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# Palladium-Catalyzed Asymmetric Benzylation of 3-Aryl Oxindoles

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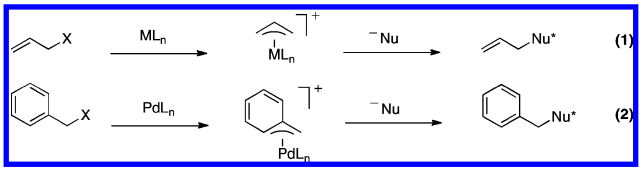
***Abstract:*** Herein we report palladium-catalyzed asymmetric benzylic alkylation with 3-aryl oxindoles as prochiral nucleophiles. Proceeding analogously to asymmetric allylic alkylation, asymmetric benzylation occurs in high yield and enantioselectivity for a variety of unprotected 3-aryl oxindoles and benzylic methyl carbonates using chiral bisphosphine ligands. This methodology represents a novel asymmetric carbon−carbon bond formation between a benzyl group and a prochiral nucleophile to generate a quaternary center.

Asymmetric allylic alkylation (AAA) is a powerful method for catalytic construction of stereocenters.[1] Proceeding through an $\eta^3$-allyl-metal complex, these reactions allow for allylic substitution with carbon, nitrogen, oxygen, and sulfur nucleophiles (eq 1). Several methods for asymmetric induction exist, and the synthetic utility of AAA has been demonstrated in multiple natural product syntheses.[1b]

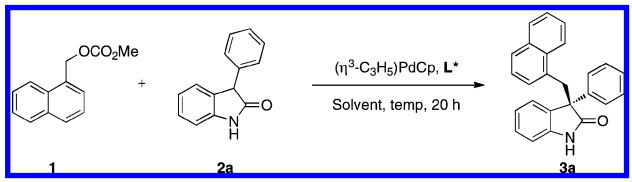
The analogous $\eta^3$-benzyl-metal species is less common since aromaticity is disrupted. However, the $\eta^3$-benzyl-palladium species has been utilized as an intermediate in catalytic benzylation[2] of carbon and heteroatom nucleophiles (eq 2).[3] Catalytic asymmetric benzylation, wherein asymmetry is introduced at the electrophile, provides high enantioselectivity only when yields are very low with 90% ee but only 11% yield as the best case.[4] Interpreting these results in part as a kinetic resolution due to the absence of a facile racemization mechanism, we began studies on asymmetric benzylation of prochiral nucleophiles to obviate such an issue.[5]




We selected oxindoles as nucleophiles for asymmetric benzylation due the prevalence of 3-tetrasubstituted oxindoles in biologically active molecules.[6] This moiety has been synthesized in a number of ways, many of which utilize the nucleophilicity of the oxindole 3-position. Asymmetric alkylation of oxindoles has been achieved via auxiliary-containing electrophiles and phase transfer catalysis; however, no catalytic asymmetric benzylations have been reported to date.[7,8] Our group has reported asymmetric allylation of oxindoles employing palladium and molybdenum catalysts.[9] Herein we report a method for palladium-catalyzed asymmetric benzylation of 3-aryl oxindoles. To the best of our knowledge, this represents the first report of asymmetric benzylation of prochiral nucleophiles. Moreover, benzylation is most efficient on unprotected oxindoles, in contrast to most methods for oxindole alkylation requiring nitrogen protection.

Our initial studies investigated the catalytic reaction between (naphthyl)methyl methyl carbonate **1** and differentially protected 3-phenyl oxindoles using 5 mol % ($\eta^3$-$C_3H_5$)PdCp and 7.5 mol % **L1** in DME. Unprotected oxindole **2a** exhibited the highest enantioselectivity and complete chemoselectivity for 3-benzylation (Table 1, entry 1). Coordinating solvents induced the highest enantioselectivity, with dioxane providing **3a** in 70% ee (Table 1, entries 1−4). Decreasing the reaction temperature was detrimental to reactivity and mildly beneficial to enantioselectivity (Table 1, entry 5). Other chiral bisphosphine ligands utilized (Figure 1) exhibited similar reactivity but lower enantioselectivity (Table 1, entries 6−8). As in previous studies on oxindole allylation,[9a] addition of 5 equiv of *tert*-butanol to the reaction mixture increased the yield and ee of **3a** (Table 1, entry 9). Increasing the reaction concentration furnished **3a** in 93% isolated yield and 86% ee (Table 1, entry 10). The isolated yield and enantioselectivity were unchanged at 6 mol % ligand loading and the 10 h reaction time (Table 1, entry 11).

***Table 1.*** Selected Optimization Experiments




| entry | L* | solvent | temp (°C) | % yield[b] | % ee[c] |
|---|---|---|---|---|---|
| 1 | **L1** | DME | 80 | 92 | 66 |
| 2 | **L1** | toluene | 80 | 41 | 63 |
| 3 | **L1** | $CH_2Cl_2$ | 35 | 86 | 45 |
| 4 | **L1** | dioxane | 80 | 93 | 70 |
| 5 | **L1** | dioxane | 25 | 11 | 77 |
| 6 | **L2** | dioxane | 25 | 17 | 43 |
| 7 | **L3** | dioxane | 25 | 6 | 38 |
| 8 | **L4** | dioxane | 25 | 9 | 12 |
| 9 | **L1** | dioxane | 25 | 24[d] | 86 |
| 10 | **L1** | dioxane | 25 | 93[d,e] | 86 |
| 11 | **LI** | dioxane | 25 | 93[d,e,f] | 86 |

[a] Reactions performed on 0.2 mmol scale at 0.2 M using 1 equiv of **1**, 1 equiv of **2a**, 5 mol % ($\eta^3$-$C_3H_5$)PdCp, and 7.5 mol % ligand for 20 h. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Reaction run with 5 equiv of *tert*-butanol. [e] Reaction performed at 0.4 M. [f] Reaction performed using 6 mol % ligand for 10 h.

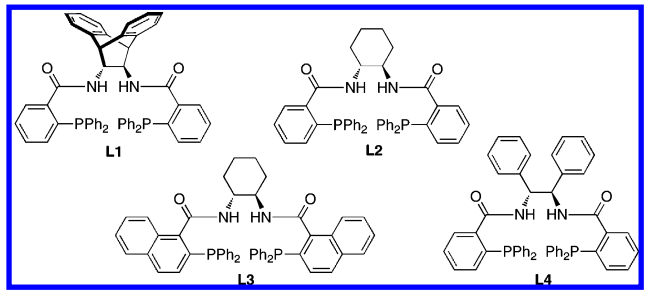
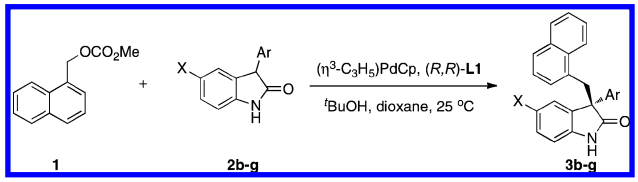
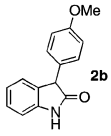
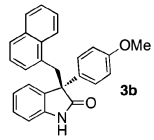
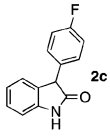
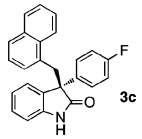
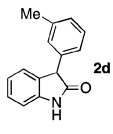
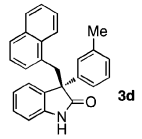
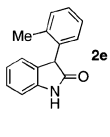
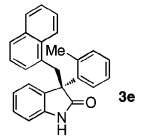
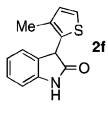
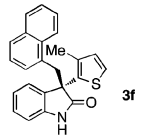
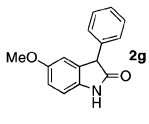
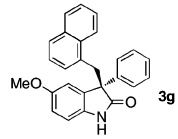



***Figure 1.*** Chiral ligands utilized for asymmetric benzylation.

Our subsequent efforts investigated the substrate scope. A variety of unprotected 3-aryl oxindoles were reacted with **1**. Introduction of an electron-donating or electron-withdrawing group at the *para*-position of the 3-phenyl group did not significantly affect the yield or enantioselectivity (Table 2, entries 1−2). A *meta*-substituted oxindole was highly reactive and provided **3d** in 77% ee. (Table 2, entry 3). *Ortho*-substitution was deleterious to reactivity, and a higher reaction temperature was required (Table 2, entry 4). A heteroaromatic substituent at the oxindole 3-position was well-tolerated (Table 1, entry 5). Substitution at the 5-position of the oxindole furnished **3g** in 83% yield and 85% ee with sonication required for complete reaction of less-soluble **2g** (Table 1, entry 6).

***Table 2.*** Asymmetric Benzylation Nucleophile Scope[a]

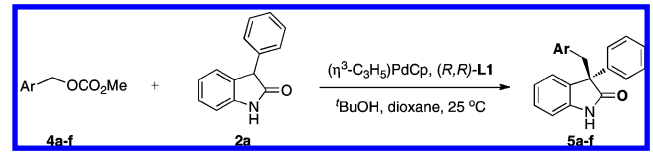


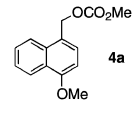
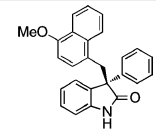
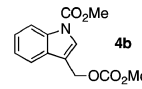
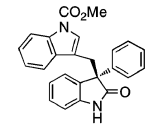
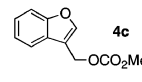
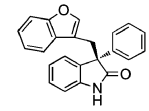
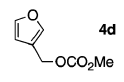
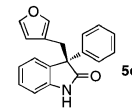
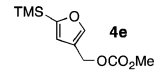
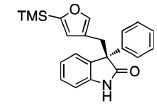
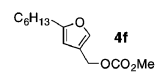
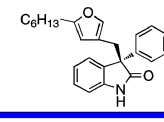

| entry | substrate | product | % yield[b] | % ee[c] |
|---|---|---|---|---|
| 1 |  **2b** |  **3b** | 81 | 80 |
| 2 |  **2c** |  **3c** | 96 | 87 |
| 3 |  **2d** |  **3d** | 84 | 77 |
| 4 |  **2e** |  **3e** | 44[d] | 76 |
| 5 |  **2f** |  **3f** | 69 | 86 |
| 6 |  **2g** |  **3g** | 83[e] | 85 |

[a] Reactions performed on 0.2 mmol scale at 0.4 M in dioxane using 1 equiv of **1**, 1 equiv of **2b**−**g**, 5 mol % ($\eta^3$-$C_3H_5$)PdCp, 6 mol % (*R,R*)-**L1**, and 5 equiv of *tert*-butanol for 10−14 h. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Reaction performed at 50 °C. [e] Reaction performed in sonicator.

We also investigated the reaction scope with respect to the electrophile (Table 3). Oxindole **2a** was reacted with a series of benzylic methyl carbonates employing the previously optimized reaction conditions. Electrophile **4a**, substituted at the 4-position of naphthalene, furnished **5a** in 80% yield and 79% ee (Table 3, entry 1). Indole and benzofuran electrophiles with the benzylic carbon at the 3-position were highly reactive and enantioselective with greater than 90% yield and ee obtained for **5b**−**c** (Table 3, entries 2−3). Furan electrophiles were competent monocyclic substrates for asymmetric benzylation of **2a** and were unaffected by substitution at the 5-position (Table 3, entries 4−6).

***Table 3.*** Asymmetric Benzylation Electrophile Scope[a]



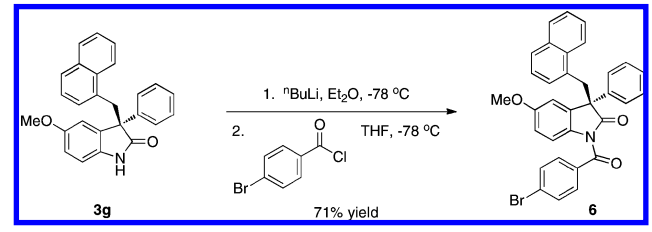

| entry | substrate | product | % yield[b] | % ee[c] |
|---|---|---|---|---|
| 1 |  **4a** |  **5a** | 80 | 79 |
| 2 |  **4b** |  **5b** | 98 | 96 |
| 3 |  **4c** |  **5c** | 91 | 93 |
| 4 |  **4d** |  **5d** | 87 | 90 |
| 5 |  **4e** |  **5e** | 94 | 91 |
| 6 |  **4f** |  **5f** | 70 | 87 |

[a] Reactions performed on 0.2 mmol scale at 0.4 M in dioxane using 1 equiv of **4a**−**f**, 1 equiv of **2a**, 5 mol % ($\eta^3$-$C_3H_5$)PdCp, 6 mol % (*R,R*)-**L1**, and 5 equiv of *tert*-butanol for 10−14 h. [b] Isolated yield. [c] Determined by chiral HPLC.

Acylation of benzylated prouduct **3g** with 4-bromobenzoyl chloride furnished **6** in 71% yield (Scheme 1). An X-ray crystal structure of **6** allowed for determination of the absolute configuration unambiguously.[10] The stereochemistry for the other examples has been assigned by analogy.

In conclusion, we have developed a method for catalytic asymmetric benzylic alkylation to generate a quaternary center. This method introduces a benzyl group at the 3-position of oxindoles in high yield and enantiomeric excess. The absence of any observable

***Scheme 1.*** Acylation of **3g**



oxindole N-benzylation is also noteworthy. Further investigations into the asymmetric benzylation scope are underway.

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**Supporting Information Available:** Experimental details and spectral data for all unknown compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(2) In the context of this publication, "benzylation" refers to reaction at the carbon attached to an aromatic ring.
(3) (a) Kuwano, R. *Synthesis* **2009**, *7*, 1049. (b) Legros, J.-Y.; Fiaud, J.-C. *Tetrahedron Lett.* **1992**, *33*, 2509. (c) Kuwano, R.; Konda, Y.; Matsuyama, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12104.
(4) (a) Legros, J.-Y.; Toffano, M.; Fiaud, J.-C. *Tetrahedron: Asymmetry* **1995**, *6*, 1899. (b) Assié, M.; Legros, J.-Y.; Fiaud, J.-C. *Tetrahedron: Asymmetry* **2005**, *16*, 1183. (c) Assie, M.; Meddour, A.; Fiaud, J.-C.; Legros, J.-Y. *Tetrahedron: Asymmetry* **2010**, *21*, 1701.
(5) (a) Trost, B. M.; Radinov, R.; Grenzer, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 7879. (b) Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 6759. (c) Trost, B. M.; Ariza, X. *Angew. Chem., Int. Ed.* **1997**, *36*, 2635. (d) Trost, B. M.; Ariza, X. *J. Am. Chem. Soc.* **1999**, *121*, 10727. (e) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6924. (f) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044. (g) Trost, B. M.; Xu, J.; Schmidt, T. *J. Am. Chem. Soc.* **2009**, *131*, 6640. (h) Trost, B. M.; Xu, J.; Reichle, M. *J. Am. Chem. Soc.* **2007**, *129*, 282. (i) Trost, B. M.; Xu, J.; Schmidt, T. *J. Am. Chem. Soc.* **2009**, *131*, 18343.
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(7) (a) Pallavicini, M.; Valoti, E.; Villa, L.; Resta, I. *Tetrahydron: Asymmetry* **1994**, *5*, 363. (b) Emura, T.; Esaki, T.; Tachibana, K.; Shimizu, M. *J. Org. Chem.* **2006**, *71*, 8559.
(8) Lee, T. B. K.; Wong, G. S. K. *J. Org. Chem.* **1991**, *56*, 872.
(9) (a) Trost, B. M.; Fredriksen, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 308. (b) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2006**, *128*, 4590. (c) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2007**, *129*, 14548.
(10) The obtained absolute stereochemistry is the opposite of that obtained in the palladium-catalyzed allylation of oxindoles (ref 9a). We believe the significantly different structure of the electrophile (benzyl vs allyl) is an important source for the change in absolute stereochemistry. The difference in the substituents on the oxindole nitrogen may also contribute since we have noted that substitution does play a role in absolute stereochemistry.

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