**Communication**

**Synthesis of C₂-Symmetric Benzimidazolium Salts and Their Application in Palladium-Catalyzed Enantioselective Intramolecular α-Arylation of Amides**

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**Abstract:** A series of C₂-symmetric chiral benzimidazolium salts, the precursor of N-heterocyclic carbene ligands, were designed and synthesized from 1,2-dibromobenzene. In situ prepared corresponding carbenes were tested in the asymmetric palladium-catalyzed intramolecular α-arylation of amides, affording chiral diarylmethanols with high yields and moderate enantioselectivities.

**Keywords:** N-heterocyclic carbene; benzimidazolium; Pd-catalyzed; asymmetric intramolecular α-arylation

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1. **Introduction**

Oxindoles (=1,3-dihydro-2H-indol-2-ones) bearing a quaternary stereogenic center at the C (3) position represent a prominent structural motif in many natural products and biologically active compounds [1–6], and the development of synthetic methods for these compounds is of great importance in organic chemistry. Consequently, asymmetric transition metal-catalyzed reactions that provide access to enantiomerically enriched 3-alkyl-3-aryl oxindoles were established over the past decade: Overman’s elegant intramolecular Heck reactions [7–9], Trost’s Pd- or Mo-mediated allylic alkylations [10–12], and the Pd-catalyzed intramolecular α-arylation of amides, which are the focus of the present study.

Pioneered by Hartwig and co-workers, the intramolecular α-arylation of amides provides efficient and direct access to chiral 3,3-disubstituted oxindoles. Bulky chiral N-heterocyclic carbene (NHC) ligands worked best for the asymmetric transformation (up to 70% ee) [13]. This study was followed by those of the groups of Glorius and Aoyama, but only moderate ee values were obtained [14–16]. A significant improvement in this Pd-catalyzed asymmetric reaction was achieved by Kündig and co-workers [17–21]. Since then, this chemistry has been expanded further and several other chiral carbene ligands have been reported to give the desired product in excellent enantioselectivities (Scheme 1). Dorta and co-workers reported new NHC ligands with chiral N-heterocycle and naphthyl side chains and their successful application in a Pd-catalyzed asymmetric reaction. A series of 3-alkyl-3-aryl [22], 3-aryl-3-aryl [23], and 3-flouro-3-aryl [24] oxindoles were synthesized. Additionally, conformationally restricted chiral ligands developed by Glorius [25] and Murakami [26] also showed
high asymmetric induction in this reaction. Despite the successes in this field, new efficient chiral NHC ligands for this reaction are still needed. In this paper, we would like to report our investigation on the enantioselective intramolecular α-arylation of amide with the new chiral carbene ligands incorporating the benzimidazole skeleton (Scheme 1).

**Scheme 1.** Representative ligands in Pd-catalyzed asymmetric intramolecular arylation of amides.

2. Results

The synthesis of the benzimidazolium salt 3a as an N-heterocyclic carbene precursor is representatively shown in Scheme 2. Buchwald-Hartwig coupling of 1,2-dibromobenzene with (S)-α-methylbenzylamine gave the disubstituted product 1a in 80% yield. Next, treatment of diamine 3a–d with NaI to give 3a. Other benzimidazolium salts 3b–d were prepared in the same manner. All of the benzimidazolium salts 3a–d were purified and fully characterized by NMR and mass spectrometry. Furthermore, this method works equally well for milligram and multigram quantities.

**Scheme 2.** Representative synthesis of benzimidazolium salt.

With the new chiral benzimidazolium salts in hand, we turned our attention to their application in the Pd-catalyzed asymmetric intramolecular arylation of amides. Ligand precursors 3a–d were tested in the intramolecular α-arylation of 4a following Hartwig's *in situ* method (Table 1) [13]. Among...
the benzimidazolium salts screened, 3c possessing a cyclohexyl group as the R substituent gave better asymmetric induction (40% ee, entry 3). With 3c as an N-heterocyclic carbene ligand precursor, the use of other solvents such as 1,4-dioxane, toluene and THF gave less satisfactory results (entries 5–7). Other bases such as KOtBu, LiOtBu, KOH, and LiOH gave no better results than NaOtBu (entries 8–11). Different palladium sources were also investigated with 3c, and [Pd(allyl)Cl]2 emerged as the best choice of catalyst precursor (entry 14). Upon lowering the reaction temperature to rt, almost no reaction occurred; however, a 41% conversion and 48% ee were observed at 50 °C (Table 1, entries 16, 17).

Table 1. Chiral carbene ligands in the Pd-catalyzed intramolecular cyclization of amide 4a to oxindole 5a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>[Pd]</th>
<th>T (°C)</th>
<th>Solvent</th>
<th>Base</th>
<th>Yield (%) b</th>
<th>ee (%) c</th>
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<td>DME</td>
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<td>14</td>
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<tr>
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<td>DME</td>
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<tr>
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<td>rt</td>
<td>DME</td>
<td>NaOtBu</td>
<td>trace</td>
<td>–</td>
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</table>

* Reaction condition: [Pd] (5 mol %), ligand (5 mol %), base (1.5 equiv), 12 h; b Isolated yields; c Determined by chiral HPLC (CHIRALCEL OD Column) analysis.

In the next step, different 2-bromoanilides were applied in the reaction with salt 3c as a catalyst precursor. As shown in Figure 1, various substrates worked well with 3c to give oxindoles in moderate to good yields (28%–99%), and the best ee value was up to 50%.

Figure 1. The asymmetric reaction products.
3. Experimental Section

3.1. General

MS spectra were measured on a Finnigan LCQDECA XP instrument and a Agilent Q-TOF 1290 LC/6224 MS system; $^1$H- and $^{13}$C-NMR spectra were obtained on Bruker AVANCE III 500 MHz and 600 MHz spectrometers (Bruker Co., Faellanden, Switzerland) with TMS as the internal standard; silica gel GF254 and H (10–40 mm, Qingdao Marine Chemical Factory, Qingdao, China) were used for TLC and CC. Unless otherwise noted, all reactions were carried out under an atmosphere of argon or nitrogen.

3.2. Procedure for the Synthesis of Compounds 1a–d

$\text{Pd}_2$($\text{dba})_2$ (73.3 mg, 0.08 mmol) and (+)-BINAP (99.6 mg, 0.16 mmol) were dissolved in mesitylene (10 mL) and the solution degassed for 15 min before being heated at 150 °C for 10 min (solution turns from deep purple to dark orange). Upon cooling sodium tert-butoxide (769 mg, 8.0 mmol), 190–0.98 (m, 28H).

1.90–0.98 (m, 28H).

1d was purified by column chromatography eluting with light petroleum/ethyl acetate (50/1). Red oil (430 mg, 68%); $^1$H-NMR spectra of 1a was identical to those reported in the literature [27].

Analogous compounds 1b–d were prepared according to the similar procedure for 1a. 1b: 82% yield; $^1$H-NMR (500 MHz, CDCl$_3$) δ: 8.31–7.39 (m, 14H), 6.41 (m, 4H), 5.35 (q, J = 6.4 Hz, 2H), 1.74 (t, J = 9.2 Hz, 6H). 1c: 85% yield; $^1$H-NMR (500 MHz, CDCl$_3$) δ: 6.84–6.48 (m, 4H), 3.41–3.20 (m, 2H), 2.51–1.75 (m, 14H), 1.47–0.77 (m, 14H); $^1$H-NMR (500 MHz, CDCl$_3$) δ: 7.31 (m, 10H), 6.51 (m, 4H), 4.25 (t, J = 6.5 Hz, 2H), 2.01–1.77 (m, 4H), 1.01 (t, J = 7.4 Hz, 6H).

3.3. Procedure for the Synthesis of Benzimidazolium Salts 3a–d

1a (411 mg, 1.3 mmol) was dissolved in 50 mL triethylorthoformate, then concentrated hydrochloric acid (37% w/w, 7.8 mmol, 656 µL of solution) was added at room temperature and the mixture was stirred for 30 min. Then the mixture was heated to 80 °C under air atmosphere for 12 h. After cooling to room temperature, ether (30 mL) was added. The precipitate was collected by filtration. The collected solids were dissolved in MeOH (10 mL) stirred with 5 equiv NaI at room temperature for 12 h. The collected solution was concentrated and the residue was allowed to react with NaI again. After evaporation of volatiles, the residue was purified by column chromatography (CH$_2$Cl$_2$/MeOH = 15/1) to give 3a (454 mg, 77%). The $^1$H-NMR and HRESIMS spectra of 3a were similar to those reported in the literature [27].

Analogous compounds 3b–d were prepared according to the similar procedure for 3a, HR-ESIMS, $^1$H- and $^{13}$C-NMR data see Supplementary Materials. 3b: 80% yield; [α]$_D^{20}$ = +157.8 (c 0.2, CH$_2$Cl$_2$); $^1$H-NMR (500 MHz, CDCl$_3$) δ: 11.47 (s, 1H), 8.16–7.25 (m, 18H), 7.08 (q, J = 6.9 Hz, 2H), 2.51 (d, J = 6.9 Hz, 6H); $^{13}$C-NMR (125 MHz, CDCl$_3$) δ: 141.13, 134.02, 132.47, 130.19, 129.52, 127.65, 126.95, 126.38, 125.48, 124.82, 121.76, 114.36, 77.29, 76.78, 56.13, 21.09; HR-ESIMS: m/z 427.2294 [M – I]$^+$ (calcld for C$_{31}$H$_{27}$N$_2$, 427.2169). 3c: 83% yield; [α]$_D^{20}$ = +0.5 (c 0.2, CH$_2$Cl$_2$); $^1$H-NMR (500 MHz, CDCl$_3$) δ: 11.23 (s, 1H), 7.71 (m, 4H), 4.91–4.81 (m, 2H), 2.51–1.75 (m, 14H), 1.47–0.77 (m, 14H); $^{13}$C-NMR (125 MHz, CDCl$_3$) δ: 141.29, 131.06, 126.91, 114.33, 77.30, 76.79, 61.42, 42.47, 29.69, 29.45, 25.66, 25.55, 25.49, 18.32; HR-ESIMS: m/z 339.3016 [M – I]$^+$ (calcld for C$_{23}$H$_{35}$N$_2$, 339.2795). 3d: 81% yield; [α]$_D^{20}$ = −19.5 (c 0.2, CH$_2$Cl$_2$); $^1$H-NMR (500 MHz, CDCl$_3$) δ: 11.82 (s, 1H), 7.66–7.32 (m, 14H), 6.03 (t, J = 7.9 Hz, 2H), 2.88–2.74 (m, 4H), 1.07 (t, J = 7.3 Hz, 6H); $^{13}$C-NMR (125 MHz, CDCl$_3$) δ: 136.21, 131.05, 129.45, 129.27, 127.40, 127.08, 114.41, 77.29, 76.78, 65.16, 27.11, 11.04; HR-ESIMS: m/z 355.2381 [M – I]$^+$ (calcld for C$_{25}$H$_{37}$N$_2$, 355.2169).
3.4. Representative Procedure for the Pd-Catalyzed Intramolecular α-Arylation of Amides

Pd$_2$(dba)$_3$ (4.6 mg, 0.005 mmol), chiral benzimidazolium iodide 3c (carbene ligand precursor) (4.7 mg, 0.01 mmol) and sodium tert-butoxide (29 mg, 0.3 mmol) were placed under N$_2$ in a dry Schlenk tube. Dimethoxyethane (DME) (0.05 M in substrate, freshly distilled over Na) was added and the mixture was stirred for 5 min. The 2-bromo-N-alkylanilide (0.2 mmol) was then added as a solution in DME (equal volume as above). The reaction was stirred at room temperature for 12 h. The reaction was treated with aq. NH$_4$Cl (2 mL) and extracted with ether (3 × 2 mL). The combined organic phases were washed with water (3 mL) and brine (3 mL), and dried over Na$_2$SO$_4$. Flash chromatography afforded the product oxindoles. The enantiomeric purity of products 5a–m was determined by chiral HPLC Analysis.

5a: 99% yield, 46% ee; The spectral data were comparable to those reported [17]. The ee was determined by HPLC analysis with Daicel Chiralcel OD-H (hexane/i-PrOH = 99/1, flow rate = 1.0 mL/min, tr (major) = 12.7 min, tr (minor) = 15.4 min); 5b: 66% yield, 44% ee; The spectral data were comparable to those reported [17]. The ee was determined by HPLC analysis with Daicel Chiralcel OD-H (hexane/i-PrOH = 99/1, flow rate = 1.0 mL/min, tr (major) = 14.5 min, tr (minor) = 16.4 min); 5c: 58% yield, 24% ee; The spectral data were comparable to those reported [25].

The ee was determined by HPLC analysis with Daicel Chiralcel OD-H (hexane/i-PrOH = 99/1, flow rate = 1.0 mL/min, tr (minor) = 13.7 min, tr (major) = 16.2 min); 5d: 99% yield, 27% ee; The spectral data were comparable to those reported [21]. The ee was determined by HPLC analysis with Daicel Chiralcel OD-H (hexane/i-PrOH = 99/1, flow rate = 1.0 mL/min, tr (minor) = 11.3 min, tr (major) = 14.2 min); 5e: 85% yield 28% ee; The spectral data were comparable to those reported [15].

The ee was determined by HPLC analysis with Daicel Chiralcel OD-H (hexane/i-PrOH = 99/1, flow rate = 1.0 mL/min, tr (minor) = 12.6 min, tr (major) = 15.7 min); 5f: 82% yield, 28% ee; The ee was determined by HPLC analysis with Daciel Chiralcel OD-H (hexane/i-PrOH = 98/2, flow rate = 1.0 mL/min, tr (minor) = 15.4 min, tr (major) = 20.2 min); 5g: 32% yield, 26% ee; The ee was determined by HPLC analysis with Daciel Chiralcel OD-H (hexane/i-PrOH = 99/1, flow rate = 1.0 mL/min, tr (major) = 10.6 min, tr (minor) = 12.2 min); 5h: 81% yield, 42% ee; The ee was determined by HPLC analysis with Daciel Chiralcel OD-H (hexane/i-PrOH = 99/1, flow rate = 1.0 mL/min, tr (major) = 10.7 min, tr (minor) = 12.1 min); 5i: 72% yield, 33% ee; The ee was determined by HPLC analysis with Daciel Chiralcel OD-H (hexane/i-PrOH = 99/1, flow rate = 1.0 mL/min, tr (minor) = 11.3 min, tr (major) = 12.2 min); 5j: 35% yield, 34% ee; The ee was determined by HPLC analysis with Daciel Chiralcel OD-H (hexane/i-PrOH = 99/1, flow rate = 1.0 mL/min, tr (major) = 11.9 min, tr (minor) = 15.3 min); 5k: 28% yield, 26% ee; The ee was determined by HPLC analysis with Daciel Chiralcel OD-H (hexane/i-PrOH = 99/1, flow rate = 1.0 mL/min, tr (minor) = 11.3 min, tr (major) = 12.7 min); 5l: 68% yield, 50% ee; The ee was determined by HPLC analysis with Daciel Chiralcel OD-H (hexane/i-PrOH = 99/1, flow rate = 1.0 mL/min, tr (major) = 11.6 min, tr (minor) = 13.6 min); 5m: 35% yield, 28% ee; The ee was determined by HPLC analysis with Daciel Chiralcel OD-H (hexane/i-PrOH = 99/1, flow rate = 1.0 mL/min, tr (minor) = 11.9 min, tr (major) = 13.2 min).

4. Conclusions

In conclusion, four chiral C$_2$-symmetric benzimidazolium salts 3a–d have been prepared. Their applicability in the Pd-catalyzed asymmetric intramolecular arylation of amides has been demonstrated, and the corresponding oxindoles were obtained with high yields and moderate enantiomeric excesses (up to 50%). Further application to other catalytic asymmetric reactions is now in progress.

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**Author Contributions:** Jie Li and Jianyou Shi were the principle investigators of the project, designed the experiments, and wrote the manuscript. Weiping He, Bihui Zhou, and Haifeng Liu performed the entire experiments. Wei Zhao, Xiangrong Li, and Linlin Li interpreted the results and helped write the manuscript.

**Conflicts of Interest:** The authors declare no conflict of interest.

**References**


**Sample Availability:** Samples of the compounds 3a–d are available from the authors.

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