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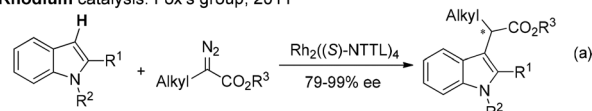
## Copper-catalyzed enantioselective C–H functionalization of indoles with an axially chiral bipyridine ligand†

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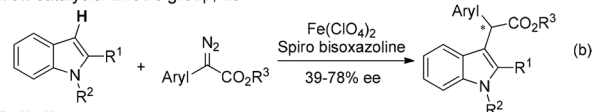
Using copper complexes with an axially chiral bipyridine ligand C4-ACBP as the catalyst, an enantioselective functionalization of indoles with diazo compounds was developed with up to 95% ee. This protocol paves the way for further applications of these ligands.

The insertion reaction of metal carbenoids represents a long-simmering topic for organic chemists.<sup>1</sup> The unique properties of the metal carbenoids, especially the dual electrophilic and nucleophilic characters, have enabled them to be established as versatile synthetic intermediates incorporated in a diverse array of valuable synthetic transformations.<sup>2</sup> In terms of their asymmetric version, particularly the C–H insertion reaction of metal carbenoids, chiral metal complexes including rhodium and copper complexes were successfully developed and applied to a wide array of substrates in the past few decades.<sup>1d–f</sup> However, with respect to indole substrates, only until recently were highly enantioselective versions disclosed. In 2011, Fox and co-workers set a major milestone by demonstrating a Rh<sub>2</sub>(S)-NTTL<sub>4</sub>-catalyzed enantioselective C–H functionalization of indoles with ethyl  $\alpha$ -alkyl- $\alpha$ -diazoacetates (79–99% ee, Scheme 1a).<sup>3</sup> Subsequently, an elegant iron-catalyzed functionalization of indoles with  $\alpha$ -aryl- $\alpha$ -diazoacetates was also reported by Zhou and co-workers, albeit with moderate enantiocontrol (39–78% ee, Scheme 1b).<sup>4</sup> Very recently, we have developed an enantioselective functionalization of indoles *via* catalysis by using a palladium complex of an axially chiral bipyridine ligand (*R*<sub>a</sub>,*S*,*S*)-C3-ACBP, and up to 98% ee could be obtained (Scheme 1c).<sup>5</sup> Although great progress has been made in this area, highly enantioselective catalytic systems are limited to rhodium and palladium catalysis, developing novel catalytic systems involving more abundant and environmentally compatible first-row transition metals for the

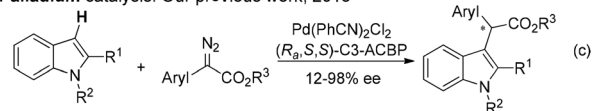
Rhodium catalysis: Fox's group, 2011



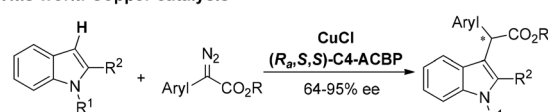
Iron catalysis: Zhou's group, 2011



Palladium catalysis: Our previous work, 2015



This work: Copper catalysis



**Scheme 1** Enantioselective C–H functionalization of indoles catalyzed by chiral metal complexes.

asymmetric functionalization of indoles by metal carbenoids is still highly desirable.<sup>6,7</sup>

Copper complexes were regarded as the catalysts of choice for carbene-related C–H insertion reactions before the advent of dirhodium tetracarboxylates.<sup>1f,8</sup> As a versatile, abundant and inexpensive transition metal, copper has been used as a metal precursor for decomposition of diazo compounds and functionalization of indoles for years.<sup>9</sup> However, the enantioselective C–H insertion reaction for the direct functionalization of indoles catalyzed by chiral copper complexes remains unsolved to date, and this is mainly ascribed to the absence of effective chiral ligands. Therefore, it is conceivable that an appropriate ligand will probably make a difference for this reaction.

Recently, we were engaged in the development of a series of axially chiral bipyridine ligands Cn-ACBP and exploration of their applications in asymmetric reactions.<sup>5,10</sup> These ligands

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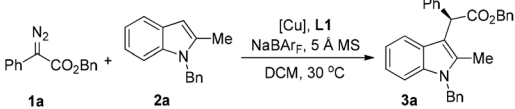
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c6ob01516f

have shown excellent stereocontrol in palladium-catalyzed carbene-related insertion reactions.<sup>5</sup> As part of our ongoing efforts in expanding the utility of these ligands and selective functionalization of indoles, herein, we report that through a copper-catalyzed enantioselective functionalization of indoles with an axially chiral bipyridine ligand, functionalized indoles can be obtained in satisfactory yields and enantioselectivities.

To initiate the study, benzyl 2-diazo-2-phenylacetate **1a** and 1-benzyl-2-methyl-1*H*-indole **2a** were chosen as model substrates for the copper-catalyzed functionalization of indoles (Table 1). Under the catalysis of CuCl/(*R*<sub>a</sub>,*S*,*S*)-C4-ACBP in dichloromethane at 30 °C, the reaction occurred in 93% ee, albeit with moderate 40% yield in 72 h (Table 1, entry 1). Alteration of copper halides to CuBr and CuI resulted in a significant increase in activity. For the precursor CuI, the reaction completed in 3 h with 92% yield and slightly diminished enantiocontrol (Table 1, entry 3). Using Cu(CH<sub>3</sub>CN)<sub>4</sub>PF<sub>6</sub> and Cu(OTf)(0.5 benzene) as precursors would further improve the reactivity; release of nitrogen gas was observed and functionalized indoles were obtained in excellent yields within 0.5 h, but the ee values dropped to 83% and 89%, respectively (Table 1, entries 4 and 5). The cupric salt Cu(OTf)<sub>2</sub> was also investigated, and both the yield and enantioselectivity decreased (Table 1, entry 6). So, CuCl was chosen as the metal precursor for further evaluations of other reaction parameters.

In order to improve the reactivity in dichloromethane, elevation of the reaction temperature to 40 °C was documented, and the yield dramatically increased to 96% without obvious loss of enantiopurity in 72 h (Table 2, entry 1). Subsequently, a brief solvent screening was carried out, and it was found that solvent was crucial to reactivity and enantioselectivity (Table 2, entries 2–5). 1,2-Dichloroethane was proved to be beneficial for the enantioselectivity, albeit comparatively low reactivity was observed (Table 2, entry 3). Surprisingly, the reaction proceeded smoothly in THF, delivering the desired product in an almost racemic fashion. Next, we focused on improving the reactivity in 1,2-dichloroethane. To our delight, by elevating the reaction temperature, an obvious

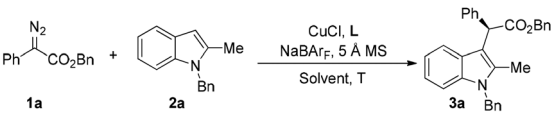
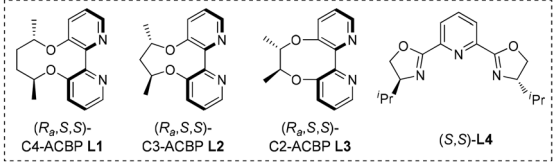
Table 1 Screening of copper salts<sup>a</sup>



Entry	[Cu]	<i>t</i> (h)	Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	CuCl	72	40	93
2	CuBr	72	63	89
3	CuI	3	92	90
4	Cu(CH <sub>3</sub> CN) <sub>4</sub> PF <sub>6</sub>	0.5	93	83
5	Cu(OTf) (0.5 benzene)	0.5	90	89
6	Cu(OTf) <sub>2</sub>	1	81	81

<sup>a</sup> Conditions: **1a** (0.20 mmol), **2a** (0.30 mmol), [Cu] (5 mol%), **L1** (5 mol%), NaBAR<sub>F</sub> (12 mol%), 5 Å MS (200 mg), 2.0 mL DCM, 30 °C. <sup>b</sup> Isolated yields. <sup>c</sup> Determined by chiral HPLC. DCM, dichloromethane.

Table 2 Condition optimization<sup>a</sup>

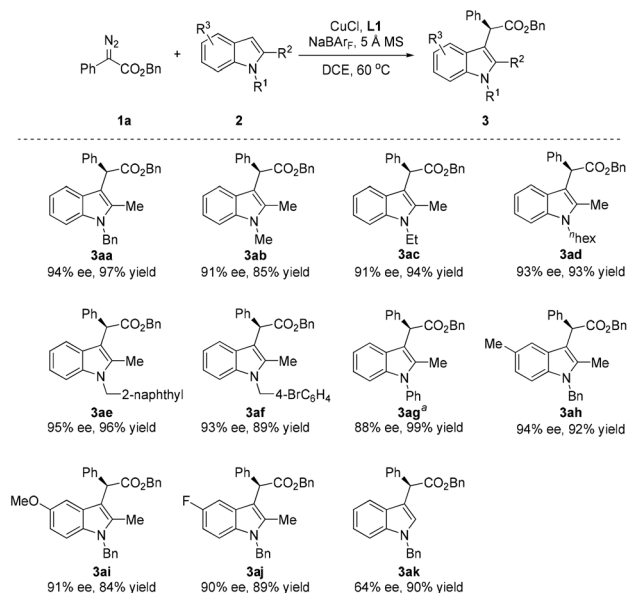



Entry	L	<i>T</i> (°C)	Solvent	<i>t</i> (h)	Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	<b>L1</b>	40	DCM	72	96	92
2	<b>L1</b>	40	CHCl <sub>3</sub>	48	93	91
3	<b>L1</b>	40	DCE	72	49	94
4	<b>L1</b>	40	Toluene	72	60	81
5	<b>L1</b>	40	THF	72	71	1
6	<b>L1</b>	50	DCE	20	96	95
7	<b>L1</b>	<b>60</b>	<b>DCE</b>	<b>2</b>	<b>97</b>	<b>94</b>
8	<b>L1</b>	70	DCE	1.5	93	93
9	<b>L2</b>	60	DCE	1.5	93	75
10	<b>L3</b>	60	DCE	2	84	61
11	<b>L4</b>	60	DCE	0.5	73	−9 <sup>d</sup>

<sup>a</sup> Conditions: **1a** (0.20 mmol), **2a** (0.30 mmol), CuCl (5 mol%), **L** (5 mol%), NaBAR<sub>F</sub> (12 mol%), 5 Å MS (200 mg), 2.0 mL of solvent. <sup>b</sup> Isolated yields. <sup>c</sup> Determined by chiral HPLC. <sup>d</sup> The opposite enantiomer was obtained. DCM, dichloromethane. DCE, 1,2-dichloroethane.

enhancement in reactivity was observed, and the reaction completed in 20 h at 50 °C, giving functionalized indoles in 96% yield and 95% ee (Table 2, entry 6). The reaction time was further shortened to a couple of hours at 60 °C and 70 °C, albeit with slightly lower ee values (Table 2, entries 7 and 8). Given the reaction efficiency and enantioselectivity, we selected 60 °C as the optimal temperature. Finally, several chiral ligands were explored, (*R*<sub>a</sub>,*S*,*S*)-C3-ACBP **L2**, which gave the best result in previously-reported Pd-catalyzed asymmetric functionalization of indoles, providing a disappointing ee value (75% ee) in this copper-catalyzed reaction (Table 2, entry 9). A commercially available pyridine-oxazoline ligand was also tested, furnishing the desired product with 9% ee (Table 2, entry 11). These phenomena reveal the special coordinative distinction of these C<sub>n</sub>-ACBP ligands with various metals in asymmetric reactions, which undoubtedly needs our further investigation.

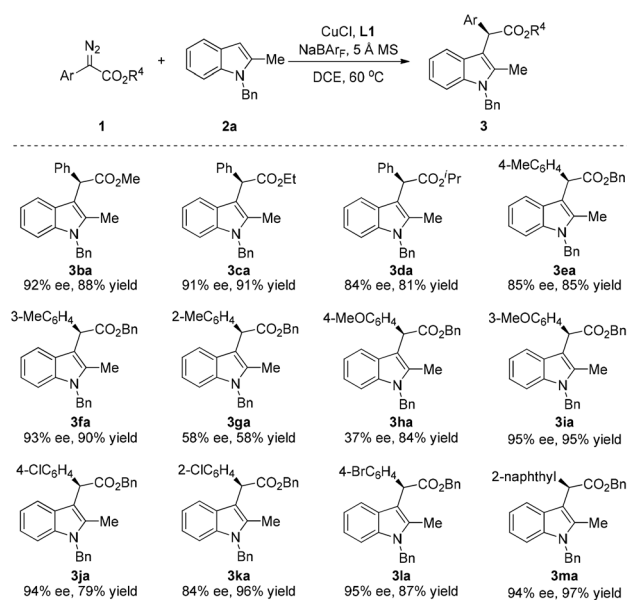
With the optimized reaction conditions in hand, we turned our attention to the investigation of the generality regarding different substituted indoles, and the results are summarized in Scheme 2. Generally speaking, alkyl group protected indoles performed quite well, delivering the desired products **3aa–3af** with high enantiomeric excess values and impressive yields. For the 1-naphthalen-2-ylmethyl protected indole **2e**, product **3ae** was obtained with the best 95% ee. 2-Methyl-1-phenyl-1*H*-indole **2g** also underwent the reaction smoothly *via* catalysis by CuI as the metal precursor instead of CuCl at 30 °C, affording **3ag** with 88% ee.<sup>11</sup> In addition, 5-substituted indoles **2h–2j** can proceed smoothly with excellent enantioselectivity and



**Scheme 2** Substrate scope: substituted indoles 2. Unless otherwise noted, all reactions were carried out under these conditions: 1a (0.20 mmol), 2 (0.30 mmol), CuCl (5 mol%), L1 (5 mol%), NaBAR<sub>f</sub> (12 mol%), 5 Å MS (200 mg), 2.0 mL DCE. <sup>a</sup> Using CuI instead of CuCl at 30 °C.

yield regardless of the electronic properties of substituents in the 5-position of indoles. Notably, we further investigated the reaction of simple 2-unsubstituted indole 2k, and moderate 64% ee was achieved, which is an obvious improvement in contrast with the one in the palladium-catalyzed reaction (12% ee).<sup>5</sup>

The initial success of the copper-catalyzed functionalization reaction with various substituted indoles prompted us to explore a wide array of diazo substrates (Scheme 3). Firstly, the reaction of diazoacetates bearing different ester groups was

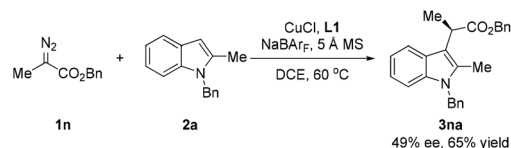


**Scheme 3** Substrate scope:  $\alpha$ -aryl- $\alpha$ -diazoacetates 1.

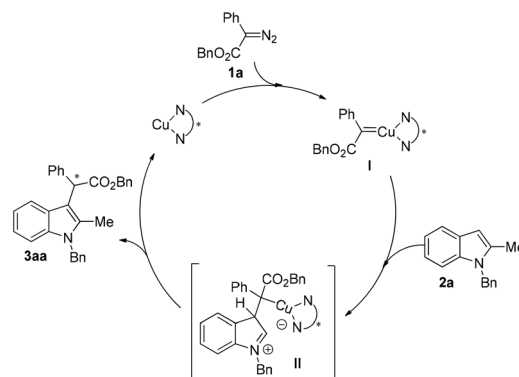
investigated, the reactions proceeded smoothly, and slightly low enantio-selectivity was observed upon increasing the steric hindrance of diazoacetates. Then, the influence of the steric and electronic properties of substituents on the phenyl rings was exploited, electron-donating groups increased the reactivity, but their detrimental effect on enantioselectivity was evident. For instance, product 3ea was obtained in 85% ee, and when the substituent placed in the *para*-position was changed into a more electron-donating methoxy group, the ee value sharply dropped to 37%, but the reason is not clear. Meanwhile, the same electron-donating groups placed in the *meta*-position barely affected yields or ee values, and 3fa and 3ia were delivered in 93% and 95% ee, respectively. For the sterically hindered substrate 1g with an *ortho*-methyl group, moderate 58% yield and 58% ee were observed. Furthermore, though electron-withdrawing groups such as Br and Cl on the phenyl rings obviously slowed down the reactions, satisfactory yields and comparable enantioselectivities were still achieved by prolonging the reaction time (3ja–3la). Additionally, 2-diazo-2-(naphthalen-2-yl)acetate 1m was also a suitable substrate for the catalytic asymmetric reaction to afford the corresponding product 3ma in 94% ee and 97% yield.

In addition to  $\alpha$ -aryl- $\alpha$ -diazoacetates,  $\alpha$ -alkyl substituted  $\alpha$ -diazoacetate 1n (benzyl  $\alpha$ -diazopropionate) was also tested in the reaction (Scheme 4), and the corresponding product could be obtained in moderate yield and 49% of enantioselectivity.

Based on the above experimental results and literature evidence,<sup>3,4,9</sup> a plausible mechanism is proposed (Scheme 5). It's likely to be analogous with that of rhodium- and iron-catalyzed reactions: the diazoester 1a was decomposed by a copper catalyst to generate copper carbene I, which reacted with indole 2a to form a metal associated zwitterionic intermediate II, and



**Scheme 4** Substrate scope:  $\alpha$ -alkyl- $\alpha$ -diazoacetates 1n.



**Scheme 5** Proposed reaction mechanism.

then proton migration from C-3 of the indole to the  $\alpha$ -position of the ester occurred to give the final product. Notably, the absolute configuration of **3aa** was the same with that of the one in the palladium-catalyzed reaction.<sup>5</sup>

## Conclusions

In summary, we have successfully developed an efficient copper-catalyzed protocol for enantioselective functionalization of indoles with an axially chiral bipyridine ligand C4-ACBP. Various chiral functionalized indoles were readily accessed in moderate to excellent yields with up to 95% ee. This reaction is featured by the employment of a copper complex CuCl/C4-ACBP as the catalyst, thus making this methodology a valuable complement to the palladium-catalyzed one. Moreover, this protocol represents a new catalytic system involving Cn-ACBP ligands and paves the way for further applications of these ligands.

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- Under the above-mentioned optimal conditions, **3ag** was obtained in 88% yield and 80% ee.