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Cobalt-Catalyzed Enantioselective Directed C–H Alkylation of Indole with Styrenes

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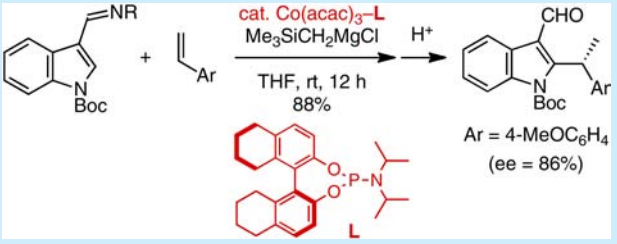
Supporting Information

ABSTRACT: A cobalt–chiral phosphoramidite catalyst promotes enantioselective imine-directed C2-alkylation of Boc-protected indoles with styrenes. The reaction affords 1,1-diarylethane products in moderate to good yields with good enantioselectivities under mild conditions. A deuterium-labeling experiment suggests that the enantioselectivity is controlled by both the styrene insertion and the C–C reductive elimination steps.



Over the last few decades, transition-metal-catalyzed, directing group-assisted addition of aromatic and vinylic C–H bonds across alkenes has gained considerable attention as a straightforward and atom-economical approach for the regioselective alkylation of arenes and alkenes.[1] Enantioselective variants of such C–H addition reactions have been achieved in intramolecular settings with rhodium catalysts first by Murai et al.[2] and then extensively by the group of Bergman and Ellman[3] with the aid of nitrogen-based directing groups. On the other hand, intermolecular directed hydroarylation of alkenes has rarely been made enantioselective, mainly because the reaction typically shows *anti*-Markovnikov selectivity with terminal olefins and thus precludes the formation of a new stereogenic center.[1,4] To our knowledge, only sporadic examples of iridium(I)–chiral diphosphine-catalyzed addition reactions to norbornene or styrene (Scheme 1a, b)[5] have been reported by the groups of Togni and Shibata as relevant intermolecular reactions involving directed C–H activation of nonprochiral aromatic substrates, while Hartwig achieved highly enantioselective iridim(I)-catalyzed addition of indole and related heteroarenes to norbornene via nondirected C–H activation (Scheme 1c).[6−8] We report here that a cobalt–chiral phosphoramidite catalyst promotes an imine-directed enantioselective addition reaction of *N*-protected indoles to styrenes (Scheme 1d). The reaction affords 1,1-diarylethane derivatives in moderate to good yields with a good level of enantioselectivity.

Recently, we developed cobalt–monophosphine catalytic systems for pyridine- or imine-directed hydroarylation reactions of styrenes that afford 1,1-diarylethane derivatives with high regioselectivity.[9,10] The reactions represent rare examples of transition-metal-catalyzed branched-selective styrene hydroarylation.[11] Thus, naturally we became interested in developing its enantioselective variant. Our study began with a screening of chiral ligands, monodentate phosphorus ligands in particular, for the cobalt-catalyzed addition of aldimine **1a-Me** derived from indole-3-carboxaldehyde[9b,12] to styrene (**2a**) (Table 1). The reaction was performed in the presence of a catalyst

Scheme 1. Directing Group-Assisted Enantioselective Intermolecular Hydroarylation of Olefins

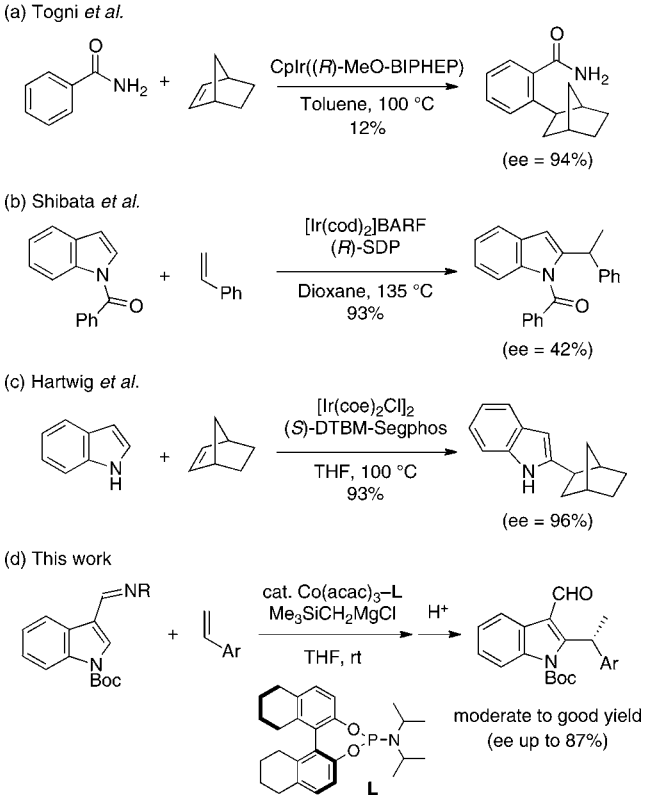


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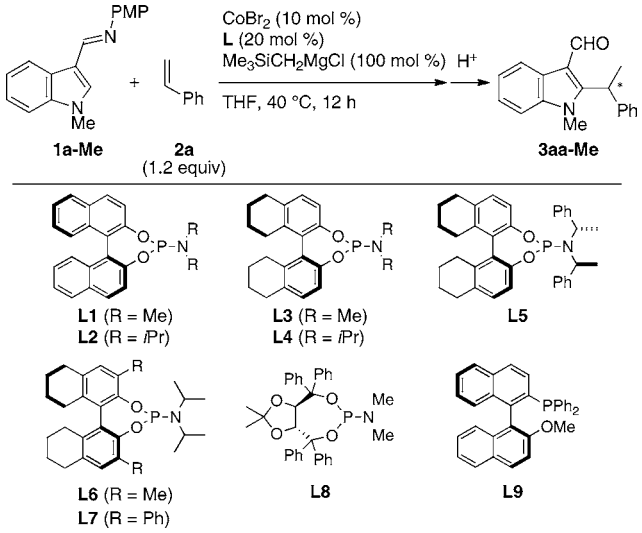
Table 1. Screening of Chiral Ligands for the Addition of Imine 1a-Me to Styrene[a]



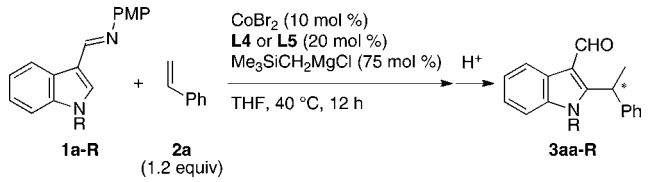
entry	ligand	yield[b] (%)	ee[c] (%)
1	**L1**	15	15
2	**L2**	69	43
3	**L3**	84	45
4	**L4**	83	47
5	**L5**	61	57
6	**L6**	66	37
7	**L7**	29	39
8	**L8**	31	3
9	**L9**	12	3
10[d]	(*S*)-BINAP	83	3
11	none	89	–

[a]The reaction was performed on a 0.15 mmol scale at a concentration of 0.4 M. [b]Estimated by GC using *n*-tridecane as an internal standard. [c]Determined by HPLC using a chiral stationary phase. [d]10 mol % of (*S*)-BINAP was used.

generated from $CoBr_2$ (10 mol %), ligand (20 mol %), and Me_3SiCH_2MgCl (100 mol %) in THF at 40 °C for 12 h. While the simplest BINOL-based phosphoramidite, (*S*)-monophos (**L1**), gave the product **3aa-Me** in low yield and enantioselectivity (Table 1, entry 1), modification of the BINOL backbone and/or the amine moiety led to substantial improvement of the catalytic performance (Table 1, entries 2−5). Thus, those having an H_8−BINOL backbone and a branched dialkylamino moiety (**L4** and **L5**) gave good conversions and moderate ee values up to 57% ee (Table 1, entries 4 and 5). Introduction of additional substituents on the 3,3′-positions had adverse effects (Table 1, entries 6 and 7). Further examination of various BINOL-based phosphoramidite ligands did not lead to an improvement of the enantioselectivity (see Table S1 in the Supporting Information). Other monodentate phosphorus ligands such as (−)-TADDOL-derived phosphoramidite **L8** and (*S*)-MOP (**L9**) gave poor conversions and very low ee values (Table 1, entries 8 and 9). (*S*)-BINAP gave a high conversion but with a low ee value (Table 1, entry 10). Note that a high conversion was achieved even under ligand-free conditions (Table 1, entry 11). Thus, some of the ligands tested (e.g., **L1**) should have decelerated the reaction.

Having identified the moderately effective ligands such as **L4** and **L5**, we next examined the effect of the indole *N*-substituent (Table 2). Using **L4**, the reaction of the *N*-Boc derivative **1a-Boc** was achieved in a moderate yield (67%) with a

Table 2. Effect of Indole N-Substituent[a]



entry	R	ligand	yield[b] (%)	ee[c] (%)
1	Boc	**L4**	67	73
2	Boc	**L5**	13[d]	ND[e]
3	Cbz	**L4**	65	67
4[f]	Ts	**L4**	19	65
5	$CONEt_2$	**L4**	0	
6	Bn	**L4**	77	53
7	Ph	**L4**	70	73
8[g]	Boc	**L4**	90	83

[a]The reaction was performed on a 0.15 mmol scale at a concentration of 0.4 M. [b]Isolated yield. [c]Determined by HPLC using a chiral stationary phase. [d]Determined by ^1H NMR using 1,1,2,2-tetrachloroethane as an internal standard. [e]Not determined. [f]The amount of Me_3SiCH_2MgCl was 100 mol %. [g]The reaction was performed at room temperature at a concentration of 0.3 M using $Co(acac)_3$ instead of $CoBr_2$.

substantially improved ee value of 73% (Table 2, entry 1), while **L5** gave rise to a diminished catalytic activity (Table 2, entry 2). Note that the loading of Me_3SiCH_2MgCl could be reduced to 75 mol %, while further reduction led to a substantial decrease in the product yield. Note also that other phosphoramidite ligands shown in Table 1 performed poorly for **1a-Boc**. The *N*-Cbz and *N*-Ts derivatives gave slightly lower ee values, the reaction of the latter being sluggish (Table 2, entries 3 and 4). The *N*-diethylcarbamoyl derivative did not afford the desired product at all (Table 2, entry 5). While the *N*-benzyl derivative smoothly participated in the reaction, the enantioselectivity was modest (Table 2, entry 6). The yield and the enantioselectivity for the *N*-phenyl derivative were comparable to that for the *N*-Boc derivative (Table 2, entry 7). Upon further modification of the reaction conditions (see Table S2, Supporting Information), the reaction of **1a-Boc** was improved by using $Co(acac)_3$ as the precatalyst and lowering the reaction temperature to room temperature (24−26 °C), affording the product **3aa-Boc** in 90% yield and 83% ee (Table 2, entry 8). In contrast to the reaction of **1a-Me** (Table 1, entry 11), the reaction of **1a-Boc** was rather sluggish in the absence of **L4**. Note that the metal/ligand ratio of 1:2 was found to be optimum and that the reaction did not take place at 0 °C.

With the $Co(acac)_3$−**L4** system in hand, we explored the scope and limitation of the enantioselective addition of 1-Boc-3-iminoindole derivatives to styrenes (Scheme 2). Styrenes bearing a *para*- or *meta*-substituent participated in the reaction with **1a-Boc** to afford the corresponding hydroarylation products in yields of 48−88% with ee values of 73−86%. High ee values (85−86%) were achieved in the reactions of 4-methoxystyrene and 4-trimethylsilylstyrene (see **3ab-Boc** and **3ac-Boc**). The former reaction could be performed on a 3 mmol scale without a significant decrease in the yield and enantioselectivity (77% yield, 85% ee). The absolute stereochemistry of the major enantiomer of **3ab-Boc** was determined

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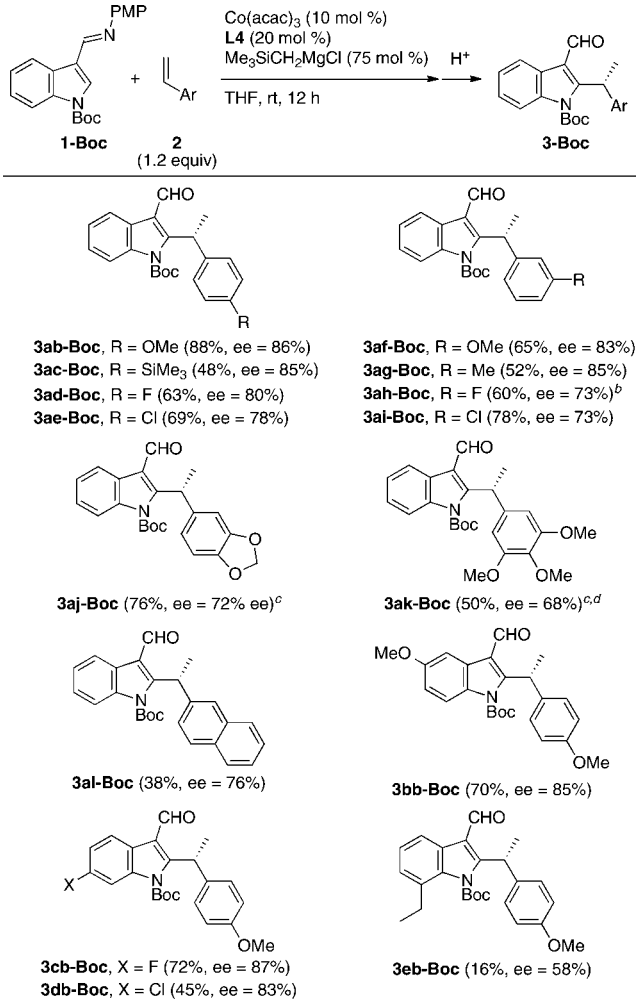
Scheme 2. Scope of the Addition of 1-Boc-3-iminoindoles to Styrenes[a]



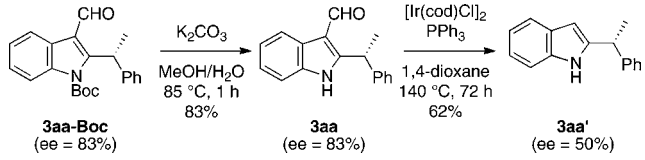
[a]The reaction was performed on a 0.15 mmol scale. Isolated yields are shown. The ee values were determined by HPLC using a chiral stationary phase. [b]The reaction time was 24 h. [c]$CoBr_2$ was used instead of $Co(acac)_3$. [d]Performed on a 0.3 mmol scale.

to be *R* by X-ray crystallographic analysis of its SAMP hydrazone derivative (see the Supporting Information). Electron-withdrawing fluoro and chloro substituents lowered the enantioselectivity down to 73% ee (see **3ah-Boc** and **3ai-Boc**). Ortho-substituted styrenes such as 2-fluorostyrene and 2-methylstyrene as well as *β*-substituted styrene such as (*Z*)-*β*-trimethylsilylstyrene failed to participate in the reaction.[13] The reactions of 3,4-methylenedioxy- and 3,4,5-trimethoxystyrene were rather sluggish when performed under the standard conditions. For these substrates, $CoBr_2$ served as a better precatalyst, affording the products **3aj-Boc** and **3ak-Boc** in moderate yields and enantioselectivities (ca. 70% ee). 2-Vinylnaphthalene afforded the desired product **3al-Boc** in a modest yield with 76% ee.

The reactions of indole substrates bearing a substituent on the 5- or 6-position with 4-methoxystyrene were achieved in moderate to good yields with enantioselectivities higher than 83% ee (see **3bb-Boc**, **3cb-Boc**, and **3db-Boc**), while the presence of a 7-ethyl substituent on indole resulted in diminished reactivity and enantioselectivity (see **3eb-Boc**). Note that in this and other cases of low to moderate yields, the unreacted starting materials were recovered without affording byproducts including a linear alkylation product (i.e., the addition reaction took place exclusively in a branched manner). Unfortunately, aromatic imines other than the indole derivatives, such as those derived from 1-napthaldehyde and acetophenone, did not participate in the reaction with styrene under the present reaction conditions.

The Boc group of the hydroarylation product **3aa-Boc** was readily removed by the treatment with K_2CO_3 in aqueous MeOH to afford the NH indole **3aa** without change of the ee value (Scheme 3). The formyl group of **3aa** could further be

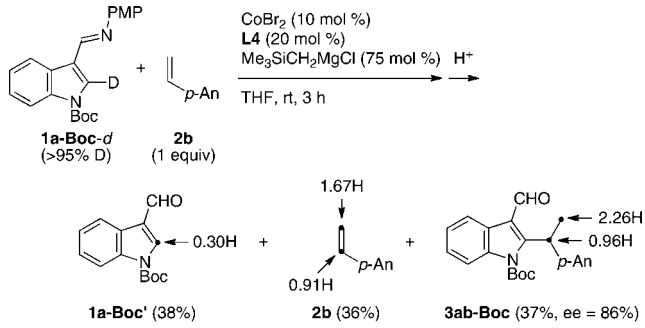
Scheme 3. Removal of Boc and Formyl Groups



removed under iridium catalysis,[14] which was, however, accompanied by a substantial erosion of the enantiomeric purity (see **3aa′**). Note that attempted decarbonylation of the same compound using some of Rh-catalyzed or Pd-catalyzed methods[15] resulted in a poor conversion, which suggests the need for further improvement of chemoselective decarbonylation methods.

To gain mechanistic insight, we performed the reaction of C2-deuterated substrate **1a-Boc-*d*** and vinylarene **2b** for 3 h, which afforded a mixture of the hydrolyzed substrate **1a-Boc′**, **2b**, and the product **3ab-Boc** (Scheme 4). Curiously, the use of

Scheme 4. Deuterium-Labeling Experiment[a]



[a]The yields and the proton contents were determined by ^1H NMR spectroscopy.

$CoBr_2$ instead of $Co(acac)_3$ was essential to achieve a reasonable conversion. Otherwise, the reaction was rather sluggish (<10% conversion after 12 h).[16] We observed a decreased deuterium content (by 30%) at the C2 position of **1a-Boc′** and a similar degree of deuterium incorporation into the methylene terminus of **2b**. The deuterium incorporation into the *α*-position of **2b** was marginal (<10%). Consistent with these observations, the methyl group of **3ab-Boc** was substantially deuterated, while deuteration at the methine moiety was negligible.

With the assumption of a catalytic cycle consisting of C−H oxidative addition, migratory insertion of styrene into the Co−H bond, and reductive elimination,[9] the result of the deuterium-labeling experiment suggests that the former two steps are reversible and that migratory insertion occurs

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predominantly in a branched manner. In addition, reductive elimination would not be significantly slower than deinsertion of styrene as judged from the limited degree of H/D exchange. Thus, we speculate that both the migratory insertion and reductive elimination steps influence the enantioselectivity of the present reaction.

In summary, we have developed an enantioselective imine-directed addition reaction of an indole C2−H bond across a styrenyl C═C bond using a cobalt−chiral phosphoramidite catalyst, affording 1,1-diarylethane derivatives in moderate to good yields with good enantioselectivities.[17] Search for more effective catalytic systems applicable to a broader range of aromatic substrates is currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization of new compounds, and crystallographic information file (CIF) for SAMP hydrazone of **3ab-Boc**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(16) Regardless of the significant difference in the catalytic activity, we speculate that the nature of the asymmetric induction process would not change depending on the cobalt precatalyst because the ee value of the model reaction is rather independent of the precatalyst (see Table S2, Supporting Information).

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