Asymmetric Conjugate Additions of Boronates to $\alpha,\beta$-Unsaturated Trifluoromethyl Ketones and Strategies Towards Asymmetric Conjugate Additions of $N$-Boc-Pyrrole Boronic Acid

by

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Authors Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.
Abstract

An important class of organic molecules are those that contain fluorine. Fluorinated molecules have found widespread use in medicinal chemistry, as well as in agrochemicals. This is due to the ability of fluorine to act as a bioisostere for hydrogen, while also imparting other, desirable properties to the molecules, such as increased lipophilicity, metabolic stability, and bioavailability. An important class of fluorinated molecules are trifluoromethyl ketones. Trifluoromethyl ketones have been used in a wide variety of applications, notably as potent enzyme inhibitors, as well as key intermediates in the synthesis of fluorinated heterocycles, medicinal compounds and natural product analogues.

Currently, there are very few methods reported for the conjugate addition to α,β-unsaturated trifluoromethyl ketones, and even fewer methods for the asymmetric conjugate addition. The majority of this thesis is focused on the development of the BINOL catalyzed asymmetric conjugate addition of organoboronates to α,β-unsaturated trifluoromethyl ketones yielding enantiomerically enriched trifluoromethyl ketones. Through this method, trifluoromethyl ketones bearing stereochemically defined β-substituents can be obtained in good yield and excellent enantioselectivity (up to 96% yield and >99.6:0.4 er). With so few protocols available for the conjugate addition to α,β-unsaturated trifluoromethyl ketones, this methodology may allow for the efficient synthesis of many novel enantiomerically enriched trifluoromethyl ketones.

The final chapter of this thesis presents preliminary studies and optimization on the asymmetric conjugate addition of N-Boc-pyrrole boronic acid to diaryl enones. Early results indicate that this may be an efficient methodology for the conjugate addition of pyrrole in a stereocontrolled manner.
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To my wife Avalon, who has provided me with so much…
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<tr>
<td>9-BBN</td>
<td>9-borabicyclo[3.3.1]nonane</td>
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<tr>
<td>BINAL-H</td>
<td>1,1′-binaphthalene-2,2′-diol modified lithium aluminum hydride</td>
</tr>
<tr>
<td>BINAP</td>
<td>2,2′-bis(diphenylphosphanyl)-1,1′-binaphthalene</td>
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<td>BINOL</td>
<td>1,1′-binaphthalene-2,2′-diol</td>
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<td>tert-butoxycarbonyl</td>
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<td>MPV</td>
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Chapter 1. Introduction and Background

1.1 Chirality in Organic Synthesis

A common challenge synthetic chemists face is the introduction of stereocenters into molecules of interest. In fact, it was only relatively recently that synthetic chemists have been able to reliably and predictably furnish stereocenters through non-enzymatic processes. This was demonstrated by Brown and Zweifel through asymmetric hydroboration of cis-2-butene in the early 1960’s.\(^1\) This demonstrated the ability to furnish new stereocenters from achiral starting materials in a controlled manner. Since the development of this reaction, many other asymmetric reactions have been developed, including those that employ catalytic additives in order to introduce asymmetry.

Historically, several different methods have been used to introduce chirality into organic molecules, the most basic of which was through the use of naturally occurring chiral molecules that are relatively easy to obtain with a high stereochemical purity. These molecules are collectively referred to as the chiral pool, and contain a wide variety of classes of compounds, including amino acids, hydroxy acids, and terpenes (Figure 1.1).\(^2\)

![Figure 1.1: Common Chiral Pool Reagents](image-url)
Another common method traditionally used for the introduction of chirality is through the use of “chiral auxiliaries” (Figure 1.2). Chiral auxiliaries are molecules which can be incorporated into an achiral molecule in order to help introduce chirality in subsequent steps, and can later be removed. Auxiliaries are often derived from chiral pool reagents, and typically use steric or other favourable interactions, such as hydrogen bonding, in order to induce a preference for a particular stereochemical outcome in a reaction.\(^3\,\,^4\)

![Diagram](image)

**Figure 1.2: Common Chiral Auxiliaries**

In 1973, Yamada *et al.* reported the use of proline esters in the asymmetric alkylation of enamines.\(^5\,\,^6\) Although these reactions led to enantiomerically enriched products, the selectivities were quite low, with enantiomeric excesses (\(ee\)) of 6-36.5\%. Later, Whitesell and coworkers showed that much higher selectivities could be attained through the use of C2 symmetric chiral enamines derived from \((S,S)-2,5\)-dimethylpyrrolidine.\(^7\,\,^8\) Alkylations of these enamines resulted in much higher selectivities (80-93% \(ee\)) than Yamada’s proline esters. This dramatic increase in selectivity was rationalized through the analysis of the diastereomeric transition states for the alkylation (Scheme 1.1).
Scheme 1.1: Observed Selectivity in the Asymmetric Alkylation of Enamines

This result demonstrated the advantage of using molecules possessing C₂-symmetry in asymmetric processes. As a result, many chiral auxiliaries and ligands possessing C₂-symmetry have been developed for use in asymmetric transformations such as asymmetric epoxidations, 1,4-conjugate additions, and hydrogenations.⁹⁻¹⁷ Some common C₂-symmetric ligands are shown in Figure 1.3.

Figure 1.3: Common C₂-Symmetric Ligands and Their Uses
1.2 BINOL and BINOL Derivatives in Asymmetric Synthesis

1,1′-Binaphthalene-2,2′-diol (BINOL) was first synthesized in 1926 by Pummerer and coworkers through the oxidative coupling of 2-naphthol with FeCl₃. However, the utility of BINOL in asymmetric synthesis remained unexplored until 1979 when Noyori and coworkers reported a highly selective asymmetric reduction of aryl ketones using a BINOL substituted aluminum hydride reagent (BINAL-H) as shown in Scheme 1.2. The selectivity observed in this reduction was rationalized through a six membered chair-like transition state, minimizing the electrostatic repulsion between a lone pair of electrons on one of the BINOL oxygens and the π-system of the aryl group (Figure 1.4).

Scheme 1.2: Asymmetric Reduction of Aryl Ketones with BINAL-H

Figure 1.4: Transition state of BINAL-H Reduction
Since Noyori’s demonstration of the potential utility of BINOL in asymmetric synthesis, many other researchers have employed BINOL and substituted BINOLs for a variety of uses such as asymmetric Diels-Alder reactions,\textsuperscript{20-22} Mannich reactions,\textsuperscript{23} and more recently as a \textsuperscript{1}H NMR chiral shift reagent\textsuperscript{24} as well as in molecular recognition.\textsuperscript{25} A review by Yudin et al. showcases many applications of BINOL and substituted BINOLs in asymmetric synthesis up until the early 2000’s.\textsuperscript{26}

1.3 1,4-Conjugate Addition

1,4-Conjugate additions have been regarded as one of the most important classes of reactions in chemical synthesis.\textsuperscript{27} This is due to the wide variety of nucleophiles that can be used along with a large range of acceptors. Additionally, there is the possibility to incorporate up to two new stereocenters.

The rich chemistry of 1,4-conjugate additions has a relatively long history, with the first example being reported by Komnenos in 1883.\textsuperscript{28} However, Michael further developed this class of reactions in 1887,\textsuperscript{29} and his name has since become synonymous with 1,4-conjugate additions. These early conjugate additions were typically performed with deprotonated 1,3-diesters or 1,3-ketoesters and alkyldienemalonates or \(\alpha,\beta\)-unsaturated esters (Scheme 1.3).\textsuperscript{28,29} It was later found that many other types of carbon nucleophiles can be used in conjugate additions including silyl enol ethers, ketene acetics, and allylsilanes, as well as some metal stabilized carbanions such as organocuprates, -rhodium and -palladium. Of these, only the organometallics will be discussed for comparison.
Scheme 1.3: Early 1,4-Conjugate Additions

1.3.1 Copper Catalyzed 1,4-Conjugate Additions

In 1941, Kharasch showed that the addition of 1 mole percent of cuprous chloride to the reaction between methylmagnesium bromide and isophorone gave almost exclusive 1,4-addition product (Scheme 1.4).\(^30\) In 1966 House et al. showed conclusively that organocuprates were the reactive species in their studies on the role of copper salts on the conjugate addition of organometallic reagents, as well as in Kharasch’s original studies.\(^31\) Although pure organocuprate compounds can be prepared, it has been found that they are typically less reactive, or completely unreactive in conjugate addition reactions.\(^32\) However, the addition of either lithium or magnesium salts to inactive, pure organocuprates would restore their reactivity in conjugate additions.\(^33\)
It has been found that the addition of trialkylhalosilanes and polar additives, such as hexamethylphosphoramide (HMPA) can increase the reactivity of the organocuprate and lead to higher yielding reactions. Corey and Boaz showed that the addition of organocuprates to enones begins through a fast, reversible d-π* complexation followed by β-cupration. The addition of trialkylhalosilanes greatly accelerated these reactions by trapping the d-π* complex forcing the β-cupration. When a cyclic enone was used, a change in stereoselectivity was also observed (Scheme 1.5). Additionally, as the resultant enolate gets trapped as the silyl enol ether, the amount of aldol condensation side product formed is greatly reduced.

Scheme 1.5: Effects of TMSCl on Addition of Organocuprates

1.3.1.1 Asymmetric 1,4-Conjugate Additions of Organocuprates

An important modification of the conjugate addition of organocuprates is the asymmetric version of the reaction. There are several methods in which one can induce asymmetry in the addition of the organocuprate, including the addition of achiral organocuprates to chiral Michael
acceptors, organocuprates containing a chiral residual ligand (a ligand that does not transfer) and through the addition of chiral ligands.

The first example of the use of a chiral ligand for asymmetric induction in organocuprate addition was shown by Kretchmer in 1972. This was accomplished through the addition of (-)-sparteine to the addition of methylmagnesium iodide to cyclohexanone or 1,3-diphenyl-2-propen-1-one (chalcone) in the presence of cuprous chloride (Scheme 1.6). Although some stereoinduction was observed in this reaction, the optical purities were very low, ranging from 3.1–6.3%. Crabbé et al. showed that (-)-N-methylephedrine could also be used as a chiral ligand in the asymmetric addition of organocuprates, but again the reaction suffered from poor optical yields. In 1980, Mukiyama showed that the use of (S)-N-methylprolinol gave much better optical yields (up to 68%) than previously employed ligands (Scheme 1.7). However, in order to achieve this level of stereoinduction, a large excess of Grignard reagent, cuprous bromide and ligand were required.

Scheme 1.6: Asymmetric Conjugate Addition of Methylcuprate with Sparteine
Scheme 1.7: Asymmetric Conjugate Addition of Methylcuprate with (S)-N-Methylprolinol

In 1997, Feringa et al. reported the first completely stereocontrolled copper catalyzed conjugate addition of dialkylzinc reagents to cyclic enones in the presence of a BINOL-derived phosphoramidite ligand containing two chiral structural units (Scheme 1.8).\textsuperscript{45} Enantioselectivities of up to >98\% were reported, when the matched \((R,R)\)-bis(1-phenylethyl) amine and \((S)\)-BINOL was used. It is interesting to note that even when the mismatched \((S,S,S)\)-L\textsubscript{1} was used, good enantioselectivities were still observed. Key to this reaction is the transfer of an alkyl fragment from the dialkylzinc reagent to the copper-ligand complex, resulting in the chiral organocuprate.

Scheme 1.8: Highly Selective Conjugate Addition of Et\textsubscript{2}Zn using a BINOL-derived Phosphoramidite Ligand

In 2001, Reiser et al. reported the first copper catalyzed asymmetric conjugate addition of diphenylzinc to cyclic enones using chiral bis(oxazolines) as ligands. However, only modest
yields and selectivities were observed (Scheme 1.9). It was found that hydroxymethylene pendant groups were required on the oxazolines, suggesting that a bimetallic complex (Figure 1.5) was operating. This restricted coordination mode explained the enantiocontrol observed in the aryl transfer, as well as the limited substrate tolerance of the catalyst.

![Scheme 1.9: Copper Catalyzed Asymmetric Conjugate Addition of Diarylzinc](image)

**Scheme 1.9: Copper Catalyzed Asymmetric Conjugate Addition of Diarylzinc**

![Figure 1.5: Proposed Binding Mode of Bifunctional Catalyst and Substrate](image)

**Figure 1.5: Proposed Binding Mode of Bifunctional Catalyst and Substrate**

Alexakis *et al.* improved upon Reiser’s method through the use of arylalanes generated through the transmetalation of arylboronic acids with triethylaluminum. It was found that a wide range of aryl substituents could be added and a range of substituted cyclic trisubstituted enones could be tolerated (Scheme 1.10). This methodology allowed for access to cyclic ketones bearing all carbon quaternary centers with a high degree of stereocontrol.
Very recently, Zhou et al. reported the copper catalyzed asymmetric conjugate addition of arylboroxines to chalcone and chalcone derivatives (Scheme 1.10).\textsuperscript{52} It was found that the spiro-phosphoramidite \textbf{L4} gave the best enantioselectivity, and that the spiro chirality was the determining factor on the enantiomer formed in this reaction. Initially, it was considered that the addition proceeded through the classic conjugate addition mechanism of diorganocuprates, consisting of oxidative addition followed by reductive elimination at the β-position of the enones. In fact, Feringa \textit{et al.} proposed a similar mechanism to this in 2006 in the (bisphosphine)copper(I) catalyzed conjugate addition of Grignard reagents.\textsuperscript{53} However, Lewis acidic metal ions, such as lithium, magnesium, and zinc, were key to stabilizing the enolates formed during the oxidative addition, and the potassium ion is not Lewis acid enough to fulfill this role.\textsuperscript{52} Additionally, reversible oxidative addition can lead to \textit{cis-to-trans} isomerization of unreacted starting material, which was not observed under the reaction conditions.

\textbf{Scheme 1.10: Asymmetric Conjugate Addition of Arylalanes}

\begin{center}
\begin{tikzpicture}
\node (n) at (0,0) {$\text{O}$};
\node (n1) at (0.5,0) {$\text{R}$};
\node (n2) at (1.5,0) {$\text{n(H}_2\text{C)}$};
\node (n3) at (2,0) {$\text{Ar}$};
\node (n4) at (2.5,0) {$\text{R}$};
\node (n5) at (3,0) {$\text{CuTC (10 mol\%)}$};
\node (n6) at (3.5,0) {$\text{L3 (11 mol\%)}$};
\node (n7) at (4,0) {$\text{59-93\%}$};
\node (n8) at (4.5,0) {$\text{82-98.6\% ee}$};
\node (n9) at (5,0) {$\text{L3}$};
\node (n10) at (0,-1) {$\text{O}$};
\node (n11) at (0.5,-1) {$\text{R}$};
\node (n12) at (1.5,-1) {$\text{n(H}_2\text{C)}$};
\node (n13) at (2,-1) {$\text{Ar}$};
\node (n14) at (2.5,-1) {$\text{R}$};
\node (n15) at (3,-1) {$\text{ArAlEt}_2$ (3 eq.) including salts}$;\end{tikzpicture}
\end{center}
Scheme 1.11: Asymmetric Conjugate Addition of Arylboroxines

In order to gain some insight into the mechanism at play, density functional theory (DFT) calculations were conducted to simulate the insertion of \((L_4)\)phenylcopper(I) to \(p\)-methylchalcone. Surprisingly, no 1,2-insertion pathway was found, and instead a rare 1,4-insertion pathway was identified, in which a six-membered transition state led directly to an O-bound copper enolate (Figure 1.6).\(^\text{52}\) It was hypothesized that the Cu-O coordination helped to stabilize the developing negative charge of the enolate in the transition state. This 1,4-insertion requires that the enone must be able to attain an \(s\text{-}cis\) conformation, which was consistent with the fact that cyclic enones did not react under the conditions used.

Figure 1.6: Proposed Transition State for 1,4-Insertion

1.3.2 Rhodium Catalyzed 1,4-Conjugate Additions

In 1990, the first rhodium catalyzed conjugate addition of terminal alkynes to \(\alpha,\beta\)-unsaturated ketones was reported.\(^\text{54}\) Soon after, it was shown that other nucleophiles could be used such as activated nitriles (Paganelli), arylstannanes (Oi) and organoboronic acids (Miyura
Miyura and Hayashi proposed that the conjugate addition of organoboronic acids proceeded through a catalytic cycle similar to that of Suzuki cross-coupling reactions. Key to this mechanism is the B-Rh transmetalation, followed by reductive elimination to give the conjugate addition product (Scheme 1.12).\textsuperscript{56}

![Scheme 1.12: Proposed Rhodium Catalyzed Conjugate Addition Catalytic Cycle](image)

### 1.3.2.1 Asymmetric Rhodium Catalyzed 1,4-Conjugate Additions

Soon after the disclosure of the racemic conjugate additions of organoboronic acids, the reaction was shown to yield enantiomerically enriched conjugate addition products when chiral phosphine ligands were used.\textsuperscript{14} It was shown that use of \((S)-2,2'-\text{bis}(\text{diphenylphosphanyl})-1,1'-\text{binaphthalene (BINAP)}\) resulted in high enantioselectivity (91-97\% ee) in a wide range of cyclic and acyclic enones (Scheme 1.13). In 2002, Hayashi \textit{et al.} confirmed that the mechanism of the asymmetric conjugate addition was the same as that proposed for the racemic addition (Scheme 1.12).\textsuperscript{17}
Scheme 1.13: Rhodium Catalyzed Asymmetric Conjugate Addition of Arylboronic Acids

This methodology was soon applied to the synthesis of pharmaceutically interesting compounds, with one of the earliest examples being reported by Helmchen.\textsuperscript{58,59} In 2008, Parker et al. showed that, with a few modifications, the conjugate addition of arylboronic acids could be efficiently scaled up to the multi-kilogram scale for use in pharmaceutical synthesis.\textsuperscript{60} It was also found that this methodology could be used to obtain the conjugate addition product of substrates that are typically poor Michael acceptors such as substituted maleimides and 4-oxobutenamides (Scheme 1.14).\textsuperscript{61,62}

Scheme 1.14: Rhodium Catalyzed Asymmetric Conjugate Additions to Maleimides and 4-Oxobutenamides
Through the modification of the chiral ligands present, a vast number of asymmetric conjugate additions can be achieved on a variety of substrate classes and several reviews have been published to exemplify the utility of this reaction.\textsuperscript{16,63,64}

Since their discovery, rhodium catalyzed reactions quickly became one of the most valuable asymmetric conjugate addition methods, owing partly to the fact that a wide variety of transformations can be achieved. Additionally, the enantioselectivities for these reactions are typically high, and the reactivity can be tuned by altering the ligands used.

1.3.3 Conjugate Additions of Organoboron Compounds

An early example of the conjugate addition of organoboron compounds was given by Brown \textit{et al.} in 1976.\textsuperscript{65} In this report, alkenylboranes obtained through the hydroboration of terminal alkynes with 9-borabicyclo[3.3.1]nonane (9-BBN) were shown to undergo smooth 1,4-addition to methyl vinyl ketone (MVK) and related ketones (Scheme 1.15). Brown hypothesized that the addition proceeded through a six-membered, cyclic transition state (Figure 1.7) as only enones able to adopt an \textit{s-cis} conformation underwent conjugate addition. Soon after, this methodology was extended to allow for the transfer of alkynyl groups in a 1,4-manner.\textsuperscript{66}

\begin{center}
\textbf{Scheme 1.15: Conjugate Addition of Alkenylborane to MVK}
\end{center}
1.3.3.1 Asymmetric Conjugate Additions of Alkynylboronates

In 2000, Chong et al. reported the first asymmetric alkynylboration of enones using alkynyl 3,3′-disubstituted-BINOL boronates. These reagents were readily prepared by the addition of an alkynyllithium to triisopropyl borate followed by treatment with a stoichiometric amount of BINOL to form an alkynyl BINOL borate salt. In analogy with previous work by Brown, it was anticipated that the treatment of this borate salt with anhydrous HCl or BF$_3$·OEt$_2$ would yield the desired boronate (Scheme 1.16). Indeed, treatment of the alkynyl BINOL borate salt and chalcone with BF$_3$·OEt$_2$ led to clean formation of the 1,4-addition product in high yields and enantioselectivities (up to 99 and >98% respectively) (Scheme 1.17).

Scheme 1.16: Synthesis of Alkynyl BINOL Borate Salts
Scheme 1.17: Asymmetric Alkynylboration of Chalcone

It was found that the stereoselectivity of these reactions could be predicted by using a six-membered cyclic transition state model similar to that proposed by Brown and Noyori for the conjugate addition of alkynyl 9-BBN reagents to enones and the asymmetric reduction of aryl ketones by BINAL-H respectively (Figure 1.8). The selectivity also correlated strongly with the substitution of the enone, with highest selectivities coming from enones bearing an aryl group on the carbonyl carbon and β-substituents containing electron-rich π-systems.

Figure 1.8: Proposed Transition State for the Asymmetric Alkynylboration

In 2004, the Chong group showed that the asymmetric alkynylboration reaction could be rendered catalytic through a rare example of a ligand accelerated reaction. It was found that, in the presence of a catalytic amount of 3,3'-disubstituted BINOL, alkynylboronates would undergo transesterification followed by conjugate addition to an enone, giving the desired products in
high yields and enantioselectivities. In order for the proposed catalytic cycle to be effective, several conditions would need to be met (Scheme 1.18). First, boronate 1 would need to readily transesterify with the BINOL ligand L5 to form boronate 2. Boronate 1 would also need to be less reactive towards the enone than boronate 2, and finally boron enolate 3 would need to disproportionate in order to reform the active boronate species.  

Scheme 1.18: Proposed Catalytic Cycle for the Asymmetric Alkynylboration of Enones

Applying what was learned in the conjugate additions of alkynylboronates with enones to N-acylimines, the Chong group showed that this methodology could be applied to the synthesis of chiral propargylamides (Scheme 1.19). However, this reaction was unable to be rendered catalytic, and stoichiometric amounts of alkynyl BINOL boronate were required. Interestingly, it
was found that when the BINOL contained strongly electron withdrawing groups in the 3,3’-positions the reaction would not go to completion. This was hypothesized to be a result of coordination of the nitrogen atom with the boron due to the increased Lewis acidity caused by the 3,3’-substituents.

![Scheme 1.19: Conjugate Addition of BINOL-Modified Alkynylboronates to N-Acylimines](image)

**Scheme 1.19: Conjugate Addition of BINOL-Modified Alkynylboronates to N-Acylimines**

**1.3.3.2 Asymmetric Conjugate Additions of $sp^2$-Boronates**

In 2007, the Chong group extended the methodology of the catalytic conjugate addition of alkynylboronates to include alkenylboronates, showing for the first time that an asymmetric conjugate alkenylation could be done in the absence of a transition metal catalyst. The alkenylboronates used in these reaction are easily prepared and showed great selectivity in the transfer to enones (Scheme 1.20).
Scheme 1.20: Asymmetric Conjugate Addition of Alkenylboronates to Enones

Several substituted BINOL catalysts were tested, all of which gave excellent selectivities. The reaction was shown to give excellent yields and selectivities to a range of enones, including those bearing electron-rich and electron-poor aromatic, heteroaromatic, and alkyl β-substituents (Table 1.1). Enones bearing relatively large β-substituents gave the highest selectivities; however, even enones bearing β-alkyl groups gave consistently high selectivities. Again, the observed enantioselectivity could be explained using the six-membered cyclic transition state proposed for the alkynylation of enones and N-acylimines.

![Proposed Transition State for the Asymmetric Alkenylboration](image)

Figure 1.9: Proposed Transition State for the Asymmetric Alkenylboration
Table 1.1: Asymmetric Conjugate Addition of Alkenylboronates to Various Enones

<table>
<thead>
<tr>
<th>R</th>
<th>Ligand (X)</th>
<th>Time (h)</th>
<th>Yield (%)$^a$</th>
<th>$er^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>L5a (H)</td>
<td>24</td>
<td>&lt;20</td>
<td>93:7</td>
</tr>
<tr>
<td>Ph</td>
<td>L5b (I)</td>
<td>36</td>
<td>93</td>
<td>98.7:1.3</td>
</tr>
<tr>
<td>Ph</td>
<td>L5c (Br)</td>
<td>12</td>
<td>92</td>
<td>98:2</td>
</tr>
<tr>
<td>Ph</td>
<td>L5e (CF₃)</td>
<td>12</td>
<td>90</td>
<td>98.6:1.4</td>
</tr>
<tr>
<td>Ph</td>
<td>L5f (Ph)</td>
<td>36</td>
<td>75</td>
<td>97.1:2.9</td>
</tr>
<tr>
<td>4-ClC₆H₄</td>
<td>L5b (I)</td>
<td>36</td>
<td>96</td>
<td>99.2:0.8</td>
</tr>
<tr>
<td>4-MeOC₆H₄</td>
<td>L5b (I)</td>
<td>48</td>
<td>86</td>
<td>99.1:0.9</td>
</tr>
<tr>
<td>2-furyl</td>
<td>L5b (I)</td>
<td>72</td>
<td>94</td>
<td>98.5:1.5</td>
</tr>
<tr>
<td>n-hexyl</td>
<td>L5b (I)</td>
<td>72</td>
<td>94</td>
<td>99.2:0.8</td>
</tr>
</tbody>
</table>

$^a$Isolated yields after flash chromatography. $^b$Determined by chiral HPLC analysis.

The conjugate addition of arylboronates proved to be difficult, and were unreactive under similar reaction conditions. However, in 2011, Turner and Chong reported the first BINOL catalyzed asymmetric conjugate addition of arylboronates (Scheme 1.21). Initial conditions, similar to those in the alkenyloboration, using up to 200 mol% of BINOL yielded only trace amounts of the desired product. After extensive screening of solvents, it was eventually found...
that the use of 4 equivalents of diethyl phenylboronate in the absence of additional solvent gave the desired product.

Scheme 1.21: Asymmetric Conjugate Arylboration of Enones

Several substituted diaryl enones, as well as alkyl enones were shown to the conjugate addition of phenyl boronate. It is interesting to note that the 3,3′-substitution was found to greatly affect the conversion and selectivity of the reaction. The parent BINOL L5a, was found to only give <50% conversion; however, a high selectivity was observed (Table 1.2). When strongly electron withdrawing groups were used, high conversions and selectivities of up to 98% ee were found. Ligand L5d was found to possess the optimal electron withdrawing ability-to-size ratio, providing the product with 100% conversion and 82% ee.
Table 1.2: BINOL Catalyzed Conjugate Addition of Arylboronates to Various Enones

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>R</th>
<th>Ligand</th>
<th>Time (h)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>er&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-MeC₆H₄</td>
<td>L₅a (H)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>96</td>
<td>&lt;50&lt;sup&gt;d&lt;/sup&gt;</td>
<td>91:9</td>
</tr>
<tr>
<td>4-MeC₆H₄</td>
<td>L₅b (I)</td>
<td>96</td>
<td>72&lt;sup&gt;d&lt;/sup&gt;</td>
<td>89:11</td>
</tr>
<tr>
<td>4-MeC₆H₄</td>
<td>L₅c (Br)</td>
<td>72</td>
<td>91&lt;sup&gt;d&lt;/sup&gt;</td>
<td>92:8</td>
</tr>
<tr>
<td>4-MeC₆H₄</td>
<td>L₅d (Cl)</td>
<td>72</td>
<td>90</td>
<td>91:9</td>
</tr>
<tr>
<td>4-MeC₆H₄</td>
<td>L₅e (CF₃)</td>
<td>72</td>
<td>36&lt;sup&gt;d&lt;/sup&gt;</td>
<td>92:8</td>
</tr>
<tr>
<td>4-MeC₆H₄</td>
<td>L₅g (CN)</td>
<td>5</td>
<td>97</td>
<td>84:16</td>
</tr>
<tr>
<td>2-MeC₆H₄</td>
<td>L₅d (Cl)</td>
<td>48</td>
<td>75</td>
<td>99:1</td>
</tr>
<tr>
<td>4-MeOC₆H₄</td>
<td>L₅d (Cl)</td>
<td>48</td>
<td>66</td>
<td>94:6</td>
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<tr>
<td>4-ClC₆H₄</td>
<td>L₅d (Cl)</td>
<td>48</td>
<td>74</td>
<td>90:10</td>
</tr>
<tr>
<td>1-naphthyl</td>
<td>L₅d (Cl)</td>
<td>32</td>
<td>86</td>
<td>98:2</td>
</tr>
<tr>
<td>n-C₄H₉</td>
<td>L₅d (Cl)</td>
<td>72</td>
<td>95</td>
<td>91:9</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yields after flash chromatography. <sup>b</sup>Determined by chiral HPLC analysis. <sup>c</sup>200 mol% used. <sup>d</sup>% Conversion based on <sup>1</sup>H NMR.

Soon after, May et al. demonstrated the conjugate addition of alkenylboronic acids to enones appended with protected, unprotected or substituted indoles. Schaus et al. developed the asymmetric propargylation of ketones using allenylboronates, and were also able to successfully perform asymmetric conjugate additions of aryl- and alkenylboronates to o-quinone methides. May et al. showed that under modified conditions, it was possible to add
alkenylboronic acids to enones containing pendant heteroaryl groups (Scheme 1.22).\textsuperscript{76} The addition of catalytic amounts of Mg(OtBu)\textsubscript{2} was found to accelerate the reaction, and it is thought that the butoxide may act as a proton transfer agent.

\[
\text{H}_{\text{Het}}\text{C} = \text{O} + \text{Het} - \text{B(OH)}_2 \rightarrow \text{H}_{\text{Het}}\text{C} = \text{O}
\]

\[
\text{Mg(OtBu)}_2 (10 \text{ mol\%)}
\]

\[
4\text{Å MS, MePh, reflux}
\]

\[
\text{H}_{\text{Het}}\text{C} = \text{O}
\]

\[
\text{Het = ♦♦♦♦♦♦♦}
\]

\[
\text{Scheme 1.22: Conjugate Addition of Alkenyl Boronic Acids to Heteroaryl Appended Enones}
\]

In a further extension of nucleophile scope, Cheung and Chong showed the conjugate addition of various heteroarylboronates to diaryl enones (Scheme 1.23).\textsuperscript{77} Similar to the arylboration described by Turner, the addition of heteroarylboronates was found to run more efficiently in the presence of excess heteroarylboronate acting as solvent. The heteroarylboronates were found to be more reactive than arylboronates, requiring a lower temperature and reaction time. The addition of heteroarylboronates also showed a higher selectivity than was observed in the arylation of enones (Table 1.3).
Scheme 1.23: Asymmetric Conjugate Heteroarylboronation of Enones

Table 1.3: BINOL Catalyzed Conjugate Addition of Heteroarylboronates to Various Enones

<table>
<thead>
<tr>
<th>R</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>S</td>
<td>O</td>
</tr>
<tr>
<td>Ph</td>
<td>24</td>
<td>30</td>
<td>83</td>
</tr>
<tr>
<td>4-MeOC₆H₄</td>
<td>48</td>
<td>30</td>
<td>84</td>
</tr>
<tr>
<td>4-BrC₆H₄</td>
<td>45</td>
<td>30</td>
<td>95</td>
</tr>
<tr>
<td>1-naphthyl</td>
<td>24</td>
<td>30</td>
<td>85</td>
</tr>
</tbody>
</table>

*a*Isolated yields after flash chromatography. *b*Determined by chiral HPLC analysis.

In order to gain further insight into the mechanism of the alkenylboronation reaction, Goodman et al. performed DFT calculations to rationalize the results observed. Transition state structures similar to those proposed by Chong and Wu were found, supporting their proposed catalytic cycle. It was also found that complexation of the boronate with the enone was the rate limited step, followed by a fast, asynchronous carbon-carbon bond formation yielding the boron enolate of the addition product. Very recently, May et al. conducted a detailed mechanistic analysis of the alkenylboronation reaction by Hammett plot analysis. It was shown that the rate of
the reaction is weakly inversely proportional to the electron withdrawing ability of β-aryl substituents ($\rho = -0.34$) and directly proportional to the electron withdrawing ability of aryl substituents on the carbonyl carbon ($\rho = 0.49$).\textsuperscript{79} Interestingly, the rate of the reaction is most strongly correlated with the electronic nature of the alkenylboronate, with electron rich aryl substituted alkenylboronic acids showing the fastest reaction rates ($\rho = -0.95$).\textsuperscript{79}

1.4 Asymmetric Conjugate Additions to Fluorinated Michael Acceptors

1.4.1 Fluorine in Organic Synthesis

Fluorinated compounds have found widespread use in both the pharmaceutical industries and as agrochemicals, with nearly 20\% of all pharmaceuticals ever released and ~30\% of agrochemicals containing at least one fluorine.\textsuperscript{80–83} Much of this results from the ability of fluorine to act as a bioisostere for hydrogen. Bioisosterism refers to the ability of atoms or groups of atoms of similar size or shape to be replaced with one another without substantially altering the biological behaviours such as binding.\textsuperscript{82} It has also been shown that replacement of hydrogen atoms with fluorine atoms can increase the lipophilicity of many compounds. This replacement also typically imparts greater metabolic stability of pharmaceuticals due to the strong C-F bond.\textsuperscript{84}

Trifluoromethyl ketones have been found of particular interest in the literature due to their interesting properties. Specifically, trifluoromethyl ketones have been found to be potent enzyme inhibitors.\textsuperscript{85–88} In addition to this, they have also been used as key intermediates in the synthesis of fluorinated heterocycles, medicinal compounds, and natural products.\textsuperscript{89–93} Due to the strong electron withdrawing ability of the CF$_3$ group, the carbonyl carbon is far more prone to nucleophilic attack.\textsuperscript{94} Additionally, the carbonyl oxygen is far less Lewis basic than non-
fluorinated congener, making trifluoromethyl enones far less reactive in Lewis acid mediated reactions.\textsuperscript{94,95}

1.4.2 Conjugate Additions to CF$_3$-containing Unsaturated Carbonyl Compounds

The first examples of conjugate additions to trifluoromethyl containing $\alpha,\beta$-unsaturated carbonyl compounds appeared in 1985 when Ogoshi reported the conjugate addition of various nucleophiles to $\beta$-CF$_3$-$\alpha,\beta$-unsaturated ketones.\textsuperscript{96} Although the reaction was quite limited in scope, it showed the utility of $\beta$-CF$_3$ enones as useful building blocks for access to trifluoromethyl substituted compounds (Scheme 1.24). In 1991, Yamazaki et al. reported a conjugate addition of lithium enolates with (E)-3-(trifluoromethyl)acrylates to give the conjugate addition products.\textsuperscript{97} This group also showed the ability of lithium enolates derived from chiral acyloxazolidinones to add diastereoselectively to $\alpha,\beta$-unsaturated $\beta$-CF$_3$ esters (Scheme 1.25).\textsuperscript{98}

Scheme 1.24: Conjugate Addition to $\beta$-CF$_3$-$\alpha,\beta$-Unsaturated Ketone

Scheme 1.25: Diastereoselective Conjugate Addition of Acyloxazolidinone Enolates
Currently, there are few examples of catalyzed conjugate additions to unsaturated trifluoromethyl ketones, with the regioselective conjugate addition of organocuprates to acetylenic ketones being one of the earliest. \(^9^9\) This reaction was shown to proceed with good regioselectivity (1,4-addition vs. 1,2-addition) and typically showed good \(E:Z\) selectivity (Scheme 1.26). In 2006, Nenajdenko \textit{et al.} reported the synthesis of trifluoromethylated \(\alpha\)-hydroxydihydropyrans through the conjugate addition of \(\alpha\)-cyanoketones to \(\alpha,\beta\)-unsaturated trifluoromethyl ketones followed by cyclization to give the product as a single diastereomer (Scheme 1.27). \(^8^9\)

![Scheme 1.26: Conjugate Addition to Acetylenic Trifluoromethyl Ketones](image)

Scheme 1.26: Conjugate Addition to Acetylenic Trifluoromethyl Ketones

![Scheme 1.27: Conjugate Addition-Cyclization of \(\alpha,\beta\)-Unsaturated Trifluoromethyl Ketones](image)

Scheme 1.27: Conjugate Addition-Cyclization of \(\alpha,\beta\)-Unsaturated Trifluoromethyl Ketones

In 2012, Konno \textit{et al.} disclosed the first practical, additive-free conjugate alkylation of \(\beta\)-trifluoromethyl enones. \(^1^0^0\) It was found that a range of alkylzinc nucleophiles could be used, including those containing esters and nitriles (Scheme 1.28). This reaction was also found to progress smoothly with a wide range of other electron deficient olefins containing the CF\(_3\) group, including amides, phosphonates, and sulphones. It was found that when trifluoromethyl olefins containing an Evans auxiliary are used, a small amount of diastereoselectivity is observed. \(^1^0^0\)
Scheme 1.28: Conjugate Addition of Alkylzinc Nucleophiles to Trifluoromethylated Electron-Deficient Olefins

1.4.2.1 Catalytic Asymmetric Conjugate Addition to β-CF₃ Enones

Shibata et al. described the first enantioselective synthesis of β-CF₃ pyrrolines through a cinchona alkaloid catalyzed asymmetric conjugate addition of nitromethane to β-trifluoromethylated enones followed by an iron mediated reduction/cyclization/dehydration sequence (Scheme 1.29). It was found that cinchona-alkaloid-thiourea derivatives efficiently catalyzed the reaction and gave the desired product in high isolated yield and ee (up to 99% and 98%, respectively). The reaction was also found to be highly general, with enones possessing a wide range of aryl-, heteroaryl-, and sterically demanding substituents being accommodated. Either enantiomer could be prepared through use of the pseudo-enantiomeric catalysts L₆ and L₇.
Akin to the methods developed in our lab, Konno et al. described the rhodium catalyzed asymmetric conjugate addition of aryl- and heteroarylboronic acids to activated β-trifluoromethyl alkenes in the presence of BINAP to give the desired product in high yield and enantioselectivity. Motivated by the initial success of the addition of organoboronic acids, this methodology was quickly expanded to include a range of organostannane nucleophiles; however, these reactions were unable to be rendered asymmetric (Scheme 1.30).
In order to test the generality of the rhodium catalyzed addition of aryl boronic acids, a variety of electron deficient β-trifluoromethyl olefins were examined. The addition to α,β-unsaturated esters and amides, as well as nitroalkenes afforded the desired product in moderate yields. However, other than the case with the α,β-unsaturated amides, enantioselectivities dropped. Reactions with vinyl phosphonates and vinyl sulphones returned very poor yields and exhibited poor enantioselectivity. When aryl stannanes were used as the nucleophile in place of aryl boronic acids, the group was able to obtain the 1,4-addition product of vinyl sulphones and phosphonates in good yields.

Up until this point, there had been no reports of catalyzed asymmetric alkynylation of β-trifluoromethyl enones. However, in 2014, Pédro et al. showed that terminal alkynes, in the presence of a copper catalyst and chiral bidentate phosphine ligands, could be transferred with good yields and enantioselectivity (Scheme 1.31). It was shown that a variety of alkynes could be used and the substrate scope was quite broad. The electronic nature of the aromatic substituent on the enones had little effect on the outcome of the reaction. Interestingly, it was found that the

Scheme 1.30: Rhodium Catalyzed Asymmetric Conjugate Addition of Aryl- Boronates and Stannanes to β-CF$_3$ Enones

In order to test the generality of the rhodium catalyzed addition of aryl boronic acids, a variety of electron deficient β-trifluoromethyl olefins were examined. The addition to α,β-unsaturated esters and amides, as well as nitroalkenes afforded the desired product in moderate yields. However, other than the case with the α,β-unsaturated amides, enantioselectivities dropped. Reactions with vinyl phosphonates and vinyl sulphones returned very poor yields and exhibited poor enantioselectivity. When aryl stannanes were used as the nucleophile in place of aryl boronic acids, the group was able to obtain the 1,4-addition product of vinyl sulphones and phosphonates in good yields.

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presence of a 2-thienyl group next to the carbonyl resulted in increased reactivity as well as selectivity. Unfortunately, aliphatic enones were shown to have much lower reactivity and resulted in products being obtained in low yield, although the selectivities remained high.\textsuperscript{103}

\begin{center}
\begin{tikzpicture}

\node[draw,shape=rectangle,minimum width=15cm,minimum height=8cm] (a) at (0,0) {
\begin{align*}
\text{Me}_2N & \quad \text{THF} \\
40^\circ C, 72 h & \quad \text{Et}_3N
\end{align*}
};

\node[draw,shape=rectangle,minimum width=1cm,minimum height=1cm] (b) at (10,0) {L8};

\node[draw,shape=rectangle,minimum width=1cm,minimum height=1cm] (c) at (0,-2) {R};

\node[draw,shape=rectangle,minimum width=1cm,minimum height=1cm] (d) at (10,-2) {R'};

\node[draw,shape=rectangle,minimum width=1cm,minimum height=1cm] (e) at (5,0) {L8 (20 mol%)};

\node[draw,shape=rectangle,minimum width=1cm,minimum height=1cm] (f) at (5,-2) {[Cu(CH_3CN)_4]BF_4 (20 mol%)};

\draw[->] (a) -- (b);
\draw[->] (b) -- (c);
\draw[->] (b) -- (d);
\draw[->] (e) -- (f);
\end{tikzpicture}
\end{center}

**Scheme 1.31: Copper Catalyzed Conjugate Alkynylation of β-CF_3 Enones**

The reaction conditions also allowed for the addition of various alkynes. Substituted phenylacetylenes bearing electron withdrawing or electron donating groups in various positions reacted smoothly with the β-trifluoromethyl enones to give the desired product with good yields and high selectivities. Aliphatic alkynes were shown to be compatible with the reaction, and although the reactions were far more sluggish, resulting in moderate yields, the enantioselectivities remained high.\textsuperscript{103}

Recently in our lab, Wawrykow developed the metal free, asymmetric conjugate addition of organoboronates to β-trifluoromethyl enones catalyzed by 3,3′-disubstituted BINOLs.\textsuperscript{104} It was found that the alkynylation showed similar selectivities to those reported by Wu and Chong for enones bearing β-alkyl groups, but were much less reactive, requiring both extended reaction times and more forcing conditions (Scheme 1.32).\textsuperscript{69,104}
Encouraged by these initial results, this methodology was extended to include additions of other organoboronate nucleophiles. The alkenylboration of β-trifluoromethyl enones was examined next. Again, the reaction showed similar selectivity to those of the β-methyl and β-isopropyl enones, further exemplifying that the trifluoromethyl group behaves similarly to an alkyl group in this chemistry.\textsuperscript{71,104} Through a simple competition experiment, in which a one-to-one mixture of β-trifluoromethyl enone and chalcone was used, it was estimated that the reaction between alkenylboronates and the β-trifluoromethyl enones is at least 100 times slower than the reaction with chalcone (Scheme 1.33).\textsuperscript{104} The addition of heteroarylboronates showed a similar trend and is summarized below in Table 1.4.
Scheme 1.33: Rate Competition Between Chalcone and β-CF<sub>3</sub> Enone

Table 1.4: BINOL Catalyzed Conjugate Addition of Organoboronates to β-CF<sub>3</sub> Enones

<table>
<thead>
<tr>
<th>Ar</th>
<th>R</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>er&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>n-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;13&lt;/sub&gt;</td>
<td>93</td>
<td>69:31</td>
</tr>
<tr>
<td>4-MeOC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>84</td>
<td>60:40</td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>n-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;13&lt;/sub&gt;</td>
<td>86</td>
<td>96:4</td>
</tr>
<tr>
<td>4-MeOC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>81</td>
<td>96:4</td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td><img src="image" alt="thiophene" /></td>
<td>72&lt;sup&gt;c&lt;/sup&gt;</td>
<td>66:34</td>
</tr>
<tr>
<td>Ph</td>
<td><img src="image" alt="oxazole" /></td>
<td>60</td>
<td>77.3:22.7</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yields after flash chromatography. <sup>b</sup>Determined by chiral HPLC analysis. <sup>c</sup>Obtained as a 4.8:1 mixture of 2 products; the minor component has been tentatively identified as the 3-thienyl addition product.

1.4.2.2 Catalytic Asymmetric Conjugate Addition to α,β-Unsaturated Trifluoromethyl Ketones

To date there are very few references in the literature on asymmetric conjugate additions to α,β-unsaturated trifluoromethyl ketones. Very recently, Pédro et al. showed the first example of an asymmetric conjugate addition of terminal diynes in the presence of a copper
This reaction was found to progress smoothly under low catalyst loadings to give the desired product in good yields and high ee. The substrate scope proved to be very broad with β-aryl groups containing electron withdrawing or electron donating groups as ortho-, meta-, or para- substituents all giving good yields and excellent selectivities. Enones containing β-alkyl groups also performed well, providing the desired product with high ee (84 – 88%), albeit in slightly diminished yield.

Scheme 1.34: Asymmetric Conjugate Addition of Diynes to α,β-Unsaturated CF₃ Ketones

In order to further probe the scope of this reaction, additional terminal diynes were also examined. Substituted phenyl-1,3-butadiynes containing electron donating or electron withdrawing groups, as well as heteroaromatic diynes, showed variable yields, but consistently provided the desired adducts with high ee. In stark contrast with the addition of aliphatic alkynes to β-trifluoromethyl enones, the additions of aliphatic diynes reacted in a manner similar to that of aromatic diynes, and gave addition products of comparable yields and high selectivities. It is also interesting to note that other non-fluorinated enones (e.g. 2-cyclohexenone, chalcone, 4-phenyl-3-buten-2-one) did not react under the optimized reaction conditions.
1.5 Thesis Proposal

With the very limited examples of conjugate additions to α,β-unsaturated trifluoromethyl ketones, and the almost non-existent asymmetric version of this reaction, we decided to investigate whether organoboronates in the presence of 3,3′-disubstituted BINOLs could be used to effect the asymmetric transfer of organic groups to trifluoromethyl enones. Previous studies in our lab on the conjugate addition of organoboronates to β-trifluoromethyl-α,β-unsaturated ketones showed that the β-trifluoromethyl group behaves similarly to a methyl or isopropyl group. We were then curious about the behaviour of α,β-unsaturated trifluoromethyl ketones in the same chemistry. If these reactions proved successful, we could also examine the affects of a trifluoromethyl group on the carbonyl carbon has on the reactivity on enones on the BINOL catalyzed asymmetric conjugate addition of other organoboronates.
2.1 Preparation of α,β-Unsaturated Trifluoromethyl Ketones

In 2000, Andrew and Mellor reported a very simple synthesis of a variety of β-substituted α,β-unsaturated trifluoromethyl ketones by the addition of Grignard reagents to trifluoromethyl enaminone 5. This enaminone can in turn be made through a two step process beginning with ethyl vinyl ether and trifluoroacetic anhydride (Scheme 2.1). Using this methodology, a variety of β-aryl α,β-unsaturated trifluoromethyl ketones containing electron donating and electron withdrawing groups, as well as the bulky 1-naphthyl group were synthesized. Enones containing β-alkyl groups were also synthesized; however, it was found that only long chain, linear alkyl Grignard reagents provided the product in high yield. This may be due to the volatility of the lower molecular weight, aliphatic trifluoromethyl enones. When iPrMgBr was used, the reaction failed and returned unidentified decomposition products. It was later found that modifying the original procedure could increase the yield of the reaction. In this modification, the freshly prepared Grignard reagent is slowly added to a solution of enaminone 5 as opposed to a solution of 5 being slowly added to the Grignard reagent, with the rest of the procedure being the same as that reported in literature. Following this modified procedure, the desired enones were obtained in good to excellent yields (Scheme 2.2).

Scheme 2.1: Preparation of Enaminone 5
Scheme 2.2: Synthesis of α,β-Unsaturated Trifluoromethyl Ketones

With enones 6a-f in hand, we were ready to test the reactivity of α,β-unsaturated trifluoromethyl ketones towards the binaphthol catalyzed conjugate addition of organoboronates.

2.2 Asymmetric Conjugate Alkenylboration of α,β-Unsaturated Trifluoromethyl Ketones

We began our efforts with the asymmetric alkenylboration chemistry previously developed in our lab. We anticipated that this chemistry would work, as it has been shown to deliver the addition product in high yield and selectivity for a variety of enones. Following a simple procedure reported by Batey et al. the alkenyl boronate was readily obtained. As the standard boronate of choice, we decided to begin with the alkenylboronates derived from 1-octyne (Scheme 2.3).
Scheme 2.3: Preparation of Alkenylboronate 8

The initial test reaction was conducted under the same reaction conditions that had previously been reported by Wu and Chong employing enone 6a and (S)-I$_2$-BINOL L$_{5b}$ (Scheme 2.4).$^{71}$

Scheme 2.4: Alkenylboronation of Enone 6a

The reaction was monitored by taking aliquots from the reaction mixture and analyzing them by $^1$H NMR. After 24 hours, the reaction had not appeared to have progressed very far and only trace amounts of addition product 9a were observed. However, when the reaction mixture was analyzed by thin layer chromatography (TLC), a new spot was seen along with starting enone 6a and (±)-I$_2$-BINOL. The reaction was allowed to stir for an additional 24 hours after
which it was quenched with DI water and extracted with DCM. Analysis by \(^1\)H NMR showed only trace amounts of product formed. However, TLC analysis showed a large streak corresponding to a new product. Purification by flash chromatography using 20:1 Hex:EtOAc afforded the product in 48% yield. The reaction was set up again; however, this time the reaction progress was monitored by the disappearance of the starting material by TLC. It was found that running the reaction at 40 °C for 72 hours gave the desired product in 86% yield. Running the reaction under these new conditions with (S)-I\(_2\)-BINOL afforded the enantioenriched addition product. However, upon analysis by chiral high performance liquid chromatography (HPLC), it was found that there were several impurities present in the sample which had gone unnoticed in the \(^1\)H NMR and \(^19\)F NMR. Due to these impurities, the enantioselectivity was unable to be determined. Repurification using 20:1 Hex:EtOAc did not alleviate the problem and, after extensive experimentation, it was found that a second column utilizing 19:1 Hex/iPrOH as the mobile phase was able to remove these impurities. HPLC analysis of this repurified product revealed an enantiomeric ratio (\(er\)) of 99.2:0.8.

Encouraged by this result, we decided to examine the effect of various groups in the 3,3\(^{\prime}\)-positions of the BINOL catalyst on the enantioselectivity (Table 2.1). It was anticipated that the I\(_2\)-BINOL catalysts would give the highest selectivity, as it had previously been proven to be the best catalyst in the binaphthol catalyzed alkenylation and alkynylation chemistry developed in our lab.\(^{69,71}\) Along with the (S)-I\(_2\)-BINOL, several other 3,3\(^{\prime}\)-disubstituted-BINOLs in enantiomerically pure form were readily available as previous lab members had made stocks for catalyst screens. The reactions were monitored by the disappearance of the starting enone by \(^1\)H NMR and TLC of the crude reaction mixture.
Table 2.1: Catalyst Screen for Asymmetric Conjugate Alkenylboration

<table>
<thead>
<tr>
<th>Ligand</th>
<th>X</th>
<th>Time (h)</th>
<th>% Yield&lt;sup&gt;a&lt;/sup&gt;</th>
<th>er&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>L5b</td>
<td>I</td>
<td>72</td>
<td>86</td>
<td>99.2:0.8</td>
</tr>
<tr>
<td>L5c</td>
<td>Br</td>
<td>72</td>
<td>93</td>
<td>98.9:1.1</td>
</tr>
<tr>
<td>L5d</td>
<td>Cl</td>
<td>72</td>
<td>88</td>
<td>97.5:2.5</td>
</tr>
<tr>
<td>L5e</td>
<td>CF₃</td>
<td>72</td>
<td>83</td>
<td>&gt;99.5:0.5&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>L5f</td>
<td>Ph&lt;sup&gt;d&lt;/sup&gt;</td>
<td>72</td>
<td>82</td>
<td>1.7:98.3</td>
</tr>
<tr>
<td>L5g</td>
<td>CN&lt;sup&gt;d&lt;/sup&gt;</td>
<td>72</td>
<td>85</td>
<td>6.4:93.6</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yields after flash chromatography. <sup>b</sup>Determined by HPLC analysis. <sup>c</sup>Minor enantiomer not detected. <sup>d</sup>[(R)-X₂-BINOL] used.

All of the ligands examined afforded the desired product with excellent selectivity and in high yield. The 3,3′-dihalo-BINOLs all performed well, giving the alkenylation product with similar yields, but varying selectivities. [(R)-Ph₂-BINOL] afforded the addition product with high selectivity, but gave the lowest isolated yield. [(R)-(CN)₂-BINOL] gave the lowest selectivity of all the ligands tested. It was hypothesized that this may be due to the low steric bulk of the cyano group. To our surprise [(S)-(CF₃)₂-BINOL] gave the best selectivity, in that the minor enantiomer was not detected by chiral HPLC analysis, although it did suffer from slightly diminished yields.
In the alkenylation of chalcone, it was found that the use of L5b and L5e provided essentially the same enantioselectivity (98.7:1.3, and 98.6:1.4 er, respectively).

It is uncertain as to why the (S)-(CF₃)₂-BINOL gave the best selectivity, but it may be due to some weak F-F interaction, which has been shown to be capable of imparting a small amount of local stabilization in a molecule.¹¹¹ This may in turn decrease the activation energy of one of the transition states, thus allowing for more of the favoured product to be formed. Due to the high selectivity observed with only a minor decrease in yield, it was decided that (S)-(CF₃)₂-BINOL would be used in all subsequent reactions.

Comparing the selectivity and reactivity with those previously reported by Wu and Chong, it appears as if the α,β-unsaturated trifluoromethyl ketone behaves similarly to diaryl enones, albeit with slightly decreased reactivity (Scheme 2.5). This decrease in reactivity was not anticipated, as the experimental mechanistic study on the BINOL catalyzed alkenylboration of diaryl enones performed by May et al. showed a small increase in rate (ρ = 0.4909) when the carbonyl substituent contained electron withdrawing groups.⁷⁹
Scheme 2.5: Comparing the Conjugate Alkenylboration of Enone 6a with (E)-Chalcone

We were interested in quantifying the reactivity difference between the trifluoromethyl enone 6a and (E)-chalcone, so a competition experiment was designed. In order to determine the relative rates of addition, equimolar amounts of (E)-chalcone, enone 6a and alkenylboronate 8 were mixed. The reaction was run under the optimized conditions found for the addition to enone 6a employing (S)-I$_2$-BINOL as the catalyst. After 48 hours, the reaction was worked up and the relative amounts of addition products were determined by $^1$H NMR. The $^1$H NMR of the crude reaction mixture showed almost exclusive addition to (E)-chalcone, with minimal amounts of 9a observed (Scheme 2.6). However, upon TLC analysis, a spot corresponding to the addition product 9a could be seen.
Scheme 2.6: Competition Experiment Between Enone 6a and Chalcone

After some experimentation, it was found that the boron enolate formed after the transfer of the alkenyl group was harder to hydrolyze than expected; with methanol, water, aqueous acid, and aqueous acid in tetrahydrofuran (THF) unable to liberate the addition product. Upon further investigation, it was found that the addition of a small amount of silica gel to the crude reaction mixture followed by filtration was the best way of freeing the addition product. With this in mind, the competition experiment was set up again in order to obtain more meaningful results. The competition experiment was set up the same way as described previously, except that the reaction was checked after 75 minutes. Upon hydrolysis with silica gel, $^1$H NMR analysis showed a product ratio of ~1:0.37 with the addition to (E)-chalcone being the major product. This implies that the rate of addition to (E)-chalcone was approximately 2.6 times faster than the addition to enone 6a.

This difference in reactivity may, in part, be explained by considering the stereoelectronic properties of the carbonyl lone pair. Due to the strong electron withdrawing ability of the trifluoromethyl group, the lone pairs on the carbonyl do not possess the same Lewis basicity; with the lone pair that is anti to the trifluoromethyl group being less basic than the lone pair that is syn. This may be caused by donation of the lone pair into the $\sigma^*$ orbital of the C-CF$_3$ bond (Figure 2.1). This would lead to the carbonyl preferentially binding to the Lewis acidic boron with the lone pair syn to the CF$_3$ group leading to an unreactive tetrahedral complex. This would
then need to equilibrate to the complex in which the lone pair *anti* to the CF$_3$ group is bound to the boron atom (Figure 2.2).

**Figure 2.1: Decreased Lewis Basicity of Lone Pair due to Donation into C-CF$_3$ $\sigma^*$ Orbital**

**Figure 2.2: Equilibrium Between Unreactive and Reactive Tetrahedral Complexes**

With (S)-(CF$_3$)$_2$-BINOL identified as the optimal catalyst, we then turned our attention to how changing the $\beta$-substituent affects the reactivity and selectivity of the reaction. We wanted to explore the effects of electron withdrawing and electron donating groups, as well as bulky and alkyl groups on the reactivity and selectivity of the alkenylation reaction (Table 2.2). The addition to $\beta$-aryl enones gave results similar to those obtained previously by Wu and Chong, with enones bearing electron rich or bulky substituents giving the highest selectivity. However, it was found that the addition to the $n$-hexyl enone **6e** returned very low isolated yields. This may have been due to the volatility of the starting material. In order to overcome this, the alkyl chain was extended, and an $n$-C$_{11}$H$_{23}$ group was used in place of the $n$-C$_6$H$_{13}$. This allowed for the
addition product to be isolated in a much higher yield (82 %). However, the enantiomers were unable to be separated by chiral HPLC and the selectivity was not determined.

We anticipate that the reaction proceeds through a transition state similar to that proposed by Wu and Chong for the alkenylation of diaryl enones, and the stereoselectivity is assumed based on the transition states shown below (Figure 2.3).

![Chemical reaction and table]

**Table 2.2: Conjugate Alkenylation of Trifluoromethyl Enones**

<table>
<thead>
<tr>
<th>Enone</th>
<th>R</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>Ph</td>
<td>72</td>
<td>83</td>
<td>&gt;99.5:0.5</td>
</tr>
<tr>
<td>6b</td>
<td>4-MeOC₆H₄</td>
<td>48</td>
<td>77</td>
<td>98.8:1.2</td>
</tr>
<tr>
<td>6c</td>
<td>4-ClC₆H₄</td>
<td>72</td>
<td>83</td>
<td>98.3:1.7</td>
</tr>
<tr>
<td>6d</td>
<td>1-Naphthyl</td>
<td>72</td>
<td>82</td>
<td>99.5:0.5</td>
</tr>
<tr>
<td>6e</td>
<td>n-C₆H₁₃</td>
<td>72</td>
<td>16</td>
<td>N.D.</td>
</tr>
<tr>
<td>6f</td>
<td>n-C₁₁H₂₃</td>
<td>72</td>
<td>82</td>
<td>N.D.</td>
</tr>
</tbody>
</table>

*Isolated yield after flash chromatography*  
*Determined by chiral HPLC analysis.*  
*“>99.5:0.5” denotes that the minor enantiomer was not observed.*  
*N.D.” denotes the er was not determined
Figure 2.3: Transition State Model to Predict the Stereoselectivity

The next steps in this study should include the determination of the selectivity of the addition to β-alkyl trifluoromethyl enones and a comparison of the selectivities to those reported by Wu and Chong should be completed. This may be accomplished through the formation of a chiral ketal \( \text{10} \) and examination of the diastereomeric mixture by \(^1\text{H}, ^{13}\text{C}\) and \(^{19}\text{F}\) NMR (Scheme 2.7). In addition to this, the synthesis of trifluoromethyl enones containing branched or cyclic β-substituents should be completed and the addition to these substrates should be done to determine the effect of alkyl and branched alkyl groups on the selectivity of this reaction.

Scheme 2.7: Potential Strategy for the Determination of the \( er \) of \( \text{9f} \)

2.3 Asymmetric Conjugate Arylboration of \( \alpha,\beta \)-Unsaturated Trifluoromethyl Ketones

Encouraged by the results obtained in the alkenylation chemistry, we next turned our attention to the arylation of trifluoromethyl enones. Preparation of the arylboronate was accomplished through a simple esterification of commercially available phenyl boronic acid with
ethanol, removing water with a Soxhlet extractor (Scheme 2.8). As a model reaction we decided to investigate the addition of diethyl phenylboronate 10 with enone 6c (Scheme 2.9). Initially the reaction was run at 30 °C in DCM, similar to the additions using the alkenylboronate. However, it was found that after 24 hours the reaction had not progressed. The temperature was increased to 40 °C and the reaction was allowed to stir for an additional 24 hours. Analysis of the crude reaction mixture showed that no reaction had occurred.

Scheme 2.8: Preparation of Diethyl Phenylboronate

Scheme 2.9: Asymmetric Conjugate Arylation of Enone 6c

The reaction was then set up again, changing the solvent from DCM to DCE and the temperature was further increased to 60 °C. After 48 hours, analysis of the crude reaction mixture again indicated that no reaction had occurred. The temperature was further increased to 120 °C and allowed to stir for an additional 48 hours. At this point it was found that the majority of the solvent had escaped from the Schlenk tube and that the reaction had finally began to progress. Using this information, the reaction was run again at 120 °C, this time employing an excess of the phenylboronate as the solvent analogous to the arylboration of diaryl enones.
reported by Turner and Chong. After 72 hours, the reaction showed complete consumption of the starting material. Purification by flash chromatography using 20:1 Hex:EtOAc gave the product in 49% yield and subsequent analysis by chiral HPLC showed that the product had an enantiomeric ratio of 93.2:6.8.

With this result in hand, we next wanted to determine the optimal catalyst for the arylation of trifluoromethyl enones. Previously, it was shown that 3,3′-Cl₂-BINOL was the optimal catalyst in the arylation of diaryl enones. However, based on the results obtained from the alkenylboration of trifluoromethyl enones, we could not rule out the possibility that a different BINOL catalyst would return higher selectivities than those reported previously. The results of the catalyst screen are summarized below (Table 2.3).

Table 2.3: Catalyst Screen for Asymmetric Conjugate Arylboration

<table>
<thead>
<tr>
<th>Ligand</th>
<th>X</th>
<th>Time (h)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>er&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>L₅b</td>
<td>I</td>
<td>72</td>
<td>49</td>
<td>93.2:6.8</td>
</tr>
<tr>
<td>L₅d</td>
<td>Cl</td>
<td>72</td>
<td>38</td>
<td>95.3:4.7</td>
</tr>
<tr>
<td>L₅e</td>
<td>CF₃</td>
<td>96</td>
<td>24</td>
<td>96:4</td>
</tr>
<tr>
<td>L₅f</td>
<td>Ph&lt;sup&gt;c&lt;/sup&gt;</td>
<td>72</td>
<td>27</td>
<td>4.6:95.4</td>
</tr>
<tr>
<td>L₅g</td>
<td>CN&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5</td>
<td>54</td>
<td>17.8:82.2</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yields after flash chromatography. <sup>b</sup>Determined by chiral HPLC analysis. <sup>c</sup>(R)-X₂-BINOL used.
This catalyst screen revealed some interesting features of this reaction. All of the catalysts tested resulted in a low to moderate isolated yield. Additionally, \((R)-(CN)_{2}\text{-BINOL}\) was shown to give a very fast reaction and the highest isolated yield. However, this ligand also resulted in the lowest enantioselectivity. The high reactivity of this ligand is thought to be a result of the strong electron withdrawing nature of the cyano group, resulting in a very electrophilic boronate, while the low selectivity may be due to the low steric bulk of the cyano group. Interestingly, both \((S)-Cl_{2}\text{-BINOL}\) and \((R)-(Ph)_{2}\text{-BINOL}\) gave comparable selectivities; however, \((R)-(Ph)_{2}\text{-BINOL}\) returned a lower yield. As with the alkenylboration, \((S)-(CF_{3})_{2}\text{-BINOL}\) resulted in the highest selectivity, although it suffered from a poor yield.

In order to determine the cause of the low yields and any possible side reactions, a control experiment was set up. This control reaction was performed in the same way as the catalyst screen, except the catalyst was omitted. Upon allowing enone \(6c\) and boronate \(11\) stir at 120 °C for 72 hours, it was found that a new product was being formed. \(^1\text{H NMR} \) analysis of the crude reaction mixture showed a 3:1 ratio of starting material to what appeared to be the 1,2-reduction product \(13\) (Scheme 2.10). Isolation of the side product by flash chromatography and subsequent analysis by \(^1\text{H NMR}\) confirmed the identity of the side product to be the 1,2-reduction product \(13\).

\[
\begin{align*}
6c \quad \text{Cl} & \quad + \quad \text{B(OEt)}_{2} \quad \text{Cl} \quad \text{B(OEt)}_{2} \quad \rightarrow \quad 6c \quad \text{Cl} & \quad + \quad \text{B(OEt)}_{2} \quad \text{Cl} \quad \text{B(OEt)}_{2} \\
\text{Cl} & \quad \text{Cl} & \quad \text{Cl} & \quad \text{Cl} & \quad \text{Cl} & \quad \text{Cl} & \quad \text{Cl} & \quad \text{Cl}
\end{align*}
\]

\[\text{3:1 ratio of starting material to 1,2-reduction product 13}\]

Scheme 2.10: 1,2-Reduction of Enone 6c in the Absence of X₂-BINOL
The presence of a side reaction leading to a 1,2-reduction product was unexpected, as the BINOL catalyzed conjugate addition of organoboronates had previously proven to be a very clean reaction. The only undesired reaction identified in previous work was a background racemic addition of the organoboronate and this was only seen in rare cases. We hypothesized that the reduction may have occurred through a β-hydride transfer from one of the ethoxy substituents of the phenylboronate occurring through a cyclic, chair-like transition state, analogous to the Meerwein-Pondorf-Verley (MPV) reduction (Scheme 2.11).

Scheme 2.11: Proposed Mechanism of 1,2-Reduction

Within the past decade, there have been a few reports by Uysal et al. of the use of secondary alkoxyborates and triethoxyborate as a catalyst for the reduction of aliphatic ketones.\textsuperscript{112–114} Due to this precedence, we decided to further investigate this reduction in order to gain a better understanding of how the reaction was progressing. We began by setting up a reaction with enone 6c solvated in triisopropyl borate at 115 °C, similar to the conditions used for the conjugate addition. After the reaction time of 72 hours, \textsuperscript{1}H NMR analysis of the reaction mixture indicated that no reaction had occurred. In order to ensure that the BINOL catalyst was not playing a role in the reduction, another control experiment was set up including the I\textsubscript{2}-BINOL (Scheme 2.12). Again, only starting material was returned. Finally, a reaction was set up using the conditions described in the literature employing catalytic amounts of B(OiPr)\textsubscript{3} with
iPrOH acting as solvent.\textsuperscript{113} Again, no reduction product was found, although the isopropyl hemiketal of enone 6c was found to be the major product of the reaction (Scheme 2.13).

Scheme 2.12: Attempted Reduction of Enone 6c Using Excess B(OiPr)\textsubscript{3}

Scheme 2.13: Formation of isopropyl Hemiketal Using Catalytic B(OiPr)\textsubscript{3}

Being unable to find other conditions that led to the reduction of enone 6c, we decided to try to minimize the amount of reduction product 13 formed by changing the boronate used. We hypothesized that if we could destabilize the transition state leading to the reduction product, we could minimize or eliminate this side reaction. To this end, we synthesized the dimethyl analogue of our boronate, anticipating that the developing positive charge on the methyl carbon would destabilize the transition state of the reduction sufficiently to minimize the contribution of this reaction. Gratifyingly, when the control experiment was conducted using the dimethyl phenylboronate 15, no reduction product was found and only starting material was recovered (Scheme 2.14). Additionally, there was no visible trace of a background racemic addition of the boronate in the absence of the BINOL catalyst.
Scheme 2.14: Control Experiment Using PhB(OMe)₂

With the 1,2-reduction of enone 6c successfully suppressed, we wanted to examine the reactivity of the dimethyl phenylboronate 15 in the conjugate addition chemistry. After some experimentation, it was found that the temperature could be dropped to 115 °C to give the addition product in much better yield (80 %) and comparable selectivity (96.5:3.5 er). With these conditions in hand, we began to explore the effects of β-substituents on the arylation reaction (Table 2.4). We began by exploring the effects of an electron rich aryl β-substituent. Pleasingly, the reaction with enone 6b proceeded smoothly, giving the addition product in 84% yield after column chromatography. However, upon analysis by chiral HPLC, it was discovered that the enantioselectivity was quite poor, with an er of 89.4:10.6. Enone 6d, containing the bulky 1-naphthyl group gave a slightly lower yield than the para- substituted enones. Enones containing a 1-naphthyl substituent in the β-position have typically returned addition products with very high enantioselectivity. Surprisingly, chiral HPLC analysis showed that the reaction had very poor selectivity, with the product having an er of 80:20. This low selectivity may be due to small energy differences in the diastereomeric transition states due to steric repulsion in one and electronic repulsion in the other (Figure 2.4).
Table 2.4: Conjugate Arylation of Trifluoromethyl Enones

\[
\begin{align*}
&\text{R-} \quad \text{CF}_3 \\
&\text{6} + \text{15} \quad \text{(S)-(CF}_3\text{)BINOL (20 mol\%)} \quad \text{Ph} \quad \text{CF}_3 \\
&\text{4A MS neat} \quad 110 \degree \text{C}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Enone</th>
<th>R</th>
<th>Time (h)</th>
<th>Yield (%)\textsuperscript{a}</th>
<th>er\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>6b</td>
<td>4-MeOC\textsubscript{6}H\textsubscript{4}</td>
<td>72</td>
<td>84</td>
<td>89.4:10.6</td>
</tr>
<tr>
<td>6c</td>
<td>4-ClC\textsubscript{6}H\textsubscript{4}</td>
<td>72</td>
<td>80</td>
<td>96.5:3.5</td>
</tr>
<tr>
<td>6d</td>
<td>1-Naphthyl</td>
<td>72</td>
<td>71</td>
<td>80:20</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Isolated yields after flash chromatography. \textsuperscript{b}Determined by chiral HPLC analysis.

Figure 2.4: Possible Transition States in the Arylation of Enone 6d

In order to better understand this reaction, the addition to enone 6f should be completed in order to examine the affect of a β-alkyl group on the selectivity of the reaction. Additionally, the addition to enone 6b and 6d should be repeated to ensure these results are not outliers. These additions should also be conducted using L5d in order to determine if higher selectivities are possible. Furthermore, conditions leading to the reduction of enone 6c should be explored further, as it may lead to an efficient method for accessing the trifluoromethylated allylic alcohol 13 (Scheme 2.15).
2.4 Asymmetric Conjugate Heteroarylboration of α,β-Unsaturated Trifluoromethyl Ketones

Looking forward, we next decided to focus our attention on the reaction of trifluoromethyl enones with heteroarylboronates. It was shown previously in our lab, that the addition of heteroaryl boronates to diaryl enones was a smooth reaction that progressed faster, and at a lower temperature than the addition of arylboronates. We began by running a test reaction with enone 6a and diethyl 2-thienylboronate 15 using (S)-(CF$_3$)$_2$-BINOL as the catalyst with the conditions described by Cheung in the addition of heteroarylboronates to diaryl enones.$^{77}$ To our delight, the addition product 16a was formed smoothly in high yield and excellent enantioselectivity (Scheme 2.16).

Scheme 2.15: Conditions Leading to Reduction of Enone 6

Scheme 2.16: Addition of 2-Thienylboronate 14 to Enone 6a

As (S)-(CF$_3$)$_2$-BINOL was shown to be the best catalyst in both the alkenylation and arylation of trifluoromethyl enones, we decided to continue using it and a catalyst screen was not completed. Motivated by the smooth reaction between enone 6a and thienylboronate 16, we
began to explore the affects that β-substituents have on the yield and selectivity of the reaction, the results of which are summarized below in Table 2.5. It can be seen that the addition of the thienyl group proceeds smoothly and with very high selectivity. Particularly interesting is the high degree of selectivity observed in the case of β-alkyl substituents, as in the addition to enone 6f. Previous research in our group has shown that enones possessing a β-alkyl substituent typically show a lower degree of enantioselectivity when compared to enones possessing β-aryl groups.

Table 2.5: Conjugate Thienylation of Trifluoromethyl Enones

<table>
<thead>
<tr>
<th>Enone</th>
<th>R</th>
<th>Time (h)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>&lt;i&gt;er&lt;/i&gt;&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>Ph</td>
<td>48</td>
<td>89</td>
<td>96.5:3.5</td>
</tr>
<tr>
<td>6b</td>
<td>4-MeOC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>48</td>
<td>85</td>
<td>98.2:1.8</td>
</tr>
<tr>
<td>6c</td>
<td>4-ClC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>48</td>
<td>79</td>
<td>93.3:6.7</td>
</tr>
<tr>
<td>6d</td>
<td>1-Naphthyl</td>
<td>48</td>
<td>75</td>
<td>99.2:0.8</td>
</tr>
<tr>
<td>6f</td>
<td>&lt;i&gt;n-C&lt;sub&gt;11&lt;/sub&gt;H&lt;sub&gt;23&lt;/sub&gt;&lt;/i&gt;</td>
<td>48</td>
<td>96</td>
<td>95.5:4.5</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yields after flash chromatography. <sup>b</sup>Determined by chiral HPLC analysis.
Encouraged by the success of the addition of the thienyl group, we wanted to further probe the reactivity of trifluoromethyl enones with other heteroaryl boronates. To this end, we began exploring the addition of furylboronate 19 with enone 6a. We anticipated that the optimized conditions used in the addition of thienylboronate would also furnish the addition product with furanyl boronate as their reactivity have been shown to be similar. Delightfully, this was true and the addition product 18a was isolated in 66% yield. HPLC analysis showed the product had an er of 94.6:5.5 (Scheme 2.17).

![Scheme 2.17: Addition of 2-Furylboronate to Enone 6a](image)

The high selectivity observed was very encouraging as the addition of furylboronate 16 to chalcone had been shown to occur with the more modest selectivity of 89:11 er. We then began to explore the effects of other substituents, the results of which are summarized below (Table 2.6). Similar to the addition of the thienyl group, the enantioselectivities were uniformly high, and good to excellent yields were obtained with all of the substrates tested. Again, enone 6f, bearing a long chain alkyl substituent, showed great selectivity. In fact, in all cases except for enone 6d, all of the addition products showed a higher enantioselectivity than when the diaryl analogue was used (Table 2.7).
Table 2.6: Conjugate Furylation of Trifluoromethyl Enones

![Reaction scheme](image)

<table>
<thead>
<tr>
<th>Enone</th>
<th>R</th>
<th>Time (h)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>er&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>Ph</td>
<td>48</td>
<td>66</td>
<td>94.6:5.4</td>
</tr>
<tr>
<td>6b</td>
<td>4-MeOC₆H₄</td>
<td>48</td>
<td>97</td>
<td>95.6:4.4</td>
</tr>
<tr>
<td>6c</td>
<td>4-ClC₆H₄</td>
<td>48</td>
<td>69</td>
<td>94.0:6.0</td>
</tr>
<tr>
<td>6d</td>
<td>1-Naphthyl</td>
<td>48</td>
<td>96</td>
<td>98.3:1.7</td>
</tr>
<tr>
<td>6f</td>
<td>n-C₃H₇</td>
<td>48</td>
<td>79</td>
<td>6.8:93.2</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yields after flash chromatography. <sup>b</sup>Determined by chiral HPLC analysis.

Table 2.7: Conjugate Addition of Furfurylboronate 16 to Diaryl Enones<sup>77</sup>

![Reaction scheme](image)

<table>
<thead>
<tr>
<th>R</th>
<th>Time (h)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>er&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>30</td>
<td>92</td>
<td>89:11</td>
</tr>
<tr>
<td>Substrate</td>
<td>% Yield</td>
<td>% ee</td>
<td>Ratio</td>
</tr>
<tr>
<td>---------------</td>
<td>--------</td>
<td>------</td>
<td>-------</td>
</tr>
<tr>
<td>4-MeOC₆H₄</td>
<td>30</td>
<td>76</td>
<td>84.4:15.6</td>
</tr>
<tr>
<td>4-BrC₆H₄</td>
<td>30</td>
<td>78</td>
<td>86:14</td>
</tr>
<tr>
<td>1-Naphthyl</td>
<td>30</td>
<td>93</td>
<td>99.9:0.1</td>
</tr>
</tbody>
</table>

*Isolated yields after flash chromatography. Determined by chiral HPLC analysis.

### 2.5 Summary and Future Work

In summary, we have accomplished the metal free asymmetric conjugate addition of alkenyl-, phenyl-, 2-thienyl-, and 2-furylboronates to a variety of α,β-unsaturated trifluoromethyl ketones. These efforts represent one of the few ways in which asymmetric conjugate additions to trifluoromethyl enones can be achieved. Additionally, this work expands upon the types of substrates compatible with the BINOL catalyzed conjugate addition of organoboronates and appears to show that trifluoromethyl enones behave similarly to aryl enones in these reactions.

Future work will include an examination of other functionalized organoboronates in order to examine the utility of this reaction for further manipulations, and an examination of the substrate functional group tolerance. Furthermore, one of the addition products should be derivatized in order to obtain an absolute configuration to ensure the proposed stereoselectivity is correct.
Chapter 3. Developing the Asymmetric Conjugate Additions of N-Boc-Pyrrole Boronic Acid

3.1 Pyrrole in Organic Synthesis

Pyrrole has been regarded as one of the most important nitrogen containing heterocycles due to its occurrence in biologically active natural products and pharmaceuticals, and as functional materials.\textsuperscript{115} It has been found to be a core feature in a number of analgesic compounds not related to classic opioids.\textsuperscript{116} In addition to this, some C-alkylated pyrroles have been shown to possess antitumor activity.\textsuperscript{117} There has been a resurgence of interest in pyrrole derivatives in recent years, partly because they are a foundational building block of biochemistry.\textsuperscript{118}

3.2 Conjugate Addition of Pyrrole to $\alpha,\beta$-Unsaturated Ketones

The conjugate addition of pyrrole has also been accomplished through the use of several different Lewis acids such as metal triflates,\textsuperscript{119} copper-,\textsuperscript{120} hafnium- and scandium salts,\textsuperscript{121} as well as through organocatalysis.\textsuperscript{117,122,123} The first enantioselective conjugate addition of pyrrole was accomplished by MacMillan and Paras in 2001.\textsuperscript{122} Using their chiral imidazolinone catalyst, they were able to achieve high yields and good enantioselectivities on a variety of $\alpha,\beta$-unsaturated aldehydes as well as with a variety of substituted pyrroles (Scheme 3.1). The reaction was operationally very simple and could be performed under aerobic conditions and using wet solvents.
Scheme 3.1: Organocatalytic Asymmetric Conjugate Addition of Pyrrole to Unsaturated Aldehydes

Recently, in 2013, Enders and Hack disclosed the asymmetric conjugate addition of unsubstituted pyrroles to α,β-unsaturated ketones catalyzed by cinchona alkaloid-derived primary amines. After extensive optimization, it was found that the addition of pyrrole to enone 21 in the presence of 20 mol% of L11 and trifluoroacetic acid (TFA), at 0 °C in chlorobenzene proceeded smoothly, furnishing the desired product in good to excellent yield and high enantioselectivities (Scheme 3.2). It is believed that the reaction proceeds via cooperative catalysis in which a trifluoroacetate anion participates in hydrogen bonding with the protonated quinuclidine and pyrrole (Figure 3.1).

Scheme 3.2: Cinchona Alkaloid Catalyzed Asymmetric Conjugate Addition of Pyrrole to Enones
Figure 3.1: Transition State for the Cinchona Alkaloid Catalyzed Conjugate Addition of Pyrrole

Similar to the research conducted in our group, May et al. recently described the conjugate addition of heteroaryl trifluoroborate salts to enones bearing β-heteroaryl groups. In particular, it was found that the addition of Boc-pyrrole trifluoroborate salt to enone 19 gave the desired addition product in good yield and high selectivity (Scheme 3.3). The reactivity of Boc-pyrrole boronic acid was also tested in this reaction. Unfortunately, poor reactivity was observed and the addition product was isolated with poor yield.

Scheme 3.3: BINOL Catalyzed Conjugate Addition of Pyrrole Trifluoroborate Salt
3.3 BINOL Catalyzed Asymmetric Conjugate Addition of N-Boc-Pyrrole Boronic Acid

We were interested in trying to develop a method through which a pyrrole boronic acid could be used in the conjugate addition to enones directly, thereby allowing the use of commercially available reagents and eliminating the need of preparing derivatives. During the studies of the addition of aryl and heteroarylboronates to enones, it was found that the use of excess boronate as the solvent was required for the reaction to proceed. This suggests that a polar, non-coordinating solvent is required to prevent coordination of the solvent with the active boronate species. Additionally, during the development of the addition of heteroarylboronates to α,β-unsaturated ketones in our lab, a variety of N-containing heteroaromatic boronates, namely the 3-pyridyl, 4-pyridyl, and 3-quinolinyl, were attempted to be prepared for use in the BINOL catalyzed conjugate addition chemistry. Unfortunately, the pyridyl boronates could not be prepared, and the 3-quinolinylboronate was unreactive.\(^{77}\)

In an effort to prevent the competitive coordination, it was thought that a trialkyl borate could be used as the solvent as it should possess similar solvating properties as a boronate. This allowed us the possibility to use solid reagents along with a boronate-like solvent. Initial conditions tested were similar to the previously optimized conditions for the addition of other heteroaromatic boronates using triisopropyl borate as the solvent. It was anticipated that the boronic acid would be less reactive than the boronate towards chalcone, so a slightly higher reaction temperature was used (Scheme 3.4).
Scheme 3.4: BINOL Catalyzed Conjugate Addition of N-Boc-Pyrrole Boronic Acid to Chalcone

To our delight, after 12 hours the reaction mixture contained a 2:1 mixture of starting material to addition product. However, upon allowing the reaction to stir for an additional 12 hours, no change in the product ratio was observed. In order to ascertain whether or not the reaction had progressed enantioselectively, the addition product was isolated and analyzed by chiral HPLC. Disappointingly, HPLC analysis found that the product had a relatively poor er of 85.9:14.1.

Encouraged by these early results, we next wanted to optimize the reaction conditions in order to maximize yield and enantioselectivity. In an earlier report, May et al. described the addition of catalytic amounts of magnesium tert-butoxide in the addition of alkenylboronic acids increased their reactivity.\textsuperscript{76} Although no firm explanation was given for the observed increase in rate, we began exploring the effects of additives on the conjugate addition of Boc-pyrrole boronic acid. Results are shown in Table 3.1 below.

The addition of 10 mol% of Mg(O-tBu)\textsubscript{2} had a negligible effect on the rate and yield of the reaction. Stoichiometric amounts of Mg(O-tBu)\textsubscript{2} showed a marked increase in both yield and selectivity, with the addition product obtained in 72% yield with an er of 95:5 (Entry 3). Cutting the alkoxide loading down to 50 mol% led to a similar yield and selectivity as stoichiometric alkoxide. Changing the alkoxide from Mg(O-tBu)\textsubscript{2} to tBuOK furnished the addition product with
a similar selectivity, although in a lower yield. However, it was also noted that some deprotected addition product was also formed. This is thought to be formed either through attack of the Boc group by t-butoxide, or through thermolysis (Figure 3.2). In order to try to prevent the loss of the Boc group, the reaction temperature was dropped to 60 °C (Entry 6). This resulted in a markedly slower reaction, with the addition product being furnished in 68% yield in 24 hours with no drop in selectivity. Finally, in an attempt to find a balance between high yield and fast reaction times, the temperature was increased to 80 °C. To our delight the addition product was formed as the major product within 12 hours and was isolated in 91% yield and 94.5:5.5 er.

Table 3.1: Optimization of Conjugate Addition of Boc-Pyrrole Boronic Acid

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>85</td>
<td>24</td>
<td>N.Dc</td>
<td>85.9:14.1</td>
</tr>
<tr>
<td>2</td>
<td>10 mol% Mg(O-tBu)₂</td>
<td>85</td>
<td>24</td>
<td>N.D.</td>
<td>N.D.</td>
</tr>
<tr>
<td>3</td>
<td>100 mol% Mg(O-tBu)₂</td>
<td>85</td>
<td>12</td>
<td>72d</td>
<td>95:5</td>
</tr>
<tr>
<td>4</td>
<td>50 mol% Mg(O-tBu)₂</td>
<td>85</td>
<td>12</td>
<td>67d</td>
<td>93:7</td>
</tr>
<tr>
<td>5</td>
<td>50 mol% tBuOK</td>
<td>85</td>
<td>12</td>
<td>48d</td>
<td>93:7</td>
</tr>
<tr>
<td>6</td>
<td>50 mol% tBuOK</td>
<td>60</td>
<td>24</td>
<td>68d</td>
<td>93:7</td>
</tr>
<tr>
<td>7</td>
<td>50 mol% tBuOK</td>
<td>80</td>
<td>12</td>
<td>91d</td>
<td>94.5:5.5</td>
</tr>
</tbody>
</table>

aIsolated yields after flash chromatography. bDetermined by chiral HPLC analysis. c“N.D.” denotes not determined. dUnreacted starting material also recovered.
With the reaction conditions optimized, we decided to investigate the rate of the racemic background reaction. This background reaction may arise from the racemic addition of the Boc-pyrrole boronic acid, or through EAS addition of Boc-pyrrole formed through the proto-deboronation of the boronic acid. In the absence of both BINOL and alkoxide, the reaction progresses to ~5:1 mixture of chalcone to addition product. Interestingly, the addition of 50 mol% tBuOK significantly suppresses the rate of this background reaction, with the crude reaction mixture showing ~12.5:1 chalcone to addition product, indicating that the background reaction can contribute up to 8% racemic material (Scheme 3.5).
With the optimized conditions in hand, we turned our attention to testing this reaction on several different substituted diaryl enones. Unfortunately, of the enones tested, only the parent chalcone showed an appreciable amount of addition product formed (Scheme 3.5).

![Scheme 3.6: Conjugate Addition of Boc-Pyrrole Boronic Acid to Substituted Chalcones](image)

Pushing forward, we decided to investigate whether the conjugate addition of N-containing heteroaromatic boronic acids to chalcone catalyzed by BINOL and tBuOK was possible. As such, the conjugate addition of 3-pyridylboronic acid and 3-quinolinylboronic acid to chalcone were examined next (Scheme 3.6). Disappointingly, the reaction conditions optimized for the addition of Boc-pyrrole boronic acid with these resulted in only recovered starting material.

![Scheme 3.7: Attempted Conjugate Addition of Pyridyl- and Quinolinyl Boronic Acids](image)
3.4 Summary and Future Work

In summary, the possibility of using Boc-pyrrole boronic acid 22 as the nucleophile in BINOL catalyzed conjugate additions has been demonstrated. The addition to chalcone can proceed in high yield and good enantioselectivity. Unfortunately, this was the only substrate found to furnish the desired addition product.

Future work will include a further optimization of reaction conditions. An interesting avenue to explore is the identification of the species present in solution in a mixture of Boc-pyrrole boronic acid, I₂-BINOL and B(O-iPr)₃. It may be found that there is a pre-equilibrium that must be established first in order to generate the reactive species. If this is the case, then an examination of the effects of pre-stirring the boronic acid and BINOL catalyst in B(O-iPr)₃ before the addition of the enone should be completed. Additionally, conditions allowing for the conjugate addition to chalcone derivatives should be sought. If this methodology proves successful, a re-examination of representative examples of the conjugate addition of other boronates should be conducted to test the possibility of using boronic acids as the nucleophile generally.

Furthermore, the conjugate addition of other N-containing heteroaromatic boronic acids should be investigated in more detail in order to ascertain whether these types of nucleophiles can be amenable to the BINOL catalyzed conjugate addition to enones.
Chapter 4. Experimental

General Experimental

All reactions were performed using flame-dried glassware under an argon atmosphere. Transfer of solvents and solutions were done using syringes following standard inert atmosphere techniques. Tetrahydrofuran and diethyl ether were freshly distilled from sodium/benzophenone. Dichloromethane was freshly distilled from calcium hydride. Molecular sieves were activated by heating under vacuum. Chiral 3,3’-disubstituted binaphthols were synthesized according to literature procedures. Alkenyl and arylboronates were prepared according to a previous report. Yields reported are isolated yields after flash chromatography. Reaction temperatures are reported as the temperature of the bath. Thin layer chromatography (TLC) was performed on Merck 0.25 mm silica gel 60 F254 plates with visualization using short wave UV light or potassium permanganate staining. Flash chromatography was performed using 40-63 μm silica gel 60 using hexane/ethyl acetate mixtures as the mobile phase unless otherwise stated. IR spectra were recorded neat for both liquids and solids using a Perkin-Elmer Spectrum Two FTIR spectrometer. \(^{1}\text{H},^{13}\text{C},^{19}\text{F}\) NMR spectra were recorded in CDCl\(_3\) at 300 MHz, 75 MHz, and 282 MHz, respectively, and are referenced to CHCl\(_3\) (δ 7.24), CDCl\(_3\) (δ 77.0) or TFA (δ -76.5) respectively, on a Bruker AVANCE 300 spectrometer. \(^{13}\text{C}\) and \(^{19}\text{F}\) NMR spectra were recorded with broadband proton decoupling. Multiplicities are reported as: ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, dd = doublet of doublets, dt = doublet of triplets, br = broad, m = multiplet. Accurate mass determinations were performed at a mass resolution of 70,000 with a ThermoFisher Scientific Q-Exactive hybrid mass spectrometer using positive ion electrospray ionization (ESI). Samples were infused at 10 μL/min in 1:1 CH\(_3\)OH/H\(_2\)O+0.1%
formic acid. Enantiomeric purities were determined by HPLC analysis (4.6 x 250 mm ChiralCel OD-H or ChiralPak AD-H) using hexane/isopropanol mixtures as the mobile phase and 254 nm detection.

**Preparation of (E)-4-(dimethylamino)-1,1,1-trifluorobut-3-en-2-one (5)¹⁰⁸,¹²⁴**

![Chemical reaction diagram](image)

In a 500 mL round bottom flask, ethyl vinyl ether (25 mL, 261 mmol, 1 eq.) was added to 250 mL dichloromethane and pyridine (4.2 mL, 52 mmol, 0.2 eq.). The reaction mixture was cooled to -78 °C in a dry ice/acetone bath. Trifluoroacetic anhydride (43 mL, 304 mmol, 1.16 eq.) was added dropwise and the reaction was allowed to stir at -78 °C for 1 hour, after which the bath was removed and the reaction was allowed to further stir at room temperature over night. The reaction mixture was then filtered through a short column of charcoal (2 in.), the solvent was removed by rotary evaporation under reduced pressure and the crude reaction mixture was placed under high vacuum for 20 minutes. The resultant dark blue oil was then diluted in 250 mL dichloromethane and cooled to -78 °C in a dry ice/acetone bath. To this stirred solution, dimethyl amine (35 mL, 528 mmol, 2 eq.) was added dropwise. The reaction was allowed to slowly warm to room temperature and stir for 24 hours. The solvent was removed by rotary evaporation under reduced pressure. The resultant orange oil was purified with a silica gel plug (200 g) using dichloromethane as the mobile phase. The title compound was afforded as a yellow crystalline powder (37.48 g, 86% yield over two steps).
General Procedure for the Preparation of α,β-Unsaturated Trifluoromethyl Ketones

Aryl or alkyl bromide (24 mmol, 1.2 eq.) was added dropwise to a 50 mL round bottom flask containing 20 mL of diethyl ether and magnesium turnings (0.535 g, 22 mmol, 1.1 eq.). The mixture was gently heated until all of the magnesium was consumed and was then allowed to cool to room temperature. In a separate 100 mL round bottom flask, (E)-4-(dimethylamino)-1,1,1-trifluorobut-3-en-2-one 5 (3.343 g, 22 mmol, 1 eq.) was dissolved in 50 mL of diethyl ether. The aryl or alkyl magnesium was then added dropwise over 10 minutes. The reaction mixture was then heated to reflux and allowed to stir for 2 hours. The reaction was cooled to room temperature and poured into cold HCl (1 M, 100 mL). The organic layer was collected, and the aqueous layer was extracted with diethyl ether (2 x 50 mL). The combined organic layer was then washed with saturated NaHCO₃ (2 x 40 mL) and finally with saturated NaCl (50 mL). The organic layer was dried over anhydrous Na₂SO₄ and concentrated by rotary evaporation under reduced pressure. The enone was then purified by flash chromatography using hexane/ethyl acetate mixtures as the mobile phase.
(E)-1,1,1-trifluoro-4-phenylbut-3-en-2-one (6a)

\[
\begin{align*}
\text{O} & \\
\text{CF}_3 & \\
\end{align*}
\]

The title compound was isolated as a clear oil in 87% yield after silica gel flash chromatography using 10:1 hexane/ethyl acetate followed by short path distillation at 60 °C at torr. Spectral data for this compound was found to match that of literature data.\(^{107}\)

(E)-4-(4-methoxyphenyl)-1,1,1-trifluorobut-3-en-2-one (6b)

\[
\begin{align*}
\text{O} & \\
\text{CF}_3 & \\
\end{align*}
\]

The title compound was isolated as a yellow powder in 95% yield after silica gel flash chromatography using 10:1 hexane/ethyl acetate followed by recrystallization with ethanol. Spectral data for this compound was found to match that of literature data.\(^{107}\)

(E)-4-(4-chlorophenyl)-1,1,1-trifluorobut-3-en-2-one (6c)

\[
\begin{align*}
\text{O} & \\
\text{CF}_3 & \\
\end{align*}
\]

The title compound was isolated as a yellow powder in 90% yield after silica gel flash chromatography using 10:1 hexane/ethyl acetate followed by recrystallization with ethanol. \(^1\text{H}\) NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.90 (1H, d, \(J = 16\) Hz), 7.56 (2H, d, \(J = 8.5\) Hz), 7.46 (2H, d, \(J = 8.5\) Hz), 6.97 (1H, d, \(J = 16\) Hz); \(^{13}\text{C}\) NMR (75 MHz, CDCl\(_3\)) \(\delta\) 179.8 (q, \(^2J_{\text{C-F}} = 35.6\) Hz), 148.5, 138.4, 131.8, 130.3, 129.5, 117.0, 116.4 (q, \(^1J_{\text{C-F}} = 290.5\) Hz); \(^{19}\text{F}\) NMR (282 MHz, CDCl\(_3\)) \(\delta\) -
77.9; IR (neat) 1713, 1601, 1590 cm$^{-1}$; mp 57.5-59 °C; HRMS m/z calcd. for C$_{10}$H$_7$ClF$_3$O ([M+H]$^+$) 235.01320, found 235.01315.

(E)-4-(1-naphthyl)-1,1,1-triflurobut-3-en-2-one (6d)

![](image)

The title compound was isolated as a yellow powder in 85% yield after silica gel flash chromatography using 20:1 hexane/ethyl acetate as the mobile phase. Spectral data was found to match that of literature data.$^{107}$

(E)-1,1,1-trifluoropentadec-3-en-2-one (6f)

![](image)

The title compound was isolated as a clear oil in 80% yield after silica gel flash chromatography using 20:1 hexane/ethyl acetate as the mobile phase. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.32 (1H, dt, $J = 15.8$, 7 Hz), 6.40 (1H, d, $J = 15.8$ Hz), 2.32 (2H, ap q, $J = 7.2$ Hz), 1.50 (2H, m), 1.25 (16H, m), 0.87 (3H, t, $J = 6.5$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 180.3 (q, $^2$J$_{C-F} = 35.5$ Hz), 157.0, 121.4, 116.2 (q, $^1$J$_{C-F} = 290.6$ Hz), 33.3, 31.9, 29.6, 29.5, 29.3, 29.2, 27.6, 22.7, 14.1; $^{19}$F NMR (282 MHz, CDCl$_3$) δ -77.7; IR (neat) 2925, 2855, 1730, 1627, 1201, 1144, 717 HRMS m/z calcd. for C$_{13}$H$_{26}$F$_3$O ([M+H]$^+$) 279.19303, found 279.19349.
General Procedure for the Conjugate Addition of Alkenylboronates to α,β-Unsaturated Trifluoromethyl Ketones

\[
\begin{align*}
\text{R} &= 6 \quad \text{CF}_3 \\
\text{n-C}_6\text{H}_{13} \quad \text{B(OMe)}_2 \quad 8 \quad \text{(S)-(CF}_3\text{)BINOL L5d} \quad \text{DCM, 40 °C} \quad \text{C}_6\text{H}_{13} \\
\text{R} &= 9 \quad \text{CF}_3
\end{align*}
\]

To an oven dried Schlenk tube was added 0.05 g of 4Å molecular sieves. The Schlenk tube was then placed under vacuum and flame dried for one minute to activate the sieves. The Schlenk tube was left to cool to room temperature under vacuum, during which time the appropriate enone (0.3 mmol, 1 eq.), and binaphthol (0.06 mmol, 0.2 eq.) were weighed out. The Schlenk tube was back-filled with argon and the enone, binaphthol and a magnetic stirring bar were added. The Schlenk tube was then evacuated and back-filled with argon three times. The alkenylboronate 8 (0.16 mL, 0.9 mmol, 3 eq.) followed by dry dichloromethane (3.0 mL) was added to the reaction mixture. The Schlenk tube was sealed and placed in a sand bath pre-heated to 40 °C and was allowed to stir until the reaction was complete. After which the crude reaction mixture was filtered through a 1 cm pad of Celite® which was rinsed with dichloromethane. The solvent was removed by rotary evaporation under reduced pressure. The crude material was purified by flash chromatography on silica gel using 20:1 hexane/ethyl acetate as the mobile phase, unless otherwise stated, to furnish the addition product. Analytically pure samples were obtained by passing the purified product through a second silica gel column using 95:5 hexane/iPrOH as the mobile phase.
(R,E)-1,1,1-trifluoro-4-phenyldodec-5-en-2-one (9a)

The title compound was prepared in 83% yield as a clear oil after silica gel chromatography.

\[ \text{H NMR (300 MHz, CDCl}_3\text{)} \delta 7.33 (2H, m), 7.25 (3H, m), 5.52 (2H, m), 3.95 (1H, ap q, } J = 6.8 \text{ Hz) 3.17 (1H, dd, } J = 18, 8 \text{ Hz), 3.07 (1H, dd, } J = 18, 6.7 \text{ Hz), 2.01 (2H, aq q, } J = 6.1 \text{ Hz), 1.28 (8H, m), 0.88 (3H, t, } J = 6.4 \text{ Hz); } ^{13}\text{C NMR (75 MHz, CDCl}_3\text{)} \delta 189.5 (q, } ^2J_{C,F} = 35.4 \text{ Hz), 142.5, 132.2, 130.7, 128.6, 127.4, 126.9, 115.8 (q, } ^1J_{C,F} = 292 \text{ Hz) 42.6, 42.5, 32.4, 31.7, 31.5, 29.1, 28.8, 22.6, 14.0; } ^{19}\text{F NMR (282 MHz, CDCl}_3\text{)} \delta -79.8; \text{ IR (neat) 2926, 1765, 1602, 1494, 1454, 1205, 1143, 698 cm}^{-1}; \text{ HRMS m/z calcd. for } C_{18}H_{24}F_3O \text{ ([M+H]}^+\text{) 313.17729, found 313.17738. The enantiomeric purity of the product was determined by HPLC using a ChiralCel OD-H column (hexanes/i-PrOH = 90:10, 0.25 mL/min flow rate), } t_R = 13.8 \text{ min (major), } t_R = 16.5 \text{ min (minor) (>99.6:0.4 } er).\]

(R,E)-4-(4-methoxyphenyl)-1,1,1-trifluorododec-5-en-2-one (9b)

The title compound was prepared in 77% yield as a clear yellow oil after silica gel chromatography.
\( ^1\text{H NMR} \) (300 MHz, CDCl\(_3\)) \( \delta \) 7.12 (2H, d, \( J = 8.4 \) Hz), 6.85 (2H, d, \( J = 8.4 \) Hz), 5.48 (2H, m), 3.90 (1H, ap q, \( J = 6.9 \) Hz), 3.78 (3H, s), 3.12 (1H, dd, \( J = 17.9, 7.6 \) Hz), 3.02 (1H, dd, \( J = 17.9, 6.8 \) Hz), 1.98 (2H, ap q, \( J = 6.3 \) Hz), 1.25 (8H, m), 0.87 (3H, t, \( J = 6.2 \) Hz); \( ^{13}\text{C NMR} \) (75 MHz, CDCl\(_3\)) \( \delta \) 189.6 (q, \( ^2J_{\text{C-F}} = 35.5 \) Hz), 158.4, 134.5, 131.8, 131.1, 128.3, 115.8 (q, \( ^1J_{\text{C-F}} = 292 \) Hz), 114.1, 55.3, 42.8, 41.7, 32.4, 31.7, 29.2, 28.8, 22.6, 14.1; \( ^{19}\text{F NMR} \) (282 MHz, CDCl\(_3\)) \( \delta \) -79.8; \( \text{IR} \) (neat) 2927, 1764, 1612, 1512, 1465, 1248, 1204, 1143 cm\(^{-1}\); \( \text{HRMS} \) m/z calcd. for C\(_{19}\)H\(_{26}\)F\(_3\)O\(_2\) ([M+H\(^+\)]\(^+\)) 343.18793, found 343.18794. The enantiomeric purity of the product was determined by HPLC using a ChiralCel OD-H column (hexanes/i-PrOH = 99.5:0.5, 0.6 mL/min flow rate), \( t_R = 11.7 \) min (major), \( t_R = 12.9 \) min (minor) (98.8:1.2 \( er \)).

\( (R,E)-4-(4\text{-chlorophenyl})-1,1,1\text{-trifluorododec-5-en-2-one (9c)} \)

![Image of the compound](image)

The title compound was prepared in 83% yield as a clear yellow oil after silica gel chromatography.

\( ^1\text{H NMR} \) (300 MHz, CDCl\(_3\)) \( \delta \) 7.35 (2H, d, \( J = 8.4 \) Hz), 7.13 (2H, d, \( J = 8.4 \) Hz), 5.54 (2H, m), 3.91 (1H, ap q, \( J = 6.1 \) Hz), 3.12 (1H, dd, \( J = 18.1, 7.5 \) Hz) 3.02 (1H, dd, \( J = 18.1, 7.1 \) Hz), 1.96 (2H, ap q, \( J = 6.1 \) Hz), 1.25, (8H, m), 0.86 (3H, t, \( J = 6.3 \) Hz); \( ^{13}\text{C NMR} \) (75 MHz, CDCl\(_3\)) \( \delta \) 189.4 (q, \( ^2J_{\text{C-F}} = 35.5 \) Hz), 140.9, 132.6, 130.3, 128.9, 128.7, 128.5, 115.8 (q, \( ^1J_{\text{C-F}} = 292.3 \) Hz), 42.4, 41.8, 32.4, 31.6, 29.1, 28.7, 22.6, 14.1; \( ^{19}\text{F NMR} \) (282 MHz, CDCl\(_3\)) \( \delta \) -79.8; \( \text{IR} \) (neat) 2927, 1765, 1492, 1205, 1144 cm\(^{-1}\); \( \text{HRMS} \) m/z calcd. for C\(_{18}\)H\(_{23}\)ClF\(_3\)O ([M+H\(^+\)]\(^+\)) 347.13835, found 347.13840. The enantiomeric purity of the product was determined by HPLC using a
ChiralCel OD-H column (hexanes/i-PrOH = 99.5:0.5, 0.5 mL/min flow rate), $t_R = 8.3$ min (minor), $t_R = 8.8$ min (major) (98.3:1.7 er).

(R,E)-1,1,1-trifluoro-4-(1-naphthyl)dodec-5-en-2-one (9d)

![Chemical Structure](image)

The title compound was prepared in 82% yield as a clear oil after silica gel chromatography.

$^1$H NMR (300 MHz, CDCl$_3$) δ 8.16 (1H, d, $J = 8.3$ Hz), 7.90 (1H, d, $J = 7.7$ Hz), 7.79 (2H, d, $J = 8$ Hz), 7.56 (2H, m), 7.47 (1H, ap t, $J = 7.6$ Hz), 7.39 (1H, d, $J = 7.1$), 5.71 (1H, dd, $J = 15.5$, 6.6 Hz), 5.60 (1H, dt, $J = 15.5$, 6.2 Hz), 4.86 (1H, dd, $J = 14.4$, 6.2 Hz), 3.36 (1H, dd, $J = 18.2$, 9 Hz), 3.22 (1H, dd, $J = 18.2$, 5 Hz), 2.04 (2H, ap q, $J = 6.6$ Hz), 1.27 (8H, m), 0.91 (3H, t, $J = 6.5$); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 190.0 (q, $^2J_{C-F} = 35.3$ Hz), 138.5, 134.1, 132.9, 131.0, 130.7, 129.1, 127.6, 126.3, 125.8, 125.6, 123.9, 123.1, 116.0 (q, $^1J_{C-F} = 291.3$ Hz), 42.6, 42.3, 37.4, 32.5, 31.7, 29.2, 28.8, 22.6, 14.1; $^{19}$F NMR (282 MHz, CDCl$_3$) δ -79.6; IR (neat) 2926, 1764, 1598, 1511, 1466, 1204, 1143, 775 cm$^{-1}$; HRMS m/z calcd. for C$_{22}$H$_{26}$F$_3$O ([M+H]$^+$) 363.19303, found 363.19306. The enantiomeric purity of the product was determined by HPLC using a ChiralCel OD-H column (hexanes/i-PrOH = 90:10, 0.5 mL/min flow rate), $t_R = 9.4$ min (major), $t_R = 11.4$ min (minor) (99.5:0.5 er).

General Procedure for the Conjugate Addition of Arylboronates to α,β-Unsaturated Trifluoromethyl Ketones

To an oven dried Schlenk tube was added 0.05 g of 4Å molecular sieves. The Schlenk tube was then placed under vacuum and flame dried for one minute to activate the sieves. The Schlenk
tube was left to cool to room temperature under vacuum, during which time the appropriate enone (0.3 mmol, 1eq.), and binaphthol (0.06 mmol, 0.2 eq.) were weighed out. The Schlenk tube was back-filled with argon and the enone, binaphthol and a magnetic stirring bar were added. The Schlenk tube was then evacuated and back-filled with argon three times. The arylboronate 14 (0.3 mL, 1.8 mmol, 6 eq.) was added to the reaction mixture and the Schlenk tube was sealed and placed in an oil bath pre-heated to 100 °C and was allowed to stir until the reaction was complete. Then the crude reaction mixture was filtered through a 1 cm pad of Celite® which was rinsed with dichloromethane. The solvent was removed by rotary evaporation under reduced pressure. The crude material was purified by flash chromatography on silica gel using 20:1 hexane/ethyl acetate as the mobile phase, unless otherwise stated, to furnish the addition product. Analytically pure samples were obtained by passing the purified product through a second silica gel column using 95:5 hexane/iPrOH as the mobile phase.

\[
\begin{align*}
\text{R}\text{=O} & \quad \text{CF}_3 & + & \quad \text{B(OMe)}_2 & \xrightarrow{(S)-(CF)_2\text{-BINOL (20 mol\%)} \quad 4\AA \text{ MS} \quad \text{neat} \quad 100 \text{ } \text{°C}} & \quad \text{R}\text{=O} & \quad \text{CF}_3 \\
\text{6} & & & \text{14} & & & \text{12}
\end{align*}
\]

\[(R)-4-(4\text{-chlorophenyl})-1,1,1\text{-trifluoro-4-phenylbutan-2-one (12b)}\]

The title compound was prepared in 84% yield as a clear yellow oil after silica gel chromatography.
1H NMR (300 MHz, CDCl3) δ 7.27 (3H, m), 7.20 (2H, ap d, J = 6.9 Hz), 7.13 (2H, d, J = 8.6 Hz), 6.82 (2H, d, 8.6 Hz), 4.61 (1H, ap t, J = 7.2 Hz), 3.76 (1H, s), 3.44 (1H, dd, J = 7.5 Hz); 13C NMR (75 MHz, CDCl3) δ 189.4 (q, 2J_C-F = 35.4 Hz), 158.4, 142.8, 134.6, 128.8, 128.5, 127.4, 126.8, 115.4 (q, 1J_C-F = 291.7 Hz), 114.2, 55.2, 43.8, 42.7; 19F NMR (282 MHz, CDCl3) δ -79.7; IR (neat) 3029, 2838, 1763, 1611, 1511, 1454, 1249, 1206, 1177, 1140, 699 cm⁻¹; HRMS m/z calcd. for C17H16F3O2 ([M+H]+), 309.10969, found 309.10965. The enantiomeric purity of the product was determined by HPLC using a ChiralCel OD-H column (hexanes/i-PrOH = 97:3, 0.3 mL/min flow rate), t_R = 9.4 min (major), t_R = 11.4 min (minor) (89.4:10.6 er).

(R)-4-(4-chlorophenyl)-1,1,1-trifluoro-4-phenylbutan-2-one (12c)

![Structure](image)

The title compound was prepared in 82% yield as a clear yellow oil after silica gel chromatography.

1H NMR (300 MHz, CDCl3) δ 7.29 (4H, m), 7.18 (5H, m), 4.62 (1H, ap t, J = 7.5 Hz), 3.45 (2H, d, J = 7.5 Hz); 13C NMR (75 MHz, CDCl3) δ 189.1 (q, 2J_C-F = 36.0 Hz), 141.9, 141.0, 132.8, 129.0, 128.9, 128.9, 127.4, 127.2, 115.4 (q, 1J_C-F = 292.1 Hz), 44.0, 42.3; 19F NMR (282 MHz, CDCl3) δ -79.7; IR (neat) 3031, 2926, 1765, 1602, 1492, 1453, 1208, 1143, 1014, 753, 698 cm⁻¹; HRMS m/z calcd. for C16H15ClF3O2 ([M+H3O]+), 331.07072 found 331.07082. The enantiomeric purity of the product was determined by HPLC using a ChiralPak AD-H column (hexanes/i-PrOH = 97:3, 0.3 mL/min flow rate), t_R = 14.1 min (major), t_R = 14.9 min (major) (93.2:6.8 er).
(R)-1,1,1-trifluoro-4-(naphthalen-1-yl)-4-phenylbutan-2-one (12d)

The title compound was prepared in 70% yield as a clear yellow oil after silica gel chromatography.

$^1$H NMR (300 MHz, CDCl$_3$) δ 8.09 (1H, d, J = 8 Hz), 7.85 (1H, d, J = 6.8 Hz), 7.76 (1H, d, J = 7.8 Hz), 7.47 (2H, m), 7.33 (1H, d, J = 6.8 Hz), 7.26 (5H, m), 7.19 (1H, m), 5.49 (1H, ap t, J = 7.3 Hz), 3.60 (2H, d, J = 7.3 Hz); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 189.4 (q, $^2$J$_{C,F}$ = 35.5 Hz), 142.2, 137.9, 134.2, 129, 128.8, 127.9, 127.8, 127, 126.5, 125.8, 125.2, 124, 123.3, 115.9 (q, $^1$J$_{C,F}$ = 290.1 Hz), 43, 40.1; $^{19}$F NMR (282 MHz, CDCl$_3$) δ -79.6; IR (neat) 3067, 2925, 1764, 1599, 1510, 1453, 1207, 1141, 1018, 782, 700 cm$^{-1}$; HRMS m/z calcd. for C$_{22}$H$_{26}$F$_3$O ([M+H]$^+$) 329.11478, found 329.11380. The enantiomeric purity of the product was determined by HPLC using a ChiralCel OD-H column (hexanes/i-PrOH = 90:10, 0.5 mL/min flow rate), t$_R$ = 10.0 min (minor), t$_R$ = 15.5 min (major) (80.3:19.7 er).

**General Procedure for the Conjugate Addition of Heteroarylboronates to α,β-Unsaturated Trifluoromethyl Ketones**

To an oven dried Schlenk tube was added 0.05 g of 4Å molecular sieves. The Schlenk tube was then placed under vacuum and flame dried for one minute to activate the sieves. The Schlenk
tube was left to cool to room temperature under vacuum, during which time the appropriate enone (0.3 mmol, 1 eq.), and binaphthol (0.06 mmol, 0.2 eq.) were weighed out. The Schlenk tube was back-filled with argon and the enone, binaphthol and a magnetic stirring bar were added. The Schlenk tube was then evacuated and back-filled with argon three times. The heteroarylboronate (16 or 19) (0.3 mL, 1.8 mmol, 6 eq.) was added to the reaction mixture and the Schlenk tube was sealed and placed in an oil bath pre-heated to 80 °C and was allowed to stir until the reaction was complete. After which the crude reaction mixture was filtered through a 1 cm pad of Celite® which was rinsed with dichloromethane. The solvent was removed by rotary evaporation under reduced pressure. The crude material was purified by flash chromatography on silica gel using 20:1 hexane/ethyl acetate as the mobile phase, unless otherwise stated, to furnish the addition product. Analytically pure samples were obtained by passing the purified product through a second silica gel column using 95:5 hexane/iPrOH as the mobile phase.

**(S)-1,1,1-trifluoro-4-phenyl-4-(thiophen-2-yl)butan-2-one (17a)**

![Chemical Structure](image)

The title compound was prepared in 89% yield as a clear yellow oil after silica gel chromatography.

**¹H NMR** (300 MHz, CDCl₃)  δ 7.31 (5H, m), 7.17 (1H, d, J = 5.2 Hz), 6.92 (1H, ap t, J = 4.2 Hz), 6.84 (1H, d, J = 3.4 Hz), 4.90 (1H, ap t, J = 7.5 Hz), 3.57 (1H, dd, J = 18.7, 7.2 Hz), 3.47 (1H, dd, J = 18.7, 7.4 Hz); **¹³C NMR** (75 MHz, CDCl₃)  δ 189.0 (q, ²J_{C-F} = 35.6 Hz), 146.4, 142.1, 128.9, 127.7, 127.4, 119.8 (q, ¹J_{C-F} = 290.6 Hz), 43.9, 40.3; **¹⁹F NMR** (282 MHz, CDCl₃)  δ -
79.6; **IR** (neat) 3031, 1764, 1602, 1495, 1454, 1205, 1140, 695 \( \text{cm}^{-1} \); **HRMS** m/z calcd. for \( \text{C}_{14}\text{H}_{12}\text{F}_3\text{OS} \) ([M+H]⁺) 285.05555, found 285.05543. The enantiomeric purity of the product was determined by HPLC using a ChiralCel OD-H column (hexanes/i-PrOH = 95:5, 0.75 mL/min flow rate), \( t_R = 10.2 \) min (major), \( t_R = 18.2 \) min (minor) (96.5:3.5 er).

**(S)-1,1,1-trifluoro-4-(4-methoxyphenyl)-4-(thiophen-2-yi)butan-2-one (17b)**

![Chemical Structure](attachment:image.png)

The title compound was prepared in 84% yield as a clear yellow oil after silica gel chromatography.

\(^1\text{H NMR}\) (300 MHz, CDCl\(_3\)) \( \delta \) 7.21 (2H, d, \( J = 8.6 \) Hz), 7.16 (1H, d, 5.1 Hz), 6.91 (1H, t, \( J = 3.5 \) Hz), 6.85 (2H, d, 8.6 Hz), 6.82 (1H, d, 3.4 Hz), 4.85 (1H, ap t, \( J = 7.5 \) Hz), 3.78 (3H, s), 3.53 (1H, dd, \( J = 18, 6.5 \) Hz), 3.44 (1H, dd, \( J = 18.9, 7.8 \) Hz); \(^{13}\text{C NMR}\) (75 MHz, CDCl\(_3\)) \( \delta \) 188.9 (q, \( ^2J_{C-F} = 36.2 \) Hz), 158.8, 147.1, 134.3, 128.5, 126.8, 124.3, 124.2, 115.9 (q, \( ^1J_{C-F} = 289.4 \) Hz), 114.2, 55.2, 44.1, 39.6; \(^{19}\text{F NMR}\) (282 MHz, CDCl\(_3\)) \( \delta \) -79.7; **IR** (neat) 2838, 1764, 1610, 1511, 1463, 1250, 1205, 1178, 1140, 697 \( \text{cm}^{-1} \); **HRMS** m/z calcd. for \( \text{C}_{15}\text{H}_{14}\text{F}_3\text{O}_2\text{S} \) ([M+H]⁺) 315.06611, found 315.06606. The enantiomeric purity of the product was determined by HPLC using a ChiralPak AD-H column (hexanes/i-PrOH = 99.7:0.3, 1.0 mL/min flow rate), \( t_R = 10.3 \) min, \( t_R = 12.6 \) min (98.2:1.8 er).
(S)-1,1,1-trifluoro-4-(4-chlorophenyl)-4-thiophen-2-yl)butan-2-one (17c)

The title compound was prepared in % yield as a clear yellow oil after silica gel chromatography.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.41 (2H, d, $J = 8.4$ Hz), 7.22 (2H, d, $J = 8.4$ Hz), 7.18 (1H, d, $J = 5.1$ Hz), 6.92 (1H, t, $J = 3.8$ Hz), 6.82 (1H, d, $J = 3.4$ Hz), 4.86 (1H, ap t, $J = 7.3$ Hz), 3.54 (1H, dd, $J = 18.8$, 7.2 Hz), 3.42 (1H, dd, $J = 18.8$, 7.7 Hz); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 188.6 (q, $^2J_{C\text{-}F} = 35.8$ Hz), 145.8, 140.6, 133.3, 129.1, 128.9, 126.9, 124.7, 124.5, 115.3 (q, $^1J_{C\text{-}F} = 291.6$ Hz), 43.8, 39.7; $^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$ -79.6; IR (neat) 1764, 1595, 1492, 1437, 1206, 1141, 697 cm$^{-1}$; HRMS m/z calcd. for C$_{14}$H$_{11}$ClF$_3$OS ([M+H]$^+$) 319.01657, found 319.01656. The enantiomeric purity of the product was determined by HPLC using a ChiralPak AD-H column (hexanes/i-PrOH = 97:3, 0.25 mL/min flow rate), $t_R$ = 17.4 min (major), $t_R$ = 18.0 min (minor) (93.3:6.7 $er$).

(S)-1,1,1-trifluoro-4-(naphthalen-1-yl)-4-(thiophen-2-yl)butan-2-one (17d)

The title compound was prepared in 75% yield as a clear yellow oil after silica gel chromatography.
**1H NMR** (300 MHz, CDCl₃) δ 8.16 (1H, d, J = 8.2 Hz), 7.89 (1H, d, J = 7.5 Hz), 7.82 (1H, d, J = 7.8 Hz), 7.54 (2H, ap quint, J = 6 Hz), 7.46 (1H, d, J = 7.7 Hz), 7.42 (1H, d, J = 6.6 Hz), 7.16 (1H, d, J = 4.9 Hz), 6.92 (1H, t, J = 3.6 Hz), 6.90 (1H, br s), 5.80 (1H, ap t, J = 6.9 Hz), 3.75 (1H, dd, J = 18.8, 8.2 Hz), 3.63 (1H, dd, J = 18.8, 6.1 Hz);

**13C NMR** (75 MHz, CDCl₃) δ 189.1 (q, 2J_{C,F} = 35.9 Hz), 146.2, 138.0, 134.1, 131.0, 129.2, 128.3, 126.9, 126.7, 126.0, 125.4, 125.1, 124.5, 124.1, 122.9, 115.6 (q, 1J_{C,F} = 292.4 Hz), 44.0, 35.5;

**19F NMR** (282 MHz, CDCl₃) δ -79.5; IR (neat) 3050, 1763, 1599, 1511, 1436, 1204, 1138, 776, 694 cm⁻¹; HRMS m/z calcd. for C₁₈H₁₄F₃O₅S ([M+H⁺]⁺) 335.07120, found 335.07114. The enantiomeric purity of the product was determined by HPLC using a ChiralCel OD-H column (hexanes/i-PrOH = 95:5, 0.5 mL/min flow rate), tᵣ = 22.9 min (major), tᵣ = 32.4 min (minor) (99.2:0.8 er).

**(R)-1,1,1-trifluoro-4-(thiophen-2-yl)pentadecan-2-one (17f)**

![Chemical Structure](image)

The title compound was prepared in 96% yield as a clear oil after silica gel chromatography.

**1H NMR** (300 MHz, CDCl₃) δ 7.15 (1H, ap d, J = 5.1 Hz), 6.91 (1H, ap t, J = 4.3 Hz), 6.83 (1H, ap d, J = 3.4 Hz), 3.56 (1H, ap quint, J = 7.1 Hz), 3.07 (1H, dd, J = 18.4, 7.2 Hz), 2.99 (1H, dd, J = 18.4, 6.6 Hz), 1.65 (2H, m), 1.23 (18H, m), 0.88 (3H, t, J = 6.4 Hz); **13C NMR** (75 MHz, CDCl₃) δ 189.78 (q, 2J_{C,F} = 35.4 Hz), 147.0, 126.7, 124.4, 123.4, 115.3 (q, 1J_{C,F} = 295.2 Hz), 44.4, 37.2, 35.2, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 27.2, 22.714.1; **19F NMR** (282 MHz, CDCl₃) δ -79.8; IR (neat) 2924, 2854, 1764, 1465, 1207, 1143, 1034, 693 cm⁻¹; HRMS m/z calcd. for C₁₉H₃₀F₅OS ([M+H⁺]⁺) 363.19640, found 363.19640. The enantiomeric purity of the product...
was determined by HPLC using a ChiralCel OD-H column (hexanes/i-PrOH = 95:5, 0.3 mL/min flow rate), \( t_R = 11.4 \text{ min (minor)}, t_R = 12.1 \text{ min (major)} (95.5:4.5 \text{ er}). \)

(S)-1,1,1-trifluoro-4-(furan-2-yl)-4-phenylbutan-2-one (20a)

The title compound was prepared in 66% yield as a clear yellow oil after silica gel chromatography.

\(^1\text{H NMR}\) (300 MHz, CDCl\(_3\)) \( \delta \) 7.33 (3H, m), 7.28 (2H, br s), 7.26 (1H, br s), 6.29 (1H, dd, \( J = 3.1, 2 \text{ Hz} \)), 6.02 (1H, d, \( J = 3.2 \)), 4.68 (1H, ap t, \( J = 7.3 \text{ Hz} \)), 3.57 (1H, dd, \( J = 18.6, 7.5 \text{ Hz} \)), 3.31 (1H, dd, \( J = 18.6, 7.1 \text{ Hz} \)); \(^{13}\text{C NMR}\) (75 MHz, CDCl\(_3\)) \( \delta \) 189.0 (q, \( ^2J_{\text{CF}} = 35.7 \)), 155.0, 141.9, 140.3, 128.9, 127.4, 115.3 (q, \( ^1J_{\text{CF}} = 292.1 \text{ Hz} \)), 106.3, 41.4, 39.1; \(^{19}\text{F NMR}\) (282 MHz, CDCl\(_3\)) \( \delta \) -79.7; \(^\text{IR}\) (neat) 1765, 1587, 1505, 1454, 1206, 1178, 1137, 700 cm\(^{-1}\); \(^\text{HRMS}\) m/z calcd. for C\(_{14}\)H\(_{12}\)F\(_3\)O\(_2\) ([M+H]\(^+\)) 269.07839, found 269.07838. The enantiomeric purity of the product was determined by HPLC using a ChiralCel OD-H column (hexanes/i-PrOH = 95:5, 0.75 mL/min flow rate), \( t_R = 6.8 \text{ min (major)}, t_R = 10.0 \text{ min (minor)} (94.6:5.4 \text{ er}). \)
(S)-1,1,1-trifluoro-4-(furan-2-yl)-4-(4-methoxyphenyl)butan-2-one (20b)

The title compound was prepared in 97% yield as a clear yellow oil after silica gel chromatography.

$^1$H NMR (300 MHz, CDCl₃) δ 7.31 (1H, br s), 7.14 (2H, d, $J = 8.7$ Hz), 6.84 (2H, $J = 8.6$ Hz), 6.27 (1H, dd, $J = 2.8, 2.4$ Hz), 5.98 (1H, d, $J = 3$), 4.61 (1H, ap t, $J =$6.6), 3.78 (3H, s), 3.51 (1H, dd, $J = 18.6, 7$ Hz), 3.26 (1H, dd, $J = 18.4, 7.4$ Hz); $^{13}$C NMR (75 MHz, CDCl₃) δ 189.1 (q, $^2J_{C-F} =$ 35.6 Hz), 158.8, 155.4, 141.9, 132.3, 128.7, 115.1 (q, $^1J_{C-F} =$ 291.9 Hz), 114.2, 110.3, 106.1, 55.2, 41.6, 38.3; $^{19}$F NMR (282 MHz, CDCl₃) δ -79.7; IR (neat) 2938, 2839, 1764, 1611, 1512, 1463, 1250, 1206, 1177, 1137, 1001, 733 cm⁻¹; HRMS m/z calcd. for C$_{15}$H$_{14}$F$_{3}$O$_{3}$ ([M+H]$^+$) 299.08896, found 299.08829. The enantiomeric purity of the product was determined by HPLC using a ChiralPak AD-H column (hexanes/i-PrOH = 99.7:0.3, 0.5 mL/min flow rate), t$_R$ = 18.0 min (minor), t$_R$ = 19.7 min (major) (95.6:4.4 er).

(S)-4-(4-chlorophenyl)-1,1,1-trifluoro-4-(furan-2-yl)butan-2-one (20c)

The title compound was prepared in 69% yield as a clear yellow oil after silica gel chromatography.
\( ^{1}H \text{NMR} \) (300 MHz, CDCl\(_3\)) \( \delta \) 7.32 (1H, br s), 7.29 (2H, d, \( J = 8.5 \) Hz), 7.20 (2H, d, \( J = 8.4 \) Hz), 6.28 (1H, dd, \( J = 3.1, 1.9 \) Hz), 6.02 (1H, d, \( J = 3.2 \) Hz), 4.64 (1H, ap t, \( J = 7.3 \)), 3.54 (1H, dd, \( J = 18.3, 7 \) Hz), 3.28 (1H, dd, \( J = 18.7, 7.5 \) Hz); \( ^{13}C \text{NMR} \) (75 MHz, CDCl\(_3\)) \( \delta \) 188.8 (q, \( 2J_{C-F} = 35.5 \)), 154.4, 142.2, 138.7, 133.3, 129.1, 129.0, 115.2 (q, \( 1J_{C-F} = 292.5 \)), 110.4, 106.5, 41.3, 38.5; \( ^{19}F \text{NMR} \) (282 MHz, CDCl\(_3\)) \( \delta \) -79.7; IR (neat) 1765, 1596, 1492, 1206, 1138, 1014, 733 cm\(^{-1}\); HRMS m/z calcd. for C\(_{14}\)H\(_{11}\)Cl\(_3\)F\(_2\)O\(_2\) ([M+H\(^+\)]\(^+\)) 303.03942, found 303.03933. The enantiomeric purity of the product was determined by HPLC using a ChiralPak AD-H column (hexanes/i-PrOH = 99:1, 0.5 mL/min flow rate), \( t_R = 9.6 \) min (minor), \( t_R = 9.9 \) min (major) (94:6 er).

(S)-1,1,1-trifluoro-4-(furan-2-yl)-4-(naphthalen-1-yl)butan-2-one (20d)

The title compound was prepared in 96% yield as a clear yellow oil after silica gel chromatography.

\( ^{1}H \text{NMR} \) (300 MHz, CDCl\(_3\)) \( \delta \) 8.13 (1H, d, \( J = 8.3 \) Hz), 7.91 (1H, d, \( J = 7.6 \) Hz), 7.84 (1H, d, \( J = 8.2 \) Hz), 7.56 (2H, quin. \( J = 8.6 \) Hz), 7.45 (1H, t, \( J = 7.5 \) Hz), 7.37 (1H, br s), 7.34 (1H, d, \( J = 7.1 \) Hz), 6.32 (1H, dd, \( J = 2.5, 2.4 \) Hz), 6.07 (1H, d, \( J = 3.2 \) Hz), 5.61 (1H, dd, \( J = 8.9, 5.4 \) Hz), 3.78 (1H, d, \( J = 18.7, 8.9 \) Hz), 3.44 (1H, dd, \( J = 18.7, 5.3 \) Hz); \( ^{13}C \text{NMR} \) (75 MHz, CDCl\(_3\)) \( \delta \) 189.2 (q, \( 2J_{C-F} = 35.9 \) Hz), 154.7, 142.0, 136.3, 134.1, 131.0, 129.2, 128.2, 126.7, 125.9, 125.5, 124.9, 122.7, 115.5 (q, \( 1J_{C-F} = 290.2 \) Hz), 110.5, 107.0, 41.2, 34.6; \( ^{19}F \text{NMR} \) (282 MHz, CDCl\(_3\)) \( \delta \) -79.5; IR (neat) 3052, 1764, 1598, 1505, 1399, 1204, 1137, 1017, 776 cm\(^{-1}\); HRMS m/z calcd. for C\(_{18}\)H\(_{14}\)F\(_3\)O\(_2\) ([M+H\(^+\)]\(^+\)) 319.09404, found 319.09409. The enantiomeric purity of the product

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was determined by HPLC using a ChiralCel OD-H column (hexanes/i-PrOH = 95:5, 0.5 mL/min flow rate), \( t_R = 13.5 \text{ min (major)} \), \( t_R = 20.8 \text{ min (minor)} \) (98.3: 1.7 \text{ er}).

(R)-1,1,1-trifluoro-4-(furan-2-yl)pentadecan-2-one (20f)

The title compound was prepared in 79\% yield as a clear yellow oil after silica gel chromatography.

\(^1\text{H NMR}\) (300 MHz, CDCl\(_3\)) \( \delta \) 7.29 (1H, m), 6.26 (1H, m), 6.03 (1H, ap d), \( J = 3.0 \text{ Hz} \), 3.35 (1H, ap quint, \( J = 6.9 \text{ Hz} \)), 3.08 (1H, dd, \( J = 18.3, 7.2 \text{ Hz} \)), 2.91 (1H, dd, \( J = 18.3, 6.4 \text{ Hz} \)), 1.62 (2H, m), 1.23 (18H, m), 0.87 (3H, t, \( J = 6.4 \text{ Hz} \)); \(^{13}\text{C NMR}\) (75 MHz, CDCl\(_3\)) \( \delta \) 190.0 (q, \( ^2J_{C,F} = 35.5 \)), 155.8, 141.3, 115.4 (q, \( ^1J_{C,F} = 294.1 \)), 110.0, 105.6, 40.8, 33.6, 33.3, 31.9, 29.6, 29.5, 29.4, 29.3, 27.0, 22.7, 14.1; \(^{19}\text{F NMR}\) (282 MHz, CDCl\(_3\)) \( \delta \) -79.8; \( \text{IR}\) (neat) 2925, 2855, 1765, 1507, 1466, 1206, 1144, 1011, 731 cm\(^{-1}\); \( \text{HRMS}\) m/z calcd. for C\(_{19}\)H\(_{30}\)F\(_3\)O\(_2\) ([M+H]\(^+\)) 347.21924, found 347.21924. The enantiomeric purity of the product was determined by HPLC using a ChiralCel OD-H column (hexanes/i-PrOH = 99.5:0.5, 0.5 mL/min flow rate), \( t_R = 7.0 \text{ min (minor)} \), \( t_R = 7.5 \text{ min (major)} \) (93.2:6.8 \text{ er}).

**General Procedure for the Conjugate Addition of N-Boc-Pyrrole Boronic Acid to Chalcone**

To an oven dried Schlenk tube was added 0.05 g of 4Å molecular sieves. The Schlenk tube was then placed under vacuum and flame dried for one minute to activate the sieves. The Schlenk tube was left to cool to room temperature under vacuum, during which time the chalcone
(0.062g, 0.3 mmol, 1eq.), I$_2$-BINOL (0.032 g, 0.06 mmol, 0.2 eq.), N-Boc-Pyrrole boronic acid 22 (0.19 g, 0.9 mmol, 3 eq.), and tBuOK (0.015 g, 0.15 mmol, 0.5 eq.) were weighed out. The Schlenk tube was back-filled with argon and the chalcone, binaphthol, boronic acid, alkoxide and a magnetic stirring bar were added. The Schlenk tube was then evacuated and back-filled with argon three times. The reaction mixture was dissolved in B(OiPr)$_3$ (0.5 mL), the Schlenk tube was sealed and placed in an oil bath pre-heated to 80 °C and was allowed to stir overnight until the reaction was complete. After which the crude reaction mixture was filtered through a 1 cm pad of Celite® which was rinsed with dichloromethane. The solvent was removed by rotary evaporation under reduced pressure. The crude material was purified by flash chromatography on silica gel using 10:1 hexane/ethyl acetate as the mobile phase, to furnish the addition product.

**Tert-butyl (S)-2-(3-oxo-1,3-diphenylpropyl)-1H-pyrrole-1-carboxylate (23)**

![Structure of 23](image)

The title compound was prepared in 91% yield as a clear yellow oil after silica gel chromatography.

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.53 (2H, d, $J = 7.9$ Hz), 7.53 (1H, ap t, $J = 7.1$ Hz), 7.43 (2H, ap t, $J = 7.6$ Hz), 7.22 (3H, ap d, $J = 6.7$ Hz), 7.15 (2H, ap d, $J = 7.2$ Hz), 6.07 (1H, ap t, $J = 3.4$ Hz), 6.03 (1H, m), 5.50 (1H, ap t, $J = 7.1$ Hz), 3.74 (1H, dd, $J = 17.1, 7.7$ Hz), 3.47 (1H, dd, $J = 17.1, 7$ Hz), 1.43 (9H, s); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 197.8, 149.1, 1143.7, 137.1, 136.8, 133.0, 128.6, 128.2, 128.1, 127.9, 126.2, 121.9, 111.6, 109.6, 83.6, 45.6, 39.127.8; IR (neat) 3067, 2936, 1740, 1687, 1597, 1491, 1449, 1327, 1123 cm$^{-1}$; HRMS m/z calcd. for C$_{24}$H$_{26}$O$_3$N
([M+H]⁺) 376.19072, found 376.19066. The enantiomeric purity of the product was determined by HPLC using a ChiralCel OD-H column (hexanes/i-PrOH = 95:5, 0.5 mL/min flow rate), t_R = 11.5 min (major), t_R = 14.0 min (minor) (94.5:5.5 er).
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