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Metal-Catalyzed Allylic Substitution & Arylation With Weakly Acidic C(sp3)–h Bonds

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Abstract
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Traditional cross coupling reactions, such as Suzuki, Negishi, Kumada, Stille and so on, require prefunctionalized coupling partners (organoboron in Suzuki, organozinc in Negishi, Grignard reagents in Kumada and organotin in Stille). The downside of such strategies is that prefunctionalization requires significant effort and time. Thus, turning C-H bond directly into cross coupling partners without any prefunctionalization is more efficient and atom-economical.

Much progress have been made the past two decades in C-H functionalization, including both sp2 and sp3 hybridized C-H bonds. Functionalization of sp2 hybridized C-H bonds has focused on arenes and heteroarenes and has been well developed. In contrast, sp3 hybridized C-H bonds are more difficult to functionalize. Early studies on sp3 hybridized C-H functionalization focused on C-H bond alpha to activating groups such ketone, ester, amide and others. Another strategy to functionalize those unactivated C-H bonds (pKa>30) is to install directing groups to facilitate reactivity and selectivity. The addition and removal of directing groups, however, may limit the utility of this strategy. To date, intermolecular cross-coupling reactions of non- or weakly acidic C(sp3)-H bonds in the absence of directing group remains a challenge.

The Walsh group set out to develop methods to for C(sp3)–H functionalization using a strategy called Deprotonative Cross Coupling Process (DCCP). DCCP takes advantage of reversible deprotonation under the conditions of the reaction as a method to achieve functionalization of weakly acidic C(sp3)-H bond using relatively mild condition. This dissertation describes two methods to functionalization of weakly acidic C(sp3)-H bonds, allylic substitution and arylation, with success on both Pd or Ni as catalyst.

The first two chapters of the dissertation describe transition metal catalyzed allylic substitution with diarylmethane pronucleophiles (pKa up to 32.3). Diarylmethane are among the least acidic pronucleophiles used to date in transition metal catalyzed allylic substitution reactions (Tsuji-Trost reaction). The widely accepted paradigm for classifying the mode of attack of nucleophiles on palladium π-allyl intermediates in the Tsuji–Trost reaction is based on the pKa of the pronucleophile: (1) stabilized or “soft” carbon nucleophiles and heteroatom nucleophiles (e.g., pronucleophiles with pKa's < 25), and (2) unstabilized or “hard” nucleophiles (those from pronucleophiles with pKa's > 25). One of the keys to the continuing development of asymmetric allylic substitution processes remains broadening the scope of “soft” nucleophiles. In Chapter 1, we successfully demonstrated the cut-off between soft and hard nucleophiles for Pd-catalyzed allylic substitution should be raised from pKa of 25 to at least 32. This discovery expands the scope of soft nucleophiles, and suggests the possibility of developing asymmetric allylic substitution for more weakly acidic substrates.

In chapter 2, we further applied Ni catalyzed allylic substitution on diarylmethanes to develop a supplement to the Pd version. We were able to prove the same nucleophile behaves as soft nucleophile in both Pd and Ni catalyzed allylic substitution. More importantly, Ni has always been paired with hard nucleophiles to perform asymmetric allylic substitution, but we were able to identify a chiral ligand SL-J204-1 to do asymmetric allylic...

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substitution using Ni as catalyst with soft nucleophile (diarylmethane) and got up to 91% yield with 92% e.e. This result suggests Ni catalyzed asymmetric allylic substitution can be done with both soft and hard nucleophiles, which makes Ni an appealing choice other than Pd for transition metal catalyzed allylic substitution.

The second part of the dissertation focus on the arylation of weakly acidic substrates such as carboxylate and toluene (pKa = 44±1). The same strategy DCCP is applied to both types of substrates, through direct metalation and subsequent cross coupling of benzylic C(sp3)-H bonds.

Chapter 3 describes alpha arylation of carboxylic acids. Significant works on alpha arylation have been done on carbonyl group containing substrates such as ketone, aldehyde, ester and amide. However, examples on alpha arylation of carboxylic acids remain scarce due to the difficulty of generating dienolate. We successfully demonstrated the reversible deprotonation could be applied to benzyl carboxylic acids and identified a catalyst system that could further cross couple dienolate with aryl chlorides and bromides.

Finally, chapter 4 describes a direct arylation of toluene derivatives benzylic C-H bond. We used an unique catalyst with deprotonatable ligand NIXANTPHOS. The deprotonated ligand would carry the counter cation (alkali metal) of the base through out the catalytic cycle. Previously, our group had developed an activation strategy using η6-coordination of arenes to tricarbonylchromium to activate toluene benzylic C-H bond. In this chapter, we developed a new strategy using η6-coordination of toluene to potassium to activate benzylic C-H bond to perform DCCP. The mechanistic study showed the crucial role of potassium cation. The method is valuable in two points: 1. Direct arylation of toluene derivatives provides a strong tool transforming cheap, inert molecule to useful molecule diarylmethane. 2. The unique mechanism would inspire us to design more heterobimetallic systems with deprotonatable ligands to activate different kind of molecules.

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Patrick j. Walsh

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Gary a. Molander

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METAL-CATALYZED ALLYLIC SUBSTITUTION & ARYLMATION
WITH WEAKLY ACIDIC $C(\text{SP}^3)\text{-H}$ BONDS

Sheng-Chun Sha

A DISSERTATION

in

Chemistry

Presented to the Faculties of the University of Pennsylvania

in

Partial Fulfillment of the Requirements for the
Degree of Doctor of Philosophy

2015

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METAL-CATALYZED ALLYLIC SUBSTITUTION & ARYLATION
WITH WEAKLY ACIDIC C(SP\(^3\))-H BONDS

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Sheng-Chun Sha
Dedicated to my family
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First of all, I would like to give my appreciation to both my advisors, Jeff and Pat. I couldn’t express how thankful I am to both of them. Jeff taught me how to think and to do experiments like a chemist, and gave me the chance to become a better scientist. I would like to thank Pat for his guidance and help through out my entire graduate school. After I joined his group in 2012, none of the days was wasted. He always motivated us to discover new things, and provided us his unparalleled insight to the questions we had. Together we have been through a wonderful and pleasant journey. Pat has been always supportive and kind to all the group members, I am really grateful to have such a wonderful advisor.

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Judy. Thank you for raising me and teaching me to be a better person. There’s nothing comparable to the love and devotion that you guys have given me. I feel really thankful and lucky to be in this family, thank you.
ABSTRACT

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WITH WEAKLY ACIDIC C(SP$^3$)-H BONDS

Sheng-Chun Sha

Professor Patrick J. Walsh

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Chapter 1
Raising the $pK_a$ Limit of “Soft” Nucleophiles in Palladium-Catalyzed Allylic Substitutions: Application of Diarylmethane Pronucleophiles

1.1. INTRODUCTION

Palladium-catalyzed C–C bond-forming reactions are among the most important and well-developed processes in modern organic chemistry.\(^1\)–\(^\text{10}\) Of these, the Tsuji–Trost allylic substitution reaction provides a useful and efficient approach to construct C–C bonds between sp\(^3\)-hybridized carbons. As a result, it has been widely used to synthesize natural products and bioactive molecules.\(^\text{11–17}\) The widely accepted paradigm for classifying the mode of attack of nucleophiles on transition metal $\eta^3$-$\pi$-allyl intermediates in the Tsuji–Trost reaction is based on the $pK_a$ of the pronucleophile.\(^\text{18}\) Nucleophiles are divided into two classes: 1) stabilized or “soft” carbon nucleophiles and heteroatom nucleophiles (e.g., enolates and those from pronucleophiles with $pK_a$‘s < 25), and (2) unstabilized or “hard” nucleophiles (those from pronucleophiles with $pK_a$‘s > 25). The distinction between these two classes is “soft” nucleophiles directly attack the $\pi$-allyl moiety while “hard” nucleophiles first attack the metal center (via transmetallation) before bond formation with the allyl group. Importantly, these two pathways lead to distinct stereochemical outcomes (soft nucleophiles result in net retention in the Tsuji–Trost allylic substitution whereas hard nucleophiles react by single inversion). The scope of “soft” nucleophiles has
received significant attention in asymmetric catalysis,\textsuperscript{11,13,14,19} although non-enantioselective Pd-catalyzed allylic substitution with “hard” nucleophiles are also known.\textsuperscript{20-22}

One of the keys to the continuing development of allylic substitution processes remains broadening the scope of “soft” nucleophiles. With this in mind, Trost and co-workers increased the reach of “soft” nucleophiles in the allylic substitution with use of 2-picoline-derived nucleophiles (p\(K_a\) = 34).\textsuperscript{23} Essential to their success was to increase the acidity of the 2-picoline CH\(_3\). This was accomplished by BF\(_3\) coordination to the pyridine nitrogen to facilitate deprotonation. The resulting “softened” nucleophile was successfully employed in Pd-catalyzed asymmetric allylic alkylation (AAA, Scheme 1A).\textsuperscript{18,24} The same group later reported no such activation was necessary with more acidic heterocycles, including pyrazine, pyrimidine, pyridazine, quinoxaline, and benzimidazole derivatives. (Scheme 1B).\textsuperscript{25}

Our group recently introduced a strategy to employ toluene derivatives (RC\(_6\)H\(_4\)–CH\(_2\)R’, p\(K_a\) ~ 44)\textsuperscript{26} as “soft” pronucleophiles in Pd-catalyzed allylic substitution reactions using Cr(CO)$_3$ to increase the acidity of the benzylic C–H’s (Scheme 1C).\textsuperscript{27} The drawback of this approach is the stoichiometric use of chromium. We, therefore, set out to develop benzylic nucleophiles in the absence of chromium activating groups.
Scheme 1.1. Palladium-Catalyzed Benzylic Allylations

A. 2-alklypyridines

\[
\begin{align*}
&\text{N} \quad \text{Nu} = \text{BF}_3 \\
&\text{R} + \text{OPG} \xrightarrow{\text{Catalyst}} \text{Ar} \quad \text{Trost 2008, 2009}
\end{align*}
\]

66 to 99% yield
88 to 99% ee
4:1 to >19:1 dr

B. Polynitrogen-containing heterocycles

\[
\begin{align*}
&\text{N} \quad \text{Nu} = \text{BF}_3 \\
&\text{N} \quad \text{R} + \text{OPG} \xrightarrow{\text{Catalyst}} \text{Ar} \quad \text{Trost 2011}
\end{align*}
\]

71% yield
97% ee

C. Chromium-stabilized toluene derivatives

\[
\begin{align*}
&\text{Nu} = \text{Cr(CO)}_3 \\
&R \quad \text{Nu} \xrightarrow{\text{Catalyst}} \text{Ar} \quad \text{Walsh 2011}
\end{align*}
\]

45 to 99% yield

D. This Work

\[
\begin{align*}
&\text{Nu} = \text{Catalyst} \\
&R \quad \text{Nu} \xrightarrow{\text{Catalyst}} \text{Ar} \quad \text{68 to 99% yield}
\end{align*}
\]

Application of unactivated diarylmethane derivatives as pronucleophiles in Pd-catalyzed allylic substitution reactions are unknown, but would have significant potential in medicinal chemistry. Hundreds of bioactive drug-like molecules contain allylated diarylmethyl motifs (Figure 1), with applications in treatment of breast cancer\textsuperscript{28}, inhibitor of HIV protease\textsuperscript{29}, blocker of human T-cells\textsuperscript{30} and antagonist of the thyroid hormone receptor,\textsuperscript{31} among others. Given these important applications, we set out to introduce diarylmethane-derived
nucleophiles for the Pd-catalyzed allylic substitution. To achieve this objective, it is essential to find conditions to deprotonate diarylmethane derivatives that are compatible with the catalyst and substrates. Based on our previous studies on deprotonative cross-coupling processes (DCCP) using diarylmethane derivatives,32-35 we hypothesized that diarylmethane derivatives could be reversibly deprotonated in situ by MN(SiMe₃)₂ (M = Li, Na, K) under mild conditions. These conditions would be more amenable to catalysis than deprotonation under traditional conditions with n-BuLi at low temperature.36 Herein we report an approach to the room temperature Pd-catalyzed allylic substitution with diarylmethane derivatives (Scheme 1D). This method enables rapid access to a variety of allylated products, including heteroaryl-containing derivatives as well as molecules bearing quaternary centers. The mild reaction conditions that have been identified employ MN(SiMe₃)₂ at room temperature and a Pd catalyst based on van Leeuwen’s Xantphos ligand.37 Surprisingly, stereochemical studies indicate that nucleophiles derived from diarylmethane derivatives (pKₐ = 25-33)26,38 behave as “soft” nucleophiles, significantly extending the range of nucleophiles undergoing the double inversion mechanism in the Tsuji–Trost allylic substitution.
Figure 1.1. Selected bioactive compounds containing the allylated diarylmethyl motif.

1.2. RESULTS AND DISCUSSION

As mentioned above, we recently disclosed a Pd–Xantphos catalyst system to promote the allylic substitution with Cr(CO)$_3$-stabilized toluene-derived nucleophiles (eq 1).$^{27}$ We hypothesized the reaction conditions in eq 1 would be a good starting point for allylic substitution with diarylmethanes and related pronucleophiles.
1.2.1. Development and Optimization of Palladium-Catalyzed Allylic Substitution with Diarylmethanes.

Given the perceived challenge to the application of diphenylmethane ($pK_a = 32.2$)\textsuperscript{39} in allylic substitutions, we initiated our studies with the more acidic 2-benzylpyridine (1a, $pK_a = 28.2$)\textsuperscript{38} under the reaction conditions in eq 1. The desired product 3aa was formed in 80% assay yield (Table 1, entry 1). Switching the base to NaN(SiMe$_3$)$_2$ led to 3aa in 99% assay yield (entry 2). The additive NEt$_3$, which proved very useful in eq 1, was not necessary for the Pd-catalyzed allylic substitution with 2-benzylpyridine (entry 3 vs 2). The allylic substitution product formed with 2-benzylpyridine was isolated in 99% yield.

We next sought to increase the $pK_a$ of the pronucleophile. The less acidic 3-benzylpyridine (1c) ($pK_a = 30.1$),\textsuperscript{38} however, led to only 27% assay yield (entry 4). We increased the assay yield of 3ca to 70% by using the more reactive base, KN(SiMe$_3$)$_2$ (entry 5). Unfortunately, further decreasing the acidity of the pronucleophile was challenging: using diphenylmethane (4aa, $pK_a = 32.3$)\textsuperscript{39} gave desired product 5aa in only 10% assay yield (entry 6). We next set out to optimize the reaction conditions for Pd-catalyzed allylic substitution with pronucleophiles with $pK_a$'s $>$30, such as diphenylmethane.
Table 1.1. Preliminary Results of Allylic Substitution Reactions

\[
\text{Ph-} \text{Ar/HetAr} + \text{OBoc} \xrightarrow{\text{5 mol \% Pd(COD)Cl}_2; \text{7.5 mol \% Xantphos; 3 equiv base}} \text{Ph-} \text{Ar/HetAr}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pronucleophiles</th>
<th>Base</th>
<th>Product</th>
<th>Yield(^b) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{d}</td>
<td>[\text{4a} ]</td>
<td>[\text{LiN(SiMe}_3\text{)_2}]</td>
<td>[\text{3aa}]</td>
<td>80</td>
</tr>
<tr>
<td>2\textsuperscript{d}</td>
<td>[\text{1a} ]</td>
<td>[\text{NaN(SiMe}_3\text{)_2}]</td>
<td>[\text{3aa}]</td>
<td>(99(^c))</td>
</tr>
<tr>
<td>3</td>
<td>[\text{1a} ]</td>
<td>[\text{NaN(SiMe}_3\text{)_2}]</td>
<td>[\text{3aa}]</td>
<td>(99(^c))</td>
</tr>
<tr>
<td>4</td>
<td>[\text{1c} ]</td>
<td>[\text{NaN(SiMe}_3\text{)_2}]</td>
<td>[\text{3ca}]</td>
<td>27</td>
</tr>
<tr>
<td>5</td>
<td>[\text{1c} ]</td>
<td>[\text{KN(SiMe}_3\text{)_2}]</td>
<td>[\text{3ca}]</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>[\text{1c} ]</td>
<td>[\text{KN(SiMe}_3\text{)_2}]</td>
<td>[\text{5aa}]</td>
<td>10</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reaction conducted on a 0.1 mmol scale with 1 equiv of pronucleophile and 2 equiv of \(2\text{a}\) at 0.1 M. \textsuperscript{b} Yield determined by \(^1\text{H NMR spectroscopy of the crude reaction mixture.}\textsuperscript{c} Isolated yield after chromatographic purification. \textsuperscript{d} 1 equiv of NEt\textsubscript{3}. 

From the results in Table 1, we hypothesized that the generation of the deprotonated diphenylmethane was problematic, and that choice of base would significantly impact the conversion. Since the traditional protocols preparing allylated diarylmethanes require strong bases (such as \(n\)-BuLi) at low temperature\textsuperscript{36} or under other harsh reaction conditions\textsuperscript{40}, we limited ourselves to
use of KN(SiMe$_3$)$_2$ as the strongest base in this study. We then screened different ethereal solvents (THF, 2-methyl THF, 1,4-dioxane, DME and CPME) and found that DME was the leading solvent of those examined (Table 2, entry 2, see the Supporting Information for details). Another important variable in optimizing Pd-catalyzed allylic substitution with diphenylmethane is the ratio of reagents. We observed decomposition of allyl tert-butyl carbonate 2a during the reaction. Increasing 2a to 3 equiv led to significant improvement in yield (entry 3). In addition, increasing the concentration of base led to higher concentrations of the nucleophile and improved yields (entries 4–5). Under these conditions, the allylic substitution product 5aa was obtained in 95% isolated yield in DME with diphenylmethane 4a as the limiting reagent, 5 equiv of KN(SiMe$_3$)$_2$ and 3 equiv of the allyl electrophile 2a. The yield dropped if the equivalence of 2a (entry 6) or the catalyst loading (entry 7) were decreased. With the optimized conditions in Tables 1 and 2, we examined various benzylic heterocycles and diarylmethanes as pronucleophiles in the allylic substitution.

**Table 1.2. Optimization of Allylic Substitution with Diphenylmethane 4a**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ratio (4a:base:2a)</th>
<th>Solvent</th>
<th>yield$^b$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:3:2</td>
<td>THF</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>1:3:2</td>
<td>DME</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>1:3:3</td>
<td>DME</td>
<td>79</td>
</tr>
<tr>
<td>4</td>
<td>1:4:3</td>
<td>DME</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>1:5:3</td>
<td>DME</td>
<td>(95$^c$)</td>
</tr>
<tr>
<td>6</td>
<td>1:5:2</td>
<td>DME</td>
<td>62</td>
</tr>
<tr>
<td>7$^d$</td>
<td>1:5:3</td>
<td>DME</td>
<td>68</td>
</tr>
</tbody>
</table>
Reaction conducted on a 0.1 mmol scale at 0.1 M. Yield determined by \(^1\)H NMR spectroscopy of the crude reaction mixture. Isolated yield after chromatographic purification. 2.5 mol % Pd(COD)Cl\(_2\)/3.75 mol % Xantphos.

1.2.2. Scope of Heterocyclic Diarylmethanes in Palladium-Catalyzed Allylic Substitution.

Based on the optimization process above, we anticipated that the choice of base would be critical to expand the scope of pronucleophiles and that each substrate class might require reexamination of bases. We first evaluated the scope of heterocyclic diarylmethanes as pronucleophiles in Pd-catalyzed allylic substitution (Table 3). The diarylmethane derivatives containing heterocycles are interesting targets in medicinal chemistry. Our method provides a rapid access to the heteroaryl-containing allylated products in good to excellent yields using 1–5 mol % catalyst loading (80–99% yield). Silylamine bases, MN(SiMe\(_3\))\(_2\) (M = Li, Na, K), were used to accommodate the wide range of pronucleophile \(pK_a\)'s. In general, LiN(SiMe\(_3\))\(_2\) was used for the most acidic pronucleophiles (\(pK_a < 28\)), NaN(SiMe\(_3\))\(_2\) for moderately acidic (\(pK_a = 28–31\)) and KN(SiMe\(_3\))\(_2\) for the least acidic (\(pK_a > 31\)). The 2-, 4- and 3-benzylpyridines underwent allylation in 91–99% yield (Table 3, entries 1–3). Xanthene (1d) derivatives are important components of dyes. Xanthene underwent monoallylation in 82% yield (entry 4). Furan and thiophene derivatives are valuable building blocks in agrochemicals and pharmaceuticals. Under the reaction conditions with KN(SiMe\(_3\))\(_2\) as the base, we observed decomposition of 2-benzylfuran (1e). Under the same reaction conditions with NaN(SiMe\(_3\))\(_2\) as the base, the desired product 3ea was obtained in only 32% yield. Using NaN(SiMe\(_3\))\(_2\), in combination with 15-crown-5 (2.5 equiv), the allylic substitution reaction afforded the
desired product 3ea in 80% yield (entry 5). This result demonstrates that the use of additives, such as crown ethers, are useful in transition metal catalyzed processes other than deprotonative cross-coupling processes. With 2-benzylthiophene (1f) the desired substitution product 3fa was isolated in 93% with NaN(SiMe₃)₂ (entry 6). Di(3-pyridyl)methane (1g) was applied to give 3ga in 85% yield (entry 7). To establish the scalability of this method, the allylation of 3-benzylpyridine (1c) was examined on a 10 mmol scale, affording the allylated product 3ca in 89% yield (eq 2).

![Chemical Reaction](image)

**Table 1.3.** Scope of Heterocyclic Diarylmethanes in the Allylic Substitution

---

Table 1.3. Scope of Heterocyclic Diarylmethanes in the Allylic Substitution

<table>
<thead>
<tr>
<th>Heterocyclic Diarylmethane</th>
<th>Yield</th>
<th>Mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>3ca</td>
<td>89%</td>
<td>1.85 g</td>
</tr>
</tbody>
</table>
HetAr + OBoc → 3equiv Base → 3aa-3ga
1a-g 2a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pronucleophiles</th>
<th>Base</th>
<th>Products</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1c</td>
<td><img src="image1" alt="1a" /></td>
<td>NaN(SiMe₃)₂</td>
<td>3aa</td>
<td>99</td>
</tr>
<tr>
<td>2c</td>
<td><img src="image2" alt="1b" /></td>
<td>LiN(SiMe₃)₂</td>
<td>3ba</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="1c" /></td>
<td>KN(SiMe₃)₂</td>
<td>3ca</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="1d" /></td>
<td>NaN(SiMe₃)₂</td>
<td>3da</td>
<td>82</td>
</tr>
<tr>
<td>5d</td>
<td><img src="image5" alt="1e" /></td>
<td>NaN(SiMe₃)₂</td>
<td>3ea</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6" alt="1f" /></td>
<td>NaN(SiMe₃)₂</td>
<td>3fa</td>
<td>93</td>
</tr>
<tr>
<td>7</td>
<td><img src="image7" alt="1g" /></td>
<td>LiN(SiMe₃)₂</td>
<td>3ga</td>
<td>85</td>
</tr>
</tbody>
</table>

*aReaction conducted on a 0.1 mmol scale with 1 equiv of 1 and 2 equiv of 2a at 0.1 M. bIsolated yield after chromatographic purification. c1 mol % Pd(COD)Cl₂, 1.5 mol % Xantphos. d2.5 equiv of NaN(SiMe₃)₂ and 2.5 equiv of 15-crown-5.*
1.2.3. Scope of Diphenylmethane Derivatives in the Allylic Substitution

Diphenylmethane derivatives are more challenging pronucleophiles due to their higher pKₐ’s.³⁹ To compensate for the less favorable equilibrium for deprotonation of these pronucleophiles, the amount of base was increased to 5 equiv. With the optimized reaction conditions for 4a (Table 4, entry 1), we investigated 4-halogenated diphenylmethanes (entries 2–4). Compounds containing fluorine are important because of their bioactivities and uses in material science.⁴⁷ The reaction with 4-fluoro diphenylmethane (4b) as pronucleophile afforded the desired product 5ba in 84% yield (entry 2). We then applied our reaction conditions to 4-bromo and 4-chloro diphenylmethanes (4c and 4d). A potential problem with these substrates lies in the competing oxidative addition of C–X (X = Cl, Br) bonds to the active Pd(0) species. We were pleased to find that Pd-catalyzed allylic substitution afforded the allylated products 5ca and 5da in 95% and 73% yield, respectively (entries 3 and 4). These results suggest that generation of the π-allyl palladium intermediate is significantly faster than the oxidative addition of C–X bonds to the Pd(0) species under our reaction conditions. Fluorene (4e) derivatives have interesting characteristics and can be used in organic light-emitting diodes.⁴⁴ By using 1.5 equiv LiN(SiMe₃)₂ and 1.1 equiv of 2a, 5ea was generated in 87% yield (entry 5). 4-Cyano diphenylmethane (4fa) is potentially problematic because benzonitriles are known to undergo additions with strong bases and organometallic reagents.⁴⁸ Nonetheless, this substrate provided the product 5fa in 90% yield (entry 6). As might be anticipated, pronucleophiles with electron donating groups are less acidic and, therefore, more difficult to deprotonate. We
found that 4-methyl diphenylmethane 4g underwent substitution to give 5ga in 68% yield at 50 °C (entry 7). Notably, 2-methyl diphenylmethane (4h) reacted to provide 5ha in 70% yield at 50 °C (entry 8). Unfortunately, 4-methoxy diphenylmethane did not react under these, or a variety of other conditions.

Table 1.4. Scope of Diphenylmethane Derivatives in Allylic Substitution Reactions
<table>
<thead>
<tr>
<th>Entry</th>
<th>Pronucleophiles</th>
<th>Products</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Image of pronucleophile 1" /></td>
<td><img src="image2" alt="Image of product 1" /></td>
<td>5aa 95</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Image of pronucleophile 2" /></td>
<td><img src="image4" alt="Image of product 2" /></td>
<td>5ba 84</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Image of pronucleophile 3" /></td>
<td><img src="image6" alt="Image of product 3" /></td>
<td>5ca 95</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Image of pronucleophile 4" /></td>
<td><img src="image8" alt="Image of product 4" /></td>
<td>5da 73</td>
</tr>
<tr>
<td>5&lt;sup&gt;c&lt;/sup&gt;</td>
<td><img src="image9" alt="Image of pronucleophile 5" /></td>
<td><img src="image10" alt="Image of product 5" /></td>
<td>5ea 87</td>
</tr>
<tr>
<td>6&lt;sup&gt;d&lt;/sup&gt;</td>
<td><img src="image11" alt="Image of pronucleophile 6" /></td>
<td><img src="image12" alt="Image of product 6" /></td>
<td>5fa 90</td>
</tr>
<tr>
<td>7&lt;sup&gt;e&lt;/sup&gt;,&lt;sup&gt;g&lt;/sup&gt;</td>
<td><img src="image13" alt="Image of pronucleophile 7" /></td>
<td><img src="image14" alt="Image of product 7" /></td>
<td>5ga 68</td>
</tr>
<tr>
<td>8&lt;sup&gt;e&lt;/sup&gt;,&lt;sup&gt;g&lt;/sup&gt;</td>
<td><img src="image15" alt="Image of pronucleophile 8" /></td>
<td><img src="image16" alt="Image of product 8" /></td>
<td>5ha 70</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reaction conducted on a 0.1 mmol scale with 1 equiv of 4 and 3 equiv of 2a at 0.1 M.  
<sup>b</sup>Isolated yield after chromatographic purification.  
<sup>c</sup>1.5 equiv of LiN(SiMe<sub>3</sub>)<sub>2</sub> and 1.1 equiv of 2a.  
<sup>d</sup>1.5 equiv of KN(SiMe<sub>3</sub>)<sub>2</sub> and 2 equiv of 2a.  
<sup>e</sup>8 equiv of KN(SiMe<sub>3</sub>)<sub>2</sub>.  
<sup>f</sup>10 equiv of KN(SiMe<sub>3</sub>)<sub>2</sub>.  
<sup>g</sup>Reaction conducted at 50 °C.
1.2.4. Dialylation with Heteroaryl Diarylmethanes

Having demonstrated the monoallylation of diarylmethanes and heteroaryl-containing derivatives, we next explored the possibility of adding a second allyl group to the allylated products prepared above. We were encouraged by the formation of small amounts of diallylation products with more acidic pronucleophiles ($pK_a < 30$) in the monoallylation optimization process. We, therefore, reoptimized the conditions to enable allylation of the purified monoallylated products. By employing 5 equiv of $KN(SiMe_3)_2$ and 3 equiv of $2a$ with the monoallylated substrates ($3aa$–$3ga$, Table 3), we obtained the corresponding diallylation products ($6aa$–$6ga$, 70–95% yield). These results indicate that the allylation chemistry outlined here can be used to establish quaternary centers.

A more efficient method to prepare the diallylated products would be from the diarylmethane derivatives. We, therefore, set out to develop a one-pot diallylation protocol. We rationalized that the conditions mentioned above for the allylation of the mono-allylated diarylmethanes would be suitable for the one-pot diallylation. This approach proved fruitful: the yields for the double allylation ranged from 65 to 85% (Table 5, entries 1–5). The one-pot syntheses were not efficient for 2-benzylpyridine (1a) and 3-benzylpyridine (1c) as pronucleophiles, because the deprotonation events are more difficult for these substrates. Nonetheless, starting from monoallylation products $3aa$ and $3ca$ we obtained the bis-allylated products $6aa$ and $6ca$ in 84 and 80% yield (entries 6–7). We were also able to use 1,1-diarylethane (e.g., 8a) as pronucleophile to install an allyl group to afford a quaternary stereocenter (entry 8). Notably, triphenylmethane (9a) was used as pronucleophile to give the sterically
congested 9aa in 90% yield (entry 9). To summarize, our method afforded diaryl- or triarylmethane products containing at least one allyl group on the quaternary carbon. Some of the products in Table 5 could presumably be employed in ring-closing metathesis reactions\textsuperscript{49} to prepare 1,1-diarylcyclopent-3-ene or Pauson-Khand type [2+2+1] reactions\textsuperscript{50} to afford bicyclic scaffolds.

**Table 1.5.** Dialylation with Diarylmethanes\textsuperscript{a}
<table>
<thead>
<tr>
<th>Entry</th>
<th>Pronucleophiles</th>
<th>Products</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 c, d</td>
<td>1b</td>
<td>6ba</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>1d</td>
<td>6da</td>
<td>65</td>
</tr>
<tr>
<td>3e</td>
<td>4e</td>
<td>7ea</td>
<td>85</td>
</tr>
<tr>
<td>4f</td>
<td>1f</td>
<td>6fa</td>
<td>70</td>
</tr>
<tr>
<td>5e</td>
<td>3aa</td>
<td>6aa</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
<td>3ca</td>
<td>6ca</td>
<td>80</td>
</tr>
<tr>
<td>7</td>
<td>8a</td>
<td>8aa</td>
<td>90</td>
</tr>
<tr>
<td>8</td>
<td>9a</td>
<td>9aa</td>
<td>90</td>
</tr>
</tbody>
</table>

*a* Reaction conducted on a 0.1 mmol scale with 1 equiv of pronucleophile and 3 equiv of 2a at 0.1 M. *b* Isolated yield after chromatographic purification. *c* Reaction conducted at 0.066 M. *d* Reaction conducted at 50 °C. *e* 3 equiv of KN(SiMe₃)₂ and 2 equiv of 2a. *f* 8 equiv of KN(SiMe₃)₂.
1.2.5. Scope of Electrophiles in Palladium-Catalyzed Allylic Substitutions

Having demonstrated that the simplest allyl electrophile can be used with a variety of pronucleophiles, we turned our attention to the nature of the electrophilic partner. We chose the more acidic pronucleophile di(3-pyridyl)methane (1g, Table 3, entry 7) and examined the influence of different leaving groups on Pd-catalyzed allylic substitution with cyclohexenyl electrophiles (2b, 2c). Both the Boc (2b) and benzoate ester (2c) derivatives gave similar yields of 10a (89 and 90% yield, entries 1–2). Changing the ring size of the electrophile from six to five (2d) resulted in 90% yield (entry 3) when the Boc analogue was used. The classic 1,3-diphenyl allyl precursor 2e afforded the allylic substitution product 10c in 87% yield with a 10:1 trans:cis ratio (entry 4).

Next, the less acidic diphenylmethane (4a) was employed as pronucleophile (entries 5–7). The Boc derived cyclohexenyl substrate 2b underwent reaction leading to the product in 85% yield (entry 5). In contrast, the benzoate derivative 2c resulted in only 20% yield (entry 6). The low yield is likely due to attack of nucleophile on the ester carbonyl. Changing the benzoate ester 2c to the pivalate ester 2f resulted in an increase in the yield to 70% (entry 7). Cyclopentenyl OBoc electrophile 2d underwent substitution in the presence of diphenylmethane in 94% yield (entry 8).

Many electrophilic partners used in allylic substitution reactions lead to unsymmetrical h3-allyl groups. We, therefore, examined the regioselectivity with unsymmetrical linear Boc-protected electrophiles such as cinnamyl alcohol (2g),
geranyl alcohol (2h) and prenyl alcohol (2i) (Table 6, entries 9–11). It is well known that \( \pi \)-allyl palladium complexes are prone to react with carbon nucleophiles at the less substituted terminus of the \( \pi \)-allyl.\textsuperscript{51} For the Pd-catalyzed allylic substitution with Boc-protected cinnamyl alcohol (2g), the linear product 10f was the major product, albeit with moderate regioselectivity (2.6:1, entry 9). The reduced regioselectivity in this case, relative to cases with less basic nucleophiles,\textsuperscript{27} is likely a manifestation of the high reactivity of the 4-benzylpyridine-derived nucleophile. Interestingly, the prenylation and geranylation exhibited opposite regioselectivities (entries 10–11). The Boc activated geranyl underwent reaction with 4-benzylpyridine slightly favoring the terminal substitution product (1.9:1.0, linear:branched). In contrast, the prenylation afforded the branched product 10h' with a linear:branched ratio of 1.0:4.5 (entry 11). We hypothesize that the origin of the regioselectivity in the prenylation is a result of the non-bonded interaction between the bulky, wide-bite angle Xantphos ligand and the more substituted carbon of the \( h^3 \)-allyl. This interaction places a larger \( d^+ \) partial change on the more substituted terminus and, therefore, nucleophilic attack at this position prevails. The additional substituent (=R) on the \( h^3 \)-allyl in the geranylation causes this group to adopt a conformation positioning it anti to the bulky (Xantphos)Pd center (Figure 2). The substituent partially obstructs the nucleophilic attack at the more substituted terminus, resulting in a shift of the regioselectivity toward the less substituted carbon of the allyl.
Figure 1.2. Proposed conformational model to explain the reversal in regioselectivity between the prenylation and geranylation (Table 2, entries 10–11). When R=H nucleophilic attack is favored at the more substituted terminus (solid arrow). When R=alkyl, attack follows the dashed arrow leading to the linear product.

Table 1.6. Scope of Electrophiles in Allylic Substitution Reactions

\[ \text{Prenylation, } R = H \]
\[ \text{Geranylation, } R = \text{CH}_2 = \text{CH}_2 \]
Entry | Electrophiles | Pronucleophiles | Products | Yield$^a$ (%) |
--- | --- | --- | --- | --- |
1$^c$ | PGO | 2b | 1g | 10a | 89 |
2$^c$ | PG = Boc | 2c | 1g | 10b | 90 |
3$^d$ | BocO | 2d | 1g | 10b | 90 |
4$^e$ | OBoc | 2e | 1g | 10c | 87 |
5$^f$ | PG = Boc | 2b | 4a | 10d | 85 |
6$^f$ | PG = Bz | 2c | 4a | 10d | 20 |
7$^f$ | PG = Piv | 2f | 4a | 10d | 70 |
8$^f$ | BocO | 2d | 4a | 10e | 94 |
9$^g, h$ | BocO | 2g | 1b | 10f | 91 |
10$^g, h$ | 2h | 1b | 10g | 88 |
11$^g, h$ | 2i | 1b | 10h | 93 |

$^a$ Yield$^a$ (%) 

Base: DME, 24 °C, 12 h

5 mol % Pd(COD)Cl$_2$
7.5 mol % Xantphos

89 (trans: cis = 10:1)$^i$

85

20

70

94

91 (L:B=2.6:1)$^j$

88 (L:B=1.9:1)$^j$

93 (L:B=1.4:5)$^j$
\(^a\) Reaction conducted on a 0.1 mmol scale at 0.1 M. \(^b\) Isolated yield after chromatographic purification. \(^c\) 3 equiv of Na(NMe\(_3\))\(_2\) and 2 equiv of \(2\). \(^d\) 3 equiv of KN(SiMe\(_3\))\(_2\) and 2 equiv of \(2\). \(^e\) 3 equiv of Li(NMe\(_3\))\(_2\) and 2 equiv of \(2\). \(^f\) 5 equiv of KN(SiMe\(_3\))\(_2\) and 3 equiv of \(2\). \(^g\) Reaction conducted at 50 °C. \(^h\) Reaction conducted at 0 °C. \(^i\) Ratio of trans:cis or linear:branched (L:B) determined by \(^1\)H NMR.

### 1.2.6. Internal vs. External Attack of Diarylmethane on \(\pi\)-Allyl Palladium Intermediate

As outlined in the Introduction, nucleophiles in allylic substitutions can directly add to the \(\pi\)-allyl or to the metal in their reactions with \([(\eta^3\text{-allyl})ML_n]^+\) intermediates. It is generally accepted that nucleophiles with conjugate acids of \(pK_a < 25\), classified as “soft” nucleophiles, undergo external attack on \(\pi\)-allyl palladium complexes. Soft nucleophiles, therefore, result in stereoretentive allylic substitutions reactions (via double inversion).\(^{52}\) On the other hand, “hard” nucleophiles, those with \(pK_a > 25\) are proposed undergo attack on the metal center of the \(\pi\)-allyl palladium complexes (i.e., transmetallation) followed by reductive elimination to afford net inversion for the allylic substitution.\(^{53}\)

To examine the mechanistic pathway of the reaction, di(3-pyridyl)methane (1g) was reacted with cis-disubstituted stereoprobe \(2j\) (Scheme 2A) and afforded cis-product 11a in 90% isolated yield as a single diastereomer (determined by \(^1\)H NMR spectroscopy). Reaction of the less acidic pronucleophile diphenylmethane (4a) (\(pK_a = 32.3\)) with \(2j\) (Scheme 2B) similarly furnished the cis-product 11b as a single diastereomer (determined by \(^1\)H NMR spectroscopy and single crystal X-ray diffraction) in 88% yield. The results
indicated both nucleophiles derived from di(3-pyridyl)methane (1g) and diphenylmethane (4a) behave as “soft” nucleophiles and that the pK_a limit for “soft” nucleophiles should be raised from 25 to 32, a change of 7 orders of magnitude.

**Scheme 1.2.** Allylic Substitution with Retention of Configuration

A. Pd-catalyzed allylic substitution of 1g with 2j

B. Pd-catalyzed allylic substitution of 4a with 2j

1.3. SUMMARY AND OUTLOOK

Herein we have developed a general method for Pd-catalyzed allylic substitution with diarylmethane derivatives at room temperature. The synthetic significance of the method is that it provides a rapid access to products containing allylated diarylmethanyl motifs. The method is general for a wide range of nucleophiles derived diarylmethanes and heteroaryl derivatives. A tandem procedure for the Pd-catalyzed allylic substitutions to afford diallylation products with quaternary centers is also described. With alkylated diarylmethanes and triarylmethanes, the method is also efficient to afford the corresponding allylated products. We anticipate that the described method will
be a valuable complement to the existing arsenal of nucleophiles in Pd-catalyzed allylic substitutions. Mechanistic studies show that diarylmethane derivatives behave as “soft” or stabilized nucleophiles. The nucleophile derived from diphenylmethane undergoes external attack on $\pi$-allyl palladium species under our reaction conditions. The results of this study indicate that the cutoff between “soft” and “hard” nucleophiles should be raised from a $pK_a$ of 25 to at least 32.

1.4. EXPERIMENTAL SECTION

General Methods. All reactions were performed under nitrogen using oven-dried glassware and standard Schlenk or vacuum line techniques. Air- and moisture-sensitive solutions were handled under nitrogen and transferred via syringe. The solvents (DME and THF) were sparged for 20 min with dry $N_2$ and dried using a commercial two-column solvent purification system comprising columns packed with neutral alumina. Unless otherwise stated, reagents were commercially available and used as purchased without further purification. Chemicals were obtained from Sigma-Aldrich, Acros, TCI America, Strem Chemicals or Matrix Scientific, and solvents were purchased from Fisher Scientific. The progress of the reactions was monitored by thin-layer chromatography using Whatman Partisil K6F 250 μm precoated 60 Å silica gel plates and visualized by short-wavelength ultraviolet light as well as by treatment potassium permanganate ($\text{KMnO}_4$) stain or iodine. Silica gel (230–400 mesh, Silicycle) was used for flash chromatography. The $^1$H NMR and $^{13}$C{$^1$H} NMR spectra were obtained using a Brüker AM-500 Fourier transform NMR spectrometer at 500 and 126 MHz, respectively. Chemical shifts are reported in
units of parts per million (ppm) downfield from tetramethylsilane (TMS), and all coupling constants are reported in hertz. The infrared spectra were obtained with KBr plates using a Perkin-Elmer Spectrum 100 Series FTIR spectrometer. High-resolution mass spectrometry (HRMS) data were obtained on a Waters LC–TOF mass spectrometer (model LCT-XE Premier) using chemical ionization (CI) or electrospray ionization (ESI) in positive or negative mode, depending on the analyte. Melting points were determined on a Unimelt Thomas-Hoover melting point apparatus and are uncorrected.

**General Procedure A: Palladium-Catalyzed Allylic Substitution with Heterocyclic Diarylmethanes Under Room Temperature.** An oven-dried 10 mL reaction vial equipped with a stir bar was charged with NaN(SiMe\(_3\))\(_2\) (55 mg, 0.30 mmol, 3 equiv) under a nitrogen atmosphere. A solution (from a stock solution) of Pd(COD)Cl\(_2\) (1.43 mg, 0.0050 mmol) and Xantphos (4.34 mg, 0.0075 mmol) in 1 mL of dry DME was taken up by syringe and added to the reaction vial. After stirring for 5 min at 24 °C, 2-benzylpyridine 1a (16 \(\mu\)L, 0.1 mmol, 1 equiv) was added to the reaction mixture followed by 2a (34 \(\mu\)L, 0.2 mmol, 2 equiv). Note that the diarylmethanes or allyl-OBoc in a solid form was added to the reaction vial prior to NaN(SiMe\(_3\))\(_2\). The reaction mixture was stirred for 12 h at 24 °C, quenched with two drops of H\(_2\)O, diluted with 3 mL of ethyl acetate and filtered over a pad of MgSO\(_4\) and silica. The pad was rinsed with additional ethyl acetate, and the solution was concentrated *in vacuo*. The crude material was loaded onto a silica gel column and purified by flash chromatography eluting with EtOAc/hexanes.
General Procedure B: Palladium-Catalyzed Allylic Substitution with Heterocyclic Diarylmethanes Under 50 °C. An oven-dried 10 mL reaction vial equipped with a stir bar was charged with KN(SiMe₃)₂ (160 mg, 0.80 mmol, 8 equiv) under a nitrogen atmosphere. A solution (from a stock solution) of Pd(COD)Cl₂ (1.43 mg, 0.0050 mmol) and Xantphos (4.34 mg, 0.0075 mmol) in 1 mL of dry DME was taken up by syringe and added to the reaction vial. After stirring for 5 min at 24 °C, 4-methyl diphenylmethane 4g (18.5 μL, 0.1 mmol, 1 equiv) was added to the reaction mixture followed by 2a (51 μL, 0.3 mmol, 3 equiv). The reaction mixture was stirred for 12 h at 50 °C, quenched with two drops of H₂O, diluted with 3 mL of ethyl acetate, and filtered over a pad of MgSO₄ and silica. The pad was rinsed with additional ethyl acetate and the solution was concentrated in vacuo. The crude material was loaded onto a silica gel column and purified by flash chromatography eluting with EtOAc/hexanes.

General Procedure C: Palladium-Catalyzed Allylic Substitution with Heterocyclic Diarylmethanes Under 0 °C. An oven-dried 10 mL reaction vial equipped with a stir bar was charged with LiN(SiMe₃)₂ (51 mg, 0.30 mmol, 3 equiv) under a nitrogen atmosphere. A solution (from a stock solution) of Pd(COD)Cl₂ (1.43 mg, 0.0050 mmol) and Xantphos (4.34 mg, 0.0075 mmol) in 1 mL of dry DME was taken up by syringe and added to the reaction vial. After stirring for 5 min at 0 °C, 4-benzylpyridine 1b (16 μL, 0.1 mmol, 1 equiv) was added to the reaction mixture followed by Boc-protected cinnamyl alcohol 2g (46 μL, 0.2 mmol, 2 equiv). The reaction mixture was stirred for 12 h at 0 °C, quenched with two drops of H₂O, diluted with 3 mL of ethyl acetate, and filtered over a pad of MgSO₄ and silica. The pad was rinsed with additional ethyl acetate
and the solution was concentrated in vacuo. The crude material was loaded onto a silica gel column and purified by flash chromatography eluting with EtOAc/hexanes

**Preparation of Diarylmethanes.**

Compounds 1e, 1f, 1g, 4f, 8a were prepared according to literature procedures.

**Preparation of Allylic Electrophiles.**

Compounds 2a, 2b, 2c, 2d, 2e, 2f, 2g, 2h, 2i, and 2j were prepared according to literature procedures.

2-(1-phenylbut-3-en-1-yl)pyridine (1.3aa): The reaction was performed following General Procedure A with 1a (16 µL, 0.1 mmol), NaN(SiMe₃)₂ (55 mg, 0.30 mmol) and 2a (34 µL, 0.2 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 10:90) to give the product (21 mg, 99% yield) as a yellow oil. Rf = 0.30 (EtOAc:hexanes = 10:90); ¹H NMR (500 MHz, CDCl₃): δ 8.57 (dt, J = 4.8, 0.9 Hz, 1H), 7.54 (td, J = 7.7, 1.8 Hz, 1H), 7.34-7.06 (m, 7H), 5.73 (dd, J = 17.1, 10.2 Hz, 1H), 5.04-4.91 (m, 2H), 4.15 (t, J = 7.8 Hz, 1H), 3.06-2.82 (m, 2H) ppm; ¹³C {¹H} NMR (126 MHz, CDCl₃): δ 163.5, 149.5, 143.5, 136.9, 136.5, 128.7, 128.3, 126.7, 123.1, 121.5, 116.5, 53.8, 39.4 ppm; IR (thin film): 3063, 3025, 3005, 2975, 2917, 1639, 1589, 1568, 1493, 1471, 1432, 994, 913, 800, 746, 699 cm⁻¹; HRMS calc’d for C₁₅H₁₆N⁺ 210.1283, observed 210.1287 [MH]⁺.

4-(1-phenylbut-3-en-1-yl)pyridine (1.3ba): The reaction was performed following General Procedure A with 1b (16 µL, 0.1 mmol),
LiN(SiMe$_3$)$_2$ (51 mg, 0.30 mmol) and 2a (34 μL, 0.2 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 30:70) to give the product (21 mg, 99% yield) as a yellow oil. R$_f$ = 0.30 (EtOAc:hexanes = 40:60); $^1$H NMR (500 MHz, CDCl$_3$): δ 8.47 (dd, J = 4.5, 1.6 Hz, 2H), 7.30-7.12 (m, 7H), 5.67 (d, J = 6.8 Hz, 1H), 5.04-4.95 (m, 2H), 3.97 (t, J = 7.9 Hz, 1H), 2.79 (ddd, J = 7.9, 6.7, 1.2 Hz, 2H) ppm; $^{13}$C {$^1$H} NMR (126 MHz, CDCl$_3$): δ 153.2, 149.8, 142.5, 135.7, 128.6, 127.9, 126.7, 123.2, 117.0, 50.5, 39.1 ppm; IR (thin film): 3064, 3026, 2977, 2925, 1640, 1595, 1557, 1494, 1452, 1413, 994, 916, 813, 746, 700 cm$^{-1}$; HRMS calc'd for C$_{15}$H$_{16}$N$^+$ 210.1283, observed 210.1292 [MH]$^+$. 

3-((1-phenylbut-3-en-1-yl)pyridine (1.3ca): The reaction was performed following General Procedure A with 1c (17 mg, 0.1 mmol), KN(SiMe$_3$)$_2$ (60 mg, 0.30 mmol) and 2a (34 μL, 0.2 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 30:70) to give the product (19 mg, 91% yield) as a yellow oil. R$_f$ = 0.40 (EtOAc:hexanes = 40:60); $^1$H NMR (500 MHz, CDCl$_3$): δ 8.50 (d, J = 2.3 Hz, 1H), 8.40 (dd, J = 4.8, 1.6 Hz, 1H), 7.48 (dt, J = 7.9, 2.0 Hz, 1H), 7.48 (dt, J = 7.9, 2.0 Hz, 1H), 7.28-7.15 (m, 6H), 5.67 (ddt, J = 17.1, 10.2, 6.8 Hz, 1H), 5.03-4.93 (m, 2H), 4.00 (t, J = 7.9 Hz, 1H), 2.86-2.74 (m, 2H) ppm; $^{13}$C {$^1$H} NMR (126 MHz, CDCl$_3$): δ 149.7, 147.7, 143.3, 139.8, 136.0, 135.3, 128.7, 127.9, 126.6, 123.4, 117.0, 48.8, 39.6 ppm; IR (thin film): 3061, 3027, 2977, 2925, 1640, 1601, 1574, 1494, 1478, 1452, 1423, 1025, 994, 916, 813, 750, 714, 700 cm$^{-1}$; HRMS calc'd for C$_{15}$H$_{16}$N$^+$ 210.1283, observed 210.1292 [MH]$^+$. 

9-allyl-9H-xanthene (1.3da): The reaction was performed following General Procedure A with 1d (18.2 mg, 0.1 mmol),
NaN(SiMe$_3$)$_2$ (55 mg, 0.30 mmol) and 2a (34 µL, 0.2 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (18 mg, 82% yield) as a colorless oil. $R_f = 0.25$ (hexanes); The NMR spectral data match the previously published data.$^67$

2-(1-phenylbut-3-en-1-yl)furan (1.3ea): The reaction was performed following General Procedure A with 1e (15 µL, 0.1 mmol), NaN(SiMe$_3$)$_2$ (45 mg, 0.25 mmol), 15-Crown-5 (50 µL, 0.25 mmol) and 2a (34 µL, 0.2 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (15.8 mg, 80% yield) as a colorless oil. $R_f = 0.25$ (hexanes); The NMR spectral data match the previously published data.$^68$

2-(1-phenylbut-3-en-1-yl)thiophene (1.3fa): The reaction was performed following General Procedure A with 1f (16 µL, 0.1 mmol), NaN(SiMe$_3$)$_2$ (55 mg, 0.30 mmol) and 2a (34 µL, 0.2 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (20 mg, 93% yield) as a colorless oil. $R_f = 0.20$ (hexanes); The NMR spectral data match the previously published data.$^69$

3,3’-(but-3-ene-1,1-diyl)dipyridine (1.3ga): The reaction was performed following General Procedure A with 1g (17 mg, 0.1 mmol), LiN(SiMe$_3$)$_2$ (51 mg, 0.30 mmol) and 2a (34 µL, 0.2 mmol). The crude material was purified by flash chromatography on silica gel (eluted with MeOH:DCM = 2.5:97.5) to give the product (18 mg, 85% yield) as a yellow oil. $R_f = 0.30$ (MeOH:DCM = 2.5:97.5); $^1$H NMR (500 MHz, CDCl$_3$): δ 8.54-8.44 (m, 4H), 7.49 (dt, J = 7.9, 1.8 Hz, 2H), 7.24-7.20 (m, 2H), 5.69-5.61 (m, 1H), 5.03-4.97 (m, 2H), 4.04
(dd, J = 10.1, 5.7 Hz, 1H), 2.81 (t, J = 7.3 Hz, 2H) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$): δ 149.5, 148.1, 138.5, 135.14, 135.02, 123.5, 117.7, 46.2, 39.2.; IR (thin film): 3078, 3032, 3001, 2978, 2852, 1641, 1589, 1575, 1479, 1423, 1178, 1132, 1047, 1025, 994, 917, 803, 775, 715 cm$^{-1}$; HRMS calc’d for C$_{14}$H$_{15}$ N$_2$ + 211.1235, observed 211.1238 [MH]$^+$

**but-3-ene-1,1-diyl dibenzene (1.5aa):** The reaction was performed following General Procedure A with 4a (17 μL, 0.1 mmol), KN(SiMe$_3$)$_2$ (100 mg, 0.50 mmol) and 2a (51 μL, 0.3 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (20 mg, 95% yield) as a colorless oil. R$_f$ = 0.25 (hexanes); The NMR spectral data match the previously published data.$^{70}$

**1-fluoro-4-(1-phenylbut-3-en-1-yl)benzene (1.5ba):** The reaction was performed following General Procedure A with 4b (17 μL, 0.1 mmol), KN(SiMe$_3$)$_2$ (100 mg, 0.50 mmol) and 2a (51 μL, 0.3 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (19 mg, 84% yield) as a colorless oil. R$_f$ = 0.25 (hexanes); $^1$H NMR (500 MHz, CDCl$_3$): δ 7.29-7.16 (m, 9H), 6.97-6.89 (m, 2H), 5.69 (dd, J = 17.1, 10.2 Hz, 1H), 5.03-4.93 (m, 2H), 3.98 (t, J = 7.8 Hz, 1H), 2.80-2.76 (m, 2H) ppm; $^{13}$C $^1$H NMR (126 MHz, CDCl$_3$): δ 161.3 (J = 244 Hz), 144.3, 140.1 (J = 3.4 Hz), 136.5, 129.26 (J = 7.6 Hz), 128.4, 127.8, 126.3, 116.4, 115.09 (J = 21.3 Hz), 50.4, 40.0 ppm; IR (thin film): 3063, 3027, 3003, 2977, 2924, 2850, 1640, 1603, 1508, 1494, 994, 915, 833, 771, 698 cm$^{-1}$; HRMS calc’d for C$_{16}$H$_{16}$F + 227.1236, observed 227.1232 [MH]$^+$.
1-chloro-4-(1-phenylbut-3-en-1-yl)benzene (1.5ca): The reaction was performed following General Procedure A with 4c (18 μL, 0.1 mmol), KN(SiMe$_3$)$_2$ (100 mg, 0.50 mmol) and 2a (51 μL, 0.3 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (23 mg, 95% yield) as a colorless oil. $R_f = 0.25$ (hexanes); The NMR spectral data match the previously published data.$^{70}$

1-bromo-4-(1-phenylbut-3-en-1-yl)benzene (1.5da): The reaction was performed following General Procedure A with 4d (18.5 μL, 0.1 mmol), KN(SiMe$_3$)$_2$ (100 mg, 0.50 mmol) and 2a (51 μL, 0.3 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (21 mg, 73% yield) as a colorless oil. $R_f = 0.25$ (hexanes); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.42-7.10 (m, 9H), 5.71 (ddt, $J = 17.1, 10.2, 6.8$ Hz, 1H), 5.06-4.96 (m, 2H), 3.99 (t, $J = 7.9$ Hz, 1H), 2.82-2.78 (m, 2H) ppm; $^{13}$C {$^1$H} NMR (126 MHz, CDCl$_3$): $\delta$ 143.9, 143.5, 136.4, 131.5, 129.8, 128.5, 127.9, 126.4, 120.0, 116.7, 50.7, 39.8 ppm; IR (thin film): 3076, 3062, 3025, 3002, 2976, 2924, 2850, 1640, 1599, 1487, 1451, 1402, 1114, 1073, 1009, 915, 815, 747, 699 cm$^{-1}$; HRMS calc’d for C$_{13}$H$_{10}$Br$^+$ 246.0044, observed 246.0163 [M-C$_3$H$_5$]$^+$.)

9-allyl-9H-fluorene (1.5ea): The reaction was performed following General Procedure A with 4e (16.7 mg, 0.1 mmol), LiN(SiMe$_3$)$_2$ (25 mg, 0.15 mmol) and 2a (19 μL, 0.11 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (18 mg, 87% yield) as a colorless oil. $R_f = 0.20$ (hexanes); The NMR spectral data match the previously published data.$^{71}$
4-(1-phenylbut-3-en-1-yl)benzonitrile (1.5fa): The reaction was performed following General Procedure A with 4f (19 mg, 0.1 mmol), KN(SiMe₃)₂ (30 mg, 0.15 mmol) and 2a (34 μL, 0.2 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 5:95) to give the product (21 mg, 90% yield) as a colorless oil. Rₖ = 0.25 (EtOAc:hexanes = 5:95); ¹H NMR (500 MHz, CDCl₃): δ 7.59-7.58 (m, 2H), 7.37-7.22 (m, 7H), 5.73-5.66 (m, 1H), 5.08-4.99 (m, 2H), 4.09 (t, J = 7.9 Hz, 1H), 2.88-2.80 (m, 2H) ppm; ¹³C {¹H} NMR (126 MHz, CDCl₃): δ 150.0, 142.9, 135.7, 132.2, 128.75, 128.67, 127.8, 126.7, 118.9, 117.1, 110.0, 51.1, 39.4 ppm; IR (thin film): 3063, 3027, 3003, 2977, 2925, 2227, 1641, 1605, 1502, 1492, 1451, 1414, 1020, 994, 916, 862, 826, 765, 730, 700 cm⁻¹; HRMS calc'd for C₁₇H₁₅NNa⁺ 256.1102, observed 256.1111 [M+Na]⁺.

1-methyl-4-(1-phenylbut-3-en-1-yl)benzene (1.5ga): The reaction was performed following General Procedure B with 4g (18.5 μL, 0.1 mmol), KN(SiMe₃)₂ (160 mg, 0.8 mmol) and 2a (51 μL, 0.3 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (15 mg, 68% yield) as a colorless oil. Rₖ = 0.20 (hexanes); The NMR spectral data match the previously published data.⁷⁰

1-methyl-2-(1-phenylbut-3-en-1-yl)benzene (1.5ha): The reaction was performed following General Procedure B with 4h (18.5 μL, 0.1 mmol), KN(SiMe₃)₂ (200 mg, 1.0 mmol) and 2a (51 μL, 0.3 mmol). The crude material was purified by flash chromatography on
silica gel (eluted with hexanes) to give the product (15.5 mg, 70% yield) as a colorless oil. \( R_f = 0.20 \) (hexanes); The NMR spectral data match the previously published data.\(^72\)

4-(4-phenylhepta-1,6-dien-4-yl)pyridine (1.6ba): The reaction was performed following General Procedure B with 1b (16 \( \mu \)L, 0.1 mmol), KN(SiMe\(_3\))\(_2\) (100 mg, 0.5 mmol) and 2a (51 \( \mu \)L, 0.3 mmol) at 0.066 M. The crude material was purified by flash chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 40:60) to give the product (21 mg, 85% yield) as a colorless oil. \( R_f = 0.25 \) (EtOAc:hexanes = 40:60); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 8.47 (dd, \( J = 4.9, 1.2 \) Hz, 2H), 7.28-7.05 (m, 7H), 5.32-5.27 (m, 2H), 5.00-4.95 (m, 4H), 2.83 (dd, \( J = 6.7, 3.4 \) Hz, 4H) ppm; \(^{13}\)C \({^1}\)H NMR (126 MHz, CDCl\(_3\)): \( \delta \) 156.9, 149.4, 145.9, 133.4, 128.1, 127.7, 126.3, 123.2, 118.6, 48.8, 41.3 ppm; IR (thin film): 3074, 3024, 2978, 2931, 2853, 1638, 1594, 1551, 1494, 1445, 1411, 996, 916, 819, 773, 749, 700, 664 cm\(^{-1}\); HRMS calc’d for C\(_{18}\)H\(_{20}\)N\(^+\) 250.1595, observed 250.1595 [MH]\(^+\).

9,9-diallyl-9H-xanthene (1.6da): The reaction was performed following General Procedure A with 1b (18.2 mg, 0.1 mmol), KN(SiMe\(_3\))\(_2\) (100 mg, 0.5 mmol) and 2a (51 \( \mu \)L, 0.3 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (17 mg, 65% yield) as a colorless oil. \( R_f = 0.25 \) (hexanes); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 7.32-6.98 (m, 9H), 5.39-5.34 (m, 2H), 4.80-4.76 (m, 4H), 2.74 (dd, \( J = 8.1, 1.0 \) Hz, 4H) ppm; \(^{13}\)C \({^1}\)H NMR (126 MHz, CDCl\(_3\)): \( \delta \) 151.7, 134.0, 127.5, 126.8, 124.7, 122.9, 117.9, 116.2, 48.0, 42.2 ppm; IR (thin film): 3074, 3005, 2978, 2923, 2852, 1639, 1599, 1572, 1480, 1447, 1326, 1303, 1266, 1232, 1130, 1098, 1042, 994, 916, 886, 749, 700, 665 cm\(^{-1}\); HRMS calc’d for C\(_{16}\)H\(_{13}\)\(^+\) 221.0967, observed 221.0963 [M-C\(_3\)H\(_5\)]\(^+\).
9,9-diallyl-9H-fluorene (1.7ea): The reaction was performed following General Procedure A with 4e (16.7 mg, 0.1 mmol), KN(SiMe$_3$)$_2$ (60 mg, 0.3 mmol) and 2a (34 μL, 0.2 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (21 mg, 85% yield) as a colorless oil. R$_f$ = 0.20 (hexanes); The NMR spectral data match the previously published data.$^{73}$

2-(4-phenylhepta-1,6-dien-4-yl)thiophene (1.6fa): The reaction was performed following General Procedure A with 1f (16 μL, 0.1 mmol), KN(SiMe$_3$)$_2$ (160 mg, 0.8 mmol) and 2a (51 μL, 0.3 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (18 mg, 70% yield) as a colorless oil. R$_f$ = 0.30 (hexanes); $^1$H NMR (500 MHz, CDCl$_3$): δ 7.28-7.24 (m, 4H), 7.20-7.15 (m, 2H), 6.91 (dd, J = 5.1, 3.6 Hz, 1H), 6.84 (dd, J = 3.6, 1.2 Hz, 1H), 5.44 (ddt, J = 17.2, 10.1, 7.0 Hz, 2H), 5.04-4.97 (m, 4H), 2.90-2.87 (m, 4H) ppm; $^{13}$C {$^1$H} NMR (126 MHz, CDCl$_3$): δ 153.7, 147.0, 134.1, 127.9, 127.3, 126.3, 126.0, 124.3, 123.8, 118.2, 47.6, 43.5 ppm; IR (thin film): 3073, 3007, 2977, 2929, 2853, 1638, 1597, 1494, 1443, 1414, 1234, 997, 915, 849, 826, 771, 743, 695, 665 cm$^{-1}$; HRMS calc’d for C$_{14}$H$_{14}$S$^+$ 214.0816, observed 214.0850 [M-C$_3$H$_5$]$^+$. 

2-(4-phenylhepta-1,6-dien-4-yl)pyridine (1.6aa): The reaction was performed following General Procedure B with 3aa (21 μL, 0.1 mmol), KN(SiMe$_3$)$_2$ (60 mg, 0.3 mmol) and 2a (34 μL, 0.2 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 5:95) to give the product (21 mg, 84% yield) as a colorless oil. R$_f$ = 0.30 (EtOAc:hexanes = 5:95); $^1$H NMR (500 MHz, CDCl$_3$): δ 8.61-8.53 (m, 1H), 7.52 (ddd, J = 8.0, 7.5, 1.9 Hz, 1H), 7.28-7.02 (m, 8H), 5.36 (ddt, J = 17.2, 10.1, 7.1 Hz,
2H), 4.99-4.91 (m, 4H), 3.04-2.93 (m, 4H) ppm; \(^{13}\)C \[^{1}\text{H}\] NMR (126 MHz, CDCl\(_3\)): \(\delta\) 166.3, 148.2, 146.7, 135.7, 134.4, 128.0, 127.6, 125.9, 123.1, 120.9, 117.8, 51.4, 41.4 ppm; IR (thin film): 3073, 3005, 2977, 2926, 2854, 1638, 1586, 1566, 1495, 1468, 1444, 1428, 1152, 994, 913, 798, 762, 748, 700, 666 cm\(^{-1}\); HRMS calc’d for C\(_{18}\)H\(_{19}\)N\(^{+}\) 249.1517, observed 249.1514 [M]+.

3-(4-phenylhepta-1,6-dien-4-yl)pyridine (1.6ca): The reaction was performed following General Procedure A with 3ca (20 \(\mu\)L, 0.1 mmol), KN(SiMe\(_3\))\(_2\) (100 mg, 0.5 mmol) and 2a (51 \(\mu\)L, 0.3 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 20:80) to give the product (20 mg, 80% yield) as a colorless oil. \(R_f = 0.20\) (EtOAc:hexanes = 20:80); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 8.45-8.41 (m, 2H), 7.41 (ddt, J = 8.0, 2.5, 1.3 Hz, 1H), 7.28-7.24 (m, 2H), 7.20-7.13 (m, 4H), 5.36-5.29 (m, 2H), 4.99-4.96 (m, 4H), 2.87 (d, J = 7.0 Hz, 4H) ppm; \(^{13}\)C \[^{1}\text{H}\] NMR (126 MHz, CDCl\(_3\)): \(\delta\) 149.5, 147.2, 146.4, 143.0, 135.5, 133.6, 128.1, 127.8, 126.2, 122.7, 118.5, 47.8, 41.7 ppm; IR (thin film): 3074, 3029, 3007, 2977, 2907, 2853, 1638, 1597, 1572, 1477, 1445, 1414, 1136, 1023, 997, 916, 809, 769, 740, 714, 700, 666 cm\(^{-1}\); HRMS calc’d for C\(_{18}\)H\(_{20}\)N\(^{+}\) 250.1595, observed 210.1606 [MH]+.

2-(2-phenylpent-4-en-2-yl)pyridine (1.8aa): The reaction was performed following General Procedure A with 8a (18 \(\mu\)L, 0.1 mmol), KN(SiMe\(_3\))\(_2\) (100 mg, 0.5 mmol) and 2a (51 \(\mu\)L, 0.3 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 5:95) to give the product (20 mg, 90% yield) as a colorless oil. \(R_f = 0.20\) (EtOAc:hexanes = 5:95); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 8.51-8.49 (m, 1H), 7.46-7.42 (m, 1H), 7.21-7.08 (m, 5H), 7.01-6.95 (m, 2H), 5.44-5.37 (m, 1H), 4.97-4.85 (m, 2H), 3.04-2.85 (m, 2H), 1.60 (s, 3H) ppm; \(^{13}\)C \[^{1}\text{H}\] NMR (126 MHz, CDCl\(_3\)): \(\delta\) 167.6,
148.3, 147.9, 135.9, 135.2, 128.0, 127.1, 125.9, 122.4, 120.8, 117.5, 48.4, 45.4, 26.1 ppm; IR (thin film): 3061, 3028, 2974, 2924, 1638, 1586, 1567, 1494, 1469, 1444, 1427, 1374, 1152, 1091, 1028, 993, 913, 788, 759, 747, 700, 665 cm$^{-1}$; HRMS calc’d for C$_{16}$H$_{18}$N$_2$ 224.1439, observed 224.1436 [MH$^+$].

**but-3-ene-1,1,1-triyltribenzene (1.9aa):** The reaction was performed following General Procedure A with 9a (24.4 mg, 0.1 mmol), KN(SiMe$_3$)$_2$ (100 mg, 0.5 mmol) and 2a (51 μL, 0.3 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (25.5 mg, 90% yield) as white solid. R$_f$ = 0.20 (hexanes); The NMR spectral data match the previously published data.$^{74}$

![but-3-ene-1,1,1-triyltribenzene](image)

3,3'-**(cyclohex-2-en-1-ylmethylene)dipyridine (1.10a):** The reaction was performed following General Procedure A with 1g (17 mg, 0.1 mmol), NaN(SiMe$_3$)$_2$ (55 mg, 0.3 mmol) and 2b (40 μL, 0.2 mmol). The crude material was purified by flash chromatography on silica gel (eluted with MeOH:DCM = 2.5:97.5) to give the product (22 mg, 89% yield) as a yellow oil. R$_f$ = 0.25 (MeOH:DCM = 2.5:97.5); $^1$H NMR (500 MHz, CDCl$_3$): δ 8.60 (dd, J = 14.6, 2.2, 2H), 8.49 (ddd, J = 6.5, 4.8, 1.6, 2H), 7.68-7.59 (m, 2H), 7.31-7.24 (m, 2H), 5.78-5.75 (m, 1H), 5.44-5.41 (m, 1H), 3.72 (d, J = 11.1 Hz, 1H), 3.06-3.02 (m, 1H), 2.05-2.02 (m, 2H), 1.79-1.74 (m, 1H), 1.68-1.54 (m, 2H), 1.33-1.23 (m, 1H) ppm; $^{13}$C [$^1$H] NMR (126 MHz, CDCl$_3$): δ 150.0, 148.04, 138.0, 135.0, 129.4, 128.2, 123.6, 52.8, 38.4, 28.0, 25.2, 21.1 ppm; IR (thin film): 3082, 3024, 2927, 2857, 2836, 1719, 1587, 1574, 1478, 1174, 1138, 1045, 1024, 902, 860, 792, 721, 680, 665 cm$^{-1}$; HRMS calc’d for C$_{17}$H$_{19}$N$_2^+$ 251.1548, observed 251.1548 [MH$^+$].
3,3'-((cyclopent-2-en-1-ylmethylene)dipyridine (1.10b): The reaction was performed following General Procedure A with 1g (17 mg, 0.1 mmol), KN(SiMe3)2 (60 mg, 0.3 mmol) and 2d (40 μL, 0.2 mmol). The crude material was purified by flash chromatography on silica gel (eluted with MeOH:DCM = 2.5:97.5) to give the product (21.2 mg, 90% yield) as a yellow oil. Rf = 0.25 (MeOH:DCM = 2.5:97.5); 1H NMR (500 MHz, CDCl3): δ 8.53 (dd, J = 10.8, 2.3 Hz, 2H), 8.41 (s, 2H), 7.55 (ddt, J = 12.5, 8.0, 2.1 Hz, 2H), 7.26-7.18 (m, 2H), 5.78 (dq, J = 5.9, 2.1 Hz, 1H), 5.42 (dq, J = 5.8, 2.0 Hz, 1H), 3.68 (d, J = 10.8 Hz, 1H), 3.56 (dtd, J = 8.4, 4.2, 2.2 Hz, 1H), 2.32-2.27 (m, 2H), 1.98 (dtd, J = 13.3, 8.1, 5.3 Hz, 1H), 1.44 (dtd, J = 13.2, 8.7, 6.5 Hz, 1H) ppm; 13C {1H} NMR (126 MHz, CDCl3): δ 149.8, 148.1, 138.9, 135.4, 132.8, 132.3, 132.3, 123.6, 52.9, 49.7, 32.0, 29.1 ppm; IR (thin film): 3051, 2928, 2849, 1574, 1478, 1421, 1177, 1105, 1025, 918, 862, 797, 718, 665 cm⁻¹; HRMS calc’d for C16H17N2+: 237.1391, observed 237.1391 [MH]+.

(E)-3,3'-((2,4-diphenylbut-3-ene-1,1-diyl)dipyridine (1.10c): The reaction was performed following General Procedure A with 1g (17 mg, 0.1 mmol), LiN(SiMe3)2 (51 mg, 0.3 mmol) and 2e (62 mg, 0.2 mmol). The crude material was purified by flash chromatography on silica gel (eluted with MeOH:DCM = 2.5:97.5) to give the product (31.5 mg, 87% yield trans:cis= 10:1) as a yellow oil. Rf = 0.20 (MeOH:DCM = 2.5:97.5); 1H NMR (500 MHz, CDCl3): δ 8.66 (d, J = 2.2 Hz, 1H), 8.44 (d, J = 1.3 Hz, 1H), 8.39 (d, J = 2.2 Hz, 1H), 8.29 (dd, J = 4.8, 1.4 Hz, 1H), 7.69 (dt, J = 8.0, 1.9 Hz, 1H), 7.46 (dt, J = 8.0, 1.9 Hz, 1H), 7.26-7.04 (m, 12H), 6.29-6.22 (m, 2H), 4.45 (d, J = 11.5 Hz, 1H), 4.29 (dd, J = 11.5, 6.2 Hz, 1H) ppm; 13C {1H} NMR (126 MHz, CDCl3): δ 150.2, 148.3, 147.8, 141.5, 137.5, 136.9, 135.9, 132.3, 131.2, 128.8, 128.2, 127.5, 126.8, 126.2, 123.6, 53.6, 52.6 ppm; IR (thin film): 3081, 3026, 2926, 1575, 1479, 1423, 1372, 1175, 1129,
1105, 1076, 1025, 966, 912, 789, 761, 664 cm\(^{-1}\); HRMS calc'd for C\(_{26}\)H\(_{23}\)N\(_2\)\(^+\) 363.1861, observed 363.1861 [MH]\(^+\).

\textbf{(cyclohex-2-en-1-ylmethylene)dibenzene (1.10d)}: The reaction was performed following General Procedure A with 4a (17 \(\mu\)L, 0.1 mmol), KN(SiMe\(_3\))\(_2\) (100 mg, 0.5 mmol) and 2b (60 \(\mu\)L, 0.3 mmol).

The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (21 mg, 85% yield) as white solid. \(R_f = 0.20\) (hexanes), KMnO\(_4\) stained; The NMR spectral data match the previously published data.\(^{75}\)

\textbf{(cyclopent-2-en-1-ylmethylene)dibenzene (1.10e)}: The reaction was performed following General Procedure B with 4a (17 \(\mu\)L, 0.1 mmol), KN(SiMe\(_3\))\(_2\) (100 mg, 0.5 mmol) and 2d (60 \(\mu\)L, 0.3 mmol).

The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (22 mg, 94% yield) as white solid. \(R_f = 0.20\) (hexanes), KMnO\(_4\) stained; The NMR spectral data match the previously published data.\(^{66}\)

\textbf{(E)-4-(1,4-diphenylbut-3-en-1-yl)pyridine (1.10f)}: The reaction was performed following General Procedure C with 1b (16 \(\mu\)L, 0.1 mmol), LiN(SiMe\(_3\))\(_2\) (51 mg, 0.3 mmol) and 2g (46 \(\mu\)L, 0.2 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 40:60) to give the product (26 mg, 91% yield) as a yellow oil. \(R_f = 0.30\) (EtOAc:hexanes = 40:60); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 8.50 (d, \(J = 4.8\) Hz, 2H), 7.34-7.08 (m, 12H), 6.39 (dd, \(J = 15.8, 0.9\) Hz, 1H), 6.05 (dtd, \(J = 15.7, 7.1, 1.1\) Hz, 1H), 4.06-4.03 (m, 1H), 2.98-2.90 (m, 2H) ppm; \(^{13}\)C {\(^1\)H} NMR (126 MHz, CDCl\(_3\)): \(\delta\) 153.2, 149.7, 142.5, 137.2, 132.2, 128.68, 128.55, 128.43, 128.29, 128.16, 127.9, 127.4, 126.8, 126.0, 123.3, 50.9, 38.4 ppm;
IR (thin film): 3059, 3025, 2922, 2851, 1945, 1878, 1805, 1594, 1557, 1493, 1451, 1413, 1279, 1072, 1029, 993, 967, 916, 810, 749, 699, 640 cm⁻¹; HRMS calc’d for C₂₁H₂₀N⁺ 286.1595, observed 286.1591 [MH]⁺

\[(E)-4-(4,8\text{-dimethyl-1-phenyl}nona-3,7\text{-dien-1-yl})pyridine\] (1.10g): The reaction was performed following General Procedure C with 1b (16 µL, 0.1 mmol), Li[N(SiMe₃)₂] (51 mg, 0.3 mmol) and 2h (56 µL, 0.2 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 40:60) to give the product (27 mg, 88% yield linear:branched = 1.9:1) as a yellow oil. R_f = 0.25 (EtOAc:hexanes = 40:60); ¹H NMR (500 MHz, CDCl₃): δ 8.49-8.46 (m, 2H), 7.39-7.14 (m, 7H), 5.03-4.97 (m, 2H), 3.92 (t, J = 7.8 Hz, 1H), 2.75-2.72 (m, 2H), 1.95 (td, J = 17.4, 10.3 Hz, 4H), 1.65 (d, J = 7.5 Hz, 3H), 1.55 (d, J = 9.8 Hz, 6H) ppm; ¹³C {¹H} NMR (126 MHz, CDCl₃): δ 153.8, 149.7, 143.2, 137.2, 131.4, 130.1, 128.6, 126.7, 125.2, 124.1, 123.5, 62.6, 51.0, 39.7, 33.6, 26.5, 25.7, 16.2 ppm; IR (thin film): 3058, 2917, 1593, 1493, 1451, 1413, 1028, 993, 699, 665 cm⁻¹; HRMS calc’d for C₂₂H₂₈N⁺ 306.2221, observed 306.2220 [MH]⁺.

\[4-(2,2\text{-dimethyl-1-phenyl}but-3-en-1-yl)pyridine\] (1.10h’): The reaction was performed following General Procedure C with 1b (16 µL, 0.1 mmol), Li[N(SiMe₃)₂] (51 mg, 0.3 mmol) and 2i (41 µL, 0.2 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 30:70) to give the product (22 mg, 93% yield linear:branched = 1:4.5) as a yellow oil. R_f = 0.30 (EtOAc:hexanes = 30:70); ¹H NMR (500 MHz, CDCl₃): δ 8.45 (d, J = 5.8 Hz, 2H), 7.33-7.18 (m, 7H), 5.99 (dd, J = 17.5, 10.8 Hz, 1H), 5.11-4.98 (m, 2H), 3.74 (s, 1H), 1.06 (s, 6H) ppm; ¹³C {¹H} NMR (126 MHz, CDCl₃): δ 151.3, 149.3, 144.8, 140.6, 129.8, 128.0, 126.7, 125.0, 113.0, 63.0, 40.2, 27.34,
27.26 ppm; IR (thin film): 3059, 3026, 2964, 2925, 2868, 1636, 1593, 1556, 1494, 1453, 1415, 1379, 1363, 1221, 1166, 1072, 1012, 994, 916, 822, 746, 701, 640 cm\(^{-1}\); HRMS calc'd for C\(_{17}\)H\(_{19}\)N\(^+\) 237.1517, observed 237.1525 [M\(^+\)].

\[3,3'-(((1R,3R)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-3-yl)methylene)dipyridine (1.11a): \]

The reaction was performed following General Procedure A with 1\(g\) (17 mg, 0.1 mmol), NaN(SiMe\(_3\))\(_2\) (55 mg, 0.3 mmol) and 2\(j\) (54 \(\mu\)L, 0.2 mmol). The crude material was purified by flash chromatography on silica gel (eluted with MeOH:DCM = 2.5:97.5) to give the product (29.4 mg, 90% yield) as a white solid (m.p. = 104-105 °C). \(R_f\) = 0.20 (MeOH:DCM = 2.5:97.5); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 8.61 (d, \(J = 2.1\) Hz, 1H), 8.56 (d, \(J = 2.1\) Hz, 1H), 8.49 (dd, \(J = 4.8, 1.6\) Hz, 1H), 8.41 (dd, \(J = 4.8, 1.6\) Hz, 1H), 7.67 (dt, \(J = 7.9, 2.0\) Hz, 1H), 7.56 (dt, \(J = 8.0, 2.0\) Hz, 1H), 7.28-7.25 (m, 3H), 7.19-7.13 (m, 3H), 5.83 (dq, \(J = 7.6, 2.6\) Hz, 1H), 5.49 (ddd, \(J = 10.2, 2.5, 1.3\) Hz, 1H), 3.70 (d, \(J = 11.0\) Hz, 1H), 3.29-3.23 (m, 1H), 2.90-2.84 (m, 1H), 2.34-2.28 (m, 1H), 2.18-2.11 (m, 1H), 1.80-1.76 (m, 1H), 1.42 (td, \(J = 12.6, 10.9\) Hz, 1H) ppm; \(^{13}\)C \({\{}^1\text{H}\}\} NMR (126 MHz, CDCl\(_3\)): \(\delta\) 150.1, 149.6, 148.2, 146.3, 138.0, 135.5, 135.1, 129.1, 128.5, 128.1, 126.8, 126.3, 123.7, 53.2, 40.57, 40.45, 36.2, 34.0 ppm; IR (thin film): 3026, 2906, 2852, 2836, 1733, 1649, 1574, 1492, 1452, 1243, 1175, 1142, 1045, 1024, 909, 849, 794, 721, 701, 666 cm\(^{-1}\); HRMS calc'd for C\(_{23}\)H\(_{23}\)N\(_2\)\(^+\) 327.1861, observed 327.1867 [MH\(^+\)].

Stereochemistry was assigned by \(^1\)H NMR analysis.\(^{66}\)

\[\text{(1R,3R)-3-benzhydryl-1,2,3,6-tetrahydro-1,1'-biphenyl (1.11b):} \]

The reaction was performed following General Procedure A with 4\(a\) (17 \(\mu\)L, 0.1 mmol), KN(SiMe\(_3\))\(_2\) (100 mg, 0.5 mmol) and 2\(j\) (81 \(\mu\)L, 0.3 mmol). The crude material was purified
by flash chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 2:98) to give the product (28.5 mg, 88% yield) as a white solid (m.p = 124-125 °C). Rr = 0.25 (EtOAc:hexanes = 2:98); 1H NMR (500 MHz, CDCl₃): δ 7.32-7.06 (m, 17H), 5.74-5.71 (m, 1H), 5.52-5.50 (m, 1H), 3.58 (d, J = 11.3, 1H), 3.24-3.18 (m, 1H), 2.86-2.79 (m, 1H), 2.27-2.22 (m, 1H), 2.13-2.05 (m, 1H), 1.80-1.76 (m, 1H), 1.40-1.33 (m, 1H) ppm; 13C {1H} NMR (126 MHz, CDCl₃): δ 147.0, 143.83, 143.72, 129.8, 128.59, 128.53, 128.38, 128.35, 127.89, 127.73, 126.9, 126.23, 126.17, 126.06, 58.4, 40.8, 36.2, 34.3 ppm; IR (thin film): 3083, 3060, 3024, 2905, 1648, 1596, 1492, 1450, 1072, 1028, 960, 906, 758, 745, 726, 698 cm⁻¹; HRMS calc'd for C₁₃H₁₁⁺ 167.0860, observed 167.0863 [M-C₁₂H₁₃]⁺.

Stereochemistry was assigned by X-Ray structure determination and by 1H NMR analysis.⁶⁶

**Screening Results of Ethereal Solvents**

<table>
<thead>
<tr>
<th>entry</th>
<th>(4a:base:2a)</th>
<th>solvent</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:3:2</td>
<td>THF</td>
<td>10%</td>
</tr>
<tr>
<td>2</td>
<td>1:3:2</td>
<td>CPME</td>
<td>9%</td>
</tr>
<tr>
<td>3</td>
<td>1:3:2</td>
<td>Dioxane</td>
<td>trace</td>
</tr>
<tr>
<td>4</td>
<td>1:3:2</td>
<td>2-Me THF</td>
<td>7%</td>
</tr>
<tr>
<td>5</td>
<td>1:3:2</td>
<td>DME</td>
<td>55%</td>
</tr>
</tbody>
</table>
a Reaction conducted on a 0.1 mmol scale with 1 equiv of 4a and 2 equiv of 2a at 0.1M. b Yield determined by ¹H NMR spectroscopy of the crude reaction mixture.

1.5. REFERENCES


(49) Kotha, S.; Manivannan, E.; Ganesh, T.; Sreenivasachary, N.; Deb, A. Synlett 1999, 10, 1618.


Chapter 2
Nickel-Catalyzed Allylic Alkylation of Diarylmethane Derivatives and Mechanistic Insight.

2.1. INTRODUCTION

Metal-catalyzed allylic substitution reactions remain one of the most efficient approaches to construct carbon-carbon bond between sp\(^3\)-hybridized carbons.\(^1\) Among the transition metals used in allylic substitution reactions, palladium has attracted the most attention and met with the greatest success. Many enantioselective catalysts have been developed and applied to the synthesis of natural products.\(^1\)\(^-\)\(^6\)

The mechanisms of allylic substitution reactions promoted by a variety of catalysts with different nucleophiles have been reported.\(^1\)\(^,\)\(^2\) From these studies, trends in reactivity and reaction pathways have emerged and are now well accepted. Importantly, the reaction pathway has been found to depend on the nature of the nucleophile.\(^1\) Thus, based on the p\(K_a\) of the pronucleophile, \(\text{Nu-H}\), anionic nucleophiles (\(\text{Nu}^-\)) are divided into two classes: carbon nucleophiles derived from pronucleophiles with p\(K_a\)'s < 25 are considered stabilized or “soft” nucleophiles while those from pronucleophiles with p\(K_a\)'s > 25 are categorized as unstabilized or “hard” nucleophiles. The difference between these two classes of nucleophiles is that soft nucleophiles attack the Pd(\(\pi\)-allyl) moiety externally while hard nucleophiles bind to the metal center (\textit{via} transmetallation) before C-
C bond formation with the allyl group. Another important distinction between these two pathways is that it has proven easier to control reactions of soft nucleophiles in asymmetric allylic substitution reactions than hard nucleophiles.\textsuperscript{1,3,7-10} With this in mind, several groups have set out to expand the scope of soft nucleophiles in palladium-catalyzed asymmetric allylic alkylation chemistry. This effort has resulted in development of successful asymmetric allylic substitution reactions with pronucleophiles with \( \text{pK}_a \)'s > 25 that behave as “soft” nucleophiles, thus challenging the boundary “soft” nucleophiles.\textsuperscript{11-15}

In contrast palladium catalyzed allylic substitutions, which have been extensively used with soft nucleophiles, nickel-based catalysts have generally been paired with hard nucleophiles, such as Grignard reagents.\textsuperscript{6,16-27} A downside to palladium catalysts is their high costs, motivating a shift from palladium to more sustainable base metal catalysts. Thus, substitution of nickel for palladium in allylic substitution reactions would be highly desirable, especially if enantioselective versions could be achieved.

Early examples of nickel catalyzed allylic substitution reactions include Hiyama and coworkers use of (\( S,S \))-chiraphos (Scheme 2.1A).\textsuperscript{16} In a clever application of achiral ligands to optimize enantioselectivity,\textsuperscript{28} Hoveyda and coworkers used the [(\( S,S \))-chiraphos]\textit{Ni}-based catalyst in the presence of \( \text{PR}_3 \) and Grignard reagents to develop an enantioselective synthesis of enol ethers (Scheme 2.1B).\textsuperscript{17} Consiglio and coworkers determined that the nucleophilic attack occurred at the nickel center (transmetallation) followed by reductive elimination to form the product.\textsuperscript{6,20} They found excellent enantioselectivity can be achieved with \( \text{EtMgBr} \), but both \( \text{MeMgBr} \) and \( (n-\text{Pr})\text{MgBr} \) exhibited significantly lower enantioselectivities (Scheme 2.1C).\textsuperscript{19} This observation highlights the
challenges in enantiocontrol via the “hard” nucleophile pathway. Unlike hard nucleophiles, soft nucleophiles that exhibit external attack in nickel-catalyzed asymmetric allylic alkylations show reduced enantioselection (up to 40% ee, Scheme 2.1D). 29

Our interest in the palladium catalyzed Tsuji-Trost reaction has been in expanding the scope of soft nucleophiles and broadening the synthetic utility of this reaction. We recently demonstrated that diarylmethane pronucleophiles behave as soft nucleophiles in allylic substitution reactions under basic conditions, raising the pKₐ limit of soft nucleophiles from 25 to at least 32.14 In the current study, we asked 1) if diarylmethane pronucleophiles were suitable substrates for nickel catalyzed allylic substitution reactions, 2) if they would react via the hard or soft nucleophile pathway, and 3) if enantioselective reactions would be possible. Herein, we communicate that these basic nucleophiles react via the soft nucleophile pathway and we present promising preliminary evidence for development of an asymmetric version of nickel-catalyzed allylic substitution reactions via the soft nucleophile pathway.

**Scheme 2.1.** Previous Works On Ni-Catalyzed Asymmetric Allylic Alkylation
A. Hiyama

\[
\text{OR} \xrightarrow{\text{Ar-MgBr}} \xrightarrow{5 \text{ mol}\% \text{ Catalyst}} \xrightarrow{\text{THF, } 0 \text{ } ^\circ\text{C}} \text{Ar}
\]
89\% \text{ ee} 50\% \text{ yield}

B. Hoveyda

\[
\text{MeO} \xrightarrow{\text{C}_2\text{H}_5\text{MgBr}} \xrightarrow{5 \text{ mol}\% \text{ Catalyst}} \xrightarrow{10 \text{ mol}\% \text{ PPh}_3, \text{ } 22 \text{ } ^\circ\text{C}} \text{C}_2\text{H}_5
\]
85\% \text{ ee} 90\% \text{ yield}

C. Consiglio

\[
\text{OPh} \xrightarrow{\text{C}_2\text{H}_5\text{MgCl}} \xrightarrow{5 \text{ mol}\% \text{ Catalyst}} \xrightarrow{22 \text{ } ^\circ\text{C}} \text{C}_2\text{H}_5
\]
84\% \text{ ee}
84\% \text{ yield}

D. Mortreux

\[
\text{OAc} \xrightarrow{\text{MeO}_2\text{C}\xrightarrow{\text{MeO}_2\text{C}}\xrightarrow{\text{4 mol}\% \text{ ligand}} \xrightarrow{\text{50 } ^\circ\text{C}} \text{MeO}_2\text{C}\xrightarrow{\text{MeO}_2\text{C}}\xrightarrow{\text{2 mol}\% \text{ Ni(COD)}_2} \text{MeO}_2\text{C}\xrightarrow{\text{MeO}_2\text{C}}\xrightarrow{\text{40 } ^\circ\text{C}} \text{MeO}_2\text{C}\xrightarrow{\text{MeO}_2\text{C}}\xrightarrow{\text{100 } ^\circ\text{C}} \text{MeO}_2\text{C}\xrightarrow{\text{MeO}_2\text{C}}\xrightarrow{\text{100 } ^\circ\text{C}}
\]
40\% \text{ ee} 100\% \text{ yield}

2.2. Results and Discussion

Given the success of our (Xantphos)Pd-catalyzed allylic substitution with diarylmethane pronucleophiles, we initiated our investigation by simply replacing Pd with Ni under the same conditions. Thus, employing Ni(COD), and van Leeuwen’s Xantphos 10 mol % each) with allylOBoc and KN(SiMe3), we were pleased that 63% yield of the allylated product was obtained (eq 2.1)
During the course of the reaction an insoluble orange precipitate formed which we suspected was Ni(Xantphos)$_2$. Therefore, 24 ligands were screened under the conditions in eq 2.1 (see Supporting Information) leading to determination that DPPF was superior to Xantphos. We then screened the nickel to ligand ratios, with 5 mol % nickel and 10 mol % DPPF we could obtain desired product in 72% yield (Table 2.1, entry 3). Solvents screening showed DME to give the best yields. Testing nickel sources NiCl$_2$ and NiBr$_2$ resulted in decreased yields (Table 2.1, entry 8 and 9) Finally, 88% isolated yield was obtained with 7.5 mol % catalyst loading. (Table 2.1, entry 10)

Table 2.1. Optimization of Allylic Alkylation with Diphenylmethane 1a
With optimized conditions in Table 2.1 (entry 10), we probed the scope of diphenylmethane derivatives (Table 2.2). We investigated 4-halogenated diphenylmethanes (Table 2.2, entries 2–4). Fluorine-containing compounds are useful because of their bioactivities and applications in material science. The reaction with 4-fluoro diphenylmethane (4b) as pronucleophile afforded the desired 4-fluoro diphenylmethane (1b) afforded the desired product 3ba in 67% yield (Table 2.2, entry 2). We then applied our reaction conditions to 4-bromo and 4-chloro diphenylmethanes (1c and 1d) with different selection of the base (NaN(SiMe$_3$)$_2$). Oxidative addition of C–X (X = Cl, Br) bonds to the

<table>
<thead>
<tr>
<th>entry</th>
<th>Ni Source</th>
<th>Ni/DPPF (mol %)</th>
<th>solvent</th>
<th>yield$^b$ (%)</th>
</tr>
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<td>1</td>
<td>Ni(COD)$_2$</td>
<td>5/5</td>
<td>DME</td>
<td>39</td>
</tr>
<tr>
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<td>Ni(COD)$_2$</td>
<td>5/7.5</td>
<td>DME</td>
<td>46</td>
</tr>
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<td>Ni(COD)$_2$</td>
<td>5/10</td>
<td>DME</td>
<td>72</td>
</tr>
<tr>
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<td>5/10</td>
<td>THF</td>
<td>46</td>
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<tr>
<td>5</td>
<td>Ni(COD)$_2$</td>
<td>5/10</td>
<td>CPME</td>
<td>&lt;5</td>
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<tr>
<td>6</td>
<td>Ni(COD)$_2$</td>
<td>5/10</td>
<td>dioxane</td>
<td>&lt;5</td>
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<tr>
<td>7</td>
<td>Ni(COD)$_2$</td>
<td>5/10</td>
<td>2-MeTHF</td>
<td>52</td>
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<td>8</td>
<td>NiCl$_2$</td>
<td>5/10</td>
<td>DME</td>
<td>35</td>
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<tr>
<td>9</td>
<td>NiBr$_2$</td>
<td>5/10</td>
<td>DME</td>
<td>51</td>
</tr>
<tr>
<td>10</td>
<td>Ni(COD)$_2$</td>
<td>7.5/15</td>
<td>DME</td>
<td>90 (88)$^c$</td>
</tr>
</tbody>
</table>

$^a$Reaction conducted on a 0.1 mmol scale. $^b$Yield determined by $^1$H NMR spectroscopy of the crude reaction mixture. $^c$Isolated yield after chromatographic purification.
active Ni(0) species could be a potentially competitive reaction pathway. Fortunately, Ni-catalyzed allylic alkylation afforded the allylated products 3ca and 3da in 98% and 89% yield, respectively (Table 2.2, entries 3 and 4). These results suggested that generation of the π-allyl nickel intermediate is faster than the oxidative addition of C-X bonds to the Ni(0) species under our reaction conditions. 4-methyl diphenylmethane (1e) gave 3ea in 61% yield (Table 2.2, entry 5). Sterically hindered substrate 2-methyl diphenylmethane (1f) reacted to provide 3fa in 65% yield (Table 2.2, entry 6). Fluorene derivatives are interesting components in material and photochemistry.\textsuperscript{32} We changed the selection of base due to the increased acidity of Fluorene (1g). With 5 equiv LiO\textsuperscript{t}Bu and 1.2 equiv of 2a, 3ga was provided in 75% yield (Table 2.2, entry 7). Unfortunately, 4-methoxy diphenylmethane gave only poor yield after efforts on optimization.

\textbf{Table 2.2.} Scope of Diphenylmethane Derivatives in Allylic Alkylation Reactions

\textsuperscript{a}
**Entry** | **Pronucleophiles** | **base** | **Products** | **ratio** | **Yield** |
--- | --- | --- | --- | --- | --- |
1 | | KHMDS | | 3aa 1:5:3 | 88% |
2 | | KHMDS | | 3ba 1:4:3 | 67% |
3 | | NaHMDS | | 3ca 1:5:3 | 98% |
4 | | NaHMDS | | 3da 1:5:3 | 89% |
5 | | KHMDS | | 3ea 1:5:3 | 61% |
6 | | KHMDS | | 3fa 1:5:3 | 65% |
7 | | LiO\text{Bu} | | 3ga 1:5:1.2 | 75% |

*aReaction conducted on a 0.1 mmol scale.*
After screening the scope of diphenylmethane derivatives, we turned our attention to biologically more interesting targets, heterocyclic diarylmethanes (Table 2.3). Pyridine containing diarylmethanes are useful in drug discovery.\textsuperscript{33} 2-benzylpyridine (4a) afforded $5\text{aa}$ in 91% yield (Table 2.3, entry 1). 4-benzylpyridine (4b) and 3-benzylpyridine (4c) provided desired products $5\text{ba}$ and $5\text{ca}$ in 93% and 91% yield (Table 2.3, entries 2 and 3). Xanthene derivatives are building blocks of dyes.\textsuperscript{32} We applied our reaction condition to Xanthene (4d) and obtained $5\text{da}$ in 81% yield (Table 2.3, entry 4). Thiophene containing products are important in agrochemicals and pharmaceuticals.\textsuperscript{34} 2-benzylthiophene (4e) rendered $5\text{ea}$ in 82% yield (Table 2.3, entry 5). Finally, 3,3′-dipyridylmethane (4f) successfully provided $5\text{fa}$ in 90% (Table 2.3, entry 6).

**Table 2.3.** Scope of Heterocyclic Diphenylmethane in Allylic Alkylation Reactions \textsuperscript{a}
Ph
HetAr +

\[ \text{4a-f} \quad \text{2a} \quad \rightarrow \quad \text{5aa-5fa} \]

5 mol % Ni(COD)_2
10 mol % DPPF
DME, 24 °C, 12 h

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pronucleophiles</th>
<th>Base</th>
<th>Products</th>
<th>4:base:2a</th>
<th>Yield ( b ) (%)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>NaN(SiMe_3)_2</td>
<td></td>
<td>5aa</td>
<td>1:2:1.2</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>LiN(SiMe_3)_2</td>
<td></td>
<td>5ba</td>
<td>1:2:1.2</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>NaN(SiMe_3)_2</td>
<td></td>
<td>5ca</td>
<td>1:3:1.2</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>LiN(SiMe_3)_2</td>
<td></td>
<td>5da</td>
<td>1:3:1.2</td>
<td>81</td>
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<tr>
<td>5</td>
<td>NaN(SiMe_3)_2</td>
<td></td>
<td>5ea</td>
<td>1:2:1.2</td>
<td>82</td>
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<tr>
<td>6</td>
<td>LiN(SiMe_3)_2</td>
<td></td>
<td>5fa</td>
<td>1:3:1.2</td>
<td>90</td>
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</tbody>
</table>

\*Reaction conducted on a 0.1 mmol scale.

With good to excellent yields demonstrated in Table 2.3, we decided to perform one-pot diallylation to construct quaternary carbon center. (Table 4) Pyridine-containing compounds such as 2-benzyl, 4-benzyl, or 3-benzyl pyridine all gave good yields (6aa – 6ca, 84%, 75%, 78%; Table 2.4, entries 1–3).
Xanthene and fluorene showed excellent reactivity of 89% and 90% yields (6da, 6ea; Table 2.4, entries 4, 5). 2-benzylthiophene provided diallylation product 6fa in 83% yield under our reaction condition. After demonstrating one-pot synthesis to construct quaternary carbon center from secondary diarylmethanes, we were also interested in starting from tertiary centers such as triarylmethane and alkylated diarylmethane. To our delight, triphenylmethane (7a) gave 8aa in 90% yield. 2-(1-phenylethyl)pyridine (7b) also underwent allylation to form 8ba in 92% yield. Overall, starting from diarylmethanes or tertiary carbon centers both gave good to excellent yields. Noteworthy, the yield-per-step was higher than 86% in each case.

Table 2.4. Scope of Diallylation of Diarylmethanes, Alkylated Diarylmethane and Triphenylmethane a
HetAr + OBOc → HetAr

5 mol % Ni(COD)$_2$
10 mol % DPPF
DME, 24 ℃, 12 h

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pronucleophiles</th>
<th>Base</th>
<th>Products</th>
<th>Yield$^\circ$ (%)</th>
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<td>KN(SiMe$_3)_2$</td>
<td>1:5:3</td>
<td>92</td>
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</table>

Entry 4: base:2a

ratio 4:base:2a

6aa-6ga, 8aa, 8ba

$^\circ$ Yield
After demonstrating diarylmethanes are suitable substrates for nickel catalyzed allylic substitution reactions, we turned our attention to the mechanistic pathway of the reaction. In order to probe the reaction pathway with cyclic electrophile 2c (eq 2.3), we first examined the reactivity of the condition on structurally similar electrophile 2b with 4f. Fortunately, the reaction condition can be applied to cyclic electrophiles 2b and the product 9fb was formed in 91% yield (eq 2.2).

\[
\begin{align*}
4f & \quad 1 \text{ equiv} \\
2b & \quad 2 \text{ equiv} \\
\text{Ni(COD)}_2 & \quad 5 \text{ mol} \% \\
\text{DPPF} & \quad 10 \text{ mol} \% \\
\text{NaHMDS} & \quad 3 \text{ equiv} \\
\text{DME, 24 °C, 12 h} & \quad 9fb \\
\end{align*}
\]

With this promising result, we would pursue the answer to our question: Does 3,3′-dipyridylmethane (4f) behave as soft nucleophiles same in Ni-catalyzed allylic alkylation as in Pd-catalyzed allylic alkylation? We were able to answer this question by performing reaction with 3,3′-dipyridylmethane (4f) and stereoprobe (2c) to determine whether the reaction proceed as double inversion pathway (soft nucleophile) or single inversion pathway (hard nucleophile). After analysis of the products, we were able to identify the nucleophiles 4f behaves as soft nucleophiles, which is identical in both Ni-catalyzed allylic alkylation and in Pd-catalyzed allylic alkylation (eq 2.3).
More importantly, we would like to know if Ni-catalyzed asymmetric allylic alkylation (AAA) could be done with soft nucleophiles in high enantiopurity. To our delight, after 252 chiral ligands screened, we were able to identify the right ligand SL-J204-1 to perform Ni-catalyzed asymmetric allylic alkylation in 91% yield with 92% e.e using optimized reaction conditions (see Supporting Information). The nucleophile 4f was proven to be soft nucleophile with SL-J204-1, which is identical with DPPF as the ligand.

**Scheme 2.2. Asymmetric Allylic Alkylation and Mechanistic Study with SL-J204-1**
2.3. SUMMARY AND OUTLOOK

To sum up, we have developed a racemic version of Ni-catalyzed allylic alkylation with diarylmethane derivatives. The protocol is robust with different nucleophiles including diphenylmethanes derivatives and heterocyclic diarylmethanes. We could also perform an one-pot synthesis from either diarylmethanes, alkylated diarylmethane or triarylmethane to construct quaternary centers. The method provides a rapid way of expanding the library of medicinally interesting targets: allylated diarylmethanes. The same soft diarylmethane nucleophiles in Pd-catalyzed allylic alkylation turned out to be soft nucleophiles as well as in Ni-catalyzed allylic alkylation. More importantly, the first Ni-catalyzed asymmetric allylic alkylation (AAA) of soft nucleophiles with high e.e. has been demonstrated. This suggested Ni-catalyzed asymmetric allylic alkylation (AAA) could be done not only with hard nucleophiles, but with soft nucleophiles as well.

2.4. EXPERIMENTAL SECTION

General Methods. All reactions were performed under nitrogen using oven-dried glassware and standard Schlenk or vacuum line techniques. Air- and moisture-sensitive solutions were handled under nitrogen and transferred via syringe. The solvent (DME) was sparged for 20 min with dry N$_2$ and dried using a commercial two-column solvent purification system comprising columns packed with neutral alumina. Unless otherwise stated, reagents were commercially available and used as purchased without further purification. Chemicals were obtained from Sigma-Aldrich, Acros, TCI America, Strem Chemicals or Matrix Scientific, and solvents were purchased from Fisher Scientific. The progress of the reactions was monitored by thin-layer chromatography using Whatman
Partisil K6F 250 μm precoated 60 Å silica gel plates and visualized by short-wavelength ultraviolet light as well as by treatment potassium permanganate (KMnO₄) stain or iodine. Silica gel (230–400 mesh, Silicycle) was used for flash chromatography. The $^1$H NMR and $^{13}$C($^1$H) NMR spectra were obtained using a Bruker AM-500 Fourier transform NMR spectrometer at 500 and 126 MHz, respectively. Chemical shifts are reported in units of parts per million (ppm) downfield from tetramethylsilane (TMS), and all coupling constants are reported in hertz. The infrared spectra were obtained with KBr plates using a Perkin-Elmer Spectrum 100 Series FTIR spectrometer. High-resolution mass spectrometry (HRMS) data were obtained on a Waters LC–TOF mass spectrometer (model LCT-XE Premier) using chemical ionization (CI) or electrospray ionization (ESI) in positive or negative mode, depending on the analyte. Melting points were determined on a Unimelt Thomas-Hoover melting point apparatus and are uncorrected.

Preparation of Diarylmethanes.
Compounds $4e^{35}, 4f^{36}, 7b^{37}$ were prepared according to literature procedures.

Preparation of Allylic Electrophiles.
Compounds $2a^{38}, 2b^{39}, 2c^{40}$ were prepared according to literature procedures.

General Procedure A: An oven-dried 10 mL reaction vial equipped with a stir bar was charged with KN(SiMe₃)₂ (100 mg, 0.50 mmol, 5 equiv) under a nitrogen atmosphere. A solution (from a stock solution) of Ni(COD)₂ (2.06 mg, 0.0075 mmol) and DPPF (8.31 mg, 0.015 mmol) in 1 mL of dry DME was taken up by syringe and added to the reaction vial. After stirring for 5 min at 24 °C, $1a$ (17 μL, 0.1 mmol, 1 equiv) was added to the reaction mixture followed by $2a$ (51 μL, 0.3 mmol, 3 equiv). Note that the diarylmethanes or allyl OBoc in a solid form was added to the reaction vial prior to KN(SiMe₃)₂. The reaction mixture was stirred for 12 h at 24 °C, quenched with two drops of H₂O, diluted with 3 mL of ethyl acetate, and filtered over a pad of MgSO₄ and silica.
The pad was rinsed with additional ethyl acetate, and the solution was concentrated in vacuo. The crude material was loaded onto a silica gel column and purified by flash chromatography eluting with EtOAc/hexanes.

**General Procedure B**: An oven-dried 10 mL reaction vial equipped with a stir bar was charged with NaN(SiMe₃)₂ (55 mg, 0.30 mmol, 3 equiv) under a nitrogen atmosphere. A solution (from a stock solution) of Ni(COD)₂ (1.37 mg, 0.005 mmol) and DPPF (5.54 mg, 0.010 mmol) in 1 mL of dry DME was taken up by syringe and added to the reaction vial. After stirring for 5 min at 24 °C, 4a (16 μL, 0.1 mmol, 1 equiv) was added to the reaction mixture followed by 2a (20.4 μL, 0.12 mmol, 1.2 equiv). Note that the diarylmethanes or allyl OBoc in a solid form was added to the reaction vial prior to NaN(SiMe₃)₂. The reaction mixture was stirred for 12 h at 24 °C, quenched with two drops of H₂O, diluted with 3 mL of ethyl acetate, and filtered over a pad of MgSO₄ and silica. The pad was rinsed with additional ethyl acetate, and the solution was concentrated in vacuo. The crude material was loaded onto a silica gel column and purified by flash chromatography eluting with EtOAc/hexanes.

**General Procedure C**: An oven-dried 10 mL reaction vial equipped with a stir bar was charged with NaN(SiMe₃)₂ (55 mg, 0.30 mmol, 3 equiv) under a nitrogen atmosphere. A solution (from a stock solution) of Ni(COD)₂ (1.37 mg, 0.005 mmol) and SL-J204-1 (3.65 mg, 0.005 mmol) in 1 mL of dry DME was taken up by syringe and added to the reaction vial. After stirring for 5 min at 24 °C, 4f (17 mg, 0.1 mmol, 1 equiv) was added to the reaction mixture followed by 2b (40 μL, 0.2 mmol, 2 equiv). Note that the diarylmethanes or allyl OBoc in a solid form was added to the reaction vial prior to NaN(SiMe₃)₂. The reaction mixture was stirred for 12 h at 0 °C, quenched with two drops of H₂O, diluted with 3 mL of ethyl acetate, and filtered over a pad of MgSO₄ and silica. The pad was rinsed with additional ethyl acetate, and the solution was concentrated in vacuo.
vacuo. The crude material was loaded onto a silica gel column and purified by flash chromatography eluting with EtOAc/hexanes.

**but-3-ene-1,1-diyl dibenzene (2.3aa):** The reaction was performed following General Procedure A with 1a (17 μL, 0.1 mmol), KN(SiMe$_3$)$_2$ (100 mg, 0.50 mmol) and 2a (51 μL, 0.3 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (18.3 mg, 88% yield) as a colorless oil. $R_f = 0.25$ (hexanes); The NMR spectral data match the previously published data.$^{41}$

**1-fluoro-4-(1-phenylbut-3-en-1-yl)benzene (2.3ba):** The reaction was performed following General Procedure A with 1b (17 μL, 0.1 mmol), KN(SiMe$_3$)$_2$ (80 mg, 0.40 mmol) and 2a (51 μL, 0.3 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (15.2 mg, 67% yield) as a colorless oil. $R_f = 0.25$ (hexanes); The NMR spectral data match the previously published data.$^{42}$

**1-chloro-4-(1-phenylbut-3-en-1-yl)benzene (2.3ca):** The reaction was performed following General Procedure A with 1c (18 μL, 0.1 mmol), NaN(SiMe$_3$)$_2$ (91 mg, 0.50 mmol) and 2a (51 μL, 0.3 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (23.8 mg, 98% yield) as a colorless oil. $R_f = 0.25$ (hexanes); The NMR spectral data match the previously published data.$^{41}$
1-bromo-4-(1-phenylbut-3-en-1-yl)benzene (2.3da): The reaction was performed following General Procedure A with 1d (18.5 μL, 0.1 mmol), NaN(SiMe₃)₂ (91 mg, 0.50 mmol) and 2a (51 μL, 0.3 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (25.5 mg, 89% yield) as a colorless oil. Rᵣ = 0.25 (hexanes); The NMR spectral data match the previously published data.⁴²

1-methyl-4-(1-phenylbut-3-en-1-yl)benzene (2.3ea): The reaction was performed following General Procedure A with 1e (18.5 μL, 0.1 mmol), KN(SiMe₃)₂ (100 mg, 0.50 mmol) and 2a (51 μL, 0.3 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (13.5 mg, 61% yield) as a colorless oil. Rᵣ = 0.20 (hexanes); The NMR spectral data match the previously published data.⁴¹

1-methyl-2-(1-phenylbut-3-en-1-yl)benzene (2.3fa): The reaction was performed following General Procedure A with 1f (18.5 μL, 0.1 mmol), KN(SiMe₃)₂ (100 mg, 0.50 mmol) and 2a (51 μL, 0.3 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (14.4 mg, 65% yield) as a colorless oil. Rᵣ = 0.20 (hexanes); The NMR spectral data match the previously published data.⁴³

9-allyl-9H-fluorene (2.3ga): The reaction was performed following General Procedure A with 1g (16.7 mg, 0.1 mmol), LiO'Bu (40 mg, 0.50 mmol) and 2a (20.4 μL, 0.12 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to
give the product (15.5 mg, 75% yield) as a colorless oil. $R_f = 0.20$ (hexanes); The NMR spectral data match the previously published data.$^{44}$

2-(1-phenylbut-3-en-1-yl)pyridine (2.5aa): The reaction was performed following General Procedure B with 4a (16 $\mu$L, 0.1 mmol), NaN(SiMe$_3$)$_2$ (36 mg, 0.20 mmol) and 2a (20.4 $\mu$L, 0.12 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 10:90) to give the product (19 mg, 91% yield) as a yellow oil. $R_f = 0.30$ (EtOAc:hexanes = 10:90); The NMR spectral data match the previously published data.$^{42}$

4-(1-phenylbut-3-en-1-yl)pyridine (2.5ba): The reaction was performed following General Procedure B with 4b (16 $\mu$L, 0.1 mmol), LiN(SiMe$_3$)$_2$ (34 mg, 0.20 mmol) and 2a (20.4 $\mu$L, 0.12 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 30:70) to give the product (19.5 mg, 93% yield) as a yellow oil. $R_f = 0.30$ (EtOAc:hexanes = 40:60); The NMR spectral data match the previously published data.$^{42}$

3-(1-phenylbut-3-en-1-yl)pyridine (2.5ca): The reaction was performed following General Procedure B with 4c (17 mg, 0.1 mmol), NaN(SiMe$_3$)$_2$ (55 mg, 0.30 mmol) and 2a (20.4 $\mu$L, 0.12 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 30:70) to give the product (19 mg, 91% yield) as a yellow oil. $R_f = 0.40$ (EtOAc:hexanes = 40:60); The NMR spectral data match the previously published data.$^{42}$

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9-allyl-9H-xanthene (2.5da): The reaction was performed following General Procedure B with 4d (18.2 mg, 0.1 mmol), LiN(SiMe₃)₂ (55 mg, 0.30 mmol) and 2a (20.4 μL, 0.12 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (18 mg, 81% yield) as a colorless oil. Rₜ = 0.25 (hexanes); The NMR spectral data match the previously published data.⁴⁵

2-(1-phenylbut-3-en-1-yl)thiophene (2.5ea): The reaction was performed following General Procedure B with 4e (16 μL, 0.1 mmol), NaN(SiMe₃)₂ (36 mg, 0.20 mmol) and 2a (20.4 μL, 0.12 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (17.6 mg, 82% yield) as a colorless oil. Rₜ = 0.20 (hexanes); The NMR spectral data match the previously published data.⁴⁶

3,3′-(but-3-ene-1,1-diyl)dipyridine (2.5fa): The reaction was performed following General Procedure B with 4f (17 mg, 0.1 mmol), LiN(SiMe₃)₂ (51 mg, 0.30 mmol) and 2a (20.4 μL, 0.12 mmol). The crude material was purified by flash chromatography on silica gel (eluted with MeOH:DCM = 2.5:97.5) to give the product (18.9 mg, 90% yield) as a yellow oil. Rₜ = 0.30 (MeOH:DCM = 2.5:97.5); The NMR spectral data match the previously published data.⁴²

2-(4-phenylhepta-1,6-dien-4-yl)pyridine (2.6aa): The reaction was performed following General Procedure B with 4a (16 μL, 0.1 mmol), KN(SiMe₃)₂ (100 mg, 0.5 mmol) and 2a (51 μL, 0.3 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 5:95) to give the product (21 mg, 84% yield) as a
colorless oil. $R_f = 0.30$ (EtOAc:hexanes = 5:95); The NMR spectral data match the previously published data.\textsuperscript{42}

4-(4-phenylhepta-1,6-dien-4-yl)pyridine (2.6ba): The reaction was performed following General Procedure B with 4b (16 $\mu$L, 0.1 mmol), KN(SiMe\textsubscript{3})\textsubscript{2} (100 mg, 0.5 mmol) and 2a (51 $\mu$L, 0.3 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 40:60) to give the product (18.7 mg, 75% yield) as a colorless oil. $R_f = 0.25$ (EtOAc:hexanes = 40:60); The NMR spectral data match the previously published data.\textsuperscript{42}

3-(4-phenylhepta-1,6-dien-4-yl)pyridine (2.6ca): The reaction was performed following General Procedure B with 4c (17 mg, 0.1 mmol), KN(SiMe\textsubscript{3})\textsubscript{2} (100 mg, 0.5 mmol) and 2a (51 $\mu$L, 0.3 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 20:80) to give the product (19.5 mg, 78% yield) as a colorless oil. $R_f = 0.20$ (EtOAc:hexanes = 20:80); The NMR spectral data match the previously published data.\textsuperscript{42}

9,9-diallyl-9H-xanthene (2.6da): The reaction was performed following General Procedure B with 4d (18.2 mg, 0.1 mmol), NaN(SiMe\textsubscript{3})\textsubscript{2} (91 mg, 0.5 mmol) and 2a (51 $\mu$L, 0.3 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (23.3 mg, 89% yield) as a colorless oil. $R_f = 0.25$ (hexanes); The NMR spectral data match the previously published data.\textsuperscript{42}
9,9-diallyl-9H-fluorene (2.6ea): The reaction was performed following General Procedure B with 1g (16.7 mg, 0.1 mmol), KN(SiMe₃)₂ (100 mg, 0.3 mmol) and 2a (51 μL, 0.3 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (22.2 mg, 90% yield) as a colorless oil. Rₜ = 0.20 (hexanes); The NMR spectral data match the previously published data.42

2-(4-phenylhepta-1,6-dien-4-yl)thiophene (2.6fa): The reaction was performed following General Procedure B with 4e (16 μL, 0.1 mmol), KN(SiMe₃)₂ (100 mg, 0.5 mmol) and 2a (51 μL, 0.3 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (21.1 mg, 83% yield) as a colorless oil. Rₜ = 0.30 (hexanes); The NMR spectral data match the previously published data.42

but-3-ene-1,1,1-triyltribenzene (2.8aa): The reaction was performed following General Procedure B with 7a (24.4 mg, 0.1 mmol), KN(SiMe₃)₂ (100 mg, 0.5 mmol) and 2a (51 μL, 0.3 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (25.5 mg, 90% yield) as white solid. Rₜ = 0.20 (hexanes); The NMR spectral data match the previously published data.42

2-(2-phenylpent-4-en-2-yl)pyridine (2.8ba): The reaction was performed following General Procedure A with 7b (18 μL, 0.1 mmol), KN(SiMe₃)₂ (100 mg, 0.5 mmol) and 2a (51 μL, 0.3 mmol). The crude material was purified by flash chromatography on silica gel (eluted with hexanes to EtOAc:hexanes = 5:95) to give the product (20.5 mg, 92% yield) as a colorless oil. Rₜ =
0.20 (EtOAc:hexanes = 5:95); The NMR spectral data match the previously published data. \(^{42}\)

\[ \text{3,3'}-(\text{cyclohex-2-en-1-ylmethylene})\text{dipyridine} \quad (2.9\text{fb}) \]

\( \text{(from DPPF): The reaction was performed following General Procedure B with 4f (17 mg, 0.1 mmol), NaN(SiMe}_3)_2 (55 mg, 0.3 \text{ mmol}) and 2b (40 } \mu\text{L, 0.2 mmol). The crude material was purified by flash chromatography on silica gel (eluted with MeOH:DCM = 2.5:97.5) to give the product (22.5 mg, 91% yield) as a yellow oil. } \text{R}_f = 0.25 \text{ (MeOH:DCM = 2.5:97.5); The NMR spectral data match the previously published data.}^{42}\]

The ee was determined by HPLC with a Daicel Chiralpak AD-H column (10% isopropanol in hexanes, 1 mL/min, 254 nm, major tr= 23.596 min, minor tr = 26.869 min).

\[ \text{3,3'}-(\text{cyclohex-2-en-1-ylmethylene})\text{dipyridine} \quad (2.9\text{fb}) \]

\( \text{(from SL-J204-1): The reaction was performed following General} \)
Procedure C with 4f (17 mg, 0.1 mmol), NaN(SiMe$_3$)$_2$ (55 mg, 0.3 mmol) and 2b (40 $\mu$L, 0.2 mmol). The crude material was purified by flash chromatography on silica gel (eluted with MeOH:DCM = 2.5:97.5) to give the product (22.5 mg, 91% yield, 92% e.e.) as a yellow oil. $R_f = 0.25$ (MeOH:DCM = 2.5:97.5); The NMR spectral data match the previously published data.$^{42}$

The ee was determined by HPLC with a Daicel Chiralpak AD-H column (10% isopropanol in hexanes, 1 mL/min, 254 nm, minor $t_r$ = 24.848 min, major $t_r$ = 26.798 min).

The reaction was performed following General Procedure B with 4f (17 mg, 0.1 mmol), NaN(SiMe$_3$)$_2$ (55 mg, 0.3 mmol) and 2c (54 $\mu$L, 0.2 mmol). The crude material was purified by flash chromatography on silica gel (eluted with MeOH:DCM = 2.5:97.5) to give the product (28.4 mg, 87% yield, cis:trans = 10:1) as a pale yellow oil. $R_f = 0.20$ (MeOH:DCM = 2.5:97.5); The NMR spectral data match the previously published data.$^{42}$

Stereochemistry was assigned by $^1$H NMR analysis.$^{40}$
3,3'-(((1\,R,3\,R)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-3-yl)methylene)dipyridine (2.10fc) (from SL-J204-1): The reaction was performed following General Procedure C with 4f (17 mg, 0.1 mmol), NaN(SiMe$_3$)$_2$ (55 mg, 0.3 mmol) and 2c (54 μL, 0.2 mmol). The crude material was purified by flash chromatography on silica gel (eluted with MeOH:DCM = 2.5:97.5) to give the product (27.1 mg, 83% yield, cis:trans = 10:1) as a pale yellow oil. R$_f$ = 0.20 (MeOH:DCM = 2.5:97.5); The NMR spectral data match the previously published data.$^{42}$

### Screening Results of Achiral Ligands

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<th>Ligand</th>
<th>Assay Yield/ Internal Standard</th>
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<tr>
<td>2-(Di-tert-butylphosphino)biphenyl (JohnPhos)</td>
<td>Xantphos: 22</td>
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<tr>
<td>4-(Di-tert-butylphosphino)-N,N-dimethylaniline (Ataphos)</td>
<td>DPPF: 46</td>
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<tr>
<td>2-Dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (Dave Phos)</td>
<td>MePhos: 11</td>
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<td>2-Di-tert-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-triisopropy1-1,1'-biphenyl (Me4tBuXPhos)</td>
<td>NiXantphos: 20</td>
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<td>Dicyclohexyl-[3,6-dimethoxy-2-(2,4,6-triisopropy1phenyl)phenyl]phosphone (BrettPhos)</td>
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<td>1,1'-Bis(diphenylphosphino)ferrocene (Dppf)</td>
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Screening Results of Achiral Ligands

1 equiv + 3 equiv

Control: Xantphos

Assay Yield/ Internal Standard
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<th>Chiral Ligands</th>
<th>Screening Results of Chiral Ligands</th>
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<tr>
<td>2-Dicyclohexylphosphino-2’-methylbiphenyl (MePhos)</td>
<td>(S,S)-bpm2: (2S,4S)-tBu-(-)-4-(Diphenylphosphino)-2-(diphenylphosphinomethyl)pyrrolidine carboxylate</td>
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<td>N-(dicyclohexylphosphino)-2-2’-tolylindole (Indole ligand)</td>
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<tr>
<td>1-[2-[Bis(tert-butyl)phosphino][phenyl]-3,5-diphenyl-1H-pyrazole (Trippy Phos)</td>
<td>(S,S)-SL-M002-1</td>
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<td>2-(Dicyclohexylphosphino)biphenyl (CyJohnPhos)</td>
<td>(S,S)-SL-M003-1</td>
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<td>2-Dicyclohexylphosphino-2’,4’,6’-tri-i-propyl-1,1’-biphenyl (Xphos)</td>
<td>(S)-BINAPINE: (3S,3’S,4S,4’S,11bS,11’bS)-(−)-4,4’-Di-t-butyl-4,4’5,5’-tetrahydro-3,3’-bi-3H-dinaphtho[2,1-c:1’,2’-e]phosphepine</td>
</tr>
<tr>
<td>Di(1-adamantyl)-2-morpholinophenylphosphine (Mor-DalPhos)</td>
<td>(S,S)-SL-T001-1</td>
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<td></td>
<td>(R,S)-SL-T002-1</td>
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<td>SL-T026-2</td>
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<td>H8-BINAM-P</td>
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<td>SL-J301-1</td>
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<td>s-f-binaphane</td>
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<td>SL-T027-2</td>
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(S)-CTH-JAFAPHOS

(R,R)-Me-DuPhos: 1,2-bis((2R,5R)-2,5-dimethylphospholano)benzene
(R,R)-i-Pr-DUPHOS: (+)-1,2-Bis((2R,5R)-2,5-di-i-propylphospholano)benzene
(R,R) Et-DuPhos: (-)-1,2-BIS((2R,5R)-2,5-DIETHYLPHOSPHOLANO)BENZENE
(R)-Prophos: (R)-(+)-(1,2-DIPHENYLPHOSPHINO)PROPANE

SL-W023-1
SL-W012-1
SL-J215-2
SL-J302-1
SL-J011-1
SL-J304-1
SL-J408-1
SL-J411-2
SL-J412-1
SL-W022-1

SL-F011-2: (Twinphos, analog of Me-BoPhoz)
SL-F013-2: (Twinphos, analog of P(cyco)-BoPhoz)
SL-J851-2: (bis SL-J001)
SL-J852-2: (bis SL-J005)
SL-J853-2: (bis SL-J013)

(S,S)-Ph-BPE: (+)-1,2-Bis((2S,5S)-2,5-diphenylphospholano)ethane

SL-W016-1
(S,S)-CHIRAPHOS: (2S,3S)-(−)-Bis(diphenylphosphino)butane

(R,R)-SL-W002-1

(S,S)-DIPAMP: (S,S)-(−)-1,2-Bis[(2-methoxyphenyl)(phenyl)phosphino]ethane

(1S,1'S,2R,2'R)-DuanPhos: (1S,1'S,2R,2'R)-2,2'-Di-t-tert-butyl-2,3,2',3'-tetrahydro-1H,
1'H-(1,1')bisphosphindolyl

(R)-BINAPHANE: (R,R)-(−)-1,2-Bis[(R)-4,5-dihydro-3H-binaphtho[1,2-c:2',1'-e]phosphino]benzene

(S,S,S)-Me-Ketalphos

(S,S,R,R)-TANGPHOS: (1S,1'S,2R,2'R)-(−)-1,1'-Di-t-butyl-[2,2']-diphyospholane

SL-W006-1

(−)-MOD DIOP

SL-W003-1

CTH-(R)-SpiroP: 1R,5R,6R-(−)-1,6-Bis(diphenylphosphinoxy)spiro[4.4]nonane

SL-W001-1

CARBOPHOS: METHYL-ALPHA-D-GLUCOPYRANOSIDE-2,6-DIBENZOATE-3,4-DI(BIS(3,5-
DIMETHYLPHENYL)PHOSPHINITE)

J430-1

(1S,2S)-(−)-Bis(methylphenylphosphino)benzene

M009-1
SL-W008-1

(S)-Me-f-Ketalphos

SL-W005-1

(R,R)-NORPHOS: (2R,3R)-(−)-2,3-BIS(DIPHENYLPHOSPHINO)BICYCLO[2.2.1]HEPT-5-ENE

catASium D (R):(3R,4R)-(−)-1-BENZYL-3,4-BIS(DIPHENYLPHOSPHINO)PYRROLIDINE

M012-1: (S,S)-(−)-2,2'-BIS[(R)-(N,N-DIMETHYLAMINO)(PHENYL)METHYL]-1,1'-BIS(DI(2-
METHYLPHENYL)PHOSPHINO)FERROCENE

CTH-(R)-3,5-xylyl-PHANEPHOS: (R)-(−)-4,12-Bis(di(3,5-xylylphosphino)-[2.2]cyclophane
(S,S)-BDPP: (2S,4S)-(-)-2,4-BIS(DIPHENYLPHOSPHINO)PENTANE
Catasium MN An(R)
Catasium MNN (R)
Catasium MN MesF (R)
Catasium MN Mes (R)
(S,S)-Me-UCAP-DTBM
(R,R)-QuinoxP*: (R,R)--2,3-Bis(tert-butylmethylphosphino)quinoxaline
(R,R)-Me-KEPHOS
(S,S,R)-Me-KEPHOS
SL-J005-1
SL-J014-1
SL-J031-1
SL-J211-1
SL-J213-1
SL-J216-1
SL-J219-1
SL-J220-1
SL-J221-1
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SL-J404-1
SL-J409-1
SL-J502-1
SL-J505-1
SL-J506-1

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<th>Chiral Ligands P2-96 ligands</th>
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<td>(R,R)-Me-BPE: (+)-1,2-Bis[(2R,5R)-2,5-dimethylphospholano]ethane</td>
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<td>(R,R)-Et-BPE: (+)-1,2-Bis[(2R,5R)-2,5-diethylphospholano]ethane</td>
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<tr>
<td>(R,R)-iPr-BPE: 1,2-Bis[(2R,5R)-2,5-diisopropylphospholano]ethane</td>
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<td>(R,R)-Me-Ferrolane: 1,1'-BIS[(2R,5R)-2,5-DIMETHYLPHOSPHOLANO]ETHANE</td>
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<tr>
<td>(R,R)-Et-Ferrolane: 1,1'-BIS[(2R,5R)-2,5-DIETHYLPHOSPHOLANO]FERROCENE</td>
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<td>(R,R)-iPr-Ferrolane: 1,1'-Bis[(2R,5R)-2,5-diisopropylphospholano]ferrocene</td>
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<td>SL-J681-1: (S, Rp, SSPO)-1-tert.-butylphosphinoyl)-2-[1-(diphenylphosphino)ethyl]ferrocene</td>
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<td>SL-J688-1: (RP)-1-[(S)-1-(DI-TERT-BUTYLPHOSPHINO)ETHYL]-2-[(S)-PHENYLPHOSPHINOYL]FERROCENE</td>
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<td>(R)-PhanePhos: (R)--4,12-BIS(DIPHENYLPHOSPHINO)-[2,2]-PARACYCLOPANE</td>
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<td>(R)-An-PhanePhos: (R)-4,12-Bis[di(4-methoxyphenyl)phosphino]-[2,2]-paracyclocphane</td>
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<td>(1S,1'S)-ethane-1,2-diylibis(tert-butyl(methyl)phosphonium) tetrafluoroborate</td>
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<tr>
<td>(R,R)-miniPHOS 2HBF4: (1R,1'R)-methylenebis(tert-butyl(methyl)phosphonium) tetrafluoroborate</td>
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<td>(R)-di-tert-butyl((tert-butyl(methyl)phosphonio)methyl)phosphonium tetrafluoroborate</td>
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<td>(S)-MaxPhos HBF4: (S)-(tert-butylmethylphosphonio)(di-tert-butylphosphino)amine tetrafluoroborate</td>
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<td>(R,R)-(+-)-1,2-Bis(t-butylmethylphosphino)benzene</td>
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Chiral Ligands P3-60 ligands

(R)-MonoPhos: (R)-(4-[N,N-DIMETHYLMINO]DINAPHTH[2,1-D:1',2'-F][1,3,2]DIOXAPHOSPHEPINE
(S)-N-Me-N-Bn-MonoPhos: (S)-(3,5-DIOX-4-PHOSPHA-CYCLOHEPTA[2,1-A:3,4-A']DINAPHTHALEN-4-YL]BENZYL(METHYL)AMINE
(S)-PipPhos: (S)-(3,5-Dioxaphosphacyclohepta[2,1-a;3,4-a']diphenalene-4-y1)piperidine
(S)-2,6-Me-MonoPhos: (S)-(2,6-Dimethyl-3,5-dioxaphosphacyclohepta[2,1-a;3,4-a']diphenalene-4-y1)dimethylamine
(S,R)-(a-MeBn)-MonoPhos: (S)-(3,5-Dioxa-4-phosphacyclohepta[2,1-a;3,4-a']diphenalene-4-y1)(1R)-1-phenylethylamine
(S,R)-(a-MeBn)2-MonoPhos: (S)-(3,5-DIOX-4-PHOSPHACYCLOHEPTA[2,1-A;3,4-A']DINAPHTHALEN-4-YL]BIS[(1R)-1-PHENYLETHYL]AMINE, DICHLORMETHANE ADDUCT
(S,S)-(a-MeBn)2-MonoPhos: (S)-(3,5-Dioxaphosphacyclohepta[2,1-a;3,4-a']diphenalene-4-y1)bis[(1S)-1-phenylethyl]amine
(S)-H8-MonoPhos: (S)-(8,9,10,11,12,13,14,15-octahydro-3,5-DIOXAPHOSPHACYCLOHEPTA[2,1-A;3,4-A']DINAPHTHALEN-4-YL]DIMETHYLAMINE
(S)-H8-PipPhos: 1-[(11bS)-8,9,10,11,12,13,14,15-octahydrodiphosphino[2,1-d:1',2'-f][1,3,2]diphenalene-4-y1)piperidine
(R)-BINOL-P-OiPr: (R)-BINAPHTHYLISOPROPYLPHOSPHITE
(R)-BINOL-P-OiBu: (R)-BINAPHTHYLISOBUTYLPHOSPHITE
(R,R)-TADDOL-P-NMe2: (3aR,8aR)-(2,2-Dimethyl-4,8,8-tetraphenyl-tetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphin-6-yl)dimethylamine
(R)-SIPHAS: (11aR)-(10,11,12,13-tetrahydrodiinden[I,1-de:1',7'-fg][1,3,2]dioxaphosphocin-5-dimethylamine
(R)-SIPHOS: (11aR)-(10,11,12,13-tetrahydrodiinden[I,1-de:1',7'-fg][1,3,2]dioxaphosphocin-5-bis[(R)-1-phenylethyl]amine
(R)-ShiP: (11aR)-(10,11,12,13-tetrahydrodiinden[I,1-de:1',7'-fg][1,3,2]dioxaphosphocin-5-phenoxo
(S,S)-Mikami Ligand: 2,10-dimethyl-N,N-bis[(1S)-1-phenylethyl]-12H-Dibenzo[d,g]1,3,2]dioxaphosphocin-6-amine
(S,S)-tBu-Mikami Ligand: 4,8-di-tert-butyl-2,10-dimethyl-N,N-bis[(1S)-1-phenylethyl]-12H-Dibenzo[d,g]1,3,2]dioxaphosphocin-6-amine
(R)-Quinap: (R)-1-(2-DIPHENYLPHOSPHINO-1-NAPHTHYL)ISOQUINOLINE
(R)-N-PINAP: (R)-(4-[2-(DIPHENYLPHOSPHINO)-1-NAPHTHALENYL]-N-[1S)-1-PHENYLETHYL]1-PHTHALAZINAMINE
(R)-MOP
(R,R)-Me-DuPhos Monoxide: (2R,5R)-1-[(2R,5R)-2,5-DIMETHYLPHOSPHOLAN-1-YL]PHENYL]-2,5-DIMETHYLPHOSPHOLAN-1-OXIDE
(S,S)-Me-RajPhos: (2S,5S)-(1)-1-[(2',3'-DIOLXONOL-2-YL]PHENYL]-2,5-DIMETHYLPHOSPHOLANE
(S,S)-Et-RajPhos: (2S,5S)-(-)-1-[(2,3'-DIOLXONOL-2-YL]PHENYL]-2,5-DIMETHYLPHOSPHOLANE
(S,S)-DiazaPhos-PPE: 2,2',3'-[(1S,3S)-2,3,5,10-tetrahydro-5,10-dioxo-2-phenyl-1H-[1,2,4]diaza phospholol[1,2b]phthalazine-1,3-diyl]bis[N-(1S)-1-phenylethyl]benzamide
(S,BINAP: (S)-(++)-2,2'-BIS(DIPHENYLPHOSPHINO)-1,1'-BINAPHTHYL
(R)-xyl-BINAP: (R)-(++)-2,2'-BIS[DI(3,5-XYLYL)PHOSPHINO]-1,1'-BINAPHTHYL
(R)-SegPhos: (R)-(++)-5,5'-BIS(DIPHENYLPHOSPHINO)-4,4'-BI-1,1'-BENZODIOXOLE
SL-J002-1
SL-J212-1
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<td>SL-W005-2</td>
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<td>(S,S)-Me-DuPhos: (+)-1,2-BIS(2S,5S)-2,5-DIMETHYLPHOSPHOLANO)BENZENE</td>
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<td>(1S,1'S,2R,2'R)-DuanPhos: (1S,1'S,2R,2'R)-2,2'-Di-tert-butyl-2,3,2',3'-tetrahydro-1H,1'H-(1,1')bisophosphindolyl</td>
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<td>(R,R)-QuinoxP*: (R,R)-2,3-Bis(tert-butylmethylphosphino)quinoxaline</td>
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<td>(R,R)-SL-M002-2 (Cy)</td>
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<td>(S,S)-Me-UCAP-DTBM</td>
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<td>(S)-(-)-7,7'-Bis(diphenylphosphino)-2,2',3,3'-tetrahydro-1,1'-spirobiindene</td>
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<td>(+)-Cy-SEGPHOS</td>
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<td>(S)-BINAPINE: (3S,3'S,4S,4'S,11bS,11'bS)-(+) -4,4'-Di-t-butyl-4,4',5,5'-tetrahydro-3',3'-bi-3H-dinaphtho[2,1-c:1',2'-e]phosphepine</td>
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<td>(S)-PipPhos: (S)-(+-)(3,5-Dioxa-4-phosphacyclohepta[2,1-a;3,4-a']dinaphthalen-4-yl)piperidine</td>
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<td>K15-0026: (1R,2R)-N,N'-BIS[2-(DIPHENYLPHOSPHINO)BENZYL]CYCLOHEXANE-1,2-DIAMINE</td>
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<td>K15-0088: (1R,2R)-N,N-Bis(2-(di-p-tolylphosphino)benzyl)cyclohexane-1,2-diamine</td>
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<td>K15-0090: (1R,2R)-N,N-Bis(2-(bis(3,5-dimethylphenyl)phosphino)benzyl)cyclohexane-1,2-diamine</td>
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<td>K15-0020: 2,2'-BIS((R-1,1'-BINAPHTHYL)-2,2'-DIMETHYL)PHOSPHINO)DIETHYLAMINE</td>
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<td>K15-0129: (R)-1-(DIPHENYLPHOSPHINO)-2-AMINO-3-METHYL BUTANE</td>
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<td>K15-0131: (R)-1-(DIPHENYLPHOSPHINO)-2-AMINO-3,3-DIMETHYL BUTANE</td>
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<td>K15-0128: (S)-1-AMINO-8-(DIPHENYLPHOSPHINO)-1,2,3,4-TETRAHYDRONAPHTHALENE</td>
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<td>K15-0046: (1R,2R)-2-(DIPHENYLPHOSPHINO)-1,2-DIPHENYLETHYLAMINE</td>
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<td>K15-0137: (1R,2R)-2-(DIPHENYLPHOSPHINO)-1-AMINOCYCLOHEXANE</td>
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<td>K15-0100: (1R,2R)-1-[(4S,11B Br)-3,5-DIHYDRO-4H-DINAPHTHIO[2,1-C:1',2'-E]PHOSPHEPIN-4-YL]-1-PHENYLPROPAN-2-AMINE</td>
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<td>(1S,2S)-(2-METHYLAMINO-1-PHENYLPROPYL)DIPHENYLPHOSPHINE</td>
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![Chemical Reaction Diagram]

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<td>61</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>SL-J204-1</td>
<td>5/10</td>
<td>24</td>
<td>85</td>
<td>73</td>
</tr>
<tr>
<td>7</td>
<td>SL-J204-1</td>
<td>5/10</td>
<td>0</td>
<td>80</td>
<td>93</td>
</tr>
<tr>
<td>8</td>
<td>SL-J204-1</td>
<td>5/7.5</td>
<td>0</td>
<td>93</td>
<td>92</td>
</tr>
<tr>
<td>9</td>
<td>SL-J204-1</td>
<td>5/5</td>
<td>0</td>
<td>92(91)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>92</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conducted on a 0.1 mmol scale.<sup>b</sup> Yield determined by <sup>1</sup>H NMR spectroscopy of the crude reaction mixture.<sup>c</sup> Crude e.e determined by chiral-HPLC. <sup>d</sup> Isolated yield.

### 2.5. REFERENCES


Chapter 3
Palladium-Catalyzed $\alpha$-Arylation of Aryl Acetic Acid Derivatives via Dienolate Intermediates with Aryl Chlorides and Bromides

3.1. INTRODUCTION

Transition metal-catalyzed $\alpha$-arylation of enolates and their derivatives is of great importance due to the diversity of compounds that can be accessed.\(^1\) In 1997 pioneering studies on palladium-catalyzed $\alpha$-arylation of ketones with aryl bromides was independently reported by the Miura\(^2\), Buchwald\(^3\) and Hartwig\(^4\) groups. Since these seminal works, intensive studies on $\alpha$-arylation of carbonyl compounds have been reported.\(^5,6\) To date, however, examples of $\alpha$-arylation of simple carboxylic acids remain scarce.\(^7,9\)

In 2007, Daugulis and co-workers studied the palladium-catalyzed ortho arylation of benzoic acids. They reported a byproduct derived from the $\alpha$-arylation of acetic acid with 3,5-dimethyl iodobenzene (Scheme 3.1A).\(^7\) The scope and mechanism of this reaction were recently investigated by Han and Zhao.\(^8\) In both cases, the reaction required use of excess acetic acid (3.5 to >50 equiv), supra-stoichiometric silver acetate, and gave poor to moderate yields (18–68%).
In 2000, Wolfe and co-workers reported reaction of phenyl acetic acid dienolate with aryl bromides and iodides in liquid ammonia under near-UV irradiation to afford alpha and para arylation products via a proposed $S_{RN1}$ process (Scheme 3.1B). The inconvenient reaction conditions ($NH_3(l)$, $hv$) preclude large-scale applications of this chemistry.

**Scheme 3.1. Previous Examples of a-Arylation of Carboxylic Acid Derivatives**

**A. Daugulis, 2007**

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\begin{array}{c}
\text{I} \\
\end{array} & \quad \begin{array}{c}
\text{OH} \\
\end{array}
\end{align*}
\]

\[+ \quad CH_3COOH \quad + \quad AgOAc \quad \xrightarrow{\text{Pd(OAc)}_2 \, (\text{cat}) \, 130 \, ^\circ C, \, 7 \, h} \]

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\begin{array}{c}
\text{OH} \\
\end{array} & \quad \begin{array}{c}
\text{OH} \\
\end{array}
\end{align*}
\]

52% yield

**B. Wolfe, 2000**

\[
\begin{align*}
\text{Ar} & \quad \text{Li}_2\text{O} \quad \text{Li}_2\text{O} \\
\end{align*}
\]

\[\xrightarrow{\text{Ar}-\text{X} \, (1 \, \text{equiv})} \quad \text{NH}_3(l), \, hv, \, 5 \, h \]

\[
\begin{align*}
\text{Ar} & \quad \text{OH}_2 \\
\end{align*}
\]

61–77% yield

**C. Mori 2014**

**D. This work**

Mori and co-workers described $\alpha$-arylation of carboxylic acids in a two-step process (Scheme 3.1C). The substrates are first irreversibly deprotonated using EtMgCl to generate dienolates followed by palladium-catalyzed $\alpha$-arylation with aryl bromides and iodides.
Our approach to the α-arylation of carboxylic acids differs from that of Mori and coworkers. We envisioned reversible deprotonation of the substrate in the presence of the catalyst, allowing the use of less reactive bases. Under these conditions, the carboxylate would be in equilibrium with the dienolate, as shown in Scheme 3.1D. To develop this approach, a few issues must be considered. Prior studies on the generation of dienolates by double deprotonation of carboxylic acids\textsuperscript{11-14} indicate strong bases (e.g. \textsuperscript{t}BuLi, LDA, Grignard reagents) are needed to achieve the second deprotonation.

Other challenges include control of chemo selectivity, undesired reactivity of the aryl acetic acid starting materials and decomposition/further reactions of the diaryl acetic acid product. As noted above, aryl acetic acid derivatives are known to undergo palladium-catalyzed ortho arylation \textit{via} a C–H activation pathway.\textsuperscript{15,16} In this process the carboxylate moiety serves as directing group to facilitate the C–H bond cleavage. For example, Yu and co-workers demonstrated that ortho-C–H activation of phenyl acetic acid derivatives by palladium could be followed by cross-coupling (Scheme 3.2A). Furthermore, aryl acetates have been reported to be unstable in the presence of palladium catalysts and undergo decarboxylative cross-coupling.\textsuperscript{17-23} This reaction pathway is exemplified by the report of Liu and co-workers, who demonstrated diarylmethanes can be formed using 2-pyridyl or nitroaryl acetates with aryl halides via palladium-catalyzed decarboxylative coupling (Scheme 3.2B).\textsuperscript{22,23} These studies indicate potential side reaction involving intermediates such as those in Scheme 3.1D that may compete with the desired α-arylation of dienolates.

Despite these issues, our experience with deprotonative cross-coupling processes (DCCP) of weakly acidic substrates ($pK_a > 25$) positioned us to pursue
the α-arylation of acids. An important feature of the DCCP is an *in situ* reversible metallation of the substrate via C–H deprotonation under catalytic cross-coupling conditions. Herein, we describe a general protocol for the palladium-catalyzed α-arylation of carboxylic acids with aryl chlorides and bromides involving reversible deprotonation of the carboxylate.

**Scheme 3.2.** Selectivity in Arylation of Aryl Acetic Acid Derivatives

A. Yu 2008-2013

B. Liu 2010

Ar= 2-Pyridyl, 2-nitrophenyl, 4-nitrophenyl

3.2. RESULTS AND DISCUSSION

The first step in our reaction development focused on deprotonation of phenyl acetic acid to form the dienolate intermediate. To evaluate bases to deprotonate the carboxylate substrate, we employed a benzylation reaction with benzyl chloride to trap the dienolate (eq 3.1).
We chose to use KN(SiMe$_3$)$_2$ as base, because it exhibits good compatibility with catalysts, reagents, and products in deprotonative cross-coupling processes.$^{28}$ Employing KN(SiMe$_3$)$_2$ at 80 °C (eq. 3.1), the benzylation product 1aa was isolated in 80% yield, indicating formation of the dienolate under these conditions. With this result in hand, we chose the NiXantphos/Pd(OAc)$_2$–based catalyst due to its ability to arylate weakly acidic substrates, such as diphenylmethanes ($pK_a = 32.3^{32}$, eq. 3.2).$^{28}$

We examined the α-arylation of phenyl acetic acid 1a (1.2 equiv) with 1-bromo-4-tert-butylbenzene 2a (limiting reagent) in the presence of KN(SiMe$_3$)$_2$ (2.5 equiv) and catalytic Pd(OAc)$_2$ (5 mol %) and NiXantphos (7.5 mol %). These studies were initiated with a solvent screen. The reaction in cyclopentyl methyl ether (CPME), an excellent solvent for DCCP’s, failed to afford arylation product (Table 3.1, entry 1). Dioxane initially appeared promising, with 56% yield (entry 2). Attempts to increase the yield, however, were unsuccessful. THF, 2-methyl-THF, and DME (entries 3–5) were examined at 80 °C with DME, giving up to 80% yield. Likewise, toluene at 110 °C afforded the product in 80% yield (entry 6). Both THF and DME resulted in generation of 5–10% of an inseparable byproduct that was not observed in toluene, making toluene a better choice for further optimization. In the reaction in toluene (entry 6), some decomposition of phenyl acetic acid was observed, presumably resulting in lower yields. To address this issue, the equivalents of aryl bromide and base were increased to 1.5 and 3,
respectively, resulting in 83% yield (entry 7). Reducing the reaction concentration to 0.05 M resulted in > 95% yield by $^1$H NMR of the crude product (entry 8). Lowering the temperature (entry 9) or catalyst loading (entry 10), resulted in lower yields.

Table 3.1. Optimization of Phenyl Acetic Acid α-Arylation

<table>
<thead>
<tr>
<th>entry</th>
<th>(1a : base)</th>
<th>temp (°C)</th>
<th>solvent</th>
<th>conc.</th>
<th>yieldb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.2 : 2.5</td>
<td>110</td>
<td>CPME</td>
<td>0.1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1.2 : 2.5</td>
<td>110</td>
<td>dioxane</td>
<td>0.1</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>1.2 : 2.5</td>
<td>80</td>
<td>THF</td>
<td>0.1</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>1.2 : 2.5</td>
<td>80</td>
<td>2-MeTHF</td>
<td>0.1</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>1.2 : 2.5</td>
<td>80</td>
<td>DME</td>
<td>0.1</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>1.2 : 2.5</td>
<td>110</td>
<td>toluene</td>
<td>0.1</td>
<td>80</td>
</tr>
<tr>
<td>7</td>
<td>1.5 : 3.0</td>
<td>110</td>
<td>toluene</td>
<td>0.1</td>
<td>83</td>
</tr>
<tr>
<td>8</td>
<td>1.5 : 3.0</td>
<td>110</td>
<td>toluene</td>
<td>0.05</td>
<td>&gt;95 (93)</td>
</tr>
<tr>
<td>9c</td>
<td>1.5 : 3.0</td>
<td>80</td>
<td>toluene</td>
<td>0.05</td>
<td>65</td>
</tr>
<tr>
<td>10c,d</td>
<td>1.5 : 3.0</td>
<td>110</td>
<td>toluene</td>
<td>0.05</td>
<td>88 (85)</td>
</tr>
</tbody>
</table>

a Reaction conducted on a 0.1 mmol scale. b Yield determined by $^1$H NMR spectroscopy of the crude reaction mixture. c Isolated yield after chromatographic purification. d 2.5 mol % Pd(OAc)$_2$/3.75 mol % NiXantphos.

With the optimized conditions of Table 3.1 (entry 8), the scope of aryl halides in the α-arylation of phenyl acetic acid was examined (Table 3.2). 1-Bromo- and 1-chloro-4-tert-butylbenzene gave 3aa in 93 and 84% yield,
respectively (entry 1). Substrates with electron donating groups, such as 4-bromo- and 4-chloroanisole, exhibited good reactivity, generating 87 and 80% yield of the arylation products (entry 2). 4-Bromo-\(N,N\)-dimethylaniline furnished 3ac in 86% yield. Aryl bromides and chlorides with electron-withdrawing groups, such as 4-F, 4-Cl, and 3-CF\(_3\), were all tolerated. 1-Bromo- and 1-chloro-4-fluorobenzene furnished diaryl acetic acid in 75 and 62% yield, respectively, while 1-bromo-4-chlorobenzene underwent coupling to give 3ae in 65% yield. In the latter case, no byproducts derived from oxidative addition of the C–Cl bond were observed. Aryl bromide bearing a 3-CF\(_3\) substituent furnished the product in 77% yield. Sterically hindered 2-bromotoluene and 1-bromonaphthalene gave 3ag and 3ah in 71% and 80% yields, respectively. In the case of 2-bromotoluene, both the aryl bromide and base equivalents were increased to 2 and 4, respectively. For the more challenging 2-chlorotoluene, 10% Pd(OAc)\(_2\) was required to render 3ag in 63% isolated yield. Heterocyclic \(N\)-methyl-5-bromoindole exhibited good reactivity with phenyl acetic acid to form 3ai in 82% yield. The TIPS silyl ether derived from 4-bromophenol was subjected to the reaction conditions and afforded 3ai in 53% yield. (Table 2, entry 10) Unfortunately, aryl bromides containing ketone, ester or amide groups failed to give desired products.

Table 3.2. Scope of Aryl Halides in the a-Arylation of Phenyl Acetic Acid\(^{a,b}\)

---

91
92

a Reaction conducted on a 0.1 mmol scale at 0.05M. b Isolated yield after chromatographic purification. c 2 equiv of 1a and 4 equiv of KN(SiMe₃)₂. d 10 mol % Pd(OAc)₂/15 mol % NiXantphos.
The scope of α-arylation with substituted aryl acetic acids was examined with 1-bromo-4-tert-butylbenzene 2a (Table 3.3). Electron neutral 2-naphthyl acetic acid afforded the coupling product in 73% yield. Electron donating 4-methoxy phenyl acetic acid underwent coupling in 86% yield. Aryl acetic acids with withdrawing 4-F, 4-Cl and 3-CF₃ groups furnished coupling products in 81, 58 and 65% yield, respectively. Sterically hindered 2-tolyl acetic acid proved to be a challenging substrate with 53% yield obtained despite repeated attempts to optimize the reaction. We next examined 3-pyridyl acetic acid in the α-arylation. With our standard reaction conditions, only decomposition of the acid was observed. We then screened bases KN(SiMe₃)₂, NaN(SiMe₃)₂, LiN(SiMe₃)₂, KO'Bu, NaO'Bu, and LiO'Bu and identified NaO'Bu as a better option, generating 70% isolated yield in the coupling (entry 7). In order to demonstrate scalability of the protocol, a gram-scale reaction was performed with 4-methoxy phenyl acetic acid (1b) and 4-tert-butyl bromobenzene (2a). The arylation product 3ba (1.1 g) was isolated in 74% (Table 3.3, entry 1).

Table 3.3. Scope of α-Arylation with Aryl Acetic Acids* b
After demonstrating the scope of aryl halides and aryl acetic acids, we turned our attention to styryl acetic acids (Scheme 3.3). *trans*-Styryl acetic acid 4a is an interesting substrate, because it has two sites that can potentially undergo arylation. After screening different bases with this substrate, we observed that with NaN(SiMe₃)₂, only one regioisomeric arylation product was
obtained. It appears that the initially formed product undergoes isomerization of the double bond to form the more conjugated product 4ap in 70% isolated yield. This product could also be envisioned to arise from a Heck reaction. We are unaware, however, of literature precedence involving trans-styryl acetic acids undergoing Heck-type reactions.

It is noteworthy that the structure of 4ap is related to Amitriptyline, a medication that has been used in the treatment of migraines,\textsuperscript{33,34} diabetic neuropathy,\textsuperscript{35} postherpetic neuralgia,\textsuperscript{36} and chronic lower back pain.\textsuperscript{35,37} In addition, Brown and co-workers reported an analog of Amitriptyline, diphenylamine DHP-362, which exhibits higher potency as a sodium channel blocker.\textsuperscript{38} The synthesis of DHP-362 is only two steps away from 4ap. We next examined the arylation of trans-styryl acetic acid 4a with different aryl bromides. Both 4-\textit{tert}-Bu and 4-F groups underwent reaction with excellent regioselectivity and afforded E/Z-mixtures in 71–78% yield.\textsuperscript{39}

**Scheme 3.3. Arylation of trans-Styryl Acetic Acid 4a**

\[
\begin{array}{c}
\text{1 equiv } \text{ArBr} \\
\begin{array}{c}
5 \text{ mol } \% \text{ Pd(OAc)}_2 \\
7.5 \text{ mol } \% \text{ NiXantphos}
\end{array}
\begin{array}{c}
3 \text{ equiv } \text{NaN(SiMe}_3\text{)}_2 \\
\text{Toluene, } 80 \degree \text{C, 12 h}
\end{array}
\end{array}
\]

\[
\begin{array}{c}
\begin{array}{c}
\text{O} \\
\text{N}
\end{array}
\begin{array}{c}
\text{OH} \\
\text{Ar}
\end{array}
\end{array}
\]

\[
\begin{array}{c}
\begin{array}{c}
\begin{array}{c}
\text{N}
\end{array}
\begin{array}{c}
\text{OH}
\end{array}
\end{array}
\begin{array}{c}
\begin{array}{c}
\text{N}
\end{array}
\begin{array}{c}
\text{OH}
\end{array}
\end{array}
\end{array}
\]

**Ar = Ph, 4ap, 70%**

**Ar = 4-\textit{Bu}-C\textsubscript{6}H\textsubscript{4}, 4aa, 78% (E:Z = 1.4:1)**

**Ar = 4-F-C\textsubscript{6}H\textsubscript{4}, 4ad, 71% (E:Z = 1:1)**

\[
\begin{array}{c}
\text{Amitriptyline} \\
\text{DHP-362}
\end{array}
\]

### 3.3. SUMMARY AND OUTLOOK

In summary, we have developed a general method for palladium-catalyzed \(\alpha\)-arylation of aryl acetic acids with aryl bromides and chlorides. The reaction also
affords product with *trans*-styryl acetic acid, which provides intermediates in route to biologically active compounds. We anticipate that this protocol will be an important complement to the existing arsenal of palladium-catalyzed a-arylation reactions.

### 3.4. EXPERIMENTAL SECTION

**General Methods.** All reactions were performed under nitrogen using oven-dried glassware and standard Schlenk or vacuum line techniques. Air- and moisture-sensitive solutions were handled under nitrogen and transferred via syringe. Toluene (anhydrous, 99.8%) was purchased from Sigma-Aldrich, THF was sparged for 20 min with dry N₂ and dried using a commercial two-column solvent purification system comprising columns packed with neutral alumina. Unless otherwise stated, reagents were commercially available and used as purchased without further purification. Chemicals were obtained from Sigma-Aldrich, Acros, TCI America, Strem Chemicals or Matrix Scientific, and solvents were purchased from Fisher Scientific. The progress of the reactions was monitored by thin-layer chromatography using Whatman Partisil K6F 250 μm precoated 60 Å silica gel plates and visualized by short-wavelength ultraviolet light as well as by treatment potassium permanganate (KMnO₄) stain or iodine. Silica gel (230–400 mesh, Silicycle) was used for flash chromatography. The ¹H NMR and ¹³C{¹H} NMR spectra were obtained using a Brüker AM-500 Fourier transform NMR spectrometer at 500 and 126 MHz, respectively. Chemical shifts are reported in units of parts per million (ppm) downfield from tetramethylsilane (TMS), and all coupling constants are reported in hertz. The infrared spectra were obtained with KBr plates using a Perkin-Elmer Spectrum 100 Series FTIR spectrometer. High-resolution mass spectrometry (HRMS) data were obtained on a Waters LC–TOF mass spectrometer (model LCT-XE Premier) using chemical ionization (CI) or electrospray ionization (ESI) in positive or negative mode,
depending on the analyte. Melting points were determined on a Unimelt Thomas-Hoover melting point apparatus and are uncorrected. Compounds 2i was prepared according to literature procedures. It is noteworthy that the acidic proton of the acid products is not observed under the $^1$H NMR conditions used in our protocol (except in one case). The acid is clearly visible in the IR and $^{13}$C($^1$H) NMR, and high resolution MS spectra.

**General Procedure**: Palladium-Catalyzed Alpha Arylation with Phenyl Acetic Acids. An oven-dried 10 mL reaction vial equipped with a stir bar was charged with KN(SiMe$_3$)$_2$ (60 mg, 0.30 mmol, 3 equiv) under a nitrogen atmosphere. A solution (from a stock solution) of Pd(OAc)$_2$ (1.12 mg, 0.0050 mmol) and NiXantphos (4.14 mg, 0.0075 mmol) in 2 mL of dry toluene was taken up by syringe and added to the reaction vial. After stirring for 5 min at 24 °C, phenyl acetic acid 1a (20.42 mg, 0.15 mmol, 1.5 equiv) was added to the reaction mixture followed by 2a (18 μL, 0.1 mmol, 1 equiv). The reaction mixture was stirred for 12 h at 110 °C, quenched with two drops of H$_2$O, diluted with 3 mL of 15% MeOH/DCM solution and filtered over a pad of MgSO$_4$ and silica. The pad was rinsed with additional 15% MeOH/DCM solution, and the solution was concentrated *in vacuo*. The crude material was loaded onto a silica gel column and purified by flash chromatography eluting with MeOH/DCM.

**2,3-Diphenylpropanoic acid (3.1aa)**: An oven-dried 10 mL reaction vial equipped with a stir bar was charged with 1a (16.3 mg, 0.12 mmol), KN(SiMe$_3$)$_2$ (60 mg, 0.30 mmol, 3 equiv) under a nitrogen atmosphere. THF (2 mL) was added followed by benzyl chloride (11.5 μL, 0.1 mmol). The reaction mixture was stirred for 12 h at 110 °C, quenched with two drops of H$_2$O, diluted with 3 mL of 15% MeOH/DCM solution and filtered over a pad of
MgSO₄ and silica. The pad was rinsed with additional 15% MeOH/DCM solution, and the solution was concentrated in vacuo. The crude material was purified by flash chromatography on silica gel (eluted with MeOH:DCM = 0.5:99.5 to MeOH:DCM = 2.5:97.5) to give the product (18 mg, 80% yield) as a colorless oil. Rf = 0.40 (MeOH:DCM = 5:95). The spectroscopic data match the previously reported data.

2-(4-(tert-Butyl)phenyl)-2-phenylacetic acid (3.3aa): The reaction was performed following the General Procedure with 1a (20.4 mg, 0.15 mmol), KN(SiMe₃)₂ (60 mg, 0.30 mmol) and 1-bromo-4-(tert-butyl)benzene (18 μL, 0.1 mmol). The crude material was purified by flash chromatography on silica gel (eluted with MeOH:DCM = 0.5:99.5 to MeOH:DCM = 2.5:97.5) to give the product (25 mg, 93% yield) as a yellow oil. Rf = 0.40 (MeOH:DCM = 5:95); ¹H NMR (500 MHz, CDCl₃): δ 7.35-7.24 (m, 9H), 5.01 (s, 1H), 1.29 (s, 9H); ¹³C {¹H} NMR (126 MHz, CDCl₃): δ 178.6, 150.6, 138.3, 135.1, 128.91, 128.84, 128.5, 127.6, 125.8, 56.8, 34.7, 31.5; IR (thin film): 3060, 3029, 2963 (br), 2904, 2708, 1708, 1600, 1514, 1496, 1454, 1408, 1364, 1307, 1285, 1269, 1215, 1174, 1108, 1019, 934, 821, 700 cm⁻¹; HRMS calc’d for C₁₈H₂₀O₂⁺ 268.1463, observed 268.1459 [MH]⁺.

2-(4-(tert-Butyl)phenyl)-2-phenylacetic acid (3.3aa) (from 1-chloro-4-(tert-butyl)benzene): The reaction was performed following the General Procedure with 1a (20.4 mg, 0.15 mmol), KN(SiMe₃)₂ (60 mg, 0.30 mmol) and 1-chloro-4-(tert-butyl)benzene (17 μL, 0.1 mmol). The crude material was purified by flash chromatography on silica gel (eluted with MeOH:DCM = 0.5:99.5 to MeOH:DCM = 2.5:97.5) to give the product (22.5 mg, 84% yield) as a yellow oil. Rf = 0.40 (MeOH:DCM = 5:95). The spectroscopic data match the previously reported data.
2-(4-Methoxyphenyl)-2-phenylacetic acid (3.3ab): The reaction was performed following the General Procedure with 1a (20.4 mg, 0.15 mmol), KN(SiMe₃)₂ (60 mg, 0.30 mmol) and 1-bromo-4-methoxybenzene (12.5 μL, 0.1 mmol). The crude material was purified by flash chromatography on silica gel (eluted with MeOH:DCM = 0.5:99.5 to MeOH:DCM = 2.5:97.5) to give the product (21 mg, 87% yield) as a colorless oil. R_f = 0.40 (MeOH:DCM = 5:95); ¹H NMR (500 MHz, CDCl₃): δ 7.31-7.22 (m, 7H), 6.85 (d, J = 8.5, 2H), 4.98 (s, 1H), 3.77 (s, 3H); ¹³C ¹H NMR (126 MHz, CDCl₃): δ 178.6, 158.9, 138.3, 130.1, 129.8, 128.66, 128.57, 127.4, 114.1, 56.2, 55.3; IR (thin film): 3029 (br), 1707, 1610, 1584, 1512, 1494, 1454, 1408, 1303, 1232, 823, 699 cm⁻¹; HRMS calc’d for C₁₅H₁₄O₃+ 242.0943, observed 242.0937 [M]+.

2-(4-Methoxyphenyl)-2-phenylacetic acid (3.3ab) (from 1-chloro-4-methoxybenzene): The reaction was performed following the General Procedure with 1a (20.4 mg, 0.15 mmol), KN(SiMe₃)₂ (60 mg, 0.30 mmol) and 1-chloro-4-methoxybenzene (12.5 μL, 0.1 mmol). The crude material was purified by flash chromatography on silica gel (eluted with MeOH:DCM = 0.5:99.5 to MeOH:DCM = 2.5:97.5) to give the product (19.5 mg, 80% yield) as a colorless oil. R_f = 0.40 (MeOH:DCM = 5:95). The spectroscopic data match the previously reported data.

2-(4-(Dimethylamino)phenyl)-2-phenylacetic acid (3.3ac): The reaction was performed following the General Procedure with 1a (20.4 mg, 0.15 mmol), KN(SiMe₃)₂ (60 mg, 0.30 mmol) and 4-bromo-N,N-dimethylaniline (20 mg, 0.1 mmol). The crude material was purified by flash chromatography on silica gel (eluted with MeOH:DCM = 0.5:99.5 to MeOH:DCM = 2.5:97.5) to give the product (22 mg, 86% yield) as a yellow oil. R_f = 0.40 (MeOH:DCM = 5:95); ¹H NMR (500 MHz, CDCl₃): δ 7.32-7.22 (m,
5H), 7.19-7.17 (m, 2H), 6.70-6.68 (m, 2H), 4.94 (s, 1H), 2.91 (s, 6H); $^{13}$C \{^1H\} NMR (126 MHz, CDCl$_3$): $\delta$ 178.9, 149.9, 138.8, 129.4, 128.60, 128.55, 127.2, 126.0, 112.9, 56.2, 40.7; IR (thin film): 3059, 3027, 2920 (br), 2803, 1953, 1719, 1612, 1565, 1521, 1495, 1453, 1351, 1282, 1196, 1165, 1032, 947, 909, 813, 728, 700 cm$^{-1}$; HRMS calc'd for C$_{16}$H$_{18}$NO$_2$ $^2$ 256.1338, observed 256.1338 [M+H$^+$].

2-(4-Fluorophenyl)-2-phenylacetic acid (3.3ad): The reaction was performed following the General Procedure with 1a (20.4 mg, 0.15 mmol), KN(SiMe$_3$)$_2$ (60 mg, 0.30 mmol) and 1-bromo-4-fluorobenzene (11 $\mu$L, 0.1 mmol). The crude material was purified by flash chromatography on silica gel (eluted with MeOH:DCM = 0.5:99.5 to MeOH:DCM = 2.5:97.5) to give the product (17.3 mg, 75% yield) as a yellow solid (m. p. = 106-108 °C). $R_f = 0.40$ (MeOH:DCM = 5:95); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.34-7.26 (m, 7H), 7.00 (t, $J$ = 8.6, 2H), 5.01 (s, 1H); $^{13}$C \{^1H\} NMR (126 MHz, CDCl$_3$): $\delta$ 178.3, 162.1 ($J$ = 247 Hz), 137.7, 133.67 ($J$ = 3.8 Hz), 130.36 ($J$ = 7.6 Hz), 128.8, 128.5, 127.7, 115.56 ($J$ = 21.4 Hz), 56.2; IR (thin film): 2923 (br), 1704, 1602, 1508, 1454, 1284, 1223, 1159, 804, 720, 695 cm$^{-1}$; HRMS calc'd for C$_{14}$H$_{16}$F$^-$ 229.0665, observed 229.0672 [M-H$^-$].

2-(4-Fluorophenyl)-2-phenylacetic acid (3.3ad) (from 1-chloro-4-fluorobenzene): The reaction was performed following the General Procedure with 1a (20.4 mg, 0.15 mmol), KN(SiMe$_3$)$_2$ (60 mg, 0.30 mmol) and 1-chloro-4-fluorobenzene (11 $\mu$L, 0.1 mmol). The crude material was purified by flash chromatography on silica gel
(eluted with MeOH:DCM = 0.5:99.5 to MeOH:DCM = 2.5:97.5) to give the product (14.3 mg, 62% yield) as a yellow solid (m. p. = 106-108 °C). \( R_f = 0.40 \) (MeOH:DCM = 5:95). The spectroscopic data match the previously reported data.

**2-(4-Chlorophenyl)-2-phenylacetic acid (3.3ae):** The reaction was performed following the General Procedure with 1a (20.4 mg, 0.15 mmol), KN(SiMe\(_3\))\(_2\) (60 mg, 0.30 mmol) and 1-bromo-4-chlorobenzene (19.14 mg, 0.1 mmol). The crude material was purified by flash chromatography on silica gel (eluted with MeOH:DCM = 0.5:99.5 to MeOH:DCM = 2.5:97.5) to give the product (16 mg, 65% yield) as a yellow oil. \( R_f = 0.40 \) (MeOH:DCM = 5:95); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 7.36-7.25 (m, 9H), 5.02 (s, 1H); \(^{13}\)C \(^{1}\)H NMR (126 MHz, CDCl\(_3\)): \( \delta \) 177.9, 137.5, 136.4, 133.5, 130, 128.8, (128.8), 128.6, 127.8, 56.3; IR (thin film): 3029 (br), 1708, 1491, 1454, 1402, 1276, 1213, 1091, 1015, 814, 699 cm\(^{-1}\); HRMS calc’d for C\(_{13}\)H\(_{10}\)Cl 201.0471, observed 201.0479 [M-COOH].

**2-Phenyl-2-(3-(trifluoromethyl)phenyl)acetic acid (3.3af):** The reaction was performed following the General Procedure with 1a (27.2 mg, 0.2 mmol), KN(SiMe\(_3\))\(_2\) (80 mg, 0.40 mmol) and 1-bromo-3-(trifluoromethyl)benzene (14 \( \mu \)L, 0.1 mmol). The crude material was purified by flash chromatography on silica gel (eluted with MeOH:DCM = 0.5:99.5 to MeOH:DCM = 2.5:97.5) to give the product (21.5 mg, 77% yield) as a yellow oil. \( R_f = 0.40 \) (MeOH:DCM = 5:95); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 7.61-7.31 (m, 9H), 5.10 (s, 1H); \(^{13}\)C \(^{1}\)H NMR (126 MHz, CDCl\(_3\)): \( \delta \) 177.7, 138.9, 137.1, 132.2, 131 (J = 32 Hz), 129.2, 129, 128.6, 127.9, 125.55 (J = 3.8 Hz), 124.48 (J = 3.8 Hz), 123.96 (J = 272.8 Hz), 56.7; IR (thin film): 3031 (br), 1712, 1600, 1496, 1450, 1412, 1330, 1215, 1165, 1125, 1098, 1077, 1032, 1003, 917, 801, 730, 700 cm\(^{-1}\); HRMS calc’d for C\(_{30}\)H\(_{21}\)O\(_4\)F\(_6\)\(^-\) 559.1344, observed 559.1343 [2M-H].
**2-Phenyl-2-(o-tolyl)acetic acid (3.3ag):** The reaction was performed following the General Procedure with 1a (20.4 mg, 0.15 mmol), KN(SiMe$_3$)$_2$ (60 mg, 0.30 mmol) and 1-bromo-2-methylbenzene (12.5 μL, 0.1 mmol). The crude material was purified by flash chromatography on silica gel (eluted with MeOH:DCM = 0.5:99.5 to MeOH:DCM = 2.5:97.5) to give the product (16 mg, 71% yield) as a yellow solid (m. p. = 87-89 °C). 

R$_f$ = 0.40 (MeOH:DCM = 5:95); $^1$H NMR (500 MHz, CDCl$_3$): δ 7.34-7.19 (m, 9H), 5.25 (s, 1H), 2.31 (s, 3H); $^{13}$C {$^1$H} NMR (126 MHz, CDCl$_3$): δ 178.3, 137.3, 136.5, 136.3, 130.8, 129.0, 128.6, 128.2, 127.61, 127.44, 126.3, 53.6, 19.9; IR (thin film): 3027 (br), 1707, 1602, 1495, 1453, 1409, 1280, 1217, 1031, 935, 747, 726, 698 cm$^{-1}$; HRMS calc'd for C$_{15}$H$_{14}$O$_2$ 226.0994, observed 226.0984 [M$^+$].

**2-Phenyl-2-(o-tolyl)acetic acid (3.3ag) (from 1-chloro-2-methylbenzene):** The reaction was performed following the General Procedure (10% Pd(OAc)$_2$ 2.24 mg and 15% NiXantphos 8.27 mg in 2mL dry toluene) with 1a (20.4 mg, 0.15 mmol), KN(SiMe$_3$)$_2$ (60 mg, 0.30 mmol) and 1-chloro-2-methylbenzene (12 μL, 0.1 mmol). The crude material was purified by flash chromatography on silica gel (eluted with MeOH:DCM = 0.5:99.5 to MeOH:DCM = 2.5:97.5) to give the product (14.3 mg, 63% yield) as a yellow solid (m. p. = 87-89 °C). R$_f$ = 0.40 (MeOH:DCM = 5:95). The spectroscopic data match the previously reported data.

**2-(Naphthalen-1-yl)-2-phenylacetic acid (3.3ah):** The reaction was performed following the General Procedure with 1a (20.4 mg, 0.15 mmol), KN(SiMe$_3$)$_2$ (60 mg, 0.30 mmol) and 1-
bromonaphthalene (14 μL, 0.1 mmol). The crude material was purified by flash chromatography on silica gel (eluted with MeOH:DCM = 0.5:99.5 to MeOH:DCM = 2.5:97.5) to give the product (21 mg, 80% yield) as a brown solid (m. p. = 128-129 °C). R_f = 0.40 (MeOH:DCM = 5:95); ¹H NMR (500 MHz, CDCl₃): δ 8.02-8.00 (m, 1H), 7.89-7.87 (m, 1H), 7.82 (d, J = 7.9, 1H), 7.51-7.29 (m, 9H), 5.82 (s, 1H); ¹³C ¹H NMR (126 MHz, CDCl₃): δ 178.4, 137.3, 134.0, 133.8, 131.6, 129.05, 129.03, 128.8, 128.5, 127.6, 126.7, 126.4, 125.8, 125.4, 123.2, 53.5; IR (thin film): 3428 (br), 2077, 1706, 1599, 1510, 1495, 1453, 1397, 1270, 1215, 1031, 790, 775, 730, 700 cm⁻¹; HRMS calc'd for C₁₈H₁₄O₂Na 285.0891, observed 285.0902 [M+Na]⁺.

2-(1-Methyl-1H-indol-5-yl)-2-phenylacetic acid (3.3ai): The reaction was performed following the General Procedure with 1a (20.4 mg, 0.15 mmol), KN(SiMe₃)₂ (60 mg, 0.30 mmol) and 5-bromo-1-methyl-indole (21 mg, 0.1 mmol). The crude material was purified by flash chromatography on silica gel (eluted with MeOH:DCM = 0.5:99.5 to MeOH:DCM = 2.5:97.5) to give the product (21.8 mg, 82% yield) as a yellow solid (m. p. = 136-138 °C). R_f = 0.40 (MeOH:DCM = 5:95); ¹H NMR (500 MHz, CDCl₃): δ 7.58-7.57 (m, 1H), 7.36-7.24 (m, 6H), 7.18 (dd, J = 8.5, 1.8, 1H), 7.02 (d, J = 3.1, 1H), 6.43 (dt, J = 3.1, 0.4, 1H), 5.16 (s, 1H), 3.75 (s, 3H); ¹³C ¹H NMR (126 MHz, CDCl₃): δ 179.3, 138.9, 136.0, 129.4, 128.86, 128.68, 128.55, 128.46, 127.1, 122.4, 120.9, 109.4, 101.1, 57.0, 32.8; IR (thin film): 3027 (br), 1703, 1511, 1493, 1449, 1421, 1339, 1246, 1079, 909, 795, 700 cm⁻¹; HRMS calc'd for C₁₇H₁₆NO₂ 266.1181, observed 266.1171 [MH]⁺.

2-(4-(tert-Butyl)phenyl)-2-(4-methoxyphenyl)acetic acid (3.3ba): The reaction was performed following the General Procedure with 2-(4-methoxyphenyl)acetic acid (25 mg, 0.15
mmol), KN(SiMe$_3$)$_2$ (60 mg, 0.30 mmol) and 2a (18 $\mu$L, 0.1 mmol). The crude material was purified by flash chromatography on silica gel (eluted with MeOH:DCM = 0.5:99.5 to MeOH:DCM = 2.5:97.5) to give the product (25.7 mg, 86% yield) as a yellow oil. \( R_f = 0.40 \) (MeOH:DCM = 5:95); \(^1\)H NMR (500 MHz, CDCl$_3$): \( \delta \) 7.33 (d, \( J = 8.2 \), 2H), 7.26-7.22 (m, 4H), 6.85 (d, \( J = 8.3 \), 2H), 4.95 (s, 1H), 3.77 (d, \( J = 0.7 \), 3H), 1.29 (d, \( J = 0.7 \), 9H); \(^{13}\)C \{\(^1\)H\} NMR (126 MHz, CDCl$_3$): \( \delta \) 179.1, 158.9, 150.3, 135.2, 130.3, 129.8, 128.2, 125.6, 114.0, 55.8, 55.3, 34.5, 31.4; IR (thin film): 3418 (br), 2962, 2835, 1707, 1611, 1584, 1511, 1463, 1441, 1406, 1363, 1303, 1251, 1215, 1179, 1109, 1035, 826 cm$^{-1}$; HRMS calc’d for C$_{19}$H$_{22}$O$_3$Na$^+$ 321.1467, observed 321.1467 [M+Na]$^+$.  

2-(4-(tert-Butyl)phenyl)-2-(4-fluorophenyl)acetic acid (3.3ca): The reaction was performed following the General Procedure with 2-(4-fluorophenyl)acetic acid (30.8 mg, 0.2 mmol), KN(SiMe$_3$)$_2$ (80 mg, 0.40 mmol) and 2a (18 $\mu$L, 0.1 mmol). The crude material was purified by flash chromatography on silica gel (eluted with MeOH:DCM = 0.5:99.5 to MeOH:DCM = 2.5:97.5) to give the product (23.2 mg, 81% yield) as a yellow oil. \( R_f = 0.40 \) (MeOH:DCM = 5:95); \(^1\)H NMR (500 MHz, CDCl$_3$): \( \delta \) 7.35-7.34 (m, 2H), 7.30 (dd, \( J = 8.8 \), 5.3, 2H), 7.23-7.22 (m, 2H), 7.00 (t, \( J = 8.7 \), 2H), 4.98 (s, 1H), 1.29 (d, \( J = 7.5 \), 9H); \(^{13}\)C \{\(^1\)H\} NMR (126 MHz, CDCl$_3$): \( \delta \) 178.5, 162.1 (\( J = 247 \) Hz), 150.6, 134.7, 133.84 (\( J = 3.4 \) Hz), 130.35 (\( J = 8.2 \) Hz), 128.2, 125.7, 115.5 (\( J = 21.3 \) Hz), 55.8, 34.5 31.3; IR (thin film): 2963 (br), 2850, 1707, 1611, 1560, 1405, 1364, 1269, 1255, 1179, 1035, 828 cm$^{-1}$; HRMS calc’d for C$_{17}$H$_{19}$O$^-$ 241.1392, observed 241.0714 [M-COOH].  

2-(4-(tert-Butyl)phenyl)-2-(4-chlorophenyl)acetic acid (3.3da): The reaction was performed following the General Procedure with 2-(4-chlorophenyl)acetic acid (25.6 mg, 0.15
mmol), KN(SiMe$_3$)$_2$ (60 mg, 0.30 mmol) and 2a (18 $\mu$L, 0.1 mmol). The crude material was purified by flash chromatography on silica gel (eluted with MeOH:DCM = 0.5:99.5 to MeOH:DCM = 2.5:97.5) to give the product (17.6 mg, 58% yield) as a yellow oil. $R_f = 0.40$ (MeOH:DCM = 5:95); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.31-7.17 (m, 8H), 4.93 (s, 1H), 1.26 (s, 9H); $^{13}$C $\{^1$H$\}$ NMR (126 MHz, CDCl$_3$): $\delta$ 178.5, 150.7, 136.6, 134.4, 133.5, 130.1, 128.8, 128.2, 125.8, 56.0, 34.5, 31.3; IR (thin film): 2963 (br), 1709, 1491, 1402, 1364, 1269, 1215, 1091, 1015, 909, 824, 734, 682 cm$^{-1}$; HRMS calc'd for C$_{18}$H$_{19}$O$_2$Cl: 302.1074, observed 302.1103 [M-COOH$^-$].

2-(4-(tert-Butyl)phenyl)-2-(o-tolyl)acetic acid (3.3ea): The reaction was performed following the General Procedure with 2-(o-tolyl)acetic acid (22.5 mg, 0.15 mmol), KN(SiMe$_3$)$_2$ (60 mg, 0.30 mmol) and 2a (18 $\mu$L, 0.1 mmol). The crude material was purified by flash chromatography on silica gel (eluted with MeOH:DCM = 0.5:99.5 to MeOH:DCM = 2.5:97.5) to give the product (15 mg, 53% yield) as a yellow paste. $R_f = 0.40$ (MeOH:DCM = 5:95); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.32 (d, J = 8.5, 3H), 7.18-7.17 (m, 5H), 5.20 (s, 1H), 2.31 (s, 3H), 1.29 (s, 9H); $^{13}$C $\{^1$H$\}$ NMR (126 MHz, CDCl$_3$): $\delta$ 178.9, 150.2, 136.5, 134.2, 130.7, 128.6, 128.2, 127.5, 126.3, 125.6, 53.1, 34.5, 31.4, 19.9; IR (thin film): 2963 (br), 1707, 1462, 1408, 1363, 1269, 1217, 1019, 910, 823, 730, 668 cm$^{-1}$; HRMS calc'd for C$_{38}$H$_{43}$O$_4$: 563.3161, observed 563.3167 [2M-H$^-$].

2-(4-(tert-Butyl)phenyl)-2-(naphthalen-2-yl)acetic acid (3.3fa): The reaction was performed following the General Procedure with 2-(naphthalen-2-yl)acetic acid (28 mg, 0.15 mmol), KN(SiMe$_3$)$_2$ (60 mg, 0.30 mmol) and 2a (18 $\mu$L, 0.1 mmol). The crude material was purified by flash chromatography on silica gel (eluted with MeOH:DCM = 0.5:99.5 to MeOH:DCM = 2.5:97.5) to give the product (20 mg, 54% yield) as a yellow oil. $R_f = 0.40$ (MeOH:DCM = 5:95); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.79-7.66 (m, 8H), 7.36-7.18 (m, 10H), 6.90 (s, 1H); $^{13}$C $\{^1$H$\}$ NMR (126 MHz, CDCl$_3$): $\delta$ 178.5, 148.5, 136.5, 134.2, 130.7, 128.6, 128.2, 127.5, 126.3, 125.6, 123.1, 121.8, 121.5, 120.9, 54.0, 34.5, 31.4, 19.9; IR (thin film): 2963 (br), 1707, 1462, 1408, 1363, 1269, 1217, 1019, 910, 823, 730, 668 cm$^{-1}$; HRMS calc'd for C$_{38}$H$_{43}$O$_4$: 563.3161, observed 563.3167 [2M-H$^-$].
product (23.3 mg, 73% yield) as a off-white solid (m.p. = 172-174 °C). R\(_f\) = 0.40 (MeOH:DCM = 5:95); \(^1\)H NMR (500 MHz, CDCl\(_3\)): δ 7.80-7.77 (m, 4H), 7.46-7.43 (m, 3H), 7.35-7.32 (m, 2H), 7.30-7.28 (m, 2H), 5.18 (s, 1H), 1.28 (s, 9H); \(^{13}\)C \{\(^1\)H\} NMR (126 MHz, CDCl\(_3\)): δ 178.8, 150.5, 135.5, 134.8, 133.4, 132.6, 128.4, 128.0, 127.64, 127.45, 126.8, 126.26, 126.13, (126.13), 125.7, 56.7, 34.5, 31.4; IR (thin film): 2962 (br), 1707, 1600, 1508, 1407, 1364, 1270, 1215, 1018, 909, 815, 748, 701 cm\(^{-1}\); HRMS calc'd for C\(_{44}\)H\(_{45}\)O\(_4\) + 637.3318, observed 637.33034 [2M+H]\(^+\).

2-(4-(tert-Butyl)phenyl)-2-(3-(trifluoromethyl)phenyl)acetic acid (3.3ga): The reaction was performed following the General Procedure with 2-(3-(trifluoromethyl)phenyl)acetic acid (40.8 mg, 0.2 mmol), KN(SiMe\(_3\))\(_2\) (80 mg, 0.40 mmol) and 2a (18 μL, 0.1 mmol). The crude material was purified by flash chromatography on silica gel (eluted with MeOH:DCM = 0.5:99.5 to MeOH:DCM = 2.5:97.5) to give the product (21.9 mg, 65% yield) as a yellow oil. R\(_f\) = 0.40 (MeOH:DCM = 5:95); \(^1\)H NMR (500 MHz, CDCl\(_3\)): δ 7.62 (s, 1H), 7.54 (t, J = 7.2, 2H), 7.44 (t, J = 7.8, 1H), 7.37-7.35 (m, 2H), 7.26-7.23 (m, 2H), 5.05 (s, 1H), 1.30 (s, 9H); \(^{13}\)C \{\(^1\)H\} NMR (126 MHz, CDCl\(_3\)): δ 177.9, 150.8, 139, 134, 132.2, 131 (J = 32 Hz), 129.1, 128.1, 125.9, 125.4 (J = 3.9 Hz), 124.4 (J = 3.9 Hz), 123.99 (J = 272.8 Hz), 56.3, 34.5, 31.3; IR (thin film): 2965 (br), 2171, 1515, 1450, 1408, 1365, 1330, 1215, 1165, 1128, 1097, 1076, 1019, 917, 828, 800, 701, 658 cm\(^{-1}\); HRMS calc’d for C\(_{38}\)H\(_{37}\)O\(_6\)F\(_6\) 672.2674, observed 672.0913 [2M].

2-(4-(tert-Butyl)phenyl)-2-(pyridin-3-yl)acetic acid (3.3ha): The reaction was performed following the General Procedure with 2-(pyridin-3-yl)acetic acid (34.7 mg, 0.2 mmol), NaO'Bu (59 mg, 0.60 mmol) and 2a (18 μL, 0.1 mmol). The crude material was purified by flash chromatography on silica gel (eluted with MeOH:DCM
= 0.5:99.5 to MeOH:DCM = 2.5:97.5) to give the product (18.9 mg, 53% yield) as a white solid (m.p. = 75-76 °C). $R_f = 0.30$ (MeOH:DCM = 5:95); $^1H$ NMR (500 MHz, CDCl$_3$): δ 9.36 (s, 1H), 8.68-8.67 (m, 1H), 8.48-8.46 (m, 1H), 7.82-7.78 (m, 1H), 7.36-7.22 (m, 4H), 5.05-5.01 (m, 1H), 1.34-1.24 (m, 9H); $^{13}C$ {¹H} NMR (126 MHz, CDCl$_3$): δ 174.7, 150.4, 147.8, 145.8, 138.6, 136.8, 134.9, 128.2, 125.8, 124.1, 55.0, 34.5, 31.3; IR (thin film in Mesitylene): 3016 (br), 2917 (br), 2860, 2729, 1757, 1711, 1607, 1471, 1374, 1165, 1037, 928, 880, 835, 687, 668 cm$^{-1}$; HRMS calc’d for C$_{17}$H$_{20}$NO$_2$: 210.1494, observed 210.1499 [M+H]$^+$. 

4,4-Diphenylbut-3-enoic acid (3.4ap): The reaction was performed following the General Procedure trans-styrylacetic acid (24.3 mg, 0.15 mmol), NaN(SiMe$_3$)$_2$ (55 mg, 0.30 mmol) and phenyl bromide (10.5 μL, 0.1 mmol). The crude material was purified by flash chromatography on silica gel (eluted with MeOH:DCM = 0.5:99.5 to MeOH:DCM = 2.5:97.5) to give the product (16.7 mg, 70% yield) as a yellow oil. $R_f = 0.40$ (MeOH:DCM = 5:95). The spectroscopic data match the previously reported data.$^{42}$

4-(4-(tert-Butyl)phenyl)-4-phenylbut-3-enoic acid (3.4aa): The reaction was performed following the General Procedure trans-styrylacetic acid (24.3 mg, 0.15 mmol), NaN(SiMe$_3$)$_2$ (55 mg, 0.30 mmol) and 2a (18 μL, 0.1 mmol). The crude material was purified by flash chromatography on silica gel (eluted with MeOH:DCM = 0.5:99.5 to MeOH:DCM = 2.5:97.5) to give the product (23 mg, 78% yield) as a yellow oil. $R_f = 0.40$ (MeOH:DCM = 5:95). The two geometric isomers are not separable. $^1H$ NMR (500 MHz, CDCl$_3$): δ 7.41-7.10 (m, 9H), 6.25-6.18 (m, 1H), 3.26-3.18 (m, 2H), 1.35-1.28 (m, 9H); $^{13}C$ {¹H} NMR (126 MHz, CDCl$_3$): δ 178.12, 178.03, 150.58, 150.39, 145.2, 145.0, 142.1, 139.2, 138.8, 135.9, 129.7, 129.4, 128.4, 128.1, 127.58, 127.44, 127.0, (127.0), 125.29, 125.10, 119.3, 118.7, 35.23, 35.15, 34.63, 34.52, 107
31.41, 31.32; IR (thin film): 3421 (br), 2962, 1705, 1493, 1461, 1480, 1362, 1269, 1217, 1109, 1073, 760, 733, 702, 650 cm\(^{-1}\); HRMS calc’d for C\(_{20}\)H\(_{23}\)O\(_2\)\(^+\) 295.1698, observed 295.1698 [M+H]\(^+\).

**4-(4-Fluorophenyl)-4-phenylbut-3-enoic acid (3.4ad):** The reaction was performed following the General Procedure trans-styrylacetic acid (24.3 mg, 0.15 mmol), NaN(SiMe\(_3\))\(_2\) (55 mg, 0.30 mmol) and 1-chloro-4-fluorobenzene (11 \(\mu\)L, 0.1 mmol). The crude material was purified by flash chromatography on silica gel (eluted with MeOH:DCM = 0.5:99.5 to MeOH:DCM = 2.5:97.5) to give the product (18.2 mg, 71% yield) as a yellow oil. \(R_f = 0.40\) (MeOH:DCM = 5:95). The two geometric isomers are not separable.

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.39-6.92 (m, 18H), 6.21 (t, \(J = 7.4, 1\)H), 6.15 (t, \(J = 7.4, 1\)H), 3.18 (dd, \(J = 7.4, 3.5, 4\)H); \(^13\)C \({\text{[}^1\text{H]}\) NMR (126 MHz, CDCl\(_3\)): \(\delta\) 178.1, 178, 162.4 (\(J = 247\) Hz), 162.2 (\(J = 247\) Hz), 144.4, 144.3, 141.6, 138.9, 137.94 (\(J = 3.5\) Hz), 137.92 (\(J = 3.5\) Hz), 131.45 (\(J = 8.2\) Hz), 129.7 (129.7), 129.07 (\(J = 8.2\) Hz), 128.6, 128.3, 127.7, 127.4, 119.7, 119.3, 115.35 (\(J = 21.4\) Hz), 115.18 (\(J = 21.4\) Hz), 35.2, 35.1; IR (thin film): 3425 (br), 1651, 1507, 1410, 1223 cm\(^{-1}\); HRMS calc’d for C\(_{32}\)H\(_{25}\)O\(_4\)F\(_2\)\(^-\) 511.1721, observed 511.1738 [2M-H].

### 3.5. REFERENCE:


Chapter 4

New Strategy in C–H Functionalizations with Bimetallic Catalysts

4.1. INTRODUCTION

Aromatic hydrocarbons are inexpensive and abundant components of petroleum distillates and have been employed as solvents and reagents on laboratory and industrial scales. They are common starting materials for the preparation of more functionalized and higher value small molecules with applications in synthesis,¹ materials science,²,³ and pharmaceutical chemistry.⁴-⁶

Inspired by the challenge of conversion of simple aromatic hydrocarbons into valuable synthetic buildings blocks, chemists have focused on transition metal promoted C–H functionalizations of simple aromatic hydrocarbons.

Among catalysts that activate C–H bonds, several different modes of C–H bond cleavage have been documented. Most common are direct oxidative addition of C–H bonds and concerted metallation deprotonation processes.⁷-¹⁰ These processes can be difficult to optimize, because the demands on the catalyst are quite stringent. Furthermore, the arene substrates usually posses multiple types of C–H’s, giving rise to selectivity problems.¹¹ Both reactivity and selectivity issues can be addressed by outfitting substrates with directing groups that bear Lewis basic centers that can bind to the catalyst and position it in the proximity C–H bond of interest.¹²-¹⁹

Strategies mentioned above focus sorely on the position or reactivity of transition metal. Main group metal, on the other hand, is often considered
innocent or is involved only in transmetallation step. For example, well known reactions such as Suzuki-Miyaura, Negishi, Kumada-Corriu, and Stille cross-coupling reactions share the same common mechanism with main group metal (M) serving as a transmetallation partner. (Figure 4.1A) However, with unique bimetallic system such as TM-NIXANTPHOS, main group metal is involved in the whole catalytic cycle.\textsuperscript{20} (Figure 4.1B) This system prompted us to pursue a new kind of strategy: activation of inert molecules using main group metal.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure4.1}
\caption{Traditional Catalytic Cycle and Heterobimetallic Catalytic Cycle}
\end{figure}

We have been interested in the introduction of methods to functionalize benzylic C–H’s of arenes and heteroarenes.\textsuperscript{21-30} A well-known method to activate benzylic positions is by coordination of the arene to a metal in an $\eta$-6-fashion. Previously we demonstrated the utility of this activation mode in the palladium catalyzed arylation of toluene derivatives and benzylic ethers and amines. This method was also applied to the catalytic enantioselective arylation of benzylic
amines to afford diarylmethylamine derivatives, which are important pharmacophores.\textsuperscript{26,31} (Scheme 4.1A)

**A. Cr Complex Benzylic Activation**

\[
\begin{align*}
\text{Cr(CO)}_3 & \quad \text{ArBr} \\
\text{[Cr]} & \quad \text{Z} = \text{H, Ar, OR, NMe}_2, \text{CH}_3
\end{align*}
\]

**B. Deprotonatable Ligand–M–Complex Benzylic Activation**

We hypothesized that use of bimetallic catalysts for C–H functionalization reactions could provide unique system to incorporate the activation of benzylic C–H with the main group metal from the counter cation of the base. The design was envisioned to benefit from cooperativity between the main group metal on the deprotonatable ligand and transition metal in the bimetallic catalysts (Scheme 4.1B).

Our previous study revealed a heterobimetallic Pd/M catalyst (M=Li, Na, K) with deprotonatable ligand NIXANTPHOS framework that demonstrates enhanced activity in the oxidative addition of aryl chlorides.\textsuperscript{20} (Figure 4.2) Importantly, the (NIXANTPHOS)Pd complex’s N–H must be deprotonated to generate the active bimetallic catalyst that achieves the room temperature
oxidative addition of aryl chlorides. This result partially supports the hypothesis of cooperativity between the main group metal on deprotonatable ligand and transition metal in the bimetallic catalysts.

![Chemical structures](image)

**Figure 4.2.** Oxidative addition of aryl chlorides by deprotonated (NIXANTPHOS)Pd(0) in the presence of base.

In this study, we focus on the benzylic C–H activation of toluene derivatives via $\eta^6$ interaction between the $\pi$ – electron of aromatic ring and the main group metal carried on the ligand. Noteworthy, no other metal species needed in the reaction than just the counter cation of the base and the Pd to functionalize toluene derivatives. A variety of diarylmethanes can be prepared from readily commercially available toluene derivatives, which mostly serve as solvents in lab or industrial use, in good to excellent yields. A novel strategy of C–H functionalization is proposed: With deprotonatable ligand, main group metal can be carried through the entire catalytic cycle and furthermore play an important role in the activation. This cooperativity between the main group metal and transition metal provides a new possibility in ligand designing and reveals the interesting feature of the main group metal.
4.2. RESULTS AND DISCUSSION

The journey began with an interesting result observed in our study on α-arylation of acetic acid derivatives. With phenyl acetic acid and aryl bromides under standard condition, desired α-arylation product was obtained in 93% yield. However, an unknown byproduct was isolated if no phenyl acetic acid added to the reaction and was later on identified as diarylmethane. (Scheme 4.2)

Scheme 4.2. Start Point of Pd-Catalyzed Arylation of Toluene.

This interesting result urged us to discover the origin of the product to the arylation of toluene in the reaction. Based on our experience on the arylation with relatively high $pK_a$ substrates (29 – 35.1), our hypothesis would be the toluene specie got deprotonated to form nucleophile and later transmetallated onto Pd to finish the cross coupling cycle. Another possible reaction pathway is through radical process, which the requirement for Pd or ligand is not necessary. Control experiments without Pd or ligand gave no desired product, which
suggested a traditional Pd catalyzed reaction mechanism is involved. (Scheme 4.3)

**Scheme 4.3.** Control Experiments of Pd-Catalyzed Arylation of Toluene.

\[
\begin{align*}
\text{Bu} & \quad \text{Br} \\
\text{Br} & \quad \text{Bu}
\end{align*}
\]

\[
\xrightarrow{5 \text{ mol } \% \text{Pd(OAc)}_2, 7.5 \text{ mol } \% \text{NiXantphos, 3 equiv KN(SiMe}_3)_2, \text{Toluene, 110 °C, 12 h}}
\]

80%

\[
\xrightarrow{\text{No Pd, 7.5 mol } \% \text{NiXantphos, 3 equiv KN(SiMe}_3)_2, \text{Toluene, 110 °C, 12 h}}
\]

No Reaction

\[
\xrightarrow{5 \text{ mol } \% \text{Pd(OAc)}_2, \text{No Ligand, 3 equiv KN(SiMe}_3)_2, \text{Toluene, 110 °C, 12 h}}
\]

No Reaction

\[
\xrightarrow{\text{No Pd, No Ligand, 3 equiv KN(SiMe}_3)_2, \text{Toluene, 110 °C, 12 h}}
\]

No Reaction

However, the traditional protocol of deprotonating toluene requires much stronger base than K[N(SiMe3)2], it is unlikely that toluene can be deprotonated only with [N(SiMe3)2]- anion since the \( pK_a \) of the two conjugate acid is in a great difference (26 vs 43). To account for this unusual reactivity, we hypothesized the counter cation of the base must not be innocent in the reaction. The hypothesis is especially reasonable with deprotonatable ligand NIXANTPHOS since the main group metal is carried through the catalytic cycle. In order to prove our hypothesis, we took a closer look to [N(SiMe3)2]− with different counter cation and found out both K[N(SiMe3)2] and Na[N(SiMe3)2] gave conversion of desired product. Lithium led to Buchwald-Hartwig type reaction.
product with \([\text{N(SiMe}_3\text{)}_2]\) anion as nucleophile instead of benzyl anion. (Scheme 4.4) We also did a ligand screening to investigate the necessity of the deprotonatable ligand NIXANTPHOS. Not surprisingly, NIXANTPHOS was the only hit out of 48 common ligands selection that gave the desired product. (See Supporting Information)

**Scheme 4.4.** Effects on Different Cation of Base in Pd-Catalyzed Arylation of Toluene.

![Scheme 4.4](image)

To this point, it’s been proven that NIXANTPHOS is required in the reaction and the main group is not innocent. To proceed, we decided to optimize the reaction condition before further exploring more details in mechanism. With efforts on the optimization, the key factors are the Pd source, temperature and concentration. We were able to get desired product in 93% isolated yield with 2.5% Pd loading. (Table 4.1)
Table 4.1. Optimization of Pd-Catalyzed Arylation of Toluene.

<table>
<thead>
<tr>
<th>entry</th>
<th>base equiv</th>
<th>temp (°C)</th>
<th>Pd source</th>
<th>ligand %</th>
<th>conc.</th>
<th>yield (^b) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>110</td>
<td>5% Pd(OAc)(_2)</td>
<td>7.5%</td>
<td>0.05</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>110</td>
<td>5% Pd(OAc)(_2)</td>
<td>7.5%</td>
<td>0.05</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>1.5</td>
<td>110</td>
<td>5% Pd(OAc)(_2)</td>
<td>7.5%</td>
<td>0.1</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>1.5</td>
<td>110</td>
<td>5% Pd(OAc)(_2)</td>
<td>7.5%</td>
<td>0.033</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td>1.5</td>
<td>110</td>
<td>5% Pd(OAc)(_2)</td>
<td>7.5%</td>
<td>0.025</td>
<td>83</td>
</tr>
<tr>
<td>6</td>
<td>1.5</td>
<td>110</td>
<td>5% Pd PreCat</td>
<td>No additional</td>
<td>0.033</td>
<td>95</td>
</tr>
<tr>
<td>7</td>
<td>1.5</td>
<td>80</td>
<td>5% Pd PreCat</td>
<td>No additional</td>
<td>0.033</td>
<td>71</td>
</tr>
<tr>
<td>8</td>
<td>1.5</td>
<td>24</td>
<td>5% Pd PreCat</td>
<td>No additional</td>
<td>0.033</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>1.2</td>
<td>110</td>
<td>5% Pd PreCat</td>
<td>No additional</td>
<td>0.033</td>
<td>65</td>
</tr>
<tr>
<td>10</td>
<td>1.5</td>
<td>110</td>
<td>2.5% Pd PreCat</td>
<td>No additional</td>
<td>0.033</td>
<td>93</td>
</tr>
<tr>
<td>11</td>
<td>1.5</td>
<td>110</td>
<td>1% Pd PreCat</td>
<td>No additional</td>
<td>0.033</td>
<td>75</td>
</tr>
</tbody>
</table>

\(^a\) Reaction conducted on a 0.1 mmol scale \(^b\) Yield determined by \(^1\)H NMR spectroscopy of the crude reaction mixture.

With the optimized reaction condition, we decided to investigate the cation effect with additives. In previous initial results, both K[N(SiMe\(_3\)]\(_2\)] and Na[N(SiMe\(_3\)]\(_2\)] gave desired product, but K[N(SiMe\(_3\)]\(_2\)] in better yield. It’s worth knowing whether this difference came from the kinetic behavior of the base (i.e. K[N(SiMe\(_3\)]\(_2\)] is more reactive than Na[N(SiMe\(_3\)]\(_2\)] and Li[N(SiMe\(_3\)]\(_2\)]), or the counter cation of the base was playing a role in the reaction. To tackle this question, we designed the experiment with additives that are capable of caging the counter cation of the base (12-crown-4 for Li, 15-crown-5 and 18-crown-6 for K) and, theoretically, increasing the reactivity of the bases. However, cases with potassium cation caged by 15-crown-5 or 18-crown-6 showed no reactivity.
as well as all lithium cases. This result suggested the potassium cation was playing an important role other than just an innocent counter cation in the reaction. (Table 4.2)

**Table 4.2.** Effect of Crown Ethers in Pd-Catalyzed Arylation of Toluene.

![Chemical Reaction Diagram]

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>additives</th>
<th>equiv.</th>
<th>yield&lt;sup&gt;b&lt;/sup&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KN(SiMe&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>18-Crown-6</td>
<td>none</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>KN(SiMe&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>18-Crown-6</td>
<td>1.5</td>
<td>64</td>
</tr>
<tr>
<td>3</td>
<td>KN(SiMe&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>18-Crown-6</td>
<td>3.0</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>KN(SiMe&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>15-Crown-5</td>
<td>1.5</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>KN(SiMe&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>15-Crown-5</td>
<td>3.0</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>KN(SiMe&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>15-Crown-5</td>
<td>5.0</td>
<td>&gt;5</td>
</tr>
<tr>
<td>7</td>
<td>KN(SiMe&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>15-Crown-5</td>
<td>10.0</td>
<td>&gt;5</td>
</tr>
<tr>
<td>8</td>
<td>LiN(SiMe&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>12-Crown-4</td>
<td>none</td>
<td>&gt;5</td>
</tr>
<tr>
<td>9</td>
<td>LiN(SiMe&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>12-Crown-4</td>
<td>1.5</td>
<td>&gt;5</td>
</tr>
<tr>
<td>10</td>
<td>LiN(SiMe&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>12-Crown-4</td>
<td>3.0</td>
<td>&gt;5</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conducted on a 0.1 mmol scale  
<sup>b</sup> Yield determined by <sup>1</sup>H NMR spectroscopy of the crude reaction mixture.

With all the evidence above, it’s now clear that deprotonatable ligand NIXANTPHOS as well potassium cation are required. To better understand the system, we came up with a model to explain the unique reactivity for the catalyst. It’s well known that Cr and other metals can form η<sup>6</sup> complex with toluene to activate benzylic protons. Potassium, on the other hand, is well known to have η<sup>6</sup> interaction with benzene ring in the crystal forms. However,
activation of benzylic protons using potassium $\eta^6$ interaction is not documented. Herein we proposed a heterobimetallic model with potassium attaching to the deprotonated ligand NIXANTPHOS as an active catalyst to perform arylation of toluene derivatives. The benzylic protons of toluene are activated due to $\eta^6$ interaction between potassium and benzene ring. We believe this model explained the role of potassium in the activation of toluene and the inhibited reactivity by addition of 15-crown-5 or 18-crown-6. Once the potassium cation is caged with crown ether, the $\eta^6$ interaction of potassium and benzene ring is inhibited, therefore shut down the activation. (Figure 4.3) Meanwhile, we believe the deprotonatable ligand NIXANTPHOS also has incremental effect to the reactivity due to the localization of potassium by the ligand. It is likely that the localization of potassium helped the transmetallation of deprotonated benzyl anion.

![Proposed Activation Pattern of Potassium](image)

**Figure 4.3.** Proposed Activation Pattern of Potassium.

In order to demonstrate the utility of the protocol, we synthesized a series of diarylmethanes from simple toluene with different aryl bromides. (Table 4.3) Aryl bromides bearing electron donating groups such as tert-buty1, methoxy group and $N,N$-dimethyl group worked in excellent yields (**3aa-3ac**, 90-95%).
Steric hindered 2-methyl-bromobenzene and 1-bromonaphthalene also gave desired product in excellent yield ($3_{ad}$, $3_{ae}$; 92% and 90%). We next explored interesting aryl bromide bearing silyl-ether, the protocol successfully gave cross coupled product $3_{af}$ in 80% yield. Heterocycle-containing diarylmethanes are valuable targets because of their uses in pharmaceuticals. We were able to produce an indole-containing diarylmethane $3_{ag}$ from corresponding aryl bromides in excellent yield (95%). Overall, the protocol is robust for different kind of aryl bromides with Pd loading as low as 2.5%.

**Table 4.3.** Scope of Aryl Bromides in Pd-Catalyzed Arylation of Toluene.
Next, we set the goal in arylation of toluene derivatives. Xylenes, for instance, are major toluene derivatives that are obtained from petroleum. Different xylenes exhibited different reactivity under the reaction condition. For
example, *ortho*-xylene (2b) reacted with 4-*tert*-butyl bromobenzene to form desired product 4ba in 99% yield. The yield dropped with *meta*-xylene (2c) and *para*-xylene (2d) to 80% and 64%. Mesitylene (2e) can also be subjected to the reaction condition to form the product 4ea in 63% yield. Both toluene derivatives with electron donating (2f) and electron withdrawing group (2g, 2h) on the *ortho*-position gave excellent yields (4fa-4ha; 90%, 85% and 81%). Noteworthy, no byproduct derived from the oxidative addition of 2-chlorotoluene (2h) was found. 3-fluorotoluene (2i) and 3-chlorotoluene (2j) also provided cross-coupled products 4ia and 4ja in 78% and 74% yields. One important example is ethyl benzene (2k), the arylation happened at the benzylic position where the most acidic protons locate and gave the branched product 4ka in 75% yield. The result is particularly interesting because it generated a chiral center, which made asymmetric transformation possible. Overall, common toluene derivatives were well tolerated under the reaction condition. However, the protocol came with limitations such as the lack of *para* substituted examples but *para*-xylene (4da). Benzene with propyl or high carbon number side chains also failed to give desired products.

**Table 4.4.** Scope of Toluene Derivative in Pd-Catalyzed Arylation of Toluene.\(^a\)
Reaction conducted on a 0.1 mmol scale
4.3. SUMMARY AND OUTLOOK

In summary, we have developed a method to directly functionalize toluene derivatives with aryl bromides to generate diarylmethanes, all of which are important building blocks in drug discovery. The mechanistic insight provides a novel point of view for the role of main group metal in the catalytic cycle. By devising the deprotonatable ligand with main group metal, new strategy of C–H functionalization can be revealed.

4.4. EXPERIMENTAL SECTION

General Methods. All reactions were performed under nitrogen using oven-dried glassware and standard Schlenk or vacuum line techniques. Air- and moisture-sensitive solutions were handled under nitrogen and transferred via syringe. Unless otherwise stated, reagents were commercially available and used as purchased without further purification. Chemicals were obtained from Sigma-Aldrich, Acros, TCI America, Strem Chemicals or Matrix Scientific, and solvents were purchased from Fisher Scientific. The progress of the reactions was monitored by thin-layer chromatography using Whatman Partisil K6F 250 μm precoated 60 Å silica gel plates and visualized by short-wavelength ultraviolet light as well as by treatment potassium permanganate (KMnO₄) stain or iodine. Silica gel (230–400 mesh, Silicycle) was used for flash chromatography. The ¹H NMR and ¹³C{¹H} NMR spectra were obtained using a Brüker AM-500 Fourier transform NMR spectrometer at 500 and 126 MHz, respectively. Chemical shifts are reported in units of parts per million (ppm) downfield from tetramethylsilane (TMS), and all coupling constants are reported in hertz. The infrared spectra were obtained with KBr plates using a Perkin-Elmer Spectrum 100 Series FTIR spectrometer. High-resolution mass spectrometry (HRMS) data were obtained on a Waters LC–TOF mass spectrometer (model LCT-XE Premier) using chemical ionization (CI) or electrospray ionization (ESI) in
positive or negative mode, depending on the analyte. Melting points were determined on a Unimelt Thomas-Hoover melting point apparatus and are uncorrected.

**Preparation of Electrophile.**

Compounds $1g^{32}$ were prepared according to literature procedures.

**General Procedure A:** An oven-dried 10 mL reaction vial equipped with a stir bar was charged with Pd Buchwald’s 3rd generation precatalyst (2.33 mg, 0.0025 mmol, 2.5 mol %), KN(SiMe$_3$)$_2$ (30 mg, 0.15 mmol, 1.5 equiv) under a nitrogen atmosphere. 3 mL of dry toluene was taken up by syringe and added to the reaction vial. 1a (18 μL, 0.1 mmol, 1 equiv) was added to the reaction mixture Note that the ArBr in a solid form was added to the reaction vial prior to KN(SiMe$_3$)$_2$. The reaction mixture was stirred for 12 h at 110 °C, quenched with two drops of H$_2$O, diluted with 3 mL of ethyl acetate, and filtered over a pad of MgSO$_4$ and silica. The pad was rinsed with additional ethyl acetate, and the solution was concentrated *in vacuo*. The crude material was loaded onto a silica gel column and purified by flash chromatography eluting with EtOAc/hexanes.

**General Procedure B:** An oven-dried 10 mL reaction vial equipped with a stir bar was charged with Pd Buchwald’s 3rd generation precatalyst (2.33 mg, 0.0025 mmol, 2.5 mol %), KN(SiMe$_3$)$_2$ (30 mg, 0.15 mmol, 1.5 equiv) under a nitrogen atmosphere. 3 mL of 2b was taken up by syringe and added to the reaction vial. 1a (18 μL, 0.1 mmol, 1 equiv) was added to the reaction mixture Note that the ArBr in a solid form was added to the reaction vial prior to KN(SiMe$_3$)$_2$. The reaction mixture was stirred for 12 h at 110 °C, quenched with two drops of H$_2$O, diluted with 3 mL of ethyl acetate, and filtered over a pad of MgSO$_4$ and silica. The pad was rinsed with additional ethyl acetate, and the solution was concentrated *in vacuo*. The crude material was loaded onto a silica gel column and purified by flash chromatography eluting with EtOAc/hexanes.
1-benzyl-4-(tert-butyl)benzene (3aa): The reaction was performed following General Procedure A with 1a (18 μL, 0.1 mmol), KN(SiMe$_3$)$_2$ (30 mg, 0.15 mmol) and toluene 2a (3mL). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (20.8 mg, 93% yield) as a colorless oil. $R_f = 0.4$ (hexanes); The NMR spectral data match the previously published data.\(^{33}\)

1-benzyl-4-methoxybenzene (3ab): The reaction was performed following General Procedure A with 1b (12.5 μL, 0.1 mmol), KN(SiMe$_3$)$_2$ (30 mg, 0.15 mmol) and toluene 2a (3mL). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (15.9 mg, 80% yield) as a colorless oil. $R_f = 0.4$ (hexanes); The NMR spectral data match the previously published data.\(^{34}\)

4-benzyl-N,N-dimethylaniline (3ac): The reaction was performed following General Procedure A with 1c (20.2 mg, 0.1 mmol), KN(SiMe$_3$)$_2$ (30 mg, 0.15 mmol) and toluene 2a (3mL). The crude material was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 5:95) to give the product (20 mg, 95% yield) as a colorless oil. $R_f = 0.25$ (EtOAc:hexanes = 5:95); The NMR spectral data match the previously published data.\(^{34}\)

1-benzyl-2-methylbenzene (3ad): The reaction was performed following General Procedure A with 1d (12 μL, 0.1 mmol), KN(SiMe$_3$)$_2$ (30 mg, 0.15 mmol) and toluene 2a (3mL). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (16.8 mg, 92% yield) as a colorless oil. $R_f = 0.4$ (hexanes); The NMR spectral data match the previously published data.\(^{35}\)
1-benzynaphthalene (3ae): The reaction was performed following General Procedure A with 1e (20.7 mg, 0.1 mmol), KN(SiMe₃)₂ (30 mg, 0.15 mmol) and toluene 2a (3mL). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (19.6 mg, 90% yield) as a colorless oil. Rₚ = 0.20 (hexanes); The NMR spectral data match the previously published data.³⁶

(4-benzylphenoxy)triisopropylsilane (3af): The reaction was performed following General Procedure A with 1f (28.5 μL, 0.1 mmol), KN(SiMe₃)₂ (30 mg, 0.15 mmol) and toluene 2a (3mL). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (27.2 mg, 80% yield) as a colorless oil. Rₚ = 0.30 (hexanes); ¹H NMR (500 MHz; CDCl₃): δ 7.28 (t, J = 7.6, 2H), 7.21-7.16 (m, 3H), 7.03 (d, J = 8.2, 2H), 6.81 (d, J = 8.3, 2H), 3.92 (s, 2H), 1.28-1.22 (m, 3H), 1.10 (d, J = 7.4, 18H); ¹³C {¹H} NMR (126 MHz, CDCl₃): δ 154.5, 141.9, 133.6, 130.0, 129.1, 128.6, 126.1, 120.0, 41.3, 18.2, 12.9 ppm; IR (thin film): 3028, 2944, 1608, 1508, 1494, 1463, 1384, 1367, 1264, 1169, 1099, 916, 883, 686 cm⁻¹; HRMS calc'd for C₂₂H₃₂OSi⁺ 340.2222, observed 340.2219 [MH⁺]

5-benzyl-1-methyl-1H-indole (3ag): The reaction was performed following General Procedure A with 1g (21 mg, 0.1 mmol), KN(SiMe₃)₂ (30 mg, 0.15 mmol) and toluene 2a (3mL). The crude material was purified by flash chromatography on silica gel (eluted with EtOAc:hexanes = 5:95) to give the product (21 mg, 95% yield) as a colorless oil. Rₚ = 0.40 (eluted with EtOAc:hexanes = 5:95); ¹H NMR (500 MHz; CDCl₃): δ 7.43 (t, J = 0.7, 1H), 7.27-7.20 (m, 5H), 7.18-7.15 (m, 1H), 7.05 (dd, J = 8.4, 1.6, 1H), 6.99 (d, J = 3.1, 1H), 6.40 (d, J = 3.1, 1H), 4.08 (s, 2H), 3.73 (s, 3H); ¹³C {¹H} NMR (126 MHz, CDCl₃): δ 142.6, 135.7, 132.2, 129.19, 129.10, 128.9, 128.5, 126.0, 123.2, 121.0, 109.4, 100.8, 42.2, 33.1
130 ppm; IR (thin film): 3024, 2903, 1658, 1601, 1512, 1492, 1448, 1421, 1339, 1303, 1244, 1154, 1079, 785, 718, 699 cm\(^{-1}\); HRMS calc’d for C\(_{16}\)H\(_{15}\)N\(^+\) 222.1282, observed 222.1251 [MH]\(^+\)

1-(4-(tert-butyl)benzyl)-2-methylbenzene (4ba): The reaction was performed following General Procedure B with 1a (18 \(\mu\)L, 0.1 mmol), KN(SiMe\(_3\))\(_2\) (30 mg, 0.15 mmol) and 2b (3mL). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (23.8 mg, 99% yield) as a colorless oil. \(R_f = 0.40\) (hexanes); \(^1\)H NMR (500 MHz; CDCl\(_3\)): \(\delta\) 7.29-7.27 (m, 2H), 7.13 (dq, J = 12.8, 4.0, 4H), 7.05 (d, J = 8.0, 2H), 3.95 (s, 2H), 2.25 (s, 3H), 1.29 (s, 9H); \(^{13}\)C \(^1\)H NMR (126 MHz, CDCl\(_3\)): \(\delta\) 148.7, 139.2, 137.3, 136.6, 130.3, 130.0, 128.4, 126.4, 126.0, 125.3, 38.9, 34.4, 31.4, 19.8 ppm; IR (thin film): 3020, 2904, 1909, 1603, 1514, 1492, 1462, 1411, 1392, 1378, 1363, 1268, 1201, 1108, 1050, 916, 805, 720 cm\(^{-1}\); HRMS calc’d for C\(_{18}\)H\(_{22}\)\(^+\) 238.1722, observed 238.1721 [M]\(^+\)

1-(4-(tert-butyl)benzyl)-3-methylbenzene (4ca): The reaction was performed following General Procedure B with 1a (18 \(\mu\)L, 0.1 mmol), KN(SiMe\(_3\))\(_2\) (30 mg, 0.15 mmol) and 2c (3mL). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (19 mg, 80% yield) as a colorless oil. \(R_f = 0.40\) (hexanes); \(^1\)H NMR (500 MHz; CDCl\(_3\)): \(\delta\) 7.28-7.25 (m, 2H), 7.14 (t, J = 7.5, 1H), 7.10-7.08 (m, 2H, 6.99-6.96 (m, 3H), 3.87 (s, 2H), 2.28 (s, 3H), 1.27 (s, 9H); \(^{13}\)C \(^1\)H NMR (126 MHz, CDCl\(_3\)): \(\delta\) 148.8, 141.2, 138.3, 138.0, 129.8, 128.51, 128.37, 126.8, 126.1, 125.4, 41.5, 34.4, 31.5, 21.5 ppm; IR (thin film): 3023, 2961, 1906, 1606, 1514, 1488, 1460, 1411, 1392, 1376, 1363, 1268, 1202, 1109, 1090, 932, 807, 700 cm\(^{-1}\); HRMS calc’d for C\(_{18}\)H\(_{22}\)\(^+\) 238.1722, observed 238.1713 [M]\(^+\)
1-(4-(tert-butyl)benzyl)-4-methylbenzene (4da): The reaction was performed following General Procedure B with 1a (18 μL, 0.1 mmol), KN(SiMe$_3$)$_2$ (30 mg, 0.15 mmol) and 2d (3mL). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (15.3 mg, 64% yield) as a colorless oil. R$_f$ = 0.40 (hexanes); $^1$H NMR (500 MHz; CDCl$_3$): δ 7.30-7.28 (m, 2H), 7.12-7.09 (m, 6H), 3.91 (s, 2H), 2.31 (d, J = 1.2, 3H), 1.29 (s, 9H); $^{13}$C {$^1$H} NMR (126 MHz, CDCl$_3$): δ 148.7, 138.42, 138.27, 135.5, 129.1, 128.9, 128.4, 125.3, 41.0, 34.4, 31.4, 21.1; IR (thin film): 3020, 2962, 1512, 1463, 1411, 1362, 1258, 1202, 1108, 1020, 846, 811, 721 cm$^{-1}$; HRMS calc’d for C$_{18}$H$_{22}$+ 238.1722, observed 238.1724 [M]$^+$

1-(4-(tert-butyl)benzyl)-3,5-dimethylbenzene (4ea):
The reaction was performed following General Procedure B with 1a (18 μL, 0.1 mmol), KN(SiMe$_3$)$_2$ (30 mg, 0.15 mmol) and 2e (3mL). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (15.9 mg, 63% yield) as a colorless oil. R$_f$ = 0.40 (hexanes); $^1$H NMR (500 MHz; CDCl$_3$): δ 7.29 (d, J = 8.3, 2H), 7.11 (d, J = 8.4, 2H), 6.82 (s, 3H), 3.86 (s, 2H), 2.26 (s, 6H), 1.29 (s, 9H); $^{13}$C {$^1$H} NMR (126 MHz, CDCl$_3$): δ 148.7, 141.2, 138.4, 137.9, 128.5, 127.7, 126.9, 125.4, 41.4, 34.4, 31.5, 21.3; IR (thin film): 3015, 2962, 1603, 1514, 1463, 1411, 1362, 1258, 1202, 1109, 1018, 855, 826, 701 cm$^{-1}$; HRMS calc’d for C$_{19}$H$_{24}$+ 252.1878, observed 252.1870 [M]$^+$

1-(4-(tert-butyl)benzyl)-2-methoxybenzene (4fa): The reaction was performed following General Procedure B with 1a (18 μL, 0.1 mmol), KN(SiMe$_3$)$_2$ (30 mg, 0.15 mmol) and 2f (3mL). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (22.9 mg, 90% yield) as a colorless oil. R$_f$ = 0.40 (hexanes); $^1$H NMR (500 MHz; CDCl$_3$): δ 7.29-7.27 (m, 2H), 7.18 (td, J = 7.8, 1.6, 1H), 7.02 (td, J = 8.1, 1.7, 1H), 6.82 (s, 3H), 3.84 (s, 2H), 3.72 (s, 3H), 2.25 (s, 6H), 1.28 (s, 9H); $^{13}$C {$^1$H} NMR (126 MHz, CDCl$_3$): δ 148.7, 141.1, 138.4, 137.9, 128.6, 127.7, 126.9, 125.4, 41.4, 34.4, 31.5, 21.3; IR (thin film): 3015, 2962, 1603, 1514, 1463, 1411, 1362, 1258, 1202, 1109, 1018, 855, 826, 701 cm$^{-1}$; HRMS calc’d for C$_{19}$H$_{24}$O+ 266.1731, observed 266.1733 [M]+.
7.15-7.13 (m, 2H), 7.08-7.06 (m, 1H), 6.88-6.85 (m, 2H), 3.94 (s, 2H), 3.81 (s, 3H), 1.29 (s, 9H); $^{13}$C {$^1$H} NMR (126 MHz, CDCl$_3$): $\delta$ 157.4, 148.5, 138.0, 130.4, 129.9, 128.6, 127.3, 125.2, 120.5, 110.4, 55.4, 35.3, 34.4, 31.5; IR (thin film): 3015, 2962, 1603, 1514, 1463, 1411, 1362, 1268, 1202, 1109, 1018, 855, 826, 701 cm$^{-1}$; HRMS calc’d for C$_{18}$H$_{22}$O$^+$ 254.1671, observed 254.1665 [M]$^+$

1-(4-(tert-butyl)benzyl)-2-fluorobenzene (4ga): The reaction was performed following General Procedure B with 1a (18 $\mu$L, 0.1 mmol), KN(SiMe$_3$)$_2$ (30 mg, 0.15 mmol) and 2g (3mL). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (20.6 mg, 85% yield) as a colorless oil. R$_f$ = 0.40 (hexanes); $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 7.31-7.29 (m, 2H), 7.20-7.13 (m, 4H), 7.06-7.00 (m, 2H), 3.97 (s, 2H), 1.29 (s, 9H); $^{13}$C {$^1$H} NMR (126 MHz, CDCl$_3$): $\delta$ 161.0 (d, JC-F = 245.7 Hz), 149.0, 136.8, 131.1 (d, JC-F = 5.0 Hz), 128.2, 127.8 (d, JC-F = 8.8 Hz), 125.4, 125.3, 124.0 (d, JC-F = 3.8 Hz), 115.3 (d, JC-F = 22.7 Hz), 34.4, 34.2 (d, JC-F = 2.5 Hz), 31.4; IR (thin film): 3014, 2962, 1584, 1515, 1491, 1455, 1412, 1363, 1268, 1230, 1203, 1118, 1091, 1019, 916, 833, 805, 754 cm$^{-1}$; HRMS calc’d for C$_{17}$H$_{19}$F$^+$ 242.1471, observed 242.1481 [M]$^+$

1-(4-(tert-butyl)benzyl)-2-chlorobenzene (4ha): The reaction was performed following General Procedure B with 1a (18 $\mu$L, 0.1 mmol), KN(SiMe$_3$)$_2$ (30 mg, 0.15 mmol) and 2h (3mL). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (21 mg, 81% yield) as a colorless oil. R$_f$ = 0.40 (hexanes); $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 7.36-7.35 (m, 1H), 7.31-7.29 (m, 2H), 7.16-7.11 (m, 5H), 4.07 (s, 2H), 1.30 (s, 9H); $^{13}$C {$^1$H} NMR (126 MHz, CDCl$_3$): $\delta$ 149.1, 138.9, 136.5, 134.3, 131.1, 129.5, 128.6, 127.6, 126.9, 125.4, 38.7, 34.4, 31.5; IR (thin film): 3057, 2962, 1570, 1514, 1470, 1442, 1411, 1363, 1268, 1201, 1109, 132
1050, 1038, 914, 841, 801, 754, 719 cm⁻¹; HRMS calc’d for C₁₇H₁₉Cl⁺ 258.1175, observed 258.1169 [M⁺]

1-(4-(tert-butyl)benzyl)-3-fluorobenzene (4ia): The reaction was performed following General Procedure B with 1a (18 μL, 0.1 mmol), KN(SiMe₃)₂ (30 mg, 0.15 mmol) and 2i (3mL). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (18.9 mg, 78% yield) as a colorless oil. Rᵣ = 0.40 (hexanes); ¹H NMR (500 MHz; CDCl₃): δ 7.32-7.30 (m, 2H), 7.24-7.22 (m, 1H), 7.10 (d, J = 8.1, 2H), 6.98 (d, J = 7.5, 1H), 6.88 (dt, J = 5.8, 2.8, 2H), 3.93 (s, 2H), 1.30 (s, 9H); ¹³C {¹H} NMR (126 MHz, CDCl₃): δ 163.0 (d, JC-F = 245.7 Hz), 149.2, 143.9 (d, JC-F = 7.5 Hz), 137.2, 129.8 (d, JC-F = 8.8 Hz), 128.5, 125.5, 124.6 (d, JC-F = 2.5 Hz), 115.8 (d, JC-F = 21.4 Hz), 112.9 (d, JC-F = 20.1 Hz), 41.1 (d, JC-F = 1.2 Hz), 34.4, 31.4; IR (thin film): 3025, 2963, 1733, 1612, 1589, 1515, 1486, 1448, 1411, 1363, 1267, 1249, 1202, 1135, 1109, 1018, 942, 835, 813, 756 cm⁻¹; HRMS calc’d for C₁₇H₁₉F⁺ 242.1471, observed 242.1470 [M⁺]

1-(4-(tert-butyl)benzyl)-3-chlorobenzene (4ja): The reaction was performed following General Procedure B with 1a (18 μL, 0.1 mmol), KN(SiMe₃)₂ (30 mg, 0.15 mmol) and 2j (3mL). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (19.1 mg, 74% yield) as a colorless oil. Rᵣ = 0.40 (hexanes); ¹H NMR (500 MHz; CDCl₃): δ 7.32-7.30 (m, 2H), 7.21-7.15 (m, 3H), 7.10-7.06 (m, 3H), 3.91 (s, 2H), 1.30 (s, 9H); ¹³C {¹H} NMR (126 MHz, CDCl₃): δ 149.2, 143.4, 137.2, 134.2, 129.7, 129.1, 128.5, 127.2, 126.3, 125.5, 41.1, 34.4, 31.4; IR (thin film): 2962, 1573, 1514, 1475, 1429, 1411, 1363, 1200, 1109, 1091, 1077, 1018, 925, 868, 804, 745, 697 cm⁻¹; HRMS calc’d for C₁₇H₁₉Cl⁺ 258.1175, observed 258.1183 [M⁺]
1-(tert-butyl)-4-(1-phenylethyl)benzene (4ka): The reaction was performed following General Procedure B with 1a (18 μL, 0.1 mmol), KN(SiMe₃)₂ (30 mg, 0.15 mmol) and 2k (3mL). The crude material was purified by flash chromatography on silica gel (eluted with hexanes) to give the product (17.9 mg, 75% yield) as a colorless oil. Rᵣ = 0.40 (hexanes); 'H NMR (500 MHz; CDCl₃): δ 7.30-7.22 (m, 6H), 7.18-7.14 (m, 3H), 4.12 (q, J = 7.2, 1H), 1.63 (d, J = 7.2, 3H), 1.29 (s, 9H); ¹³C {¹H} NMR (126 MHz, CDCl₃): δ 148.7, 146.6, 143.3, 128.4, 127.7, 127.2, 126.0, 125.2, 44.4, 34.4, 31.4, 21.9; IR (thin film): 3025, 2964, 1600, 1514, 1492, 1451, 1409, 1363, 1268, 1201, 1111, 1016, 835, 779, 754, 699 cm⁻¹; HRMS calc’d for C₁₈H₂₄⁺ 238.1722, observed 238.1717 [M⁺]

Ligands Screening Results

Experiments were set up inside a glovebox under a nitrogen atmosphere. Two 24-well aluminum block containing 1 mL glass vials was predosed with Buchwald type precatalyst dimer (0.5 μmol) and the phosphine ligands (2 μmol for monodentate ligands and 1 μmol for bidentate ligands) in THF. The solvent was removed to dryness using a GeneVac and 4-tert-butylbromobenzene (10 μmol) wos dosed into each reaction vial as a solution in Toluene (50 μL, 0.2 M). KN(SiMe₃)₂ (15 μmol) in Toluene (50 μL, 0.2 M) was added. Total reaction scale is 100 μL, 0.1 M. The 24-well plate was then sealed and stirred for 12 h at 110°C.

Work up:
Upon opening the plate to air, 500 μL of a solution of Biphenyl (used as internal standard to measure HPLC yields) in acetonitrile (0.002 mol/L) was added into each vial. The plate was covered again and the vials stirred for 10 min. to ensure good homogenization.
Into a separate 96-well LC block was added 700 μL of acetonitrile, followed by 25 μL of the diluted reaction mixtures. The LC block was then sealed with a silicon-rubber storage mat and mounted on an automated HPLC instrument for analysis.

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4.5. REFERENCES

(10) Mkhaliid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. Chem. Rev. 2010, 110, 890.


Appendix A1. NMR Spectra Relevant to Chapter 1
Figure A1.1 500 MHz $^1$H and 125 MHz $^{13}$C{$^1$H} NMR of 1.3aa in CDCl$_3$
Figure A1.2 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 1.3ba in CDCl$_3$
Figure A1.3 500 MHz $^1$H and 125 MHz $^{13}$C{$^1$H} NMR of 1.3ca in CDCl$_3$
Figure A1.4 500 MHz $^1$H and 125 MHz $^{13}$C{[^1]H} NMR of 1.3da in CDCl$_3$
Figure A1.5 500 MHz $^1$H and 125 MHz $^{13}$C{$^1$H} NMR of 1.3ea in CDCl$_3$
Figure A1.6 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 1.3fa in CDCl$_3$
Figure A1.7 500 MHz $^1$H and 125 MHz $^{13}$C{$^1$H} NMR of 1.3ga in CDCl$_3$
Figure A1.8 500 MHz $^1$H and 125 MHz $^{13}$C$^1$H NMR of 1.5aa in CDCl$_3$
Figure A1.9 500 MHz $^1$H and 125 MHz $^{13}$C{$^1$H} NMR of 1.5ba in CDCl$_3$
Figure A1.10 500 MHz $^1$H and 125 MHz $^{13}$C{H} NMR of 1.5ca in CDCl$_3$
Figure A1.11 500 MHz $^1$H and 125 MHz $^{13}$C[$^1$H] NMR of 1.5da in CDCl$_3$
Figure A1.12 500 MHz $^1$H and 125 MHz $^{13}$C{$^1$H} NMR of 1.5ea in CDCl$_3$
Figure A1.13 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 1.5fa in CDCl$_3$
Figure A1.14 500 MHz $^1$H and 125 MHz $^{13}$C{$^1$H} NMR of 1.5ga in CDCl$_3$
Figure A1.15 500 MHz $^1$H and 125 MHz $^{13}$C[$^1$H] NMR of 1.5ha in CDCl$_3$
Figure A1.16 500 MHz $^1$H and 125 MHz $^{13}$C[$^1$H] NMR of 1.6ba in CDCl$_3$
Figure A1.17 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 1.6da in CDCl$_3$
Figure A1.18 500 MHz $^1$H and 125 MHz $^{13}C$ NMR of 1.7ea in CDCl$_3$
Figure A1.19 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 1.6fa in CDCl$_3$
Figure A1.20 500 MHz $^1$H and 125 MHz $^{13}$C{$^1$H} NMR of 1.6aa in CDCl$_3$
Figure A1.21 500 MHz $^1$H and 125 MHz $^{13}$C$^1$H NMR of 1.6ca in CDCl$_3$
**Figure A1.22** 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 1.8aa in CDCl$_3$
Figure A1.23 500 MHz $^1$H and 125 MHz $^{13}$C{H} NMR of 1.9aa in CDCl$_3$
Figure A1.24 500 MHz $^1$H and 125 MHz $^{13}$C$\{^1\text{H}\}$ NMR of 1.10a in CDCl$_3$
Figure A1.25 500 MHz $^1$H and 125 MHz $^{13}$C{$^1$H} NMR of 1.10b in CDCl$_3$
Figure A1.26 500 MHz $^1$H and 125 MHz $^{13}$C{$^1$H} NMR of 1.10c in CDCl$_3$
Figure A1.27 500 MHz $^1$H and 125 MHz $^{13}$C{$^1$H} NMR of 1.10d in CDCl$_3$
Figure A1.28 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 1.10e in CDCl$_3$
**Figure A1.29** 500 MHz $^1$H and 125 MHz $^{13}$C{$^1$H} NMR of 1.10f in CDCl$_3$
Figure A1.30 500 MHz $^1$H and 125 MHz $^{13}$C$\{^1$H$\}$ NMR of 1.10g in CDCl$_3$
Figure A1.31 500 MHz $^1$H and 125 MHz $^{13}$C{$^1$H} NMR of 1.10h in CDCl$_3$
Figure A1.32 500 MHz $^1$H and 125 MHz $^{13}$C($^1$H) NMR of 1.11a in CDCl$_3$
Figure A1.33 500 MHz $^1$H and 125 MHz $^{13}\text{C}[^1\text{H}]$ NMR of 1.11b in CDCl$_3$
Figure A2.1 500 MHz $^1$H NMR of 2.3aa in CDCl$_3$
Figure A2.2 125 MHz $^{13}$C{\textsuperscript{1}H} NMR of 2.3aa in CDCl$_3$
Figure A2.3 500 MHz $^1$H NMR of 2.3ba in CDCl$_3$
Figure A2.4 125 MHz $^{13}\text{C}[^1\text{H}]$ NMR of 2.3ba in CDCl$_3$
Figure A2.5 500 MHz $^1$H NMR of 2.3ca in CDCl$_3$
**Figure A2.6** 125 MHz $^{13}$C{$^1$H} NMR of 2.3ca in CDCl$_3$
Figure A2.7  500 MHz $^1$H NMR of 2.3da in CDCl$_3$
Figure A2.8 125 MHz $^{13}$C$\{^1\text{H}\}$ NMR of 2.3da in CDCl$_3$
Figure A2.9 500 MHz $^1$H NMR of 2.3ea in CDCl$_3$
Figure A2.10 125 MHz $^{13}\text{C}^\text{1}{\text{H}}$ NMR of 2.3ea in CDCl$_3$
Figure A2.11 500 MHz $^1$H NMR of 2.3fa in CDCl$_3$
Figure A2.12 125 MHz $^{13}\text{C}\{^1\text{H}\}$ NMR of 2.3fa in CDCl$_3$
Figure A2.13 500 MHz $^1$H NMR of 2.3ga in CDCl$_3$
Figure A2.14 125 MHz $^{13}\text{C}[^1\text{H}]$ NMR of 2.3ga in CDCl$_3$
Figure A2.15 500 MHz $^1$H NMR of 2.5aa in CDCl$_3$
Figure A2.16 125 MHz $^{13}\text{C}\{^1\text{H}\}$ NMR of 2.5aa in CDCl$_3$
Figure A2.17 500 MHz $^1$H NMR of 2.5ba in CDCl$_3$
Figure A2.18 125 MHz $^{13}\text{C}^{1}\text{H}$ NMR of 2.5ba in CDCl$_3$
Figure A2.19 500 MHz $^1$H NMR of 2.5ca in CDCl$_3$
Figure A2.20 125 MHz $^{13}C^{1}H$ NMR of 2.5ca in CDCl$_3$
Figure A2.21 500 MHz $^1$H NMR of 2.5da in CDCl$_3$
Figure A2.22 125 MHz $^{13}$C{\textsuperscript{1}H} NMR of 2.5da in CDCl$_3$
Figure A2.23 500 MHz $^1$H NMR of 2.5ea in CDCl$_3$
Figure A2.24 125 MHz $^{13}\text{C}[^1\text{H}]$ NMR of 2.5ea in CDCl$_3$
Figure A2.25 500 MHz $^1$H NMR of 2.5fa in CDCl$_3$
Figure A2.26 125 MHz $^{13}\text{C}[^1\text{H}]$ NMR of 2.5fa in CDCl$_3$
Figure A2.27 500 MHz $^1$H NMR of 2.6aa in CDCl$_3$
Figure A2.28 125 MHz $^{13}$C{^1}H NMR of 2.6aa in CDCl$_3$
Figure A2.29 500 MHz $^1$H NMR of 2.6ba in CDCl$_3$
Figure A2.30 125 MHz $^{13}$C-$^1$H NMR of 2.6ba in CDCl$_3$
Figure A2.31 500 MHz $^1$H NMR of 2.6ca in CDCl$_3$
Figure A2.32 125 MHz $^{13}$C-$^1$H NMR of 2.6ca in CDCl$_3$
Figure A2.33 500 MHz $^1$H NMR of 2.6da in CDCl$_3$
Figure A2.34 125 MHz $^{13}$C{H} NMR of 2.6da in CDCl$_3$
Figure A2.35 500 MHz $^1$H NMR of 2.6ea in CDCl$_3$
Figure A2.36 125 MHz $^{13}\text{C}^1\text{H}$ NMR of 2.6ea in CDCl$_3$
Figure A2.37 500 MHz $^1$H NMR of 2.6fa in CDCl$_3$
Figure A2.38 125 MHz $^{13}\text{C}[^1\text{H}]$ NMR of 2.6fa in CDCl$_3$
Figure A2.39 500 MHz $^1$H NMR of 2.8aa in CDCl$_3$
Figure A2.40 125 MHz $^{13}$C$\{^{1}H\}$ NMR of 2.8aa in CDCl$_3$
Figure A2.41 500 MHz $^1$H NMR of 2.8ba in CDCl$_3$
Figure A2.42 125 MHz $^{13}\text{C}[^1\text{H}]$ NMR of 2.8ba in CDCl$_3$
Figure A2.43 500 MHz $^1$H NMR of 2.9fb in CDCl$_3$
Figure A2.44 125 MHz $^{13}\text{C}\{^1\text{H}\}$ NMR of 2.9fb in CDCl$_3$
Figure A2.45 500 MHz $^1$H NMR of 2.10fc in CDCl$_3$
Contains 10% of trans product from 2c impurity

Figure A2.46 125 MHz $^{13}$C{${}^1$H} NMR of 2.10fc in CDCl$_3$
Figure A3.1 500 MHz $^1$H NMR of 3.1aa in CDCl$_3$
Figure A3.2 125 MHz $^{13}\text{C}[^1\text{H}]$ NMR of 3.1aa in CDCl$_3$
Figure A3.3 500 MHz $^1$H NMR of 3.3aa in CDCl$_3$
Figure A3.4 125 MHz $^{13}$C-$[^1]$H NMR of 3.3aa in CDCl$_3$
Figure A3.5 500 MHz $^1$H NMR of 3.3ab in CDCl$_3$
Figure A3.6 125 MHz $^{13}$C{^1}H NMR of 3.3ab in CDCl$_3$
Figure A3.7 500 MHz $^1$H NMR of 3.3ac in CDCl$_3$
Figure A3.8 125 MHz $^{13}$C-$^1$H NMR of 3.3ac in CDCl$_3$
Figure A3.9 500 MHz $^1$H NMR of 3.3ad in CDCl$_3$
Figure A3.10 125 MHz $^{13}$C-$^1$H NMR of 3.3ad in CDCl$_3$
Figure A3.11 500 MHz $^1$H NMR of 3.3ae in CDCl$_3$
Figure A3.12 125 MHz $^{13}$C{^1}H NMR of 3.3ae in CDCl$_3$
Figure A3.13 500 MHz $^1$H NMR of 3.3af in CDCl$_3$
Figure A3.14 125 MHz $^{13}$C{$^1$H} NMR of 3.3af in CDCl$_3$
Figure A3.15 500 MHz $^1$H NMR of 3.3ag in CDCl$_3$
Figure A3.16 125 MHz $^{13}$C-$^1$H NMR of 3.3ag in CDCl$_3$
Figure A3.17 500 MHz $^1$H NMR of 3.3ah in CDCl$_3$
Figure A3.18 125 MHz $^{13}\text{C}[^1\text{H}]$ NMR of 3.3ah in CDCl₃
Figure A3.19 500 MHz $^1$H NMR of 3.3ai in CDCl$_3$
Figure A3.20 125 MHz $^{13}$C\{H\} NMR of 3.3ai in CDCl$_3$
Figure A3.21 500 MHz $^1$H NMR of 3.3ba in CDCl$_3$
Figure A3.22 125 MHz $^{13}$C-$^1$H NMR of 3.3ba in CDCl$_3$
Figure A3.23 500 MHz $^1$H NMR of 3.3ca in CDCl$_3$
Figure A3.24 125 MHz $^{13}$C-$^1$H NMR of 3.3ca in CDCl$_3$
Figure A3.25 500 MHz NMR of 3.3da in CDCl₃
Figure A3.26 125 MHz $^{13}$C-'H' NMR of 3.3da in CDCl$_3$
Figure A3.27 500 MHz $^1\text{H}$ NMR of 3.3ea in CDCl$_3$
Figure A3.28 125 MHz $^{13}$C{^1}H NMR of 3.3ea in CDCl$_3$
Figure A3.29 500 MHz $^1$H NMR of 3.3fa in CDCl$_3$
Figure A3.30 125 MHz $^{13}$C{''H} NMR of 3.3fa in CDCl$_3$
Figure A3.31 500 MHz $^1$H NMR of 3.3ga in CDCl$_3$
Figure A3.32 125 MHz $^{13}$C-$^{1}$H NMR of 3.3ga in CDCl$_3$
Figure A3.33 500 MHz $^1$H NMR of 3.3ha in CDCl$_3$
Figure A3.34 125 MHz $^{13}$C[{'H}] NMR of 3.3ha in CDCl$_3$
Figure A3.35 500 MHz $^1$H NMR of 3.4ap in CDCl$_3$
Figure A3.36 125 MHz $^{13}\text{C}[^1\text{H}]$ NMR of 3.4ap in CDCl$_3$
Figure A3.37 500 MHz $^1$H NMR of 3.4aa in CDCl$_3$
Figure A3.38 125 MHz $^{13}$C-{H} NMR of 3.4aa in CDCl$_3$
Figure A3.39 500 MHz $^1$H NMR of 3.4ad in CDCl$_3$
Figure A3.40 125 MHz $^{13}$C($^1$H) NMR of 3.4ad in CDCl$_3$
Appendix A4. NMR Spectra Relevant to Chapter 4
Figure A4.1 500 MHz $^1$H NMR of 4.3aa in CDCl$_3$
Figure A4.2 125 MHz $^{13}$C{$^1$H} NMR of 4.3aa in CDCl$_3$
Figure A4.3 500 MHz $^1$H NMR of 4.3ab in CDCl$_3$
Figure A4.4 125 MHz $^{13}$C$^{1}$H NMR of 4.3ab in CDCl$_3$
Figure A4.5 500 MHz $^1$H NMR of 4.3ac in CDCl$_3$
Figure A4.6 125 MHz $^{13}\text{C}\{^1\text{H}\}$ NMR of 4.3ac in CDCl$_3$
Figure A4.7 500 MHz $^1$H NMR of 4.3ad in CDCl$_3$
Figure A4.8 125 MHz $^{13}\text{C}^{1\text{H}}$ NMR of 4.3ad in CDCl$_3$
Figure A4. 500 MHz $^1$H NMR of 4.3ae in CDCl$_3$
Figure A4.10 125 MHz $^{13}$C$^1$H NMR of 4.3ae in CDCl$_3$
Figure A4.11 500 MHz $^1$H NMR of 4.3af in CDCl$_3$
Figure A4.12 125 MHz $^{13}$C{H} NMR of 4.3af in CDCl$_3$
Figure A4.13 500 MHz $^1$H NMR of 4.3ag in CDCl$_3$
Figure A4.14 125 MHz $^{13}$C\textsuperscript{1}H NMR of 4.3ag in CDCl\textsubscript{3}
Figure A4.15 500 MHz $^1$H NMR of 4.4ba in CDCl$_3$
Figure A4.16 125 MHz $^{13}$C-$^{1}$H NMR of 4.4ba in CDCl$_3$
Figure A4.17 500 MHz $^1$H NMR of 4.4ca in CDCl$_3$
Figure A4.18 125 MHz $^{13}$C{$^1$H} NMR of 4.4ca in CDCl$_3$
Figure A4.19 500 MHz $^1$H NMR of 4.4da in CDCl$_3$
Figure A4.20  125 MHz $^{13}$C{\textsuperscript{1}H} NMR of 4.4da in CDCl\textsubscript{3}
Figure A4.21 500 MHz $^1$H NMR of 4,4ea in CDCl$_3$
Figure A4.22 125 MHz $^{13}$C{$^1$H} NMR of 4.4ea in CDCl$_3$
**Figure A4.23** 500 MHz $^1$H NMR of 4.4fa in CDCl$_3$
Figure A4.24 125 MHz $^{13}$C{$^1$H} NMR of 4.4fa in CDCl$_3$
Figure A4.25 500 MHz $^1$H NMR of 4.4ga in CDCl$_3$
Figure A4.26 125 MHz $^{13}$C{$^{1}$H} NMR of 4.4ga in CDCl$_3$
Figure A4.27 500 MHz $^1$H NMR of 4.4ha in CDCl$_3$
Figure A4.28 125 MHz $^{13}\text{C}\{^1\text{H}\}$ NMR of 4.4ha in CDCl$_3$
Figure A4.29 500 MHz $^1$H NMR of 4.4ia in CDCl$_3$
Figure A4.30 125 MHz $^{13}$C{$^1$H} NMR of 4.4ia in CDCl$_3$
Figure A4.31 500 MHz $^1$H NMR of 4.4ja in CDCl$_3$
Figure A4.32 125 MHz $^{13}\text{C}\{^1\text{H}\}$ NMR of 4.4ja in CDCl$_3$
Figure A4.33 500 MHz $^1$H NMR of 4.4ka in CDCl$_3$
Figure A4.34 125 MHz $^{13}$C{^1}H NMR of 4.4ka in CDCl$_3$
Appendix B. X-ray Structure Reports
Compound 11b, C_{25}H_{24}, crystallizes in the monoclinic space group P2\(_1\)/c (systematic absences 0k0: k=odd and h0l: l=odd) with a=18.8031(14)Å, b=5.8211(5)Å, c=17.3207(13)Å, \(b=103.022(4)^\circ\), \(V=1847.1(3)\text{Å}^3\), \(Z=4\), and \(d_{\text{calc}}=1.167\text{ g/cm}^3\). X-ray intensity data were collected on a Bruker APEXII CCD area detector employing graphite-monochromated Mo-Ka radiation (\(l=0.71073\text{ Å}\)) at a temperature of 143(1)K. Preliminary indexing was performed from a series of thirty-six 0.5° rotation frames with exposures of 10 seconds. A total of 2591 frames were collected with a crystal to detector distance of 37.6 mm, rotation widths of 0.5° and exposures of 30 seconds:

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<th>f</th>
<th>c</th>
<th>frames</th>
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<td>8.28</td>
<td>19.46</td>
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</tr>
<tr>
<td>w</td>
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<td>28.88</td>
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<tr>
<td>f</td>
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<td>59.55</td>
<td>348.71</td>
<td>-26.26</td>
<td>559</td>
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Rotation frames were integrated using SAINT\(^i\), producing a listing of unaveraged \(F^2\) and \(s(F^2)\) values which were then passed to the SHELXTL\(^ii\) program package for further processing and structure solution. A total of 38765 reflections were measured over the ranges 2.22 \(\leq q \leq 25.42^\circ\), -22 \(\leq h \leq 22\), -7 \(\leq k \leq 7\), -14 \(\leq l \leq 20\) yielding 3315 unique reflections (Rint = 0.0633). The intensity data were corrected for Lorentz and polarization effects and for absorption using SADABS\(^iii\) (minimum and maximum
The structure was solved by direct methods (SHELXS-97iv). Refinement was by full-matrix least squares based on $F^2$ using SHELXL-97.v All reflections were used during refinement. The weighting scheme used was $w=1/\left[ s^2(F_o^2) + (0.0781P)^2 + 1.2783P \right]$ where $P = (F_o^2 + 2F_c^2)/3$. Non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined using a riding model. Refinement converged to $R1=0.0597$ and $wR2=0.1474$ for 2336 observed reflections for which $F > 4s(F)$ and $R1=0.0922$ and $wR2=0.1680$ and GOF =1.029 for all 3315 unique, non-zero reflections and 226 variables.vi The maximum D/s in the final cycle of least squares was 0.000 and the two most prominent peaks in the final difference Fourier were +0.647 and -0.268 e/Å³.

Table S1. lists cell information, data collection parameters, and refinement data. Final positional and equivalent isotropic thermal parameters are given in Tables S2. and S3. Anisotropic thermal parameters are in Table S4. Tables S5. and S6. list bond distances and bond angles. Figure 1. is an ORTEPvii representation of the molecule with 30% probability thermal ellipsoids displayed.
Figure S1. ORTEP drawing of the title compound with 30% probability thermal ellipsoids.
Table S1. Summary of Structure Determination of Compound 11b

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<td>Wavelength</td>
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<td>Crystal system</td>
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<tr>
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<td>Cell constants:</td>
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<tr>
<td>b</td>
<td>5.8211(5) Å</td>
</tr>
<tr>
<td>c</td>
<td>17.3207(13) Å</td>
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<td>b</td>
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<td>Crystal size</td>
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<td>Theta range for data collection</td>
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<tr>
<td>Independent reflections</td>
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<td>Completeness to theta = 25.42°</td>
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<td>Absorption correction</td>
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<td>Max. and min. transmission</td>
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<td>Refinement method</td>
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<td>Data / restraints / parameters</td>
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<tr>
<td>Goodness-of-fit on F²</td>
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<tr>
<td>Final R indices [I&gt;2sigma(I)]</td>
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<tr>
<td>R indices (all data)</td>
<td>R1 = 0.0922, wR2 = 0.1680</td>
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<tr>
<td>Largest diff. peak and hole</td>
<td>0.647 and -0.268 e.Å⁻³</td>
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### Table S2. Refined Positional Parameters for Compound 11b

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<tr>
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<tr>
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Ueq=\frac{1}{3}(U_{11}(aa^*)^2+U_{22}(bb^*)^2+U_{33}(cc^*)^2+2U_{12}aa^*bb^*+2U_{13}aa^*cc^*+2U_{23}bb^*cc^*)^\frac{1}{2}

### Table S3. Positional Parameters for Hydrogens in Compound 11b

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<tr>
<th>Atom</th>
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<th>y</th>
<th>z</th>
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<td>0.3948</td>
<td>0.045</td>
</tr>
<tr>
<td>H2a</td>
<td>0.3407</td>
<td>0.5349</td>
<td>0.3149</td>
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</tr>
<tr>
<td>H2b</td>
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<td>0.7935</td>
<td>0.3094</td>
<td>0.039</td>
</tr>
<tr>
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</tr>
<tr>
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<td>0.9223</td>
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<td>0.047</td>
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<tr>
<td>H5</td>
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<td>0.9879</td>
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<tr>
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<td>0.7542</td>
<td>0.4550</td>
<td>0.044</td>
</tr>
<tr>
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<td>0.7543</td>
<td>0.2859</td>
<td>0.045</td>
</tr>
<tr>
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<td>0.1703</td>
<td>0.2932</td>
<td>0.042</td>
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<tr>
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<td>0.1816</td>
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<td>0.1001</td>
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<td>0.6713</td>
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<tr>
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</tr>
<tr>
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<tr>
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<tr>
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Table S4. Refined Thermal Parameters (U's) for Compound 11b

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<th>Atom</th>
<th>$U_{11}$</th>
<th>$U_{22}$</th>
<th>$U_{33}$</th>
<th>$U_{23}$</th>
<th>$U_{13}$</th>
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<tr>
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<td>0.0107(10)</td>
<td>-0.0005(10)</td>
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<td>0.0546(16)</td>
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<tr>
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<td>-0.0019(12)</td>
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<tr>
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<tr>
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The form of the anisotropic displacement parameter is:

$$\exp[-2p^2(a^2U_{11}h^2+b^2U_{22}k^2+c^2U_{33}l^2+2abU_{23}kl+2acU_{13}hl+2a^2bU_{12}hk)]$$
Table S5. Bond Distances in Compound 11b, Å

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<thead>
<tr>
<th>Bond</th>
<th>Distance (Å)</th>
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<td>C4-C5</td>
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<td>C7-C14</td>
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<td>C9-C10</td>
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<td>C18-C19</td>
<td>1.385(4)</td>
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<tr>
<td>C21-C22</td>
<td>1.378(3)</td>
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<tr>
<td>C24-C25</td>
<td>1.395(3)</td>
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<tr>
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<td>C5-C6</td>
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Table S6. Bond Angles in Compound 11b, °

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<tr>
<td>C3-C2-C1</td>
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<tr>
<td>C4-C3-C20</td>
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<td>C5-C6-C1</td>
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<tr>
<td>C8-C7-C14</td>
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<tr>
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<tr>
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<td>119.8(2)</td>
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1Bruker (2009) SAINT. Bruker AXS Inc., Madison, Wisconsin, USA.
3Sheldrick, G.M. (2007) SADABS. University of Gottingen, Germany.
\[ R_1 = \sum ||F_o|| - ||F_c|| / \sum ||F_o|| \]
\[ wR^2 = \left( \sum w(F_o^2 - F_c^2)^2 / \sum w(F_o^2)^2 \right)^{1/2} \]
\[ GOF = \left[ \sum w(F_o^2 - F_c^2)^2 / (n - p) \right]^{1/2} \]
where \( n \) = the number of reflections and \( p \) = the number of parameters refined.


---

\(^i\)Bruker (2009) SAINT. Bruker AXS Inc., Madison, Wisconsin, USA.
\(^iii\)Sheldrick, G.M. (2007) SADABS. University of Göttingen, Germany.

\(^vi\)R1 = \( \sum ||F_o|| - ||F_c|| / \sum ||F_o|| \)
\[ wR^2 = \left( \sum w(F_o^2 - F_c^2)^2 / \sum w(F_o^2)^2 \right)^{1/2} \]
\[ GOF = \left[ \sum w(F_o^2 - F_c^2)^2 / (n - p) \right]^{1/2} \]
where \( n \) = the number of reflections and \( p \) = the number of parameters refined.