Published in final edited form as:
J Am Chem Soc. 2009 July 29; 131(29): 9900–9901. doi:10.1021/ja903880q.

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

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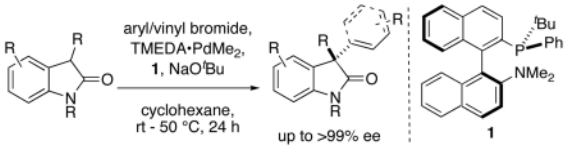
Abstract



The enantioselective α-arylation and α-vinylation of oxindoles catalyzed by Pd and a biarylmonophosphine ligand with both axial and phosphorous-based chirogenicity is reported. The resultant quaternary carbon stereocenters are formed in high enantiomeric excess, and the conditions tolerate a range of substitution on both the oxindole and the aryl/vinyl coupling partners.

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, substrate scope remains limited in intermolecular reactions; there has been only one example of the 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, or 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.

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

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 and promising levels of enantiomeric excess (Figure 1, conditions as described in Table 1). Interestingly, of all the ligands screened, only biaryl monosphosphines were found to promote the reaction in appreciable yield or enantioselectivity. Based on 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.

Having identified **1** as the optimal ligand, we explored the substrate scope with regard to the aryl bromide coupling partner. Both electron-rich and electron-deficient aryl bromides reacted with high enantioselectivity and in good yield (Table 1, entries 1 and 2), as did 2-bromonaphthalene (Table 1, entry 3). Substituted aryl bromides, including 3-chloro, 2-dioxolanyl, and those with alkyl substituents, also were transformed to the corresponding products with high selectivity (Table 1, entries 4, 5, and 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, a trend 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, of all of the products of this reaction.

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 in the only asymmetric example of such a coupling with a heterocyclic aryl halide that we are aware of.

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. 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 phosphorous-based chirogenicity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the National Institutes of Health (NIH) (GM46059) for funding this project. R.A.A. acknowledges an NIH predoctoral fellowship (F31GM081905). We thank Amgen, Boehringer-Ingelheim, Merck, Nippon Chemical, and BASF (Pd compounds) for additional support. We thank Dr. Patrick Bazinet for obtaining the crystal structure of ent-**4**.

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10. TMEDA•$PdMe_2$ is an air-stable Pd precatalyst that is readily prepared in two steps from $PdCl_2$•MeCN. For details, see the supporting information and Biscoe MR, Fors BP, Buchwald SL. J Am Chem Soc 2008;130:6686. [PubMed: 18447360]
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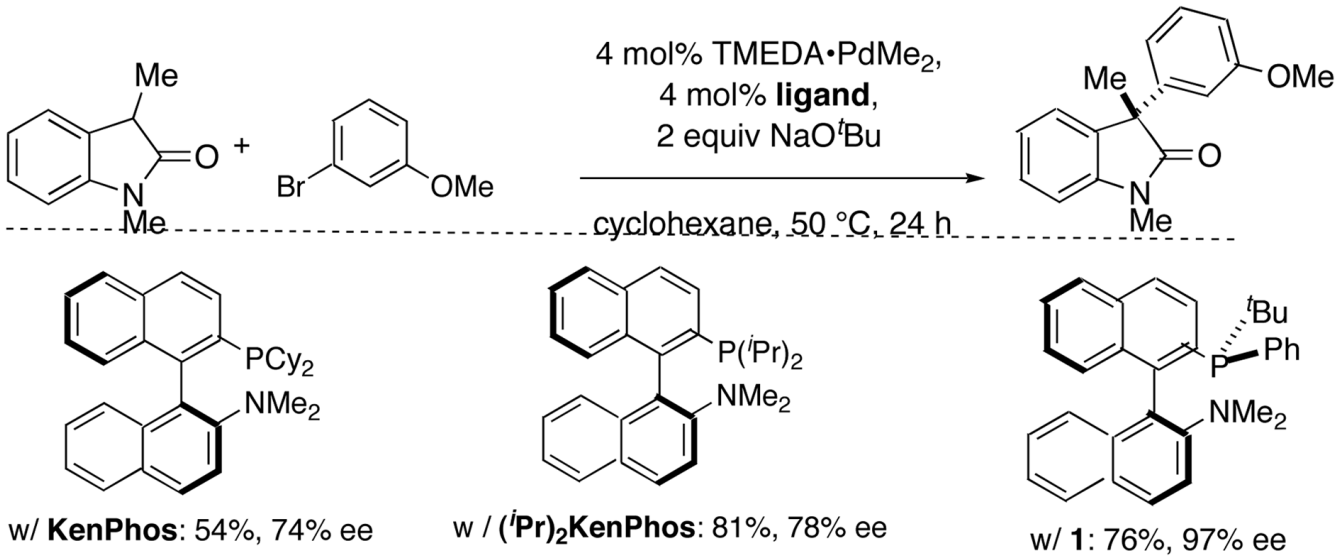
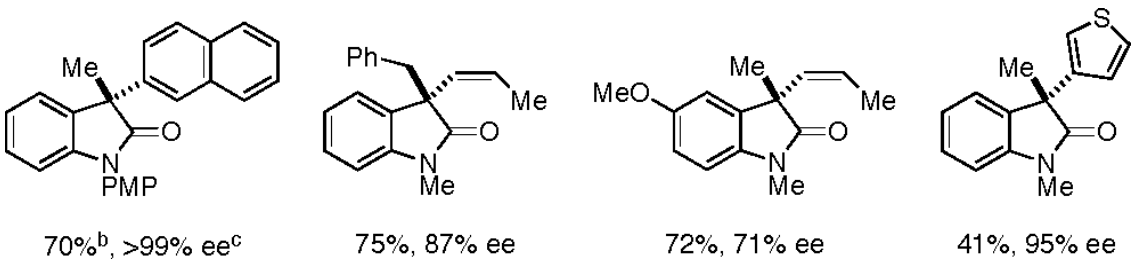


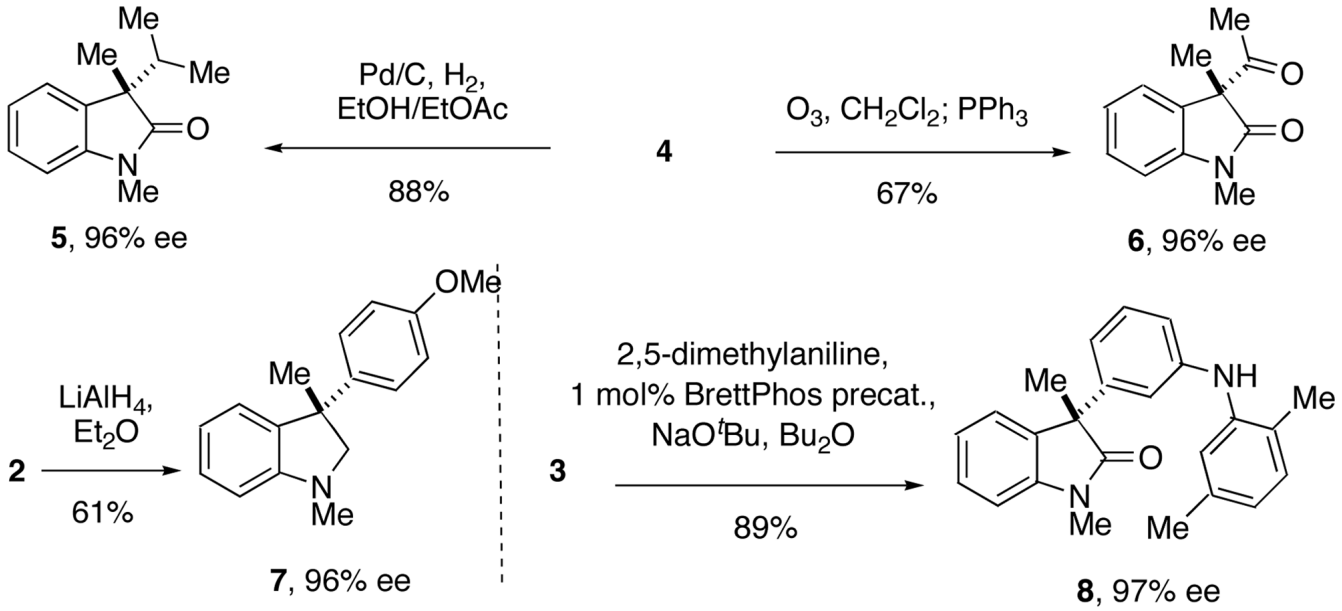
Figure 1.
Pd-catalyzed enantioselective α-arylation of 1,3-dimethyl oxindole with an axially-chiral, P-chirogenic ligand.



70%[b], >99% ee[c] 75%, 87% ee 72%, 71% ee 41%, 95% ee

Figure 2. Reactions to form other substituted oxindoles.[a]

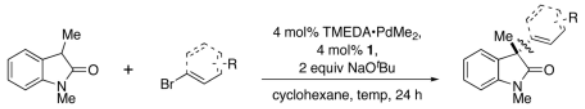
[a]Reactions were run at 50 °C using the same conditions as shown for Table 1. Results shown are the average of two runs. [b]Yields of isolated material. [c]Enantiomeric excesses determined by chiral HPLC.



Scheme 1.
Derivatization of α-aryl and α-vinyl oxindole products.

Table 1

Enantioselective α-arylation and α-vinylation of 1,3-dimethyloxindole.[a]



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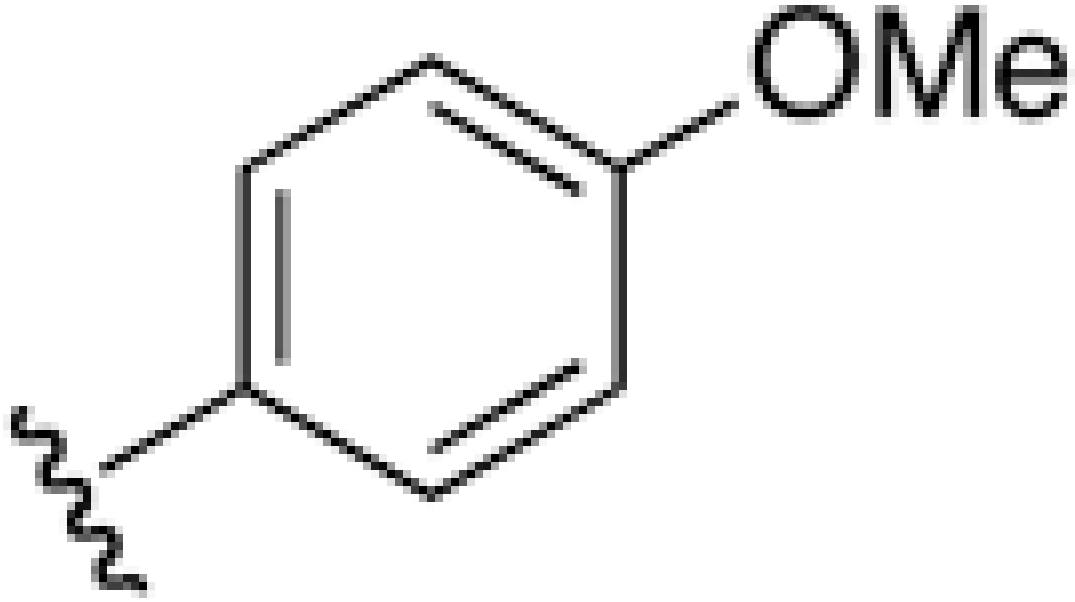
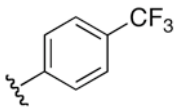
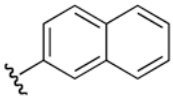
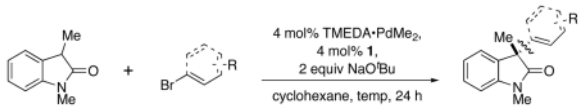
1		50	74	96
2	(2) 	50	63	95
3		50	79	96



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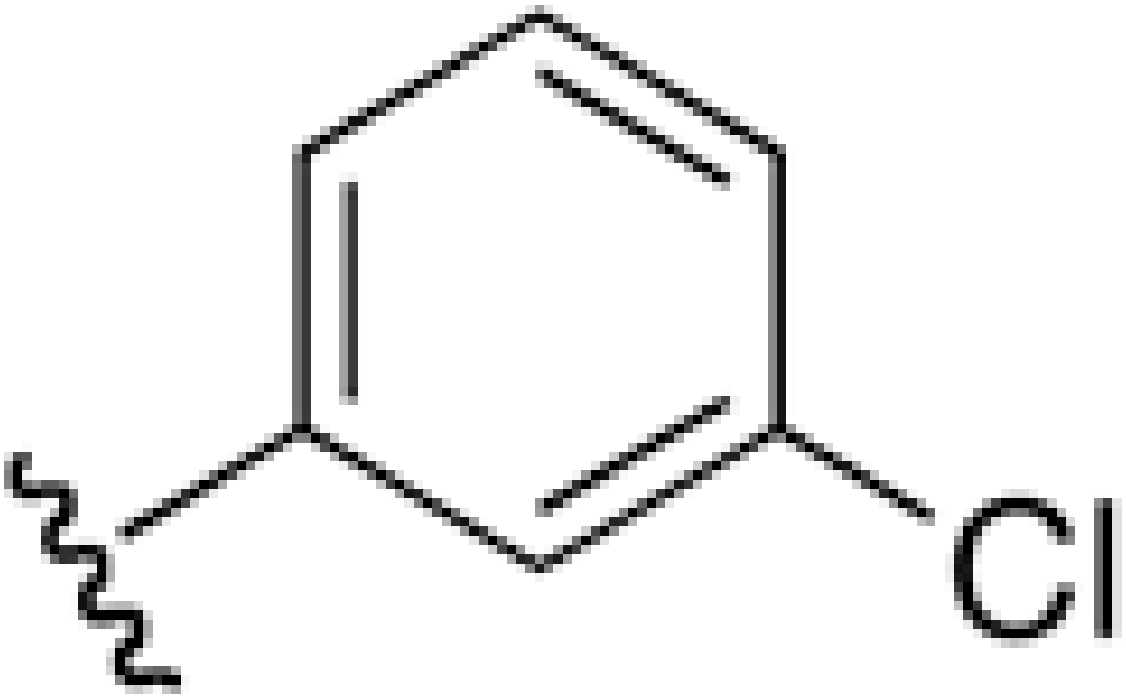
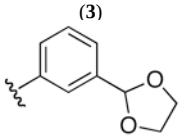
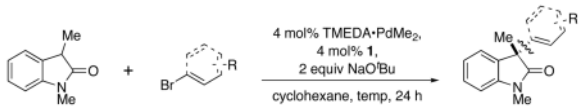
4[d]		50	62	97
5	**(3)** 	50	62	97



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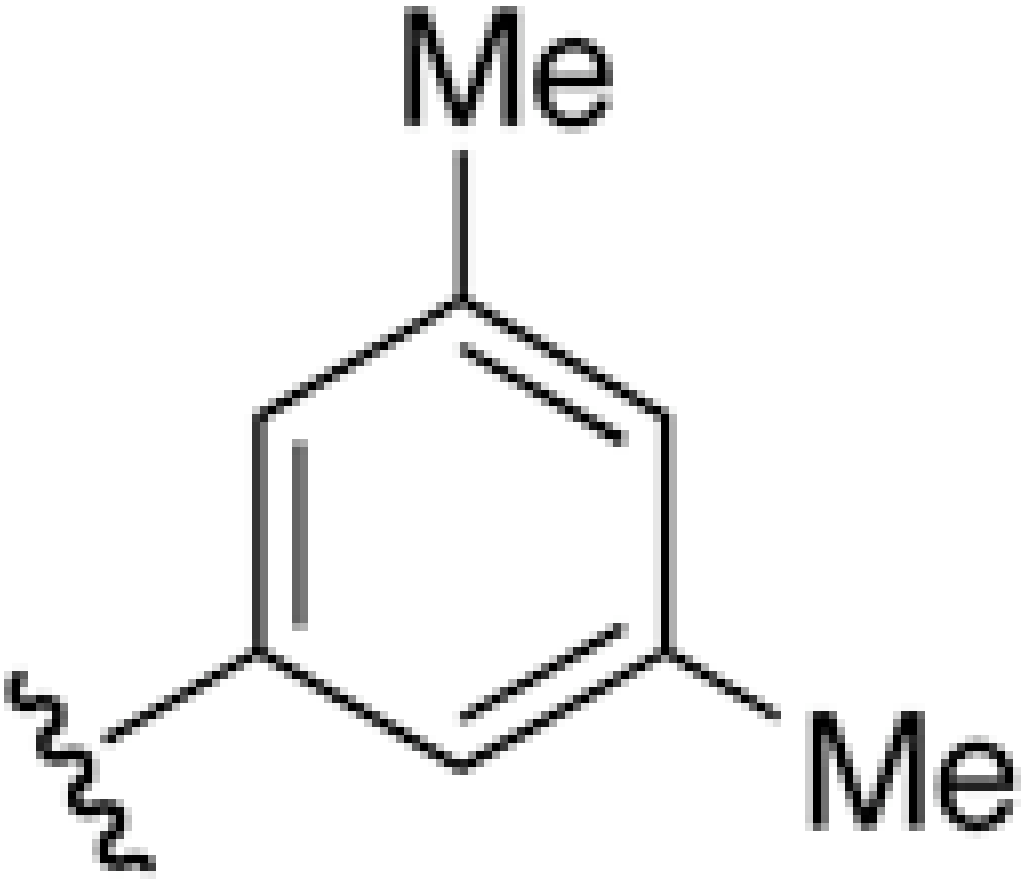
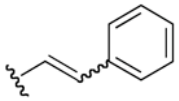
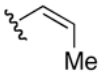
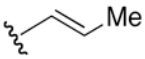
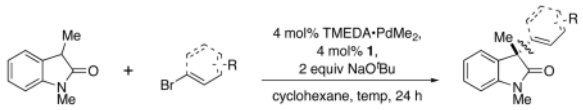
6		50	79	97
7[e]		rt	73 *trans* 10 *cis*	78 *tr* 98 *c*
8		rt	79	94
9		rt	87	54



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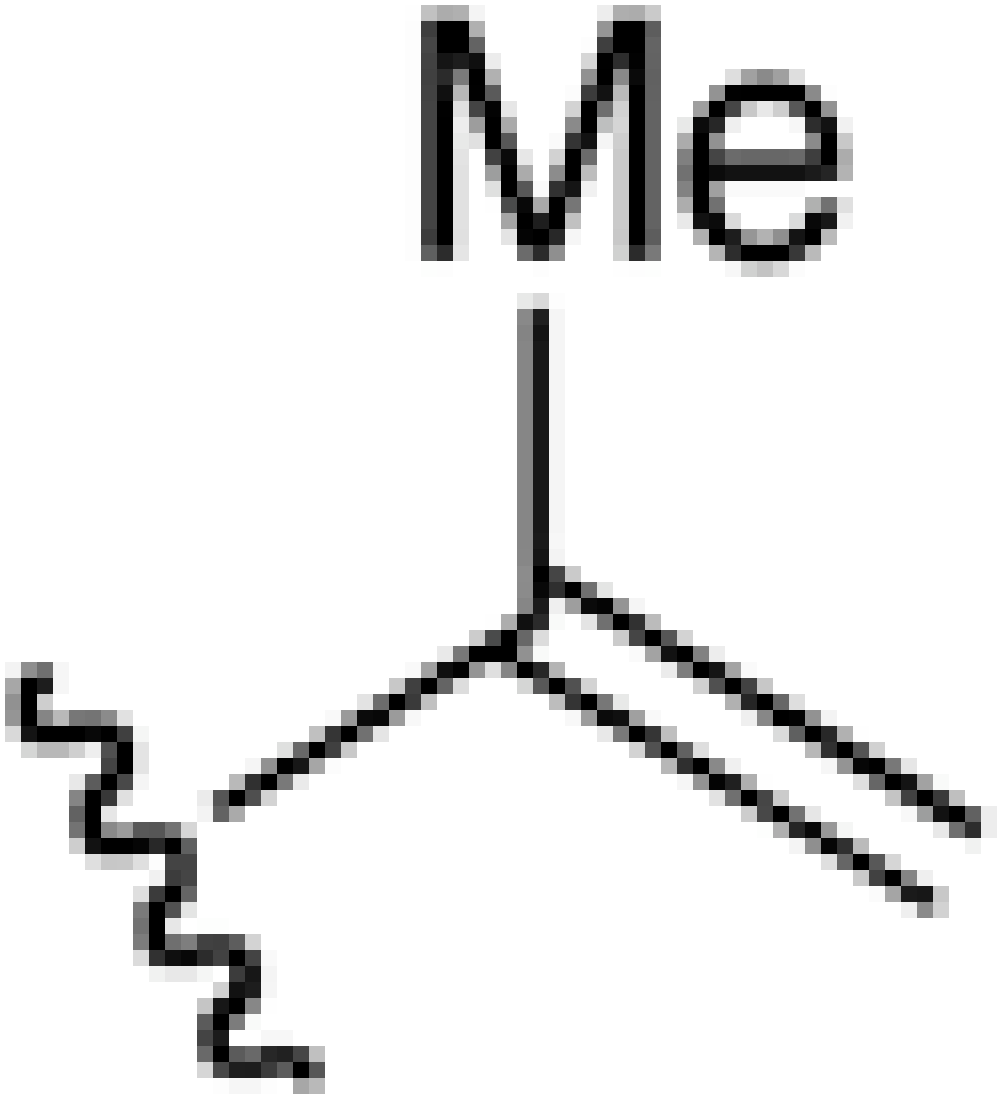
10		50	63	96

(**4**)

[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^tBu (1.0 mmol, 2 equiv) in cyclohexane (1 mL) at temperature shown. Results shown are the average of two runs, in which all starting material was consumed.

[b] Yield of isolated material.

[c] Determined by chiral HPLC.

[d] 18 h reaction time.

[e] Vinyl bromide used as a 4.5:1 *trans:cis* mixture.

[f] Determined following reduction with H_2 and Pd/C.