Copper(I) Iodide-Catalyzed Asymmetric Synthesis of Optically Active Tertiary α-Allenols

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Abstract A facile CuI-catalyzed asymmetric synthesis of chiral tertiary α-allenols with up to 95% ee starting from common tertiary propargylic alcohols and aldehydes has been developed. The amount of chiral ligand used in this transformation can be as low as 2.5 mol%.

Key words copper catalysis, asymmetric synthesis, allenols, propargylic alcohols, aldehydes

Due to their unique structural properties, reactivities, and potential applications in medicine, allenes have attracted much attention from organic chemists, materials scientists, and pharmacists over the last few decades.1,2 A particular challenge in allene chemistry is to construct axially chiral allenes efficiently.3 Several strategies have been applied to achieve this goal.4,5

In 2012, our group reported a two-step approach for the synthesis of optically active allenes from propargylic alcohols and aldehydes in which a catalytic amount of CuBr and a chiral 4-[(2-diphenylphosphanyl)naphthyl]-N-[1-phenylethyl]phthalazin-1-amine (N-PINAP) ligand6 are responsible for the highly enantioselective formation of a propargylic amine. After filtration to remove Cu(I), we used ZnI₂ (0.45 equiv) and NaI (0.5 equiv) to convert the optically active propargylic amine into an allene through a stereodefined anti-1,5-hydride shift (Scheme 1).5a Later, we observed that CdI₂ works in harmony with CuBr to realize this transformation without filtration (Scheme 1).5a However, both methods required a rather high loading of metal salts to promote the formation of allenes from the optically active propargylic amines generated in situ. Moreover, the stepwise addition of chemicals is not operationally friendly. Therefore, approaches to the enantioselective allylation of terminal alkynes (EATA) that use a chiral catalyst operating in both steps are highly desired. Here, we report the realization of such a concept (Scheme 1).

On the basis of our previous observation that the dialkylamine played a vital role in the CuI-catalyzed synthesis of allenes from terminal alkynes and aldehydes,7 we reasoned that long-chain dialkylamines or structurally similar cyclic amines might be viable reactants for an enantioselective reaction of this type. After preliminary screening of a series of dialkylamines and cyclic amines, we were glad to find that the commercially available cyclic amine azocane was the most effective reactant in this EATA reaction (Table 1).8 When the reaction was carried out with propargylic alcohol (1a), 1.6 equivalents of cyclohexanal (2a), and 1.4 equiv of azocane with 10 mol% of CuI and 10 mol% of (R,S)-N-PINAP as the catalyst system at room temperature for 0.5 hours and then at 130 °C for five hours, the desired allenol (S)-3aa was formed in 76% yield and 86% ee (entry 7). Although a series of dialkylamines reacted smoothly to produce the corresponding propargylic amines, the second step to form the allene was not efficient (entries 1–3). In comparison, for cyclic amines, the second step became much easier on increasing the ring size from five to eight (entries 4–7). However, the yield of (S)-3aa decreased to 37% for azonane (entry 8), which was attributed to the fact that azonane is more similar to an open-chain dialkylamine.
Encouraged by these preliminary results, we started to optimize the reaction conditions for the highly stereoselective formation of allene \((\text{S})-3\text{aa}\). Surprisingly, we observed that the metal/ligand ratio had an obvious effect on the enantioselectivity. When the metal/ligand ratio was adjusted from 10:10 to 10:2.5, the ee value of \((\text{S})-3\text{aa}\) increased from 86% to 90% (Table 2, entries 1–4); however, a further reduction in the ratio of ligand led to a lower ee (entry 5). Increasing the ratio of CuI made no difference to the yield or the ee (entry 6). Furthermore, when the reaction temperature for the second step was lowered to 120 °C, the ee value slightly increased, but the yield of \((\text{S})-3\text{aa}\) dropped to 59% (entry 7). When the reaction time for the second step was extended from 8 to 12 hours, the yield of \((\text{R})-4\text{aa}\) dropped from 6% to 4%, and the yield of \((\text{S})-3\text{aa}\) increased from 76% to 79%; however, the ee for \((\text{S})-3\text{aa}\) dropped from 90% to 87% (entry 8). After solvent screening, it was observed that 1,4-dioxane still provided the best yield and ee (entries 9–13). Thus, the optimized reaction conditions were as follows: a mixture of CuI (10 mol%), \((\text{R,S})-\text{N-PINAP}\) (10 mol%), \(\text{CuBr}\) (2.5 mol%), \(\text{CdI}_2\) (0.6 equiv), \(\text{ZnI}_2\) (0.45 equiv), \(\text{NaI}\) (0.5 equiv) were stirred at room temperature in toluene for 1 h, then 130 °C, 8 h.

Table 1: Amines Screened and Preliminary Resultsa

<table>
<thead>
<tr>
<th>Entry</th>
<th>R, R</th>
<th>Timeb (h)</th>
<th>Yieldc (%) of ((\text{S})-3\text{aa})</th>
<th>Yieldc (%) of ((\text{S})-4\text{aa})</th>
<th>Dee (%) of ((\text{S})-3\text{aa})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>i-Bu, i-Bu</td>
<td>24</td>
<td>6</td>
<td>78</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>Bu, Bu</td>
<td>22</td>
<td>14</td>
<td>82</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>((\pm)-\text{CH}_2\text{CH(Et)}\text{Bu}, \text{CH}_2\text{CH(Et)}\text{Bu})</td>
<td>18</td>
<td>4</td>
<td>76</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>((\pm)-\text{CH}_3\text{Bu})</td>
<td>1</td>
<td>0</td>
<td>54</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>((\pm)-\text{CH}_3\text{Bu})</td>
<td>2</td>
<td>10</td>
<td>84</td>
<td>76</td>
</tr>
<tr>
<td>6</td>
<td>((\pm)-\text{CH}_3\text{Bu})</td>
<td>1</td>
<td>35</td>
<td>52</td>
<td>76</td>
</tr>
<tr>
<td>7</td>
<td>((\pm)-\text{CH}_3\text{Bu})</td>
<td>0.5</td>
<td>76</td>
<td>12</td>
<td>86</td>
</tr>
<tr>
<td>8</td>
<td>((\pm)-\text{CH}_3\text{Bu})</td>
<td>1</td>
<td>37</td>
<td>65</td>
<td>88</td>
</tr>
</tbody>
</table>

* The reaction was carried out on a 0.2 mmol scale in 1,4-dioxane (1.6 mL).
* Reaction time for the first step.
* Determined by 1H NMR analysis with CH$_2$Br$_2$ as the internal standard.
* Determined by chiral HPLC analysis of the isolated product.
* Not determined.
until the first step was complete (as monitored by TLC), and then the reaction tube was directly placed in an oil bath at 130 °C for the second step (entry 4).

The reaction was easily conducted on a 1 mmol scale (Table 3, entry 1). When (R,Sa)-N-PINAP was employed (Condition B), the enantiomer (R)-3aa was produced in a slightly higher ee (Table 3, entry 2). With the optimized conditions in hand, we started to investigate the scope of the reaction.10 In general, both cyclic and acyclic tertiary propargylic alcohols 1a–d reacted with secondary alkyl aldehydes 2a–d to give the corresponding allenols (S)-3aa to (R)-4aa in 40–73% yields and in 81–95% ee (entries 1–8). The enantioselectivity was sensitive to the R 3 group of the aldehyde: increasing the steric bulk of the R 3 group was beneficial to the enantiocontrol of the reaction (entries 7 and 8). The linear alkyl aldehyde 2e also gave the corresponding allene (S)-3ce in 53% yield, albeit with only 63% ee (entry 9). The first step of the reaction of aromatic aldehyde 2f proved sluggish, and allene (S)-3af was obtained in 66% yield and with 65% ee (entry 10).

For the primary propargylic alcohol 1e and the secondary propargylic alcohol 1f, chiral α-allenols (S)-3ea and (S, S)-3fa were obtained in 52 and 69% yield, respectively; however, the ee values decreased to 60% and 41%, respectively (Scheme 2).

The absolute configurations of the allenols were assigned by comparison with authentic samples prepared by following the protocol described in a previous report5 and by applying the Lowe–Brewster rule.11 A plausible model is proposed to predict the absolute configuration of the allenes (Scheme 3). First, the chiral alkynyl copper species (R,Sa)-5, generated in situ, reacts with the iminonium intermediate 6, also generated in situ from the aldehyde and azocane, to form the corresponding propargylic amine (R)-4 enantioselectively.6 Subsequently Cu(I) coordinates to the C≡C triple bond with the assistance of the proximal hydroxy group to form complex 7, which undergoes highly stereoselective anti-1,5-hydride transfer and anti-β-elimination to afford the corresponding allene (S)-3.

In summary, we have developed a catalytic EATA reaction to synthesize optically active tertiary α-allenols from common tertiary propargylic alcohols and aldehydes by using only 10 mol% of Cul and 2.5 mol% of N-PINAP ligand. The medium-sized cyclic amine azocane plays an important role in the reaction, providing a suitable environment for the reaction.
role in determining both the yield and enantioselectivity of this transformation. Another crucial factor affecting the stereoselectivity of the reaction is the metal/ligand ratio; however, it should be noted that the results for secondary terminal propargylic alcohols or normal terminal alkynes and aromatic/linear aliphatic aldehydes are still disappointing. Further studies, including the design of new ligands for such transformations, are being conducted in our laboratory.

**Funding Information**

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**Acknowledgment**

We thank Mr. Yuchen Zhang in this group for reproducing the syntheses of (R)-3ca, (S)-3cc, and (R)-3dc presented in Table 3.

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**Table 3 The Scope of the CuI/N-PINAP-catalyzed EATA Reaction**

<table>
<thead>
<tr>
<th>entry</th>
<th>R1, R2 (1)</th>
<th>R3 (2)</th>
<th>Condition</th>
<th>Yield (%) of 3</th>
<th>ee (%) of 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>−(CH3)− (1a)</td>
<td>Cy (2a)</td>
<td>A</td>
<td>72 [(S)-3aa]</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>−(CH3)− (1a)</td>
<td>Cy (2a)</td>
<td>B</td>
<td>73 [(R)-3aa]</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>−(CH3)− (1a)</td>
<td>i-Pr (2b)</td>
<td>A</td>
<td>54 [(S)-3ab]</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>−(CH3)− (1a)</td>
<td>i-Pr (2b)</td>
<td>B</td>
<td>45 [(R)-3bb]</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>Me, Me (1c)</td>
<td>Cy (2a)</td>
<td>B</td>
<td>65 [(R)-3ca]</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
<td>Me, Me (1c)</td>
<td>CHET2 (2c)</td>
<td>A</td>
<td>50 [(S)-3cc]</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>Et, Et (1d)</td>
<td>cyclopentyl (2d)</td>
<td>B</td>
<td>54 [(R)-3dd]</td>
<td>81</td>
</tr>
<tr>
<td>8</td>
<td>Et, Et (1d)</td>
<td>CHET2 (2c)</td>
<td>B</td>
<td>40 [(R)-3dc]</td>
<td>93</td>
</tr>
<tr>
<td>9</td>
<td>Me, Me (1c)</td>
<td>(CH3)3Me (2e)</td>
<td>A</td>
<td>53 [(S)-3ce]</td>
<td>63</td>
</tr>
<tr>
<td>10</td>
<td>−(CH3)− (1a)</td>
<td>Ph (2f)</td>
<td>A</td>
<td>66 [(S)-3af]</td>
<td>65</td>
</tr>
</tbody>
</table>

*Condition A: 1 (1 mmol), 2 (1.6 equiv), azocane (1.4 equiv), CuI (10 mol%), (R,Sa)-N-PINAP (2.5 mol%), 1,4-dioxane (8 mL), r.t., 1 h, then 130 °C, 8 h; Condition B: As Condition A, but with ligand (R,Ra)-N-PINAP (2.5 mol%). The reaction was carried out on a 1 mmol scale in 1,4-dioxane (8 mL).*

* Determined by chiral HPLC analysis.

* The reaction time for the first step was 24 h.

* The reaction time for the first step was 48 h.

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**Scheme 2 EATA Reaction with alkyne 1d and 1e**
Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611641.

References and Notes


(8) Due to the difficulty of isolating (R)-4, the structures of (R)-4 were assigned by comparison with the structure of (R)-4aa. The NMR yields of (R)-4 were determined by 1H NMR analysis of the crude reaction mixture. The characteristic peak of (R)-4 appeared at about δ = 3.20–2.90 ppm.


(10) 1-(15S)-4-Methylpent-1-2,4-dien-1-yl)cyclohexanol ([S]-3ab);

Typical Procedure
A flame-dried Schlenk tube with a poly(tetrafluoroethylene) plug was charged with Cul (19.1 mg, 0.1 mmol), (R,S)-N-PINAP (14.1 mg, 0.025 mmol), and 1,4-dioxane (5 mL) under argon, and the mixture was stirred at rt for 30 min. Propargylic alcohol 1a (123.7 mg, 1 mmol)/1,4-dioxane (1 mL), aldehyde 2b (115.8 mg, 1.6 mmol)/1,4-dioxane (1 mL), and azocane (161.9 mg, 1.4 mmol)/1,4-dioxane (1 mL) were then added sequentially under argon. The mixture was then stirred at rt until the reaction was complete (TLC, ~1 h). The Schlenk tube was then placed in a preheated oil bath at 130 °C with stirring. After 8 h, the crude mixture was diluted with Et2O (10 mL) and washed with 3 M aq HCl (10 mL). The organic layer was separated, and the aqueous layer was extracted with Et2O (2 x 10 mL). The combined organic layer was washed with brine, dried (Na2SO4), filtered, and concentrated to give a residue that was purified by chromatography [silica gel, PE–EtOAc (20:1)] to give a liquid; yield: 97.0 mg (54%, 92% ee); [α]D20 = +80.8 (c 1.005, CHCl3); HPLC [Chiralcel AS-H column, hexane–EtOAc (20:1)]: δ = 214 nm; tR(major) = 11.8 min; tR(minor) = 10.9 min. IR (neat): 3343, 2958, 2927, 2859, 1961, 1494, 1463, 1446, 1410, 1380, 1360, 1345, 1318, 1297, 1246, 1192, 1176, 1163, 1146, 1112, 1088, 1058, 1038 cm⁻¹. 1H NMR (400 MHz, CDCl3): δ = 5.38-5.30 (m, 2 H, CH=C=CH), 2.41-2.27 (m, 1 H, CH), 1.79-1.41 (m, 10 H, protons from 5 × CH2 + OH), 1.40-1.25 (m, 1 H, proton from CH3). 13C NMR (100 MHz, CDCl3): δ = 199.6, 102.3, 101.6, 70.5, 66.6, 60.5, 55.4, 54.2, 48.2, 41.1, 38.3, 33.4, 31.9, 30.0, 27.6, 25.2, 22.5, 22.4, 20.5. MS (EI): m/z (%) = 180 (M⁺, 15.1), 99 (100). HRMS: m/z [M⁺] calcd for C12H20O: 180.1514; found: 180.1512.