Ligand Design

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Enantioselective Palladium-Catalyzed C–H Functionalization of Indoles Using an Axially Chiral 2,2′-Bipyridine Ligand

*Xiang Gao, Bo Wu, Wen-Xue Huang, Mu-Wang Chen, and Yong-Gui Zhou**

Abstract: *A palladium-catalyzed enantioselective C–H functionalization of indoles was achieved with an axially chiral 2,2′-bipyridine ligand, thus providing the desired indol-3-acetate derivatives with up to 98 % ee. Moreover, the reaction protocol was also effective for asymmetric O–H insertion reaction of phenols using α-aryl-α-diazoacetates. This represents the first successful application of bipyridine ligands with axial chirality in palladium-catalyzed carbene migratory insertion reactions.*

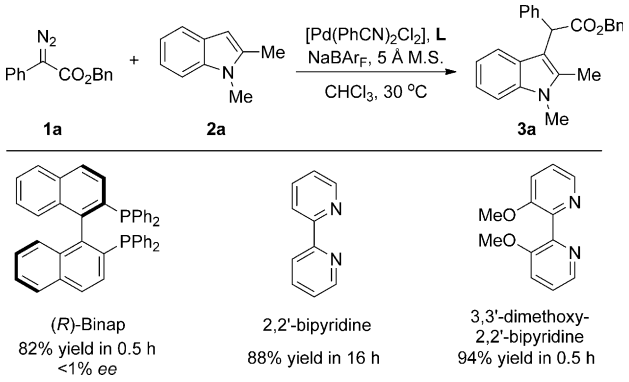
Functionalized indoles are ubiquitous structural motifs in a myriad of biologically active alkaloids and pharmaceuticals.[1] To access these privileged building blocks, the most straightforward approach is direct functionalization of simple and commercially available indoles. Among the enormous efforts devoted to this area, transition-metal-catalyzed C–H functionalization by diazo compounds stands out because of its convenience in constructing indol-3-acetate derivatives with high medicinal value.[2] The groups of Fox[2c] and Hashimoto[2d] disclosed rhodium-catalyzed direct C–H functionalization of indoles by carbenoids, derived from α-alkyl-α-diazo-acetates, with excellent enantioselectivity. But when α-aryl-α-diazoacetates were used, neither iron[2e] nor rhodium catalysts[2f] gave satisfactory results in terms of enantioselectivity (Scheme 1). An interesting protocol to acquire chiral indol-3-acetate derivatives was developed by the group of Hu through enantioselective trapping of zwitterionic intermediates.[2g,h] Despite the progress made recently, developing an enantioselective method for the direct functionalization of indoles using α-aryl-α-diazoacetates is still challenging and highly desirable.

Palladium is an indispensable and versatile catalyst in modern organic synthesis.[3] Palladium-catalyzed carbene-transfer reactions based on migratory insertion have received considerable attention recently,[4,5] but asymmetric versions are underexplored. The few catalytic systems developed by the groups of Hu,[6a] Feng[6b] and Zhou[6c] were successfully applied in palladium-catalyzed asymmetric carbene-transfer reactions, but stagnation in the design of efficient ligands impeded development of this area. From these previous works, we saw an opportunity for realizing the direct palladium-catalyzed enantioselective functionalization of indoles by α-aryl-α-diazoacetates with the aid of a proper ligand. In this context, we report a highly efficient palladium-catalyzed method for the enantioselective C–H functionalization of indoles with an axially chiral 2,2′-bipyridine ligand. In addition, this catalytic system is also effective for asymmetric O–H-insertion reaction of phenols.

Group	[M]	R	*ee* [%]
Fox	Rh	Alkyl	79–99
Hashimoto	Rh	Alkyl	58–86
Zhou	Fe	Aryl	39–78
Davies	Rh	Aryl	< 5
This work	Pd	Aryl	up to 98

Scheme 1. Enantioselective C–H functionalization of indoles.

At the outset, we examined the catalytic performance of the palladium complex, coordinated with the classical diphosphine ligand (*R*)-Binap, in the C–H functionalization of 1,2-dimethylindole (**2a**) by benzyl 2-diazo-2-phenylacetate (**1a**; Figure 1). The reaction was complete in 0.5 hours and delivered the desired product in 82 % yield, albeit in racemic fashion. Gratifyingly, the palladium complex with bipyridines also catalyzed the reaction, and 2,2′-bipyridine, bearing electron-donating methoxy substituents at the 3,3′-positions, significantly increased the reactivity to give the product **3a** in 94 % yield after 0.5 hours. Inspired by this finding, we envisioned that a chiral electron-rich bipyridine ligand could effectively promote the asymmetric reaction.



1a **2a** **3a**

(*R*)-Binap
82% yield in 0.5 h
<1% *ee*

2,2'-bipyridine
88% yield in 16 h

3,3'-dimethoxy-2,2'-bipyridine
94% yield in 0.5 h

Figure 1. C–H functionalization of 2-methylindole with (*R*)-binap and achiral bipyridines. M.S. = molecular sieves.

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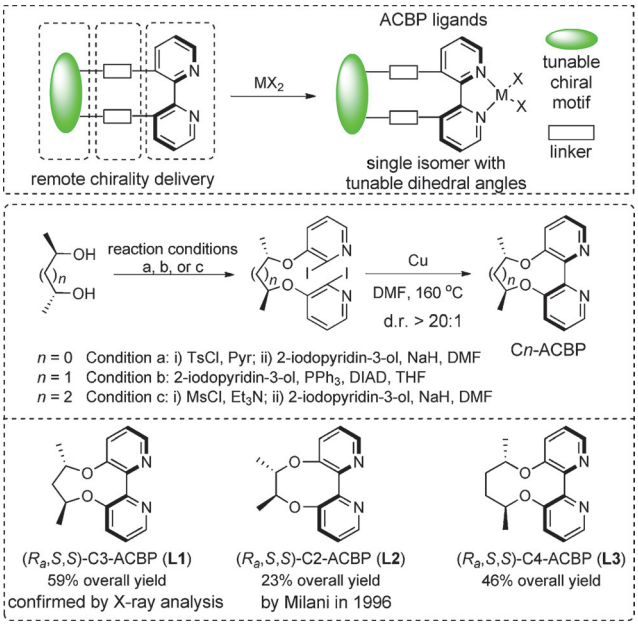
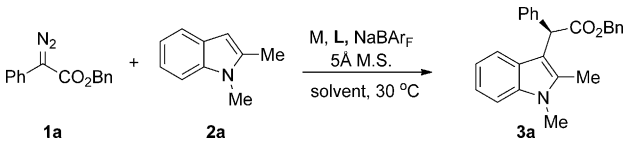


Scheme 2. Synthesis of tunable axially chiral bipyridine ligands C*n*-ACBP and palladium complex. DMF = *N*,*N*-dimethylformamide, Ts = 4-toluenesulfonyl.

Table 1: Enantioselective palladium-catalyzed C–H functionalization of indoles: Optimization of reaction conditions.[a]



Entry	M	Solvent	Ligand	Yield [%][b]	*ee* [%][c]
1	CuCl	$CHCl_3$	**L1**	88	73
2	$PdCl_2$	$CHCl_3$	**L1**	86	76
3	$[Pd(CH_3CN)_2Cl_2]$	$CHCl_3$	**L1**	86	82
4	$[Pd(PhCN)_2Cl_2]$	$CHCl_3$	**L1**	92	95
5	$[Pd(PhCN)_2Cl_2]$	CH_2Cl_2	**L1**	93	97
6	$[Pd(PhCN)_2Cl_2]$	$ClCH_2CH_2Cl$	**L1**	89	96
7	$[Pd(PhCN)_2Cl_2]$	toluene	**L1**	90	96
8[d]	$[Pd(PhCN)_2Cl_2]$	CH_2Cl_2	**L1**	61	8
9	$[Pd(PhCN)_2Cl_2]$	CH_2Cl_2	**L2**	90	86
10	$[Pd(PhCN)_2Cl_2]$	CH_2Cl_2	**L3**	92	96

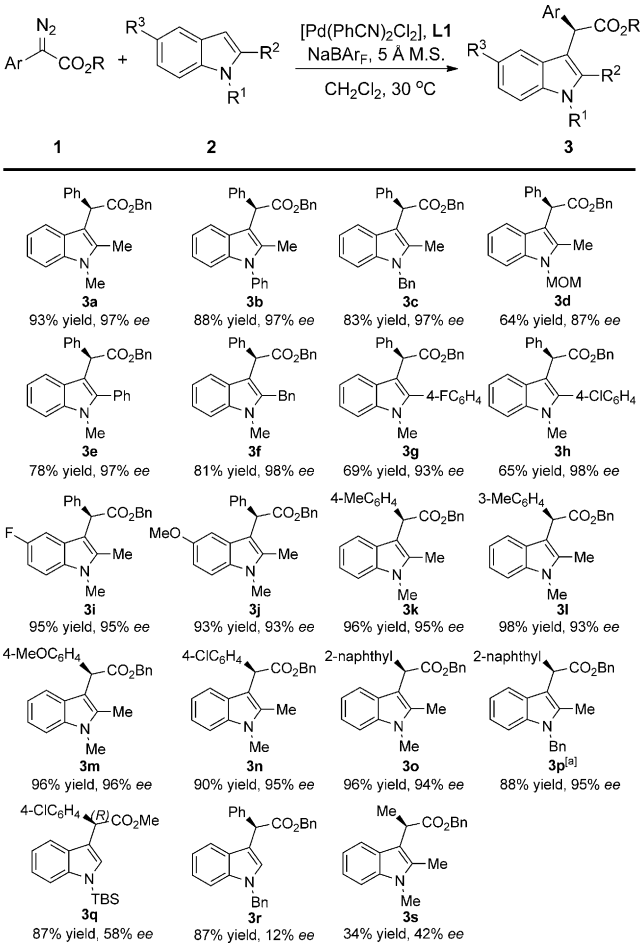
[a] Reaction conditions: **1a** (0.30 mmol), **2a** (0.45 mmol), M (5.0 mol%), **L** (5.0 mol%), $NaBAr_F$ (12.0 mol%), 5 Å M.S. (300 mg), solvent (3.0 mL), 2–19 h. [b] Yield of isolated product. [c] Determined by HPLC analysis using a chiral stationary phase. [d] Without $NaBAr_F$.

2,2′-Bipyridines and their metal complexes have found widespread applications in organic synthesis and organometallics.[7,8] Among various chiral bipyridine ligands reported in the literature, 2,2′-bipyridine ligands with axial chirality have not been well explored in asymmetric catalysis and do not deliver high enantioselectivity. In 1996, Milani and co-workers synthesized an atropisomeric bipyridine ligand, namely (−)-(*S*,*S*)-3,3′-(1,2-dimethylethylenedioxy)-2,2′-bipyridine (**L2**) by using chiral diols, as stereocontrolling elements, to induce chirality (Scheme 2), but attempts to apply it in catalytic asymmetric reactions were unsuccessful.[9,10] The low asymmetric induction is mainly attributed to the loss of the atropisomeric nature of the ligand because of its almost-planar conformation upon coordination to palladium. As is well demonstrated in the literature, tunable dihedral angles, enabled by the ligand structure, dramatically affect the chiral environment in catalytic asymmetric reactions.[11] Stimulated by the pioneering work, we synthesized two bipyridine ligands, **L1** and **L3**, starting from 2-iodopyridin-3-ol and optically active diols of various lengths. Through either a Mitsunobu reaction or S_N2 reaction, and subsequent Ullmann coupling, these ligands were obtained in moderate yields.[12] Subsequently, we started to investigate their performance in palladium-catalyzed enantioselective C–H functionalization of indoles.

Initially, we focused our attention on the establishment of the optimal reaction conditions for the C–H functionalization of **2a** using **1a**. To our gratification, by employing **L1** as a ligand, the reaction proceeded smoothly under the catalysis of $[Pd(PhCN)_2Cl_2]$ in CH_2Cl_2, thus giving the desired product with 97% *ee* (Table 1, entries 1–8). The evaluation of ligands showed that the previously reported **L2** also promoted the reaction, but because of its small dihedral angel upon chelation, 86% *ee* was obtained (entry 9). With a bigger dihedral angle, **L3** gave the desired product with 96% *ee* (entry 10). Finally, we chose **L1** as the model ligand for further investigation of the substrate scope because it is easier to access.

With the optimized reaction conditions in hand, the substrate scope was then studied and the results depicted in Scheme 3. As expected, various substrates performed very well under the standard reaction conditions. The reaction is successful for different N-protected indoles, thus providing the corresponding products in 87–97% *ee* and satisfactory yields (**3a–d**). Various 2-substituted indoles were also suitable reaction partners, thus giving the functionalized indoles in moderate to high yields and excellent enantioselectivities (**3e–h**). Regardless of the electronic properties, indoles with 5-F and 5-MeO substituents also underwent the reaction smoothly to give the corresponding products in 95% and 93% *ee*, respectively (**3i,j**). Subsequently, diazoesters bearing a variety of substituted aromatic groups were examined, and high yields (88–98%) and enantioselectivities (93–96%) could be obtained (**3k–p**). In addition, we found that substituents at the indole C2-position was crucial for achieving high enantioselectivity, and the use of 2-unsubstituted indole resulted in low to moderate *ee* values (**3q,r**). Benzyl 2-diazopropanoate reacted with 1,2-dimethylindole, albeit in a moderate 31% yield and 42% *ee* (**3s**).

The initial success of our C*n*-ACBP ligands in the enantioselective C–H functionalization of indoles encouraged us to further evaluate their practical utility. The α-aryl-α-aryloxyacetate moiety is ubiquitous in biologically active molecules, thus developing highly enantioselective catalytic asymmetric methods for preparing these important compounds is highly desirable.[13] Zhou and co-workers disclosed an elegant work by employing palladium and chiral spiro-bisoxazoline ligands for the enantioselective synthesis of α-aryl-α-diazoacetates.[6c] We decided to further evaluate these ligands in palladium-catalyzed enantioselective insertion of α-



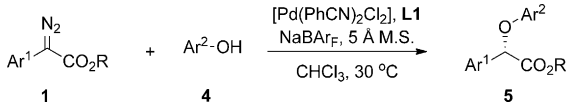
Scheme 3. Palladium-catalyzed enantioselective C–H functionalization of indoles. Reaction conditions: **1** (0.30 mmol), **2** (0.45 mmol), [Pd(PhCN)$_2$Cl$_2$] (5.0 mol%), (R_a,*S*,*S*)-C3-ACBP (**L1**; 5.0 mol%), NaBAr$_F$ (12.0 mol%), CH_2Cl_2 (3.0 mL), 5 Å M.S. (300 mg), 2–5 h. [a] **1** (1.20 mmol), **2** (1.80 mmol).

aryl-α-diazoacetates into the O–H bonds of phenols for the rapid installation of α-aryl-α-aryloxy acetates.[14]

Firstly, establishment of the optimal reaction conditions was carried out. The best result in terms of yield and enantioselectivity was obtained under the catalysis of [Pd(PhCN)$_2$Cl$_2$] and **L1** in $CHCl_3$ at 30 °C, thus giving the desired product with 90% yield and 94% *ee*. (see Table S1 in the Supporting Information for details). Evaluation of previously synthesized ligands indicated that **L2** gave a moderate enantioselectivity (50% *ee*), and when **L3** was used, the *ee* value increased to 81%. The highest *ee* value (94%) was obtained by employing **L1** as a ligand.

Having established the optimal reaction conditions for the asymmetric insertion of ethyl α-diazo-α-phenylacetate into the O–H bond of phenol, we then explored the substrate scope of this transformation (Table 2). Ethyl α-diazo-α-phenylacetate reacted with phenol smoothly to afford the target product **5a** in 90% yield and 94% *ee* (entry 1). The less sterically hindered methyl ester and more sterically hindered isopropyl ester afforded products with satisfactory yields and excellent enantioselectivities (entries 2 and 3). Impressively,

Table 2: Palladium-catalyzed enantioselective insertion of the α-aryl-α-diazoacetates **1** into O–H bonds of phenols **4**.[a]



Entry	Ar^1/R	Ar^2	Yield [%][b]	*ee* [%][c]
1	Ph/Et	Ph	90 (**5a**)	94 (+)
2	Ph/Me	Ph	86 (**5b**)	94 (+)
3	Ph/*i*Pr	Ph	80 (**5c**)	93 (+)
4	Ph/Bn	Ph	96 (**5d**)	98 (+)
5	4-MeC_6H_4/Bn	Ph	87 (**5e**)	96 (+)
6	4-ClC_6H_4/Bn	Ph	96 (**5f**)	93 (+)
7	2-naphthyl/Bn	Ph	85 (**5g**)	99 (+)
8	Ph/Bn	4-MeC_6H_4	96 (**5h**)	94 (+)
9	Ph/Bn	4-MeOC_6H_4	91 (**5i**)	98 (+)
10	Ph/Bn	4-FC_6H_4	85 (**5j**)	96 (+)
11	Ph/Bn	4-ClC_6H_4	78 (**5k**)	94 (+)
12	Ph/Bn	4-PhC_6H_4	89 (**5l**)	95 (+)
13	Ph/Bn	3-MeC_6H_4	94 (**5m**)	96 (+)
14	Ph/Bn	2-MeC_6H_4	48 (**5n**)	92 (+)
15	Ph/Bn	2-naphthyl	99 (**5o**)	98 (+)

[a] Reaction conditions: **1** (0.60 mmol), **4** (0.40 mmol), [Pd(PhCN)$_2$Cl$_2$] (5.0 mol%), (R_a,*S*,*S*)-C3-ACBP (**L1**; 5.0 mol%), NaBAr$_F$ (12.0 mol%), 5 Å M.S. (400 mg), $CHCl_3$ (4.0 mL), 5–18 h. [b] Yield of isolated product. [c] Determined by HPLC analysis using a chiral stationary phase.

the benzyl ester gave 96% yield and 98% enantioselectivity (entry 4). The success of the initial results prompted us to explore a wide variety of related substrates. Several benzyl α-aryl-α-diazoacetates were evaluated. To our delight, excellent enantioselectivities could be maintained (entries 5–7), and high enantioselectivity (up to 99% *ee*) was obtained for benzyl 2-diazo-2-(naphthalen-2-yl)acetate. All substituted phenols exhibited moderate to excellent yields and excellent enantioselectivities (entries 8–15). The electronic properties of phenols had a negligible effect on the enantioselectivities. The sterics of *ortho*-substituted phenol dramatically affected the yield, and 48% yield was obtained for *o*-cresol (entry 14). However, the enantioselectivity remained excellent (92% *ee*).

In summary, by using an axially chiral bipyridine ligand, we have successfully developed the first palladium-catalyzed enantioselective C–H functionalization of indoles by α-aryl-α-diazoacetates with up to 98% *ee*. Additionally, this reaction protocol is applicable to the enantioselective insertion of α-aryl-α-diazoacetates into the O–H bonds of phenols, thus providing the corresponding α-aryl-α-aryloxy acetates with up to 99% *ee*. This study is expected to be a stepping stone to unlocking the potential of axially chiral 2,2′-bipyridine ligands in asymmetric catalysis. Further studies, regarding the catalytic performance of C*n*-ACBP ligands in other catalytic asymmetric reactions, are underway in our group and will be reported in the near future.

Experimental Section

General procedure for palladium-catalyzed enantioselective functionalization of indoles: The powdered [Pd(PhCN)$_2$Cl$_2$] (5.8 mg, 0.015 mmol, 5.0 mol%), (R_a,*S*,*S*)-C3-ACBP (**L1**; 3.8 mg, 0.015 mmol, 5.0 mol%), NaBAr$_F$ (31.9 mg, 0.036 mmol, 12.0 mol%), and 300 mg

5 Å molecular sieves were introduced into an oven-dried Schlenk tube under nitrogen. After dichloromethane (3.0 mL) was injected into the Schlenk tube, the solution was stirred at 30 °C under nitrogen for 2 h. 1,2-Dimethylindole (**2a**; 65 mg, 0.45 mmol) and benzyl 2-diazo-2-phenylacetate (**1a**; 76 mg, 0.30 mmol) was then introduced in one portion. The resulting mixture was stirred at 30 °C until **1a** was fully consumed. After filtering and removing solvent under vacuum, the pure product was isolated by flash chromatography (petroleum ether/ethyl acetate = 30:1, v/v).

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[12] **L1** and its palladium complex [Pd(**L1**)$(OCOCF_3)_2$] were confirmed by X-ray crystallography, the dihedral angle of **L1** is 49.05° and it is reduced to 22.14° upon chelation. CCDC 1024794 and 1024795 contain the supplementary crystallographic data respectively, these data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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