed flask equipped with a stirrer bar was charged with dry THF (50 mL) and 1-bromo-2,4,6-trifluorobenzene (2.95 mL, 5.27 g, 25 mmol, 1.0 equiv.). ^{i}PrMgCl (12.5 mL, 25 mmol, 1.0 equiv., 2 M in THF) was added dropwise at -20 °C. The solution was stirred for an additional hour at rt. Next, a solution of $BF_3.Et_2O$ (1.03 mL, 1.18 g, 8.33 mmol, 0.33 equiv.) and dry THF (10 mL) was added dropwise at -78 °C, and the resulting mixture was left to stir at rt for 1 h. The resulting crude solid was sublimed at 130 °C, washed with pentane, and dried to deliver pure $B(H_2C_6F_3)_3$ as a white solid (920 mg, 27%). **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 6.58-6.70 (6H, m, ArC(3,5)*H*); **^{11}B NMR ($CDCl_3$, 160 MHz)** δ_B: 59.0; **^{19}F NMR (471 MHz $CDCl_3$)** δ_F: -95.8 (d, *J* 10.5, ArC(2,6)*F*), -100.3 (t, *J* 10.4, ArC(4)*F*). Spectroscopic data in accordance with the literature.[3]

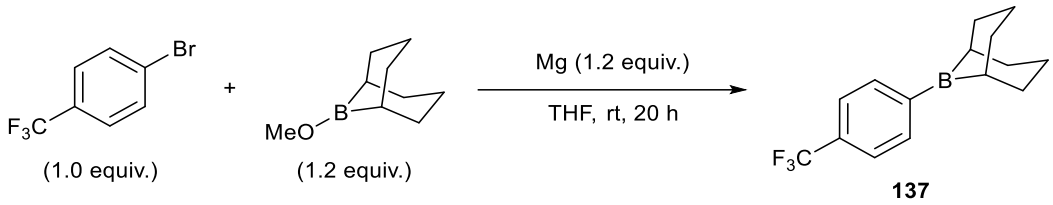
(1s,5s)-9-Hexyl-9-borabicyclo[3.3.1]nonane



The title compound was prepared according to a procedure stated in the literature.[6] In an argon-filled glovebox, a flame dried 50 mL Schlenk tube equipped with a magnetic stirrer bar was charged with degassed 1-hexene (2.8 mL, 1.77 g, 21 mmol,

1.05 equiv.). This was followed by the addition of 9-OMe-BBN (40 mL, 20 mmol, 0.5 M in THF, 1.0 equiv) at 0 °C under nitrogen. After the mixture was left to stir at rt for 16 h, the volatiles were removed under vacuum. Purification of the crude mixture was attempted using Kugelrohr distillation apparatus. **^{11}B NMR ($CDCl_3$, 160 MHz)** δ_B: found ca. 88 ppm, but not isolated pure.

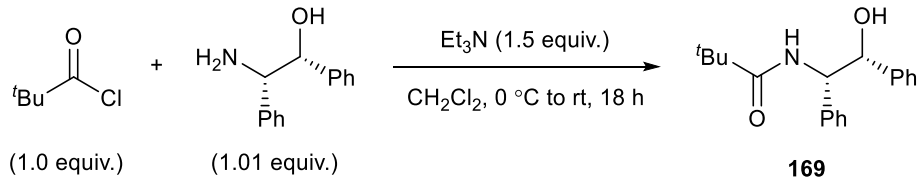
(1s,5s)-9-(4-(Trifluoromethyl)phenyl)-9-borabicyclo[3.3.1]nonane (137)



The title compound was prepared according to a procedure stated in the literature.[5] Under nitrogen, a flame dried 50 mL Schlenk tube was charged with 9-OMe-BBN (16 mL, 16 mmol, 1.0 M in hexane, 1.2 equiv.). The volatiles were removed under vacuum and THF (10 mL) was added. Under nitrogen, a second flame dried 50 mL Schlenk tube equipped with a magnetic stirrer bar was charged with magnesium turnings (384 mg, 16 mmol, 1.2 equiv.), *p*-$CF_3C_6H_5Br$ (1.86 mL, 3.0 g, 13.3 mmol, 1.0 equiv.) and the prepared 9-OMe-BBN solution THF. After the mixture was left to stir at rt for 20 h, the volatiles were removed under vacuum. Purification of the crude mixture was attempted using Kugelrohr distillation apparatus. **^{11}B NMR ($CDCl_3$, 160 MHz)** δ_B: found ca. 80 ppm, but not isolated pure.

7.2 Synthesis of Lewis Bases

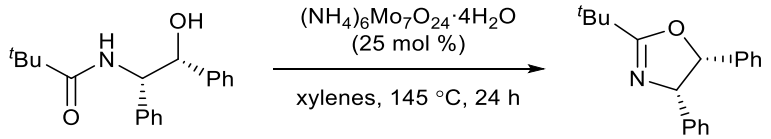
N-((1S,2R)-2-Hydroxy-1,2-diphenylethyl)pivalamide (169)



The title compound was prepared according to a procedure stated in the literature.[7] Under nitrogen, a flame-dried 100 mL round-bottomed flask equipped with a stirrer bar was charged with pivaloyl chloride (1.85 mL, 1.81 g, 15.0 mmol, 1.0 equiv.) and dry CH_2Cl_2 (15 mL). The solution was added dropwise to a mixture of (1*R*,2*S*)-2-

amino-1,2,-diphenylethanol (3.24 g, 15.2 mmol, 1.01 equiv.) and Et_3N (3.12 mL, 2.28 g, 22.5 mmol, 1.5 equiv.) at 0 °C. The reaction mixture was warmed to rt and stirred for 18 h. The mixture was then transferred to a separatory funnel, quenched with H_2O (50 mL), diluted with EtOAc (100 mL), and washed with brine (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the title compound as an off-white solid (3.80 g, 85%); $[\alpha]_D^{20}$ -32.0 (c 1.0, $CHCl_3$) {lit.[7] $[\alpha]_D^{20}$ -31.4 (c 1.0, $CHCl_3$)}; mp 61-63 °C (lit. 61-63 °C).[7] The title compound was used in the next step without any further purification. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.18 (9H, s, C(C*H*$_3$)$_2$), 3.37 (1H, d, *J* 4.3 O*H*), 5.01-5.07 (1H, m, C*H*OH), 5.32 (1H, dd, *J* 7.8, 4.0, C*H*NH), 6.33 (1H, *J* 7.8, N*H*), 6.95-7.06 (4H, m, 4×Ar*H*), 7.15-7.33 (6H, m, 6×Ar*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 27.6 (C(*C*H$_3$)$_3$), 39.0 (*C*CH$_3$)$_3$), 59.4 (*C*HNH), 76.9 (*C*HOH), 126.8 (2×Ar*C*), 127.6 (2×Ar*C*), 127.8 (Ar*C*), 128.0 (Ar*C*), 128.1 (2×Ar*C*), 128.4 (2×Ar*C*), 137.7 (Ar*C*), 139.7 (Ar*C*), 178.9 (*C*=O). Spectroscopic data in accordance with the literature.[7]

(4S,5R)-2-(tert-Butyl)-4,5-diphenyl-4,5-dihydrooxazole (135)

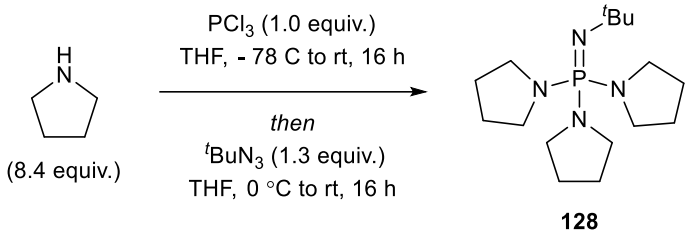


169 **135**

The title compound was prepared according to a procedure stated in the literature.[7] Under nitrogen, a flame-dried 250 mL round-bottomed flask equipped with a stirrer bar was charged with amide **169** (3.00 g, 10.1 mmol, 1.0 equiv.), ammonium heptamolybdate tetrahydrate (3.09 g, 2.5 mmol, 25 mol %) and xylenes (120 mL). The mixture was heated at reflux using a Dean Stark Apparatus for 24 h. The volatiles were removed *in vacuo* to give a crude solid. Purification by flash silica chromatography (eluent = 5-20% EtOAc in hexanes, 50 × 200 mm silica) gave the title compound as a white solid (903 mg, 32%); mp 168-170 °C (lit. 170-174 °C);[7] R_f: 0.10 (eluent =20% EtOAc in hexanes); (3.80 g, 85%); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.30 (9H, s, C(C*H*$_3$)$_3$), 4.89 (1H, d, *J* 7.1, C*H*), 5.10 (1H, d, *J* 7.1, C*H*), 7.09-7.13 (2H, m, 2×Ar*H*), 7.14-7.32 (8H, m, 8×Ar*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 28.1 (C*C*H$_3$), 33.7 (*C*CH$_3$), 74.1 (*C*H), 85.3 (*C*H), 126.4 (2xAr*C*), 127.0 (2xAr*C*), 127.1 (Ar*C*), 127.3 (Ar*C*),

127.7 (Ar*C*), 127.8 (2xAr*C*), 127.9 (2xAr*C*), 137.3 (Ar*C*), 138.3 (Ar*C*), 175.4 (*C*=N). Spectroscopic data in accordance with the literature.[7]

tert-Butylimino-tri(pyrrolidino)phosphorane (128)



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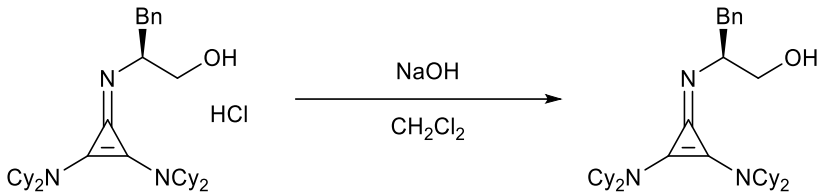
The title compound was prepared according to a procedure stated in the literature.[8] Under nitrogen, a flame-dried 250 mL Schlenk flask was charged with freshly distilled pyrrolidine (19.7 mL, 17.1 g, 240 mmol, 8.4 equiv.), and dry THF (80 mL), followed by the dropwise addition of PCl_3 (2.5 mL, 3.9 g, 28.6 mmol, 1.0 equiv.) at -78 °C. The reaction mixture was slowly warmed to rt and left to stir overnight. It was then cooled in an ice-water bath before adding *tert*-butyl azide (3.7 g, 37.3 mmol, 1.3 equiv.) dropwise. The reaction was again warmed to rt and left to stir overnight. The mixture was poured into a solution of chilled water (60 mL), hexanes/toluene (63/32 mL) and triethylamine (5 mL) The organic layer was collected, and the aqueous layer was washed with hexanes (20 mL × 3). The combined organic layers were dried over solid KOH pellets with stirring for 2 h, and then placed in a freezer for 3 h. The organic layer was decanted from the frozen alkaline layer and evaporated *in vacuo* to deliver the phosphazide intermediate as a crude solid. The solid was heated at 145 °C for 3 days under nitrogen to give a crude material. Purification of the crude mixture was attempted using Kugelrohr distillation apparatus. BTTP was obtained as a yellow oil (1.87 g, 21%). **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.34 (9H, d, *J* 0.9, 3×C*H*$_3$), 1.83-1.90 (12H, m, N(CH$_2$)$_2$(C*H*$_2$)$_2$), 3.22-3.30 (12H, m, N(C*H*$_2$)$_2$(CH$_2$)$_2$); **^{31}P NMR ($CDCl_3$, 202 MHz)** δ_C: 22.4; **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 26.1 (d, *J* 8.1, N(CH$_2$)$_2$(*C*H$_2$)$_2$), 31.5 (d, *J* 4.6, 3×*C*H$_3$), 47.8 (d, *J* 5.1, N(*C*H$_2$)$_2$(CH$_2$)$_2$), 52.5 (d, *J* 1.4, *C*(CH$_3$)$_4$). Spectroscopic data in accordance with the literature.[9]

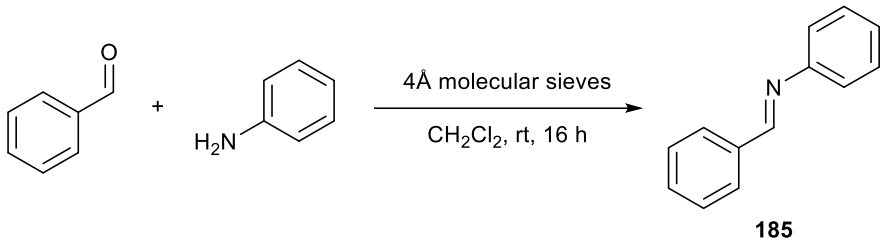
(S)-2-((2,3-Bis(dicyclohexylamino)cycloprop-2-en-1-ylidene)amino)-3-phenylpropan-1-ol (172)



175 **172**

Compound **175** was synthesised by Shyam Basak according to a procedure from the literature.[10] Free cyclopropenimine **172** was obtained from hydrochloride salt **175**, stored in the freezer, and used within 2 days. Compound **175** (100 mg, 0.17 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (15 mL) and washed with 1.0 M NaOH (3 × 10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound as an off-white solid (70 mg, 75%). **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.05-1.95 (40H, m, Cy*H*), 2.70-2.86 (2H, m), 3.00-3.17 (4H, NCy*H*), 3.39-3.46 (1H, m), 3.36-3.53 (1H, m), 3.75-7.83 (1H, m), 7.10-7.16 (1H, m, 4×Ar*H*), 7.18-7.30 (4H, m, 4×Ar*H*). Absent O*H*. Spectroscopic data in accordance with the literature.[10]

7.3 Substrate Synthesis



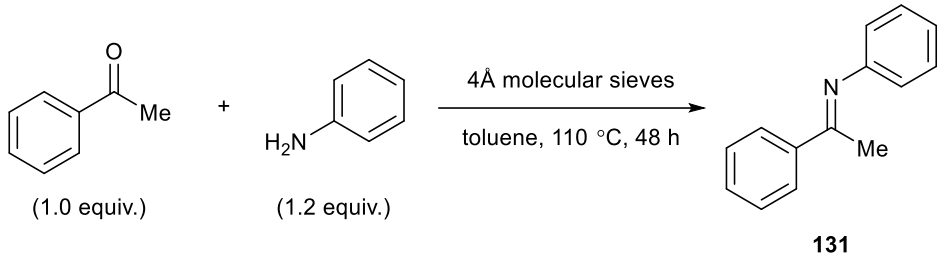
185

(E)-N,1-Diphenylmethanimine (185)

Under nitrogen, a flame-dried 250 mL round-bottomed flask was charged with 4Å molecular sieves (1 g), dry CH_2Cl_2 (100 mL), benzaldehyde (2.04 mL, 2.12 g, 20 mmol, 1.0 equiv.) and aniline (1.83 mL, 1.86 g, 20 mmol, 1.0 equiv.). The reaction mixture was left to stir at rt for 16 h. The molecular sieves were filtered off, and all volatiles were removed under vacuum. Purification by recrystallisation with ethanol yielded a yellow solid (1.20 g, 33%); mp 51-53 °C (lit. 50-51 °C);[11] R_f = 0.75 (eluent = 10% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 7.20-7.26 (3H, m, ArC(3',4',5')*H*), 7.38-7.43 (2H, m, ArC(2',6')*H*), 7.47-7.52 (3H, m, ArC(3,4,5)*H*), 7.89-7.93 (2H, m,

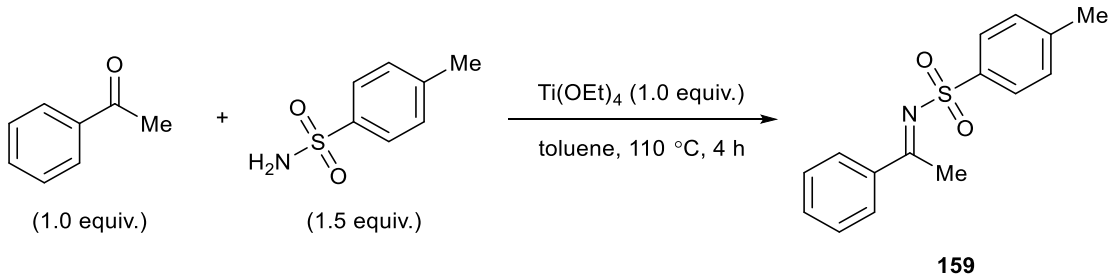
ArC(2,6)*H*), 8.47 (1H, s, *H*C=N); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 121.0 (Ar*C*(3',5')), 126.04 (Ar*C*(4')), 128.9 (ArC(3,5)), 128.9 (ArC(2,6)), 129.3 (Ar*C*(2',6')), 131.5 (Ar*C*(4)), 136.4 (Ar*C*(1)), 152.2 (Ar*C*(1')), 160.5 (H*C*=N). Spectroscopic data in accordance with the literature.[11]

(*E*)-N,1-Diphenylethan-1-imine (131)



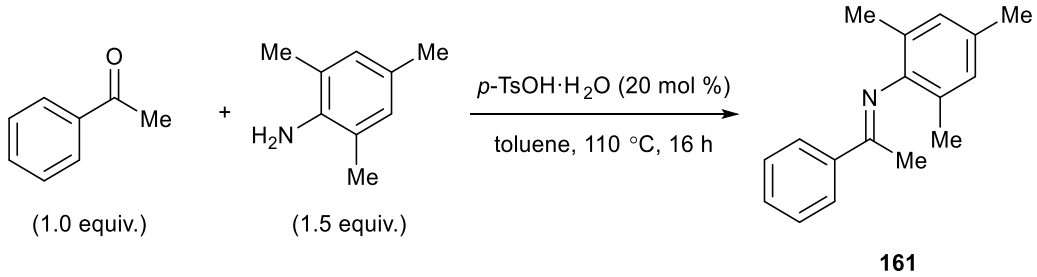
Under nitrogen, a flame-dried 250 mL round-bottomed flask was charged with 4Å molecular sieves (25 g), dry toluene (60 mL), acetophenone (5.83 mL, 6.01 g, 50 mmol, 1.0 equiv.) and aniline (5.48 mL, 5.59 g, 60 mmol, 1.2 equiv.). The reaction mixture was left to reflux at 110 °C for 48 h. The reaction was cooled, the molecular sieves filtered off, and all volatiles were removed under vacuum. Purification by recrystallisation with ethanol yielded a yellow solid (2.20 g, 23%); mp 38-40 °C (lit. 40-41 °C);[12] R_f = 0.36 (eluent = 5% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 2.24 (3H, s, CH_3), 6.79-6.83 (2H, m, ArC(2',6')*H*), 7.07-7.12 (1H, m, ArC(4')*H*), 7.33-7.38 (2H, m, ArC(3,5)*H*), 7.41-7.50 (3H, m, ArC(3,4,5)*H*), 7.96-8.01 (2H, m, ArC(2,6)*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 17.53 (*C*H$_3$), 119.5 (Ar*C*(2',6')), 123.3 (Ar*C*(4')), 127.3 (Ar*C*(2,6)), 128.5 (Ar*C*(3,5)), 129.1 (Ar*C*(3'5')), 130.6 (Ar*C*(1)), 139.6 (Ar*C*(4)), 151.8 (Ar*C*(1')), 165.6 (*C*=N). Spectroscopic data in accordance with the literature.[12]

(*E*)-4-Methyl-N-(1-phenylethylidene)benzenesulfonamide (159)



Under nitrogen, a flame-dried 100 mL round-bottomed flask was charged with dry toluene (30 mL), acetophenone (2.33 mL, 2.40 g, 20 mmol, 1.0 equiv.) and *p*-toluenesulfonamide (5.14 g, 30 mmol, 1.5 equiv.), followed by the careful addition of $Ti(OEt)_4$ (5.30 mL, 5.76 g, 20 mmol, 1.0 equiv.) with stirring at rt. The reaction mixture was left to reflux at 110 °C for 16 h. After completion, the reaction mixture was cooled to rt, transferred to a large conical flask, diluted with EtOAc (30 mL), quenched with $NaHCO_3$ solution (30 mL), and filtered through a pad of celite. The filtrate was transferred to a separatory funnel. The organic layer was collected, and the aqueous phase was washed with EtOAc (2 × 20 mL). The organics were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by recrystallisation with ethanol yielded a crystalline white solid (945 mg, 17%); mp 85-87 °C (lit. 89-90 °C);[13] R_f = 0.26 (eluent = 10% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 2.45 (3H, s, C*H*$_3$), 2.99 (3H, s, C*H*$_3$), 7.32-7.37 (2H, m, 2×Ar*H*), 7.38-7.44 (2H, m, 2×Ar*H*), 7.50-7.56 (1H, m, ArC(4)*H*), 7.86-7.96 (4H, m, ArC(2',3',5'6')*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 21.3 (*C*H$_3$), 21.7 (*C*H$_3$), 127.2 (2×Ar*C*), 128.4 (2×Ar*C*), 128.7 (2×Ar*C*), 129.6 (2×Ar*C*), 133.3 (Ar*C*), 137.7 (Ar*C*), 138.9 (Ar*C*), 143.7 (Ar*C*), 180.0 (*C*=N). Spectroscopic data in accordance with the literature.[13]

(E)-N-Mesityl-1-phenylethan-1-imine (161)

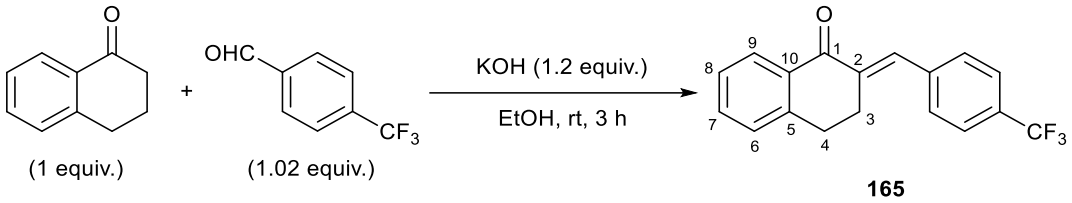


161

Under nitrogen, a flame-dried 100 mL round-bottomed flask was charged with dry toluene (30 mL), acetophenone (2.33 mL, 2.40 g, 20 mmol, 1.0 equiv.) and 2,4,6-trimethylaniline (2.81 mL, 2.70 g, 20 mmol, 1.0 equiv.). The reaction mixture was left to reflux at 110 °C for 16 h. The reaction was cooled and quenched with $NaHCO_3$ (20 mL). The mixture was transferred to a separatory funnel. The organic phase was collected, and the aqueous phase was washed with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (1 × 25 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash alumina chromatography (eluent = 1-2%

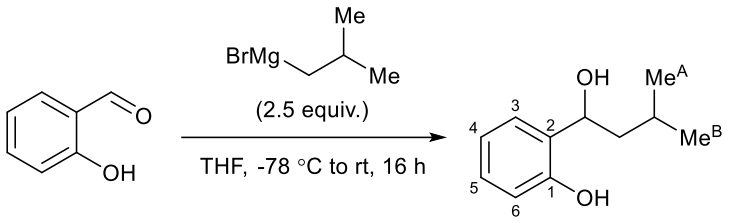
EtOAc in hexanes, 40 × 200 mm silica) gave the title compound as an orange oil (255 mg, 5%); R_f = 0.69 (eluent = 10% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.99 (6H, s, *o*-CH_3), 2.07 (3H, s, *p*-CH_3), 2.29 (3H, s, N=CCH_3), 6.86-6.89 (2H, m, ArC(3',5')*H*), 7.43-7.51 (3H, m, ArC(3,4,5)*H*), 7.99-8.06 (2H, m, ArC(2,6)*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 17.6 (2×*C*H_3), 18.0 (*C*H_3), 20.8 (*C*H_3), 125.7 (2×Ar*C*), 127.2 (2×Ar*C*), 128.4 (2×Ar*C*), 129.0 (2×Ar*C*), 130.3 (Ar*C*), 132.0 (Ar*C*), 139.4 (Ar*C*), 146.8 (Ar*C*), 165.5 (C=N). Spectroscopic data in accordance with the literature.[14]

(E)-2-(4-(Trifluoromethyl)benzylidene)-3,4-dihydronaphthalen-1(2H)-one (165)



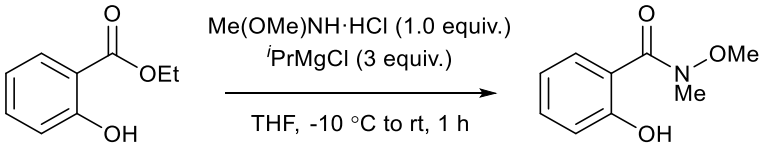
The title compound was prepared according to a procedure stated in the literature.[15] To a 250 mL round-bottomed flask equipped with a stirrer bar was charged *α*-tetralone (2.66 mL, 2.92 g, 20 mmol, 1 equiv.), 4-(trifluoromethyl)benzaldehyde (2.79 mL, 3.55 g, 20.4 mmol, 1.02 equiv.) and ethanol (40 mL). KOH (1.35 g, 24 mmol, 1.2 equiv.) in ethanol (40 mL) was then added dropwise to the mixture, with stirring. The mixture was left to stir at rt for 3 h before being poured into ice-cold water (100 mL). The resulting white precipitate was filtered off, washed with more ice-cold water, and dried under vacuum to yield a beige solid (5.99 g, 99%); mp 176-178 °C (lit. 177-178 °C);[15] R_f = 0.37 (eluent = 10% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 2.94-3.00 (2H, m, C(4)H_2), 3.08-3.14 (2H, m, C(3)H_2), 7.25-7.29 (1H, m, *C*(8)*H*), 7.36-7.41 (1H, m, C(6)*H*), 7.49-7.55 (3H, m, ArC(2',6')*H* and C(7)*H*), 7.65-7.70 (2H, d, *J* 8.2, ArC(3',5')*H*), 7.85 (1H, s, C=C*H*), 8.12-8.17 (1H, m, C(9)*H*); **^{19}F NMR (471 MHz $CDCl_3$)** δ_F: -62.7; **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 27.3 (*C*(4)H_2), 29.0 (*C*(3)H_2), 124.1 (q, *J* 273, *C*F_3), 125.5 (q, J 3.8, Ar*C*(3',5')), 127.3 (*C*(6)), 128.4 (*C*(8)), 128.5 (Ar*C*(2',6')), 130.0 (C(2)=*C*H), 130.3 (q, *J* 32.6, Ar*C*(4')), 133.4 (*C*(5)), 133.7 (*C*(9)), 134.8 (C(7)), 137.5, (*C*(2)), 139.6 (Ar*C*(1')), 143.3 (*C*(10)), 187.7 (*C*=O). Spectroscopic data in accordance with the literature.[16]

2-(1-Hydroxy-3-methylbutyl)phenol



Under nitrogen, a flame-dried 250 mL round-bottomed flask with a stirrer bar was charged with dry THF (100 mL) and salicylaldehyde (4.18 mL, 4.88 g, 40 mmol, 1 equiv.), followed by the dropwise addition of *iso*-butylmagnesium bromide (50 mL, 100 mmol, 2.5 equiv., 2 M in THF) at -78 °C with stirring. The reaction was warmed to room temperature and left to stir overnight. The reaction was quenched with sat. aq. NH_4Cl (25 mL) and H_2O (25 mL). EtOAc (10 mL) was added, and the mixture was transferred to a separatory funnel. The organic layer was collected, and the aqueous phase was washed with EtOAc (2 × 25 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 40 × 150 mm silica) gave the title compound as a colourless oil (6.51 mg, 90%); R_f: 0.32 (eluent = 10% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 0.95 (3H, d, J 6.6, CH_3^A), 0.98 (3H, d, J 6.6, CH_3^B), 1.54-1.63 (1H, m, C*H*H), 1.73 (1H, non, *J* 13.1, 6.5, $CH_2CH(CH_3)_2$), 1.88 (1H, ddd, *J* 13.9, 8.9, 5.8, CH*H*), 2.54 (1H, d, *J* 3.4, CHO*H*), 4.91 (1H, ddd, *J* 8.9, 5.3, 3.5, C*H*OH), 6.82 (1H, dt, *J* 7.4, 1.1, ArC(5)*H*), 6.87 (1H, dd, *J* 8.1, 1.0, ArC(3)*H*), 6.95 (1H, dd, *J* 7.5, 1.6, ArC(6)*H*), 7.17 (1H, dt, *J* 8.1, 1.7, ArC(4)*H*), 7.90 (1H, s, ArC(1)O*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 22.0 (*C*H_3^B), 23.1 (*C*H_3^A),24.6 (*C*H$(CH_3)_2$), 46.0 (*C*H_2), 74.3 (*C*HOH), 117.2 (Ar*C*(5)), 119.7 (Ar*C*(3)), 126.9 (Ar*C*(4)), 127.8 (Ar*C*(2)), 128.9 (Ar*C*(6)), 155.6 (Ar*C*(1)OH). Spectroscopic data in accordance with the literature.[17]

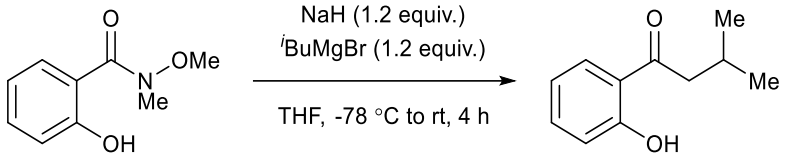
2-Hydroxy-N-methoxy-N-methylbenzamide



The title compound was prepared according to a procedure stated in the literature.[18] Under nitrogen, a flame-dried 250 mL round-bottomed flask with a stirrer bar was charged with dry THF (30 mL), methyl salicylate (3.90 mL, 4.56 g, 30 mmol, 1.0 equiv.), and Me(OMe)NH·HCl (2.93 g, 30 mmol, 1.0 equiv.), followed by the slow

addition of iPrMgCl (45 mL, 90 mmol, 3 equiv., 2M in THF) at -10 °C. The reaction mixture was stirred at -10 °C for 1 h, warmed to rt, quenched with NH_4Cl solution (30 mL) and transferred to a separatory funnel. The organic layer was collected, and the aqueous phase was washed with EtOAc (2 × 25 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 40 × 150 mm silica) gave the title compound as a colourless oil (2.39 mg, 44%); R_f: 0.26 (eluent = 10% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 3.41 (3H, s, C*H*$_3$), 3.65 (3H, m, C*H*$_3$), 6.84 (1H, ddd, *J* 8.2, 7.2, 1.3, Ar*H*), 6.99 (1H, dd, *J* 8.3, 1.2, Ar*H*), 7.37 (1H, ddd, *J* 8.5, 7.3, 1.7, Ar*H*), 7.95 (1H, dd, *J* 8.1, 1.7, Ar*H*), 11.17 (1H, s, ArO*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 34.2 (*C*H$_3$), 61.4 (*C*H$_3$), 114.5 (Ar*C*), 118.1 (Ar*C*), 118.7 (Ar*C*), 129.6 (Ar*C*), 133.9 (Ar*C*), 161.1 (Ar*C*), 170.0 (*C*=O). Spectroscopic data in accordance with the literature.[19]

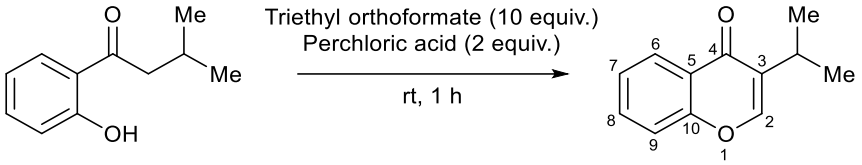
1-(2-Hydroxyphenyl)-3-methylbutan-1-one



The title compound was prepared according to a procedure stated in the literature.[18] Under nitrogen, a flame-dried 100 mL round-bottomed flask with a stirrer bar was charged with dry THF (20 mL) and 2-hydroxy-N-methoxy-N-methylbenzamide (2.0 g, 11 mmol, 1.0 equiv.), followed by the addition of NaH (0.53 g, 13.25 mmol, 1.2 equiv., 60% dispersion in mineral oil) at -78 °C. The reaction mixture was stirred vigorously for 10 min, followed by the addition of ^{i}BuMgBr (6.6 mL, 13.25 mmol, 1.2 equiv., 2M in THF) at -78 °C. The reaction mixture was warmed to rt and stirred for 4 h before quenching with NH_4Cl solution (20 mL). The mixture was transferred to a separatory funnel. The organic layer was collected, and the aqueous phase was washed with EtOAc (2 × 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 35 × 150 mm silica) gave the title compound as a colourless oil (0.92 g, 46%); R_f: 0.89 (eluent = 10% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.02 (6H, d, *J* 6.7, CH(C*H*$_3$)$_2$), 2.30 (1H, non, *J* 6.7, CH$_2$C*H*(CH$_3$)$_2$), 2.85 (2H, d, *J* 6.9,

C*H*$_2$), 6.89 (1H, ddd, *J* 8.1, 7.2, 1.2, Ar*H*), 6.98 (1H, dd, *J* 8.4, 1.2, Ar*H*), 7.46 (1H, ddd, *J* 8.4, 7.1, 1.6, Ar*H*), 7.76 (1H, dd, *J* 8.0, 1.7, Ar*H*), 12.47 (1H, s, ArO*H*); **^{13}C NMR (CDCl$_3$, 126 MHz)** δ_C: 22.9 (CH(*C*H$_3$)$_2$), 25.7 (*C*H(CH$_3$)$_2$), 47.2 (*C*H$_2$), 118.7 (Ar*C*), 118.9 (Ar*C*), 119.8 (Ar*C*), 130.3 (Ar*C*), 136.4 (Ar*C*), 162.7 (Ar*C*), 206.8 (*C*=O). Spectroscopic data in accordance with the literature.[19]

3-Isopropyl-4H-chromen-4-one (164)



164

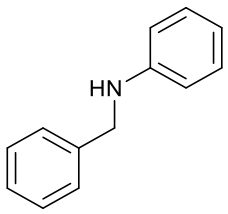
Preparation of the title compound was adapted from a procedure stated in the literature.[20] Perchloric acid (0.43 mL, 0.77 g, 7.63 mmol, 2.0 equiv., 70% solution) was added dropwise to a suspension of 1-(2-hydroxyphenyl)-3-methylbutan-1-one (680 mg, 3.81 mmol, 1.0 equiv.) and triethyl orthoformate (6.34 mL, 5.65 g, 38.1 mL, 10 equiv.). The solution went from pale orange to dark red after stirring for 5 min. After 1 h stirring at rt, Et$_2$O (15 mL) was added to precipitate the intermediate oxonium perchlorate salt, which was subsequently hydrolyzed with hot H$_2$O (25 mL). The mixture was transferred to a separatory funnel. The organic layer was collected, and the aqueous phase was washed with Et$_2$O (2 × 10 mL). The organic layers were combined, dried over MgSO$_4$, filtered, and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 1-3% EtOAc in hexanes, 35 × 150 mm silica) gave the title compound as a colourless oil (244 mg, 34%); R_f: 0.35 (eluent = 5% EtOAc in hexanes); **^{1}H NMR (CDCl$_3$, 500 MHz)** δ_H: 1.24 (6H, d, *J* 6.9, CH(C*H*$_3$)$_2$), 3.17 (1H, dhept, *J* 6.9, 0.9, C*H*(CH$_3$)$_2$), 7.37 (1H, ddd, *J* 8.1, 7.1, 1.1, ArC(7)*H*), 7.42 (1H, ddd, J 8.5, 1.0, 0.5, ArC(9)*H*), 7.63 (1H, dd, *J* 8.6, 7.1, 1.7, ArC(8)*H*), 7.72 (1H, d, *J* 1.0, ArC(2)*H*), 8.24 (1H, ddd, *J* 8.0, 1.7, 0.5, ArC(6)*H*); **^{13}C NMR (CDCl$_3$, 126 MHz)** δ_C: 21.7 (CH(*C*H$_3$)$_2$), 25.2 (*C*H(CH$_3$)$_2$), 118.1 (Ar*C*(9)), 124.2 (Ar*C*(3)), 124.9 (Ar*C*(7)), 126.1 (Ar*C*(6)), 130.3 (Ar*C*(5)), 133.4 (Ar*C*(8)), 151.4 (Ar*C*(2)), 156.4 (Ar*C*(10)), 177.5 (*C*=O). Spectroscopic data in accordance with the literature.[21]

7.4 Synthesis of Products

General procedure 1: Hydrogenation of Substrates

Inside an argon-filled glovebox, to an oven-dried 5 mL sample vial with a stirrer bar was added substrate (x mmol, 1.0 equiv.), Lewis base (x mol %), Lewis acid (x mol %) and solvent (x mL). The vial was partially sealed using a screw-top cap possessing several pierced holes. The vial was placed inside a Parr reactor, which was then sealed. The Parr reactor was removed from the glovebox, placed upon a fitted heating block behind a blast shield, and filled with H_2 gas slightly below required reaction pressure (x bar). The reaction mixture was heated to the specified temperature (°C) followed by any necessary adjustment in pressure. After the reaction mixture had been left to stir for the specified reaction time (h), the reactor was cooled, slowly vented, and disconnected to retrieve the vial. Mesitylene (1 equiv.) was added to the crude mixture for subsequent ^{1}H NMR analysis.

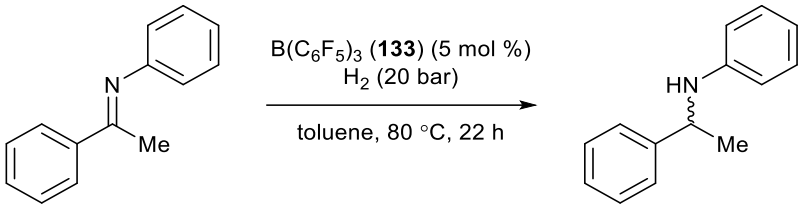
N-Benzylaniline (186)



186

The title compound was prepared according to general procedure 1 using (E)-*N*,1-diphenylmethanimine (**184**) (90.6 mg, 0.5 mmol, 1.0 equiv.), 9-Hexyl BBN (5.2 mg, 0.025 mmol, 5 mol%), Verkade's base (**129**) (5.4 mg, 0.025 mmol, 5 mol %) and toluene (2 mL). The crude ^{1}H NMR showed 13% conversion to **186**. Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 25 × 150 mm silica) gave the title compound as a crystalline solid (12 mg, 25%); R_f: 0.5 (eluent = 5% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 4.04 (1H, br s, N*H*), 4.37 (2H, s, CH_2), 6.62-6.68 (2H, m, 2×Ar*H*), 6.70-6.75 (1H, m, Ar*H*), 7.15-7.22 (2H, m, 2×Ar*H*), 7.26-7.31 (1H, m, Ar*H*), 7.32-7.42 (4H, m, 4×Ar*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 48.5 (*C*H_2), 113.0 (2×Ar*C*), 117.7 (Ar*C*), 127.4 (2×Ar*C*), 127.6 (Ar*C*), 128.8 (2×Ar*C*), 129.4 (2×Ar*C*), 139.6 (Ar*C*), 148.3 (Ar*C*). Spectroscopic data in accordance with the literature.[22]

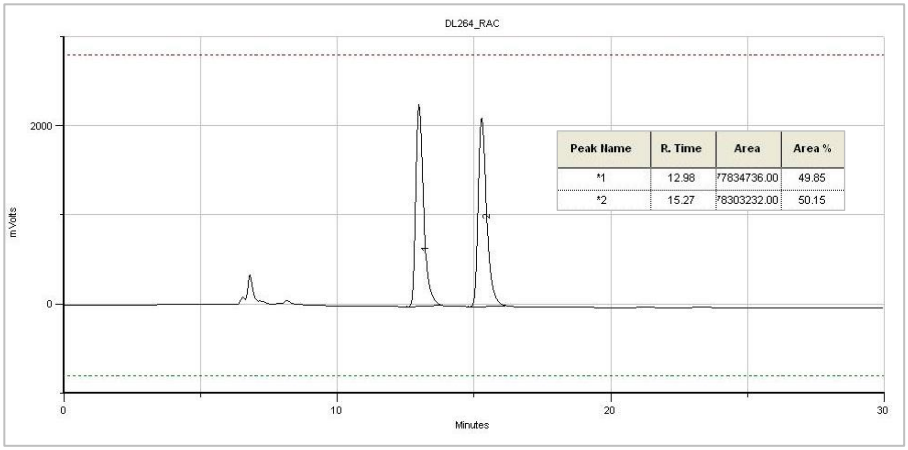
N-(1-Phenylethyl)aniline (±134)



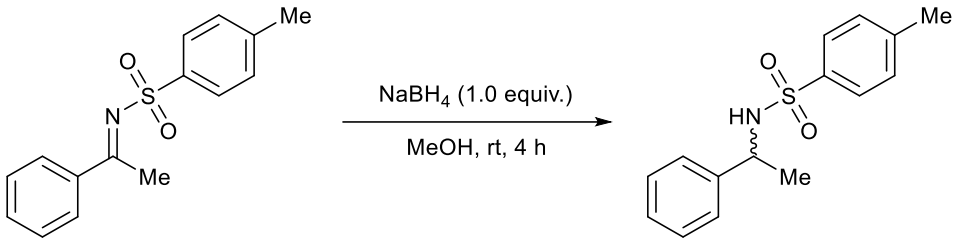
131 **±134**

The title compound was prepared according to general procedure 1 using *N*,1-diphenylethan-1-imine (**131**) (97.6 mg, 0.5 mmol, 1.0 equiv.), $B(C_6F_5)_3$ (**133**) (12.8 mg, 0.025 mmol, 5 mol%), and toluene (2 mL). Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 25 × 150 mm silica) gave the title compound as a pale-yellow oil (98 mg, 87%); R_f: 0.5 (eluent = 5% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.52 (3H, d, *J* 6.7, C*H*$_3$), 4.04 (1H, br s, N*H*), 4.49 (1H, q, *J* 6.7, C*H*CH$_3$), 6.49-6.54 (2H, m, 2×Ar*H*), 6.62-6.67 (1H, m, Ar*H*), 7.06-7.12 (2H, m, 2×Ar*H*), 7.20-7.25 (1H, m, Ar*H*), 7.29-7.35 (2H, m, 2×Ar*H*), 7.35-7.40 (2H, m, 2×Ar*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 25.2 (*C*H$_3$), 53.6 (*C*HCH$_3$), 113.4 (2×Ar*C*), 117.4 (Ar*C*), 126.0 (2×Ar*C*), 127.0 (Ar*C*), 128.8 (2×Ar*C*), 129.2 (2×Ar*C*), 145.4 (Ar*C*), 147.4 (Ar*C*). Spectroscopic data in accordance with the literature.[23]

HPLC data for racemate: Chiralpak IB (Gilson method 6) = 95:5 Hexane:IPA, 0.5 mL/min, 211 nm, 12.98 and 15.27 min.



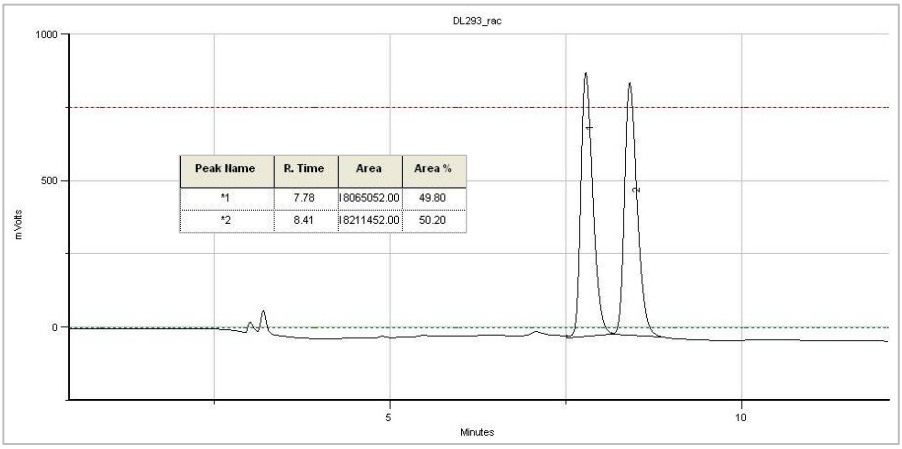
4-Methyl-N-(1-phenylethyl)benzenesulfonamide (±160)



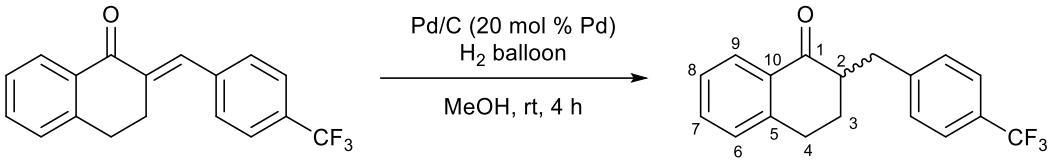
159 **±160**

Under nitrogen, a flame dried 10 mL round-bottomed flask equipped with a stirrer bar was charged with (*E*)-4-methyl-N-(1-phenylethylidene)benzenesulfonamide (**159**) (137 mg, 0.5 mmol, 1.0 equiv.) and MeOH (1 mL), followed by the portion-wise addition of $NaBH_4$ (18.9 mg, 0.5 mmol, 1.0 equiv.). The mixture was left to stir at rt for 4 h. The reaction was quenched with saturated NH_4Cl solution (1 mL) and diluted with EtOAc (10 mL). The mixture was transferred to a separatory funnel containing brine (10 mL). The organic layer was collected, and the aqueous phase washed with EtOAc (2 × 10 mL). The organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 10-20% EtOAc in hexanes, 25 × 150 mm silica) gave the title compound as a crystalline off-white solid (116 mg, 85%); mp 78-80 °C (lit. 79-80 °C);[24] R_f: 0.27 (eluent = 20% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.43 (3H, d, *J* 6.9, CHC*H*$_3$), 2.39 (3H, s, $C_6H_4CH_3$), 4.46 (1H, quint, *J* 6.7, C*H*CH$_3$), 4.75 (1H, d, *J* 6.9, N*H*), 7.07-7.13 (2H, m, ArC(3',5')*H*), 7.15-7.23 (5H, m, ArC(2,3,4,5,6)*H*), 7.59-7.64 (2H, m, Ar(2',6')*H*); **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 21.6 (*C*H$_3$), 23.7 (*C*H$_3$), 53.8 (*C*HCH$_3$), 126.2 (2×Ar*C*), 127.2 (2×Ar*C*), 127.6 (Ar*C*(4)), 128.7 (2×Ar*C*), 129.6 (2×Ar*C*), 137.8 (Ar*C*), 142.1 (Ar*C*), 143.2 (Ar*C*). Spectroscopic data in accordance with the literature[24]

HPLC data for racemate: Chiralpak IB (Gilson method 62) = 80:20 Hexane:IPA, 2.0 mL/min, 211 nm, 7.78 and 8.41 min.



2-(4-(Trifluoromethyl)benzyl)-3,4-dihydronaphthalen-1(2H)-one (±147)

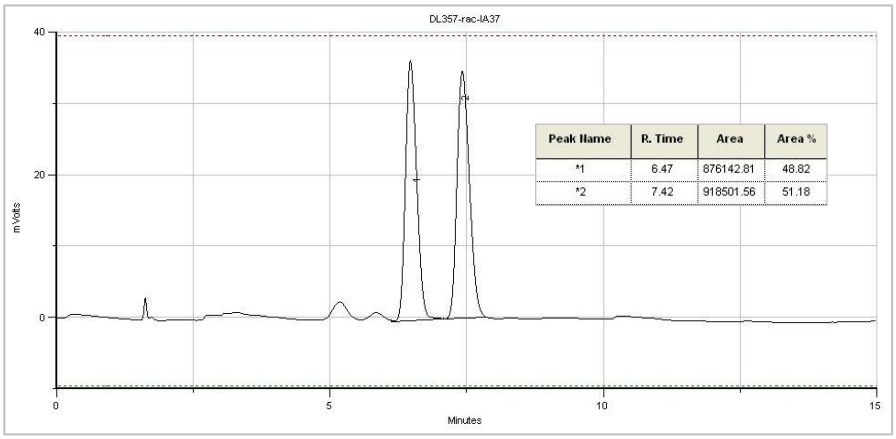


165 **±147**

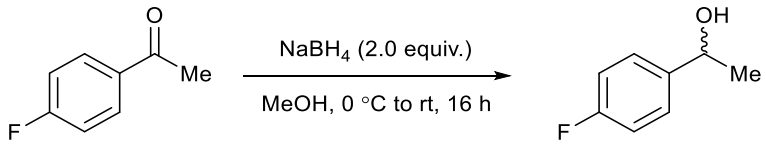
Under nitrogen, a flame-dried 100 mL round-bottomed flask equipped with a stirrer bar was charged with (E)-2-(4-(trifluoromethyl)benzylidene)-3,4-dihydronaphthalen-1(2H)-one (**5.36**) (302 mg, 1.0 mmol, 1.0 equiv.) and degassed MeOH (40 mL). 5% Pd on charcoal (426 mg, 0.2 mmol Pd, 20 mol % Pd) was then added rapidly in small portions with stirring. The flask was purged with H_2 gas (×3) and the contents were left to stir at rt for 4 h under the pressure of a hydrogen-filled balloon (1-2 bar). Upon completion, the contents were filtered through a pad of celite with additional MeOH to keep the filter cake wet. Care was taken to avoid drying out the filter cake, before disposing the solids into special Pd/C waste. The filtrate was collected and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 0.5-2% EtOAc in hexanes, 25 × 200 mm silica) gave the title compound as a white solid (160 mg, 53%); R_f: 0.27 (eluent = 20% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.75-1.87 (1H, m, C_6H_4CH*H*), 2.06-2.14 (1H, m, C_6H_4C*H*H), 2.70-2.82 (2H, m, C(3)H_2), 2.92-3.01 (2H, m, C(4)H_2), 3.48-3.58 (1H, m, C(2)*H*), 7.23 (1H, d, *J* 7.7, ArC(6)*H*), 7.32 (1H, t, *J* 7.8, ArC(8)*H*), 7.36 (2H, d, *J* 8.0, ArC(2',6')H), 7.48 (1H, dt, *J* 7.5, 1.3, ArC(7)*H*), 7.56 (2H, d, *J* 8.0, ArC(3'5')*H*), 8.07 (1H, dd, *J* 7.9, 1.4, ArC(9)*H*); **^{19}F NMR (471 MHz $CDCl_3$)** δ_F: -62.3; **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 28.1 (*C*(4)H_2), 28.9 (*C*(3)H_2), 35.8 (C_6H_4*C*H_2), 49.4 (*C*(2)H), 124.4 (q, *J* 272, *C*F_3), 125.5 (q, J 3.8, Ar*C*(3'5')), 126.9 (*C*(6)), 127.7 (*C*(8)), 128.7 (q, J 32.4, Ar*C*(4')CF_3), 128.9 (*C*(7)), 129.7

(Ar*C*(2'6')), 132.5 (*C*(5)), 133.6 (*C*(9)), 144.0 (*C*(1')), 144.5 (*C*(10)), 198.9 (*C*=O). Spectroscopic data in accordance with the literature.[7]

HPLC data for racemate: Chiralpak IA (Gilson method 37) = 99:1 Hexane:IPA, 2.0 mL/min, 211 nm, 6.47 and 7.42 min.



1-(4-Fluorophenyl)ethan-1-ol (±171)

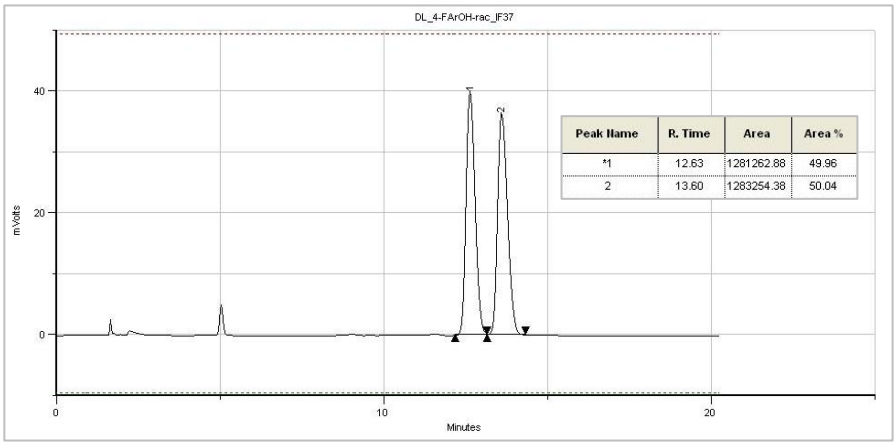


170 **±171**

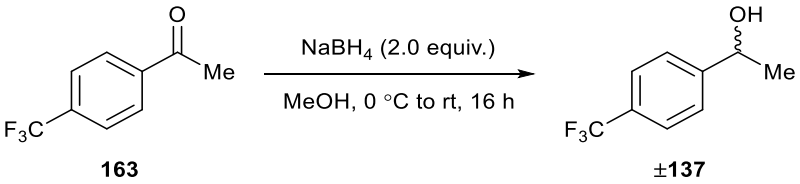
Under nitrogen, a flame dried 100 mL round-bottomed flask equipped with a stirrer bar was charged with 1-(4-fluorophenyl)ethan-1-one (276 mg, 2.0 mmol, 1.0 equiv.) and MeOH (20 mL), followed by the portion-wise addition of $NaBH_4$ (151 mg, 4 mmol, 2.0 equiv.) at 0 °C. The mixture was left to stir at rt for 16 h. The reaction was quenched with saturated NH_4Cl solution (20 mL) and the mixture was transferred to a separatory funnel. The organic layer was collected, and the aqueous phase washed with EtOAc (2 × 20 mL). The organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 10-20% EtOAc in hexanes, 30 × 150 mm silica) gave the title compound as a colourless oil (264 mg, 94%); R_f: 0.30 (eluent = 20% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.48 (3H, d, *J* 6.4, CHC*H*$_3$), 1.78 (1H, br s, CHO*H*), 4.89 (1H, q, *J* 6.4, C*H*CH$_3$), 7.00-7.06 (2H, m, 2×Ar*H*) 7.31-7.37 (2H, m, 2×Ar*H*); **^{19}F NMR (471 MHz $CDCl_3$)** δ_F: -115.2; **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: **25.4 (*C*H$_3$), 69.9 (*C*HOH), 115.4 (d, *J* 21.3,**

Ar*C*(3,5)), 127.18 (d, *J* 8.1, Ar*C*(2,6)), 141.6 (d, *J* 3.0, Ar*C*(1)), 162.3 (d, *J* 245.2, Ar*C*(4)). Spectroscopic data in accordance with the literature.[25]

HPLC data for racemate: Chiralpak IF (Gilson method 37) = 99:1 Hexane:IPA, 2.0 mL/min, 211 nm. 12.63 and 13.60 min.



1-(4-(Trifluoromethyl)phenyl)ethan-1-ol (±137)

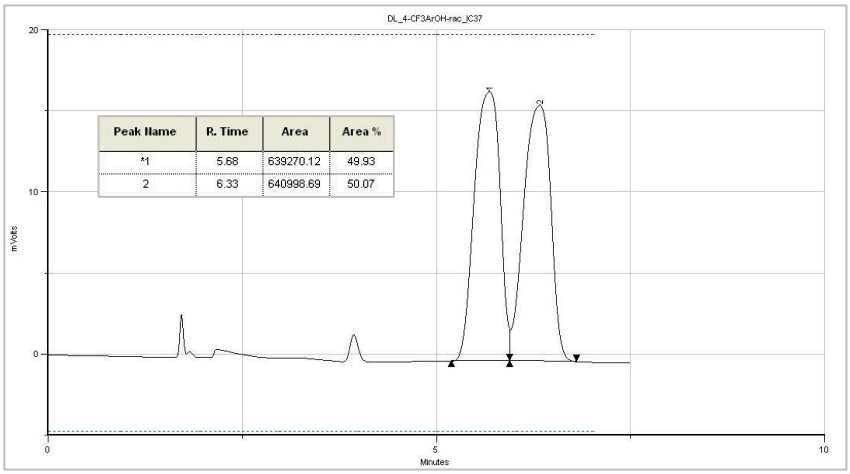


163 **±137**

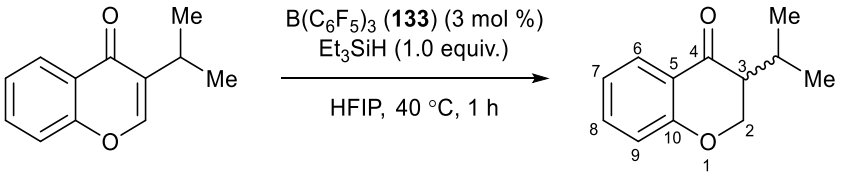
Under nitrogen, a flame dried 100 mL round-bottomed flask equipped with a stirrer bar was charged with 1-(4-(trifluoromethyl)phenyl)ethan-1-one (941 mg, 5.0 mmol, 1.0 equiv.) and MeOH (25 mL), followed by the portion-wise addition of $NaBH_4$ (378 mg, 10 mmol, 2.0 equiv.) at 0 °C. The mixture was left to stir at rt for 16 h. The reaction was quenched with saturated NH_4Cl solution (25 mL) and the mixture was transferred to a separatory funnel. The organic layer was collected, and the aqueous phase washed with EtOAc (2 × 20 mL). The organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 10-20% EtOAc in hexanes, 30 × 150 mm silica) gave the title compound as a colourless oil 808 mg, 85%); R_f: 0.27 (eluent = 20% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.53 (3H, d, *J* 6.5, CHC*H*$_3$), 1.87 (1H, br s, CHO*H*), 5.00 (1H, q, *J* 6.5, C*H*CH$_3$), 7.50-7.54 (2H, m, 2×Ar*H*) 7.61-7.66 (2H, m, 2×Ar*H*); **^{19}F NMR (471 MHz $CDCl_3$)** δ_F: -62.7; **^{13}C NMR ($CDCl_3$, 126 MHz)** δ_C: 25.6 (CH*C*H$_3$), 70.0 (*C*HCH$_3$), 124.3

(q, *J* 272, CF_3), 125.6 (q, *J* 3.8, Ar*C*(3,5)), 125.8 (Ar*C*(2,6)), 129.8 (q, *J* 32, Ar*C*(4)), 149.8 (Ar*C*(1)). Spectroscopic data in accordance with the literature.[26]

HPLC data for racemate: Chiralpak IC (Gilson method 37) = 99:1 Hexane:IPA, 2.0 mL/min, 211 nm, 5.68 and 6.33 min.



3-Isopropylchroman-4-one (±145)

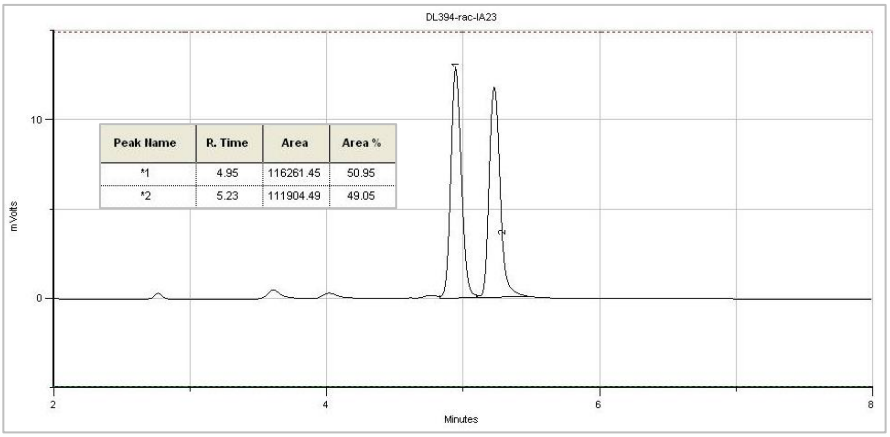


164 **±145**

Preparation of the title compound was adapted from a procedure stated in the literature.[27] Inside an argon-filled glovebox, to an oven-dried 5 mL sample vial with a stirrer bar was added **164** (94.1 mg, 0.5 mmol, 1.0 equiv.), triethylsilane (42 µL, 58 mg, 0.5 mmol, 1 .0 equiv.), $B(C_6F_5)_3$ (**133**) (7.7 mg, 0.015 mmol, 3 mol %) and degassed HFIP (1 mL). The vial was sealed with an aluminium cap and removed from the glovebox. Using a hotplate, the contents were heated at 40 °C for 1 h. The reaction mixture was diluted with EtOAc and transferred to a separatory funnel containing brine (20 mL). The organic layer was collected, and the aqueous phase was washed with EtOAc (2 × 10 mL). The organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 1-2% EtOAc in hexanes, 25 × 200 mm silica) gave the title compound as a pale yellow oil (14 mg, 15%); R_f: 0.63 (eluent = 10% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)**

δ_H: 1.01 (3H, d, *J* 6.8, CH(CH_3^ACH_3^B)), 1.04 (3H, d, *J* 6.8, CH(CH_3^ACH_3^B)), 2.31 (1H, d, *J* 6.8, C*H*(CH_3)$_2$), 2.35-2.40 (1H, m, COC*H*), 4.50 (2H, d, *J* 5.3, CH_2), 6.94 (1H, ddd, *J* 8.4, 1.0, 0.4, ArC(9)*H*), 7.01 (1H, ddd, J 7.9, 7.2, 1.1, ArC(7)*H*), 7.45 (1H, ddd, *J* 8.4, 7.2, 1.8, ArC(8)*H*), 7.89 (1H, ddd, *J* 7.9, 1.8, 0.4, ArC(6)*H*); **^{13}C NMR (CDCl$_3$, 126 MHz)** δ_C: 19.8 (CH_3^A*C*H_3^B)), 20.7 (*C*H_3^ACH_3^B), 25.7 (*C*H(CH_3)$_2$), 52.4 (CO*C*H), 68.7 (*C*H_2), 117.7 (Ar*C*(9)), 121.2 (Ar*C*(5)), 121.4 (Ar*C*(7)), 127.5 (Ar*C*(6)), 135.8 (Ar*C*(8)), 161.5 (Ar*C*(10)), 194.5 (*C*=O). Spectroscopic data in accordance with the literature.[7]

HPLC data for racemate: Chiralpak IA (Gilson method 23) = 99.5:0.5 Hexane:IPA, 2.0 mL/min, 211 nm. 4.95 and 5.23 min.



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