



Communication

Synthesis of planar chiral isoquinolinone-fused ferrocenes through palladium-catalyzed C–H functionalization reaction



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ABSTRACT

(*S,S*)-Me-BI-DIME/Pd(0)-catalyzed enantioselective C–H functionalization of *N*-ferrocenyl *o*-bromobenzanilides has been realized, affording isoquinolinone-fused ferrocenes with up to 97% *ee*. The products can be transformed into planar chiral ferrocenyl monophosphines, which demonstrate their preliminary application.

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Compounds containing a phenanthridinone skeleton possess remarkable biological and pharmaceutical properties, such as antilymphoma, antileukemia, antitumor, antiviral and inhibitor of HIV-1 integrase, *etc.* [1]. Replacement of aryl rings by ferrocenyl moieties usually improves the properties of a given biomolecule dramatically [2]. Hence, the synthesis of planar-chiral isoquinolinone-fused ferrocenes, phenanthridinone analogues, are worth expecting for biochemists and pharmaceutical chemists.

On the other hand, planar chiral ferrocenes have been extensively utilized as privileged chiral catalyst and ligands in asymmetric catalysis (Fig. 1) [3]. Therefore, intensive efforts have been devoted to their asymmetric synthesis, and significant progress has been achieved using transition-metal-catalysts [4]. Recently, asymmetric C–H bond functionalization [5] enables the concise synthesis of planar chiral ferrocenes [6–18]. The Binap/Pd catalyzed intramolecular cyclization of ferrocenyl (*o*-bromo)aryl ketones, independently developed by You group and Gu *et al.*, enabled the elegant synthesis of planar chiral ferrocenes (Scheme 1a) [8a,8b]. Then, the synthesis

of planar chiral quinolinoferrrocenes, with moderate enantioselectivity in some cases, was realized with (*R,Sa*)-*O*-PINAP as the ligand [8c]. Soon after that, our group reported the asymmetric synthesis of these scaffolds in excellent enantioselectivity with TADDOL-derived phosphoramidite as ligand [8d]. Stereospecific synthesis of them could also be realized *via* a metallocenic radical pathway [8j]. Planar-chiral lactam-fused ferrocenes, can serve as precursors of useful planar-chiral pyridines. The planar-chiral lactam-fused ferrocenes with the nitrogen atom directly linked with ferrocenyl ring, are more attractive [16,17]. Very recently, a wonderful asymmetric oxidative annulation of twofold C–H bonds and alkynes was realized by using chiral Ni–Al bimetallic catalyst, providing such kind of planar-chiral lactam-fused ferrocenes in excellent *ee* values (Scheme 1b) [18]. Despite the significant achievement, the efficient asymmetric synthesis of the planar-chiral lactam-fused ferrocenes in a catalytic manner is still highly desirable. Inspired by the previous works on Pd(0)-catalyzed enantioselective C–H activation, we report herein the synthesis of planar-chiral isoquinolinone-fused ferrocenes *via* Pd(0)-catalyzed C–H functionalization reaction (Scheme 1c). (*S,S*)-Me-BI-DIME, *P*-chiral monophosphorus ligands developed by Tang group [19], proved to be critical, delivering the desired products with up 97% *ee*.

Readily available *N*-ferrocenyl *o*-bromobenzanilides **1a** was selected as model substrate for the optimization of reaction conditions (Table 1). However, it is very difficult to control the

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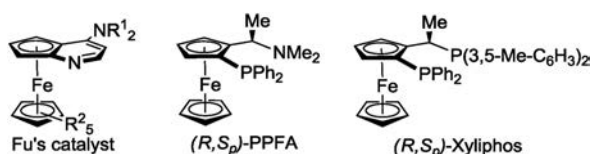
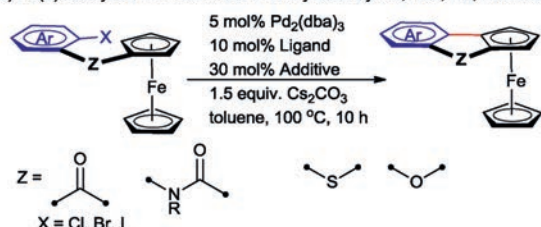


Fig. 1. Excellent catalyst and chiral ligands based on planar-chiral ferrocenes.

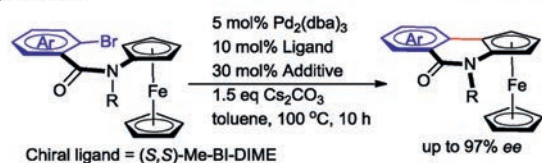
a) Pd(0)-catalyzed intramolecular C-H arylation by Gu, You, Liu, Duan *et al.*



b) Ni-Al bimetallic catalyzed oxidative annulations by Ye



c) This work



Scheme 1. Synthesis of planar chiral ferrocenes via C-H functionalization.

enantioselectivity. The catalytic systems, used in the above mentioned reactions, are not suitable for this reaction [8]. For example, the combination of TADDOL-derived phosphoramidite **L1** with $\text{Pd}_2(\text{dba})_3$ which gave excellent enantioselectivity in the synthesis of planar chiral quinilinoferrocenes [8d], afforded **2a** in just 38% yield with 57% *ee* (Table 1, entry 1) [20]. Although excellent yields were obtained by using **L2** and **L3**, the *ee* values were even poorer (Table 1, entries 2 and 3). Both H_8 -BINOL-derived phosphoramidite **L4** and BINOL-derived phosphoramidite **L5** showed very poor enantioselectivities (Table 1, entries 4 and 5). The P-chiral birayl monoposphorus ligands developed by Tang group were then evaluated in the reaction (Table 1, entries 6–13). Ligands **L6–L8** containing one P-chiral centre gave desired product in very poor *ee* (Table 1, entries 6–8). Pleasingly, both **L9** and **L10**, with an additional chiral center, gave **2a** in good to excellent yields (95%) and with excellent enantioselectivities (94%) (Table 1, entries 9 and 10). The addition of PivOH improved yield and enantioselectivity of the reaction (Table 1, entry 10 vs. 11). Although lower or higher temperature led to lower yields, the enantioselectivity was still excellent (Table 1, entries 12 and 13).

Under the optimized reaction conditions, the scope of *N*-ferrocenyl *o*-bromobenzanilides **1** was investigated and the result is listed in Scheme 2. The substrates, **1a–1d**, with different *N*-protecting groups such as Et-, Bn-, *n*Bu- and *p*-MeO- C_6H_4 - groups reacted smoothly to furnish the desired products, **2a–2d**, in good to excellent yields and with excellent enantioselectivity (94%–97% *ee*). The substrates, with substituents at the 5-position of the phenyl rings, yielded products **2e** and **2f** in good to excellent yields with excellent enantioselectivity (96% and 94% *ee*). Although substrate **1g**, with a methyl group at the 4-position of the phenyl rings, led to moderate yield, the substrates with the Cl- and F-substituents on the same positions, afforded products **2h** and **2i** in

Table 1
Optimization of reaction conditions for asymmetric transformation.^a

Entry	L	Temp. (°C)	Yield (%) ^b	<i>ee</i> (%) ^c
1	L1	100	38	57
2	L2	100	98	30
3	L3	100	95	10
4	L4	100	80	1
5	L5	100	64	7
6	L6	100	83	17
7	L7	100	35	1
8	L8	100	86	26
9	L9	100	88	91
10	L10	100	95	94
11 ^d	L10	100	77	90
12	L10	80	79	94
13	L10	110	83	95

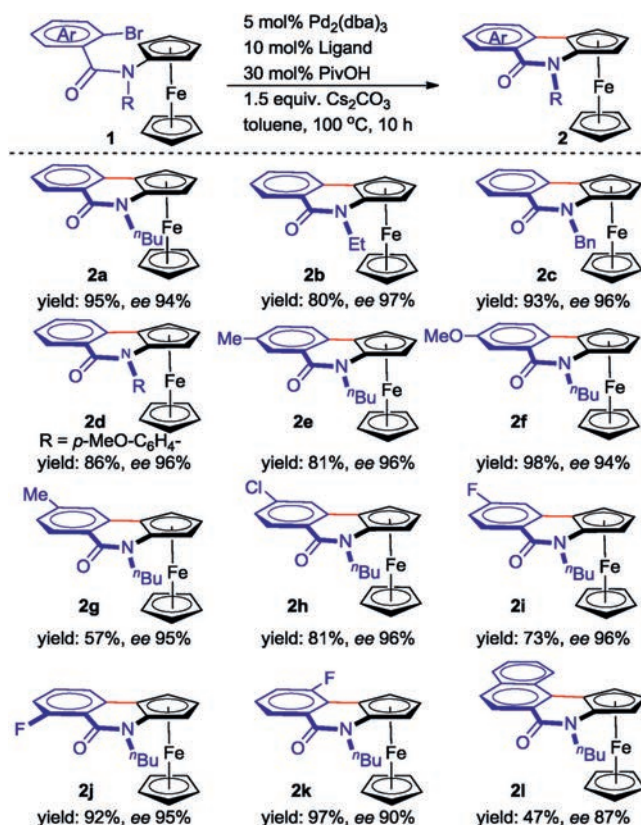
^a Reaction conditions: amide **1a** (0.10 mmol, 1.0 equiv.), $\text{Pd}_2(\text{dba})_3$ (5 mol%), **L** (10 mol%), Cs_2CO_3 (0.15 mmol, 1.5 equiv.), toluene (1 mL), under N_2 for 10 h.

^b Isolated yields.

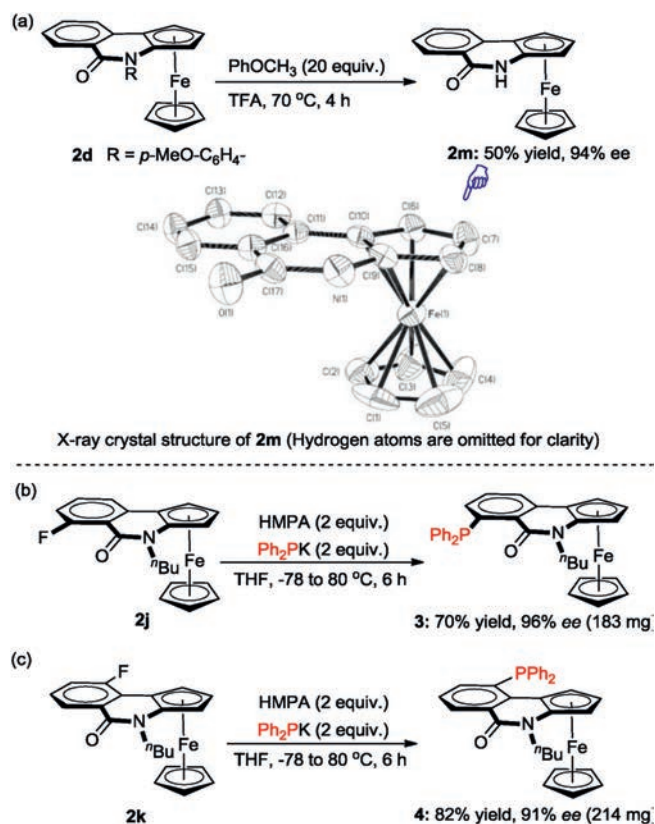
^c Determined by chiral HPLC.

^d Without pivalic acid.

good isolated yields with excellent enantioselectivity. Regardless of their steric effect, the substrates with the F-substituents reacted smoothly to give products **2i–2k** in excellent *ee* value (90%–96% *ee*). Product **2l**, with polycyclic rings, could also be obtained in good *ee*.



Scheme 2. The scope of substrates. Reaction conditions: amide **1a** (0.10 mmol, 1.0 equiv.), $\text{Pd}_2(\text{dba})_3$ (5 mol%), **L** (10 mol%), Cs_2CO_3 (0.15 mmol, 1.5 equiv.), toluene (1 mL), under N_2 for 10 h. Isolated yields determined by chiral HPLC. **2j** and **2k** are in 0.20 mmol scale.



Scheme 3. Deprotection of **2d** (a), and synthesis of planar ferrocene-based phosphines **3** (b), as well as **4** (c).

The preliminary synthetic utilization of the products were carried out, and the result was listed in Scheme 3. Treatment with 20 equiv. of PhOCH_3 in TFA at 70°C for 4 h, **2d** was transformed to **2m**, a useful synthetic building block, in 50% isolated yield with 94% ee (Scheme 3a). The absolute configuration of **2m** was assigned as S_p by X-ray crystallographic analysis (CCDC: 2024984). Planar chiral phosphines have proved to be privileged ligands in transition-metal catalysed asymmetric catalysis, and for example, (R,S_p)-xyliphos shown in Fig. 1 have been successfully utilized in industrial chemistry for the manufacture of (*S*)-metolachlor. Therefore it is highly desirable to transform the products to useful planar chiral phosphines. To our delight, **2j** and **2k** worked well with Ph_2PK in the presence of HMPA, generating planar ferrocene-based phosphines **3** and **4** in good yields without any erosion in enantioselectivity.

In conclusion, an efficient and highly enantioselective synthesis of planar chiral isoquinolinone-fused ferrocenes has been realized via palladium-catalyzed C–H functionalization reaction under mild condition. *P*-chiral biaryl monophosphorus ligand, (*S,S*)-Me-BI-DIME, is crucial for the enantioselectivity. Moreover, the chiral products with F-substituent could be transformed to planar ferrocene-based phosphines in one step. Further applications of the method are currently underway in our laboratory.

Declaration of competing interest

The authors report no declarations of interest.

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