The Synthetic Utility of Allylic Trifluoroborate Salts: Reactions of Ketones and Indoles using Montmorillonite, Indium and Lewis Acid

by

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A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
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University of Toronto

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Abstract

Chapter 1 briefly covers the development and utility of allylboron reagents in organic synthesis. Transition models proposed for addition to carbonyl groups and imines are discussed and selected examples of the utility of these reagents to the synthesis of complex molecule covered.

In chapter 2 the allylation and crotylation of ketones using allyl- and crotyltrifluoroborates and montmorillonite K-10 are described. The method is scalable and utilizes a reliable catalyst with high functional group tolerance. A conventional work-up is not required for further purification, since the boric acid by-product of the reagent remains trapped in the cavity of the K-10. The method is quite robust and provides an operationally straightforward procedure for the allylation of a range of ketones using the air and moisture stable potassium allyltrifluoroborate.

In Chapter 3, the first indium-mediated highly chemo- and diastereoselective allylation of α,β-epoxyketones using allyltrifluoroborate was developed. It was shown in the case of simple ketone substrates, the loading of indium can be reduced to catalytic quantities without a diminishment in yield. The stereochemical nature of the epoxy homoallylic alcohols was
unequivocally established through Payne rearrangement. Mechanistic studies indicate that the reaction proceeds through an allylindium species; although the nature of the indium species was not fully elucidated.

Finally, in chapter 4 regioselective allylation and diastereoselective crotylation of various indoles are discussed using BF$_3$·Et$_2$O as a promoter. It was shown that the electronic effects of the substituents on the indole ring had little effect on the outcome of the reaction. However, steric factors were more influential on the yields and reactivity of the substrates. Stereospecific addition of the $E$- and $Z$-crotyltrifluoroborates could also be achieved under the reaction conditions, providing the corresponding anti and syn products, respectively.
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<tr>
<td>[α]D</td>
<td>specific rotation measured at 589 nm</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
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<tr>
<td>aq</td>
<td>aqueous</td>
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<tr>
<td>9-BBN</td>
<td>9-borabicyclo[3.3.1]nonane</td>
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<td>BINOL</td>
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<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>br</td>
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<td>h</td>
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<td>------------------------------------------------</td>
</tr>
<tr>
<td>$H_o$</td>
<td>Hammett acidity function</td>
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<td>HMDS</td>
<td>hexamethyldisilazane</td>
</tr>
<tr>
<td>HOMO</td>
<td>highest occupied molecular orbital</td>
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<tr>
<td>MHz</td>
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<td>min</td>
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<td>M.P.</td>
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<td>tetrabutylammonium fluoride</td>
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<td>TBS</td>
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<td>TBDPS</td>
<td>tert-butylidiphenylsilyl</td>
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<td>Abbreviation</td>
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<td>triethylsilyl</td>
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<td>tetrahydrofuran</td>
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Chapter 1
Allylboron Reagents: General Aspects

1 Introduction

1.1 Allyl Organometallic Reagents

Additions of allyl anions and their equivalents to carbonyl compounds has become one of the most important methods for C–C bond formation, owing to the versatile reactivity and transformations available for alkene double bonds. For example the C=C bond can be further manipulated through oxidation, epoxidation, olefin metathesis and various transition-metal catalyzed cross-coupling reactions allowing access to a wide range of synthetically useful intermediates.¹ Allyl metal complexes of various metals such as magnesium, lithium, boron, silicon, tin, indium, zinc, nickel and copper have been extensively studied.² Allylation of carbonyl groups has become one of the major tools in the synthesis of natural products and biologically active molecules.³ This brief review will be limited to the reactivity and synthesis of allyl metalloids with the emphasis on allylboron reagents. Attention will be paid to their nucleophilicity towards the carbonyl groups. The reactivity of other allyl metals will not be discussed.

1.2 Allyl Alkali and Alkaline Earth Metal Reagents

It is important to gain insight into the structure and the reactivity of allyl alkali and alkaline earth metals because they are predominantly the original allyl agents used for the synthesis of other allylmetalloids such as allylboron, allylsilane and allyltin derivatives; generated by addition to the corresponding electrophiles. These classes of reagents undergo facile 1,3-haptotropic rearrangements. In the case of unsymmetrical allylic reagents, their addition to electrophiles will

afford two regioisomeric products. The structure of the allyl alkali and alkaline earth metal reagents varies significantly, depending on the metal bearing the allyl moiety. The intrinsic nature of the metal binding to the allyl group is a property of the metal radius; whereas the nucleophilicity of the metal-allyl is governed primarily by the steric demands of the allyl moiety. For example, lithium with its small ionic radius exhibits two different bond lengths to the allylic termini indicative of unsymmetrical binding, whereas magnesium is bound to the allyl moiety through an unconventional $\sigma$-bond. However, upon increasing the size of the alkali metal, the interaction between the metal and the allyl termini becomes symmetrical through $\pi$-complexes similar to that of transition metals (Figure 1.1).

![Figure 1.1 Allyl Metal Binding Models](image)

It is important to control the alkene configuration of the generated allyl metalloids. Schlosser has shown in the generation of $E$ and $Z$ crotyl metal reagents that the $Z$ isomer is preferred with increasing size of the metal cation. Although the $E/Z$ isomerization is rapid for lithium and magnesium allyl reagents, similar isomerization is much slower for the crotylpotassium reagents, allowing access to configurationally well-defined crotyl metal reagents upon reaction with suitable electrophiles (Figure 1.2).

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7 West, P.; Purmort, J. I.; McKinley, S. V. J. Am. Chem. Soc. 1968, 90, 797–798.
1.2.1 Stability of Allyl Organometallic Reagents

The stability of the allyl metals has an inverse relation with their reactivity, with allyl alkali and allyl alkaline earth metals being the most reactive species. These reagents are prepared immediately prior to use in order to achieve the best results partially due to their reactivity towards oxygen and moisture. The reactivity of the allyl metal towards electrophiles decreases with decreasing ionic character of the metal allyl bond. For example, while allyllithium is very reactive towards water, allylsilanes, allylboronates, allylindiums and allyltins are stable species in aqueous media and in the case of allyl indium, water is essential for most of the transformations to occur.

Allylboron stability is directly related to the Lewis-acidity of the boron center, which can be altered through the nature of the ligands directly attached to it. Electron-withdrawing groups increase the reactivity, while electron-donating groups decrease it. For example, allylic boronates are more stable to atmospheric oxidation and, thus are much easier to handle than the corresponding allylic boranes. As a result, most allylic boronates (i.e., pinacol or catechol derived boronates) can be purified by column chromatography on silica gel.

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1.2.2 Classification of Allyl Organometallic Reagents

The development of allyl organometallic reagents for addition to the carbonyl functionality was largely in parallel to the aldol reaction, primarily due to the interest in acyclic stereocontrol for the synthesis of polyketide derivatives, since allylation and subsequent oxidation of the C=C bond provides an alternative to the aldol reaction (construction of β-hydroxy carbonyl compounds) (Figure 1.3).

![Figure 1.3 The Allyl Metal Alternative to the Aldol Condensation](image)

The use of allylic organometallic reagents in acyclic stereocontrolled transformations was not common until late 1970’s, when three major discoveries inspired their widespread application.\(^\text{14}\) Buss and Heathcock reported that a crotylchromium reagent underwent highly 1,2-anti diastereoselective addition to aldehydes.\(^\text{15}\) Hoffmann and Zeiss reported that Z-crotylboronates, upon addition to aldehydes, afforded 1,2-syn homoallylic alcohols exclusively.\(^\text{16}\) Yamamoto and co-workers discovered that crotylstannane reagents, upon activation with Lewis acid, underwent addition to aldehydes affording 1,2-syn homoallylic alcohols, irrespective of the double bond.


geometry of the tin reagent.\textsuperscript{17} It was the predictability of the stereochemistry of the products in these reactions that inspired the synthetic community to apply these reagents in polyketides synthesis. Denmark and Weber classified allylmetallic reagents in three major categories, primarily based on the observed 1,2-\textit{syn} versus 1,2-\textit{anti} diastereoselectivity upon addition to the aldehydes (Figure 1.4).\textsuperscript{18} Type I reagents undergo stereospecific addition to aldehydes, in which \textit{E}- and \textit{Z}-crotyl reagents afford 1,2-\textit{anti} and 1,2-\textit{syn} diastereoselectivity respectively. This class includes B, Al and heteroatom-substituted silicon and tin reagents. It is generally accepted that the crotylation by these reagents occurs though a cyclic, six-membered, chair-like transition state. Type II reagents including trialkyl/triaryl-Si and Sn derivatives undergo addition to carbonyl functionality through an open transition state affording 1,2-\textit{syn} selectivity regardless of the configuration of double bond in the reagents. Type III reagents, which are mostly generated \textit{in situ} from allylhalides and early transition metals such as titanium, chromium and zirconium undergo addition to carbonyl functionality leading to 1,2-\textit{anti} diastereoselectivity irrespective of the geometry of the double bond in allyl halides. This is attributed to fast 1,3-isomerization of the \textit{in situ} generated allylorganometals (1,3-metallotropic rearrangement), affording the thermodynamically more favored \textit{E}-isomer, which upon subsequent stereospecific addition results in the formation of \textit{anti} products.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.4.png}
\caption{Different Classes of Allyl Organometallic Reagents}
\end{figure}


1.3 Organoboron Reagents

Bubnov was the pioneer in using triallylboron for additions to carbonyl compounds.\(^\text{19}\) A key organoboron chemistry discovery was reported by Hoffmann, who observed the stereospecific additions of \(E\)‐ and \(Z\)‐crotylboronates to aldehydes, affording 1,2-\(\text{anti}\) and 1,2-\(\text{syn}\) homoallylic alcohols respectively. Since this discovery, along with progress of stereoselective transformations in a variety of other areas,\(^\text{20}\) this field saw tremendous growth through the chemistry of Hoffmann,\(^\text{21}\) Brown,\(^\text{22}\) Roush,\(^\text{23}\) Masamune\(^\text{24}\) and Corey,\(^\text{25}\) with the primary focus on practicality and stereoselective transformations using a variety of chiral allyl- and crotylboron reagents. Over the last decade, the focus on allyl and crotylboron addition reactions has shifted towards Lewis acid catalyzed transformations using achiral boronates.\(^\text{26}\)

1.3.1 Early Investigations

Preliminary studies of allylboron reagents were focused on increasing the stability of the reagents through installing electron-donating groups as ligands on boron. To suit this need a variety of diols were examined.\(^\text{27}\) The relative reactivity of organoboron compounds can be summarized based on the following trends involving the substituents on boron, whereby triallylboron is the most reactive and allylboronate is the least reactive species (Figure 1.5).\(^\text{28}\) This observation was essential to develop a procedure for practical preparation of crotyl

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reagents, where the high purity of the reagents is crucial to achieve high diastereoselectivity upon addition to the aldehydes. This was attributed to the fact that fast 1,3-borotropic isomerization was observed with increasing reactivity of the boron reagents.

![Figure 1.5 The Reactivity Pattern of Allylboron Reagents of Addition to Cabonyl Compounds](image)

Figure 1.5 The Reactivity Pattern of Allylboron Reagents of Addition to Cabonyl Compounds

To date the most widely applied procedure for the preparation of crotyl reagents is the use of Schlosser’s super base for the \textit{in situ} generation of \textit{E}- or \textit{Z}-crotyl potassium reagents from \textit{trans} and \textit{cis}-2-butene, respectively. Subsequent treatment with trimethylborate affords the high purity \textit{E}- or \textit{Z}-crotylboron species; this requires precise control of the temperature during transmetalation step. Unfortunately, this procedure is only suitable for deprotonation of symmetric olefins where there are limited allylic hydrogens available on the substrates. For example, substrates like 2-methyl-2-butene with multiple allylic hydrogens afford a mixture of products using Schlosser’s base. In order to avoid the aforementioned problem, Matteson developed a one-carbon homologation procedure using chloromethyllithium and vinylboronates. It is generally accepted that nucleophilic attack occurs at the boron center and subsequent migration of the vinyl group with concomitant extrusion of the halogen affords the homologated allylboron reagent (Scheme 1.1). This procedure is especially useful for the

synthesis of Z-crotylboronates using Z-vinylboronates, some of which are not possible to synthesize through other methods.\textsuperscript{33} Matteson and co-workers have applied this method for the synthesis of chiral $\alpha$-halo or $\alpha$-alkyl crotyl boronates.\textsuperscript{34}

\begin{equation}
\text{Scheme 1.1 Matteson Homologation}
\end{equation}

1.3.2 Chiral Allyl and Crotylboron Reagents

The majority of the chiral reagents were developed using naturally abundant diols as ligands or through a simple transformation (i.e., hydroboration) of commercially available substrates (Figure 1.6). For example, Hoffmann applied a camphor-derived ligand for the preparation of chiral allylboronates that has been utilized successfully for the addition to the carbonyl compounds.\textsuperscript{35} Roush and co-workers reported diisopropyltartrate as a chiral ligand for the synthesis of chiral allylboronates, which undergo highly enantioselective addition to carbonyl compounds.\textsuperscript{36} Brown’s reagent diisopinocampheylallylborane was prepared through hydroboration of $\alpha$- or $\beta$-pinene.\textsuperscript{37} Chong reported a BINOL-derived chiral allylboron reagent for the enantioselective allylation of ketones.\textsuperscript{38} Soderquist has applied Matteson homologation for ring expansion using 9-BBN and lithium trimethylsilyldiazomethane and subsequent resolution using ephedrine to generate the chiral reagent 1.038.\textsuperscript{39}

1.4  Mechanisms of Additions to Carbonyl Compounds

The observed stereoselectivity of nucleophilic addition to C=O bonds can be influenced by substrate control or reagent control, referring to the path in which the substrates or reagents dictate the outcome of a particular reaction. For example, in the case of 1,2-nucleophilic addition to a C=O group under substrate control, the cyclic ketone geometry or topology of the ketone determines stereoselectivity, whereas for acyclic ketones the geometry of the adjacent carbon dictates the stereochemistry of addition. Over the last five decades a variety of models have been proposed to rationalize the outcome of the 1,2- nucleophilic addition to acyclic ketones bearing an α-chiral center. Cram,40 Cornforth,41 Karabatsos42 and Felkin43 have proposed several models to rationalize the 1,2-asymmetric induction based on steric, electronic and electrostatic effects. However, none of the proposed models is able to rationalize all the results of stereoselective

additions (Figure 1.6). The Felkin model later improved by Anh’s\textsuperscript{44} orbital consideration and also with the incorporation of the Bürgi-Dunitz trajectory\textsuperscript{45} for the nucleophilic attack has become the most applied model. Although the Felkin-Anh model is the most accepted one, it remains quite challenging to predict the stereochemical outcome of 1,2-addition based only on this model, and the debate continues\textsuperscript{46} as to which characteristic properties of the substrate such as steric, electronic, and stereoelectronic, ultimately control the outcome of the addition.

Figure 1.7 Proposed Models for 1,2-Asymmetric Induction for Ketones with α-Chiral Centers

Allyl boron reagents are classified as type I allyl metals and it is generally accepted that addition to carbonyl compounds proceeds through a rigid cyclic Zimmerman-Traxler chair-like transition state (Figure 1.8).\textsuperscript{47} This addition exhibits a superb reagent control for diastereoselective crotyl addition to the carbonyl functionality. The observed stereospecific addition of \textit{E}- and \textit{Z}-crotylboron reagents occurs with nearly perfect reagent configuration transfer to the products,

which is consistent with a cyclic closed transition state. In the accepted model, coordination of
the Lewis acidic boron reagent activates the aldehyde, similarly, coordination of the aldehyde as
a Lewis base increases the reactivity of the allylboron reagents. In the accepted six-membered
transition state model, the aldehyde substituent adopts a pseudo equatorial position, minimizing
the unfavorable 1,3-diaxial interactions inherent with the alternative arrangements. Because the
observed diastereoselectivity directly correlates to the geometry of the double bond, the purity of
the starting allylboron is crucial to achieve the high diastereoselectivity.

![Figure 1.8 Addition of E-Crotylboron Reagents to Aldehyde](image)

Unlike crotylboron reagents, crotylsilanes and –stannanes are less reactive and consequently
require external Lewis acid activation for addition to aldehydes, affording the 1,2–syn product
predominantly regardless of the geometry of the reagents. These reagents are classified as type
II reagents, and open transition states have been proposed for these reagents with antiperiplanar
orientation of the C=O and incoming nucleophilic C=C bonds with the aim of minimizing the

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steric interaction between the methyl group from the reagents and R group of the aldehydes (Figure 1.9). \(^{50}\)

![Diagram](image)

**Figure 1.9** Open Transition State Models for Addition of Crotylsilane and -Stannane Reagents

Based on this model, due to the several gauche interactions, the reaction is sensitive to the bulkiness of Lewis acids and the reagents. Denmark and Weber performed a controlled intramolecular addition of allylsilane and -stannane reagents to aldehydes using a variety of Lewis acids and observed high \textit{syn} selectivity irrespective of the size of the Lewis acids or reagents. \(^{51}\) Based on these observations they propose a preference for a synclinal orientation over the antiperiplanar geometry. The increased gauche interaction in this model was rationalized based on the secondary orbital interactions between the HOMO of the reagents and the LUMO of the carbonyl group (Figure 1.10). \(^{52}\) However, Keck reported that the geometry of the crotylstannanes can have a significant role in determining the stereoselectivity and stronger

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Lewis acids (i.e., TiCl$_4$) prefer the synclinal geometry, where as weaker ones react through an antiperiplanar trajectory.\textsuperscript{53}

![Diagram of Frontier Molecular Orbitals](image)

**Figure 1.10** Proposed Synclinal Transition State and Frontier Molecular Orbitals

1.4.1 Addition of Organoboron Reagents to C=N functionality

The reactivity of allylboronates with imine derivatives is considerably lower than for the corresponding carbonyl functionality.\textsuperscript{54} This is attributed to the lower electronegativity of the nitrogen atom of imines; to circumvent this and increase reactivity towards addition, an electron withdrawing group on the imine or $\alpha$-carbon of the aldimine functionality is usually applied.\textsuperscript{55} Unlike the corresponding carbonyl compounds, where the selectivity of crotylboron addition is governed predominantly by the reagent, the reactivity and observed selectivity of the imine functionality is influenced by additional parameters, such as the geometry of the imine, and the size and electronic character of the substituents on the nitrogen. For example, Yamamoto observed the steric effect of imine functionality on the diastereoselectivity of addition of crotyl-9-BBN (Figure 1.11).\textsuperscript{56}

Crotylation of the benzylideneaniline using crotyl-BBN-afforded the 1,2-anti product 1.055 exclusively, where as the aliphatic linear substrates afforded 1,2-syn products 1.053 and 1.054. Yamamoto rationalized the observed syn-selectivity based on the cyclic transition state 1.057 where both crotyl and imine have E-geometry. The decreased syn selectivity with increasing the size of the group on imine is attributed to increased 1,3-diaxial non-bonding interactions favoring transition state 1.058 to afford the anti products (Figure 1.12). It can be said with some certainty that all of these four plausible transition states can be operative depending on the size of the alkyl chain on the imine functionality, the geometry of the imine and boron reagents, and the bulkiness of the boron reagents. For example, the 1,2-anti product can be achieved using Z-crotyl-9-BBN presumably through the chair-like transition state 1.059, whereas 1,2-syn selectivity is observed using E-crotyl-9-BBN through boat-like transition 1.058. The observed diastereoselectivity for imines is opposite to that of the corresponding aldehydes using E-and Z-crotylboron reagents as expected, except for well-defined Z-imines which give similar diastereoselectivity.

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**Figure 1.11 Diastereoselective Crotylation of Aldimines**

\[ \begin{array}{c}
\text{N}^+R^1\text{R}^2 + \text{Me}_{\text{B}}\text{L}_{\text{B}}\text{L} \rightarrow \text{HN}^+\text{R}^2 \text{R}^1\text{Me} + \text{HN}^+\text{R}^2 \text{R}^1\text{Me} \\
\text{R}^1 = n\text{-Pr}, \text{Ph} \\
\text{R}^2 = n\text{-Pr}, i\text{-Pr}, \text{Ph} \\
\end{array} \]

\[ \begin{array}{c}
\text{R}^1 = R^2 = n\text{-Pr} \textbf{1.053} \\
\text{R}^1 = n\text{-Pr}, R^2 = i\text{-Pr} \textbf{1.054} \\
\text{R}^1 = R^2 = \text{Ph} \textbf{1.055} \\
\text{R}^1 = \text{Ph}, R^2 = n\text{-Pr} \textbf{1.056} \\
\end{array} \]

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1.4.2 Catalytic Transformations

Addition of allylstannane and allylsilane reagents to the carbonyl compounds requires external activation due to the lower reactivity of the reagents. Catalytic addition of these reagents has been well developed and several Lewis acid catalyzed (i.e., Ti(OPr)$_4$/BINOL) approaches have been reported for the enantioselective addition of allylstannane to ketones.\textsuperscript{58} In contrast to the allylstannane reagents, catalytic allylation of ketones using allylboronates has been overlooked. Shibasaki and coworkers reported copper catalyzed activation of allylboronates in additions to ketones.\textsuperscript{59} Hall and co-workers reported a rationally designed chiral diol which upon coordination to SnCl$_4$ generated a Brønsted acid in situ for the activation of an aldehyde and allylboronate affording homoallylic alcohols in excellent yields and enantioselectivities (Scheme 1.2).\textsuperscript{60} The catalytic system was applied successfully for aldehydes having a wide range of functional groups, as well as for the addition of $E$- and $Z$-crotylboronates affording the corresponding homoallylic alcohols in excellent yield and selectivities. The authors later applied an electron deficient version of the ligand for the allylation of less reactive aliphatic aldehydes to improve the enantioselectivity. This system has not been applied to ketones and six linear steps are required for the synthesis of diol, which are the major drawbacks of this catalytic system.


Schaus reported an 3,3′-Br$_2$-BINOL catalytic system for the allylation and crotylation of the ketones. The system was mild and a wide range of functional groups were tolerated affording the tertiary homoallylic alcohols in good yields. This work was inspired by Hall’s report on the effect of Brønsted acids in rate accelerations of allylations and Chong’s observation of the 3,3′-substitution effect on increasing the BINOL ligand stereoselectivity. Various ketones were allylated using this system to give homoallylic alcohols in good yields and enantiomeric ratios. Mechanistic studies indicated that a reversible ligand exchange in the catalytic system was crucial for activation of the allylboronate.

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It was also observed that the reaction had a first order rate dependence on the chiral naphthols 1.063 and liberating the ligands from 1.062 was the rate determining step in the reaction. It was observed that increased concentration of the species 1.062 was detrimental to the stereoinduction; hence increasing the concentration of external alcohol (i.e, i-PrOH) accelerates the reaction by liberating 1.063. Using non-coordinating t-BuOH and cyclic boronates, the catalyst loading can be reduced to 2.0 mol% without diminishing yields or enantioselectivity. Based on these observations the authors proposed the following catalytic cycle (Figure 1.13).

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The reported catalytic systems using allyl or crotyl boronate addition to ketones are very limited and have not been developed significantly due to the inherent difficulty associated with these reagents. Further studies and investigations are necessary to develop an economically viable catalytic system for practical use.

1.5 Potassium Allyltrifluoroborates

Vedejs and co-workers showed the synthesis of functionalized amino acid derivatives using crystallization-induced asymmetric transformation (AT) starting from amino acid-derived amidine carboxylates. It is known in the literature that boron complexes have been used for the crystallization and purification of the “ate” complexes. As part of their studies Vedejs and co-workers were interested in developing a procedure for in situ generation of boron difluorides for this purpose which would avoid the problems associated with the storage and handling of these reagents. Kaufman had shown through $^{11}$B NMR studies that the boron difluoride (Ipc)BF$_2$ can

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be generated *in situ* from K(Ipc)BF$_3$ upon treatment with BF$_3$·OEt$_2$ in acetonitrile.$^{64}$ It was also known in the literature that KHF$_2$ can be utilized as a source of fluoride anion exemplified in the synthesis of KPh$_2$BF$_2$ from Ph$_2$BOH.$^{65}$ Vedejs and co-workers synthesized a wide range of ArBF$_3$K salts from the corresponding boronic acids using KHF$_2$ and successfully applied them for *in situ* generation of the corresponding ArBF$_2$ species using strong fluorophiles (Scheme1.4).$^{64}$ Thus, amino acid-derived amidine carboxylates reacted with aryltrifluoroborates in the presence of trimethyl silylchloride affording the thermodynamically favored diastereomer 1.077, which upon treatment with strong base and subsequent reaction with an electrophile, formed enantiomerically pure functionalized α-amino acids after hydrolysis.

![Scheme 1.4 Vedejs’ Synthesis of Aryltrifluoroborates and Their Application Toward the Synthesis of α-Amino Acids](image)

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The authors rationalized the observed high enantioselectivity of 1.080 based on the self replication of chirality in amino acids as observed by Seebach in related systems.\textsuperscript{66} Since this report, organotrifluoroborates have become a stable surrogate for boronic acids and have been applied in various transformations.\textsuperscript{67} In particular, Batey and co-workers reported the synthesis of potassium allyl and crotyl trifluoroborates and demonstrated their use in additions to aldehydes and imines.\textsuperscript{68} Activating conditions were required using Lewis acid as well as phase-transfer catalyst.

1.6 Applications of Allylation to Total Synthesis

Boron-mediated transformations are one of the most powerful in organic synthesis.\textsuperscript{69} Allylboration in particular plays an important role in the total synthesis of various natural products where there is a need to achieve defined acyclic stereocontrol. Shown here are selected examples to demonstrate the utility of allylboron reagents and their application in the synthesis of natural products. Due to the lack of practical catalytic systems, the most applied system for an enantioselective transformation is Brown’s chiral allylboron reagents. Roush and co-workers reported an application of the asymmetric allylboration of an aldehyde using Brown’s allyl isopinocampheyl for the synthesis of (+)-superstolide A \textsuperscript{1.084} (Scheme 1.5).\textsuperscript{70} The homoallylic alcohol 1.082 was converted through further transformations into the cis decaline component of the target molecule.

\begin{thebibliography}{99}
\end{thebibliography}
Smith and co-workers applied isopinocampheyl allylboron reagent for the allylation of aldehyde 1.085 in the total synthesis of (+)-spongistatin 1. They utilized Brown’s asymmetric crotylation of aldehyde 1.085 to form homoallylic alcohol 1.086 in good yields and excellent diastereoselectivity (Scheme 1.6). The alcohol 1.086 was further subjected to several functional group manipulations to achieve the synthesis of (+)-spongistatin 1.

Scheme 1.5 Roush’s Total Synthesis of (+)-Superstolide A

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Scheme 1.6 Smith’s Total Synthesis of (+)-Spongistatin 1

Hall and coworkers developed procedures for tandem allylboration/lactonization using β-ester allylboronates, which has recently been applied to the total synthesis of (+)-chinensiolide B (Scheme 1.7).

Carvone-derived aldehyde 1.088 underwent BF₃·Et₂O catalyzed key tandem allylboration/lactonization sequence, using a 3.5:1(Z:E) isomeric mixture of functionalized allylboronate 1.089 affording the bicyclic lactone 1.090 in good yield and excellent diastereoselectivity. The observed high diastereoselectivity was surprising, considering the low isomeric purity of employed allylboronate 1.089. The authors rationalized that the reaction was E/Z selective and the E-1.089 was inert to the reaction conditions. The lactone 1.090 was further

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modified through functional group manipulations to achieve the total synthesis of (+)-chinesiolide B.

\[
\begin{align*}
\text{TBSO} \cdot \begin{array}{c}
\text{Me} \\
\text{Me} \\
\text{H} \\
\text{O}
\end{array} 
& \quad + \quad \text{TBDPSO} \cdot \begin{array}{c}
\text{CO}_2\text{Me} \\
\text{BPin}
\end{array} 
\quad \text{BF}_3\text{Et}_2\text{O} \quad (2.5 \text{ mol}\%)
\quad \text{Toluene, 0 °C, 48 h}
\rightarrow \\
\text{Me} \quad \begin{array}{c}
\text{H} \\
\text{Me} \\
\text{O}
\end{array} 
& \quad \text{Me} \quad \begin{array}{c}
\text{H} \\
\text{O}
\end{array} 
\quad \text{OTBDPS} 
\quad 87\% \quad (19:1 \text{ dr})
\end{align*}
\]

\((+)-\text{Chinesiolide B}\)

**Scheme 1.7** Hall’s Total Synthesis of (+)-Chinesiolide B

Batey and co-workers reported the total synthesis of the (−)-tetrahydrolipstatin using potassium \((2E)\)-nonenyltrifluoroborate in the presence of phase-transfer-catalyst (Scheme 1.8).\(^{73}\) Addition of crotylboron \(1.093\) to the aldehyde \(1.092\) was occurred in the presence of 10 mol% \(\text{Bu}_4\text{NI}\) providing a 3:1 mixture of 1,2-\textit{anti}-2,4-\textit{anti} and 1,2-\textit{anti}-2,4-\textit{syn} diastereomers of \(1.094\). The desired homoallylic alcohol 1,2-\textit{anti}-2,4-\textit{anti} \(1.094\) was separated and subjected to further functional group manipulations to achieve the total synthesis of (−)-tetrahydrolipstatin.

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1.7 Conclusion

Allylation and crotylation of carbonyl compounds play a pivotal role in carbon-carbon bond formation reactions in organic synthesis, owing to the versatile transformations available to the alkene functionality. Boron reagents are widely used for this purpose due to their stereoselectivity and lower toxicity. Addition of allylboron to aldehydes have been well established and it is generally accepted that the addition proceed through a cyclic chair-like transition state. Similarly the addition of E-and Z-crotylboron reagents proceed stereospecifically, affording 1,2-anti and 1,2-syn homoallylic alcohols, respectively. The catalytic enantioselective transformations for addition of allyl and crotylboron reagents to aldehydes have been attempted but a robust practical procedure is still lacking and most of the practical applications of allylation for enantioselective transformations still rely on the use of stoichiometric chiral boron reagents, with Brown’s reagents being the most used. The additions of allyl and crotylboron reagents to ketones are more challenging due to lower reactivity and steric congestion around the carbonyl group. Additions of allyl and crotyl boron reagents to ketones have not yet been well developed, with the majority of methods being reported over the last decade. The catalytic enantioselective transformations have been attempted using achiral allyl and crotylboronates and Schaus’ biphenol system is currently the most promising method.
Chapter 2
Montmorillonite Catalyzed Allylation and Crotylation of Ketones and Aldehydes Using Potassium Organotrifluoroborate Salts

2 Introduction

2.1 Structure and Properties of Montmorillonite K-10

Environmental concerns have prompted the necessity for greener chemical transformations and have forced scientists to look for alternative catalysts which will minimize environmental impact.\(^1\) Solid acid catalysts and reagents are becoming increasingly important alternatives to the traditional aqueous systems.\(^2\) Although heterogeneously catalyzed transformations have been widely used in petrochemical processes,\(^3\) they have been mainly limited to hydrogenation in the pharmaceutical and fine chemical industries. Homogenous transformations have been the main focus in the pharmaceutical industry, primarily to maximize yields with historically less emphasis placed on reducing waste generation and environmental impact. The use of Montmorillonite and related reagents represent an attractive alternative for many classical homogenous-acid-catalyzed transformations offering significant advantages over traditional methods. They are non-corrosive, easy to handle, thermally and mechanically stable, environmentally benign and economically viable. Often they are recyclable and reusable in the process without diminishing the yield or efficiency.\(^4\)

From now on the term “K-10” will refer to the natural Montmorillonite K-10 and will be used throughout the thesis for simplicity.

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2.1.1 Structure

K-10 is a layered alumina silicate which is constituted of octahedral AlO$_6$ and tetrahedral SiO$_4$ units. The octahedral AlO$_6$ unit is surrounded in two dimensions by two layers of tetrahedral SiO$_4$ units to form sandwich-like layers. The apical oxygen of the tetrahedral sheet is subjected to the octahedral layer (Figure 2.1). These platelets stack on top of each other to form a finely defined structure. The internal layer of each platelet is surrounded by water and/or exchangeable cations which are responsible for most observable properties of unaltered or modified K-10. The space between the layers can be varied significantly depending on the size of cations or the quantity of water. K-10 has been used mostly as a Brønsted acid catalyst. However, the catalytic activity of K-10 can be modified to act as a Lewis acid through the use of exchangeable cations. Modification of K-10 is done through cation exchange and doping by salt deposition.

![Figure 2.1 The Montmorillonite Structure](http://en.wikipedia.org/wiki/Montmorillonite May 2008)

2.1.2 Acidity

The Brønsted acidity of K-10 is attributed to the terminal hydroxyl or bridging oxygen atoms and has been reported relative to the standard Hammett acidity scale. The Hammett acidity function

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(\(H_a\)) of natural K-10 with Na\(^+\) or NH\(_4\)\(^+\) as exchangeable cations is \(H_a = +1.5 - 3.0\), however treatment of K-10 with acidic solution (H\(_2\)SO\(_4\), 30%) increases the acidity to \(H_a = -6.0 - 8.0\) which is in the range of concentrated nitric (\(H_a = -5.0\)) and sulfuric acids (\(H_a = -12.0\)).\(^6\) The Lewis acidic properties of K-10 can be altered through cation-exchange by equilibrating the solid in a solution of the desired cation (e.g., Fe, Zn, Cu, Pd, and Rh) in aqueous medium at room temperature.

### 2.2 Applications in Organic Reactions

K-10 and its derivatives have been applied in various acid catalyzed organic transformations.\(^8\) This review will be limited to the acid catalyzed transformations in heterogeneous media using natural K-10, some of which were not possible using Brønsted or Lewis-acids. Reactions involving the use of modified K-10 will not be discussed.\(^9\)

#### 2.2.1 Regioselective Hydrochlorination of Olefins

A typical addition of hydrochloric acid to olefins requires elevated reaction temperatures and prolonged reaction time in order to achieve full conversion. Laszlo and Delaude reported the hydrochlorination of 1-methyl cyclohexene 2.001 in the presence of K-10 using sulfuryl chloride (SO\(_2\)Cl\(_2\)) as a mild chloride source (Scheme 2.1).\(^10\) The formal Markovnikov product 2.002 was obtained as the major product under mild reaction conditions in a short time.

![Scheme 2.1 Laszlo's Hydrochlorination of Olefins](image-url)

---

2.2.2 K-10 Catalyzed Friedel-Crafts Reactions

Since their introduction in 1877, Friedel-Crafts reactions have become one of the most important C–C bond forming reactions in organic synthesis. A variety of methods including the use of Lewis acid and Brønsted acids have been applied for these transformations. Onaka and co-workers reported the application of K-10 for the synthesis of porphyrins using one of the most acid labile intermediates. Under the reaction conditions, K-10 catalyzed multiple Friedel-Crafts reactions simultaneously between pyrrole and hexanal which was followed by one-pot chloranil oxidation to afford the desired porphyrin 2.006 in 46% isolated yield (Scheme 2.2). The main advantage of this procedure was surpassing the extremely high dilution typically required for porphyrin synthesis. Additionally, it provided a simpler method for isolation and purification of the product. It is noteworthy to mention that the yields were lower under identical reaction conditions using conventional homogenous acids such as BF₃·Et₂O or trifluoroacetic acid.

Scheme 2.2 Onaka’s Porphyrin Synthesis

---

Baran and Richter reported an intramolecular Friedel–Crafts alkylation in the total synthesis of (−)-fischerindole G.\textsuperscript{15} While several acid catalysts were screened to achieve Friedel–Crafts cyclization of intermediate 2.007 to 2.008, many provided low isolated yields of 2.008 along with a number of side products. The use of K-10 and microwave heating provided a clean reaction to give 2.008 in acceptable isolated yield as a single diastereomer after a single recycling of unreacted starting material (Scheme 2.3).

\textbf{Scheme 2.3} Baran’s Total Synthesis of (−)-Fischerindole G

Nair and co-workers reported the Friedel-Crafts alkylation of tetracyclic 2.010 with various aromatic and heteroaromatics to furnish the desired addition products in good yields (Scheme 2.4).\textsuperscript{16} The regioselectivity of the observed addition products can be rationalized by activation of the enone carbonyl moiety with K-10 and subsequent nucleophilic addition of the aromatic or heteroaromatics to afford the products.

\textbf{Scheme 2.4} Nair’s Friedel-Crafts Alkylation of Tetracyclic Enones


2.2.3 K-10 Catalyzed Synthesis of Heterocycles

Heterocycles are important not only due to their abundance, but because of their widespread application and utilities in chemistry, biology, pharmaceuticals and agrochemicals. Heterocycles are prevalent in many natural products, such as vitamins, hormones, antibiotics and alkaloids. It can be said with some certainty that our modern life would have been impossible without the progress of the heterocyclic chemistry. Thus, many synthetic as well as natural compounds which are considered valuable medicinal agents, agrochemicals, and plastics precursors are based on heterocycles. Medicinal chemistry in particular is associated intimately with heterocyclic compounds and the top ten selling pharmaceuticals have heterocyclic frameworks. It is these values that inspire scientists to develop and/or improve synthetic routes to access heterocyclic cores.

2.2.3.1 Diastereoselective Synthesis of Aziridines

The smallest azaheterocycle moiety, aziridines, not only occur in a variety of biologically active natural products, but also have been utilized for the synthesis of useful intermediates through regio- and stereoselective transformations. Török and coworkers reported a K-10 catalyzed diastereoselective synthesis of N-substituted cis-aziridines from imines and ethyl diazoacetate (Scheme 2.5). A wide range of imines were efficiently converted to their corresponding aziridines. However, strong electron withdrawing groups on either side of the aniline or aldehyde component of the Schiff bases failed to give the desired products in significant quantity. It is important to note that the major byproduct of this class of reactions is β-enamine acetate which was not observed under the K-10 conditions. K-10 was recovered from the reaction mixture by filtration upon completion of the reaction and was subjected to three consecutive reactions, without diminishing the yields or selectivity. The significance of this procedure was its simplicity, mild reaction conditions, reusability of the K-10 and short reaction times.

---

2.2.3.2 Synthesis of Quinoxaline Derivatives

Quinoxalines or benzopyrazines are an important class of nitrogen heterocycles that have a wide range of biological activities including anti-bacterial, anti-cancer and kinase inhibition. Benzopyrazines occur in several natural products, modern pharmaceuticals and peptide antibiotics such as echinomycin. Various methods have been developed for the synthesis of the benzopyrazine core. Lu and co-workers reported a K-10 catalyzed condensation of 1,2-diamines with α-dicarbonyls to afford substituted benzopyrazines under mild reaction conditions (Scheme 2.6). The acid-sensitive furan diketone also gave the desired quinoxoline and polymerization products were not observed under the reaction conditions. The condensation was highly substrate dependent since anilines bearing electron withdrawing groups gave lower yields and prolonged reaction times were required to achieve a full conversion.

Scheme 2.5 K-10 Catalyzed Diastereoselective Synthesis of cis-Aziridines

2.2.3.3 Synthesis of Multifunctionalized Pyrimidines

Functionalized pyrimidines are widespread naturally occurring organic molecules that occur in nucleic acids and vitamin B1. Functionalized synthetic analogues have been applied widely as pharmaceutical and agrochemical agents. Yadav and Rai reported a multi-component condensation protocol using K-10 as a catalyst to synthesize multi-functionalized fused-ring pyrimidines (Scheme 2.7). Unprotected D-xylose, amidine/guanidine and activated glycine were subjected to the K-10 catalysis under microwave heating conditions to afford bicyclic iminosugar systems. The products were isolated after recrystallization from ethanol as a single diastereomers. Notably, erosion of chirality in the carbohydrate backbone was not observed.

Scheme 2.6 K-10 Catalyzed Synthesis of Benzopyrazines

\[
\begin{align*}
\text{H}_2\text{O, rt} & \quad \text{K-10} \\
\text{Ar} & \quad \text{Ar} \\
\text{X} = \text{H, Ar} = \text{Ph} & \quad (100\%) \quad 2.024 \\
\text{Me, Ar} = \text{Ph} & \quad (100\%) \quad 2.025 \\
\text{NO}_2, \text{Ar} = \text{Ph} (78\%) & \quad 2.026 \\
\text{H, Ar} = \text{furyl} (95\%) & \quad 2.027
\end{align*}
\]

---

Scheme 2.7 K-10 Catalyzed Synthesis of Functionalized Pyrimidines

2.2.3.4 Synthesis of Coumarins

Coumarins are another important class of heterocycles which occur in many natural and synthetic organic compounds. Many synthetic routes have been developed for the synthesis of the coumarin core including the Pechmann, Wittig, Perkin and Knoevenagel reactions. The Pechmann reaction is probably the most widely used method due to its simplicity and the availability of starting materials which allows access to various classes of substituted coumarins. Li and co-workers reported using K-10 as a reusable catalyst for Pechmann-type condensation between phenols 2.035 and ethyl acetoacetate, permitting access to a wide range of mono and disubstituted coumarins in good yields (Scheme 2.8). The major drawback of this procedure was that phenols bearing electron withdrawing functionalities failed to provide the desired products.

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36 Narasimhan, N. S.; Mali, R. S.; Barve, M. V. Synthesis 1979, 906–909.
2.2.4 K-10 Catalyzed Formation and Cleavage of the Ketals

K-10 has been applied for the protection of carbonyl groups as ketals,\textsuperscript{40} acetics and thioacetals.\textsuperscript{41} The cleavage of the acetal groups for acid-sensitive substrates was also reported using K-10 under mild conditions.\textsuperscript{42} Reddy and Falck reported a K-10 catalyzed deprotection of the acetonoid moiety in their total synthesis of the antineoplastic Fostriecin (Scheme 2.9).\textsuperscript{43} The acid labile ketal 2.042 was subjected to K-10 catalysis at room temperature to give the desired product 2.043 as a single product. It is interesting to note that under the reaction conditions epimerization of the allylic tertiary alcohol was not observed.

\begin{center}
\includegraphics[width=\textwidth]{scheme_2.9.png}
\end{center}

\textbf{Scheme 2.9} Falck’s Total Synthesis of Fostriecin

2.3 Results and Discussion

2.3.1 Project Objectives

The first synthesis and application of potassium allyl and crotyltrifluoroborates was reported\textsuperscript{44} by Batey and co-workers in 1999 shortly after the introduction of organotrifluoroborates as stable surrogates for boronic acids by Vedejs.\textsuperscript{45} Potassium allyltrifluoroborate was synthesized from the addition of allylmagnesium bromide to trimethylborate\textsuperscript{46} followed by acidic hydrolysis to afford the allylboronic acid. The boronic acid was not directly isolated but rather treated with saturated KHF\textsubscript{2} to afford the allytrifluoroborate as a white powder which was purified by dissolution and filtration from dry acetonitrile (Scheme 2.10). The crotyl trifluoroborates\textsuperscript{47} were synthesized from \textit{E}– or \textit{Z}–crotylpotassium reagents, generated \textit{in situ} from trans or cis-2-butenes \texttt{2.047} and \texttt{2.049} respectively according to the Schlosser procedure.\textsuperscript{48} Precise control of the internal temperature was critical to maintain the stereochemical configuration of crotylpotassium reagents during lithium to potassium transmetalation. High degrees of control of the olefin geometry of the crotylboron reagents are essential to ensure high diasterocontrol upon addition to carbonyl compounds.

\begin{center}
\begin{tikzpicture}

\node (a) at (0,0) {\text{\ce{\text{MgBr} \quad 2.045}}};
\node (b) at (2,0) {\text{\ce{\text{BF}_3K \quad 78\% \quad 2.046}}};
\node (c) at (0,-1) {\text{\ce{\text{R}^1 \quad \text{R}^2}}};
\node (d) at (2,-1) {\text{\ce{\text{R}^1 \quad \text{BF}_3K}}};
\node (e) at (0,-2) {\text{\ce{\text{R}^1 = H, \text{R}^2 = Me \quad 2.047}}};
\node (f) at (2,-2) {\text{\ce{\text{R}^1 = H, \text{R}^2 = Me, E-crotyl (70\%) \quad 2.049}}};
\node (g) at (0,-3) {\text{\ce{\text{R}^1 = Me, \text{R}^2 = H \quad 2.048}}};
\node (h) at (2,-3) {\text{\ce{\text{R}^1 = Me, \text{R}^2 = H, Z-crotyl (71\%) \quad 2.050}}};

\draw[->] (a) -- (b) node[midway, above] {\text{i) \text{B(OMe)}_3, \text{\textdegree}78 \text{C}}}
\draw[->] (a) -- (b) node[midway, above] {\text{ii) \text{HCl (aq)}}};
\draw[->] (b) -- (c) node[midway, above] {\text{iii) \text{KHF}_2 (aq)}};
\draw[->] (c) -- (d) node[midway, above] {\text{i) \text{\textdegree}78 \text{C}}}
\draw[->] (d) -- (e) node[midway, above] {\text{i) \text{\textdegree}78 \text{C}}}
\draw[->] (d) -- (f) node[midway, above] {\text{ii) \text{B(OPr)}_3}};
\draw[->] (d) -- (g) node[midway, above] {\text{ii) \text{B(OPr)}_3}};
\draw[->] (d) -- (h) node[midway, above] {\text{ii) \text{B(OPr)}_3}};
\draw[->] (d) -- (h) node[midway, above] {\text{iii) \text{HCl (aq)}}};
\draw[->] (d) -- (h) node[midway, above] {\text{iv) \text{KHF}_2 (aq)}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 2.10} Synthesis of Potassium Organotrifluoroborate Reagents

Batey and Thadani reported a phase–transfer-catalyzed allylation and crotylation of aldehydes using allyl and crotyltrifluoroborates.\textsuperscript{49} Attempts were made to apply the phase-transfer-catalyzed procedure for addition to ketones, and while this method was successful for cyclic ketones it failed to give satisfactory results with less reactive acyclic ketones even with increased amounts of the allyl reagent (Scheme 2.11).\textsuperscript{50}

\begin{center}
\begin{tikzpicture}
\draw[thick,->] (0,0) -- (2,0) node[black,above] {2.051} node[black,below] {Cyclohexane};
\draw[thick,->] (2,0) -- (4,0) node[black,above] {2.046} node[black,below] {\(\text{BF}_3\text{K}\) (1.5 equiv.)};
\draw[thick,->] (4,0) -- (6,0) node[black,above] {\(\text{H}_2\text{O}\), 16 h, rt} node[black,below] {\(\text{nBuNI}\) (1.0 equiv.)} node[black,above] {CH\(_2\)Cl\(_2\)};
\draw[thick,->] (6,0) -- (8,0) node[black,above] {\(\text{HO}\) \(\text{CH}=\text{CH}\) \(\text{OH}\) \(\text{HO}\)} node[black,below] {2.052} node[black,above] {72\%};
\draw[thick,->] (0,-2) -- (2,-2) node[black,above] {2.053} node[black,below] {\(\text{Me}\) \(\text{Ph}\) \(\text{O}\)};
\draw[thick,->] (2,-2) -- (4,-2) node[black,above] {2.046} node[black,below] {\(\text{BF}_3\text{K}\) (5.0 equiv.)};
\draw[thick,->] (4,-2) -- (6,-2) node[black,above] {CH\(_2\)Cl\(_2\), H\(_2\)O, 16 h, rt} node[black,below] {\(\text{nBuNI}\) (1.0 equiv.)} node[black,above] {CH\(_2\)Cl\(_2\)};
\draw[thick,->] (6,-2) -- (8,-2) node[black,above] {\(\text{HO}\) \(\text{Me}\) \(\text{CH}=\text{CH}\) \(\text{HO}\)} node[black,below] {2.053} node[black,above] {30\%};
\end{tikzpicture}
\end{center}

**Scheme 2.11** Phase Transfer Catalyzed Allylation of Ketones

It was this that inspired us to develop a robust method for this transformation in aqueous media that: 1) can be applied for the ketone allylation, 2) would avoid the problems associated with the removal of phase-transfer-catalysts, 3) would preclude the requirement of using an inert atmosphere or any special requirements, and 4) can be applied to substrates bearing potentially labile stereocenters without erosion of chirality. We were also interested to know about the behaviors of the group 13 elements (B to In) in the presence of each other. It is noteworthy to mention that boron to indium transmetallation was unknown in the literature at the time of this investigation. A communication including the preliminary results from this section has been published.\textsuperscript{51}

### 2.3.2 Reaction Optimization

Organometalloid reagents are known to be stable in aqueous media and various methods have been developed for Barbier-like nucleophilic addition to carbonyl compounds.\(^{52}\) During the course of our early investigations of allylation of 4-bromoacetophenone using indium and allyltrifluoroborate, it was observed that indium morphology changed from powder to granules after the completion of the reaction.\(^{53}\) To our surprise when the recovered granules were utilized as an indium source, addition occurred at a more sluggish rate. Addition of KF to the reaction media in the presence of indium retarded the reaction (Table 2.1, entry 4) which may indicate that a dissociative mechanism was operative; the addition of fluoride ions suppressed the dissociation of 2.046 into tricoordinate allylboron species via the common ion effect and led to a slower rate of reaction.\(^{54}\) It was postulated that the reaction proceeded via the same intermediate as the phase-transfer-catalyzed pathway and the indium surface was the \textit{in situ} activator of the potassium allyltrifluoroborate. During the course of this investigation the transmetallation of the group 13 elements (B to In or In to B) was unknown in the literature. In order to rule out the possibility of an allylindium intermediate via boron to indium transmetallation, a variety of solid reagents that could only function by facilitating KF dissociation from 2.046 were screened (Table 2.1, entries 5–11). K-10 and neutral alumina demonstrated the greatest activity using a water/chloroform solvent system (Table 2.1, entries 5 and 7). Further investigation revealed that water and two equivalents of the allyltrifluoroborate reagent 2.046 were essential to achieve full conversion (Table 2.1, entries 5–7). The most effective additives were applied for the crotylation using 2.049 under identical conditions to give the desired product 2.055 with excellent diastereoselectivity (Table 2.1, entry 12–13). However, only K-10 gave satisfactory results with the more acid sensitive (Z)-crotyltrifluoroborate 2.050, giving full conversion in CD\(_2\)Cl\(_2\) solvent (Table 2.1, entry 16). For the scope of this reaction dichloromethane was used as solvent for both allylation and crotylation because conversions and/or diastereoselectivities were lower using other solvents such as toluene, H\(_2\)O, THF, CH\(_3\)CN, CHCl\(_3\), DMF or MeOH.


\(^{53}\) Indium-catalyzed method and its possible mechanistic pathway will be discussed in chapter 3.

Table 2.1 Optimization of the Reaction Using Potassium Allyltrifluoroborates 2.046, 2.049 and 2.050

<table>
<thead>
<tr>
<th>Entry</th>
<th>RBF₃K</th>
<th>Additive (0.1 g)</th>
<th>Solvent (Volume, mL)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.046</td>
<td>-</td>
<td>D₂O (1.0)</td>
<td>≤ 2</td>
</tr>
<tr>
<td>2</td>
<td>2.046</td>
<td>In (1.0)</td>
<td>D₂O (1.0)</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>2.046</td>
<td>In (1.0), Bu₄NI (1.0)</td>
<td>D₂O (1.0)</td>
<td>3 (62)</td>
</tr>
<tr>
<td>4</td>
<td>2.046</td>
<td>In (1.0), KF (2.0)</td>
<td>D₂O (0.1) : CDCl₃ (1.4)</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>2.046</td>
<td>K-10</td>
<td>D₂O (0.1) : CDCl₃ (1.4)</td>
<td>96</td>
</tr>
<tr>
<td>6</td>
<td>2.046</td>
<td>K-10</td>
<td>CDCl₃ (1.5)</td>
<td>66</td>
</tr>
<tr>
<td>7</td>
<td>2.046</td>
<td>alumina(N)</td>
<td>D₂O (0.1) : CDCl₃ (1.4)</td>
<td>quant</td>
</tr>
<tr>
<td>8</td>
<td>2.046</td>
<td>alumina(A)</td>
<td>D₂O (0.1) : CDCl₃ (1.4)</td>
<td>67</td>
</tr>
<tr>
<td>9</td>
<td>2.046</td>
<td>charcoal</td>
<td>D₂O (0.1) : CDCl₃ (1.4)</td>
<td>11</td>
</tr>
<tr>
<td>10</td>
<td>2.046</td>
<td>Amberlite</td>
<td>D₂O (0.1) : CDCl₃ (1.4)</td>
<td>≤ 5</td>
</tr>
<tr>
<td>11</td>
<td>2.046</td>
<td>silica gel</td>
<td>D₂O (0.1) : CDCl₃ (1.4)</td>
<td>37</td>
</tr>
<tr>
<td>12</td>
<td>2.049</td>
<td>K-10</td>
<td>D₂O (0.1) : CDCl₃ (1.4)</td>
<td>98</td>
</tr>
<tr>
<td>13</td>
<td>2.049</td>
<td>alumina(N)</td>
<td>D₂O (0.1) : CDCl₃ (1.4)</td>
<td>98</td>
</tr>
<tr>
<td>14</td>
<td>2.050</td>
<td>K-10</td>
<td>D₂O (0.1) : CDCl₃ (1.4)</td>
<td>73</td>
</tr>
<tr>
<td>15</td>
<td>2.050</td>
<td>alumina(N)</td>
<td>D₂O (0.1) : CDCl₃ (1.4)</td>
<td>≤ 5</td>
</tr>
<tr>
<td>16</td>
<td>2.050</td>
<td>K-10</td>
<td>D₂O (0.1) : CD₂Cl₂ (1.4)</td>
<td>98</td>
</tr>
</tbody>
</table>

a) Yield of the products determined by ¹H NMR using an internal standard. b) 3% isolated yield of 2.054 after 3 h and 62% after 48 h. c) Entries 1–11 gave product 2.054, entries 12–13 gave 2.055 (dr ≥ 98:2), and entries 14–16 gave 2.056 (dr ≥ 95:5).

With the optimized reaction conditions in hand, the scope and limitations of this transformation were investigated. Aromatic ketones with various functional groups were allylated under the reaction conditions. Steric and electronic effect of the substitutions on the aromatic rings did not significantly influence the outcome of the reactions and the allylated products were obtained in good to excellent yields (Table 2.2, entries 1–4). Reaction of aliphatic ketones such as 2.060 took
place in good yields, with the more sterically demanding pinacolone 2.061 being fully converted to its allylated product. However, a lower isolated yield is attributed to the difficulty in isolation of the product due to its volatility (Table 2.2, entries 5 and 6). The allylation of substituted ketones 2.062 and 2.063 and enone 2.065 occurred in good to excellent yields (Table 2.2, entries 7–10). Acid sensitive heteroaromatics 2.066 and 2.067 were allylated under mild conditions to afford the desired tertiary homoallylic alcohols in excellent yields (Table 2.2, Entries 11-12).

**Table 2.2** Substrate Scope of the K-10 Catalyzed Allylation of Ketones Using Potassium Allyltrifluoroborate 2.046

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketone</th>
<th>Product</th>
<th>Yield *</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.053 (X = p-Br)</td>
<td>2.054 (X = p-Br)</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>2.057 (X = o-OMe)</td>
<td>2.070 (X = o-OMe)</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>2.058 (X = m-NH2)</td>
<td>2.071 (X = m-NH2)</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>2.059 (X = p-NO2)</td>
<td>2.072 (X = p-NO2)</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td>2.060</td>
<td>2.073</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>2.061</td>
<td>2.074</td>
<td>59</td>
</tr>
<tr>
<td>7</td>
<td>2.062</td>
<td>2.075</td>
<td>98</td>
</tr>
</tbody>
</table>
The newly developed procedure has significant advantages over the previously reported methods. In addition, reactions using K-10 were faster than those methods previously reported by Batey and co-workers. Purification is straightforward and avoids problems associated with the removal of phase-transfer catalysts. Additionally the use of an inert atmosphere or special
conditions is not required. However, some acid-labile functional groups such as epoxides or ketals were not compatible and lower isolated yields or multiple products were observed.\textsuperscript{55}

2.3.3 Diastereoselective Allylation and Crotylation of Ketones

It was then of interest to investigate the limit and scope of this method for a variety of cyclic and acyclic systems. Nucleophilic addition to cyclic ketones is known to be influenced by the conformational properties\textsuperscript{56} of the ketone, especially those bearing an $\alpha$-substituent, giving significantly different results depending on the size and nature of the substituents. It was observed that under the reaction conditions 2-norbornanone \textbf{2.083} was allylated to give the exo-homoallyl alcohol \textbf{2.089} in high yield and diastereoselectivity (Table 2.3, entry 1). The conformationally rigid ketone \textbf{2.084} was allylated under the reaction conditions to give \textbf{2.091} as a major product. The observed diastereoselectivity was consistent with pseudo-equatorial nucleophilic attack of \textbf{2.046}, minimizing 1,3-diaxial interactions to give \textbf{2.091} and leading to the allyl group adopting an equatorial position. In order to test the feasibility of the K-10 method, $\alpha$-silyloxy and alkoxy ketones \textbf{2.085-2.088} were synthesized according to known literature procedures.\textsuperscript{57,58,59}

\textsuperscript{55} The details of acid liable compounds will be covered in chapter 3.
Table 2.3 Substrate Scope of the K-10 Catalyzed Allylation of Ketones Using Potassium Allyltrifluoroborate 2.046

![Chemical Reaction](attachment:image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketone</th>
<th>Products</th>
<th>(dr.)&lt;sup&gt;a&lt;/sup&gt; Yield(%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="" alt="Image" /> 2.083</td>
<td><img src="" alt="Image" /> 2.089 <img src="" alt="Image" /> 2.090</td>
<td>95:5 93</td>
</tr>
<tr>
<td>2</td>
<td><img src="" alt="Image" /> 2.084</td>
<td><img src="" alt="Image" /> 2.091 <img src="" alt="Image" /> 2.092</td>
<td>82:18 93</td>
</tr>
<tr>
<td>3</td>
<td><img src="" alt="Image" /> 2.085</td>
<td><img src="" alt="Image" /> 2.093 <img src="" alt="Image" /> 2.094</td>
<td>78:22 92</td>
</tr>
<tr>
<td>4</td>
<td><img src="" alt="Image" /> 2.086</td>
<td><img src="" alt="Image" /> 2.095 <img src="" alt="Image" /> 2.096</td>
<td>80:20 94</td>
</tr>
<tr>
<td>5</td>
<td><img src="" alt="Image" /> 2.087</td>
<td><img src="" alt="Image" /> 2.097 <img src="" alt="Image" /> 2.098</td>
<td>36:64 91</td>
</tr>
<tr>
<td>6</td>
<td><img src="" alt="Image" /> 2.088</td>
<td><img src="" alt="Image" /> 2.099 <img src="" alt="Image" /> 2.100</td>
<td>28:72 92</td>
</tr>
</tbody>
</table>

<sup>a</sup> the diasteromeric ratios were determined by GC or <sup>1</sup>H NMR analysis on crude products. <sup>b</sup> Yield of products isolated after silica gel chromatography.
Allylation of the α-silyloxy- or benzyloxyketones 2.085 and 2.086 were accomplished in high yields and moderate to good diastereoselectivity affording the anti-products (Table 2.3, entries 3 and 4). Moderate diastereoselectivity was observed for allylation of the α-methoxy cyclohexanone giving the axial homoallylic alcohol 2.098 as the major product. Increasing the size of the alkoxy group to an α-benzyloxy group had little impact on the observed diastereoselectivity (Table 2.3, entries 5 and 6).

Hoffman and co-workers performed extensive studies on addition of allyl and E- and Z-crotyl boronates to α-benzyloxy propanal (Figure 2.2). It was observed that allylboron addition to aldehyde 2.101 afforded alcohols 2.105 and 2.106 with poor diastereoselectivity. Surprisingly, the crotylation of 2.101 using E-crotylboronate 2.103 was unselective, whereas Z-crotylboronate 2.104 was afforded 88:12 diastereoselectivity favouring the product 2.109.

Hoffmann and Roush have rationalized these observations based on Cornforth- and Felkin-Anh-like models with the aim of minimization of the gauche pentane (coloured red and blue) interactions in the cyclic transition states (Figure 2.3). Transition states 2.111 and 2.115 were identified to have the minimum interactions in the reactions using E-and Z-crotylboronates. Transition state 2.115, with a Cornforth-like conformation of the chiral centre, has the minimum non-bonding interactions using Z-crotylboronates. However, with allylboronation there are fewer gauche pentane interactions and, the debate continues as to which transition state 2.112 (Felkin

![Figure 2.2 Allylation and Crotylation of α-Benzyloxypropanal](image)

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type) and 2.115 (Cornforth-like) dominates. Based on these arguments the observed \textit{anti}-
selectivity for the allylation of the substrates 2.085 and 2.086 can be rationalized by both
Cornforth and Felkin-Anh like transition state (Figure 2.4).

\textbf{Figure 2.3} Plausible Transition States for Crotylation of 2.101
The K-10 promoted crotylation of acyclic ketones using 2.049 and 2.050 was studied. The diastereoselective crotylations of ketones are more challenging than aldehydes due to increased steric congestion of the carbonyl group. The crotylation of various ketones was achieved in high yields and diastereoselectivity. Diastereosepecific additions were achieved with \((E)\)- and \((Z)\)-crotyl reagents 2.049 and 2.050 affording the \textit{anti} and \textit{syn} products, respectively (Scheme 2.12). Homoallylic alcohols 2.055, 2.120, 2.122 and 2.124 were obtained using \((E)\)-crotyltrifluoroborate, whereas products 2.056, 2.121, 2.123 and 2.125 were obtained using \((Z)\)-crotyltrifluoroborate. This selectivity is consistent with reaction of tricoordinate allylboron species through cyclic Zimmerman-Traxler-like transition states. The requisite tricoordinate allylboron species can be formed by fluoride ion abstraction or hydrolysis from 2.046 under K-10 conditions. The exact nature of the actual species involved is not known but the observed products are consistent with tricoordinate boron species. As expected, a lower diastereoselectivity was observed for 2-heptanone due to lower steric differentiation of the substituents (i.e., methyl versus pentyl).\(^{62}\)

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2.3.4 Allylation and Diastereoselective Crotylation of Aldehydes

During the course of investigation on aldehyde substrates, it was observed that 1.2 equivalents of organotrifluoroborates with respect to aldehydes were sufficient to achieve full conversion in a short time. Under modified conditions the desired homoallylic secondary alcohols were obtained in excellent yields and diastereoselectivity (Scheme 2.13). Diastereospecific additions were achieved with (E)- and (Z)-crotyl reagents 2.049 and 2.050 affording the anti and syn products, respectively. Using (E)-crotyltrifluoroborate, additions occurred efficiently affording alcohols 2.132–2.135 in good yields and high diastereoselectivity. Compounds 1.138 and 2.139 were obtained using (Z)-crotyltrifluoroborate.

Scheme 2.12 Scope of the K-10 Catalyzed Crotylation of Ketones
2.4 Practical Applications

A significant advantage of this procedure over existing procedures is its simplicity. The developed method does not require inert atmosphere conditions which are often required for the traditional boron reagents, and the work up is straightforward. Monitoring the reaction is very simple; as a sign of completion of the reaction, the originally murky and heterogeneous mixture becomes completely clear and K-10 settles to the bottom of the reaction mixture once it has absorbed water. The heterogeneous mixture becomes a clear biphasic solution and the organic products were isolated via simple filtration through Celite. The procedure is scalable and
independent of the steric/electronic nature of the substrate reagents and consistent results were obtained using different trifluoroborates (Scheme 2.14). The major drawback of this method is the lack of possibility of enantioselective addition, since the in situ generated achiral tricoordinated boron spices is very reactive. However, starting from enantiopure α-substituted substrates it was possible to prepare enantiopure homoallyl alcohols. As an example of this method, the α-(tert-butyldimethylsilyloxy)aldehyde 2.142 was subjected to the reaction conditions using (Z)-non-2-enyltrifluoroborate 2.143 to afford 2.144 in good yield and diastereoselectivity. The syn-homoallylic alcohol 2.144 was further elaborated for the synthesis of (+)-Antimycin A₁₁b.⁶³

![Scheme 2.14 Synthetic Application of the K-10 Catalyzed Allylation](image)

⁶³ This experiment was done by John Janetzko B.Sc. 2011.
2.5 Mechanistic Studies

During the optimization of K-10 catalyzed reactions, it was observed that allylation and protodeboration of allyltrifluoroborate were competing reactions. The decomposition pathway was attributed to the acidic properties of the K-10. During the preliminary investigation of the allylation reactions of ketones, it was realized that in order to achieve full conversion, two equivalents of the trifluoroborate reagents were required. In previous reports, the activation of potassium allyltrifluoroborate was implicated as occurring through dissociation of fluoride to generate an active tricoordinate allylboron reagent. Under the reaction conditions the dissociation of fluoride anion was required to generate the active boron reagent, although the exact nature of it was not elucidated. In order to confirm the boron intermediate, potassium α,α-bis(deutero)allyltrifluoroborate was synthesized according to the reported method. Vinyl magnesium bromide reacted with trimethylborate followed by hydrolysis to give vinylboronic acid 2.147, which was immediately treated with pinacol to afford the volatile vinylboronic acid pinacolester 2.148. Pinacol ester 2.148 was then subjected to Matteson’s homologation conditions, which upon hydrolysis and treatment with KHF$_2$ afforded an inseparable mixture of the desired product 2.150 and potassium vinyl trifluoroborate 2.149 in an 82:18 ratio (Scheme 2.15).

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In a control reaction, 4'-bromoacetophenone underwent selective allylation using the aforementioned mixture 2.149/2.150 to give compound 2.152 as essentially the sole product (Scheme 2.16).

Scheme 2.15 Potassium α,α-Bis(deutero)allyltrifluoroborate

In this case the acidic K-10 presumably abstracts fluoride to generate a tricoordinate allylboron species which subsequently reacts with 4'-bromoacetophenone to afford the product 2.152. This result is consistent with reaction of the ketone with an allylboron species through a closed, chair-like Zimmerman-Traxler transition state (Scheme 2.17).
2.6 Conclusions

A new K-10 catalyzed allylation and crotylation of carbonyl groups has been developed and the scope of the diastereoselective allylation and crotylation reactions examined for aldehydes and ketones. The method is robust, scalable and reliable with high functional group tolerance. Substituents on aromatics and heteroaromatics rings were found to have little effect on the outcome of the reaction. The conventional work-up was not required for further purification, since the boric acid by-product of the reagent remains trapped in the cavity of the K-10. The problems associated with the removal of phase-transfer catalysts and the requirement of an inert atmosphere were avoided. Though this reaction was not performed enantioselectively, the epimerization of the α-chiral substrates was not observed under the reaction conditions, as exemplified in the synthesis of Antimycin A₁₆. Mechanistic studies revealed that the reaction proceeds though a boron intermediate via a closed transition state.

In comparison to known boron-based allylation and crotylation methods, the newly developed method can be performed at ambient temperature and it does not require the use of an inert atmosphere or anhydrous conditions, due to stability of the reagent. Moreover, a wide range of functional groups are tolerated providing a useful allylation protocol of substrates with sensitive functional groups (e.g., CN, NO₂) which often do not work well using classical allylmetal nucleophiles. However, acid labile functional groups such as acetals and epoxides are not...
compatible under the reaction conditions. The major disadvantage of this method is the inability to perform enantioselective allylation. However, starting from compounds with preexisting stereocentres, such as $\alpha$-chiral ketones or aldehydes, diastereoselective additions can occur, thus providing a means to form single enantiomer products with high enantiomeric purity from chiral single enantiomer precursors. Further development of this procedure is envisaged to other substrate classes, and the development of sequential reactions. For example, amine and ketone condensation results in the formation of an imine and water, which may then afford homoallylic amines.

2.7 Experimental Procedures

Reaction solvents were distilled under an inert atmosphere before use and transferred via syringe using standard techniques unless otherwise stated. CH$_2$Cl$_2$ was distilled from CaH$_2$ under nitrogen. All reagents, unless otherwise stated, were used as received (Aldrich, Fisher Scientific Ltd. or Lancaster). Commercially available potassium allyl trifluoroborate (2.046), and crotyltrifluoroborate salts 2.049 and 2.050 were prepared by known procedures.\(^{67}\) Montmorillonite K-10 was purchased from Aldrich, and was used without activation.

IR spectra were obtained on a Perkin-Elmer Spectrum 1000, with samples loaded as films on NaCl plates or as KBr discs. \(^1\)H and \(^{13}\)C NMR spectra were obtained on Varian Mercury 300 or Unity 400 or 500 spectrometers as solutions in CDCl$_3$ (unless otherwise indicated). Chemical shifts are expressed in ppm values. Spectra were referenced to 7.26 ppm for CHCl$_3$ for proton chemical shifts and 77.00 ppm for CDCl$_3$ for carbon chemical shifts. Peak multiplicities are designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad (this abbreviation is also used for designation of IR peaks); r, rotamer; \(J\), coupling constant in Hz (rounded to the nearest 0.5 Hz). Low resolution mass spectra (MS) were recorded on a Bell and Howell 21-490 spectrometer. High resolution mass spectra (HRMS) were recorded on an AEI MS3074 spectrometer. Melting points were obtained on a Fisher-Johns melting point apparatus and are uncorrected.

Flash column chromatography on silica gel (60 Å, 230-400 mesh, obtained from Silicycle Inc.) was performed with distilled hexanes, or reagent grade solvents. Analytical thin-layer chromatography (TLC) was performed on pre-coated aluminum-backed silica gel plates (Alugram SIL G/UV<sub>254</sub> purchased from Silicycle Inc.), visualized with a UV lamp (254 nm), iodine, ninhydrin, potassium permanganate, phosphomolybdic acid (Aldrich), or vanillin. References following the compound names indicate literature articles where <sup>1</sup>H and <sup>13</sup>C NMR data have previously been reported. References following the compound names indicate literature articles where full characterizations of spectral and physical properties have previously been reported.

**General Procedure for Addition of Potassium Trifluoroborate Salts 2.046, 2.049 and 2.050 to Ketones under Montmorillonite K10 Conditions**

To ketone (0.50 mmol), potassium allyl or crotyltrifluoroborate salts 2.046, 2.049 or 2.050 (1.0 mmol) and K-10 (0.1 g) in a 5 mL round bottom flask was added CH<sub>2</sub>Cl<sub>2</sub> (1.4 mL) and water (0.1 mL). The biphasic reaction mixture was vigorously stirred at rt until reaction conversion was complete as monitored by TLC analysis. The reaction mixture was then filtered to separate the solid phase and washed with CH<sub>2</sub>Cl<sub>2</sub> (3 x 5 mL). The solvent was evaporated and the concentrated organic mixture was passed through a short plug of silica gel using EtOAc/hexane as an eluent. The resulting eluate was concentrated *in vacuo* to afford the product alcohol.

**Analytical Data for Homoallylic Alcohols**

2-(4-Bromophenyl)pent-4-en-2-ol (2.054).<sup>68</sup> Isolated as a clear, colourless oil; (117 mg, 97%); R<sub>f</sub> = 0.35 (20% v/v EtOAc in hexanes); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 7.43 (2H, d, <i>J</i> = 9.0 Hz), 7.29 (2H, d, <i>J</i> = 9.0 Hz), 5.60 (1H, dddd, <i>J</i> = 18.0, 9.5, 8.0, 6.5 Hz), 5.15-5.10 (2H, m), 2.63 (1H, dd, <i>J</i> = 14.0, 6.5 Hz).

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Hz), 2.46 (1H, dd, $J = 14.0$, 8.0 Hz), 2.07 (1H, s), 1.51 (3H, s); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 146.9, 133.4, 131.4, 126.9, 120.8, 120.1, 73.6, 48.5, 30.1.

(2S*,3S*)-2-(4-Bromophenyl)-3-methylpent-4-en-2-ol (2.055). Isolated as a clear, colourless oil (124 mg, 97%); crude dr $\geq$ 98:2; $R_f = 0.53$ (20% v/v EtOAc in hexanes); $^1$H NMR (CDCl$_3$, 400 MHz) δ 7.45 (2H, $d$, $J = 8.5$ Hz), 7.30 (2H, $d$, $J = 8.5$ Hz), 5.66 (1H, $ddd$, $J = 18.0$, 9.5, 7.5 Hz), 5.14-5.05 (2H, m), 2.60-2.48 (1H, m), 1.95 (1H, br s), 1.50 (3H, s), 0.96 (3H, d, $J = 7.0$ Hz); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 146.3, 139.8, 132.1, 127.7, 120.8, 117.3, 75.7, 49.0, 26.2, 14.3; IR (film) $\nu_{\text{max}}$ 3473, 3074, 2975, 2933, 1636, 1486, 1454, 1394, 1372, 1161, 1078, 1008, 919, 934, 815, 720, 665 cm$^{-1}$; MS (EI) $m/z$ 202 (15), 201 (98), 200 (16), 199 (100), 195 (10), 182 (10); HRMS (EI) $m/z$ calcd. for C$_{12}$H$_{14}$Br [M-OH]$^+$ 237.0279, found 237.0290. The dr was determined by analysis of the crude $^1$H NMR, using the signals of the 3-methyl group.

(2S*,3R*)-2-(4-Bromophenyl)-3-methylpent-4-en-2-ol (2.056). Isolated as a clear, colourless oil (120 mg, 94%); crude dr ≥95:5; $R_f = 0.55$ (20% v/v EtOAc in hexanes); $^1$H NMR (CDCl$_3$, 400 MHz) δ 7.45 (2H, $d$, $J = 8.5$ Hz), 7.28 (2H, $d$, $J = 8.5$ Hz), 5.79 (1H, $ddd$, $J = 17.0$, 10.5, 8.0 Hz), 5.16-5.06 (2H, m), 2.50 (1H, dq, $J = 7.5$, 7.0 Hz), 1.50 (1H, br s), 1.55 (3H, s), 0.85 (3H, d, $J = 7.0$ Hz); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 146.3, 139.6, 131.2, 127.7, 127.4, 120.6, 117, 75.8, 49.0, 28.7, 14.9.; IR (film) $\nu_{\text{max}}$ 3405, 3079, 2972, 2929, 2877, 1639, 1592, 1488, 1456, 1404, 1094, 1071, 1010, 917, 823, 665 cm$^{-1}$; MS (EI) $m/z$ 202 (14), 201 (98), 200 (15), 199 (100), 185 (10), 183 (10); HRMS (EI) $m/z$ calcd. for C$_{12}$H$_{14}$Br [M-OH]$^+$ 237.0279, found 237.0269. The dr was determined by analysis of the crude $^1$H NMR, using the signals of the 3-methyl group.
2-(2-Methoxyphenyl)pent-4-en-2-ol (2.070). Isolated as a clear, colourless oil (86 mg, 89%); R_f = 0.28 (30% v/v EtOAc in hexanes); ^1H NMR (CDCl_3, 400 MHz) δ 7.31 (1H, dd, J = 7.5, 2.0 Hz), 7.24 (1H, dddd, J = 8.0, 7.5, 2.0 Hz), 6.95 (1H, dddd, J = 7.5, 7.5, 1.5 Hz), 6.92 (1H, dd, J = 8.0, 1.5 Hz), 5.64 (1H, dddd, J = 17.0, 10.0, 7.5, 7.0 Hz), 5.08-4.99 (2H, m), 3.87 (3H, s), 2.82 (1H, dddd, J = 14.0, 7.0, 1.0, 1.0 Hz), 2.60 (1H, dddd, J = 14.0, 7.5, 1.0, 1.0 Hz), 1.57 (3H, s); ^13C NMR (CDCl_3, 100 MHz) δ 156.9, 135.0, 134.8, 128.4, 127.0, 121.0, 118.0, 111.5, 74.4, 55.5, 46.8, 27.2.

2-(3-Aminophenyl)pent-4-en-2-ol (2.071). Isolated as a pale yellow oil (70 mg, 78%); R_f = 0.38 (80% v/v EtOAc in hexanes); ^1H NMR (CDCl_3, 400 MHz) δ 7.10 (1H, dd, J = 7.5, 7.5 Hz), 6.82-6.76 (2H, m), 6.53 (1H, d, J = 7.5 Hz), 5.64 (1H, dddd, J = 17.0, 10.0, 8.5, 6.5 Hz), 5.15-5.08 (2H, m), 3.31 (3H, br s), 2.62 (1H, dd, J = 13.5, 6.5 Hz), 2.43 (1H, dd, J = 13.5, 8.5 Hz), 1.49 (3H, s); ^13C NMR (CDCl_3, 100 MHz) δ 149.3, 146.5, 134.1, 129.3, 119.51, 115.4, 113.6, 112.0, 73.8, 46.6, 30.1; IR (film) ν_max 3590, 3480, 3071, 2980, 2930, 2890, 1641, 1620, 1110, 1005, 831, 707 cm^-1; MS (EI) m/z 178 (3), 177 (5), 160 (15), 159 (20), 151 (13), 139 (29), 125 (17), 108 (100), 98 (77), 95 (50); HRMS (EI) m/z calcd. for C_{11}H_{15}NO [M]^+ 177.1526, found 177.1533.

2-(4-Nitrophenyl)pent-4-en-2-ol (2.072). Isolated as a yellow oil (99 mg, 96%); R_f = 0.26 (30 v/v EtOAc in hexanes); ^1H NMR (CDCl_3, 400 MHz) δ 8.18 (2H, d, J = 9.0 Hz), 7.62 (2H, d, J = 9.0 Hz), 5.60 (1H, dddd, J = 16.5, 11.0, 8.0, 6.5 Hz), 5.17-5.12 (2H, m), 2.68 (1H, dd, J = 14.0, 6.5 Hz), 2.54 (1H, dd, J = 14.0, 8.0 Hz), 2.31 (1H, bs), 1.58 (3H, s); ^13C NMR (CDCl_3, 100 MHz) δ 155.3, 146.9, 132.7, 126.2, 123.6, 120.6, 73.9, 48.5, 30.0.

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2,3-Dimethylhex-5-en-3-ol (2.073).\textsuperscript{71} Isolated as a clear, colourless oil (60 mg, 94%); \( R_f = 0.22 \) (20% v/v EtOAc in hexanes); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 5.89 (1H, dddd, \( J = 17.0, 10.5, 7.5, 7.0 \) Hz), 5.17-5.10 (1H, m), 2.29-2.18 (2H, m), 1.75-1.65 (1H, qq, \( J = 6.5, 6.5 \) Hz), 1.39 (1H, s), 1.09 (3H, s), 0.95 (3H, d, \( J = 6.5 \) Hz), 0.92 (3H, d, \( J = 6.5 \) Hz); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \( \delta \) 134.3, 118.8, 74.4, 44.4, 37.1, 23.1, 17.7, 17.1.

2,2,3-Trimethylhex-5-en-3-ol (2.074).\textsuperscript{72} Isolated as a clear, colourless oil (42 mg, 59%); \( R_f = 0.46 \) (20% v/v EtOAc in hexanes); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 5.98-5.91 (1H, m), 5.17-5.08 (2H, m), 2.35 (1H, dd, \( J = 13.5, 7.5 \) Hz), 2.20 (1H, dd, \( J = 13.5, 7.5 \) Hz), 1.16 (3H, s), 0.94 (9H, s); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \( \delta \) 135.4, 118.7, 75.9, 41.2, 38.0, 25.5, 21.9.

Methyl 2-Hydroxy-2-phenylpent-4-enoate (2.075).\textsuperscript{73} Isolated as a clear, colourless oil (101 mg, 98%); \( R_f = 0.31 \) (40% v/v EtOAc in hexanes); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 7.60-7.57 (2H, m), 7.40-7.29 (3H, m), 5.79 (1H, dddd, \( J = 16.0, 11.0, 7.5, 6.5 \) Hz), 5.22-5.12 (2H, m), 3.78 (3H, s), 3.71 (1H, br s), 2.98 (1H, dd, \( J = 14.0, 7.5 \) Hz), 2.77 (1H, ddt, \( J = 14.0, 6.5, 1.5 \) Hz); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \( \delta \) 175.3, 141.5, 132.6, 128.5, 128.1, 125.8, 119.6, 78.4, 53.4, 44.4.

Ethyl 2-Hydroxy-2-methylpent-4-enoate (2.076).\textsuperscript{74} Isolated a clear, colourless oil (72 mg, 91%); \( R_f = 0.33 \) (25% v/v EtOAc in hexanes); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 5.77 (1H, dddd, \( J = 16.0, 11.0, 7.5, 7.5 \) Hz), 5.13-5.05 (2H, m), 4.26-4.15 (2H, m), 3.20 (1H, br s), 2.49 (1H, dd, \( J = 14.0, 7.5 \) Hz), 2.37 (1H, dddd, \( J =


14.0, 7.5, 1.0, 1.0 Hz), 1.40 (3H, s), 1.28 (3H, dd, J = 7.0 Hz); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 176.4, 132.3, 119.0, 74.2, 61.8, 44.6, 25.5, 14.2.

**Ethyl 3-Hydroxy-3-methylhex-5-enoate (2.077).**$^{75}$ Isolated as a clear, colourless oil (85 mg, 98%); $R_f$ = 0.56 (30% v/v EtOAc in hexanes); $^1$H NMR (CDCl$_3$, 400 MHz) δ 5.86 (1H, dddd, J = 17.0, 10.5, 7.5, 7.0 Hz), 5.15-5.04 (2H, m), 4.18 (2H, q, J = 7.0 Hz), 3.61 (1H, br s), 2.43 (2H, dd, J = 16.0 Hz), 2.29 (2H, d, J = 7.5 Hz), 1.28 (3H, dd, J = 7.0, 7.0 Hz), 1.24 (3H, s); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 173.2, 133.9, 118.7, 70.9, 60.8, 46.7.0, 44.5, 27.0, 14.4.

**3-Methyl-1-phenylhexa-1,5-dien-3-ol (2.078).**$^{76}$ Isolated as a clear, colourless oil (78 mg, 83%); $R_f$ = 0.29 (30% v/v EtOAc in hexanes); $^1$H NMR (CDCl$_3$, 400 MHz) δ 7.37 (2H, d, J = 8.0 Hz), 7.30 (2H, dd, J = 8.0, 7.5 Hz), 7.20 (1H, t, J = 7.5 Hz), 6.61 (1H, d, J = 16.0 Hz), 6.31 (1H, d, J = 16.0 Hz), 5.93-5.77 (1H, m), 5.22-5.12 (2H, m), 2.46 (1H, dddd, J = 13.5, 6.5, 1.0, 1.0 Hz), 2.37 (1H, dddd, J = 13.5, 8.0, 1.0, 1.0 Hz), 1.83 (1H, br s), 1.40 (3H, s); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 137.2, 136.5, 133.8, 128.8, 127.7, 126.7, 119.5, 72.6, 47.6, 28.2 (one signal missing).

**2-(Furan-2-yl)pent-4-en-2-ol (2.079).**$^{77}$ Isolated as a clear, colourless oil (68 mg, 90%); $R_f$ = 0.54 (20% v/v EtOAc in hexanes); $^1$H NMR (CDCl$_3$, 400 MHz) δ 7.35 (1H, dd, J = 2.0, 1.0 Hz), 6.30 (1H, dd, J = 3.5, 2.0 Hz), 6.19 (1H, dd, J = 3.5, 1.0 Hz), 5.62-5.73 (1H, m), 5.10-5.16 (2H, m), 2.69 (1H, dd, J = 13.5, 7.0 Hz), 2.54 (1H, dd, J = 13.5, 8.0 Hz), 2.13 (1H, s), 1.53 (3H, s); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 159.5, 141.8, 133.5, 119.4, 110.2, 104.9, 71.0, 46.4, 26.8.

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2-(5-Bromothiophen-2-yl)pent-4-en-2-ol (2.080). Isolated as a yellow viscose oil (116 mg, 94%); R_f = 0.54 (30% v/v EtOAc in hexanes); ^1H NMR (CDCl_3, 400 MHz) δ 6.87 (1H, d, J = 4.0 Hz), 6.64 (1H, d, J = 4.0 Hz), 5.71 (1H, dddd, J = 17.0, 10.5, 8.0, 6.5 Hz), 5.13-5.19 (2H, m), 2.64 (1H, dd, J = 13.5, 6.5 Hz), 2.50 (1H, dd, J = 14.0, 8.0 Hz), 2.32 (1H, s), 1.56 (3H, s); ^13C NMR (CDCl_3, 100 MHz) δ 154.8, 133.0, 129.8, 122.7, 120.4, 110.8, 73.2, 49.0, 30.4; IR (film) ν_max 3480, 3071, 2980, 2930, 2890, 1641, 1620, 1326, 1110, 1005, 831, 707 cm⁻¹; MS (EI) m/z 230 (3), 208.9 (4), 207.9 (6.9), 206.9 (100), 205.9 (7.3), 204.9 (95.8), 190.9 (8.7), 188.9 (11.3), 149.0 (10.7), 134 (7.7); HRMS (EI) m/z calcld. for C_{9}H_{9}S_{79}Br [M-H_{2}O] 227.9608, found 227.9620.

3-Allyl-3-hydroxyindolin-2-one (2.081).^78 Isolated as a light yellow solid (87 mg, 93%); R_f = 0.36 (30% v/v EtOAc in hexanes); ^1H NMR (DMSO-d_6, 400 MHz) δ 10.17 (1H, s), 7.21 (1H, d, J = 7.0 Hz), 7.14 (1H, t, J = 8.0 Hz), 6.91 (1H, t, J = 7.5 Hz), 6.73 (1H, d, J = 7.5 Hz), 5.91 (1H, s), 5.35-5.45 (1H, m), 4.87-4.91 (2H, m), 2.55 (1H, dd, J = 13.0, 6.5 Hz), 2.40 (1H, dd, J = 13.5, 8.0 Hz); ^13C NMR (DMSO-d_6, 100 MHz) δ 179.4, 142.3, 132.4, 132.2, 129.5, 124.8, 122.1, 119.5, 110.1, 75.9, 42.8.

2-(Pyridin-4-yl)pent-4-en-2-ol (2.082).^70 Isolated as a clear, colourless oil (44 mg, 54%); R_f = 0.42 (EtOAc); ^1H NMR (CDCl_3, 400 MHz) δ 8.46 (2H, dd, J = 4.5, 1.5 Hz, 2H), 7.36 (2H, d, J = 5.5 Hz), 5.60 (1H, dddd, J = 16.0, 11.0, 8.0, 6.5 Hz), 5.11-5.15 (2H, m), 2.80 (1H, s), 2.63 (1H, dd, J = 14.0, 6.5 Hz), 2.50 (1H, dd, J = 14.0, 8.0 Hz), 1.54 (3H, s); ^13C NMR (CDCl_3, 100 MHz) δ 157.0, 149.3, 133.2, 120.8, 73.6, 47.7, 29.8.

Synthesis of α-substituted ketones

3-[(tert-Butyldiphenylsilyloxy)-butan-2-one (2.085).\(^{57}\)

\[
\text{C}_6\text{H}_{14}\text{O} + \text{Imidazole} + \text{CH}_2\text{Cl}_2 \rightarrow \text{O} \quad \text{TBDPS} \quad 90\% \quad 2.085
\]

To a solution of 3-(hydroxy)-butan-2-one (0.881 g, 10.0 mmol) in THF (15 ml) were added imidazole (1.7 g, 25 mmol) and tert-butyldiphenylsilylchloride (2.6 mL, 10 mmol). The heterogeneous mixture stirred for 12 h, and then filtered to separate the solids. The solids were washed with diethyl ether (20.0 mL), and the combined organics concentrated to afford a viscose solid/oil. This mixture was purified on silica gel column chromatography (5% v/v EtOAc in hexanes) to give the product as a clear, viscous oil (2.95 g, 90%); \( R_f = 0.29 \) (5% v/v EtOAc in hexanes); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 7.61-7.66 (4H, m), 7.25-7.45 (6H, m), 4.18 (1H, q, \( J = 6.5 \) Hz), 2.16 (3H, s), 1.19 (3H, d, \( J = 6.5 \) Hz), 1.1 (9H, s); \(^1^3\)C NMR (CDCl\(_3\), 100 MHz) \( \delta \) 212.0, 135.9, 133.8, 133.2, 130.2, 130.1, 128.0, 127.9, 76.0, 27.1, 25.2, 20.8, 19.5.

3-(Benzyloxy) butan-2-one (2.086).\(^{58}\)

\[
\text{C}_6\text{H}_{14}\text{O} + \text{NaH} + \text{PhBr} \rightarrow \text{O} \quad \text{PCC} \quad \text{CH}_2\text{Cl}_2 \quad 52\% \quad 2.086
\]

To a 50 mL flame-dried, round-bottomed flask under positive argon pressure, sodium hydride (0.80 g, 20.0 mmol), THF (40 mL) and 2,3-butanediol (1.80 mL, 20.0 mmol) were added. The mixture was stirred at room temperature for 30 min and cooled to 0 °C. Benzyl bromide was added in one portion and the solution was stirred for 2 h at room temperature. After completion of the reaction (as monitored by TLC), the reaction mixture was quenched with H\(_2\)O (10 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (2x15 mL). The organic layers were combined, dried over sodium sulfate and concentrated in vacuo to afford light yellow mixture. The crude product was dissolved in CH\(_2\)Cl\(_2\) (20 mL), and powdered...
3Å molecular sieves (4.0 g) and PCC (2.6 g, 12.0 mmol) were added. After stirring for 12 h, ether (50 mL) was added slowly with vigorous stirring and the solution was filtered under vacuum through a pad of celite. The solution was concentrated in vacuo, and the product purified by silica gel column chromatography (90:10 v/v hexanes in ethyl acetate) to afford 2.086 (0.93 g, 52% yield). ¹H NMR (CDCl₃, 400 MHz) δ 7.28-7.38 (5H, m), 4.55 (1H, d, J = 11.5 Hz), 4.50 (1H, d, J = 11.5 Hz), 3.90 (1H, q, J = 7.0 Hz), 2.20 (3H, s), 1.35 (3H, d, J = 7.0 Hz).

2-(Benzyloxy)cyclohexanone (2.088).⁵⁹

A solution of 2-hydroxycyclohexanone dimer (2.28 g, 10.0 mmol), benzylalcohol (3.24 g, 30.0 mmol), toluene (4.0 mL) and conc. hydrochloric acid (1.0 mL, 12.0 M) was refluxed for 2 h using a Dean–Stark apparatus. The reaction was cooled to room temperature, diluted with diethyl ether (20 mL) and washed with water (2×10 mL). The combined organic layers were evaporated and the yellowish oily residue purified using silica gel chromatography (86:14 v/v ethyl acetate in hexane) affording 2.088 (1.56 g, 76%) as a clear colorless oil; ¹H NMR (CDCl₃, 400 MHz) δ 7.28-7.38 (5H, m), 4.76 (1H, d, J = 12.0 Hz), 4.48 (1H, d, J = 12.0 Hz), 3.88 (1H, qd, J = 5.5, 1.0 Hz), 2.45-2.51 (1H, m), 2.18-2.26 (2H, m), 1.60-1.98 (5H, m); ¹³C NMR (CDCl₃, 100 MHz) δ 210.2, 137.9, 128.4, 127.75, 125.7, 81.7, 71.6, 40.6, 34.5, 27.6, 23.1.

**endo-2- Allylbicyclo[2.2.1]hepten-2-ol (2.089).**\(^{80}\) Isolated as a clear, colourless oil (60 mg, 79%); crude dr ≥ 95:5; R\(_f\) = 0.50 (20% v/v EtOAc in hexanes); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 5.90 (1H, dddd, \(J\) = 16.0, 10.5, 9.5, 7.5 Hz), 5.18-5.08 (2H, m), 2.32-2.21 (2H, m), 2.20-2.15 (1H, m), 2.09-2.04 (1H, m), 2.02-1.90 (1H, m), 1.66 (1H, br s), 1.63-1.44 (3H, m), 1.35-1.23 (3H, m), 1.08 (1H, dd, \(J\) = 13.0, 3.5 Hz); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 134.2, 119.4, 78.6, 46.8, 46.5, 45.7, 38.8, 37.4, 28.7, 22.3.

**1-Allyl-4-**\(^{\text{tert}}\)-butylcyclohexanol (2.091 and 2.092).\(^{81}\) The dr. was determined to be 2.091: 2.092 [82:18], by analysis of the crude \(^1\)H NMR, using the signals of the allylic hydrogens. 2.091 (major diastereomer) isolated after flash chromatography (20% v/v ethyl acetate in hexanes) as a clear, colourless oil (76 mg, 77%); R\(_f\) = 0.49 (20% v/v EtOAc in hexanes); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 5.89 (1H, dddd, \(J\) = 17.5, 10.0, 7.5, 7.0 Hz), 5.15-5.02 (2H, m), 2.14 (2H, d, \(J\) = 7.5 Hz), 1.72-1.48 (4H, m), 1.44-1.22 (5H, m), 0.96-0.86 (1H, m), 0.85 (9H, s); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 134.1, 118.8, 70.4, 48.8, 48.2, 37.7, 32.3, 27.5, 22.4.

2.092: (minor diastereomer) isolated as a clear, colourless crystalline solid (15 mg, 15%); mp = 59-60 °C (CHCl\(_3\)) (ref. 81, mp = 59.5-60.5 °C); R\(_f\) = 0.36 (20 v/v EtOAc in hexanes); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 5.87 (1H, dddd, \(J\) = 17.5, 10.5, 7.5, 7.0 Hz), 5.20-5.09 (2H, m), 2.29 (2H, d, \(J\) = 7.5 Hz), 1.84-1.56 (5H, m), 1.44-1.33 (2H, m), 1.16-0.99 (3H, m), 0.86 (9H, s); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 133.7, 118.8, 71.7, 47.4, 40.9, 38.5, 32.2, 27.6, 24.2.

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2-(tert-Butyldiphenylsilyloxy)-3-methylhex-5-en-3-ol (2.093). The dr was determined to be 78:22 by analysis of the crude $^1$H NMR, using the signals of the most upfield methyl groups. 2.093 was isolated after flash chromatography (5% v/v ethyl acetate in hexanes) as a clear, colourless oil (125 mg, 68%); $R_f = 0.29$ (5% v/v EtOAc in hexanes); $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.82-7.75 (4H, m), 7.50-7.40 (6H, m), 6.03-5.91 (1H, m), 5.18-5.11 (2H, m), 3.80 (1H, q, $J = 6.5$ Hz), 2.53 (1H, dd, $J = 14.0$, 6.5 Hz), 2.38 (1H, br s), 2.25 (1H, dd, $J = 14.0$, 8.0 Hz), 1.18 (3H, s), 1.14 (9H, s), 1.06 (3H, d, $J = 6.5$ Hz); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 135.9, 135.8, 134.2, 134.2, 133.2, 129.7, 129.5, 127.6, 127.4, 117.9, 76.3, 74.4, 41.5, 27.0, 22.9, 19.3, 17.9; IR (film) $\nu_{max}$ 3569, 3472, 3134, 3072, 3049, 2961, 2892, 2857, 1960, 1891, 1826, 1639, 1589, 172, 1427, 1378, 1111, 975, 821, 740, 702, 611 cm$^{-1}$; MS (EI) $m/z$ 313 (5), 312 (19), 311 (58), 283 (10), 249 (12), 200 (26), 199 (100), 197 (16), 181 (15), 139 (18), 135 (23); HRMS (EI) $m/z$ calcd. for C$_{23}$H$_{31}$OSi [M-OH]$^+$ 351.2144, found 351.2145.

The crude diastereomeric ratios for the compounds 2.095 to 2.100 were determined using following GC analysis method:

Column: Polyethylene glycol HP INNOwax Agilant 19091N-136 column was used. Initial temperature was 140 °C with increasing rate 20 °C/ min to reach the final temperature 220 °C and it was hold at this temperature for 5 min. Detector air flow was 400 mL/ min. Helium flow was 0.5 mL/ min and the pressure was 16.29 psi. Hydrogen flow was 30.0 mL/min.

(2S*,3R*)-2-(Benzyloxy)-3-methylhex-5-en-3-ol (2.095). Isolated after flash chromatography (5% v/v ethyl acetate in hexanes) as a clear, colourless oil (103 mg, 94%); crude dr = 20:80 using the aforementioned GC method. $^1$H NMR (CDCl$_3$, 400 MHz, major diastereomer) $\delta$ 7.25-7.36 (5H, m), 5.83-5.94 (1H, m), 5.03-5.11 (2H, m), 4.65 (1H, d, $J = 11.5$ Hz), 4.43 (1H, d, $J = 11.5$ Hz), 3.40 (1H, q, $J = 6.5$ Hz), 2.40 (1H, dd, $J = 14.0$, 6.5 Hz), 2.30 (1H, s), 2.16 (1H, dd, $J = 14.0$, 8.0 Hz), 1.20 (3H, d, $J = 6.5$ Hz), 1.15 (3H, s); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ = 138.8, 134.4, 128.6, 127.9, 118.3, 81.4, 80.2, 74.3, 71.6, 43.6, 41.9, 23.4, 13.8.
1-Allyl-2-methoxycyclohexanol (2.097 and 2.098). The crude dr was determined to be 2.097: 2.098 [36:64] using the aforementioned GC method. 2.097 was isolated after flash chromatography (5% v/v ethyl acetate in hexanes) as a clear, colourless oil (20 mg, 24%); (1S*,2S*)-1-Allyl-2-methoxycyclohexanol (2.097).\(^{82}\) \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 5.90 (1H, m), 5.04-5.09 (2H, m), 3.36 (3H, s), 3.01 (1H, dd, \(J = 8.5, 4.0\) Hz), 2.26-2.38 (3H, m), 1.15-1.80 (8H, m); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 134.4, 117.9, 82.1, 73.2, 56.8, 43.6, 34.5, 25.4, 22.9, 21.6.

(1R*,2S*)-1-Allyl-2-methoxycyclohexanol (2.098).\(^{82}\) Isolated as clear, colourless oil (57 mg, 67%) \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 5.90 (1H, dddd, \(J = 17.0, 10.5, 8.0, 6.5\) Hz), 5.09-5.16 (2H, m), 3.36 (3H, s), 3.08 (1H, dd, \(J = 8.5, 3.5\) Hz), 2.40 (1H, dd, \(J = 14.5, 7.0\) Hz), 2.25 (1H, dd, \(J = 14.0, 8.0\) Hz), 2.01 (1H, s), 1.84-1.91 (1H, m), 1.72-1.77 (1H, m), 1.25-1.60 (6H, m); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 134.0, 118.7, 84.7, 73.7, 57.2, 39.3, 34.2, 25.6, 22.5, 22.0.

1-Allyl-2-(benzyloxy)cyclohexanol (2.099 and 2.100). The crude dr was determined to be 2.099: 2.100 [28:72] using the aforementioned GC method. 2.099 was isolated after flash chromatography (5% v/v ethyl acetate in hexanes) as a clear, colourless oil (113 mg, 92%). The structures were further elucidated by presence/absence of strong correlations in ROESY spectroscopy between the allylic hydrogen and the \(\alpha\)-benzyloxy hydrogen shown in red. (1S*,2S*)-1-Allyl-2-(benzyloxy)cyclohexanol (2.099). Isolated as a clear, colourless oil (27 mg, 22%). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 7.27-7.37 (5H, m), 5.85 (1H, dddd, \(J = 17.0, 10.5, 8.0, 7.0\) Hz), 5.01-5.09 (2H, m), 4.66 (1H, d, \(J = 11.5\) Hz), 4.43 (1H, d, \(J = 11.5\) Hz), 3.25 (1H, dd, \(J = 9.0, 4.0\) Hz), 2.38 (1H, dd, \(J = 14.0, 7.0\) Hz), 2.32 (1H, dd, \(J = 14.0, 8.0\) Hz), 2.28 (1H, s), 1.80-1.85 (1H, m), 1.65-1.84 (3H, m), 1.50-1.59 (1H, m), 1.17-1.42 (3H, m); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) = 138.8, 134.5, 128.6, 128.0, 117.9, 80.4, 73.3, 70.9, 43.9, 34.5, 26.2, 23.2, 21.5 (one carbon signal is missing).

(1R*,2S*)-1-Allyl-2-(benzyloxy)cyclohexanol (2.100). Isolated as clear, colourless oil (86 mg, 70%); ¹H NMR (CDCl₃, 400 MHz) δ = 7.27-7.35 (5H, m), 5.90 (1H, dddd, J = 17.0, 10.5, 8.0, 6.5 Hz), 5.08-5.15 (2H, m), 4.65 (1H, d, J = 11.5 Hz), 4.44 (1H, d, J = 11.5 Hz), 3.32 (1H, dd, J = 7.5, 3.0 Hz), 2.48 (1H, dd, J = 14.0, 6.5 Hz), 2.30 (1H, dd, J = 14.0, 8.0 Hz), 1.94 (1H, s), 1.85-1.91 (1H, m), 1.76-1.81 (1H, m), 1.27-1.68 (6H, m); ¹³C NMR (CDCl₃, 100 MHz) δ = 139.2, 134.1, 128.6, 127.7, 127.67, 118.8, 82.1, 73.7, 71.2, 40.0, 34.1, 26.2, 22.4, 21.9 (one carbon signal is missing).

(2S*,3S*)-3-Methyl-2-phenylpent-4-en-2-ol (2.120). Isolated as a clear, colourless oil (83 mg, 94%); The dr was determined to be 95:5 by analysis of the crude ¹H NMR, using the signals of the 3-methyl group; Rᵢ = 0.62 (20 % v/v EtOAc in hexanes); ¹H NMR (CDCl₃, 400 MHz) δ 7.43 (2H, d, J = 8.5 Hz), 7.34 (2H, t, J = 7.5 Hz), 7.24 (1H, t, J = 7.5 Hz), 5.80 (1H, ddd, J = 18.0, 10.5, 7.5 Hz), 5.15-5.07 (2H, m), 2.54 (1H, dq, J = 7.5, 7.0 Hz), 1.97 (1H, br s), 1.53 (3H, s), 0.97 (3H, d, J = 7.0 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 147.3, 140.2, 128.1, 126.8, 125.7, 116.8, 75.9, 49.0, 26.1, 14.3.

(2S*,3R*)-3-Methyl-2-phenylpent-4-en-2-ol (2.121). Isolated as a clear, colourless oil (80 mg, 91%); The dr was determined to be 95:5 by analysis of the crude ¹H NMR, using the signals of the 3-methyl group; Rᵢ = 0.58 (20% v/v EtOAc in hexanes); ¹H NMR (CDCl₃, 400 MHz) δ 7.43 (2H, dd, J = 8.0, 1.5 Hz), 7.36 (2H, t, J = 7.5 Hz), 7.26 (1H, t, J = 7.5, 1.5 Hz), 5.84 (1H, ddd, J = 17.0, 11.0, 8.5 Hz), 5.16-5.09 (2H, m), 2.66 (1H, dq, J = 7.5, 7.5 Hz), 1.98 (1H, br s), 1.55 (3H, s), 0.89 (3H, d, J = 7.0 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 147.2, 140.1, 128.1, 126.7, 125.4, 116.5, 76.0, 49.2, 28.7, 15.0.
(2S*,3S*)-Ethyl 2-hydroxy-2,3-dimethylpent-4-enoate (2.122). Isolated as a clear, colourless oil (80 mg, 93%); The dr was determined to be ≥95:5 by analysis of the crude 1H NMR, using the signals of the 3-methyl group.; Rf = 0.45 (20% v/v EtOAc in hexanes); 1H NMR (CDCl3, 400 MHz) δ = 5.73 (1H, ddd, J = 17.0, 11.5, 8.5 Hz), 5.02-4.94 (2H, m), 4.18 (2H, m), 3.15 (1H, br s), 2.50-2.40 (1H, m), 1.34 (3H, s), 1.26 (3H, t, J = 7.0 Hz), 1.04 (3H, d, J = 7.0 Hz); 13C NMR (CDCl3, 100 MHz) δ = 177.1, 139.5, 116.1, 76.5, 62.0, 46.3, 23.7, 14.4, 13.7.

(2S*,3R*)-Ethyl 2-hydroxy-2,3-dimethylpent-4-enoate (2.123). Isolated as a clear, colourless oil (78 mg, 91%); The dr was determined to be ≥ 95:5 by analysis of the crude 1H NMR, using the signals of the 3-methyl group.; Rf = 0.41 (20% v/v EtOAc in hexanes); 1H NMR (CDCl3, 400 MHz) δ = 5.76 (dd, J = 17.0, 11.0, 9.0 Hz, 1H), 5.12-5.05 (m, 2H), 4.24 (m, 2H), 3.16 (br s, 1H), 2.49-2.40 (m, 1H), 1.33 (s, 3H), 1.30 (t, J = 7.0 Hz, 3H), 0.94 (d, J = 7.0 Hz, 3H); 13C NMR (CDCl3, 100 MHz) δ = 177.0, 138.5, 116.7, 76.0, 61.8, 46.2, 24.2, 15.2, 14.2.

3,4-Dimethylnon-1-en-4-ol (2.124 and 2.125). Isolated as a clear, colourless oil (81 mg, 95%); The dr was determined to be 53:47 by analysis of the crude 1H NMR, using the signals of the 4-methyl group.; Rf = 0.49 (15% v/v EtOAc in hexanes); Major (2.124, A), Minor (2.125, B), 1H NMR (CDCl3, 400 MHz) δ 5.89-5.75 (1H+1H, m, A+B), 5.12-5.04 (2H+2H, m, A+B), 2.26 (2H+2H, m), 1.48-1.24 (8H+8H, m, A+B), 1.11 (3H, s, B), 1.09 (3H, s, A), 1.03 (3H, d, J = 7.0 Hz, B), 1.00 (3H, d, J = 7.0 Hz, A), 0.89 (3H+3H, t, J = 7.0 Hz, A+B); 13C NMR (CDCl3, 100 MHz) δ 140.8 (B), 140.6 (A), 116.4 (A), 115.9 (B), 74.0 (B), 73.9 (A), 48.0 (B), 47.4 (A), 40.2 (A), 39.7 (B), 32.7 (B), 32.6 (A), 24.3 (B), 23.8 (A), 23.2 (B), 23.1 (A), 22.9 (A), 15.1 (B), 14.7 (B), 14.3 (A), 14.2 (B). (A/B 13C

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signals distinguished based on the relative intensity of the major $^{13}$C/ minor $^{13}$C peaks and comparison to the product obtained from the (E)-crotyltrifluoroborate which gave a 62:38 ratio of 2.124:2.125).

**General Procedure for Addition of Potassium Trifluoroborate salts 2.046 or 2.049 or 2.050 to Aldehydes under Montmorillonite K10 Conditions**

To aldehyde (0.50 mmol), potassium allyl or crotyltrifluoroborate salts 2.046 or 2.049 or 2.050 (0.60 mmol) and montmorillonite K10 (0.1 g) in a 5 mL round bottom flask was added CH$_2$Cl$_2$ (1.4 mL) and water (0.1 mL). The biphasic reaction mixture was vigorously stirred at rt for 10 min, at which point reaction conversion was complete as monitored by TLC analysis. The reaction mixture was then filtered and washed with CH$_2$Cl$_2$ (3 x 5 mL). The filtrate was concentrated *in vacuo* and the concentrated organic mixture was passed through a short plug of silica gel using EtOAc/Hexane as the eluent. The resulting eluate was concentrated *in vacuo* to afford the product alcohol.

1-(4-Nitrophenyl)but-3-en-1-ol (2.126).$^{84}$ Isolated as a pale yellow oil (91 mg, 95%); $^1$H NMR (CDCl$_3$, 400 MHz) δ 8.20 (2H, d, $J = 8.5$ Hz), 7.54 (2H, d, $J = 8.5$ Hz), 5.78 (1H, dddd, $J = 16.5, 11.5, 7.5, 6.5$ Hz), 5.20-5.14 (2H, m), 4.85 (1H, dd, $J = 7.5, 5.0$ Hz), 2.41 (1H, br s), 2.59-2.38 (2H, m); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 151.4, 147.4, 133.4, 126.9, 123.8, 119.8, 72.4, 44.1.

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4-(1-Hydroxybut-3-enyl)benzonitrile (2.127). Isolated as a clear, colourless oil (83 mg, 96%); $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.63 (2H, d, $J$ = 8.0 Hz), 7.46 (2H, d, $J$ = 8.0 Hz), 5.77 (1H, dddd, $J$ = 16.5, 10.5, 7.5, 6.5 Hz), 5.18-5.13 (2H, m), 4.78 (1H, dd, $J$ = 7.5, 5.0 Hz), 2.43 (1H, br s), 2.52-2.36 (2H, m); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 149.4, 133.6, 132.4, 126.7, 119.6, 119.1, 111.3, 72.6, 44.0.

1-(4-Methoxyphenyl)but-3-en-1-ol (2.128). Isolated as a clear, colourless oil (86 mg, 97%); $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.27 (2H, d, $J$ = 8.5 Hz), 6.87 (2H, d, $J$ = 8.5 Hz), 5.77 (1H, dddd, $J$ = 18.0, 10.0, 7.0, 6.5 Hz), 5.16-5.09 (2H, m), 4.67 (1H, t, $J$ = 6.5 Hz), 3.79 (3H, s), 2.48 (2H, t, $J$ = 7.0 Hz), 2.24 (1H, br s); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 159.2, 136.3, 134.9, 127.3, 118.3, 114.0, 73.2, 55.5, 43.9.

(E)-1-Phenylhexa-1,5-dien-3-ol (2.130). Isolated as a clear, colorless oil (85 mg, 97%); $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.41-7.36 (2H, m), 7.31 (2H, t, $J$ = 7.5 Hz), 7.27-7.21 (1H, m), 6.60 (1H, d, $J$ = 16.0 Hz), 6.24 (1H, dd, $J$ = 16.0, 6.5 Hz), 5.93-5.80 (1H, m), 5.23-5.16 (2H, m), 4.35 (1H, q, $J$ = 6.5 Hz), 2.48-2.34 (2H, m), 2.03 (1H, br s); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 136.6, 134.0, 131.5, 130.2, 128.49, 127.6, 126.4, 118.4, 71.6, 41.9.

1-Cyclohexylbut-3-en-1-ol (2.131). Isolated as a clear, colorless oil (75 mg, 97%); $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 5.88-5.76 (1H, m), 5.15-5.07 (2H, m), 3.37 (1H, ddd, $J$ = 9.0, 6.0, 3.5 Hz), 2.36-2.26 (1H, m), 2.16-2.00 (2H, m), 1.88-1.60 (5H, m), 1.40-0.95 (6H, m); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 135.7, 118.1, 75.0, 43.3, 39.0, 29.3, 28.3, 26.7, 26.5, 26.3.

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(1S*,2S*)-2-Methyl-1-phenylbut-3-en-1-ol (2.132). Isolated as a clear, colourless oil (81 mg, 100%); The dr was determined to be ≥ 98:2 by analysis of the crude $^1$H NMR, using the signals of the 2-methyl group.; $^1$H NMR (CDCl$_3$, 400 MHz) δ 7.35-7.24 (5H, m), 5.81 (1H, ddd, $J$ = 17.0, 10.5, 8.0 Hz), 5.21-5.12 (2H, m), 4.34 (1H, dd, $J$ = 8.0, 3.0 Hz), 2.48 (1H, ddq, $J$ = 8.0, 7.0, 7.0 Hz), 2.19 (1H, br s), 0.87 (3H, d, $J$ = 7.0 Hz); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 142.7, 140.9, 128.4, 127.8, 127.1, 117.0, 78.1, 46.5, 16.7.

(1S*,2S*)-1-(4-Methoxyphenyl)-2-methylbut-3-en-1-ol (2.133). Isolated as a clear, colourless oil (95 mg, 99%); The dr was determined to be ≥ 98:2 by analysis of the crude $^1$H NMR, using the signals of the 2-methyl group.; $^1$H NMR (CDCl$_3$, 400 MHz) δ 7.25 (2H, d, $J$ = 9.0 Hz), 6.88 (2H, d, $J$ = 9.0 Hz), 5.81 (1H, ddd, $J$ = 17.5, 10.0, 8.0 Hz), 5.21-5.14 (2H, m), 4.28 (1H, d, $J$ = 8.0 Hz), 3.79 (3H, s), 2.58-2.50 (1H, m), 2.18 (1H, d, $J$ = 3.0 Hz), 0.83 (3H, d, $J$ = 7.0 Hz); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 159.3, 141.2, 134.8, 128.2, 116.8, 113.9, 77.0, 55.5, 46.6, 16.8.

(3S*,4S*)-4-Methyl-1-phenylhexa-1,5-dien-3-ol (2.136). Isolated as a clear, colorless oil (93.2 mg, 99%); The dr was determined to be ≥ 98:2 by analysis of the crude $^1$H NMR, using the signals of the 4-methyl group.; $^1$H NMR (CDCl$_3$, 400 MHz) δ 7.21-7.39 (5H, m), 6.56 (1H, d, $J$ = 16.0 Hz), 6.20 (1H, dd, $J$ = 16.0, 7.0 Hz), 5.81 (1H, ddd, $J$ = 17.0, 10.5, 8.0 Hz), 5.14-5.19 (2H, m), 4.05 (1H, dd, $J$ = 7.0, 7.0 Hz), 2.32-2.40 (1H, m), 1.93 (1H, br s), 1.05 (3H, d, $J$ = 7.0 Hz); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 140.4, 137.0, 131.9, 130.5, 128.8, 127.9, 126.7, 116.9, 76.4, 44.9, 15.3.

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\((3S^*,4R^*)\)-4-Methyl-1-phenylhexa-1,5-dien-3-ol (2.138).\textsuperscript{86} Isolated as a clear, colorless oil (93 mg, 98%); crude dr \( \geq 98:2 \). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta = 7.20 - 7.38 \) (5H, m), 6.59 (1H, d, \( J = 16.0 \) Hz), 6.20 (1H, dd, \( J = 16.0, 6.5 \) Hz), 5.82 (1H, ddd, \( J = 17.0, 10.5, 7.5 \) Hz), 5.10 - 5.15 (2H, m), 4.05 (1H, dd, \( J = 6.5, 6.5 \) Hz), 2.42 - 2.50 (1H, m), 1.88 (1H, br s), 1.08 (3H, d, \( J = 7.0 \) Hz); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \( \delta = 140.2, 137.0, 131.4, 130.2, 128.8, 127.8, 126.7, 116.2, 76.0, 44.1, 15.1.\n
\((1S^*,2R^*)\)-1-(4-Methoxyphenyl)-2-methylbut-3-en-1-ol (2.139).\textsuperscript{88} Isolated as a clear, colourless oil (92 mg, 96%); The dr was determined to be \( \geq 98:2 \) by analysis of the crude \(^1\)H NMR, using the signals of the 2-methyl group.; \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta = 7.21 \) (2H, d, \( J = 8.5 \) Hz), 6.86 (2H, d, \( J = 8.5 \) Hz), 5.80 (1H, ddd, \( J = 17.5, 10.0, 7.0 \) Hz), 5.21-5.20 (1H, m), 5.17-5.14 (1H, m), 4.28 (1H, dd, \( J = 6.0, 3.0 \) Hz), 3.79 (3H, s), 2.45 (1H, ddq, \( J = 8.0, 7.0, 7.0 \) Hz), 1.98 (1H, d, \( J = 3.0 \) Hz), 1.02 (3H, d, \( J = 7.0 \) Hz); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \( \delta = 159.1, 140.6, 135.0, 127.9, 115.6, 113.6, 76.9, 55.4, 44.8, 14.6.\n
\((1S^*,2S^*)\)-1-(Benzo[d][1,3]dioxol-5-yl)-2-methylbut-3-en-1-ol (2.141). In a 100-mL round-bottomed flask equipped with magnetic stir bar, piperonal (3.75 g, 25.0 mmol) dissolved in CH\(_2\)Cl\(_2\) (37.5 mL). (E)-potassium crotyltrifluoroborate salt (4.86 g, 30.0 mmol), K-10 (2.5 g) and H\(_2\)O (2.5 mL) were added. The biphasic reaction mixture was vigorously stirred at rt for 15 min at which point the reaction mixture became clear as a sign of complete conversion as monitored by TLC analysis. The reaction mixture was then filtered though fritted funnel silica gel (10.0 g) pad and washed with CH\(_2\)Cl\(_2\) (4 \( \times \) 25 mL). The solvent was concentrated in vacuo (40 °C, water bath temp., 400 mmHg) and dried under vacuum (0.5 mmHg, 25 °C) overnight to afford 5.21 g 2.141 as a clear colorless oil. The crude diastereomeric ratio was determined to be 90:1(anti:syn)
using the following quantitative $^1$H NMR technique.$^{89}$ The quantitative $^1$H NMR was acquired using 90° pulse tip angles, recovery delay 25 s, acquisition time of 5.112 s, spectral width 6410.3 Hz and processed without apodization functions. Comparison of integrations of $^{13}$C-$^1$H satellite peak of major diastereomer to the $^{12}$C-$^1$H peak of minor diastereomer gave the diastereomeric ratio 90:1. The organic mixture was further purified using silica gel (127.0 g slurred using 20 % v/v ethyl acetate in hexane). The crude oil transferred directly to the column and the flask rinsed with (3× 2mL) and internal layer of the column washed with (3×2mL). The column was flushed with 20 % v/v ethyl acetate in Hexane and the fraction collected in 13 mL test tubes. The resulting fractions (tubes 49-90) were concentrated in vacuo and dried under vacuum (0.5 mmHg, 25 °C) overnight to afford clear colorless solid (4.84 g, 94% yield).; M.p. = 32-34 °C; $R_f = 0.61$ (20% v/v ethyl acetate in hexanes); IR (neat) $\nu_{\text{max}}$ 3325, 2980, 2906, 1643, 1503, 1485, 1437, 1373, 1246, 1227, 1193, 1094, 1035, 991, 932, 920, 877, 802, 679 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 6.86 (1H, s), 6.76 (2H, d, $J = 1.0$ Hz), 5.95 (2H, s), 5.80 (1H, ddd, $J = 17.0, 10.5, 8.0$ Hz), 5.20-5.23 (2H, m), 4.25 (1H, dd, $J = 8.0, 2.5$ Hz), 2.42 (1H, ddq, $J = 8.0, 7.5, 7.0$ Hz), 2.15 (1H, s), 0.85 (3H, d, $J = 6.5$ Hz); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 147.9, 147.3, 141.0, 136.6, 120.7, 117.1, 108.1, 101.2, 77.9, 46.7, 16.8; LRMS (EI) $m/z$ 206.1 (4.7), 188.1 (94.2), 173.1 (62.1), 158.1 (13.3, 151.0 (100.0), 143.0 (12.2), 130.1 (19.0), 129.1 (27.2), 123.0 (12.5), 115.1 (32.6), 93.0 (23.8); HRMS (EI) $m/z$ calc’d. for C$_{12}$H$_{14}$O$_3$ [M]$^+$ 206.0943, found 206.0949.

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4,4,5,5-Tetramethyl-2-vinyl-1,3,2-dioxaborolane (2.148).\(^{90}\)

\[ \text{MgBr} \xrightarrow{i) \text{B(OME)}_3, \text{THF }, -78 \, ^\circ\text{C}} \text{2.146} \rightarrow \xrightarrow{\text{ii) HCl (5.0N)}} \text{2.147} \xrightarrow{\text{Pinacol, 4Å MS, EtO}} \text{2.148} \]

To a 100 ml flame-dried, round-bottomed flask under positive argon pressure, trimethyl borate (3.4 mL, 30.0 mmol) and diethyl ether (20.0 mL) were added via syringe. The flask was placed in a dry ice/acetone bath to reach the internal temperature of -78 °C (controlled using Fischer scientific K-type probe), and vinylmagnesium (68 mL, 0.5 M in THF, 34 mmol) was added drop wise using a syringe pump over 15 min. The reaction was allowed to stir for 1 h at -78 °C, at which point the reaction was warmed up to -40 °C using an acetonitrile/dry ice bath and quenched with 5N aqueous HCl (6mL). After being stirred for 10 min, the solution was poured into separation funnel and extracted with diethyl ether (3×60 mL). The organic layers were combined and dried with sodium sulfate, and the solution was concentrated in vacuo to a volume of about 20 mL. It is important to control the concentration since at high concentration the acid 2.147 is prone to proto-deboration or polymerization. The solution was transferred to a flask containing diethyl ether (30 mL), activated 4 Å molecular sieves (4.0 g) and pinacol (4.0 g, 34.0 mmol). The heterogeneous mixture was stirred at room temperature for 10 h and was filtered to separate the solids and the solvents distilled at atmospheric pressure at 40 °C since 2.148 is very volatile. The crude product was further purified using silica gel column chromatography (9:1 v/v pentane/diethyl ether). \(^1\)HNMR (CDCl\(_3\), 400 MHz) \(\delta\) 5.81-5.89 (1H, m), 4.94-5.02 (2H, m), 1.25 (12H, s). \(^{11}\)B NMR (CDCl\(_3\), 128 MHz) \(\delta\) 32.94.

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Potassium α,α-bis(deutero) allyltrifluoroborate (2.150).\textsuperscript{91}

\[
\begin{align*}
\text{B} & \quad \text{O} \quad \text{O} \quad \text{B} \\
\text{O} & \quad \text{B} \quad \text{F}_3 \quad \text{K} \\
\end{align*}
\]

To a 50 mL flame-dried, round-bottomed flask under positive argon pressure, 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (1.348 g, 8.74 mmol), CD\textsubscript{2}I\textsubscript{2} (0.71 mL, 8.74 mmol) and diethyl ether (25.0 mL) were added via syringe. The flask was placed in a dry ice/acetone bath to reach the internal temperature -78 °C (controlled using Fischer scientific K-type probe), and n-butyl lithium (4.2 mL, 2.08 M in THF, 8.74 mmol) was added drop wise using a syringe pump over 15 min. The reaction was then allowed to stir for 1.5 h at -78 °C and the reaction was slowly warmed up to room temperature. After stirring for 12 h before, the reaction mixture was filtered through a medium porosity fritted funnel to separate the solids. The ether was evaporated at 40 °C at atmospheric pressure. The clear colourless volatile mixture was further purified by silica gel column chromatography (1:1 v/v pentane/CH\textsubscript{2}Cl\textsubscript{2}). The solvent was concentrated and evaporated using a freeze drying technique and the ratio of the desired product versus unreacted vinyl boronate was determined to be (82:18) using \textsuperscript{1}H NMR and \textsuperscript{11}B NMR. The product mixture was diluted with diethyl ether (5.0 mL) and treated with aqueous KHF\textsubscript{2} (2.0 g, 26.2 mmol in 2.0 mL H\textsubscript{2}O) and stirred for 1 h. The solvents were evaporated at room temperature and the solids were dried under vacuum over 12 h. The solid mixture was dissolved in hot dry acetonitrile (50 mL) and filtered through a fritted funnel. The acetonitrile was evaporated and the white solid was washed with cold ether to afford 2.149 and 2.150 (0.708 g, 54% yield) as an inseparable mixture of 82:18 ratio; \textsuperscript{1}H NMR (CD\textsubscript{3}CN, 400 MHz) δ 5.81-5.89 (1H, m), 4.94-5.02 (2H, m); \textsuperscript{11}B NMR (CD\textsubscript{3}CN, 128 MHz) δ 4.0 (q, \textit{J}_{B-F} = 61.0 Hz); \textsuperscript{19}F NMR (CD\textsubscript{3}CN, 128 MHz) δ -140.50 (q, \textit{J}_{F-B} = 60.0 Hz).

5,5-Dideutero-2(4'-bromophenyl)-4-penten-2-ol (2.152). Isolated as a clear, colorless oil: Rf = 0.35 (60% v/v ethyl acetate in hexanes); 1H NMR (CDCl3, 400 MHz) δ 7.46 (2H, d, J = 9.0 Hz), 7.30 (2H, d, J = 9.0 Hz), 5.60 (1H, m), 2.63 (1H, dd, J = 14.0, 6.5 Hz), 2.46 (1H, dd, J = 14.0, 8.5 Hz), 2.03(1H, s), 1.52 (3H, s); 13C NMR (CDCl3, 100 MHz) δ 146.7, 133.9, 131.2, 126.7, 120.6, 73.4, 48.2, 29.9 (one carbon peak missing); IR (neat) νmax 3433 (br), 2978, 2932, 2361, 1906, 1597, 1451, 1273, 1234, 1011, 910, 733 cm⁻¹; LRMS (EI) m/z 201.0 (94.6), 199.0 (100.0), 182.9 (16.2), 145.1 (59.1), 130.1 (55.2), 129.1 (20.2), 102.0 (15.2), 77.0 (10.0), 43.0 (13.0); HRMS (ESI) m/z calc’d. for C_{11}H_{9}^{79}BrD_{2} [M-H_{2}O]^+ 224.0170, found 224.0174.
Chapter 3
Indium-Promoted Chemo- and Diastereoselective Allylation of Ketones and $\alpha,\beta$-Epoxyketones

3 Introduction

Indium metal has been known since 1863, however its utility in organic synthesis was initiated only three decades ago when Butsugan reported the application of indium in Reformatsky reactions. Diphenyl indium chloride was the first synthesized organoindium compound that was used as a nucleophile in addition reactions to carbonyl groups and Michael acceptors. Most of the early investigations on indium were largely limited to the use of activated indium in Reformatsky-type transformations.

3.1 Indium in Organic Chemistry

Arguably the breakthrough application for the utility of indium in organic synthesis occured in 1988, when Araki and Butsugan recognized that inactivated indium powder can be used for the preparation of organoindium reagents from alkyl bromide and iodides. Another important step in the development of organoindium chemistry was reported by Chan and Li, in their application of the effectiveness of nucleophilic addition of organoindium reagents to carbonyl compounds in aqueous media. These discoveries opened a new area in organoindium chemistry.

3.1.1 Indium Mediated Barbier-Type Reactions

The Barbier reaction involves nucleophilic addition of organometalloids to carbonyl functionalities, which are typically generated in situ. These reactions often take place in an aqueous medium or have water as a co-solvent. In contrast to organolithium or Grignard reagents, the addition of organometalloids under Barbier reaction conditions provides several

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advantages over conventional methods. They avoid the requirement of an inert atmosphere for the transformations and often avoid the protection of functional groups such as hydroxyl and amine groups. Moreover, the transformations in aqueous media can be applied for substrates with low solubility in organic solvents such as carbohydrates or peptides. The first indium-mediated Barber reaction was reported by Chan in 1991 and since then a widespread application of this method has been seen. The Barbier reaction using other metals or metalloids such as Zn, Sn, Bi and Sm was known at the time of this report; however, the unique properties of indium metal made it the most efficient metal for this transformation. Commercially available indium is not cheap with a cost comparable to that of silver. A characteristic property of indium is the low ionization potential that is directly proportional to its ability to release a valence electron. In fact, indium has a lower ionization potential (5.79 eV), than that of magnesium (7.65 eV) while benefitting from higher stability towards oxygen and aqueous media. Indium has been reported for allylation and propargylation under various Barbier-type reaction conditions, and recently an asymmetric variant of the indium-mediated allylation has been reported.

3.1.2 Mechanism of Indium Mediated transformations

The current mechanistic understanding for the indium-mediated Barbier transformation is far from satisfactory. In order to elucidate the precise nature of the organoindium species, a combination of factors such solvents, substrates and allyl halides must be considered. In the case of indium-mediated allylation, it was believed that the reaction occurred at the surface of the metal through a single electron transfer (SET)-type mechanism involving transfer of an electron from the metal to the allyl halide to generate an active radical anion. This postulate was challenged based on the experimental observation of Whitesides and co-workers who reported that in situ generation of allylindium from allylmagnesium bromide and indium trichloride gave

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11 The Aldrich price for 10.0 g of indium or silver with 99.9% purity is $65.5 (2011 catalog price).
similar results to the use of indium metal with allyl bromide in the allylation of carbohydrates. In 1999 Chan and Yang reported an extensive $^1$H NMR study on the nature of allylindium intermediates in different solvents. This study established that (at least in the case of allylindium in D$_2$O) allyl bromide reacts rapidly to form the allylindium(I) instead of the more stable allylindium(III) species. The formation of indium(I) intermediates over the indium(III) intermediates was attributed to the substantially lower first ionization potential relative to the second and third ionization potentials for indium. This observation was strictly dependent on the solvent, as performing the reaction in THF or DMF resulted in the formation of a mixture of indium(I) and indium(III) intermediates. The authors were unable to rule out the possibility of the parallel process occurring at the surface of the metal to generate a radical anion. Paquette and co-workers reported the addition of allylindium reagents to various $\alpha$-heteroatom substituted carbonyl compounds. Based on the observed results, the authors rationalized that allylindium(III) or a radical anion was the actual intermediate for the indium mediated allylation reaction. Koszinowski utilized a combination of $^1$H NMR spectroscopy, electrospray–ionization (ESI) mass spectrometry and electrical conductivity measurements to probe the allylindium species formed using indium metal and allyl bromide in various solvents. It is believed that indium(I) and indium(III) intermediates are in equilibrium, depending on the nature of the applied solvents, and a variety of allylindium(III) species that had coordinated solvent were identified.

3.1.3 Regio- and Stereoselectivity of Indium Mediated Allylation Reactions

It is known that the transfer of an allyl group from an allyl metal species can occur either via the $\alpha$– or $\gamma$–positions of the allyl fragment, and in most scenarios the C–C bond formation occurs at the most substituted carbon of the alkyl halides. The regiocontrol of the addition is primarily governed by steric effects causing nucleophilic attack to occur via the less hindered side of the allyl moiety. The relative configuration of the addition products can be modified significantly by the appropriate choice of solvent. It is believed that the addition of allylindium reagents to

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carbonyl compounds occur via an open transition state affording predominantly products with syn relative configuration. However, bulky substituents at the γ-position of the reagent can alter the stereoselectivity to predominantly give the anti product in certain cases. Reliable syn selectivity can be achieved through a strong chelating group on substrate, and this approach has been used widely in numerous total syntheses.

3.2 Applications in Total Synthesis

Indium-mediated allylation of carbonyl compounds has been extensively used for C–C bond formation in organic synthesis. Some representative examples are shown below to demonstrate the usefulness of this method. Chan and Li reported the synthesis of sialic acid KDN in which they applied an indium-mediated allyl nucleophile addition to an aldehyde derived from D-(+)-mannose to afford the syn homoallylic alcohol 3.003 (Scheme 3.1). The polyol 3.003 was then further elaborated to synthesize the target KDN. It is interesting to note that the applied reaction conditions avoided the requirement of tedious protection and subsequent deprotection of the hydroxyl groups, permitting the product to be isolated via simple recrystallization. The observed high diastereoselectivity can be rationalized by a Cram-chelation model.

![Scheme 3.1 Chan’s Total Synthesis of Sialic Acid KDN](image)

Li and co-workers applied an indium-mediated diastereoselective allenylation as a key step in their total synthesis of (+)-Goniofurfurone. It is known that allenyl metaloids are in equilibrium

with the respective propargyl metalloids; in aqueous media both exhibit similar reactivity towards nucleophilic additions. Surprisingly, under the reaction conditions predominantly the desired allenylation products with high diastereoselectivity were observed (Scheme 3.2). The regioselectivity was rationalized based on the steric and electronic effects and the high observed stereoselectivity was attributed to chelation control.

Scheme 3.2 Li’s Total Synthesis of (+)-Goniofufurone

Madsen and co-workers reported a concise synthesis of (+)-cyclophellitol using an indium-mediated crotylation.21 The aldehyde 3.010 was synthesized over two steps from d-xylose and subjected to the indium-mediated allylation in the presence of lanthanum triflate to form the desired homoallylic alcohol 3.012 as a single diastereomer (Scheme 3.3).

Scheme 3.3 Madsen’s Total Synthesis of (+)-Cyclophellitol

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Loh and co-workers reported the synthesis of a key intermediate 3.016 using an indium-mediated allylation of an aldehyde with a primary allyl bromide (Scheme 3.4).\textsuperscript{22} The homoallyl alcohol 3.016 was further elaborated in the total synthesis of antillatoxin and its derivatives. It is noteworthy to mention that the practical aspect of indium mediated allylation reaction provided an easy access to a variety of antillatoxin analogs.

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {3.014};
\node (b) at (2,0) {3.015};
\node (c) at (4,0) {3.016};
\node (d) at (6,0) {\text{syn : anti (93:7)}};
\node (e) at (1,0) {$\text{MeO}_2\text{C}$};
\node (f) at (2,0) {$\text{Br}$};
\node (g) at (3,0) {$\text{In} \cdot \text{NH}_4\text{Cl} \cdot \text{sat. aq.}$};
\node (h) at (0,-2) {\text{(4S,5S)-Antillatoxin 3.017}};
\node (i) at (0,-4) {\text{Scheme 3.4 Loh’s Total Synthesis of Antillatoxin}};
\node (j) at (-3,-4) {\text{3.3 Indium to Boron Transmetalation}};
\end{tikzpicture}
\end{center}

Organoindium reagents have been successfully applied for a variety of traditional cross-coupling reactions with transition metals.\textsuperscript{23} However, transmetalation of organoindium to another group 13 element was unknown until 2007 when Kobayashi and Schneider reported the transmetalation

\begin{thebibliography}{9}
\end{thebibliography}
of allylboronic acid pinacol ester to indium(I) iodide and subsequent addition to various ketones (Scheme 3.5). A strictly inert atmosphere was required for this transformation since the indium(I) is highly prone to disproportionate to the more stable indium(0) and indium(III) species. The reported method failed to give the desired product using crotlylboronic acid pinacol ester or potassium allyltrifluoroborate. The mechanism of this transmetalation was merely speculated upon at the time of report.

\[
\begin{align*}
\text{R} & \quad \text{Me}^+ \\
\text{(1.5 equiv.)} & \quad \text{B(pin)} \\
\text{InI (5.0 mol %)} & \quad \text{THF, 40}^\circ\text{C, 24h}
\end{align*}
\]

\[\text{R} = \text{Ph} \quad (88\%) \quad 3.019\]
\[2-\text{Br-C}_6\text{H}_4 \quad (97\%) \quad 3.020\]
\[4-\text{NH}_2-C_6\text{H}_4 \quad (99\%) \quad 3.021\]
\[2-\text{Naphthyl} \quad (98\%) \quad 3.022\]
\[4-\text{Pyridyl} \quad (56\%) \quad 3.021\]
\[2-\text{Furyl} \quad (92\%) \quad 3.022\]

\textbf{Scheme 3.5 Indium(I) Iodide Catalyzed Allylation of Ketones with Allylboronate}

Kobayashi and co-workers reported the use of catalytic indium(0) for the C–C bond formation reaction in aqueous media. The developed procedure has been applied for nucleophilic additions to various carbonyl and imine derivatives.

### 3.4 Results and Discussion

#### 3.4.1 Objective of This Study

Nucleophilic addition of allylboron reagents to carbonyl compounds bearing epoxide functionality has been limited to α,β-epoxyaldehydes, and additions to epoxyketones remain a

---

significant challenge.\textsuperscript{28} It was of interest to developing a robust method for the allylation of epoxyketones in aqueous media that would preclude the requirement of using an inert atmosphere or any special requirements, and that could be applied to substrates bearing potentially labile stereocenters without erosion of chirality. It was also of interested to know about the transmetallation behavior of the group 13 elements (B to In or In to B). It is noteworthy to mention that evidence for a direct transmetallation of B to In (or the reverse) was unknown in the literature at the time of this investigation.

3.4.2 Reaction Optimization

It is well established that organometalloid reagents are stable in aqueous media and various methods have been developed for Barbier-type nucleophilic addition to carbonyl compounds.\textsuperscript{29} It was of interest of developing a robust method for the allylation of ketone substrates in aqueous media. Batey and Thadani had previously reported a phase-transfer-catalyzed reaction for the allylation of aldehydes using potassium allyltrifluoroborate salts. The authors showed that the reaction likely preceded via tri-coordinated allylboron species though dissociation of KF from the allyltrifluoroborate. Unfortunately, the phase-transfer-catalyzed allylation reaction conditions that were successful for aldehydes failed to give full conversion for the allylation of 4-bromoacetophenone (a model ketone substrate). During the course of preliminary investigations pertaining to the allylaton of 4-bromoacetophenone using indium and potassium allyltrifluoroborate, it was observed that indium powder changed morphology to granules as the reaction approached completion. Interestingly, when the recovered granules were utilized as the indium source for subsequent reactions, addition was still observed, albeit at a more sluggish rate.\textsuperscript{30} The addition of KF or phase-transfer catalyst to the reaction media in the presence of indium retarded the reaction (Table 3.1, entries 4 and 5). The former observation suggests that a

\textsuperscript{30} For detailed studies see section 3.5.2.
dissociative mechanism is operative; the addition of fluoride ions suppressing the dissociation of \( 2.046 \) into a tricoordinate allylboron species and leading to a slower rate of reaction via the common ion effect.\(^{31}\) It was postulated that the reaction proceeded via the same intermediate as in the phase-transfer-catalyzed pathway and the indium surface was the \textit{in situ} activator of the potassium allyltrifluoroborate. Attempts to obtain the indium-mediated allylation in solely aqueous media failed to give satisfactory results.

Table 3.1 Optimization of the Reaction Using Potassium Allyltrifluoroborates 3.024 and 3.025

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive (equiv.)</th>
<th>Solvent (Volume, mL)</th>
<th>Yield (%)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{Bu}_4\text{Ni} (1.0) )</td>
<td>( \text{D}_2\text{O} (1.0) )</td>
<td>49</td>
</tr>
<tr>
<td>2</td>
<td>None</td>
<td>( \text{D}_2\text{O} (1.0) )</td>
<td>( \leq 2 )</td>
</tr>
<tr>
<td>3</td>
<td>In (1.0)</td>
<td>( \text{D}_2\text{O} (1.0) )</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>In (1.0)/KF (2.0)</td>
<td>( \text{D}_2\text{O} (0.1) : \text{CDCl}_3 (1.4) )</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>In (1.0)/( \text{Bu}_4\text{Ni} (1.0) )</td>
<td>( \text{D}_2\text{O} (1.0) )</td>
<td>3 (62)(^c)</td>
</tr>
<tr>
<td>6</td>
<td>In (1.0)</td>
<td>( \text{CDCl}_3 (1.0) )</td>
<td>( \leq 5 )</td>
</tr>
<tr>
<td>7</td>
<td>In (1.0)</td>
<td>( \text{D}_2\text{O} (0.1) : \text{CDCl}_3 (1.4) )</td>
<td>quant</td>
</tr>
<tr>
<td>8</td>
<td>In (0.1)</td>
<td>( \text{D}_2\text{O} (0.025) : \text{CDCl}_3 (1.5) )</td>
<td>98(^c)</td>
</tr>
<tr>
<td>9</td>
<td>Zn (1.0)</td>
<td>( \text{D}_2\text{O} (0.1) : \text{CDCl}_3 (1.4) )</td>
<td>( \leq 5 )</td>
</tr>
<tr>
<td>10</td>
<td>Sn (1.0)</td>
<td>( \text{D}_2\text{O} (0.1) : \text{CDCl}_3 (1.4) )</td>
<td>( \leq 5 )</td>
</tr>
<tr>
<td>11</td>
<td>In (1.0)</td>
<td>( \text{D}_2\text{O} (0.1) : \text{CDCl}_3 (1.4) )</td>
<td>52 (dr 98:2)(^d)</td>
</tr>
</tbody>
</table>

\(^a\) \( ^1\text{H} \) NMR yield using internal standard. \(^b\) 3.0 equivalents of allyltrifluoroborate were used. \(^c\) 36 hours was required to achieve full conversion. \(^d\) \( E \)-crotlytrifluoroborate 3.025 was used for 60 hours.

However, controlled experiments revealed that water was not only essential to achieve full conversion, but the quantity of water was crucial as well (Table 3.1, entries 6-8),\textsuperscript{32} since the reaction failed to give meaningful conversion under rigorously dry conditions (Table 3.1, entry 6). In order to achieve full conversion the amount of water was minimized through use of an organic co-solvent. A high yield of the desired homoallylic alcohol was obtained using CH$_2$Cl$_2$/H$_2$O or CHCl$_3$/H$_2$O solvent systems. Efficient addition also occurred using catalytic quantities of metallic indium, albeit with a lower reaction rate (Table 3.1, entry 8). The optimized stoichiometric indium conditions failed to give full conversion for the crotylation of 4-bromoacetophenone using potassium E-crotyltrifluoroborate (Table 3.1, entry 11).

With the optimized reaction conditions in hand the scope and limitations of this transformation were investigated using catalytic indium and a CH$_2$Cl$_2$/H$_2$O solvent system. Aromatic ketones with various functional groups were smoothly allylated under the reaction conditions. Steric or electronic effect of substitutions on the aromatic rings did not influence the outcome of the reaction and the allylated products were obtained in good to excellent yields (Table 3.2, entries 1–4). The reaction of aliphatic ketone 3.031 took place with good yield, however, the more sterically demanding pinacolone 3.032 failed to give the desired homoallylic alcohol. The allylation of substituted ketones 3.033-3.035 as well as an enone 3.036 occurred in good to excellent yields (Table 3.2, entries 7–10).

\textsuperscript{32} For the detailed experiments on the role of water: see section 3.4.1.
Table 3.2 Substrate Scope of the Indium-Catalyzed Allylation of Ketones Using 3.024

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketone</th>
<th>Product</th>
<th>Yield a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.023 (X = p-Br)</td>
<td>3.026 (X = p-Br)</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>3.028 (X = o-OMe)</td>
<td>3.037 (X = o-OMe)</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>3.029 (X = m-NH₂)</td>
<td>3.038 (X = m-NH₂)</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>3.030 (X = p-NO₂)</td>
<td>3.039 (X = p-NO₂)</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>3.031 (X = Br)</td>
<td>3.040</td>
<td>66</td>
</tr>
<tr>
<td>6</td>
<td>3.032 (X = OMe)</td>
<td>3.041</td>
<td>≤ 5b</td>
</tr>
<tr>
<td>7</td>
<td>3.033 (X = CO₂Me)</td>
<td>3.042</td>
<td>93</td>
</tr>
<tr>
<td>8</td>
<td>3.034 (X = CO₂Et)</td>
<td>3.043</td>
<td>84</td>
</tr>
<tr>
<td>9</td>
<td>3.035 (X = Et)</td>
<td>3.044</td>
<td>91</td>
</tr>
<tr>
<td>10</td>
<td>3.036 (X = Br)</td>
<td>3.045</td>
<td>95</td>
</tr>
</tbody>
</table>

a) Yield of product isolated after silica gel chromatography. b) Yield of 3.041 estimated by ¹H NMR analysis.
3.4.3 Allylation of Epoxy Ketones

The epoxyketone project was undertaken in collaboration with John Janetzko, during his second year of undergraduate study. Under my supervision he contributed experimental results and this contribution will be acknowledged as it appears throughout the remainder of this chapter. The majority of the epoxy ketone results have been published and some of the experimental data is not included in this thesis.\(^{33}\)

Although chemoselective reactions of \(\alpha,\beta\)-epoxyaldehydes have been studied using chiral allylboron reagents,\(^{34}\) additions to epoxyketones remain a significant challenge.\(^{35}\) Diastereoselective addition of allylstannanes to \(\alpha,\beta\)-epoxyketones has been achieved using boron trifluoride diethyletherate or lead(II) iodide activation. Unfortunately these methods utilize toxic tin reagents and exhibit limited substrate scope. One draw-back of these methods that struck us as interesting was that they occur with diminished yields for cyclic \(\alpha,\beta\)-epoxyketones or epoxyketones bearing a terminal epoxide. To circumvent the challenge of chemoselectivity in the preparation of epoxy homoallylic alcohols, Walsh and co-workers utilized a one-pot sequential asymmetric allylation, directed epoxidation affording \(\text{syn}\)-epoxy homoallylic alcohols. While this system works well for cyclic enones, substitution at the \(\alpha\)-carbon of the enone was necessary to obtain high selectivity.\(^{36}\)

Initial attempts to apply previously developed protocols for \textit{in situ} activation of potassium allyltrifluoroborate using the model substrate 2,3-epoxycyclohexanone \(3.046\), gave only moderate yields of epoxy alcohol \(3.047\) due to competing side reactions of \(3.046\) (Table 3.3, entries 1-2). Therefore, alternative conditions using a variety of Lewis acids, fluorophiles and solid additives were examined in order to establish a protocol suitable for achieving controlled addition while minimizing by-product formation. Attempts to activate potassium allyltrifluoroborate with a variety of fluorophiles such as TBDPSCI, TBSCI, TIPSOTf and HMDS afforded only a complex mixture of the products. Several other Lewis acids were capable of promoting addition to \(3.046\), but product yields were disappointing (Table 3.3, entries 3–5). Intriguingly metallic


Indium (1.0 equiv.) was demonstrated to be an effective promoter with no evidence of side-product formation, but only in the presence of water as a co-solvent (Table 3.3, entries 6–7). The use of other metals such as Sn, Zn, Mg and Ag were unsuccessful. Reaction of 3.046 in the absence of water revealed that the reaction did not occur (<5% conversion), even after 24 h at room temperature. Reaction using methanol, as an alternative protic solvent additive was unsuccessful, while the use of MeCN as an alternative to dichloromethane afforded lower yields of 3.047 (Table 3.3, entries 8–9).

Table 3.3 Allylation of α,β-Epoxycyclohexanone 3.046 with Potassium Allyltrifluoroborate.\(^{37}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Solvent (Volume, mL)</th>
<th>Yield(^a) (d.r.(^b))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K10 (0.1 g)</td>
<td>CH(_2)Cl(_2)/H(_2)O (1.4:0.1)</td>
<td>62 (98:2)</td>
</tr>
<tr>
<td>2</td>
<td>BF(_3)-OEt(_2) (0.1 equiv.)</td>
<td>CH(_2)Cl(_2) (1.5)</td>
<td>64 (98:2)</td>
</tr>
<tr>
<td>3</td>
<td>In(OTf)(_3) (0.1 equiv.)</td>
<td>CH(_2)Cl(_2) (1.5)</td>
<td>23 (82:18)</td>
</tr>
<tr>
<td>4</td>
<td>Cu(OTf)(_2) (0.1 equiv.)</td>
<td>CH(_2)Cl(_2) (1.5)</td>
<td>48 (91:9)</td>
</tr>
<tr>
<td>5</td>
<td>B(O(_\text{i\text{Pr}}))(_3) (0.1 equiv.)</td>
<td>CH(_2)Cl(_2) (1.5)</td>
<td>43 (98:2)</td>
</tr>
<tr>
<td>6</td>
<td>In (1.0 equiv.)</td>
<td>CH(_2)Cl(_2)/H(_2)O (1.4:0.1)</td>
<td>77 (93:7)</td>
</tr>
<tr>
<td>7</td>
<td>In (1.0 equiv.)</td>
<td>CH(_2)Cl(_2) (1.5)</td>
<td>N. R.</td>
</tr>
<tr>
<td>8</td>
<td>In (1.0 equiv.)</td>
<td>CH(_2)Cl(_2)/MeOH (1.4:0.1)</td>
<td>N. R.</td>
</tr>
<tr>
<td>9</td>
<td>In (1.0 equiv.)</td>
<td>MeCN/H(_2)O (1.45:0.05)</td>
<td>33 (91:9)</td>
</tr>
<tr>
<td>10</td>
<td>In (1.0 equiv.)</td>
<td>CH(_2)Cl(_2)/H(_2)O (1.45:0.05)</td>
<td>83 (95:5)</td>
</tr>
<tr>
<td>11</td>
<td>In (1.0 equiv.)</td>
<td>THF/H(_2)O (1.45:0.05)</td>
<td>76 (94:6)</td>
</tr>
<tr>
<td>12</td>
<td>In (0.1 equiv.)</td>
<td>CH(_2)Cl(_2)/H(_2)O (1.45:0.05)</td>
<td>41 (95:5)</td>
</tr>
<tr>
<td>13</td>
<td>In (1.0 equiv.)</td>
<td>CH(_2)Cl(_2)/H(_2)O (1.45:0.05)</td>
<td>73(^c) (92:8)</td>
</tr>
</tbody>
</table>

a) Yield of product isolated after silica gel chromatography. b) dr was determined by the integration of the α-epoxide C–H signal in the crude mixture. c) Allylboronic acid pinacol ester (2.0 equiv.) was used instead of potassium allyltrifluoroborate.

\(^{37}\) Experiments were performed by John Janetzko.
Further optimization of the conditions revealed that the amount of water present has a significant influence on the reaction outcome, and needed to be strictly controlled to achieve full conversion and optimal yields of 3.047 (Table 3.3, entry 10). While potassium allyltrifluoroborate is stable in water; showing less than 5% decomposition over 24 hours in the absence of a reactive substrate (i.e. ketone), the presence of metallic indium leads to initially rapid formation of propene gas. The use of more water resulted in faster decomposition of the potassium allyltrifluoroborate reagent and concomitantly lowers yields of 3.047. The use of a lower loading of indium in catalytic quantity was successful although a lower yield of 3.047 was obtained (Table 3.3, entry 12). Stoichiometric quantities of indium were therefore used for subsequent studies on the reaction of α,β-epoxyketones. Attempts to use the pinacol ester of allylboronic acid also failed to afford full conversion to the desired product under otherwise identical conditions and led to a reduced yield and slightly lower diastereoselectivity of 3.047 (Table 3.3, entry 13). The use of the indium promoted method was then examined with a wider range of α,β-epoxyketones in order to establish the generality of the protocol and the effect of the substrate on the selectivity of the addition. In all cases examined the products were obtained in excellent yields and with high diastereoselectivity (Table 3.4). The presence of α-, β- and γ-substitution on the epoxyketones was well tolerated (Table 3.4, entries 2–4). The presence of an α-methyl substituent in 3.049 resulted in slower reaction presumably due to steric constraints, and a modest increase to 2.5 equiv. of the potassium allyltrifluoroborate was therefore necessary to achieve full consumption of the starting material within 24 h (Table 3.4, entry 3). The presence of the α-methyl substituent in 3.049 also did not lead to a loss in diastereoselectivity. Chemoselective allylation of the less sterically encumbered carbonyl group of 3.052 occurred under the reaction conditions (Table 3.4, entry 6). Due to the mild nature of the protocol various functional groups were well tolerated. For example, the reaction could be achieved in the presence of an acid labile dimethylketal in 3.053 that had previously been shown to hydrolyze in the presence of K-10 (Table 3.4, entry 7). Reaction of the bis(epoxide) 3.053, which constitutes the protected core of the natural product aranorosin, had previously been shown to result in

38 Stability of the potassium allyl trifluoroborate was monitored by 1H, 11B and 19F NMR. In the presence of metallic indium, propene gas was observed by 1H and 13C NMR (See Chapter 3.5.1 for details).


several products using organometallic reagents.\textsuperscript{41} Reaction of seven and five-membered ring α,β-epoxyketones 3.054 and 3.055 occurred in good to excellent yields (Table 3.4, entries 8 and 9). In the case of reaction of the five-membered ring epoxyketone the diastereoselectivity of 3.063 was modest, favoring the cis-epoxy alcohol stereoisomer (\textit{vide infra}). Despite the highly reducing nature of indium metal\textsuperscript{42} it is noteworthy that competitive reductive deoxygenation of the epoxide functionality did not occur under the reaction conditions for any of the cyclic substrates studied.

\textbf{Table 3.4 Stereoselective Synthesis of Cyclic Epoxy Alcohols}\textsuperscript{37}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield\textsuperscript{a} (d.r.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>O</td>
<td>HO</td>
<td>83 (95:5)</td>
</tr>
<tr>
<td></td>
<td>3.046</td>
<td>3.047</td>
<td>79\textsuperscript{c} (94:6)</td>
</tr>
<tr>
<td>2</td>
<td>O</td>
<td>HO</td>
<td>85 (93:7)</td>
</tr>
<tr>
<td></td>
<td>3.048</td>
<td>3.056</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>O</td>
<td>HO</td>
<td>97\textsuperscript{d} (≥ 99:1)</td>
</tr>
<tr>
<td></td>
<td>3.049</td>
<td>3.057</td>
<td></td>
</tr>
</tbody>
</table>


\textsuperscript{41} Mahesh, M.; Murphy, J. A.; Wessel, H. P. \textit{J. Org. Chem.} 2005, 70, 4118–4123.
The reactions of acyclic $\alpha,\beta$-epoxyketones were also examined using the indium-promoted protocol (Table 3.5, entries 1–8). Again the $\alpha,\beta$-epoxyketone precursors are readily synthesized by epoxidation of the corresponding enones or allylic alcohols. Variation of the $\beta$-substituent in the $\alpha,\beta$-epoxyphenylketones 3.064-3.066 was found to have little effect on the reaction (Table 3.5, entries 1–3). The products were all obtained in high yield and with excellent selectivity.
even in the case of the reaction of the more challenging unsubstituted terminal epoxide 3.066, which had previously given a poor result using PbI₂ promoted addition of diallyldibutylstannane (Table 3.5, entry 3). Reaction of the epoxy methyl ketone 3.067 occurred with a noticeable drop in diastereoselectivity of 7:1 (Table 3.5, entry 4) relative to that obtained with corresponding phenyl ketone 3.064. The steric effect of the other carbonyl substituent was further examined using substrates 3.068, 3.069 and 3.070 (Table 3.5, entries 5–7). Reaction of the least sterically encumbered compound, the α,β-epoxyaldehyde 3.068, occurred to give 3.075 in an *ca.* 1.2:1 ratio. Reaction of the ethyl ketone 3.069 and *iso*-propyl ketone 3.070 occurred with *ca.* 19:1 and > 50:1 diastereomeric product ratios respectively. Thus, the product diastereoselectivity was observed to increase as the substituent size increased on the carbonyl group. Finally, reaction of an enantiomerically enriched version of compound 3.064 (*−*)-enantiomer occurred without loss of stereochemical fidelity (Table 3.5, entry 8). In the case of the acyclic examples investigated, deoxygenated products were not observed for the reactions of 3.064-3.066, while reaction of the alkyl substituted cases 3.067, 3.069 and 3.070 resulted in small amounts (less than 7%) of reductively deoxygenated products after reaction at room temperature.
Table 3.5 Stereoselective Synthesis of Acyclic Epoxy Alcohols

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield(^a) (d.r.)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Substrate 1" /></td>
<td><img src="image2" alt="Product 1" /></td>
<td>92 (97:3)</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Substrate 2" /></td>
<td><img src="image4" alt="Product 2" /></td>
<td>95 (≥ 99:1)</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Substrate 3" /></td>
<td><img src="image6" alt="Product 3" /></td>
<td>96 (97:3)</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Substrate 4" /></td>
<td><img src="image8" alt="Product 4" /></td>
<td>85 (86:14)</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="Substrate 5" /></td>
<td><img src="image10" alt="Product 5" /></td>
<td>59 (54:46)</td>
</tr>
<tr>
<td>6</td>
<td><img src="image11" alt="Substrate 6" /></td>
<td><img src="image12" alt="Product 6" /></td>
<td>93(^c) (95:5)</td>
</tr>
<tr>
<td>7</td>
<td><img src="image13" alt="Substrate 7" /></td>
<td><img src="image14" alt="Product 7" /></td>
<td>83(^d) (≥ 99:1)</td>
</tr>
<tr>
<td>8</td>
<td><img src="image15" alt="Substrate 8" /></td>
<td><img src="image16" alt="Product 8" /></td>
<td>94(^e) (97:3)</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yield of the major diastereomer after silica gel chromatography. \(^b\) d.r’s were determined by \(^1\)H NMR intergration of the α-epoxide C–H’s in the crude reaction mixture. \(^c\) 2.5 equiv of potassium allyltrifluoroborate was used to ensure full conversion. \(^d\) The starting material was used as a mixture of enantiomers (e.r. = 93:7, as determined by HPLC). The respective product had the same optical purity by HPLC.
3.5 Mechanistic Studies

The mode by which the indium metal acts to facilitate the addition of the potassium organotrifluoroborate salt was not clear at the outset of this study. In previous reports the activation of potassium allyltrifluoroborate was implicated to occur through dissociation of fluoride to generate an active tricoordinate allylboron reagent. However, in the case of the reaction of ketones with potassium allyltrifluoroborate under the indium promoted conditions the intermediacy of either an allylboron or allylindium species could be envisaged. Therefore, in order to gain further insight on the nature of the activation, mechanistic studies were undertaken using either 4’-bromoacetophenone or 2,3-epoxycyclohexanone as model substrates.

3.5.1 Effect of Water

During the course of the reaction optimization it was found that the presence of water was critical, since reaction did not occur under rigorously dry conditions (< 5% conversion) after 24 hours at room temperature (Table 3.1, entry 6). While potassium allyltrifluoroborate is stable in water, showing less than 5% decomposition over 24 h in the absence of the ketone, the presence of metallic indium leads to initially rapid formation of propene gas.\textsuperscript{43} Observation of propene formation in the presence of indium and water as a co-solvent suggested a competitive proto-deboration reaction could occur under the reaction conditions. Reaction of potassium allyltrifluoroborate in the absence of ketones using indium in neat water also led to rapid proto-deboration to give propene 3.078 which was trapped and characterized at low temperature. Similar reaction with D\textsubscript{2}O led to the formation of 3-deuteriopropene 3.079 (Scheme 3.6).

\textsuperscript{43} Stability of the potassium allyl trifluoroborate was monitored by \textsuperscript{1}H, \textsuperscript{11}B and \textsuperscript{19}F NMR. In the presence of metallic indium, propene gas was observed by \textsuperscript{1}H and \textsuperscript{13}C NMR.
Scheme 3.6 Decomposition of Potassium Allyl- and Crotyltrifluoroborates in the Presence of Indium

Similar proto-or deutoro-deboration pathways were observed for the (E)-crotyltrifluoroborate, albeit with lower reaction rate. Such a protodeboration reaction also suggests the possible intermediacy of an organoindium intermediate, rather than reaction via a direct protonation of an organoboron species. A plot of conversion for the allylation of 4’-bromoacetophenone versus the amount of water revealed that 2.76 equivalents of water (relative to the substrate) led to full conversion, the use of less water led to lower product conversion (e.g. ≈ 47% with 2.2 equiv.), while the use of more equivalents of water led to gradual decrease in conversion, dropping to 52% conversion with 11.0 equivalents (Figure 3.1).
As a qualitative observation, at the beginning of a reaction with a ketone using indium metal, the indium was present as a fine powder (mesh size = 100 or 300), however rapid agglomeration occurred to give indium granules as the reaction was stirred vigorously with a magnetic stir bar. The initial amount of indium powder was 57.5 mg (0.5 mmol) and the isolated amount of granules after the reaction was 55.8 ± 1.8 as obtained by the following procedure: Upon reaction completion, the organic layer was filtered through cotton and washed with CH$_2$Cl$_2$ (3 × 5 mL). The remaining white/gray solid was washed sequentially with acetone/H$_2$O (v/v, 1:1) (10 mL), H$_2$O (10 mL) and CH$_2$Cl$_2$ to obtain pure indium granules. The indium was further dried under high vacuum for 30 min prior to re-use. The isolated granules were applied for four consecutive reactions and showed no diminishment in the isolated yield of 3.026. However, the reactivity of isolated indium granules was lower than that of commercial indium powder (100-mesh). The reactions required longer times (12 h versus 5 h) in order to achieve full conversion, presumably due to the lower active surface area. It should be noted that stirring commercial indium with the reaction solvent system (CH$_2$Cl$_2$/H$_2$O) in the absence of potassium allyltrifluoroborate and
ketone for 5 hours resulted in granule formation of similar activity to those obtained after the reaction.

Table 3.6 Allylation Reaction Using Recovered Indium

<table>
<thead>
<tr>
<th>Entry</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>93</td>
</tr>
</tbody>
</table>

3.5.3 Indium Mediated Crotylation Using Potassium Crotyltrifluoroborates

Crotylation reactions under similar conditions were also investigated (Scheme 3.7). It is well established that crotylindium reagents react with carbonyl groups through an open transition state to afford a syn addition product predominately, while (E)- and (Z)-crotyltrifluoroborates react via a closed chair-like transition state to give the anti and syn addition products, respectively. Reaction of (E)-crotylindium using (E)-bromobut-2-ene and indium metal in THF/water with 4’-bromoacetophenone confirmed a preference for syn-selectivity yielding 3.027 and 3.083 in a 17:83 ratio. Conversely, reaction of potassium (E)-crotyltrifluoroborate with 4’-bromoacetophenone occurred slowly under the optimized indium-based reaction conditions giving a 98:2 ratio of 3.027 and 3.083 with high anti-selectivity. Likewise, crotylation of 4’-bromoacetophenone using potassium (Z)-crotyltrifluoroborate afforded a 98:2 ratio of 3.083 and 3.027 with high syn-selectivity (Scheme 3.7).

To examine the possibility of the reaction proceeding via a classical allylindium(III) type species for epoxy ketones, \( 3.046 \) was subjected to reaction with allylindium (prepared in situ from allyl bromide). A complex mixture of products resulted, \(^{45}\) including an approximately 2:1 ratio of products resulting from addition to the carbonyl group versus products arising from attack at the β-position of the epoxide (Scheme 3.8). These results suggest that reaction of the (E)- or (Z)-crotyltrifluoroborate salts do not occur via the same crotylindium species involved under Classical Barbier-like conditions.

\[ \text{Scheme 3.8 Addition of Allylindium(III) to Epoxyketone} \]
Indeed, the high stereospecific results observed for the crotylation reactions of the \((E)\)- or \((Z)\)-crotyltrifluoroborate salts are consistent with reaction via an organoboron species rather than an indium intermediate. This may indicate that the presence of the methyl group on the \((E)\)- or \((Z)\)-crotyltrifluoroborate reagents prevent effective transmetallation to indium and that a more conventional reaction via an \((E)\)- or \((Z)\)-crotylboron intermediate is more feasible under these conditions. The complex mixture obtained under classical allylindium(III)-type nucleophiles for a model epoxy ketone, suggests that allylation of epoxy ketones using indium and allyltrifluoroborate does not proceed via known allylindium(III) species.

### 3.5.4 Deuterium Labeling Experiments

The stereo- and regiochemical outcome of the addition of an \(\eta^1\)-allylmetal species to a carbonyl group, depends on whether the nucleophilic addition is faster or slower than the 1,3-metallotropic rearrangements.\(^{46}\) It is known that this haptotropic rearrangement is faster than nucleophilic addition in allylmetal compounds such as lithium, magnesium, zinc, chromium, samarium and indium.\(^{47}\) If the allylindium species was operative under the optimized reaction conditions, upon haptotropic rearrangement one would expect to observe two distinct addition products using potassium \(\alpha,\alpha\)-bis(deutero)allyltrifluoroborate. In order to test this hypothesis, potassium \(\alpha-d_2\)-allyltrifluoroborate was synthesized according to the literature procedure.\(^{48}\) Reaction of 3.023 with deuterium labeled compound revealed unequivocally that direct addition via an organoboron compound was not occurring under indium-promoted conditions (Scheme 3.9). In a control experiment 4'-bromoacetophenone underwent selective allylation to give product 3.090 as essentially the sole product using K-10 promoted conditions.\(^{49}\) This result is consistent with reaction of the ketone with an allylboron species through a closed, chair-like Zimmerman-Traxler transition state. On the other hand, reaction using the metallic indium-promoted conditions led to a roughly 1:1 mixture of the allylated compounds 3.089 and 3.090, which differ in the position of the deuterium label at either the allylic methylene position or the

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\(^{49}\) See chapter 2.5.
terminal alkene position (Scheme 3.9). This observation of label scrambling is consistent with transmetallation of the \( \alpha,\alpha \)-bis(deutero)allyltrifluoroborate to an unidentified allylindium species and likely rules out a direct allylboron addition as occurs with the K-10-promoted conditions. The putative allylindium species perhaps exists as a surface bound species, which would be capable of rapid 1,3-metallotropic rearrangements. Such an allylindium species could then undergo addition to the ketone to give a mixture of 3.089 and 3.090 or could undergo protodeboration reaction with water. Alternatively the indium may promote scrambling of the 3.088 through the intermediacy of an allylindium species (capable of 1,3-metallotropic rearrangement) which then regenerate the scrambled allyltrifluoroborate species.

![Scheme 3.9](image)

**Scheme 3.9** Addition of \( \alpha-d_2 \)-Potassium Allyltrifluoroborate Using Indium

3.5.5 Indium Surface Effect

As the recovered mass of indium metal was almost quantitative, and the recovered indium could be used to promote addition reactions to ketones; this suggested a surface indium-mediated activation process is plausible. Addition of KF to the reaction media resulted in the complete loss of reactivity, which is consistent with either deactivation of the indium surface by the fluoride ions, or implies that activation of the allyltrifluoroborate anion by initial fluoride ion dissociation is necessary for indium activation to occur.\(^\text{31}\) In order to elucidate the indium surface composition, a scanning transmission electron microscopy (STEM) analysis on indium powder (mesh size = 100) and recovered indium nuggets were conducted. The STEM analytical data revealed that the indium to oxygen ratio (87:13) was identical for both samples. This result indicates that the composition of the indium surface remained constant through out the reaction and raised a question as to whether the indium oxide on the surface is responsible for the transformation. In order to answer the aforementioned question, a variety of metal oxides
including indium oxide were screened under catalytic reaction conditions. Surprisingly, only indium oxide gave a result comparable to the indium powder. This result supports the hypothesis that indium oxide on the surface of the metallic indium is responsible for promoting ketone allylation.

Table 3.7 The Effect of Metal Oxides on Allylation Reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metal oxide (10.0 mol %)</th>
<th>Conv. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>In$_2$O$_3$</td>
<td>96 (93)</td>
</tr>
<tr>
<td>2</td>
<td>ZnO</td>
<td>39</td>
</tr>
<tr>
<td>3</td>
<td>Fe$_2$O$_3$</td>
<td>19</td>
</tr>
<tr>
<td>4</td>
<td>Ag$_2$O</td>
<td>17</td>
</tr>
<tr>
<td>5</td>
<td>CuO</td>
<td>8</td>
</tr>
</tbody>
</table>

3.5.6 Investigating the Chelation Effect

It is known that the addition of allylindium reagents to $\alpha$-substituted carbonyl groups proceed in a chelation-controlled fashion.$^{14}$ Despite their practical application in organic synthesis, the mechanistic understanding and the nature of allylindium reagents is far from satisfactory. Paquette reported the detailed investigations of chelation effects operative during diastereoselective addition of allylindium reagents to $\alpha$-heteroatom substituted aldehydes and cyclohexanones. In order to understand the mode of action and role of the epoxide moiety under indium catalyzed conditions, epoxy ketone 3.066 was subjected to K-10 and indium catalyzed allylation conditions to afford the syn epoxy homoallylalcohol 3.091 and anti products 3.073 respectively.
The observed reversal of diastereocontrol under the different reactions conditions, reveals that the two different pathways must occur via different intermediates and must follow different stereochemical models; raising the question whether the indium catalyzed reaction proceeded through chelation-controlled pathway.

Paquette reported the addition of allylindium to an \( \alpha,\beta \)-epoxyaldehyde to achieve non-chelation controlled product with moderate selectivity.\(^{14}\) In order to test the scope of the observed results, the \( \alpha \)-heteroatom substituted ketones 3.092–3.095 were synthesized according to literature methods and subjected to the indium-catalyzed reaction conditions. Allylation of the \( \alpha \)-silyloxyketone 3.092 was accomplished in high yield and moderate diastereoselectivity affording the \textit{syn}-product (Table 3.8, entries 3 and 4). The observed \textit{syn} product was rationalized based on the Felkin-Ahn model, with the \( \alpha \)-silyloxy group serving as the large substituent (as expected). Allylation of the \( \alpha \)-benzyloxy ketone 3.093 was accomplished in high yields with very poor diastereoselectivity (\textit{ca.} d.r. 1:1) even with a stoichiometric quantity of indium (Table 3.8, entries 2 and 3). Moderate diastereoselectivity was observed for the allylation of \( \alpha \)-methoxy cyclohexanone 3.094 giving the equatorial homoallyl alcohol 3.100 as the major product. This result is consistent with the reported chelation-controlled model.\(^{14a}\) Surprisingly, using allylboronic acid pinacol ester 3.018 instead of the corresponding potassium allyl trifluoroborate 3.024 led to a marked increase in the diastereoselectivity of 3.100.
Table 3.8 Substrate Scope of the Indium Catalyzed Allylation of α-Substituted Ketones Using Potassium allyltrifluoroborate 3.024

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketone</th>
<th>Products</th>
<th>(dr)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOSi^t^BuPh$_2$</td>
<td>HO$_2$Me, MeCH=CH$_2$, HO$_2$Me</td>
<td>24:76</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>MeO$_2$Me</td>
<td>HO$_2$Me, MeCH=CH$_2$, HO$_2$Me</td>
<td>49:51</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>MeOBn</td>
<td>HO$_2$Me, MeCH=CH$_2$, HO$_2$Me</td>
<td>48:52</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>OOMe</td>
<td>68:32</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>OMe</td>
<td>94:6</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>OBn</td>
<td>45:55</td>
<td>86</td>
<td></td>
</tr>
</tbody>
</table>

a) The diastereomeric ratios were determined by GC or $^1$H NMR analysis on crude products. b) Yield of products isolated after silica gel chromatography. c) Stochiometric indium was used. d) Allylboronate pinacol (2.0 equiv.) ester used.
Under K-10 promoted allylation conditions the allylation presumably proceeds through a tricoordinated allylboron intermediate, which given the requirement for a water additive most likely is allylboronic acid $A$, which then undergoes addition to the ketones to afford the homoallylic alcohol products (Figure 3.2). However, in the case of the indium catalyzed/promoted methods the exact nature of the intermediate has not been definitively established. It is possible that the reaction occurs on the indium surface through an allylboron to allylindium transmetallation. The deuterium scrambling data using indium suggests the general intermediate $B$ which then undergoes allylation of the ketone or a competitive proto-deboration reaction. The reaction using indium oxide may suggest that the active surface species using indium metal is in fact indium oxide. Further mechanistic studies will be required to elucidate the surface effects in these reactions.
3.6 Stereoselectivity of Additions

There have been relatively few investigations on the diastereoselectivity of addition reactions of organometal or organometalloid compounds to $\alpha,\beta$-epoxyketones.\(^{50}\) Allylation of acyclic substrates such as 3.064 and 3.065 using diallyldibutylstannane were shown to occur with syn-selectivity. Similarly, the reaction of the cyclic $\alpha,\beta$-epoxyketone 3.046 led to 3.047 where the stereochemical relationship between the epoxide and the tertiary alcohol have an anti relationship. These results were rationalized by Baba and co-workers as resulting from a Cram chelation model. Similar selectivities were observed in our additions, based on NMR analysis (including n.O.e. experiments) of the products. Confirmation of the anti-selectivity observed for cyclic substrates was established via the observation of Payne rearrangement\(^{51}\) of 3.047 under basic conditions, giving the more highly substituted epoxide 3.104 in excellent yield (Scheme 3.11). Since Payne rearrangement is known to occur via intramolecular alkoxide attack through an $S_N2$ mechanism, only the anti-diastereomer of 3.047 would be capable of undergoing rearrangement. This observation provided independent verification of the anti-selectivity obtained for the allylated products. However, treatment of the crude mixture of diastereomers 3.063 under the same conditions, led only to rearrangement of the minor isomer affording 3.107. This revealed that formation of 3.063 occurred preferentially as the syn-diastereoisomer rather than the anti-selectivity as observed for reactions of the six-membered ring cases.


Scheme 3.11 Payne Rearrangement of Cyclic and Acyclic Epoxy Alcohols

The major diastereomers obtained using the indium based protocol were the same for the substrates examined by Baba and co-workers using lead(II) catalyzed addition of allylstannanes through a chelation controlled model. Whereas the addition of allylindium species to α-
oxygenated ketones has previously been reported to afford \textit{syn} products consistent with chelation control,\textsuperscript{14} to the best of our knowledge this has not been reported in the case of epoxides.

It is highly unlikely that chelation control could be in effect for an allylboron species, since chelation-controlled addition is not known for organoboron species. Thus, it is not clear whether such a chelation-controlled model is appropriate for the indium-promoted addition of potassium allyltrifluoroborate species to epoxyketones described herein. An alternative rationale for the diastereocontrol of these substrates may be required.

Among the few examples in the literature of nucleophilic additions (e.g., cyanide) to \(\alpha,\beta\)-epoxy carbonyl compounds, no relationship between ring-size and \textit{anti}/\textit{syn} selectivity has been observed.\textsuperscript{52} For the allylation reactions of cyclic \(\alpha,\beta\)-epoxyketones, the observed diastereoselectivity can be rationalized using the model \textbf{3.111} (Figure 3.2) based upon previously reported conformational analyses;\textsuperscript{53,54} matching well with the steric and electronic factors previously examined by Plumet and co-workers\textsuperscript{55} Approach via the pseudo-equatorial trajectory B is favored over the pseudo-axial trajectory A. The reactions of \textbf{3.053} and the cyclopentanone oxide \textbf{3.055} occur from nucleophile addition \textit{anti} to the epoxide leading to the \textit{cis}-substituted epoxy alcohols, presumably as a result of steric factors.

![Figure 3.3 Stereochemical Model for the Diastereoselective Addition to Cyclic \(\alpha,\beta\)-Epoxyketones](image)

\textbf{Figure 3.3} Stereochemical Model for the Diastereoselective Addition to Cyclic \(\alpha,\beta\)-Epoxyketones


The selectivity of the addition reactions of the acyclic epoxyketones 3.064-3.070 is consistent with a Felkin-Anh-like selectivity,\textsuperscript{56} where the oxirane oxygen, the \( \alpha \)-epoxide carbon and the \( \alpha \)-epoxide hydrogen serve as the “large”, “medium” and “small” substituents respectively. In this respect the “large” electronegative epoxide C–O bond adopts an orientation orthogonal to the carbonyl group, and attack of the nucleophile occurs through the trajectory 3.112 rather than 3.113 (Figure 3.3). The increased steric interaction present in 3.065 occurs between the \( R^1 \) ketone substituent and the \( \alpha \)-epoxide carbon substituent (i.e., \( C\beta - R^2 \)). Consistent with this notion is the drop in diastereoselectivity observed as the size of the \( R^1 \) substituent decreases along the series iso-Pr > Ph > Et > Me > H for the reactions of 3.070, 3.064, 3.069, 3.067 and 3.066 respectively.

![Figure 3.4 Stereochemical Model for the Diastereoselective Addition to Acyclic \( \alpha,\beta \)-Epoxyketones 3.064-3.070.](image)

### 3.7 Conclusions

In summary, we have developed the first indium-mediated, highly chemo- and diastereoselective allylation of \( \alpha,\beta \)-epoxyketones, and shown that in the case of simple ketone substrates the loading of indium can be reduced to catalytic quantities without a diminution in yield. The method is quite robust and provides an operationally straightforward procedure for the allylation of a range of ketones using the air and moisture stable potassium allyltrifluoroborate salt. It precludes the requirement for reaction under inert atmosphere conditions using indium-catalyzed reactions of allylboronic acid pinacol ester. The method constitutes an environmentally

benign alternative to the use of toxic stannanes previously employed for these transformations, operates under ambient conditions allowing for higher functional group tolerance, and is readily scalable to 6 mmol (largest scale examined to date) without reduction in yield or diastereoselectivity. The diastereoselectivity of addition to cyclic substrates is complementary to that obtained with the alternative sequential allylation/directed epoxidation protocols. In addition, this method is suitable for acyclic substrates giving products that would be difficult to obtain selectively through a sequential allylation/directed epoxidation protocol. The reaction requires the use of a small amount of water as an additive. We have shown unequivocally the relative configuration of the epoxy homoallylic alcohols through a variety of stereospecific rearrangements and have proposed appropriate models to rationalise the obtained stereoisomers. Mechanistic analysis suggests that it is unlikely that the reaction proceeds exclusively via an allylboron type intermediate. The requirement for water to be present and inhibition by added fluoride anion (by KF) suggest that fluoride dissociation is required for the reaction to occur. However, the scrambling observed for the addition reaction of a deuterium labeled allyltrifluoroborate salt, suggests that transmetallation may be occurring perhaps via a surface bound allylindium species. The STEM analysis and metal oxide screening experiments indicate that indium oxide might be the actual catalytic species. The high chemo- and diastereoselectivity obtained in the addition reactions, in addition to the ready access to precursor epoxyketones should render this an efficient and general C–C bond formation method.

This method provides a complementary route to access anti tertiary homoallylic epoxy alcohols, which are difficult to obtain using classical chelation-controlled allylic epoxidation methods. The mild reaction conditions allow allylation reactions to be performed on multifunctionalized intermediates at a late stage in multistep syntheses. The allylation / Payne rearrangement affords tetra-substituted anti epoxy alcohols, which cannot be obtained through classical procedure due to steric congestion of the tetra-substituted olefins. Future studies in this area will involve investigations on the scope of the allylation of various substrates using indium oxide as a catalyst/ promoter, and the use of the method in complex molecule synthesis.

57 For example, poor selectivity has been observed for enantioselective allylboration for ketones where the two ketone substituents are of similar size, see: Carnales, E.; P. Ganeshwar, K.; Soderquist, J. A. J. Am. Chem. Soc. 2005, 127, 11572–11573.
3.8 Experimental Procedures

The following general experimental considerations apply for all experiments described in this chapter. Unless otherwise stated, all reactions were performed under nitrogen or argon atmosphere using oven (140 °C) and flame dried glassware. Reaction solvents were distilled under an inert atmosphere before use and transferred via syringe using standard techniques. Dichloromethane (CH$_2$Cl$_2$) was distilled from CaH$_2$ under nitrogen. Tetrahydrofuran (THF) and diethyl ether (ether) were distilled from sodium under nitrogen. Anhydrous methanol was used as received from Aldrich. Anhydrous tert-butanol was either freshly distilled from sodium under argon, and stored under argon over activated 4Å molecular sieves or obtained from Aldrich and used as delivered. All reagents, unless otherwise stated, were used as received from their respective providers (Aldrich, Alfa Aesar, STREM or ACP). Commercially available potassium allyltrifluoroborate was prepared by known procedure.$^{58}$ Indium metal 99.99% trace metal basis, 100-mesh was purchased from Aldrich, and used without activation.

Infrared spectra were recorded on a Perkin-Elmer Spectrum 100 FT-IR with universal ATR attachment as neat samples or using a Shimadzu FT-IR 8400S spectrometer for thin film samples. $^1$H and $^{13}$C NMR spectra were obtained on a Varian Mercury 400 MHz spectrometer as a solution in chloroform-$d$, and chemical shifts are expressed in parts per million (ppm) relative to TMS. Peak multiplicities are designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; dt, doublet of triplets and so forth; br, broad (this abbreviation is also used for designation of IR peaks); $J$, coupling constant in hertz (Hz); str denoted a strong IR band. An asterisk immediately following an absolute configuration label denotes a racemic mixture. Mass spectra, both low-resolution (LRMS) and high resolution (HRMS) where recorded on either an AB/Sciex QStar mass spectrometer (ESI) or a Waters GC ToF mass spectrometer (EI). LRMS includes only peaks of significant relative intensity, whose relative intensity is given in parenthesis. Accurate masses where determined within ± 5 ppm of the calculated mass. Optical Rotations were recorded on an AutoPol IV automatic polarimeter cell used. Melting points were obtained on a Fisher-Johns melting point apparatus and are uncorrected.

Flash column chromatography on silica gel (60Å, 230-400 mesh, obtained from Silicycle Inc.) was performed reagent grade solvents. Analytical thin-layer chromatography (TLC) was performed on pre-coated aluminum-backed silica gel plates (Alugram SIL G/UV$_{254}$ purchased from Silicycle Inc.), visualized with a UV lamp (254 nm), iodine, ninhydrin, potassium permanganate, $p$-anisaldehyde, phosphomolybdic acid (Aldrich), or vanillin. References following the compound names indicate literature articles where full characterizations of spectral and physical properties have previously been reported.

**General procedure for addition of potassium allyltrifluoroborate to simple ketones under catalytic indium conditions**

To ketone (0.50 mmol), potassium allyl or crotyl trifluoroborate salt (1.0 mmol) and indium (10 mol%, 5.7 mg) was added CH$_2$Cl$_2$ (1.5 mL) and water (25 µL). The reaction mixture was vigorously stirred at room temperature until full conversion was reached as monitored by TLC analysis. The reaction mixture was then filtered to separate the solid-phase and washed with CH$_2$Cl$_2$ (3 x 5 mL). The solvent was evaporated and the concentrated organic mixture was passed through a short plug of silica gel using EtOAc/Hexane as the eluent. The resulting eluate was concentrated *in vacuo* to afford the product alcohol.

**General procedure for the allylation of α,β-epoxyketones**

To an oven dried 5 mL round-bottomed flask was added α,β-epoxyketone (0.5 mmol), potassium allyltrifluoroborate (1.0 mmol), indium (0.5 mmol) dichloromethane (1.45 mL) and distilled water (0.05 mL), followed by vigorous stirring at room temperature. The reaction was monitored by TLC, and upon completion it was filtered through a pad of silica gel, and washed with ethyl acetate (50 mL). The solvent was removed *in vacuo* to afford the crude epoxy homoallylic alcohol, which was subsequently purified by flash column chromatography on silica gel.
Analytical data for homoallylic alcohols:

Diastereomeric ratios were determined by the relative intensities of epoxide protons in the crude products. In most cases the diastereomeric ratio were also confirmed by GC analysis.

Analytical data for compounds 3.026, 3.037–3.45 and 3.096–3.103 were reported in chapter 2.7 and will not be duplicated here.

(1R*,2S*,6R*)-2-(Prop-2-en-1-yl)-7-oxabicyclo[4.1.0]heptan-2-ol (3.047). After 25 h at room temperature, followed by standard work-up, 3.047 was isolated after flash chromatography (20% v/v ethyl acetate in hexanes) as a clear, colorless oil; (64 mg, 83%). crude dr = 95:5; Rf = 0.23 (20% v/v ethyl acetate in hexanes); 1H NMR (CDCl3, 400 MHz) δ 5.97 (1H, dddd, J = 17.0, 10.0, 8.0, 7.0 Hz), 5.19-5.28 (2H, m), 3.27 (1H, ddd, J = 3.5, 3.5, 1.5 Hz), 2.91 (1H, d, J = 3.5 Hz), 2.55 (1H, dddd, J = 13.5, 7.0, 1.0, 1.0 Hz), 2.25 (1H, dd, J = 13.5, 8.0 Hz), 1.82-1.94 (3H, m), 1.46-1.61 (2H, m), 1.29-1.36 (2H, m); 13C NMR (CDCl3, 100 MHz) δ 132.7, 120.1, 69.4, 57.4, 53.7, 44.3, 32.9, 23.6, 15.7.

(1R*)-1-[(2S*)-Oxiran-2-yl]-1-phenylbut-3-en-1-ol (3.073). After 6 h at room temperature, followed by standard work-up, 3.073 was isolated after flash chromatography (30% v/v ethyl acetate in hexanes) as an opaque, off-white wax (92 mg, 96%). crude dr = 97:3; Rf = 0.52 (30% v/v ethyl acetate in hexanes); 1H NMR (CDCl3, 400 MHz) δ = 7.42-7.50 (2H, m), 7.34-7.40 (2H, m), 7.25-7.32 (1H, m), 5.77 (1H, dddd, J = 17.5, 10.5, 7.5, 6.0 Hz), 5.11-5.20 (2H, m), 3.33 (1H, dd, J = 4.0, 3.0 Hz), 2.76-2.81 (3H, m), 2.63 (1H, dd, J = 5.5, 4.0 Hz), 2.29 (1H, s); 13C NMR (CDCl3, 100 MHz) δ 142.6, 132.7, 128.6, 127.6, 125.3, 119.9, 72.2, 57.9, 46.2, 43.6.
Procedure for indium accelerated hydro/deuterodeboration of potassium allyl- and crotyltrifluoroborate

To potassium allyltrifluoroborate (1.0 mmol, 0.148 g) and indium (0.115 g) in a 5 mL round bottom flask was added distilled water or D₂O (1.0 mL). The reaction mixture was vigorously stirred at room temperature while any evolved gases were trapped via cannulation into a cooled J. Young NMR tube at -78 °C containing CD₂Cl₂ (1 mL). The NMR tube was sealed after 1 h and ¹H NMR and ¹³C NMR analysis was performed immediately either at room temperature or at –50 °C to show either 3.078 (H₂O) or 3.079 (D₂O).

Prop-1-ene (3.078). ¹H NMR (CD₂Cl₂, 400 MHz) δ 5.79-5.85 (1H, m), 4.99-5.05 (1H, m), 4.90-4.94 (1H, m), 1.71 (3H, d, J = 6.5, 1.0 Hz); ¹³C NMR (CD₂Cl₂, 100 MHz) δ 134.0, 115.4, 19.2.

3-Deuteroprop-1-ene (3.079). ¹H NMR (CD₂Cl₂, 500 MHz, -50 °C) δ 5.74-5.82 (1H, m), 4.96 (1H, dd, J = 17.0, 1.5 Hz), 4.85 (1H, dd, J = 10.0, 1.5 Hz), 1.62 (2H, m); ¹³C NMR (CD₂Cl₂, 125 MHz) δ 134.3, 115.6, 19.5 (t, J_C-D = 19.5 Hz).

But-1-ene (3.080). ¹H NMR (CD₂Cl₂, 500 MHz, -30 °C) δ 5.79-5.84 (1H, m), 4.93 (1H, dd, J = 17.0, 2.0 Hz), 4.83 (1H, dd, J = 10.0, 2.0 Hz), 1.95-2.01 (2H, m), 0.91 (1H, d, J = 7.5 Hz); ¹³C NMR (CD₂Cl₂, 125 MHz, -30 °C) δ 142.7, 114.8, 28.7, 14.9.

Procedure for crotylation of 4’-bromoacetophenone utilizing trans-1-bromo-2-butene with indium

To 4’-bromoacetophenone (0.50 mmol, 0.100 g), trans-1-bromo-2-butene (1.0 mmol, 0.135 g) and indium (0.115 g) in a 5 mL round bottom flask was added THF (2 mL) and water (2 mL). The reaction mixture was vigorously stirred at room temperature for 2 h. Subsequently the
reaction mixture was quenched with HCl (2 mL, 2.0 M). The organic layer was extracted with Et₂O (3 x 5 mL) and dried with Na₂SO₄. The solvent was evaporated in vacuo to yield a mixture of 3.027 and 3.083 (0.107 g, 85 %, 17:83 [3.027:3.083]).

Procedure for crotylation of 4’-bromoacetophenone utilizing E-or Z-potassium crotyltrifluoroborates activated with indium

To 4’-bromoacetophenone (0.50 mmol, 0.100 g), potassium E–crotyltrifluoroborate (1.0 mmol, 0.162 g) and indium (0.115 g) in a 5 mL round bottom flask was added CH₂Cl₂ (1.4 mL) and water (0.1 mL). The reaction mixture was vigorously stirred at room temperature for 24 h. The reaction mixture was then filtered to separate the solid phase and washed with CH₂Cl₂ (3 x 5 mL). The solvent was evaporated in vacuo to give a mixture of 3.027 and 3.083 (52%, ≥ 98:2 [3.027:3.083]). Identical procedure was followed using Z–crotyltrifluoroborate for 60 h and afforded 3.083 as essentially a sole product (32%, ≥ 98:2 [3.083:3.027]).

Procedure for allylation of 4’-bromoacetophenone utilizing α,α-bis(deutero)allyltrifluoroborate with indium

To 4’-bromoacetophenone (0.50 mmol, 0.100 g), potassium α,α-bis(deutero)allyltrifluoroborate (1.0 mmol, 0.150 g) and indium (5.7 mg) in a 5 mL round bottom flask was added CH₂Cl₂ (1.5 mL) and water (25.0 μL). The reaction mixture was vigorously stirred at room temperature for 24 h. The reaction mixture was then filtered to separate the solid phase and washed with CH₂Cl₂ (3 x 5 mL). The solvent was evaporated in vacuo affording an inseparable mixture 3.089 and 3.090, which was further purified by flash chromatography (10% v/v ethyl acetate in hexanes) to obtain the mixture as a clear liquid (89 mg, 73%); ratio = 51.5:48.5; ¹H NMR (CDCl₃, 400 MHz) δ 7.43-7.46 (2H+2H, m, A+B), 7.29-7.32 (2H+2H, m, A+B), 5.55-5.22 (1H+1H, m, A+B), 5.10-5.15 (2H, dd, J = 17.0, 11.0 Hz, A ), 2.62 (1H, dd, J = 13.5, 6.5 Hz, B), 2.47 (1H, dd, J = 13.5, 8.5 Hz, B), 2.07 & 2.07
(1H+1H, 2×s, A B), 1.51 (3H+3H, s, A+B); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 146.9 (A+B), 133.3 (B), 133.2 (A), 131.4 (A+B), 126.9 (A+B), 120.7 (B), 120.1 (A), 73.6 (A), 73.5 (B), 48.4 (A+B), 30.1 (A), 30.0 (B), one carbon peak is missing for each compound.; $^2$H NMR (CHCl$_3$, 100 MHz) δ -2.15 (2$^2$H, s), -4.69 (1$^2$H, s), -4.84 (1$^2$H, s) referenced to CDCl$_3$.

**General procedure for the effect of metal oxides on allylation of 3.023 using potassium allyltrifluoroborate** To ketone 3.023 (0.50 mmol, 99.5 mg), potassium allyltrifluoroborate (1.0 mmol, 0.147 g) and metal oxide (10.0 mol%) was added CH$_2$Cl$_2$ (1.5 mL) and water (25.0 µL). The reaction mixture was vigorously stirred at room temperature until full conversion was reached as monitored by TLC analysis. The reaction mixture was then filtered to separate the solid-phase and washed with CH$_2$Cl$_2$ (3 x 5 mL). The solvent was evaporated and the concentrated organic mixture was passed through a short plug of silica gel using EtOAc/Hexane as the eluent. The resulting eluate was concentrated *in vacuo* to afford the product alcohol.

(1$^S$*)-1-[(2$^S$*)-Oxiran-2-yl]-1-phenylbut-3-en-1-ol (3.091). Isolated after flash chromatography (30% v/v ethyl acetate in hexanes) as clear liquid (57 mg, 60%); crude dr = 84:16; R$_f$ = 0.59 (30% v/v ethyl acetate in hexanes); $^1$H NMR (CDCl$_3$, 400 MHz) δ 7.45-7.52 (2H, m), 7.35-7.40 (2H, m), 7.25-7.32 (1H, m), 5.66 (1H, ddd, J = 17.0, 10.5, 7.5, 7.0 Hz), 5.05-5.16 (2H, m), 3.42 (1H, dd, J = 4.0, 3.0 Hz), 2.87 (1H, dd, J = 5.0, 3.0 Hz), 2.81 (1H, dd, J = 4.0, 5.0 Hz), 2.70 (1H, ddt, J = 14.5, 8.0, 1.5 Hz), 2.60 (1H, dd, J = 14.5, 8.0 Hz), 2.32 (1H, s); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 143.6, 132.4, 128.3, 127.4, 125.4, 119.1, 73.0, 57.3, 44.6, 43.7; IR (neat) $\nu_{max}$ 3457 (br), 3073, 3000, 2980, 2925, 2360, 2341, 1955, 1815, 1642, 1601, 1582, 1496, 1415, 1397, 1337, 1266, 1208, 1187, 1133, 1044, 992, 915, 889, 867, 803, 765, 730, 679 cm$^{-1}$; LRMS (EI) m/z 172.1 (1.5), 149.1 (30.7), 105.0 (100.0), 103.1 (10.2), 91.1 (8.9), 77.0 (15.4); HRMS (EI) m/z calc’d. for C$_{12}$H$_{14}$O$_2$ [M]$^+$ 190.0994, found 190.0992.
General procedure for Payne rearrangement

To epoxy homoallyl alcohol (0.28 mmol) and dry tBuOH (5 mL) was added sodium hydroxide (0.30 mmol, 12.5 mg). The reaction mixture was vigorously stirred at 30 °C until full conversion was achieved as monitored by TLC analysis. The reaction mixture was then quenched with saturated NH₄Cl (5mL) and extracted with ethyl acetate (3 × 12 mL). The solvent was evaporated and the concentrated organic mixture was passed through a short plug of silica gel using EtOAc/Hexane as the eluent. The resulting eluate was concentrated in vacuo to afford the product alcohol.

\((1R^*,2S^*,6R^*)-6-(\text{Prop-2-en-1-yl})-7\text{-oxabicyclo[4.1.0]heptan-2-ol} \quad (3.104)\).

Prepared from 3.047 by the general procedure, isolated after flash chromatography (50% v/v ethyl acetate in hexanes) as clear colorless oil (52 mg, 84%); \(R_f = 0.64\) (50% v/v ethyl acetate in hexanes); \(^1\)H NMR (CDCl₃, 400 MHz) \(\delta\) 5.79 (1H, dddd, \(J = 17.5, 10.5, 7.5, 7.0\) Hz), 5.08-5.16 (2H, m), 4.03 (1H, dd, \(J = 7.5, 6.0\) Hz), 2.95 (1H, s), 2.36 (1H, dd, \(J = 14.5, 7.0\) Hz), 2.31 (1H, dd, \(J = 14.5, 7.0\) Hz), 1.82-1.95 (2H, m), 1.66-1.76 (2H, m), 1.42-1.52 (1H, m), 1.23-1.36 (1H, m), 1.12-1.22 (1H, m); \(^1^3\)C NMR (CDCl₃, 100 MHz) \(\delta\) 132.9, 118.2, 66.6, 61.6, 60.7, 41.3, 30.0, 27.5, 15.5; IR (neat) \(\nu_{\text{max}}\) 3428 (br), 2939, 2871, 1641, 1449, 1427, 1353, 1286, 1230, 1162, 1079, 1064, 1045, 1025, 997, 916, 877, 824, 791, 715 cm\(^{-1}\); LRMS (El) \(m/z\) 113.1 (12.1), 108.1 (25.4), 92.1 (20.1), 84.1 (26.4), 83.1 (25.5), 80.1 (31.1), 68.0 (22.6), 65.0 (16.6), 58.0 (14.5), 57.0 (84.9), 55.0 (100.0), 53.0 (16.0), 52.0 (10.6); HRMS (El) \(m/z\) calc’d. for C₉H₁₄O₂ [M]+ 154.0994, found 154.0986.

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(1S,2R,4R,6R)-6-Allyl-1-methyl-4-(prop-1-en-2-yl)-7-oxabicyclo[4.1.0]heptan-2-ol (3.105). Prepared from 3.057 by Payne rearrangement, isolated after flash chromatography (20% v/v ethyl acetate in hexanes) as clear colorless oil (52 mg, 89%); R_f = 0.35 (20% v/v ethyl acetate in hexanes); a mixture of diastereomers (Major Isomer = A, Minor Isomer = B) in a ratio of 93:7 consistent with the ratio of epoxide diastereomers in 3.057 by GC. (vide supra) (52 mg, 89%) isolated as clear, colorless oil; Crude dr ≥ 99:1; Certain peaks of the minor diastereomer that overlapped with the major diastereomer and could not be distinguished and have been omitted. ^1H NMR (CDCl_3, 400 MHz): (Major Isomer = A) δ = 5.97 (1H, dddd, J = 17.0, 10.0, 8.5, 7.0 Hz), 5.17-5.25 (2H, m), 4.71-4.79 (2H, m), 3.10 (1H, m), 2.61 (1H, dd, J = 13.5, 7.0 Hz), 2.25 (1H, dd, J = 14.0, 8.5 Hz), 2.06-2.18 (2H, m), 2.07 (1H, br s), 1.67-1.77 (2H, m), 1.71 (3H, s), 1.36 (3H, s), 1.25 (1H, t, J = 13.0 Hz), (Minor Isomer = B) δ 5.90 (1H, dddd, J = 17.0, 10.5, 8.5, 6.5 Hz), 4.67-4.70 (2H, m), 3.07 (1H, d, J = 5.5 Hz), 2.35-2.52 (2H, m); ^13C NMR (CDCl_3, 100 MHz): (Major Isomer = A) δ 148.76, 133.6, 120.18, 109.73, 71.92, 62.2, 61.7, 41.6, 40.3, 34.7, 31.1, 21.1, 19.4 (Minor Isomer = B) δ 132.9, 119.8, 118.1, 71.2, 65.1, 63.2, 61.6, 60.7, 43.2, , 40.1, 37.0, 35.3, 34.2, 33.1, 29.1, 20.5, 17.1 16.6; IR (neat) ν max 3465 (br), 2973, 2933, 1644, 1435, 1375, 1073, 1025, 914, 888, 769, 731 cm⁻¹; LRMS (EI) m/z 167.1 (43.4), 149.1 (99.4), 131.1 (6.3), 125.1 (19.9), 123.1 (20.7), 121.1 (40.1), 109.1 (19.1), 107.1 (100.0), 105.1 (21.3), 97.1 (11.8), 95.1(19.6), 93.1 (34.2), 91.1 (31.6), 81.1 (22.0), 79.1 (36.8), 77.0 (15.0), 71.1 (19.3), 67.1 (22.2), 55.0 (20.3), 53.0 (14.4), 43.0 (77.0); HRMS (EI) m/z calc’d. for C_{13}H_{18}O [M-H_2O]^+ 190.1358, found 190.1356; Optical rotation of mixture [α]_{D}^{27} = - 45.07° (c = 1.15, CHCl_3).

(1S*,2R*,7S*)-7-Allyl-8-oxabicyclo[5.1.0]octan-2-ol (3.108). Prepared from 3.062, isolated after flash chromatography as a clear colorless oil (40 mg, 85%); Crude dr ≥ 95:5; R_f = 0.2 (25% v/v ethyl acetate in hexanes); ^1H NMR (CDCl_3, 400 MHz) δ 5.71-5.82 (1H, m), 5.09-5.14 (2H, m), 3.75-3.80 (1H, m), 2.93(1H, d, J = 5.5 Hz), 2.41-2.48 (2H, m), 2.26 (1H, dd, J = 14.5, 7.0 Hz ), 2.09-2.17 (1H, m), 1.71-1.83 (3H, m), 1.61-1.69 (1H, m), 1.31-1.43 (3H, m); ^13C NMR (CDCl_3, 100 MHz): δ 133.0, 118.7,
73.9, 66.6, 61.8, 40.8, 34.9, 33.8, 27.3, 24.4; IR (neat) \( \nu_{\text{max}} \) 3386 (br), 2923, 2855, 1641, 1456, 1353, 1103, 1032, 1002, 917, 882, 802, 735 cm\(^{-1}\); LRMS (EI) m/z 150.1 (14.3), 132.1 (15.4), 122.1 (12.5), 121.1 (21.6), 117.1 (16.4), 115.1 (17.2), 109.1 (13.0), 107.1 (16.0), 104.1 (21.4), 97.1 (12.6), 95.1 (10.8), 93.1 (33.6), 91.1 (54.8), 83.0 (11.9), 81.1 (61.30), 80.1 (13.50), 79.1 (100.0), 78.0 (10.9), 77.1 (36.1), 67.1 (30.2), 65.0 (14.5), 55 (21.8), 53.0 (14.2); HRMS (EI) m/z calc’d. for C\(_{10}\)H\(_{14}\)O [M-H\(_2\)O]\(^+\) 150.1045, found 150.1043.

\((R^\ast)-1-((2S^\ast,3R^\ast)-3-Allyl-3-phenyloxiran-2-yl)ethanol \ (3.109)\). Prepared from 3.072 and isolated after flash chromatography (20% v/v ethyl acetate in hexanes) as a colorless oil (50 mg, 88%), Crude dr ≥ 99:1; \( R_f = 0.43 \) (20% ethyl acetate in hexanes); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 7.25-7.37 (5H, m), 5.75 (1H, dddd, \( J = 17.5, 10.5, 7.0, 6.5 \) Hz), 5.08-5.16 (2H, m), 3.85-3.92 (1H, dq, \( J = 8.0, 6.0 \) Hz), 2.76-2.79 (2H, m), 1.41(3H, d, \( J = 6.5 \) Hz); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \( \delta \) 140.6, 133.8, 128.5, 127.8, 126.4, 118.4, 68.9, 66.3, 64.5, 36.8, 21.0.; IR (neat) \( \nu_{\text{max}} \) 3415 (br), 2973, 1642, 1496, 1448, 1371, 1264, 1139, 1068, 994, 914, 757, 721, 698 cm\(^{-1}\); LRMS (EI) m/z 160.1 (16.0), 145.1 (26.5), 131.1 (75.0), 128.1 (42.3), 127.1 (16.3), 120.1 (23.1), 117.1 (20.0), 116.1 (18.5), 115.1 (48.2), 105.0 (100.0), 103.1 (13.6), 91.1 (75.6), 77.0 (38.8); HRMS (EI) m/z calc’d. for C\(_{13}\)H\(_{15}\)O\(_2\) [M]\(^+\) 203.1072, found 203.1071.

\(((2S^\ast, 3R^\ast)-3-Allyl-3-phenyloxiran-2-yl)methanol (3.110)\). Prepared from 3.073 and isolated after flash chromatography (20% v/v ethyl acetate in hexanes) as a colorless oil (50 mg, 94%). \( R_f = 0.29 \) (20% v/v ethyl acetate in hexanes); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 7.25-7.37 (5H, m), 5.72-5.82 (1H, dddd, \( J = 17.0, 10.5, 7.0, 6.5 \) Hz), 5.06-5.12 (2H, m), 3.97 (1H, d, \( J = 12.0 \) Hz), 3.84-3.94(1H, dd, \( J = 12.5, 6.5 \) Hz), 3.16(1H, dd, \( J = 6.5, 4.5 \) Hz), 2.80-2.86 (1H, ddt, \( J = 15.5, 7.0, 1.5 \) Hz), 2.68 (1H, ddt, \( J = 15.5, 6.5, 1.5 \) Hz), 2.10 (1H, s); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \( \delta \) 140.5, 133.2, 128.5, 127.9, 126.3, 118.5, 65.7, 64.0, 61.3, 36.8. IR (neat) \( \nu_{\text{max}} \) 3381 (br), 2890, 1641, 1496, 1448, 1291, 1037, 960, 917, 763, 699 cm\(^{-1}\); LRMS (EI) m/z 160.1 (12.6), 145.1 (13.0), 131.1 (87.1), 129.1 (76.1), 128.1 (49.5), 127.1 (16.5), 120.1 (21.6), 117.1 (11.9), 116.1 (18.9), 115.1 (48.4), 105.0

Prepared by subjecting mixture 3.063 to general Payne rearrangement conditions to afford a crude mixture of 3.107 and the major component of 3.063 in a ratio of 42:58. Separation by flash column chromatography (50% v/v ethyl acetate in hexanes) proved challenging, and only one pure fraction was obtained to give 3.107 (1.2 mg, 5% [based on starting mixture, 87% crude yield of mixture.]) as clear colorless oil, containing traces of hexanes; R<sub>f</sub> = 0.35 (50% v/v ethyl acetate in hexanes); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 5.82 (1H, dddd, J = 17.0, 10.0, 7.0, 7.0 Hz), 5.08-5.21 (2H, m), 4.3 (1H br s), 3.3 (1H, s), 2.50-2.63 (2H, m), 0.95-1.90 (5H, m); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 27.1, 30.7, 35.9, 63.2, 66.9, 72.3, 117.9, 133.1; IR (neat) ν<sub>max</sub> 3420 (br), 2926, 2851, 1712, 1643, 1424, 1312, 1231, 1168, 1059, 982, 919, 836, 713 cm<sup>-1</sup>; LRMS (EI) m/z 123.1 (1.2), 122.1 (6.0), 99.0 (19.3), 91.1 (14.5), 86.0 (41.0), 84.0 (68.1), 81.0 (13.2), 79.1 (46.1), 77.0 (23.0), 71.0 (10.5), 67.1 (31.3), 66.1 (10.5), 65.0 (14.8), 57.0 (15.1), 55.0 (10.8), 53.0 (25.9), 51.0 (45.2), 50 (10.0), 49.0 (100.0), 48.0 (14.5), 47.0 (30.4); HRMS (EI) m/z calc’d. for C<sub>8</sub>H<sub>10</sub>O [M – H<sub>2</sub>O]<sup>+</sup> 122.073, found 122.0736.
Chapter 4
Regioselective Allylation of Indoles Using Potassium Organotrifluoroborates

4 Introduction

4.1 Indole

The name ‘indole’ originates from a combination of indigo and oleum which refers to the method of isolation of aromatic compounds by treatment of the natural indigo dye with a sulfuric acid/sulfuric anhydride mixture. Numerous methods have been developed for the synthesis of indole and its substituted derivatives. Progress in transition metal-catalyzed chemistry has led to the development of several catalytic procedures for the synthesis of indoles with various substituents. The development of various procedures enabling access to new indole structures, and the importance of indole as synthetic targets has resulted in significant interest indole chemistry. For example, the indole alkaloid reserpine has been used for the treatment of central nervous system disorders and is still used as part of a combination of drugs for the treatment of hypertension. Applications of indole alkaloids are not limited to the pharmaceuticals. For example, they are widely used as pigments, in agricultural and in material science. Since the first synthesis of indole over a hundred years ago, its synthesis and functionalization has progressed steadily and various practical methods have been developed to date, many of which have

industrial applications.\textsuperscript{5} While the primary focus of process chemists is to develop mild synthetic methods that are practical, safe, and scalable for large-scale preparation, little research has been devoted to the catalytic functionalization of indoles on an industrial scale. With increasing environmental concerns, economical feasibility and sustainability, the functionalization of indole to achieve valuable intermediates, natural products and biologically active molecules, has become an emerging research area over the last three decades.

4.2 Indole Functionalization

Indole has three sites of primary reactivity; the N1-, C2- and C3-positions of the heterocyclic system. The C3-position is the most reactive side, with reactivity $10^{13}$ times more than the benzene ring (Figure 4.1).\textsuperscript{6} In indole the N–H bond has $pK_a$(N–H) values ranging from 12.36 to 19.5 in H$_2$O\textsuperscript{7} and deprotonation of N1-H is necessary to achieve selective reaction between N1 and electrophiles. The regioselective functionalization of the C2-position in indole is quite challenging and can usually be considered only after the protection of the N1 and C3 positions.

\begin{center}
\textbf{Figure 4.1} The Most Reactive Positions of Indole for Electrophilic Attack
\end{center}

The most reliable and frequently used procedure for the functionalization at C2 of indole is the use of directed ortho metalation (DOM). The use of a directing group at N1 permits facile deprotonation of the C2-position, and the resulting anion can be trapped with various electrophiles. However, the major disadvantages of DOM approaches are the additional steps required for installation and removal of the directing groups. Selected examples of catalytic indole functionalization in aforementioned positions are shown in the following sections to illustrate the scope and limitations of existing methods.

4.2.1 C–N Bond Formation

The regioselective functionalization of indole is arguably the most efficient route to access a diverse range of indole derivatives. The major problem associated with the regioselective functionalization of indole is attributed to the fact that nucleophilicity of the C3-position of indole, is greater relative to that of N1, largely due to the larger HOMO coefficient at C3. Over the last three decades scientist have overcome the issue of regiocontrol through the installation of an electron-withdrawing substituent at C2, such that the substituent decreases the nucleophilicity at C3 through steric interaction, while also increasing the acidity of the N–H proton. However, this strategy suffers from major drawbacks, such as limited substrate scope and the additional steps required for installing/removing the electron-withdrawing groups. Another approach which has been used extensively is to block the C3 position. Buchwald and co-workers reported a copper catalyzed N-arylation of indoles using aryl iodides and trans-N,N'-dimethyl-1,2-cyclohexanediamine as a ligand (Scheme 4.1). A variety of N-phenyl indole substrates can be prepared using this method and a wide range of functional groups were tolerated. Despite the success of this system, this procedure suffers from several limitations. For example, 2-substituted indoles or ortho substituted aryl iodide failed to give the desired cross-coupling products. Competitive cross-coupling reactions were observed using indole substrates bearing an acetimide functionality and lower yields were observed using aryl bromides instead of aryl iodides as coupling partners.

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Hartwig and co-workers reported an iridium–phosphoramidite catalyzed asymmetric N-allylation of indoles.\textsuperscript{10} A screen of a variety of catalysts revealed that the iridium–phosphoramidite (Figure 4.2) was the most efficient catalyst for N-allylation providing high ratios of branched-to-linear adducts with tert-butylcinnamyl carbonate. It is interesting to note that steric or electronic properties of the tert-butylcinnamyl carbonate had little impact on the observed yields or chemoselectivity and stereoselectivity. However, the presence of electron-withdrawing substituents at the C2- and C3-positions of indole was necessary to form the desired products with good yields and chemoselectivity (Table 4.1). For example, a low yield was observed for the N-allylation of 3-phenyl indole (Table 4.1, entry 5).

\textbf{Figure 4.2} Iridium–Phosphoramidite Catalyst

Table 4.1 Hartwig’s Iridium-Catalyzed N- Allylation of 3-Substituted Indoles

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate X</th>
<th>Product</th>
<th>4.015/4.016 (Yield %)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.017 CO₂Me</td>
<td>4.022</td>
<td>96:4 84</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>4.018 CHO</td>
<td>4.023</td>
<td>94:6 87</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>4.019 C(O)Me</td>
<td>4.024</td>
<td>98:2 88</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>4.020 CN</td>
<td>4.025</td>
<td>96:4 93</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td>4.021 Ph</td>
<td>4.026</td>
<td>99:1 21</td>
<td>97</td>
</tr>
</tbody>
</table>

4.2.2 C–C Bond Formation

4.2.2.1 C₂–C Bond Formation

Sames and co-workers reported the first catalytic functionalization of N-substituted indoles. Sames and co-workers reported the first catalytic functionalization of N-substituted indoles. It was demonstrated that precise control of the substrate to catalyst ratio was necessary to achieve good yields since the major by-product was biphenyl formed through homo-coupling of aryl iodide. An inverse relationship between the catalyst loading and the chemical yields was observed and the optimum catalyst loading was found to be 0.5 mol%. The procedure developed exhibited a high degree of functional group tolerance.

Scheme 4.2 Sames’ C₂-Arylation of N-Methyl Indoles

However, lower yields were observed for indoles bearing methoxy or phenylsulfonamide substituents. The mechanism of this transformation has not yet been fully elucidated. Based on the observed regioselectivity, the authors postulated that nucleophilic palladation or carabopalladation were plausible mechanisms for this transformation. Fagnou and co-workers reported an oxidative cross-coupling of arenes with \( N \)-pivalyl indole.\(^\text{12}\) After an extensive screen of oxidants, bases and substituents on the indole nitrogen, optimal yields of C2-coupling products were obtained using palladium triflate, silver acetate as base, a pivalyl \( N \)-protecting group and pivalic acid as an additive (Scheme 4.3). The optimized reaction condition was compatible with various functional groups on the indole ring and the electronic properties of the substituents had little impact on the outcome of the reaction. It is interesting to note that upon using copper(II) salts as oxidants, the observed regioselectivity of this transformation was altered entirely to achieve C3-coupling products predominantly.

\[
\begin{align*}
\text{Scheme 4.3 Fagnou's Oxidative Cross-Coupling of Benzene with } N\text{-Pivalyl Indole}
\end{align*}
\]

\[\text{4.2.2.2 C3–C bond formation}\]

Due to the high nucleophilicity at the C3-position, various methods have been developed for C3–C bond formation of indoles through reaction with carbon electrophiles.\(^\text{13}\) Widely utilized transformations for this purpose are Friedel-Crafts acylation, Friedel-Crafts alkylation and

\[\text{References:}\]
Michael additions to α,β-unsaturated carbonyl compounds. Although the C3-position is the most reactive towards electrophilic aromatic substitution, competitive functionalization at N1 and C2 positions can be observed. In order to achieve high regioselectivity, the reactivity of the N1 and C2 should be altered to minimize potential side products. Tamarau and co-workers reported an elegant method for modifying the N1 and C2 reactivity for the allylation of the C3-position of indoles using triethylborane.\textsuperscript{14} The actual role of the triethylborane is not fully understood. The developed procedure has significant advantages over classical alkylation methods. For example, alcohols were used as the alkylating agents instead of using traditional alkyl halides and various functional groups on indole rings were tolerated, some of which require protection under traditional alkylation methods. However, the method was synthetically useful for the allylation, although a combination of linear and branched alkylation products were observed using alcohols with a higher degree of substitution. The observed linear- to- branched ratio was influenced by steric factors. With increasing size of the R group on allyl donor, the linear product 4.040 was isolated as a major product. Interestingly, N-methyl indole failed to give allylation product under the reaction conditions.

\textbf{Scheme 4.4} Tamarau’s Allylation of C3-Position of Indoles Using Triethylborane

Trost and Quancard applied the modified version of the Tamarau’s procedure for enantioselective allylation of C3-substituted indoles to generate quaternary centers at the C3 position.\textsuperscript{15}

4.3 Boron-Based Functionalization of Indoles

Allylation of imines is one of the most important C–C bond formation methods in organic synthesis, owing to the versatile transformations available for alkene bond. For example, the homoallylic amine products can be further manipulated to access useful β-amino acids. However, addition of the allyl nucleophiles to imines poses several challenges such as: lower reactivity of the imine functionality relative to the corresponding carbonyl, potential E/Z isomerization of linear imines and tautomerization of imines bearing α-protons. Boron-based reagents have unique properties to circumvent the aforementioned challenges, for example, the high Lewis acidity of boron reagents increases the reactivity of the imine functionality, and the lower basicity of the boron reagents minimizes the potential tautomerization of imines with α-protons.\textsuperscript{16} The allylation of nitriles can be achieved using triallylboranes.\textsuperscript{17} Bubnov and co-workers have applied identical conditions for the allylation of heterocycles using triallylboranes.\textsuperscript{18} These heterocycles have lower reactivity than imines towards nucleophilic addition and, successful addition was achieved only using highly reactive triallylborane at elevated temperatures. For example, pyridines underwent allylation to afford trans-α,α′-diallylation which upon subsequent treatment with triallylborane and base afforded the thermodynamically more stable cis-α,α′-diallyl-tetrahydropryridine (Scheme 4.5).

Most indole functionalization has utilized the unique nucleophilic properties of indole and very little attention has been devoted to umpolung properties of the indole, whereby the indole ring will act as an electrophile. Indole is in equilibrium with $3H$-indole, which can be subjected to a number of irreversible bond forming reactions (Figure 4.3). The equilibrium constant in aqueous solution for the tautomerization of indole $\text{4.001}$ to $3H$-indole $\text{4.047}$ is $pK_T = 5.8 \pm 0.2$. The tautomerization can be catalyzed by acid or base, however, the tautomerization is less efficient under basic conditions.

Bubnov utilized this strategy and reported the nucleophilic allylation of indole at the C2-position to generate 2-allyl indolines (Scheme 4.6).\textsuperscript{18} Substituents on the indole rings had little impact on the yield of the reaction and substituents at the C3-position of indole led to the formation of anti addition products predominantly. This same procedure has been applied for other boron reagents namely prenylboron reagents.\textsuperscript{20}

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4.4 Applications of Boron-Based Functionalization of Indoles

Substituted indole scaffolds are among the most commonly occurring alkaloids in nature. Owing to their biological properties, prenylated indole alkaloids have been extensively investigated. Danishefsky and co-workers reported the total synthesis of gypsetin using boron-based reverse prenylation reaction at the C2-position of an N-phthaloyl-protected tryptophan. Treatment of 4.053 with tert-butylhypochlorite and triethylamine afforded the unstable 3-chloroindolenine 4.054 which was subsequently reacted with freshly prepared prenyl-9-BBN yielding the intermediate 4.055 (Scheme 4.7). Intermediate 4.055 was further subjected to functional group manipulations in order to achieve the total synthesis of gypsetin. Interestingly, under identical reaction conditions using other prenyl nucleophile sources such as prenyl tri(n-butyl)stannane and prenyl trimethylsilane failed to give the desired product with the chloroindolenine 4.054.

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Trauner and co-workers applied the reverse prenylation method for the total synthesis of variecolortide A.\textsuperscript{24} \textit{In situ} generated 3-chloro indolenine from 5-prenyl indole and \textit{N}-chlorosuccinimide, upon treatment with 9-prenyl-BBN, afforded the 2,5-bisprenylated indole \textbf{4.058} (Scheme 4.8). The intermediate \textbf{4.058} was further elaborated to achieve the total synthesis of variecolortide A.

\textbf{Scheme 4.7} Danishefsky’s Total Synthesis of Gypsetin

\textbf{Scheme 4.8} Trauner’s Total Synthesis of Variecolortide A

The prenyl-9-BBN procedure has been applied by Williams and co-workers in the total synthesis of notoamide J. Electrophilic chlorination of Boc-protected 5-hydroindole afforded the 3-chloroindole, which was reacted with prenyl-9-BBN in the presence of triethylamine to afford the 2-prenylindole in 48% isolated yield. The low isolated yield was attributed to the difficulties associated with the complete removal of excess prenylboron reagents.

Scheme 4.9 Williams’ Total Synthesis of Notoamide J

4.5 Results and discussion

4.5.1 Objectives

The major disadvantages of Bubnov’s procedures for the allylation and prenylation of indoles are in the use of triallylborane or triprenylborane reagents. Specific precautions are required for the preparation and handling of these reagents since they are oxygen sensitive pyrophoric substances. Triallylborane is very reactive towards various functional groups and generally is prepared immediately prior to use. Danishefsky attempted to increase the stability of the triprenylborane using prenyl-9-BBN. However, the major problem associated with his procedure,

is the use of 3-methylbuta-1,2-diene gas and 9-BBN for the preparation of the reagent, and the sequential distillation required for purification of the product. Additionally, activation of the indole ring and excess amounts of the prenyl-9-BBN reagent are necessary to achieve acceptable yields.

Batey and Thadani reported the synthesis of potassium-allyl and crotyltrifluoroborates as stable surrogates for the allyl and crotylorganoboron reagents. Later, Batey and Li reported diastereoselective allylation and crotylations of N-tosylimines using potassium-allyl and crotyltrifluoroborates in the presence of catalytic BF$_3$·Et$_2$O. It was of interest to develop a method for the regioselective allylation- and crotylation of indoles using potassium-allyl and crotyltrifluoroborates. Because of the stability of organotrifluoroborates, it was anticipated that a procedure based on these reagents would preclude the requirement of using an inert atmosphere or the special requirements, which are necessary using trialkylborane reagents.

4.5.2 Reaction Optimization

Following prior success with K-10 and indium for \textit{in situ} activation of potassium allyltrifluoroborate towards nucleophilic addition to carbonyl compounds, these protocols for nucleophilic addition to indole gave only moderate conversions of indole to 2-allyl indoline due to competing side reactions (Table 4.2, entries 1-2). Increasing the reaction times beyond 48 hours did not improve the yield. The optimal indium procedure developed for ketones, failed to give the desired product (Table 4.2, entry 3). Therefore, alternative conditions using a variety of Lewis acids and solid additives were examined in order to establish a protocol suitable for achieving controlled addition at the C2-position while minimizing by-product formation. Control experiments indicated that a competing reaction dominated at higher concentration (Table 4.2, entries 6–7). For example, using a catalytic amount of BF$_3$·Et$_2$O under 0.33 M conditions with respect to indole, dimerization of the indole was a major by-product. It is well established that indole derivatives undergo dimerization under acid conditions. Decreasing the concentration to 0.1 M, eliminated the dimerization pathway, but failed to give full conversion. A screen of variety of other Lewis acids revealed that Sc(OTf)$_3$, In(OTf)$_3$, Yb(OTf)$_3$ and BF$_3$·Et$_2$O were

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capable of promoting addition to 4.001, however the isolated yields of 4.049 were disappointing (Table 4.2, entries 9–12). Attempts to increase the solubility of the Lewis acids failed to achieve full conversion (Table 4.2, entries 13–14). Using allyl boronic acid pinacol ester instead of allyltrifluoroborate gave poor results (Table 4.2, entries 16–18). Inconsistent results were observed using a catalytic amount of Lewis acid and the results were substrate/reagent dependent. For example, allylation of indoles bearing substituents at the 2- and 3-positions failed to achieve full conversion using a catalytic amount of Lewis acid (Table 4.3, entries 9, 12 and 13). Additionally, low yields or incomplete conversions were observed using less reactive E- and Z-crotyltrifluoroborates under catalytic conditions (Table 4.3, entries 4 and 6).

Table 4.2 Optimization of Nucleophilic Allylation of Indole Using Potassium Allyltrifluoroborate

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Conv.(Yield %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K-10, CH₂Cl₂, H₂O</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>K-10, CH₂Cl₂, H₂O</td>
<td>50ᵇ</td>
</tr>
<tr>
<td>3</td>
<td>In (1.0 equiv.), CH₂Cl₂, H₂O</td>
<td>≤ 5</td>
</tr>
<tr>
<td>4</td>
<td>Cu(OAc)₂ (10 mol%), 4Å MS, CH₂Cl₂, H₂O</td>
<td>≤ 5</td>
</tr>
<tr>
<td>5</td>
<td>Al₂O₃ (0.1 g), CH₂Cl₂, H₂O</td>
<td>≤ 5</td>
</tr>
<tr>
<td>6</td>
<td>BF₃·Et₂O (15.0 mol%), CH₂Cl₂</td>
<td>45ᶜ</td>
</tr>
<tr>
<td>7</td>
<td>BF₃·Et₂O (15.0 mol%), CH₂Cl₂</td>
<td>25ᵈ</td>
</tr>
<tr>
<td>8</td>
<td>Cu(OTf)₂ (15.0 mol%), CH₂Cl₂</td>
<td>21 (-)</td>
</tr>
<tr>
<td>9</td>
<td>Sc(OTf)₃ (15.0 mol%), CH₂Cl₂</td>
<td>100 (72)</td>
</tr>
<tr>
<td>10</td>
<td>In(OTf)₃ (15.0 mol%), CH₂Cl₂</td>
<td>80 (68)</td>
</tr>
<tr>
<td>11</td>
<td>Yb(OTf)₃ (15.0 mol%), CH₂Cl₂</td>
<td>100 (79)ᵉ</td>
</tr>
<tr>
<td>12</td>
<td>BF₃·Et₂O (100 mol%), CH₂Cl₂</td>
<td>100 (92)</td>
</tr>
<tr>
<td>13</td>
<td>Sc(OTf)₃ (15.0 mol%), CH₃CN</td>
<td>28</td>
</tr>
<tr>
<td>14</td>
<td>Sc(OTf)₃ (15.0 mol%), CH₂Cl₂, H₂O</td>
<td>≤ 5</td>
</tr>
<tr>
<td>15</td>
<td>Ag OTf (15.0 mol%), CH₂Cl₂</td>
<td>10⁹</td>
</tr>
<tr>
<td>16</td>
<td>In(OTf)₃ (15.0 mol%), CH₂Cl₂</td>
<td>≤ 5⁹</td>
</tr>
<tr>
<td>17</td>
<td>Sc(OTf)₃ (15.0 mol%), CH₂Cl₂</td>
<td>≤ 5⁹</td>
</tr>
<tr>
<td>18</td>
<td>In (1.0 equiv.) CH₂Cl₂, H₂O</td>
<td>≤ 5⁹</td>
</tr>
</tbody>
</table>

a) The conversion was monitored using ¹H NMR of the crude products. b) The reaction was performed under inert atmosphere for 48 h. c) The reaction was performed at 0.33 M with respect to indole. Dimerization of indole was a major by-product. d) The indole concentration was 0.1 M, 36 h. e) Full conversion was observed after 12 h. f) Allyl boronic acid pinacol ester was used as the allylating agent.
Fortunately, consistent results were obtained using a stoichiometric amount of BF₃·Et₂O as an additive for *in situ* activation of organotrifluoroborates 4.064-4.066 (Table 4.3, entries 3, 5, 8, 11 and 14). However, 2-methyl indole and reactions using Z-crotyl trifluoroborate were slower and longer reaction times were required to achieve full conversions. It is interesting to note that N-methylindole failed to give the desired product even under the stoichiometric amount of BF₃·Et₂O conditions (Table 4.3, entry 16).

**Table 4.3 Optimization of the Reaction for Substituted Indoles with Allyl- and Crotyltrifluoroborates 4.064, 4.065 and 4.066**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R-BF₃K</th>
<th>Conditions</th>
<th>Product</th>
<th>Conv. (Yield %)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.065</td>
<td>K-10, CH₂Cl₂, H₂O</td>
<td>4.070</td>
<td>100 (72)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4.066</td>
<td>K-10, CH₂Cl₂, H₂O</td>
<td>4.071</td>
<td>&lt; 10</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4.065</td>
<td>BF₃·Et₂O (100 mol%), CH₂Cl₂</td>
<td>4.070</td>
<td>100 (88)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4.066</td>
<td>Sc(OTf)₃ (15 mol%), CH₂Cl₂</td>
<td>4.071</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>4.066</td>
<td>BF₃·Et₂O (100 mol%), CH₂Cl₂</td>
<td>4.071</td>
<td>100 (89)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4.066</td>
<td>Yb(OTf)₃ (15 mol%), CH₂Cl₂</td>
<td>4.071</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>4.064</td>
<td>BF₃·Et₂O (100 mol%), CH₂Cl₂</td>
<td>4.072</td>
<td>≤ 5</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>4.064</td>
<td>Yb(OTf)₃ (15 mol%), CH₂Cl₂</td>
<td>4.072</td>
<td>100 (83)b</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>4.064</td>
<td>Yb(OTf)₃ (15 mol%), CH₂Cl₂</td>
<td>4.072</td>
<td>65 (-)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>4.064</td>
<td>K-10, CH₂Cl₂, H₂O</td>
<td>4.073</td>
<td>≤ 5</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>4.064</td>
<td>BF₃·Et₂O (100 mol%), CH₂Cl₂</td>
<td>4.073</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>4.064</td>
<td>Sc(OTf)₃ (15 mol%), CH₂Cl₂</td>
<td>4.073</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>4.064</td>
<td>Yb(OTf)₃ (15 mol%), CH₂Cl₂</td>
<td>4.073</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>4.065</td>
<td>BF₃·Et₂O (100 mol%), CH₂Cl₂</td>
<td>4.074</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>4.064</td>
<td>K-10, CH₂Cl₂, H₂O</td>
<td>4.075</td>
<td>≤ 5</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>4.064</td>
<td>BF₃·Et₂O (100 mol%), CH₂Cl₂</td>
<td>4.075</td>
<td>≤ 5</td>
<td></td>
</tr>
</tbody>
</table>

a) Isolated yield. b) Observed dr was 2.1:1 based on the crude ¹H NMR. c) Observed dr was 1.7:1 based on the ¹H NMR of the crude product.
The optimal reaction conditions were found to utilize stoichiometric BF$_3$·Et$_2$O with respect to substrate, two equivalents of organotrifluoroborates and dichloromethane as a solvent (Table 4.3).

With optimized conditions developed, it became of interest to evaluate the scope of the allylation of various substituted indoles (Table 4.4). Electronic effects had little impact on outcome of the allylation reaction and indoles bearing various electron-donating and electron-withdrawing substituents were allylated efficiently, affording the desired products in excellent yields (Table 4.4, entries 1-6). Steric effects of substituents on the indole ring were detrimental to the reaction progress and significantly longer reaction times were required to achieve full conversion. For example, full conversion was observed only after 72 hours for the 7-methyl, 3-methyl and 2-methyl substrates (Table 4.4, entries 7-9). The lower reactivity of the 7-methyl indole can be attributed to the unfavorable syn-pentane-like interactions between the methyl and BF$_2$ groups in the transition state 4.105 and 4.108 (see Figure 4.6). The corresponding allylated product from 3-methyl indole 4.072 was obtained in good yield but poor diastereoselectivity, favoring the anti relative configuration (Table 4.4, entry 8). Substitution at the C2-position slowed reaction progress and longer reaction time and/or larger quantities of reagents were necessary to achieve full conversion (Table 4.4, entries 9-10). For example, 2-phenyl indole required 3.0 equivalents of allyltrifluoroborates and BF$_3$·Et$_2$O over 74 h to afford 4.091 in 85% isolated yield. Allylation of sterically demanding 4.083 was very slow and 54% conversion observed after 74 hours (Table 4.4, entry 11). Attempts to mono-allylate 3-chloroindole were unsuccessful and using excess allyltrifluoroborate (4.0 equiv.), α,α-diallylated 4.093 was obtained as the sole product (Table 4.4, entry 12).
Table 4.4 Substrate Scope for the Allylation of Indoles Using Allytrifluoroborates

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)€</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(X = H)</td>
<td>(X = H)</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>(X = 5-Br)</td>
<td>(X = 5-Br)</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>(X = 5-Cl)</td>
<td>(X = 5-Cl)</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>(X = 5-F )</td>
<td>(X = 5-F )</td>
<td>79</td>
</tr>
<tr>
<td>5</td>
<td>(X = 5-OH)</td>
<td>(X = 5-OH)</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>(X = 5-CO₂Me)</td>
<td>(X = 5-CO₂Me)</td>
<td>86</td>
</tr>
<tr>
<td>7</td>
<td>(X = 7-Me)</td>
<td>(X = 7-Me)</td>
<td>87€</td>
</tr>
<tr>
<td>8</td>
<td>(X = 3-Me)</td>
<td>(X = 3-Me)</td>
<td>87(2.1:1)</td>
</tr>
<tr>
<td>9</td>
<td>(X = 2-Me)</td>
<td>(X = 2-Me)</td>
<td>91</td>
</tr>
<tr>
<td>10</td>
<td>(X = 2-Ph)</td>
<td>(X = 2-Ph)</td>
<td>85€</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td></td>
<td>38€</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td>88€</td>
</tr>
</tbody>
</table>

a) Indole substrates (0.5 mmol), potassium allyltrifluoroborate (0.147 g, 1.0 mmol), BF₃·Et₂O (62.0 μL, 0.5 mmol) and CH₂Cl₂ (4.0 mL, 0.125 M). b) Isolated yields. c) 3.0 equivalents of potassium allyltrifluoroborate and BF₃·Et₂O were required over 62 h to achieve full conversion. d) Yield of combined anti:syn diastereomers and the dr was 2.1:1 based on the crude ¹H NMR. e) Conversion was 52% after 74 h. f) 4.0 equivalents of potassium allyltrifluoroborate were used.

The scope of the procedure using other organotrifluoroborate salts was then investigated. Although prenylation and allylation of indoles have been studied extensively, little investigation has been devoted to regioselective crotylation and propargylation of indole at the C2-position. The developed procedure was successfully applied for the crotylation of indole using E- and Z-crotyltrifluoroborates, affording the anti and syn products 4.070 and 4.071 respectively in good yields and excellent diastereoselectivities (Table 4.5, entries 1-2).
Table 4.5 Substrate Scope with Respect to the Allylating Agent

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R-BF₃K</th>
<th>Product</th>
<th>Yield (%) [dr]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Substrate 1" /></td>
<td>Me <img src="image2.png" alt="BF₃K" /></td>
<td><img src="image3.png" alt="Product 1" /></td>
<td>95 (≥ 95:5)</td>
</tr>
<tr>
<td>2</td>
<td><img src="image4.png" alt="Substrate 2" /></td>
<td>Me <img src="image5.png" alt="BF₃K" /></td>
<td><img src="image6.png" alt="Product 2" /></td>
<td>83 (≥ 95:5)</td>
</tr>
<tr>
<td>3</td>
<td><img src="image7.png" alt="Substrate 3" /></td>
<td><img src="image8.png" alt="Me" /> <img src="image9.png" alt="BF₃K" /></td>
<td><img src="image10.png" alt="Product 3" /></td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td><img src="image11.png" alt="Substrate 4" /></td>
<td><img src="image12.png" alt="Me" /> <img src="image13.png" alt="BF₃K" /></td>
<td><img src="image14.png" alt="Product 4" /></td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td><img src="image15.png" alt="Substrate 5" /></td>
<td>Me <img src="image16.png" alt="BF₃K" /></td>
<td><img src="image17.png" alt="Product 5" /></td>
<td>91(95:5)</td>
</tr>
</tbody>
</table>

a) Isolated yields. b) Diastereomeric ratio determined by ¹H NMR analysis of the crude products by comparison of the most up-field methyl chemical shift. c) Full conversion achieved using 3.0 equivalents of trifluoroborate salt and BF₃·Et₂O (2.0 equiv.) over 74 h.
However, reaction using potassium Z-crotyltrifluoroborate required a larger quantity of the reagents and longer reaction time to achieve full conversion. Using potassium allenyltrifluoroborate under identical conditions, led to propargylation of indole to afford 4.097 as the sole product. This is the first example of propargylation of indole using an allenelylboron reagent, perhaps because allenylboron reagents are known to decompose at temperatures above -20 °C.29

4.5.3 Stereochemistry of Crotylation

In order to unambiguously elucidate the relative configuration of the crotylation products, 4.070 and 4.071 were treated with acryloyl chloride in the presence of Hüning’s base to afford the 4.099 and 4.102, that were further subjected to ring closing metathesis using Grubbs catalyst 4.100, resulting in the formation of tricyclic amides 4.101 and 4.103 respectively in excellent yields (Scheme 4.10). To determine the relative configuration of the C9 methyl and C9a hydrogen in compounds 4.101 and 4.103, crystallization attempts failed to give satisfactory results.

![Scheme 4.10 Preparations of Lactams from 4.070 and 4.071](image)

Through-space NMR techniques (n.O.e.) were applied to clarify the relative stereochemistry. The observed n.O.e. data alone was not sufficient to elucidate unambiguously the relative

stereochemistry. The combination of $^3J$ and $^4J$ ($^1H$, $^1H$) and n.o.e. methods have been used to elucidate the relative stereochemistry of rigid cyclic systems. During the last decade several universal $J$-based NMR databases have been developed for the assignment of relative configuration of acyclic,\textsuperscript{30} polyketide\textsuperscript{31} and chlorinated natural products.\textsuperscript{32} Since the pioneering studies by Barfield and others,\textsuperscript{33} extensive theoretical and experimental investigations on the $^1H$-$^1H$ allylic coupling have also been published.\textsuperscript{34} These studies indicated that the sign and magnitude of allylic coupling is dependent upon the dihedral angle ($\phi$),\textsuperscript{35} which by Barfield’s definition is the angle between allylic C-H and the plane of $\pi$-orbitals as illustrated below for \textbf{4.103} (Figure 4.4).

\begin{align*}
    ^3J_{\pi\sigma} & \approx 6.6 \cos^2 \phi + 2.6 \sin^2 \phi \ (0^\circ \leq \phi \leq 90^\circ) \\
    ^3J_{\pi\sigma} & \approx 11.6 \cos^2 \phi + 2.6 \sin^2 \phi \ (180^\circ \geq \phi \geq 90^\circ) \\
    ^4J_{\pi\sigma} & \approx -1.3 \cos^2 \phi - 2.6 \sin^2 \phi \ (0^\circ \leq \phi \leq 90^\circ) \\
    ^4J_{\pi\sigma} & \approx -2.6 \sin^2 \phi \ (180^\circ \geq \phi \geq 90^\circ)
\end{align*}

\textbf{Figure 4.4} Coupling Constant Relationship to Dihedral Angle

Figure 4.5 Data for Elucidation of 4.101 and 4.103 Relative Stereochemistry. (A) B3LYP/6-31G* Minimized Structure.\(^{36}\) (B) Observed n.O.e. data. (C) Observed and calculated coupling constant data.

\(^{36}\) 4.101 is 1.4 kcal/mol lower in energy at the B3LYP/6-31G* level of theory (gas state, Spartan 04 Macintosh).
The 3D structures of 4.101 and 4.103 are shown above (Figure 4.5 A), showing a twisted cyclohexene geometry. Analysis of the n.O.e. experiments, $^3J(1^H, 1^H)$ and $^4J(1^H, 1^H)$ were sufficient to elucidate the relative stereochemistry. Strong n.O.e. correlations were observed between the C9a-$H$ and C9-$H$ in both compounds. However, the most useful information from the n.O.e. data analysis was the presence of a strong n.O.e. correlation between the C9a-$H$ and C9-$Me$ in compound 4.101, which was absent in the compound 4.103 (Figure 4.5 B). This observation indicates that the C9a-$H$ and C9-$Me$ have syn and anti relationships in the compounds 4.101 and 4.103 respectively. This conclusion was further confirmed by an analysis of corresponding $^3J(1^H, 1^H)$ and $^4J(1^H, 1^H)$ coupling constants (Figure 4.5 C) and the related dihedral angles of the protons from the minimized structure computed at the B3LYP/6-31G* level of theory and using the formula in Figure 4.4. The observed large $^3J(1^H, 1^H)$ coupling constant of 12.7 Hz between C9-$H$ and C9a-$H$ in 4.101 correlates well with the calculated $^3J(1^H, 1^H)$ with a dihedral angle of -172° and the observed small $^3J(1^H, 1^H)$ coupling constant of 4.5 Hz between C9-$H$ and C9a-$H$ in 4.103 is consistent with the calculated $^3J(1^H, 1^H)$ with a small dihedral angle of 45°. A small $^4J(1^H, 1^H)$ coupling constant of 1.7 Hz is observed between C7-$H$ and C9-$H$ for compound 4.101, and correlates well with the corresponding dihedral angle. Surprisingly, similar coupling was not observed for the compound 4.103 suggesting a very small (unobservable) coupling constant which is consistent with the calculated $^4J(1^H, 1^H)$. This data indicates anti and syn relative stereochemistry for the products 4.070 and 4.071 respectively.

It is known that the addition of crotylboron reagents to aldimines and ketimines varies significantly and in the case of acyclic aldimines, the stereospecific addition of E-and Z-crotylborons occurs to afford syn and anti products respectively. The observed opposite diastereoselectivity relative to the aldehydes analogues, is rationalized based on minimizing the steric interaction of the imine substituents and boron reagents in the transition states. However, for the crotylation of indole using E- and Z-crotyltrifluoroborates, the diastereoselective additions occurred stereospecifically, affording anti and syn products respectively, consistent with an allylboron difluoride intermediate, as observed in the crotylation of aldehydes. These results can be attributed to the rigid Z-configuration of the imine geometry (rather than an E-configuration for an acyclic imine), with reaction presumably proceeding though a Zimmerman–

Traxler–like transition state. Four plausible transitions states are shown below for reactions via $E$- and $Z$-crotyltrifluoroborates (Figure 4.6). Chair-like transition states 4.105 and 4.108 are favored over boat-like transition states 4.106 and 4.107 due to reduced syn pentane-like interactions. These cyclic transition states rationalize many of the observed results. For example, the transition state 4.108 can also be used to rationalize the lower reactivity of the $Z$-crotyltrifluoroborate because of the steric interaction between the methyl group of trifluoroborate and the C3H-indole. A similar rationale can be applied for the lower reactivity of the C7-substituted indole derivatives due to syn pentane-like interaction between the substituent and the B–F in the transition state 4.105. Additionally, the cyclic transition state can be used to rationalize the need for a free imine for addition to occur, as N-methyl indole failed to give any conversion.

![Figure 4.6 Plausible Transition States for Crotylation of Indole](image)

4.6 Conclusions

A regioselective allylation- and crotylation procedure of indoles using organotrifluoroborates has been developed. Because of the stability of organotrifluoroborates, the requirements of using an inert atmosphere or any special equipment usually necessary using trialkylborane reagents are avoided. Regioselective allylation and diastereoselective crotylation of various indoles were
achieved efficiently in good yields, showing that the electronic effects of the substituents on the indole ring had little effect on the outcome of the reaction. However, steric factors were more influential on the reactivity of the substrates and yields of products. Stereospecific and diastereoselective addition of the E- and Z-crotyltrifluoroborates could also be achieved under the reaction conditions, providing the corresponding anti and syn products, respectively. The method is quite robust and provides an operationally straightforward procedure for the allylation of a range of indoles using the air and moisture stable potassium allyl and crotyltrifluoroborate salts. It precludes the requirement for reaction under inert atmosphere conditions which is required for triallyboron and prenyl-9-BBN reagents. The reaction mechanism presumably involves the reaction of an allylboron difluoride intermediate with an imine, since the reaction occurs under anhydrous conditions but requires the presence of boron trifluoride etherate for fluoride ion abstraction to activate the nucleophile.

It will be interesting to expand the scope of this method for the synthesis of natural alkaloids. Expansion of this method using various substituted crotyl reagents will also be valuable, since crotylation of indole and subsequent oxidation of the intermediates should provides access to indoles having branched alkyl chain at the C2-position. Ultimately expansion of this method to a one-pot allylation (or crotylation) / metal-catalyzed oxidation should allow access to 2-substituted indoles, in a procedure that is an alternative to C2-H activation.

4.7 Experimental Procedures

The following general experimental considerations apply for all experiments described in this section. Unless otherwise stated, all reactions were performed under nitrogen or argon atmosphere using oven (140 °C) and flame dried glassware. Reaction solvents were distilled under an inert atmosphere before use and transferred via syringe using standard techniques. Dichloromethane (CH$_2$Cl$_2$) was distilled from CaH$_2$ under nitrogen. Tetrahydrofuran (THF) and diethyl ether (ether) were distilled from sodium under nitrogen. Anhydrous methanol was used as received from Aldrich. All reagents, unless otherwise stated, were used as received from their respective providers (Aldrich, Alfa Aesar, STREM or ACP). Commercially available potassium allyltrifluoroborate was prepared by the known procedure.$^{26}$ Indium metal 99.99% trace metal basis, 100-mesh was purchased from Aldrich, and used without activation.
Infrared spectra were recorded on a Perkin-Elmer Spectrum 100 FT-IR with universal ATR attachment as neat samples or using a Shimadzu FT-IR 8400S spectrometer for thin film samples. $^1$H and $^{13}$C NMR spectra were obtained on a Varian Mercury 400 MHz spectrometer as a solution in chloroform-$d$, and chemical shifts are expressed in parts per million (ppm) relative to TMS. Peak multiplicities are designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; dt, doublet of triplets and so forth; br, broad (this abbreviation is also used for designation of IR peaks); $J$, coupling constant in Hertz (Hz); str denoted a strong IR band. High resolution mass spectra (HRMS) were recorded on direct analysis in real time (DART) technique using JEOL AccuTOF and accurate masses were determined within ± 5 ppm of the calculated mass. Melting points were obtained on a Fisher-Johns melting point apparatus and are uncorrected.

Flash column chromatography on silica gel (60Å, 230 - 400 mesh, obtained from Silicycle Inc.) was performed using reagent grade solvents. Analytical thin-layer chromatography (TLC) was performed on pre-coated aluminum-backed silica gel plates (Alugram SIL G/UV$_{254}$ purchased from EMD Inc.), visualized with a UV lamp (254 nm), iodine, ninhydrin, potassium permanganate, $p$-anisaldehyde, phosphomolybdic acid (Aldrich), or vanillin. References following the compound names indicate literature articles where full characterization of all spectral and physical properties has previously been reported.

**General procedure for the preparation of 2-substituted indolines:**

To an oven dried 5 mL round-bottomed flask was added indole (0.5 mmol), potassium allyltrifluoroborate (1.00 mmol), BF$_3$·Et$_2$O (62 μL, 0.50 mmol) and dichloromethane (4.0 mL), followed by vigorous stirring at room temperature. The reaction was monitored by TLC, and upon completion it was quenched by addition of HCl (3.0 mL, 1N). The mixture was neutralized by addition of saturated NaHCO$_3$ and extracted with Et$_2$O (3×10 mL) and dried over MgSO$_4$. The solvent was removed in vacuo to afford the crude indoline, that was subsequently purified by flash column chromatography on silica gel.
Analytical data for 2-substituted indolines:

Diastereomeric ratios were determined by the relative intensities of distinct protons in the crude products. The indoline derivatives are prone to oxidation upon standing at room temperature and characterization was done immediately after isolation. The purified samples are stable at -20 °C.

2-Allylindoline (4.049). After reaction at 12 h at room temperature, followed by standard work-up, 4.049 was isolated after flash chromatography (20% v/v ethyl acetate in hexanes) as a clear, colorless oil; (73 mg, 92%); R<sub>f</sub> = 0.70 (20% v/v ethyl acetate in hexanes);<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 7.06 (1H, dd, J = 7.5, 1.0 Hz), 6.98 (1H, ddd, J = 7.5, 7.5, 1.0 Hz), 6.66 (1H, ddd, J = 7.5, 7.5, 1.0 Hz), 6.58 (1H, d, J = 7.5 Hz), 5.76-5.86 (1H, m), 5.08-5.13 (2H, m), 3.88 (2H, dddd, J = 8.5, 7.5, 7.5, 6.0 Hz), 3.12 (1H, dd, J = 15.5, 8.5 Hz), 2.72 (1H, dd, J = 15.5, 7.5 Hz), 2.24-2.39 (2H, m);<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 150.6, 135.2, 128.4, 127.3, 124.7, 118.5, 117.5, 109.2, 58.6, 40.9, 35.6.

(S<sup>*</sup>)-2-((S<sup>*</sup>)-But-3-en-2-yl)indoline (4.070). After reaction at 25 h at room temperature, followed by standard work-up, 4.070 was isolated after flash chromatography (20% v/v ethyl acetate in hexanes) as a clear, colorless oil; (83 mg, 95%). Crude dr = 95:5; R<sub>f</sub> = 0.23 (50% v/v ethyl acetate in hexanes);<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 7.04 (1H, dd, J = 7.0, 1.0 Hz), 6.98 (1H, ddd, J = 7.5, 7.5, 1.0 Hz), 6.66 (1H, ddd, J = 7.5, 7.5, 1.0 Hz), 6.56 (1H, d, J = 7.5 Hz), 5.72 (1H, ddd, J = 17.0, 10.0, 8.5 Hz), 5.06-5.13 (2H, m), 3.95 (1H, br s), 3.60 (1H, dd, J = 8.5, 8.5, 8.5 Hz), 3.06 (1H, dd, J = 15.5, 8.5 Hz), 2.76 (1H, dd, J = 15.5, 8.5 Hz), 2.25 (1H, ddq, J = 8.5, 8.5, 6.5 Hz), 1.04 (3H, d, J = 6.5 Hz);<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 150.9, 141.6, 128.6, 127.3, 124.6, 118.3, 115.5, 108.8, 64.1, 44.0, 33.9, 16.8; IR (neat) ν<sub>max</sub> 3373, 3055, 2966, 1608, 1485, 1463, 1402, 1375, 1319, 1246, 1018, 1000, 915, 745 cm<sup>-1</sup>; HRMS (DART) m/z calc’d. for C<sub>12</sub>H<sub>16</sub><sup>14</sup>N [M+H]<sup>+</sup> 174.1282, found 174.1287.
(S*)-2-((R*)-But-3-en-2-yl)indoline (4.071). After reaction at 74 h at room temperature, followed by standard work-up, 4.071 was isolated after flash chromatography (20% v/v ethyl acetate in hexanes) as a clear, colorless oil; (72 mg, 83%). Crude dr = 95:5; \[ R_f = 0.23 \] (50% v/v ethyl acetate in hexanes); \[^1\]H NMR (CDCl\(_3\), 400 MHz) \[ \delta \] 7.04 (1H, dd, \[ J \] = 7.0, 1.0 Hz), 6.98 (1H, ddd, \[ J \] = 7.5, 7.5, 1.0 Hz), 6.66 (1H, ddd, \[ J \] = 7.5, 7.5, 1.0 Hz), 6.57 (1H, d, \[ J \] = 7.5 Hz), 5.80 (1H, ddd, \[ J \] = 17.5, 10.5, 7.0 Hz), 5.03-5.11 (2H, m), 3.89 (1H, br s), 3.73 (1H, ddd, \[ J \] = 9.0, 9.0, 7.0 Hz), 3.05 (1H, dd, \[ J \] = 16.0, 9.0 Hz), 2.78 (1H, dd, \[ J \] = 16.0, 9.0 Hz), 2.35 (1H, ddd, \[ J \] = 7.0, 7.0, 7.0 Hz), 1.07 (3H, d, \[ J \] = 7.0 Hz); \[^13\]C NMR (CDCl\(_3\), 100 MHz) \[ \delta \] 151.3, 141.1, 129.1, 127.4, 118.6, 115.0, 109.1, 64.3, 43.7, 34.3, 16.5; IR (neat) \[ \nu_{\text{max}} \] 3373, 3049, 2966, 1608, 1485, 1463, 1405, 1371, 1319, 1246, 1018, 1000, 914, 746 cm\(^{-1}\); HRMS (DART) \[ m/z \] calc’d. for C\(_{12}\)H\(_{16}\)\(^{14}\)N [M+H]\(^+\) 174.1282, found 174.1284.

(2S,3R)-2-Allyl-3-methylindoline (4.072). After reaction at 25 h at room temperature, followed by standard work-up, 4.072 was isolated after flash chromatography (20% v/v ethyl acetate in hexanes) as a clear, colorless oil; (64 mg, 83%). Crude dr = 2.1:1; \[ R_f = 0.23 \] (50% v/v ethyl acetate in hexanes); \[^1\]H NMR (CDCl\(_3\), 400 MHz) \[ \delta \] 6.98-7.04 (2H, m), 6.72 (1H, dt, \[ J \] = 8.5, 1.0 Hz), 6.59 (1H, d, \[ J \] = 8.0 Hz), 5.80-5.91 (1H, m), 5.09-5.17 (2H, m), 3.91 (1H, bs), 3.42 (1H, ddd, \[ J \] = 8.5, 8.0, 4.5 Hz), 2.95 (1H, sept., \[ J \] = 7.0 Hz), 2.40-2.47 (1H, m), 2.24-2.32 (1H, m), 1.30 (3H, d, \[ J \] = 7.0 Hz); IR (neat) \[ \nu_{\text{max}} \] 3367, 3053, 2960, 2923, 2869, 1640, 1608, 1483, 1464, 1402, 1359, 1310, 1245, 1151, 1091, 1015, 991, 914, 877, 746 cm\(^{-1}\); \[^13\]C NMR (CDCl\(_3\), 100 MHz) \[ \delta \] 150.3, 135.7, 134.1, 127.6, 123.7, 118.7, 117.6, 109.3, 67.4, 42.5, 40.1, 18.5; HRMS (DART) \[ m/z \] calc’d. for C\(_{12}\)H\(_{16}\)\(^{14}\)N [M+H]\(^+\) 174.1282, found 174.1284.
2-Allyl-2-methylindoline (4.073). After reaction at 6 h at room temperature, followed by standard work-up, 4.073 was isolated after flash chromatography (20% v/v ethyl acetate in hexanes) as a clear, colorless oil; (79 mg, 91%) , Rf = 0.23 (50% v/v ethyl acetate in hexanes); 1H NMR (CDCl3, 400 MHz) δ 7.04 (1H, dd, J = 7.0, 1.0 Hz), 6.98 (1H, ddd, J = 7.5, 7.5, 1.0 Hz), 6.68 (1H, ddd, J = 7.5, 7.5, 1.0 Hz), 6.55 (1H, d, J = 7.5 Hz), 5.86 (1H, dddd, J = 17.5, 10.5, 7.5, 6.5 Hz), 5.04-5.13 (2H, m), 3.71 (1H, br s), 2.90 (1H, d, J = 15.5 Hz), 2.76 (1H, d, J = 15.5 Hz), 2.30 (2H, d, J = 7.5 Hz), 1.28 (3H, s); 13C NMR (CDCl3, 100 MHz) δ 150.3, 134.6, 128.4, 127.5, 125.2, 118.6, 118.5, 109.4, 63.4, 46.3, 42.7, 27.2. IR (neat) νmax 3361, 2962, 2906, 1638, 1608, 1484, 1463, 1393, 1374, 1321, 1252, 1149, 1018, 996, 914, 814, 746 cm⁻¹; HRMS (DART) m/z calc’d. for C12H1614N [M+H]⁺ 174.1282, found 174.1290.

(R*)-2-((S*)-But-3-en-2-yl)-2-methylindoline (4.074). After reaction at 25 h at room temperature, followed by standard work-up, 4.074 was isolated after flash chromatography (20% v/v ethyl acetate in hexanes) as a clear, colorless oil; (85 mg, 91%). Crude dr = 95:5; Rf = 0.46 (20% v/v ethyl acetate in hexanes); 1H NMR (CDCl3, 400 MHz) δ 7.03 (1H, dd, J = 7.5, 1.0 Hz), 6.98 (1H, ddd, J = 7.5, 7.5, 1.0 Hz), 6.66 (1H, ddd, J = 7.5, 7.5, 1.0 Hz), 6.54(1H, d, J = 7.5 Hz), 5.80 (1H, ddd, J = 17.5, 10.0, 8.5 Hz), 5.06-5.11 (2H, m), 3.74 (1H, br s), 2.98 (1H, d, J = 15.5 Hz), 2.70 (1H, d, J = 15.5 Hz), 2.32-2.42 (1H, m), 1.17 (3H, s), 1.04 (3H, d, J = 7.0 Hz); 13C NMR (CDCl3, 100 MHz) δ 150.3, 140.8, 128.3, 127.5, 125.1, 118.3, 116.4, 109.2, 66.2, 47.8, 41.4, 23.5, 15.9; IR (neat) νmax 3373, 2963, 1608, 1485, 1464, 1393, 1322, 1250, 1153, 1088, 1019, 998, 915, 814, 745 cm⁻¹; HRMS (DART) m/z calc’d. for C13H1814N [M+H]⁺ 188.1439, found 188.1443.
3-Chloro-1H-indole (3.084). To a solution of indole (1.17 g, 10.0 mmol) in DMF (10 mL) at 0 °C, N-Chlorosuccinimide (1.40 g, 10.5 mmol) was added. The reaction mixture temperature was raised to room temperature and stirred for an additional 3.5 h, and then the reaction mixture was poured in 75 g of ice-cold water. The precipitate was filtered, dissolved in CH₂Cl₂ (15 mL) and extracted with H₂O (4 × 15 mL). The organic phase was then dried over Na₂SO₄ and concentrated at 48 °C. The residual yellowish solid turned green under high vacuum, and showed spectroscopic data corresponding to 3-chloroindole according to the ref.38; (1.11 g, 73%), compound 3.084 decomposed upon heating. \( ^1\)H NMR (CDCl₃, 400 MHz) \( \delta \) 8.02 (1H, bs), 7.64 (1H, d, \( J = 7.5 \) Hz), 7.34 (1H, d, \( J = 8.0 \) Hz), 7.17-7.26 (2H, m), 7.14 (1H, d, \( J = 2.5 \) Hz);

2-Allyl-5-bromoindoline (4.085). After reaction at 16 h at room temperature, followed by standard work-up, 4.085 was isolated after flash chromatography (20% v/v ethyl acetate in hexanes) as a clear, colorless oil; (107 mg, 90%); \( R_f = 0.50 \) (20% v/v ethyl acetate in hexanes); \( ^1\)H NMR (CDCl₃, 400 MHz) \( \delta \) 7.14 (1H, m), 7.07 (1H, dd, \( J = 8.0, 2.0 \) Hz), 6.42 (1H, d, \( J = 8.0 \) Hz), 5.73-5.83 (1H, m), 5.08-5.13 (2H, m), 3.90 (2 H, dddd, \( J = 9.0, 7.5, 7.0, 6.0 \) Hz), 3.10 (1H, dd, \( J = 16.0, 9.0 \) Hz), 2.70 (1 H, dd, \( J = 16.0, 7.0 \) Hz), 2.23-2.36 (2 H, m); \( ^{13}\)C NMR (CDCl₃, 100 MHz) \( \delta \) 149.9, 135.0, 131.1, 130.1, 127.9, 118.2, 110.5, 110.1, 59.1, 41.0, 35.6; IR (neat) \( \nu_{max} \) 3381, 3075, 2899, 2842, 1640, 1602, 1477, 1422, 1318, 1281, 1246, 1161, 1055, 994, 912, 804, 732 cm\(^{-1}\); HRMS (DART) \( m/z \) calc’d. for C₁₁H₁₃\(^{79}\)Br\(^{14}\)N [M+H]\(^+\) 238.0231, found 238.0239.

2-Allyl-5-chloroindoline (4.086). After reaction at 16 h at room temperature, followed by standard work-up, 4.086 was isolated after flash chromatography (20% v/v ethyl acetate in hexanes) as a clear, colorless oil; (89 mg, 92%); \( R_f = 0.46 \) (20% v/v ethyl acetate in hexanes); \( ^1\)H NMR (CDCl₃, 400 MHz) \( \delta \) 7.01 (1H, m), 6.93 (1H, dd, \( J = 8.0, 2.0 \) Hz), 6.46 (1H, d, \( J = 8.0 \) Hz), 5.74-5.84 (1H, m),

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5.08-5.13 (2H, m), 3.90 (2H, dddd, J = 8.5, 7.5, 7.0, 6.0 Hz), 3.10 (1H, dd, J = 16.0, 8.5 Hz), 2.70 (1H, dd, J = 16.0, 7.0 Hz), 2.24-2.34 (2H, m); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 149.5, 135.0, 130.6, 127.2, 125.1, 123.1, 118.0, 109.9, 59.2, 41.0, 35.7; IR (neat) $\nu$$_{\text{max}}$ 3378, 2906, 1640, 1605, 1480, 1426, 1318, 1281, 1247, 1178, 1110, 1066, 994, 917, 869, 805, 734 cm$^{-1}$; HRMS (DART) m/z calc’d. for C$_{11}$H$_{13}^{35}$Cl$^{14}$N $[\text{M+H}]^+$ 194.0736, found 194.0731.

2-Allyl-5-flouroindoline (4.087). After reaction at 18 h at room temperature, followed by standard work-up, 4.087 was isolated after flash chromatography (20% v/v ethyl acetate in hexanes) as a clear, colorless oil; (70 mg, 79%); R$_f$ = 0.45 (20% v/v ethyl acetate in hexanes); $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 6.78 (1H, ddd, J = 8.5, 1.5 Hz), 6.69 (1H, dd, J = 8.0, 2.0 Hz), 6.48 (1H, dd, J = 8.5, 4.5 Hz), 5.75-5.85 (1H, m), 5.08-5.14 (2H, m), 3.90 (2H, dddd, J = 9.0, 7.5, 7.0, 6.0 Hz), 3.78 (1H, br s), 3.10 (1H, dd, J = 16.0, 9.0 Hz), 2.70 (1H, dd, J = 16.0, 7.0 Hz), 2.25-2.38 (2H, m); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 157.0 (d, J = 234 Hz), 146.8, 135.2, 130.4, 117.8, 113.4 (d, J = 24.0 Hz), 112.3 (d, J = 24.0 Hz), 109.4, 59.5, 36.1; IR (neat) $\nu$$_{\text{max}}$ 3376, 2906, 2842, 1640, 1603, 1493, 1448, 1221, 1124, 995, 917, 861, 804, 745 cm$^{-1}$; HRMS (DART) m/z calc’d. for C$_{11}$H$_{13}^{19}$F$^{14}$N $[\text{M+H}]^+$ 178.1032, found 178.1038.

2-Allylindolin-5-ol (4.088). After reaction at 14 h at room temperature, followed by standard work-up, 4.088 was isolated after flash chromatography (50% v/v ethyl acetate in hexanes) as a clear, colorless oil; (70 mg, 90%); R$_f$ = 0.48 (50% v/v ethyl acetate in hexanes); $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 6.58 (1H, d, J = 2.0 Hz), 6.48 (1H, d, J = 8.0 Hz), 6.44 (1H, dd, J = 8.0, 2.0 Hz), 5.74-5.85 (1H, m), 5.08-5.13 (2H, m), 4.62 (2H, br s), 3.84 (1H, dddd, J = 8.5, 7.5, 7.0, 6.0 Hz), 3.07 (1H, dd, J = 16.0, 8.5 Hz), 2.67 (1H, dd, J = 16.0, 7.0 Hz), 2.26-2.33 (2H, m); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 149.7, 143.7, 135.3, 130.9, 117.8, 114.0, 113.0, 110.9, 59.3, 40.9, 36.3; IR (neat) $\nu$$_{\text{max}}$ 3295, 3051, 2935, 2843, 1640, 1603, 1493, 1461, 1363, 1265, 1219, 1133, 1029, 994, 918, 861, 808, 735 cm$^{-1}$; HRMS (DART) m/z calc’d. for C$_{11}$H$_{14}^{14}$N$^{16}$O $[\text{M+H}]^+$ 176.1075, found 176.1078.
Methyl 2-allylindoline-5-carboxylate (4.089). After reaction at 24 h at room temperature, followed by standard work-up, 4.089 was isolated after flash chromatography (20% v/v ethyl acetate in hexanes) as a clear, colorless oil; (93 mg, 86%); R_f = 0.45 (20% v/v ethyl acetate in hexanes); ^1H NMR (CDCl_3, 400 MHz) δ 7.74 (1H, dd, J = 8.0, 1.5 Hz), 7.72 (1H, d, J = 1.5 Hz), 6.50 (1H, d, J = 8.0Hz), 5.74-5.85 (1H, m), 5.09-5.15 (2H, m), 4.30 (1H, br s), 3.92-4.07 (1H, m), 3.84 (3H, s), 3.16 (1H, dd, J = 16.0, 9.0 Hz), 2.73 (1H, dd, J = 16.0, 6.5 Hz), 2.25-2.38 (2H, m); ^13C NMR (CDCl_3, 100 MHz) δ 167.6, 155.1, 134.7, 131.0, 128.1, 126.5, 119.8, 118.2, 107.5, 58.9, 51.7, 41.2, 34.9; IR (neat) ν_max 3359, 2945, 2860, 1682, 1609, 1494, 1452, 1431, 1281, 1256, 1220, 1192, 1170, 1129, 1091, 982, 906, 865, 832, 769, 722 cm⁻¹; HRMS (DART) m/z calc’d. for C_{11}H_{13}F_{14}N_{16}O_{2} [M+H]^+ 218.1181, found 218.1187.

2-Allyl-7-methylindoline (4.090). After reaction at 62 h at room temperature, followed by standard work-up, 4.090 was isolated after flash chromatography (20% v/v ethyl acetate in hexanes) as a clear, colorless oil; (75 mg, 87%); R_f = 0.45 (20% v/v ethyl acetate in hexanes); ^1H NMR (CDCl_3, 400 MHz) δ 6.94 (1H, d, J = 7.0 Hz), 6.84 (1H, d, J = 7.5 Hz), 6.63 (1H, dd, J = 7.5, 7.0 Hz), 5.85 (1H, dddd, J = 17.0, 10.0, 7.5, 6.5 Hz ), 5.08-5.14 (2H, m ), 3.90 (1H, ddd, J = 9.0, 7.5, 7.0, 6.0 Hz), 3.74 (1H, br s), 3.16 (1H, dd, J = 15.5, 9.0 Hz), 2.74 (1H, dd, J = 15.5, 7.0 Hz), 2.27-2.37 (2H, m), 1.46-1.61 (2H, m), 2.11 (3H, s); ^13C NMR (CDCl_3, 100 MHz) δ 149.1, 135.3, 128.2, 127.7, 122.2, 118.7, 118.6, 117.4, 58.4, 71.1, 36.0, 16.8; IR (neat) ν_max 3362, 3050, 2921, 2845, 1639, 1601, 1467, 1436, 1397, 1323, 1306, 1257, 1218, 1070, 995, 914, 753 cm⁻¹; HRMS (DART) m/z calc’d. for C_{12}H_{16}^{14}N [M+H]^+ 174.1282, found 174.1291.

2-Allyl-2-phenylindoline (4.091). After reaction at 64 h at room temperature, followed by standard work-up, 4.091 was isolated after flash chromatography (20% v/v ethyl acetate in hexanes) as a clear, colorless oil; (100 mg, 85%). R_f = 0.71 (20% v/v ethyl acetate in hexanes); ^1H NMR (CDCl_3, 400 MHz) δ 7.43 (2H, dd, J = 7.5, 1.0 Hz), 7.33 (2H, dd, J = 8.0, 8.0 Hz), 7.22 (1H, t, J = 7.5 Hz), 7.06 (2H, m),
6.70 (1H, t, J = 7.5 Hz), 5.75-5.85 (1H, dddd, J = 15.5, 12.0, 9.0, 5.5 Hz), 5.00-5.07 (2H, m), 4.35(1H, brs), 3.28 (1H, d, J = 15.5Hz), 3.20 (1H, d, J = 15.5 Hz), 2.62 (1H, dd, J = 13.5, 9.0 Hz), 2.72 (1H, ddt, J = 13.5, 5.5, 1.0 Hz), 2.62 (1H, dd, J = 13.5, 9.0 Hz); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 150.1, 147.0, 133.9, 128.6, 127.8, 127.7, 126.7, 125.9, 125.1, 119.4, 118.9, 109.6, 68.5, 46.0, 45.0 (two carbon peaks are missing); IR (neat) $\nu_{max}$ 3355, 3026, 2916, 1608, 1485, 1463, 1393, 1323, 1252, 919, 746 cm$^{-1}$; HRMS (DART) m/z calc’d. for C$_{17}$H$_{18}$N [M+H]$^+$ 236.1439, found 236.1449.

2-Allyl-2,3-dihydro-1H-benzo[g]indole (4.092). After reaction at 74 h at room temperature, followed by standard work-up, 4.092 was isolated after flash chromatography (20% v/v ethyl acetate in hexanes) as a clear, colorless oil; (38 mg, 38%); $R_f$ = 0.43 (20% v/v ethyl acetate in hexanes);

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.75-7.79 (1H, m), 7.58-7.63 (1H, m), 7.35-7.39 (2H, m), 7.24-7.29 (2H, m), 5.83-5.93 (1H, m), 5.11-5.16 (2H, m), 4.08 (1H, dddd, J = 9.0, 8.5, 7.5, 6.5 Hz), 3.34 (1H, dd, J = 15.5, 9.0 Hz), 2.92 (1H, dd, J = 15.5, 6.5 Hz), 2.34-2.45 (2H, m); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 146.2, 135.3, 133.7, 128.7, 125.2, 124.9, 123.8, 122.3, 121.6, 120.9, 118.9, 117.9, 59.2, 41.5, 36.8; IR (neat) $\nu_{max}$ 3357, 3056, 2924, 2842, 1640, 1574, 1520, 1446, 1418, 1370, 1287, 1073, 1020, 996, 916, 858, 796, 771, 737 cm$^{-1}$; HRMS (DART) m/z calc’d. for C$_{15}$H$_{16}$N [M+H]$^+$ 210.1283, found 210.1287.

2,2-Diallylindoline (4.093). After reaction at 12 h at room temperature, followed by standard work-up, 4.093 was isolated after flash chromatography (20% v/v ethyl acetate in hexanes) as a clear, colorless oil; (88 mg, 88%); $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 6.99-7.04 (2H, m), 6.66 (1H, ddd, J = 7.5, 7.5, 1.0 Hz), 6.55(1H, d, J = 8.0 Hz), 5.79-5.90 (1H, m), 5.06-5.13 (2H, m), 3.86 (1H, br s), 2.87 (2H, s), 2.33 (4H, m); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 150.3, 134.2, 128.3, 127.6, 125.1, 118.7, 118.5, 109.3, 65.5, 43.9, 40.4.
Potassium trifluoro(propa-1,2-dien-1-yl)borate (4.095).\(^\text{39}\) To a flame-dried 100 mL flask, HgCl\(_2\) (0.4 g, 1.44 mmol) and magnesium (22.8 g, 950 mmol) were added and the mixture heated to remove moisture. The flask was then cooled and transferred to an ice-bath. Freshly distilled diethyl ether (75 mL) was added to the mixture and propargyl bromide (7.4 mL, 50 mmol, 80% in toluene) added drop wise.\(^\text{40}\) As a sign of formation of the Grignard reagent, the mixture started boiling and throughout the addition the temperature was kept at 0-5 °C. In another 250 mL flame-dried flask under positive pressure of argon, dry diethyl ether (75 mL) and trimethylborate (5.6 mL, 50.0 mmol) were added.\(^\text{29}\) The flask was transferred to an acetone/dry ice bath to reach the internal temperature (controlled by thermal probe type-K, Fischer scientific) below -75 °C. The allenyl Grignard reagent from the first flask was canulated to the second flask over 30 min., and the mixture stirred at this temperature for an additional 40 min before internal temperature rose to -40 °C. It was then quenched by addition of diluted sulfuric acid (25 mL, 0.6 M), the ether layer was separated, and the aqueous layer was extracted with diethyl ether (2×20 mL). The combined ether layers were dried over magnesium sulfate and concentrated to a volume about 10 mL, at which point solid KHF\(_2\) (11.7 g, 150 mmol) and water (2.5 mL) were added. A white crystalline solid formed which was filtered and dried immediately since it decomposes in the presence of water to unknown orange species. The solids was further purified by dissolution/precipitation in a dry acetonitrile/ether solvent systems affording 4.095; (3.8 g, 52%); \(^1\)H NMR (CD\(_3\)CN, 400 MHz) \(\delta \) 4.60 (br m, 1H), 4.08 (br m, 2H); \(^{13}\)C NMR (CD\(_3\)CN, 100 MHz) \(\delta \) 210.9, 117.7, 65.3; \(^{11}\)B NMR (CD\(_3\)CN, 128 MHz) \(\delta \) 2.5 (q, \(J_{B-F} = 50 \text{ Hz})\); \(^{19}\)F NMR (CD\(_3\)CN, 376 MHz) \(\delta \) -138.2 (q, \(J_{F-B} = 50 \text{ Hz})\).

2-(2-Methylbut-3-en-2-yl)indoline (4.096).\(^\text{20}\) After reaction at 25 h at room temperature, followed by standard work-up, 4.096 was isolated after flash chromatography (15 % v/v ethyl acetate in hexanes) as a clear, colorless oil; (83mg, 89%); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta \) 7.02 (1H, d, \(J = 7.5 \text{ Hz} \), 6.98 (1H, ddd, \(J = 7.5, 7.5, 1.0 \text{ Hz} \)), 6.68 (1H, ddd, \(J = 7.5, 7.5, 1.0 \text{ Hz} \)), 6.55 (1H, d, \(J = 8.0 \text{ Hz} \)), 5.88 (1H, dd, \(J = 18.0, 10.5 \text{ Hz} \)), 5.02-5.06 (2H, \(J = 18.0, 10.5, 2.0 \text{ Hz} \)), 3.83 (1H, br s),

3.72 (1H, dd, $J = 9.5, 9.5$ Hz), 2.93 (1H, dd, $J = 15.5, 9.0$ Hz), 2.82 (1H, dd, $J = 16.0, 9.5$ Hz), 1.04 (3H, s), 1.02 (3H, s); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 151.3, 145.6, 128.8, 127.2, 124.5, 118.1, 112.5, 108.5, 67.8, 40.2, 31.4, 24.2, 21.9.

2-(Prop-2-yn-1-yl)indoline (4.097). After reaction at 25 h at room temperature, followed by standard work-up, 4.097 was isolated after flash chromatography (20% v/v ethyl acetate in hexanes) as a clear, colorless oil; (65 mg, 83%); $R_f$ = 0.48 (20% v/v ethyl acetate in hexanes); $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.08 (1H, d, $J = 7.0$ Hz), 7.02 (1H, t, $J = 7.5$ Hz), 6.69 (1H, dt, $J = 7.5, 1.0$ Hz), 6.62 (1H, d, $J = 8.0$ Hz), 4.12 (1H, br s), 4.03 (1H, ddt, $J = 13.5, 8.5, 6.5$ Hz), 3.18 (1H, dd, $J = 16.0, 8.5$ Hz), 2.77 (1H, dd, $J = 16.0, 6.5$ Hz), 2.42 (1H, t, $J = 2.5$ Hz), 2.40 (1H, dd, $J = 2.5, 1.0$ Hz), 2.08 (1H, t, $J = 2.5$ Hz); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 150.4, 128.0, 127.7, 127.5, 119.0, 109.5, 81.8, 70.3, 58.3, 35.8, 26.2; IR (neat) $\nu_{max}$ 3363, 3284, 2905, 1608, 1483, 1466, 1403, 1322, 1245, 1151, 1054, 1018, 879, 748 cm$^{-1}$; HRMS (DART) m/z calc’d. for C$_{11}$H$_{12}$N [M+H]$^+$ 158.0969, found 158.0972.

1-((R*)-2-((S*)-But-3-en-2-yl)indolin-1-yl)prop-2-en-1-one (4.099). To a 25 mL round-bottomed flask were added THF (10.0 mL), 4.070 (0.26 g, 1.5 mmol), iPrE$_2$N (0.39 mL, 2.25 mmol) and acryloyl chloride (0.18 mL, 2.25 mmol). The mixture stirred at rt for 1 hour at which point the mixture filtered though fritted funnel and the solid washed with ether (15mL). The organic layer concentrated and the crude was further purified by flash chromatography (15%v/v ethyl acetate in hexanes) as a light yellowish solid (0.27 g, 80%).

$^1$H NMR (C$_6$D$_8$, 400 MHz, 50 °C) $\delta$ 8.31 (1H, br s), 6.82-6.87 (2H, m), 6.53 (1H, dd, $J = 16.5, 2.0$ Hz), 6.33-6.40 (1H, m), 5.52 (1H, ddd, $J = 17.0, 10.0, 6.5$ Hz), 5.40 (1H, dd, $J = 10.0, 2.0$ Hz), 4.92 (1H, td, $J = 10.0, 1.5$ Hz), 4.83 (1H, td, $J = 17.0, 1.5$ Hz), 4.21 (1H, bs), 3.70 (1H, d, $J = 16.5, 10.0$ Hz), 2.47 (1H, dd, $J = 16.5, 1.5$ Hz), 0.61 (3H, d, $J = 6.5$Hz); $^{13}$C NMR (C$_6$D$_8$, 100 MHz) $\delta$ 139.2, 133.6, 129.2, 127.8, 127.4, 123.7, 115.1, 61.6, 42.2, 29.4, 11.3; IR (neat) $\nu_{max}$ 2981, 2862, 1648, 1594, 1480, 1461, 1419, 1376, 1283, 1243, 1215, 1167, 1141, 1024, 984, 949,
922, 841, 789, 749, 716 cm⁻¹; HRMS (DART) m/z calc’d. for C₁₅H₁₈¹⁴N₁₆O[M+H]⁺ 228.13884, found 228.13857.

(9S*,9aR*)-9-methyl-9a,10-dihydropyrido[1,2-a]indol-6(9H)-one (4.101). Compound 4.099 (0.091 g, 0.4 mmol) and catalyst 4.100 (3.4 mg, 1.0 mol %) were dissolved in dichloromethane (12 mL) and the mixture refluxed for 12 h. The reaction stopped and the volatiles evaporated. The brown crude was further purified by flash chromatography (40% v/v ethyl acetate in hexanes) as a colorless solid (78 mg, 98%); ¹H NMR (CDCl₃, 400 MHz) δ 8.21 (1H, d, J = 8.0 Hz), 7.23 (2H, t, J = 8.5 Hz), 7.03 (1H, dt, J = 8.5, 1.0 Hz), 6.45 (1H, dd, J = 9.5, 1.5 Hz), 6.05 (1H, dd, J = 9.5, 3.0 Hz), 3.85 (1H, ddd, J = 12.5, 10.5, 8.5 Hz), 3.30 (1H, dd, J = 15.5, 8.5 Hz), 2.86 (1H, dd, J = 15.5, 10.5 Hz), 2.58 (1H, ddq, J = 14.5, 9.5, 7.5, 2.5 Hz), 1.25 (3H, d, J = 7.5 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 162.3, 145.9, 142.7, 129.6, 128.0, 126.1, 124.7, 123.8, 116.2, 64.1, 37.0, 35.2, 16.8.; IR (neat) ν max 2967, 2879, 2841, 1661, 1593, 1478, 1459, 1416, 1357, 1311, 1245, 1142, 1088, 1017, 926, 814, 800, 767, 754 cm⁻¹; HRMS (DART) m/z calc’d. for C₁₃H₁₄¹⁴N₁₆O[M+H]⁺ 200.10754, found 200.10809.

1-((R*)-2-((R*)-but-3-yl)indolin-1-yl)prop-2-en-1-one (4.102).

To a 25 mL round-bottomed flask were added THF (10.0 mL), 4.071 (0.19 g, 1.14 mmol), iPr₂E(N (0.31 mL, 1.71 mmol) and acryloyl chloride (0.14 mL, 1.71 mmol). The mixture stirred at rt for 1 hour at which point the mixture filtered through a fritted funnel and the solid washed with ether (15 mL). The organic layer concentrated and the crude was further purified by flash chromatography (20% v/v ethyl acetate in hexanes) as a light yellowish solid (0.23 g, 92%).

¹H NMR (CD₄D₈, 400 MHz, 55 °C) δ 8.21 (1H, br s), 6.81-6.87 (2H, m), 6.52 (1H, dd, J = 16.5, 2.0 Hz), 6.32-6.42 (2H, m), 5.37-5.42 (2H, m), 4.74 (2H, dd, J = 17.0, 10.0 Hz), 4.10 (1H, br s), 2.70 (1H, dd, J = 16.5, 9.0 Hz), 2.42-2.52 (2H, m), 2.06-2.08 (1H, m), 0.79 (3H, d, J = 6.5 Hz); IR (neat) νmax 2949, 2922, 1648, 1608, 1594, 1478, 1460, 1420, 1379, 1339, 1292, 1280, 1245,
1213, 1167, 1111, 1055, 107, 986, 948, 912, 844, 789, 749, 716 cm\(^{-1}\); HRMS (DART) \(m/z\) calc’d. for \(C_{13}H_{18}^{14}N^{16}O[M+H]^+\) 228.13884, found 228.13857.

(9R\*,9aR\*)-9-methyl-9a,10-dihydropyrido[1,2-a]indol-6(9H)-one (4.103).

Identical procedure for 4.101 was followed and 4.103 isolated as a colorless solid (84 mg, 96%); \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 8.21 (1H, d, \(J = 7.5\) Hz), 7.22 (2H, t, \(J = 7.5\) Hz), 7.02 (1H, t, \(J = 7.5\) Hz), 6.74 (1H, dd, \(J = 10.0, 6.5\) Hz), 6.00 (1H, d, \(J = 10.0\) Hz), 4.54 (1H, ddd, \(J = 10.0, 10.0, 4.5\) Hz), 3.17 (1H, dd, \(J = 16.0, 10.5\) Hz), 3.10 (1H, dd, \(J = 16.0, 9.5\) Hz), 2.86 (1H, dd, \(J = 15.5, 10.5\) Hz), 2.58 (1H, ddq, \(J = 10.0, 7.0, 4.5\) Hz), 1.07 (3H, d, \(J = 7.0\) Hz); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 162.5, 145.8, 142.7, 129.8, 127.9, 125.2, 124.8, 123.8, 116.2, 60.9, 32.0, 30.9, 12.1.; IR (neat) \(\nu_{max}\) 2967, 2935, 2879, 1655, 1611, 1590, 1480, 1459, 1412, 1355, 1340, 1305, 1248, 1226, 1140, 1112, 1071, 1033, 951, 919, 809, 751, 720 cm\(^{-1}\); HRMS (DART) \(m/z\) calc’d. for \(C_{13}H_{14}^{14}N^{16}O[M+H]^+\) 200.10754, found 200.10830.
Chapter 2
Sample: PW3_916
Sample ID: e_20071205_01
File: timothy/students/forescare/data/20071205-PW3_916_Protion-001.fid

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Solvent: cdcl3
Temp: 23.0 C / 298.1 K
Operator: forescare
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VENDOR = "peakline.chem.utoronto.ca"

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16 repetitions
Carrier: 398.7460153 MHz
DARK SUPPRESSING
Line broadening 0.2 Hz
FT size 65536
Total time 1 min. 4 sec

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Sample: PW3_914
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Operator: forescare
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Power 40 dB
continuously on
MULTI-36 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 1024
Total time 1.3 min. 16 sec.
Sample: PRL_028
Sample ID: e.20071215.03
File: /home/christine/pnr-000.20071215-PRL_028-Proton-001.fid

Pulse Sequence: zpul
Solvent: d6d2
Temp: 25.0 C / 296.1 K
Operator: Sincere
File: 20071215-PRL_028_Proton-001

Noise: 0.000 sec
Pulse 45.0 degrees
Acq. time 2.95M sec
Wtch 44:0.0 s
100 repetitions
Chemical shift: 0.0 ppm
Data Processing
Line broadening: 0.2 Hz
FT size 4096
Total time 1 min. 4 sec

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Sample: PRL_028
Sample ID: e.20071215.02
File: /home/christine/pnr-000.20071215-PRL_028-Carbon-001.fid

Pulse Sequence: zpul

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Sample: FN3_998
Sample ID: a.20080214_52
File: timothy/student/fmurenaenum/data/FN3/20080215-FN3_998_Halon-002.fid

Pulse Sequence: sdpul
Solvent: cdcl3
Temp: 298.0 / 298.1 K
Sample #66, Operator: Flurnox
File: 20080215-FN3_998_Halon-002
VNMRS-600 "speakle.500"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Avg. time 2.920 sec
Width 61.390.0 Hz
16 repetitions

OBSERVE 81, 399.994000 MHz
DATA PROCESSING
Line broadening 0.2 Hz
SF size 65536
Total time 1 min. 12 sec

Sample: FN3_998
Sample ID: a.20080214_52
File: timothy/student/fmurenaenum/data/FN3/20080215-FN3_998_Carbon-001.fid

Pulse Sequence: sdpul

[Image of NMR spectra]
Sample: FNL_R100
Sample ID: a.20460911.38
File: timothy/Students/fmnsunxsvmsrnm/data/20460917-FNL_R100_FKHZMS-002.fid

Pulse Sequence: alppul
Solvent: cdc13
Temp. 25.0 C / 298.1 K
Sample #40, Operator: fmnus
File: 20460917-FNL_R100_FKHZMS-002
NMRD-400 "pabiki.chem.ubc.ca"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.992 sec
Width 239.0 Hz
16 repetitions
comment st. 395.954061 sec
DATA PROCESSING
Line broadening 0.2 Hz
FT size 65536
Total time 3 min. 12 sec

Sample: FNL_R100
Sample ID: a.20460917.28
File: timothy/Students/fmnsunxsvmsrnm/data/20460917-FNL_R100_Carbon-001.fid

Pulse Sequence: alppul
Solvent: cdc13
Temp. 25.0 C / 298.1 K
Sample #40, Operator: fmnus
File: 20460917-FNL_R100_Carbon-001
NMRD-400 "pabiki.chem.ubc.ca"

Relax. delay 0.200 sec
Pulse 35.0 degrees
Acq. time 1.500 sec
Width 2409.4 Hz
128 repetitions
GAIN LEVEL C13, 1.0,1750873 MHz
B1SPECTRUM HI, 395.950943 MHz
Power 40 dB
continuously on
WALD-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 12 min. 63 sec
Sample: P03_P110
Sample ID: k_20083232_46
File: timothy/studenta/Escherichia/spectra/data/20083232-P03_P110_ROTON-002.fid

Pulse sequence: edj11
Solvent: d6-dcl3
Temp: 298.1 K
Sample #: 100, Operator: Escherichia

Relax: delay 1.000 sec
Acq. time 2.992 sec
Match 0.0 Hz
16 repetitions

Spectrum: X0, 500.198 MHz
Data 199032309
Line broadening 0.2 Hz
FT size 65396
Total time 1 min, 12 sec.

Sample: P03_P110
Sample ID: k_20083232_46
File: timothy/studenta/Escherichia/spectra/data/20083232-P03_P110_Carbon-001.fid

Pulse sequence: edj11
Sample: PH4_P14
Sample ID: s_20080618_G1
File: timothy/Students/Froweses/average/data/20080618-PH4_P14_Proton-002.fid

Pulse Sequence: e2pul
Solvent: d2o
Temp. 25.0 C / 298.1 K
Operator: Froweses
File: 20080618-PH4_P14_Proton-002

Delay: 1.020 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 500.0 Hz
16 repetitions

Spectrum: H1. 397.74M317 MHz

Data Processing
Line broadening 0.2 Hz
FT size 65536
Total time 1 min, 6 sec

---

Sample: PH4_P14
Sample ID: s_20080618_G2
File: timothy/Students/Froweses/average/data/20080618-PH4_P14_Carbon-001.fid

Pulse Sequence: e2pul
Solvent: d2o
Temp. 25.0 C / 298.1 K
Operator: Froweses
File: 20080618-PH4_P14_Carbon-001

Delay: 0.210 sec
Pulse 45.0 degrees
Acq. time 1.337 sec
Width 6450.0 Hz
128 repetitions

Spectrum: C13. 70.515MHz MHz

Data Processing
Line broadening 0.5 Hz
Total time 13 min, 15 sec
Sample: PHE_916
Sample ID: s_2000618_93
File: timothy/students/exsorces/venseymy/data/2000618-PHE_916_Proton-001.fid

Pulse Sequence: alpul
Solvent: ocmcl3
Temp: 29.0 C / 298.1 K Operation: fluorous
File: 2000618-PHE_916_Proton-001
VMRIS-400 "pahkih.chem.stanford.edu"

Relax delay 1.000 sec
Pulse 45.0 degrees
Acq. Time 2.356 sec
Width 5612.3 Hz
16 repetitions
CRESTTE R1, 339.742612 MHz
DATA ACQUISITION
Line broadening 0.2 Hz
FT size 65536
Total time 1 min. 4 sec

STANDARD 38 OBSERVE - profile
Sample: PHE_916
Sample ID: s_2000618_93
File: timothy/students/exsorces/venseymy/data/2000618-PHE_916_Carbon-001.fid

Pulse sequence: alpul
Solvent: ocmcl3
Temp: 23.9 C / 298.1 K
Operation: fluorous
File: 2000618-PHE_916_Carbon-001
VMRIS-400 "pahkih.chem.stanford.edu"

Relax delay 0.200 sec
Pulse 45.0 degrees
Acq. Time 2.537 sec
Width 24509 Hz
16 repetitions
OBSERVE R1, 150.512092 MHz
DSSCANN XL, 359.742641 MHz
Power 45 dB
continuously on
WMRSC-34 modulated
DATA ACQUISITION
Line broadening 0.5 Hz
FT size 65536
Total time 1 min. 8 sec
Sample: PMA.250
Sample ID: s_2008707_88
File: timothy/students/fluorocross/spectra/data/2008707-PMA_420_Carbono-001.fld

Pulse Sequence: alipal
Solvent: cdcl3
Temp: 25.0 C / 298.1 K
Sample #7, Operator: Fluorocross
File: 2008707-PMA_300_Carbono-002
VNMRS-400 "publib.chem.stanford.edu"

Pulse delay 1.000 sec
Pulse 45.0 degrees
Avg. time 2.592 sec
Match 6298.0 Hz
16 repetitions
OBSERV - XL; 599.574143 Mm
DATA PROCESSING
Line broadening 0.2 Hz
FP size 614592
Total time 1 min. 11 sec

INDEX FREQUENCY PPM HEIGHT
1 13797.5 136.926 28.8
2 13579.9 134.244 23.1
3 13349.1 132.550 47.7
4 13113.9 130.953 99.9
5 12873.6 129.357 133.1
6 12633.1 127.752 98.1
7 12392.8 126.148 119.5
8 12152.5 124.544 47.9
9 7805.3 77.121 16.8
10 7248.9 75.522 17.4
11 7176.8 75.005 17.0
12 7237.7 72.977 49.9
13 6245.4 62.354 69.8

Sample: PMA.250
Sample ID: s_2008707_88
File: timothy/students/fluorocross/spectra/data/2008707-PMA_420_Carbono-001.fld

Pulse Sequence: alipal
Solvent: cdcl3
Temp: 25.0 C / 298.1 K
Sample #7, Operator: Fluorocross
File: 2008707-PMA_300_Carbono-002
VNMRS-400 "publib.chem.stanford.edu"

Pulse delay 1.000 sec
Pulse 45.0 degrees
Avg. time 3.150 sec
Match 24656.4 Hz
612 repetitions
OVERLAP C12, 50.672952 Mhz
OVERLAP 10, 50.576019 Mhz
Power: 39.00
continuously on
WCU3-16 modulator
DATA PROCESSING
Line broadening 0.5 Hz
FP size 131072
Total time 10 min. 93 sec
Sample: PHN_P34
Sample ID: S0080723_36
File: Timothy/Students/Ferenczy/AnaPapers/data/20080723-PHN_P34_FeNO3-002.fld

Pulse Sequence: sglpul
Solvent: ccd3j
Temp: 25.0 °C / 298.1 K
Sample type: FeNO3
File: 20080723-PHN_P34_FeNO3-002

VNRGS-90: "pablos@chem.utoronto.ca"

Delay: 1.000 sec
Pulse: 45.6 degrees
Ampl. time: 0.292 sec
Width: 3934.0 Hz
16 repetitions

Observe: XL 300 MHz, 655250 Hz

Data Processing:
Line broadening: 0.5 Hz
PT size: 65536
Total time: 1 min, 13 sec

Sample: PHN_P34
Sample ID: S0080703_34
File: Timothy/Students/Ferenczy/AnaPapers/data/20080703-PHN_P34_Carbon-001.fld

Pulse Sequence: sglpul
Solvent: ccd3j
Temp: 29.5 °C / 326.1 K
Sample type: FeNO3
File: 20080703-PHN_P34_Carbon-001

VNRGS-90: "pablos@chem.utoronto.ca"

Delay: 0.000 sec
Pulse: 45.6 degrees
Ampl. time: 0.292 sec
Width: 3456 Hz
31 repetitions
Observe: XL 300 MHz, 655250 Hz

Data Processing:
Line broadening: 0.5 Hz
PT size: 65536
Total time: 1 min, 13 sec
Chapter 3
STANDARD PACTIM PARAMETERS

File: timothy/student/loweeyes/data/FM_P36_50.txt

Pulse sequence: aaryl

Solvent: d6-dmso
Temp: -30.0 °C / 243.2 K
Operator: loweeyes
File: FM_P36_50

Wavenum: 400 MHz

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 3.000 sec
WATER 7.000.0 Hz
64 repetitions

COMMENTS: H1 495.847207 MHz

Spectral Properties
FT size 131072
Total time 4 min, 14 sec
Sample: 13C613D, deuterium
Sample ID: 13C613D_01
File: timothy/∼/students/∼/chemys/data/RFID/13C613D_01_deuterium_deuterium-001.fid

Pulsed Sequence: nmr

Delay: 25.0 µs / 250.0 Hz
Operator: deuterium
File: 13C613D_01_deuterium_deuterium-001

VNMRS-600 "pekke.net"

Delay, delay 1.000 sec
Pulse 90.0 degrees
Acq. time 1.000 sec
Wait 300.0 Hz

190 repetitions

CHEMFILE: 1k, 61.564135 MHz
SPECTRUM: 1k, 61.564135 MHz
Power 40 dB

Off during acquisition
OFF during delay
MULTI-14 modulated

Line broadening: 0.5 Hz

Total time 30 min, 5 sec
Sample: PWT_P116
Sample ID: a_20100911_97
File: timsthy/students/foxover/foxover/data/20100911-PWT_P116_Proton-002.fid
Pulse Sequence: alyp1
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #02, Operator: foxover
File: 20100911-PWT_P116_Proton-002
VENDOR: “pakka.mnr”

Relax. delay 1.000 sec
Pulse 45.5 degrees
Acq. time 2.932 sec
Width 6.957 Hz
16 repetitions

RESOLVE K1, 399.4405522 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 8358
Total time 1 min. 12 sec

Sample: PWT_P116
Sample ID: a_20100911_97
File: timsthy/students/foxover/foxover/data/20100911-PWT_P116_Carbon-001.fid
Pulse Sequence: alyp1
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #02, Operator: foxover
File: 20100911-PWT_P116_Carbon-001
VENDOR: “pakka.mnr”

Relax. delay 0.200 sec
Pulse 35.0 degrees
Acq. time 1.300 sec
Width 24096.4 Hz
512 repetitions

RESOLVE K1, 100.4393845 MHz
DECOUPL K1. 399.4405512 MHz
Power 40 dB
continuously on
MASER-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 151672
Total time 12 min. 43 sec
Sample: PW7.P156
Sample ID: s_20100911_06

Pulse Sequence: zgul
Solvent: ccd12
Temp: 293.0 C / 298.1 K
Sample #0, Operator: Xenovac
VNMRS-600 "peklo.mx"

Relax: delay 1.000 sec
Pulse 90.0 degrees
Avg. time 3.932 sec
Width 6390.7 Hz
16 repetitions
Sweep E1, 319.4005556 MHz
DATA PROCESSING
Line Broadening 0.5 Hz
FT size 65,536
Total time 1 min. 12 sec

---

Sample: PW7.P156
Sample ID: s_20100911_06

Pulse Sequence: zgul
Solvent: ccd12
Temp: 293.0 C / 298.1 K
Sample #0, Operator: Xenovac
File: 20100911-PW7.P156_Carbon-001
VNMRS-600 "peklo.mx"

Relax: delay 0.200 sec
Pulse 37.5 degrees
Avg. time 3.100 sec
Width 26094.4 Hz
512 repetitions
Sweep E1, 319.4005556 MHz
Sweep E2, 319.4420502 MHz
Power 40 dB
continuously on
Wave-14 modulated
DATA PROCESSING
Line Broadening 0.5 Hz
FT size 153,247
Total time 12 min. 53 sec
Chapter 4
Sample: FNB_P142_after_column
Sample ID: a_20110322_02
File: timothy/students/Inoue/Research/data/20110322-FNB_P142_after_column_proton-001.fid

Pulse Sequence: xpol
Solvent: dcd13
Temp. 29.0 °C / 298.1 K
Operator: Inoue
File: 20110322-FNB_P142_after_column_proton-001
VNMRS-400 "pekke.ren"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.554 sec
Width 6410.3 Hz
16 repetitions

OBSERVE H1, 399.7480446 MHz
DATA PROCESSING
FFT size 32768
Total time 1 min, 4 sec

Sample: FNB_P142_after_column
Sample ID: a_20110322_02
File: timothy/students/Inoue/Research/data/20110322-FNB_P142_after_column_carbon-001.fid

Pulse Sequence: xpol
Solvent: dcd13
Temp. 29.0 °C / 298.1 K
Operator: Inoue
File: 20110322-FNB_P142_after_column_carbon-001
VNMRS-400 "pekke.ren"

Relax. delay 0.200 sec
Pulse 35.0 degrees
Acq. time 1.337 sec
Width 24509.8 Hz
112 repetitions

OBSERVE C13, 100.5147238 MHz
DECouple H1, 399.7480446 MHz
Power 45 dB
continuously on
WALTZ-14 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FFT size 89392
Total time 13 min, 11 sec

H 4.049

0.94 0.98 1.00 1.05 1.17
0.97 0.97 2.15 2.15 2.31

ppm
Sample: PBR_918
Sample ID: a_20131101_34
File: timothy/students/fmoforus/vnmrays/data/20131101-PBR_918_Proton-002.fid

Pulse Sequence: mpul
Solvent: dd13
Temp. 298.1 K
Sample #55. Operator: fmoforus
File: 20131101-PBR_918_Proton-002
VNMRS-400 "pekkle.mso"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.922 sec
Width 6355.7 Hz
16 repetitions

Spectrum: H1, 399.485618 MHz
DATA PROCESSING
Line broadening 0.8 Hz
FT size 65536
Total time 1 min, 12 sec

Sample: PBR_918
Sample ID: a_20131101_37
File: timothy/students/fmoforus/vnmrays/data/20131101-PBR_918_Carbon-002.fid

Pulse Sequence: mpul
Solvent: dd13
Temp. 298.1 K
Sample #55. Operator: fmoforus
File: 20131101-PBR_918_Carbon-002
VNMRS-400 "pekkle.mso"

Relax. delay 0.200 sec
Pulse 90.0 degrees
Acq. time 1.300 sec
Width 24056.4 Hz
512 repetitions

Spectrum: C13, 100.631298 MHz
DECOUPLE H1, 399.485618 MHz
Power 49 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.8 Hz
FT size 131072
Total time 15 min, 53 sec
Sample: PRH.PI166
Sample ID: a_20110326_06
File: timothy/student/foxmurus/data/20110326-PRH.PI166_Proton-002.fid

Pulse Sequence: s2pul
Solvent: dcd13
Temp: 25.0 C / 298.1 K
Sample 991, Operator: foxmurus
File: 20110326-PRH.PI166_Proton-002
VNMRD-400 "peckle.nmr"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.992 sec
Width 6389.7 Hz
16 repetitions

RESOLVE C13, 399.4040835 MHz
DATA PROCESSING
Line broadening 0.8 Hz
FT size 65536
Total time 3 min, 12 sec

Sample: PRH.PI166
Sample ID: a_20110326_06
File: timothy/student/foxmurus/data/20110326-PRH.PI166_Carbon-001.fid

Pulse Sequence: s2pul
Solvent: dcd13
Temp: 25.0 C / 298.1 K
Sample 991, Operator: foxmurus
File: 20110326-PRH.PI166_Carbon-001
VNMRD-400 "peckle.nmr"

Relax. delay 0.200 sec
Pulse 35.0 degrees
Acq. time 1.305 sec
Width 24094.4 Hz
512 repetitions

RESOLVE C13, 110.4302115 MHz
DECOUPLING C13, 399.4060951 MHz
Power 40 dB
continuously on
MULTI-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 51270
Total time 12 min, 53 sec
Sample: FNR_P140
Sample ID: a_20110326_05
File: timing/hs/projects/fmzren/daten/20110326-FNR_P140_Carbon-001.fid

Pulse Sequence: zpul
Solvent: cdcl3
Temp: 25.0 °C / 298.1 K
Sample #80. Operator: fmzren
File: 20110326-FNR_P140_Carbon-001

Rest delay: 0.200 sec
Pulses 35.0 degrees
Acq. time 1.350 sec
Width 340.65 Hz
512 repetitions

Data Processing
Line broadening 0.5 Hz
Total time 11 min, 13 sec

---

Sample: FNR_P140
Sample ID: a_20110326_05
File: timing/hs/projects/fmzren/daten/20110326-FNR_P140_Proton-002.fid

Pulse Sequence: zpul
Solvent: cdcl3
Temp: 25.0 °C / 298.1 K
Sample #80. Operator: fmzren
File: 20110326-FNR_P140_Proton-002

Rest delay: 1.000 sec
Pulses 45.0 degrees
Acq. time 2.992 sec
Width 635.7 Hz
16 repetitions

Data Processing
SI 399.40000 MHz
Line broadening 0.2 Hz
FT size 65536
Total time 1 min, 13 sec
Sample: PW3_P122
Sample ID: s_20080401_02
File: timothy/studenta/fournoueux/vnmrsyst/data/PW3/20080401-PW3_P122_Fluorine-001.fid

Pulse Sequence: edpi1
Solvent: cdcl3
Temp: 25.0 C / 298.1 K
Operator: fournoueux
File: 20080401-PW3_P122_Fluorine-001
VNMRS-650 "pakele.unc"

Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 0.444 sec
Width 125.0 kHz
16 repetitions
OBSERVE F13, 376.1410982 MHz
DATA PROCESSING
Line broadening 0.9 Hz
Shim apodization 0.4 Hz
FT size 262144
Total time 1 min. 50 sec

---

Sample: PW3_P1132
Sample ID: s_20080355_01
File: timothy/studenta/fournoueux/vnmrsyst/data/PW3/20080355-PW3_P1132_Boron-001.fid

Pulse Sequence: edpi1
Solvent: dmso
Temp: 25.0 C / 298.1 K
Operator: fournoueux
File: 20080355-PW3_P1132_Boron-001
VNMRS-650 "pakele.unc"

Relax. delay 0.100 sec
Pulse 50.0 degrees
Acq. time 1.097 sec
Width 23148.1 Hz
Single scan
OBSERVE F13, 129.255544 MHz
DECORDER X, 353.7113945 MHz
Power 49 dB
continuously on
WASTE-18 modulated
data racemess
Line broadening 0.5 Hz
FT size 121072
Total time 2 min. 1 sec
Sample: PWM_P22
Sample ID: w_29116057_29
File: timberby_students/fossorox/veracruz/data/20110617-PWR_P22_Proton-010.fid

Pulse Sequence: splex

Solvent: ocd13
Temp: 25.0 °C / 286.1 K
Sample P17, Operator: Fossorox
File: 20110617-PWR_P22_Proton-010
VMRSD-405 "pekule.mnr"

Relax. delay 1.010 sec
Pulse 45.0 degrees
Acq. time 2.992 sec
WDT 6.5 T Hertz
256 repetitions
Kaiser 91, 399.3000159 MHz
DATA PROCESSING
Line broadening 12 Hz
PT size 2048
Total time 1 min, 11 sec

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Sample: PWM_P22
Sample ID: w_29116057_29
File: timberby_students/fossorox/veracruz/data/20110617-PWR_P22_Carbon-001.fid

Pulse Sequence: splex

Solvent: ocd13
Temp: 25.0 °C / 286.1 K
Sample P17, Operator: Fossorox
File: 20110617-PWR_P22_Carbon-001
VMRSD-405 "pekule.mnr"

Relax. delay 0.200 sec
Pulse 90.0 degrees
Acq. time 1.505 sec
Width 240.494.4 Hz
256 repetitions
Kaiser 91, 399.3000159 MHz
DATA PROCESSING
Line broadening 0.5 Hz
PT size 135172
Total time 10 min, 53 sec
Sample: FW9_P24
Sample ID: e Fare 016_01
File: 20110916_P24_Fvot-001.fid

Pulse Sequence: 90pul
Solvent: toluene
Temp. 35.0 C / 100.1 K
Operator: Gaussian
File: 20110916_P24_Fvot-001

Relax. delay 1.100 sec
Pulse 45.0 degrees
Acq. time 2.995 sec
Width 4411.3 Hz
10 repetitions
OVERRES X1, 399.750000 Hz
PART 8950S81560
FT size 30160
Total time 1 min. 4 sec