Development of Biisoquinoline-Based Chiral Diaminocarbene Ligands: Enantioselective S_N_2 Allylic Alkylation Catalyzed by Copper—Carbene Complexes

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Chiral biisoquinoline-based diaminocarbene ligands (BIQ) were designed to create a chiral environment extended toward the metal center, which was confirmed by an X-ray structure. The concise ligand synthesis is highlighted by a modified Bischler–Napieralski cyclization of bisamides prepared from readily available chiral phenethylamines, and allows easy variation of the stereodifferentiating groups. The cyclohexyl-BIQ–copper complex is an efficient catalyst for enantioselective S_N_2 allylic alkylation with Grignard reagents showing S_N_2 regioselectivity higher than 5:1 and enantioselectivity in the range of 68–77% ee.

Since the discovery and isolation of several types of stable singlet carbones, tremendous research efforts have been made to develop N-heterocyclic carbene (NHC) ancillary ligands. NHCs are powerful σ-donating and weak π-accepting ligands, and their metal complexes generally show better air and thermal stability than phosphine complexes. Nevertheless, the development of chiral carbene ligands is still in its early stages. Structural diversity in the chiral carbene ligands has not been fully explored. The chiral Ru complex (I) developed by Grubbs and co-workers represents one of the best “monodentate” designs, accounting for over 90% ee in asymmetric ring closing metathesis reactions (Figure 1). However, a substrate dependence on enantioselectivity in these reactions might suggest that the chiral space created by the ligand is remote from the metal center, and therefore less discriminating for less sterically demanding substrates. In addition, the X-ray crystal structure shows that the aryl groups on the nitrogens are pointing orthogonal to the plane of NHC–Ru. Therefore, it would be interesting to extend and reposition the stereodifferentiating groups more toward the metal center. We envisioned that this possibility could be explored through the tricyclic biisoquinoline-based chiral carbene 2 featuring stereogenic centers at the positions α to the nitrogen atoms (Figure 1). Related tricyclic carbene structures have been reported. During the course of our study, Herrmann reported a phenyl-substituted biisoquinoline-based carbene ligand and its Rh and Ir complexes. Herein we report a concise synthesis of chiral biisoquinoline-based carbene ligands (BIQ) and our results on enantioselective allylic alkylation catalyzed by Cu–carbene complexes.

Figure 1. Design of tricyclic carbene ligands featuring an extended chiral pocket around the metal center.


(5) Herrmann reported that during the preparation of the saturated NHC–Rh or –Ir complexes via transmetalation, the unsaturated NHC–metal complexes were unexpectedly formed in moderate yields when bromide was counterion in the imidazolium salt.


SCHEME 1. Synthesis of Chiral Imidazoliums

\[
\begin{align*}
\text{NH}_{2} & \quad \text{oxalyl chloride} \\
R & \quad \text{EtN, THF} \\
0^\circ C & \quad \text{to rt, 12 h} \\
3a-(S) & \quad (R = i-Bu) \\
3b-(R) & \quad (R = i-Pr) \\
3c-(S) & \quad (R = Cy) \\
\text{PCl}_{5} & \quad \text{Zn(OTf)}_{2} \\
\text{toluene} & \quad 65^\circ C, 12 h \\
5a-(S,S) & \quad (85\%) \\
5b-(R,R) & \quad (83\%)^a \\
5c-(S,S) & \quad (81\%)^a
\end{align*}
\]

\( ^a \) Opposite enantiomer shown for compounds 3c, 4c, 5c, and 6c.

SCHEME 2. Synthesis of Metal–Carbene Complexes

\[
\begin{align*}
\text{N} & \quad \text{Cl} \\
1) & \quad \text{Ag}_{2}O, \text{CH}_{2}Cl_{2} \\
& \quad \text{rt, 12 h} \\
2) & \quad [\text{Pd(cinnamyl)}Cl]_2 \\
& \quad \text{CH}_{2}Cl_{2}, \text{rt 3 h} \\
6a-(S,S) & \quad \text{53\% (two steps)} \\
1) & \quad \text{Ag}_{2}O, \text{CH}_{2}Cl_{2} \\
& \quad \text{rt, 12 h} \\
2) & \quad \text{CuCl}, \text{CH}_{2}Cl_{2} \\
& \quad \text{rt 1 h} \\
6a-(S,S) & \quad \text{R = i-Bu} \\
6b-(R,R) & \quad \text{R = i-Pr} \\
6c-(S,S) & \quad \text{R = Cy} \\
8a & \quad [[\text{S}-\text{i-Bu-BIQ}]\text{CuCl}] (91\%) \\
8b & \quad [[\text{R}-\text{i-Pr-BIQ}]\text{CuCl}] (55\%) \\
8c & \quad [[\text{S}-\text{Cy-BIQ}]\text{CuCl}] (71\%)^a
\end{align*}
\]

\( ^a \) Opposite enantiomer shown for compounds 6c and 8c.

potentially interesting \( C_2 \)-symmetric chiral bisimine ligands. Standard reaction of the bisimines (5) with chloromethyl ethyl ether smoothly produced the \( C_2 \)-symmetric imidazolium salts (6) in excellent yield.\(^8\)

Palladium(II) and copper(I) complexes were successfully synthesized from the chiral imidazoliums (6) via a transmeta-
lution route\(^6\) (Scheme 2) and single crystals of carbene–Pd(II) complex (7a-Pd) suitable for X-ray diffraction were easily obtained.\(^10\) The X-ray structure of 7a-Pd confirmed our design hypothesis showing that the stereodifferentiating groups (i-Bu) are projected toward the Pd metal center in this \( C_2 \)-symmetric ligand structure (Figure 2).

The carbene–copper(I) complexes (8a–c) were tested in asymmetric allylic alkylation (AAA) reactions\(^11\) (Table 1). Cu-


other reported copper catalysts. The initial optimization of the reaction conditions was mostly performed with 3 mol % [(S)-i-Bu-BIQ]CuCl catalyst (8a) on naphthyl substrates (9). Interestingly, the BIQ-CuCl catalysts show better regioselectivity and enantioselectivity with ester leaving groups such as acetate (OAc) or pivaloate (OPiv) (entries 6, 14, and 15 vs entries 1–5). This is in contrast to the phosphoramidite ligands which typically use allylic halide substrates for Grignard reagent alkylations. Diethyl ether was selected as the optimum solvent after a brief survey where changing the solvent to THF or CH2Cl2 significantly lowered regioselectivity and enantioselectivity (entries 1, 11, and 13). The enantioselectivity was rather insensitive to temperature; however, lower yields were obtained at -78 °C (entries 9 and 10). When the ligand structure is varied, the cyclohexyl complex (8c) gives the best regioselectivity (88:12) and enantioselectivity (72% ee). The reaction scope was studied under the optimized conditions (Table 2). Other alkyl Grignard reagents can be used without significantly decreasing reaction yield, regioselectivity, or enantioselectivity (entries 1–3). However, use of phenyl Grignard reagent affords the SN2 product exclusively, implying a possible change in mechanism. The reaction was also effective for the formation of a quaternary chiral center (entry 5). The aryl substrates also tolerate electron-donating (entry 6) and electron-withdrawing substituents (entry 7), as well as ortho-substituents (entry 8).

In summary, we have synthesized chiral biisoquinoline-based tricyclic chiral diaminocarbene ligands (BIQ) and their Pd and Cu complexes. The chiral environment is created in close proximity to the metal center, which is confirmed by an X-ray crystal structure. The concise ligand synthesis allows easy variation of stereodifferentiating groups from readily accessible starting materials. The cyclohexyl-BIQ—copper complex is an efficient catalyst for enantioselective SN2′ allylic alkylation with Grignard reagents and the BIQ carbene ligands can be applied to other asymmetric catalyses. Application of BIQ carbene and imine ligands in other asymmetric transformations is currently in progress in our laboratory.

### Experimental Section


**TABLE 1. Optimization of Reaction Conditions**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Leaving Group [X]</th>
<th>Solvent</th>
<th>Catalyst</th>
<th>Yield (%)</th>
<th>γ : α</th>
<th>% ee (config)</th>
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<tr>
<td>1</td>
<td>Cl</td>
<td>CH2Cl2</td>
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<td>78</td>
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<td>2</td>
<td>Cl</td>
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<td>8b</td>
<td>98</td>
<td>64:36</td>
<td>35, (S)</td>
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<tr>
<td>3</td>
<td>O</td>
<td>Et2O</td>
<td>8a</td>
<td>98</td>
<td>51:49</td>
<td>45, (S)</td>
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<tr>
<td>4</td>
<td>O</td>
<td>OCOMe</td>
<td>8a</td>
<td>98</td>
<td>44:56</td>
<td>55, (S)</td>
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<tr>
<td>5</td>
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<td>Et2O</td>
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<td>80</td>
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<tr>
<td>6</td>
<td>OAc</td>
<td>Et2O</td>
<td>8a</td>
<td>98</td>
<td>77:23</td>
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<tr>
<td>7</td>
<td>OAc</td>
<td>Et2O</td>
<td>8b</td>
<td>98</td>
<td>78:22</td>
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<td>8</td>
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<td>98</td>
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<td>98</td>
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<td>11</td>
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<td>OPiv</td>
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<td>16</td>
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<td>Et2O</td>
<td>8a</td>
<td>99</td>
<td>88:12</td>
<td>72, (R)</td>
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* Isolated yield. † Determined by 1H NMR. ‡ Determined by chiral HPLC. Absolute configuration is determined by the optical rotation value (see the Supporting Information for details).

**TABLE 2. Reaction Scope**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R3MgBr</th>
<th>Yield (%)</th>
<th>γ : α</th>
<th>% ee</th>
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<td></td>
<td>Et</td>
<td>99</td>
<td>88:12</td>
<td>72</td>
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<tr>
<td>2</td>
<td></td>
<td>n-Hex</td>
<td>91</td>
<td>85:15</td>
<td>77</td>
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<td>3</td>
<td></td>
<td>cyclopentyl</td>
<td>91</td>
<td>84:16</td>
<td>68</td>
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<tr>
<td>4</td>
<td></td>
<td>Ph</td>
<td>95</td>
<td>&lt;2:98</td>
<td>N/A</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>Et</td>
<td>91</td>
<td>85:15</td>
<td>76</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>Et</td>
<td>91</td>
<td>85:15</td>
<td>76</td>
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<tr>
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<td></td>
<td>n-Hex</td>
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<td>77:23</td>
<td>75</td>
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<td></td>
<td>n-Hex</td>
<td>77</td>
<td>75:25</td>
<td>70</td>
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</table>

* Isolated yield. † Determined by 1H NMR. ‡ Determined by chiral HPLC (see the Supporting Information for details).
under argon was added oxalyl chloride (0.096 mL, 1.1 mmol) dropwise at 0 °C. The reaction mixture was allowed to warm to room temperature and was then stirred for 12 h. The reaction mixture was cooled to 0 °C before quenching with water (10 mL). The mixture was extracted with CHCl₃ (3 × 15 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 3:1 chloroform/hexane) to afford 4c (0.349 g, 0.778 mmol, 71% yield). ¹H NMR (300 MHz, CDCl₃) δ 7.27–7.09 (m, 12H), 3.95 (m, 2H), 2.88 (dd, J = 5.6, 14 Hz, 2H), 2.66 (dd, J = 8.3, 14 Hz, 2H), 1.78–1.58 (m, 10H), 1.44 (m, 2H), 1.24–1.02 (m, 10H); ¹³C NMR (75 MHz, CDCl₃) δ 159.5, 138.2, 129.3, 128.6, 126.6, 56.1, 41.0, 38.2, 30.3, 28.3, 26.5, 26.3, 26.2. HRMS-ESI (m/z) [M + H]⁺ calculated for C₃₉H₃₇ClN₂: 437.2951, found 437.2952.

(3S,5S)-3,3′-Dicyclohexyl-1,3',4,4′-tetrahydro-1,1'-bis(oquino-line), 5c-(S,S). To a solution of 4c (619 mg, 1.38 mmol) in toluene (60 mL) under nitrogen was added Zn(OtBu)₂ (1.51 g, 4.14 mmol) and PCl₃ (1.72 g, 8.28 mmol). The reaction mixture was stirred at 85 °C for 12 h and then cooled to room temperature before quenching with a 30% aqueous NH₄Cl solution (20 mL). The mixture was extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification of the crude product by flash column chromatography (silica gel, 7:1 hexanes/EtOAc) afforded 5c (357 mg, 0.841 mmol, 61% yield). ¹H NMR (300 MHz, CDCl₃) δ 7.26–7.05 (m, 8H), 3.40 (m, 2H), 2.69 (m, 4H), 1.93–1.54 (m, 12H), 1.29–1.09 (m, 10H); ¹³C NMR (75 MHz, CDCl₃) δ 163.9, 138.2, 130.9, 128.5, 127.8, 62.0, 42.9, 30.4, 29.2, 27.9, 26.8, 26.7, 26.6. HRMS-ESI (m/z) [M + H]⁺ calculated for C₃₁H₄₀N₂O₂: 461.3163, found 461.3164.

[6S,8S)-Dicyclohexyl-1,6,8,9-tetrahydro-6a,7a-diaza-dibenzo[c,e][fluorenum] Chloride, 6c-(S,S). To a solution of 5c (0.0822 g, 0.194 mmol) in THF (8 mL) was added chloromethyl ethyl ether (0.110 mL, 1.18 mmol). The reaction mixture was stirred for 12 h. Volatiles were removed at reduced pressure and the resulting sticky residue was purified by flash column chromatography (silica gel, 10:1 CH₃Cl/MeOH) to afford 6c (0.0750 g, 0.159 mmol, 82% yield). ¹H NMR (300 MHz, CDCl₃) δ 11.31 (s, 1H), 7.92 (d, J = 7.2 Hz, 2H), 7.39–7.32 (m, 6H), 7.17 (m, 2H), 3.34 (dd, J = 5.5, 16.1 Hz, 2H), 3.20 (d, J = 15.9 Hz, 2H), 1.73–0.82 (m, 20H); ¹³C NMR (75 MHz, CDCl₃) δ 137.2, 132.8, 130.7, 129.9, 127.9, 124.5, 124.1, 124.0, 60.1, 38.3, 31.6, 29.5, 29.4, 25.9, 25.7, 25.6. HRMS-ESI (m/z) [M – Cl]⁺ calculated for C₃₂H₃₇ClN₂: 473.2957, found 473.2957.

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Supporting Information Available: Detailed synthetic procedures and analytical data for new compounds (pdf) and X-ray crystallographic data for 7a-Pd (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.