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To be cited as: *Chem. Asian J.* 10.1002/asia.201800121

Link to VoR: http://dx.doi.org/10.1002/asia.201800121

A Journal of

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10.1002/asia.201800121

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Copper-Catalyzed Asymmetric Synthesis of Borylated *cis*-Disubstituted Indolines

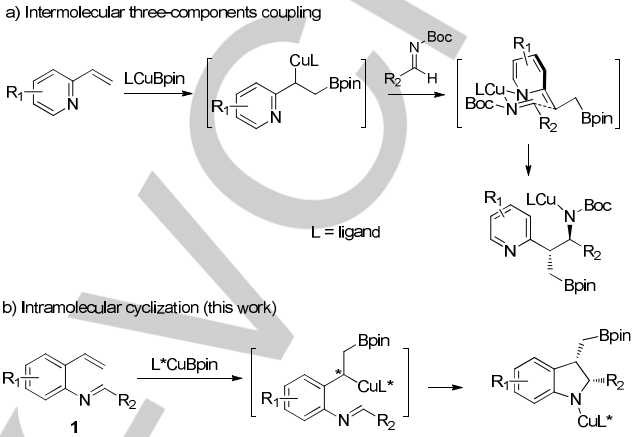
DingXi Li,[a] Jiwon Kim,[a] Jung Woon Yang,[b] and Jaesook Yun*[a]

Dedication ((optional))

Abstract: A copper-catalyzed, intramolecular borylative cyclization of vinyl arenes with imines is reported, which affords enantio-enriched indolines as a single diastereomer under mild conditions. A benzylcopper species is generated by Cu−Bpin addition to the alkene, which then acts as a nucleophile for intramolecular imine addition. The reaction is applicable to various vinyl arenes with an imine moiety at the *ortho*-position, including heterocycles, for formation of borylated indolines in good yields and *ee* up to 90%.

Chiral indolines are important structural motifs that are frequently found in biologically active natural products and pharmaceuticals.[1] In addition, they have been widely applied in a variety of asymmetric transformations as chiral auxiliaries or organocatalysts.[2] Diverse methodologies have been developed to obtain these molecules based on kinetic resolution,[3] asymmetric catalytic reduction of functionalized indoles,[4] [3+2] cycloaddition,[5a,b] asymmetric allylation of indole boronates,[5c] and intramolecular cyclization of various precursors.[1c,6]

Over the last decade, the copper-catalyzed borylative coupling reactions of unsaturated carbon–carbon bonds have been developed with various electrophiles, including aldehydes,[7] ketones,[7b] acyl halides,[8] alkyl halides,[9] and allylphosphates.[10] Meanwhile, borylative coupling with imines has only been reported for allenes, dienes, and azaarenes,[11] forming copper–allyl intermediates or their equivalents after copper–boron addition to the unsaturated substrates (Scheme 1 a). Thus, a six-membered-ring chair transition state could easily be adopted during the reaction of the C–C unsaturated substrates, diboranes, and imines. However, an efficient asymmetric borylative intramolecular cyclization has not yet been reported.[12] We envisioned that the generated L*Cu–Bpin catalyst could react with styrene tethered to an imine group (**1**) to afford the desired indolines (Scheme 1 b). Herein, we report an efficient methodology for the synthesis of indolines via copper-catalyzed borylative intramolecular cyclization of vinyl arenes (**1**).



Scheme 1. Cu-catalyzed asymmetric borylative coupling of vinyl arenes and imines.

We initially examined various chiral bidentate phosphine ligands, as summarized in Table 1. In all cases, a single diastereomer of indoline **2a**[13] was obtained by reacting *N*-benzylidene-2-vinylaniline **1a** with bis(pinacolato)diboron in the presence of a catalytic copper chloride, LiO*t*Bu, and phosphine ligands. With the C_2-symmetric bisphosphine ligands **L1**–**L3**, low enantioselectivities or poor yields were obtained (entries 1–3). In particular, the bulky **L3** ligand was not efficient for product formation. The short-tethered bisphosphine ligands **L4**–**L6** gave high yields of **2a** with moderate *ee* values (entries 4–6). Ferrocene-based bidentate phosphine ligands (**L7** and **L8**) were not beneficial, with only slightly increased *ee* values (entries 7 and 8). However, the (*S,S*)-Ph-BPE ligand (**L9**) showed promising reactivity and enantioselectivity (entry 9). Decreasing the reaction temperature to 0 °C led to a slight increase in enantioselectivity and reduced yield (entry 10). Solvent screening demonstrated diethyl ether to be the best choice. Finally, we obtained the corresponding indoline in good yield and high enantioselectivity (entry 13).

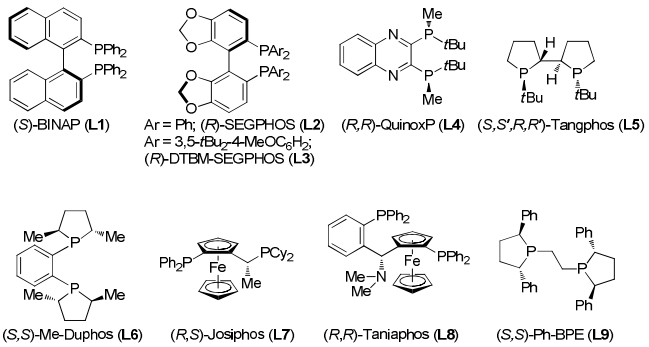


Figure 1. Ligand structures.

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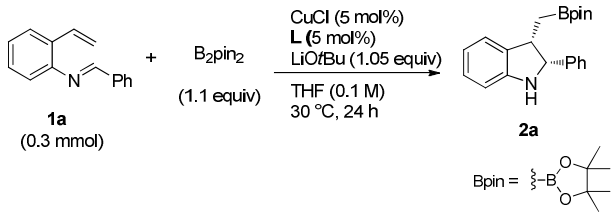
10.1002/asia.201800121

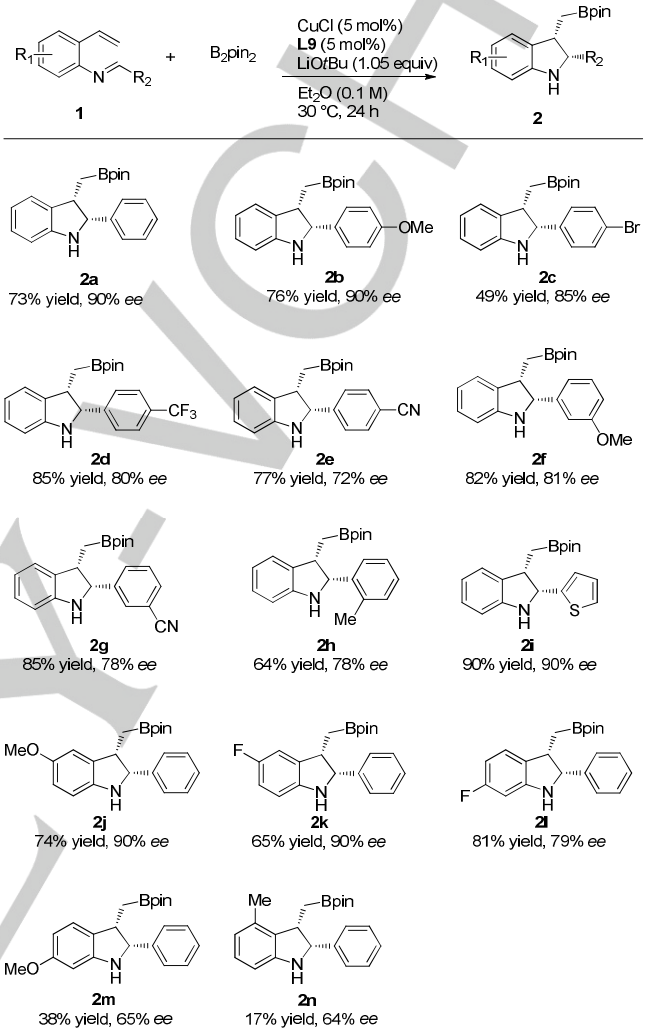
Table 1. Optimization of copper-catalyzed borylative cyclization.



Entry	L	Solvent	NMR [%][a]	yield	*ee* [%][b]
1	**L1**	THF	68		-8
2	**L2**	THF	81		14
3	**L3**	THF	13		ND[c]
4	**L4**	THF	80		52
5	**L5**	THF	90		50
6	**L6**	THF	92		-52
7	**L7**	THF	87		54
8	**L8**	THF	51		59
9	**L9**	THF	90		84
10[d]	**L9**	THF	85		86
11	**L9**	toluene	82		87
12	**L9**	MTBE	79		88
13	**L9**	diethyl ether	85 (73)		90

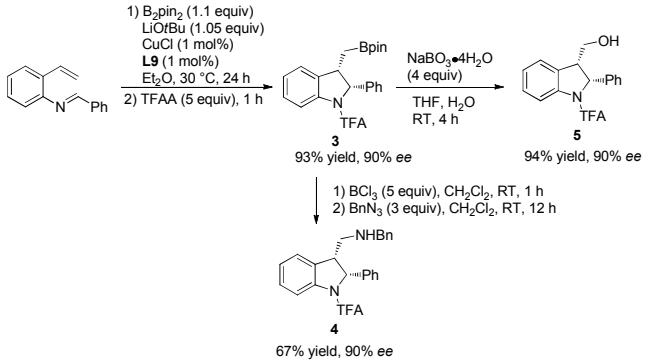
[a] Yields were determined by ^{1}H NMR analysis of the crude reaction mixture using DMF as an internal standard. The isolated yield of **2a** is shown in parentheses. [b] The *ee* values were determined by chiral HPLC analysis. [c] Not determined. [d] Reaction temperature was 0 °C.

Using these optimal reaction conditions, we investigated a variety of vinyl arenes with a tethered imine group (Scheme 2). The electron-donating methoxy group at the *para*-position of the imine moiety gave the corresponding borylated indoline (**2b**) with high yield and enantioselectivity. However, an electron-withdrawing substituent on the aromatic ring of the imine affected the enantioselectivity and slightly decreased *ee* values of the desired indoline products (**2c**–**2g**). Substrates with an electron-withdrawing substituent such as -Br, -CF_3, or -CN at the *para*-position resulted in slightly decreased enantioselectivities (**2c**–**2e**). Both *meta*-methoxy and nitrile substituents on the imine phenyl ring gave moderate enantioselectivity (**2f** and **2g**). With increased steric hindrance at the *ortho*-position, a higher temperature was required for complete conversion and the desired indoline (**2h**) was produced in 78% ee. The reaction of imines containing thiophene afforded the corresponding indoline (**2i**) in 90% yield and 90% *ee*. Next, different substituents on the phenyl ring of vinyl arene were examined. Substrates with electron-donating or electron-withdrawing substituents at the 4-position to the imine moiety produced **2j** and **2k**, but a substrate with a F-substituent at the 5-position showed decreased enantioselectivity (**2l**). Unfortunately, an electron-donating methoxy substituent at the *para*-position (**1m**) and a methyl substituent at the *ortho*-position (**1n**) to the vinyl arenes resulted in low yields even at higher temperatures.

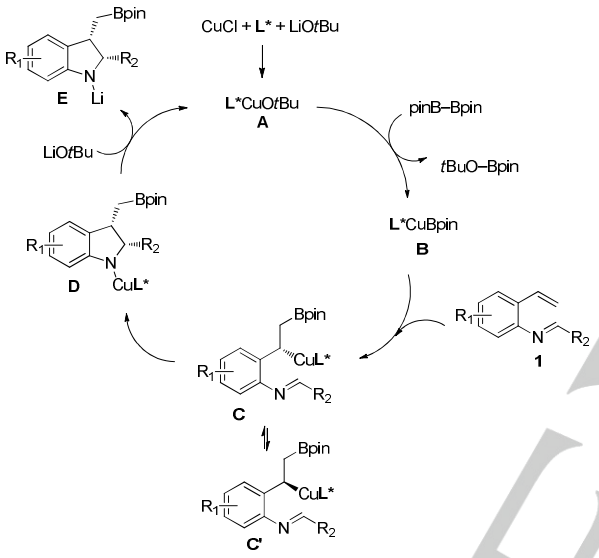


Scheme 2. Substrate scope of the copper-catalyzed borylative cyclization. Reaction conditions: **1** (0.3 mmol), B_2pin_2 (1.1 equiv), CuCl (5 mol%), **L9** (5 mol%), and LiO*t*Bu (1.05 equiv) in diethyl ether at 30 °C. Yields of isolated product are shown. The *ee* values were determined by HPLC analysis. Reactions of **1h**, **1m**, and **1n** were carried out at 50 °C.

Organic transformations of borylated indoline **3** were then briefly studied. The protected indoline (**3**) could be prepared in high yield in a one-pot synthesis by adding trifluoroacetic anhydride after catalytic cyclization with 1 mol% catalyst (Scheme 3). Hydroxylation ($NaBO_3$•$4H_2O$/THF/H_2O) of **3** afforded the corresponding hydroxyl-substituted indoline **5**[13] at excellent yield (94%), with conservation of the *ee*. Moreover, amination[14] of **3** was performed with BCl_3 and BnN_3 in dichloromethane to yield the conforming indoline **4** in 67% yield with the same *ee*.



Scheme 3. Functionalization of borylated *cis*-2,3-disubstituted indolines.



Scheme 4. Proposed catalytic cycle.

The proposed catalytic cycle is shown in Scheme 4. The **L***CuO*t*Bu species (**A**) is generated from the reaction of CuCl, ligand (**L***), and a base, which subsequently reacts with B_2pin_2 to afford the **L***Cu–Bpin species (**B**). This species then undergoes addition to the styrene in an *anti*-Markovnikov fashion to produce a chiral *β*-boryl benzylcopper intermediate **C**,[15] which could epimerize to **C'** in solution.[16] Electron-withdrawing groups at the *ortho*- or *para*-position of the vinyl arene have been reported to lead to facile epimerization,[17] which could explain the variable enantioselectivities observed in our study. The chiral benzylcopper **C** adds to the imine intramolecularly to form a cyclized indoline **D**. Finally, the catalytic cycle is closed by ligand exchange with LiO*t*Bu.

In summary, we have developed a copper-catalyzed borylative cyclization method of alkenes with imines, leading to enantio-enriched borylated *cis*-indolines in good to high yields. This methodology accommodates a range of functionalized vinyl arenes with an imine group including a heterocycle. Further studies on this class of reactions are ongoing.

Experimental Section

A mixture of CuCl (0.015 mmol, 1.5 mg), LiO*t*Bu (0.315 mmol, 25.2 mg), (*S,S*)-Ph-BPE (0.015 mmol, 7.6 mg), and bis(pinacolato)diboron (0.33 mmol, 83.8 mg) in anhydrous diethyl ether (1 mL) was stirred for 5 min in a Schlenk tube under an atmosphere of N_2. Starting material **1** (0.3 mmol) dissolved in anhydrous diethyl ether (1 mL) was added. The reaction tube was washed with anhydrous diethyl ether (1 mL), sealed, moved to an oil bath of 30 °C, and stirred for 24 h, until the reaction was completed as indicated by TLC. The reaction mixture was quenched with H_2O (5 mL), extracted with ethyl acetate (3 x 10 mL), dried with $MgSO_4$, filtered, and concentrated. The resulting crude sample was purified by flash column chromatography on silica gel to obtain the product **2**.

Acknowledgements ((optional))

This research was supported by National Research Foundation of Korea (NRF) grants (NRF-2016R1A2B4011719 and NRF-2016R1A4A1011451), funded by the Korean government (MEST). D. Li thanks the China Scholarship Council (201508260066).

Keywords: asymmetric catalysis • borylative coupling • copper • indolines • intramolecular cyclization

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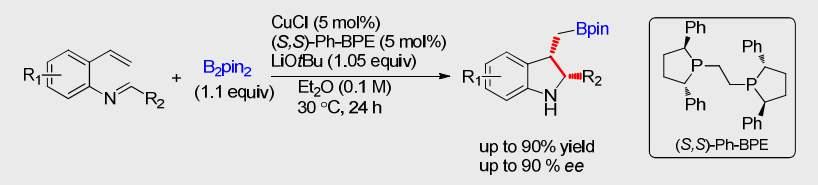

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