CuH-Catalyzed Enantioselective Ketone Allylation with 1,3-Dienes: Scope, Mechanism, and Applications

Chengxi Li\textsuperscript{1}, Richard Y. Liu\textsuperscript{1}, Luke T. Jesikiewicz\textsuperscript{2}, Yang Yang\textsuperscript{1}, Peng Liu\textsuperscript{2,*}, and Stephen L. Buchwald\textsuperscript{1,*}

\textsuperscript{1}Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States
\textsuperscript{2}Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States

ABSTRACT: Chiral tertiary alcohols are important building blocks for the synthesis of pharmaceutical agents and biologically active natural products. The addition of carbon nucleophiles to ketones is the most common approach to tertiary alcohol synthesis, but traditionally relies on stoichiometric organometallic reagents that are difficult to prepare, sensitive, and uneconomical. We describe a mild and efficient method for the copper-catalyzed allylation of ketones, using widely available 1,3-dienes as allylmetal surrogates. Homoolylic alcohols bearing a wide range of functional groups are obtained in high yield and with good regio-, diastereoselectivity, and enantioselectivity. Mechanistic investigations using density functional theory (DFT) implicate the in situ formation of a rapidly equilibrating mixture of isomeric copper(I) allyl complexes, from which Curtin-Hammett kinetics determine the major isomer of product. A stereochemical model is provided to explain the high diastereo- and enantioselectivity of this process. Finally, this method was applied toward the preparation of an important drug, (R)-Procyclidine, and a key intermediate in the synthesis of several pharmaceuticals.

\section*{INTRODUCTION}

Enantiomerically enriched tertiary alcohols and their derivatives feature prominently in a variety of important pharmaceutical agents and complex natural products.\textsuperscript{1} Consequently, their efficient synthesis has attracted great attention from synthetic chemists.\textsuperscript{2} Traditionally, the addition of organomagnesium (Grignard) reagents to ketones has been a popular method to obtain tertiary alcohols in racemic form.\textsuperscript{3} However, the harsh methods required to prepare these organometallic reagents, as well as their instability and Brønsted basicity, have limited the tolerance of these reagents toward polar functional groups. Furthermore, the necessity to use stoichiometric organometallic reagents, and often, chiral auxiliaries for enantioselective transformations, is intrinsically inefficient and operationally complicating. Thus, the development of highly efficient catalytic, asymmetric strategies for constructing tertiary alcohols remains a goal of high priority in organic synthesis.\textsuperscript{4}

1,3-\textit{i}enes are important industrial raw materials that are produced on an enormous scale annually (Figure 1a). These chemicals include butadiene\textsuperscript{5} (about 13 \times 10^6 ton/year production), isoprene\textsuperscript{6} (about 8 \times 10^5 ton/year) and myrcene\textsuperscript{7} (about 2500 ton/year). Recently, a number of groups have proposed that these inexpensive and stable compounds could serve as ideal surrogates for stoichiometric organometallic reagents in carbonyl addition reactions. In 2005, a pioneering report by Gendre and Moïse\textsuperscript{8} demonstrated the first titanium-catalyzed aldehyde allylation using conjugated dienes as reagents (Figure 1b), although due to the highly reactive nature of the titanium-allyl species, the functional group tolerance was limited. Subsequently, Kirschke\textsuperscript{9} has developed ruthenium-catalyzed stereoselective aldehyde (or alcohol) allylations with 1,3-butadiene (Figure 1c). Unfortunately, the same method cannot be generally applied to ketones for the synthesis of tertiary alcohols. Despite reports of a number of other transition-metal-catalyzed reductive couplings (Ni\textsuperscript{9}, Ru\textsuperscript{10}, Rh\textsuperscript{11} and Ir\textsuperscript{12}) with conjugated dienes, reactions involving ketones, rather than aldehydes, remain challenging, even in a non-stereoselective manner.

\begin{tabular}{|c|c|c|}
\hline
(a) Industrial production of 1,3-dienes & \\
\hline
1,3-butadiene & Me & Me \\
\hline
isoprene & -1.3 \times 10^7 ton/year & -8 \times 10^7 ton/year \\
\hline
myrcene & -2.5 \times 10^7 ton/year & \\
\hline
(b) Ti-catalyzed allylation of aldehydes with 1,3-dienes (Gendre, Moïse) & \\
\hline
R&H & + & R&= & [Ti] & OH & R&= & Me \\
\hline
(c) Ru-catalyzed asymmetric allylation of aldehydes with 1,3-dienes (Kirschke) & \\
\hline
R&H & or & R&H & + & CH=CH & [Ru] & OH & Me \\
\hline
(d) Cu-catalyzed asymmetric ketone allylation with 1,3-dienes (this work) & \\
\hline
R&H & + & R&H & + & L\textsuperscript{*}CuH & R&= & Me \\
\hline
\end{tabular}

\textsuperscript{*}feedstock reagents \hspace{1cm} \textsuperscript{**}high branched selectivity
\textsuperscript{***}high diastereoenantioselectivity \hspace{1cm} formation of adjacent stereocenters

Figure 1. Overview of 1,3-dienes in industry and in catalytic allylation processes.

Over the past several years, a number of research groups, including ours, have reported approaches for the copper-catalyzed hydroamination of unsaturated substrates through the in situ generation of alkylcopper nucleophiles.\textsuperscript{13} Using this strategy, activated pronucleophiles such as enynes and allenes were
successfully engaged in nucleophilic addition reactions with ketones.\textsuperscript{14} This reactivity pattern has since also been extended to the reductive coupling of olefin prounucleophiles with imines.\textsuperscript{20,21}

Following this general concept, herein we describe a highly regio- and enantioselective copper-catalyzed method for the allylation of ketones using readily available 1,3-dienes (Figure 1d). Previously, we had reported a single, unoptimized example of this transformation.\textsuperscript{14} In addition, we report a computational study of the mechanism of this class of transformations, revealing a complex kinetic basis for diastereo- and enantioselectivity resulting from an equilibrating mixture of allylcopper intermediates of similar energy. Furthermore, we propose a stereochemical model for these allylation processes using non-C$_2$-symmetric JOSIPHOS-derived chiral ligands. Finally, we apply our method toward an efficient and concise synthesis of the pharmaceutical agent (R)-procyclidine and key intermediates in the synthesis of (R)-Oxyphencyclidine, (R)-Oxybutynin and (R)-Oxypenthionin bromide.

### RESULTS AND DISCUSSION

We began by studying the reaction between 4-methoxyacetophenone (1a) and 1,3-butadiene (1b) under conditions previously reported for Cu-catalyzed reductive coupling reactions (Table 1, entry 1).\textsuperscript{14} With (R)-DTBM-SEGPHOS (L1) as the ligand, homoallylic alcohol 1 was obtained with 44% yield, 1:2:1 dr and 83:5.16:5 er for the major diastereomer (65.5:34.5 er for the minor). Based on 'H NMR analysis of the crude reaction mixture, the remainder of the ketone underwent direct reduction by copper hydride. When the ligand was exchanged for (S,S)-Ph-BPE (L2), this reduction pathway was suppressed,\textsuperscript{14a} and a 96% yield of 1 was obtained with moderate dr and ee (Table 1, entry 2). Further ligand screening revealed that use of the commercially available JOSIPHOS\textsuperscript{16} derivative SL-J011-1 further improved the stereoselectivity to 4:1 dr and 97:3 er (96:4 er for the minor diastereomer, Table 1, entry 3).

Table 1. Evaluation of Reaction Conditions for the CuH-Catalyzed Allylation of 4-Methoxyacetophenone.\textsuperscript{16}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Yield$^a$ (%)</th>
<th>dr$^b$</th>
<th>er$^c$ (major)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L1</td>
<td>PhMe</td>
<td>25</td>
<td>44</td>
<td>1:2:1</td>
<td>83.5:16.5 (65.5:34.5)</td>
</tr>
<tr>
<td>2</td>
<td>L2</td>
<td>PhMe</td>
<td>25</td>
<td>96</td>
<td>3:1:1</td>
<td>86.5:13.5 (84:16)</td>
</tr>
<tr>
<td>3</td>
<td>L3</td>
<td>PhMe</td>
<td>25</td>
<td>90</td>
<td>4:1</td>
<td>97:3 (96:4)</td>
</tr>
<tr>
<td>4</td>
<td>L3</td>
<td>CyH</td>
<td>25</td>
<td>71</td>
<td>3:1</td>
<td>96.5:3.5 (94:6)</td>
</tr>
<tr>
<td>5</td>
<td>L3</td>
<td>THF</td>
<td>25</td>
<td>88</td>
<td>4:1</td>
<td>96.5:3.5 (94:6)</td>
</tr>
<tr>
<td>6</td>
<td>L3</td>
<td>MTBE</td>
<td>25</td>
<td>83</td>
<td>3:4:1</td>
<td>97:3 (94:55:5)</td>
</tr>
<tr>
<td>7</td>
<td>L3</td>
<td>Dioxane</td>
<td>25</td>
<td>55</td>
<td>3:9:1</td>
<td>96.5:3.5 (94:6)</td>
</tr>
<tr>
<td>8</td>
<td>L3</td>
<td>PhMe</td>
<td>40</td>
<td>75</td>
<td>3:6:1</td>
<td>95:5 (93:7)</td>
</tr>
</tbody>
</table>

$^a$Conditions: 0.2 mmol ketone (1 equiv), 1,3-butadiene (2 equiv), copper(II) acetate (0.05 equiv), ligand (0.06 equiv), dimethoxy(methyl)silane (4 equiv) in solvent (0.2 mL), ketone was added slowly by syringe pump; see the Supporting Information for details. $^b$Yield and diastereomeric ratio were determined by 1H NMR spectroscopy of the crude mixture, using dibromomethane as an internal standard. $^c$Enantiomeric ratio was determined by HPLC or SFC analysis on commercial chiral columns, and the relative configuration of 1 was determined by comparing its NMR data with reported data.\textsuperscript{17}

Evaluation of the reaction solvent (Table 1, entry 4-7) indicated that toluene was optimal for this transformation. The results were very sensitive to the reaction temperature: the yield, dr, and er were all diminished at slightly elevated temperatures (40 °C, Table 1, entry 8). However, excellent yield (94%), dr (4:1), and er (98:2 and 97:3 respectively for the major and minor diastereomers) were achieved when the reaction was performed at 0 °C (Table 1, entry 9). Further lowering of the reaction temperature (-20 °C) significantly decreased the dr again (Table 1, entry 10).

Next, the substrate scope of the asymmetric reductive coupling of diverse ketones with acyclic 1,3-dienes was examined (Table 2). A range of chiral homoallylic tertiary alcohols were prepared with excellent yields and enantiomeric purity (>94:6 er). The reaction was compatible with ether (1), alcohol (2), secondary (3) and tertiary amine (4) groups, as well as aromatic heterocycles (5, 6). Cyclic ketones such as 7a reacted with particularly good diastereoselectivity, as well as excellent yield and enantioselectivity. Using acetylferrocene, we obtained enantioenriched ferrocene 8. In addition to butadiene, isoprene was also found to react with good yield and excellent enantioselectivity (9).

We also surveyed the scope of ketone allylation using cyclic 1,3-dienes. However, under the conditions used for acyclic dienes, the yield of the desired product was unsatisfactory, and direct reduction of the ketone was instead the major reaction that was observed (see Supporting Information for details). We hypothesized that in the case of cyclic dienes, the L3-ligated CuH is unable to react with the diene at a rate competitive with direct ketone reduction. Revisiting our initial ligand evaluation data, we noticed that the use of (S,S)-Ph-BPE (L2) provided less ketone reduction byproduct than with L3 (Table 1, entries 2 and 3).\textsuperscript{14a} Accordingly, we hypothesized that substituting L2 for L3 might be useful in these cases where ketone reduction is a problem: indeed, the catalyst derived from L2 provided greatly improved yields with cyclic diene substrates.
Table 2. Evaluation of the Scope of the Ketone Allylation with Acyclic Dienes.\textsuperscript{a}

\begin{tabular}{cccc}
\hline
$R^1$ & $R^2$ & $R^3$ & Yield (dr) \tabularnewline
\hline
\textbullet{} & \textbullet{} & \textbullet{} & 94% (95:5) \text{ er} \tabularnewline
\textbullet{} & \textbullet{} & \textbullet{} & 94% (96:4) \text{ er} \tabularnewline
\textbullet{} & \textbullet{} & \textbullet{} & 92% (95:5) \text{ er} \tabularnewline
\textbullet{} & \textbullet{} & \textbullet{} & 94% (96:4) \text{ er} \tabularnewline
\textbullet{} & \textbullet{} & \textbullet{} & 95% (95:5) \text{ er} \tabularnewline
\textbullet{} & \textbullet{} & \textbullet{} & 91% (95:5) \text{ er} \tabularnewline
\textbullet{} & \textbullet{} & \textbullet{} & 94% (96:4) \text{ er} \tabularnewline
\textbullet{} & \textbullet{} & \textbullet{} & 92% (95:5) \text{ er} \tabularnewline
\textbullet{} & \textbullet{} & \textbullet{} & 91% (95:5) \text{ er} \tabularnewline
\textbullet{} & \textbullet{} & \textbullet{} & 94% (95:5) \text{ er} \tabularnewline
\end{tabular}

\textsuperscript{a}Yields indicate the isolated yield of product as a mixture of two diastereomers on a 1.0 mmol scale. Diastereomeric ratios were determined by \textsuperscript{1}H NMR spectroscopy for both the crude and purified products; enantiomeric ratios were determined by HPLC or SFC analysis on commercial chiral columns; enantiomeric ratios of minor diastereomers are indicated in parentheses after those of the major diastereomers. Yields, diastereomeric ratios, and enantiomeric ratios are the averages for two identical runs. See Supporting Information for full details.

Table 3. Scope Evaluation of Ketone Allylation with Cyclic Dienes.\textsuperscript{a}

\begin{tabular}{cccc}
\hline
$R^1$ & $R^2$ & $R^3$ & Yield (dr) \tabularnewline
\hline
\textbullet{} & \textbullet{} & \textbullet{} & 92% (95:5) \text{ er} \tabularnewline
\textbullet{} & \textbullet{} & \textbullet{} & 94% (96:4) \text{ er} \tabularnewline
\textbullet{} & \textbullet{} & \textbullet{} & 94% (96:4) \text{ er} \tabularnewline
\textbullet{} & \textbullet{} & \textbullet{} & 92% (95:5) \text{ er} \tabularnewline
\textbullet{} & \textbullet{} & \textbullet{} & 91% (95:5) \text{ er} \tabularnewline
\textbullet{} & \textbullet{} & \textbullet{} & 94% (96:4) \text{ er} \tabularnewline
\textbullet{} & \textbullet{} & \textbullet{} & 92% (95:5) \text{ er} \tabularnewline
\textbullet{} & \textbullet{} & \textbullet{} & 91% (95:5) \text{ er} \tabularnewline
\textbullet{} & \textbullet{} & \textbullet{} & 94% (95:5) \text{ er} \tabularnewline
\textbullet{} & \textbullet{} & \textbullet{} & 92% (95:5) \text{ er} \tabularnewline
\end{tabular}

\textsuperscript{a}Yields indicate the isolated yield of product as a mixture of two diastereomers on a 1.0 mmol scale. Diastereomeric ratios were determined by \textsuperscript{1}H NMR spectroscopy for both the crude and purified products; enantiomeric ratios were determined by HPLC or SFC analysis on commercial chiral columns; enantiomeric ratios of minor diastereomers are indicated in parentheses after those of the major diastereomers. Yields, diastereomeric ratios, and enantiomeric ratios are the averages for two identical runs. See Supporting Information for full details.

Using L2, several classes of ketones were coupled with cyclic 1,3-dienes in high regio- and enantioselectivity (Table 3). The reaction is most efficient for aryl methyl ketones. A broad range of aromatic carbonyl substituents, including an ortho-substituted arene (11), a pyridine (15), a pyrrole (16), a bromopyrazole (17), and a ferrocene (20) were evaluated, all providing good results. Several additional types of ketones were converted with high yield and stereoselectivity under the same conditions. For instance, a dialkyl ketone (13) and a vinyl methyl ketone (14) underwent allylation with high enantioselectivity. We proposed that the low diastereoselectivity observed in the case of 13 may be due to the minimal steric differentiation between the methyl and methylene groups attached to the carbonyl. Accordingly, we found that our method can be particularly useful on symmetric dialkyl ketones, which react to form homoallylic alcohol products with exceptionally high yield and enantioselectivity (18, 19). Finally, a larger ring diene, 1,3-cycloheptadiene, is also an effective reagent, providing 21 with moderate yield and excellent stereoselectivity.

\section*{MECHANISTIC STUDIES}

The proposed catalytic cycle of this CuH-catalyzed allylation reaction is summarized in Figure 2. We envisioned that a primary allylic copper intermediate (III) might be formed by hydrocupration of a diene. Selectivity-determining nucleophilic addition of III to the ketone would provide copper alkoxide V. Subsequently, σ-bond metathesis with a hydrosilane VI should rapidly regenerate the copper hydride catalyst I, with concomitant formation of the silylated homoallylic alcohol (VII) in a process that is well precedented.\textsuperscript{14a}
We performed density functional theory (DFT) calculations to investigate several aspects of this proposed reaction mechanism. First, a comparison of the candidate hydrocupration mechanisms was performed to understand the mechanism of generation of the key allylcopper intermediate. Next, the energies and interconversion barriers of several possible allylic complexes were evaluated. From here, a thorough consideration of possible insertion transition states for the addition of the allylcopper intermediate to ketones was undertaken to reveal the origin the observed diastereoselectivity. Finally, we sought to explain the π-facial selectivity with respect to the ketone. While the mechanism of chiral induction in enantioselective reactions utilizing C₂-symmetric ligands such as Ph-BPE has been frequently rationalized using quadrant-diagrams,¹⁸ analogous intuitive models for less symmetric ligands such as JOSIPHOS derivatives are rare.¹⁸d Therefore, we focused on developing an understanding of the high enantioselectivity observed with L₃-supported copper catalysts.

We started our computational investigation with a conformational search on the L₃-supported CuH catalyst. Two lowest-energy conformers with almost identical energies (22a and 22b, Figure 3) were located. These conformers differ in the arrangement of the six-membered chelate ring. In 22a, the chiral carbon center is puckered out-of-plane, while the two phosphorus atoms and the Cu are nearly co-planar with one of the Cp rings of the ferrocene. In contrast, in 22b, the Cu is puckered out-of-plane, while the two phosphorus atoms and the chiral carbon are nearly co-planar with the ferrocene Cp ring. As a result, the P-tBu and P-aryl substituents in 22a and 22b adopt different orientations, and thus create distinct steric environments around the Cu center. In 22a, the P-tBu group in quadrant IV and the P-aryl group in quadrant II are placed closer proximity to the Cu center, while the P-tBu and P-aryl groups in quadrants I and III are more distal from the Cu. Therefore, the steric environment of this conformer resembles those of C₂-symmetric ligands. In contrast, conformer 22b is pseudo-C₂-symmetric. The P-tBu and P-aryl groups in quadrants IV and III are placed closer to the Cu center, while quadrants I and II are relatively unoccupied by the ligand as the P-substituents in these quadrants are placed further away from the Cu. Considering the similar stability of 22a and 22b, both ligand conformations were considered when locating the transition states in the proposed catalytic cycle. Our calculations indicated the hydrocupration, 1,3-migration, and ketone addition transition states all are lower in energy when the ligand adopts the conformation in 22a, which has a pseudo-C₂-symmetric steric environment (see below). This is consistent with the high efficiency of CuH catalysts with C₂-symmetric ligands such as Ph-BPE in promoting similar transformations.

Figure 2. Proposed catalytic cycle.

Figure 3. Conformers of the CuH catalyst supported by the SL-J011-1 ligand (L₃). The P-Ar and P-tBu groups proximal to the Cu center are highlighted in red.

Figure 4. Optimized geometries of the 1,2- and 1,4-hydrocupration transition states. The diene is highlighted in yellow. The P-aryl and P-tBu groups “proximal” to the Cu center are highlighted in red in Figure 4a.

We selected 2-acetonaphthone and 1,3-butadiene as the model substrates for our computational investigation of the catalytic cycle. Experimentally, this pair of substrates react with 95% yield, 2.5:1 dr, and 93:7 er (for the major diastereomer,
90.5:9.5 er for the minor diastereomer) under the standard reaction conditions (see Supporting Information for details). We hypothesized that, initially, the hydrocupration of 1,3-butadiene might proceed via either direct 1,4-hydrocupration of the diene or via 1,2-hydrocupration followed by a 1,3-migration. Our calculations suggest that this process strongly prefers to occur through the 1,2-addition pathway (TS1a, Figure 4) to form a secondary allylcopper intermediate (23, Figure 5). In comparison, the 1,4-hydrocupration of the diene requires 9.6 kcal/mol higher activation energy (TS1c, Figure 4b). The 1,2-hydrocupration proceeds with moderate π-facial selectivity (ΔΔG° = 0.8 kcal/mol, Figure 4a) leading initially to an (S)-allylcopper intermediate. However, this stereocenter is rapidly ablated: the secondary allyl complex 23 undergoes facile 1,3-migration via either TS2-cis or TS2-trans to form primary allylcopper intermediates 24-cis and 24-trans, which are similar in energy to each other, and both more stable than 23 (Figure 5). This 1,3-migration step requires a very low barrier and is reversible. Therefore, the cis/trans isomers of the primary allylcopper intermediates exist in equilibrium with each other, and with the branched isomers, prior to the nucleophilic addition to the ketone.

The enantio- and diastereoselectivity are both determined in the subsequent ketone addition step. We found that the ketone addition occurs through a six-membered Zimmerman-Traxler-type transition state.19 After exhaustive computational investigation of possible transition state isomers, TS3a and TS3b were identified as the most favorable pathways for the ketone additions (see SI for other less favorable TS structures). In both TS3a and TS3b, the bulkier aryl group on the ketone is placed in a pseudo-equatorial orientation, and the methyl substituent is pseudo-axial. Counterintuitively, the preferred pathway for reaction with the ketone takes place from the cis-allylcopper species 24-cis via TS3a, which places the terminal methyl substituent of the allyl group pseudo-axial.19 In comparison, the ketone addition process from 24-trans, which involves a pseudo-equatorial methyl substituent, requires an additional 1.3 kcal/mol of activation energy (TS3b). An examination of TS3b reveals the origin of this destabilization: the methyl substituent on the C=C double bond is placed between the aryl and methyl groups of the ketone, and thus induces greater steric repulsions at the forming C–C bond. On the other hand, the 1,3-diaxial repulsions with the same methyl substituent in TS3a are relatively weak because only one H…Me interaction is expected to contribute. The most favorable ketone addition transition state TS3a leads to the alkoxy copper intermediate 26a, from which rapid σ-bond metathesis with a silane generates the observed major product in silyl-protected form (27a). This step is known to be very rapid for copper alkoxides, which renders the ketone addition step effectively irreversible.14a

Figure 5. Computed energy profiles of the CuH-catalyzed allylation of 2-acetonaphthone 25. The calculations were performed at the M06-2X/SDD–6–311+G(d,p)/SMD(toluene)//B3LYP/SDD–6–31G(d) level of theory. All energies are with respect to the separate L*CuH catalyst (22a) and reactants (1b and 25).

We next turned our attention to the enantioselectivity of this process, which is determined by the π-facial selectivity of the ketone addition step as dictated by the ligand. Relative to favored transition state structure TS3a, disfavored structure TS3c involves the addition to the opposite face of the ketone (Figure 6). In TS3c, the α-methylene group and the pseudo-axial methyl group of the ketone are both placed in the two quadrants occupied by the “proximal” P-aryl and P-t-Bu groups (highlighted in red in Figure 6). As such, TS3c is destabilized by the steric repulsions with the ligand. In contrast, in the more stable transition state TS3a, the α-methylene group and the pseudo-axial methyl group are both placed in the “unoccupied” quadrants, in which the P-substituents are further away (“distal”) from the Cu center and the substrate. Due to the diminished ligand-substrate steric repulsions, TS3a is 4.0 kcal/mol more stable than TS3c, which is in qualitative agreement with the high levels of enantioselectivity observed in the experiment.
APPLICATIONS

To demonstrate the synthetic utility of this asymmetric transformation, we sought to prepare chiral tertiary alcohol 30, a key intermediate in the synthesis of anticholinergic agents (R)-Oxybutynin, (R)-Oxyphenonium bromide, and (R)-Oxyphencyclidine. Currently, these drugs are typically administered in their racemic form, which is synthesized through the addition of a cyclohexyl Grignard reagent to a ketone. However, motivated by the decreased side effects and higher efficiency associated with the single enantiomer forms, several groups have developed synthetic routes to enantioenriched key chiral intermediate 30 using chiral auxiliaries, chiral pool synthesis, an organocatalytic aldol-elimination-hydrogenation-deprotection sequence, or palladium-catalyzed asymmetric allylic alkylation followed by functional group interconversions. Using our method, we devised an alternative, catalytic, enantioselective synthetic route to this key chiral intermediate (Scheme 1) that yields enantiopure product and does not require the purification of intermediates. From commercially available starting material 28, after CuH-catalyzed coupling with cyclohexadiene, reduction, hydrolysis, and recrystallization, 30 was obtained in 53% overall yield and with over 99.5:0.5 er in a one-pot sequence without the need for chromatography.

We also applied our method toward a new synthetic route to (R)-Procyclidine, a treatment for Parkinson’s disease. Biological testing suggests that (R)-Procyclidine has a higher affinity for the relevant muscarinic receptor both in humans and in animal models. Thus, an efficient asymmetric synthesis of (R)-Procyclidine would be valuable. We studied the copper-catalyzed allylation of commercially available ketone 31, which provided chiral tertiary alcohol 32. Again, without requiring chromatographic purification, the mixture containing 32 was subjected to simple hydrogenation and direct crystallization to yield (R)-Procyclidine (33) in 58% overall yield and over 99.5:0.5 er.

In summary, we have developed a highly efficient copper-catalyzed allylation of ketones with feedstock linear and cyclic conjugated dienes. A large variety of chiral tertiary alcohols were prepared in excellent yield, regio-, and enantioselectivity, and with a high level of functional group compatibility. Guided by DFT calculations, a rationale explaining the factors responsible for the enantio- and diastereoselectivity of this transformation was derived. From a mixture of rapidly equilibrating allylcopper intermediates of similar energy, selective reaction of the cis-allyl complex generates the observed diastereomer. Furthermore, a model for the enantioselectivity of the addition of the allylcopper intermediates to ketones was proposed for catalysts bearing the non-C₃-symmetric JOSIPHOS ligands. Our method also enabled a new, concise, and enantioselective
synthesis of pharmaceutically important drug (R)-Procyclidine and a key intermediate for anticholinergic drugs (R)-Oxyphenylcymline, (R)-Oxybutynin and (R)-Oxyphenonium bromide.

**ASSOCIATED CONTENT**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.1c04756.

Experimental procedures and characterization data for all compounds (PDF)
NMR spectra (PDF)
SFC and HPLC traces (PDF)
Computational details and Cartesian coordinates of optimized geometries (PDF)

**AUTHOR INFORMATION**

**Corresponding Author**
*sbuchwal@mui.edu, *pengliu@pitt.edu

**ORCID**
Chengxi Li: 0000-0003-3904-0299
Richard Y. Liu: 0000-0003-0951-6487
Luke T. Jesikiewicz: 0000-0002-8020-7006
Yang Yang: 0000-0002-4956-2034
Peng Liu: 0000-0002-8188-632X
Stephen L. Buchwald: 0000-0003-3875-4775

**Notes**
The authors declare no competing financial interest.

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**REFERENCES**


