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Palladium-Catalyzed Enantioselective α-Arylation and α-Vinylation of Oxindoles Facilitated by an Axially Chiral P-Stereogenic Ligand

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All-carbon quaternary centers are found in numerous biologically active small molecules, and their efficient construction remains a challenge in organic synthesis.[1] In that context, methods for the asymmetric α-arylation and α-vinylation of carbonyl enolates hold particular promise because of their ability to form highly substituted centers adjacent to a functional group that can be readily manipulated. Recent reports have described the asymmetric α-arylation of enolates derived from ketones[2] and, in an intramolecular reaction, aldehydes.[3] Despite the progress in this field, however, the substrate scope remains limited in intermolecular reactions; there has been only one example of enantioselective α-arylation of lactones,[4] for example, and to the best of our knowledge, there have been no reports to date of general methods for the intermolecular enantioselective α-arylation or α-vinylation of amide, ester, and other non-ketone carbonyl enolates.[5]

Recently, we reported conditions that allow for the selective N- or C-arylation of oxindoles based on the application of either Cu or Pd catalysts.[6] The oxindole core and its derivatives are found in many natural products and other biologically active compounds,[7] and methods for their asymmetric formation and transformation are of considerable interest.[8,9] The Pd-catalyzed conditions we described were capable of forming quaternary centers from 3-substituted oxindoles in racemic fashion, and we set out to explore an asymmetric variant of that method. Herein we describe the highly enantioselective Pd-catalyzed intermolecular coupling of oxindoles and aryl and vinyl bromides facilitated by a biaryl monophosphine ligand that contains two sources of asymmetry.

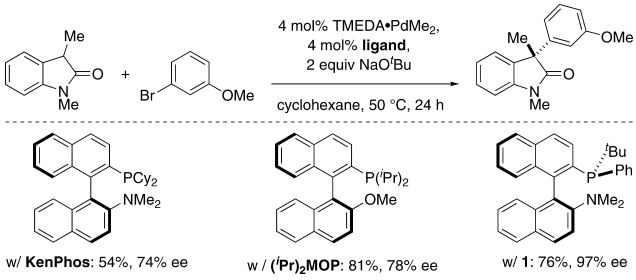
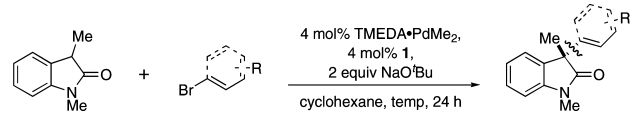
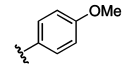
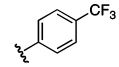
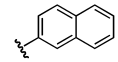
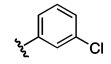
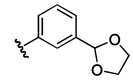
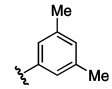
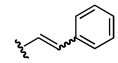
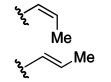
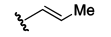
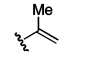


Figure 1. Pd-catalyzed enantioselective α-arylation of 1,3-dimethyloxindole with an axially chiral, P-chirogenic ligand.

Following an initial survey of ligands and optimization of Pd sources, we found that KenPhos and (^{i}Pr)$_2$MOP promoted the coupling of 1,3-dimethyloxindole with 3-bromoanisole in the presence of TMEDA·PdMe$_2$[10] and NaO^{t}Bu in good yield with promising levels of enantiomeric excess (Figure 1, with the conditions described in Table 1). Interestingly, of all the ligands screened, only biaryl monosphosphines were found to promote the reaction in appreciable yield or enantioselectivity. On the basis of our results, we hypothesized that a ligand similar to KenPhos but with an additional asymmetric element would lead to a more enantioselective coupling process. Indeed, we observed that **1** facilitated the coupling under the same conditions in 76% yield and 97% ee. Ligand **1** was reported by our group several years ago as the first example of an axially chiral, P-stereogenic ligand,[11] and although it was examined in several cross-coupling reactions at that time, including α-arylation and α-vinylation reactions, it was not superior to simpler ligands and has not been reported in an application since that time.

Table 1. Enantioselective α-Arylation and α-Vinylation of 1,3-Dimethyloxindole[a]



entry	ArBr/ vinylBr		temp (°C)	yield (%)[b]	ee (%)[c]
1		(**2**)	50	74	96
2			50	63	95
3			50	79	96
4[d]		(**3**)	50	62	97
5			50	62	97
6			50	79	97
7[e]			rt	73 *trans* 10 *cis*	78 *trans* 98 *cis*[f]
8			rt	79	94
9			rt	87	54
10		(**4**)	50	63	96[f]

[a] Reaction conditions: oxindole (0.65 mmol, 1.3 equiv), aryl/vinyl bromide (0.5 mmol, 1 equiv), TMEDA·PdMe$_2$ (4 mol %), **1** (4 mol %), NaO^{t}Bu (1.0 mmol, 2 equiv) in cyclohexane (1 mL) at the temperature shown. Each result shown is the average of two runs in which all of the starting material was consumed. [b] Yield of isolated material. [c] Determined by chiral HPLC. [d] Using a reaction time of 18 h. [e] Vinyl bromide was used as a 4.5:1 trans/cis mixture. [f] Determined following reduction with H$_2$ and Pd/C.

Having identified **1** as the optimal ligand, we explored the substrate scope with regard to the aryl bromide coupling partner.

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Both electron-rich and electron-deficient aryl bromides reacted in good yield with high enantioselectivity (Table 1, entries 1 and 2), as did 2-bromonaphthalene (Table 1, entry 3). Substituted aryl bromides, including those with 3-chloro, 2-dioxolanyl, and alkyl substituents, also were transformed to the corresponding products with high selectivity (Table 1, entries 4−6). In general, aryl halides with substituents positioned meta or para to the bromine reacted effectively, whereas reactions of those with ortho substituents led to low yields; this trend is often seen in intermolecular asymmetric enolate arylation.[2a,12]

Vinyl bromides were also efficient coupling partners under these conditions. For instance, we found that application of a *cis/trans* mixture of β-bromostyrene formed a separable mixture of the corresponding *cis*- and *trans*-styrenyl oxindole products under the reaction conditions, although the cis isomer was formed with significantly higher enantioselectivity (Table 1, entry 7). Similarly, *cis*-1-bromo-1-propene gave product more enantioselectively than *trans*-1-bromo-1-propene (Table 1, entries 8 and 9). Use of 2-bromopropene formed the corresponding isopropenyl oxindole in good yield and high enantiomeric excess (Table 1, entry 10). Single-crystal X-ray diffraction of the enantiomer of that product (ent-**4**, formed with the enantiomer of ligand **1**) was used to determine the absolute stereochemistry of that compound and, by inference, those of all of the products of this reaction.

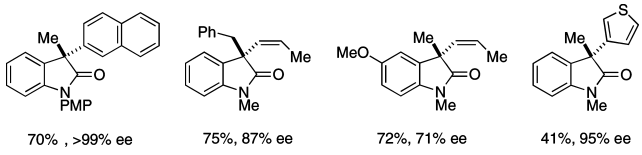
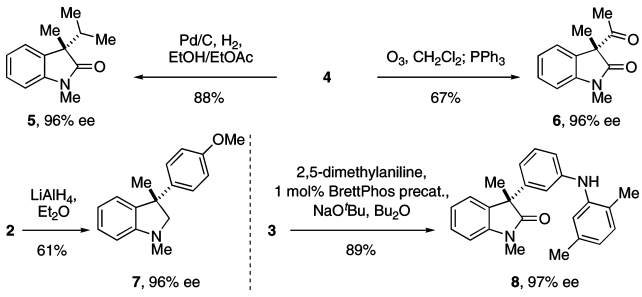


Figure 2. Products of reactions to form other substituted oxindoles. Reactions were run at 50 °C using the same conditions as shown in Table 1. Results shown are averages of two runs. The first value below each structure is the yield of isolated material, and the second is the enantiomeric excess determined by chiral HPLC.

To examine the generality of these reaction conditions, we applied them to substrates bearing different substituents on the oxindole backbone (Figure 2). α-Arylation proceeded in good yield and excellent enantioselectivity with an *N*-aryl oxindole. A 3-benzyl-containing substrate was well-tolerated, as was one with a 5-methoxy group, a motif commonly found in bioactive oxindole-based compounds, although this substrate reacted with lower enantioselectivity. Also, α-arylation with 3-bromothiophene formed the corresponding product in high enantiomeric excess; this is the only asymmetric example of such a coupling with a heterocyclic aryl halide of which we are aware.

Scheme 1. Derivatization of α-Aryl and α-Vinyl Oxindole Products



As shown in Scheme 1, vinyl oxindole **4** was readily converted into either the related saturated compound **5** or the 3-acetyl derivative **6** by reduction or ozonolysis, respectively. Access to enantiomerically enriched compounds of this type would be difficult using conventional methodology. 3-Aryl oxindole **2** was converted into the corresponding indoline **7** with $LiAlH_4$, and **3** was employed in a Pd-catalyzed C−N cross-coupling reaction to give **8**.[13] All of these reactions took place with no loss of optical activity.

In conclusion, we have developed conditions for the Pd-catalyzed enantioselective α-arylation and α-vinylation of oxindoles using a ligand with both axial and phosphorus-based chirogenicity.

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Supporting Information Available: Experimental procedures, characterization data for all new compounds, spectral data, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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