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Enantioselective Synthesis of Planar Chiral Ferrocenes via Pd(0)-Catalyzed Intramolecular Direct C−H Bond Arylation

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Supporting Information

ABSTRACT: A highly efficient synthesis of planar chiral ferrocenes by enantioselective Pd(0)-catalyzed direct C−H arylation from readily available starting materials under mild reaction conditions was developed (up to 99% yield, 99% ee). The products can be easily transformed to the highly efficient planar ferrocene ligands, which have demonstrated high efficiency in Pd-catalyzed asymmetric allylic alkylation and amination reactions.

Ferrocene now serves as a widely applicable organometallic scaffold for the preparation of functional molecules in catalysis, material science, and, more recently, biomedicinal chemistry.[1] Particularly, ferrocenes with planar chirality have been widely employed as ligands or catalysts in asymmetric catalysis.[2] Some of them have found industrial applications in the production of pharmaceuticals and agrochemicals (Josiphos and PPFA, Figure 1). Therefore, considerable efforts have been

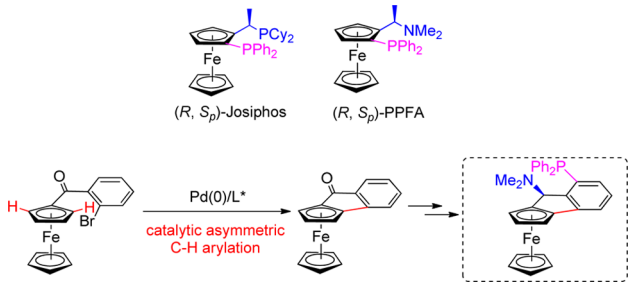

Figure 1. Chiral ferrocene ligands and newly designed enantioselective C−H arylation.

devoted to the synthesis of planar chiral ferrocenes.[3,4] In this regard, the methods employed extensively involve diastereoselective directed *ortho*-metalation (DoM),[5] enantioselective DoM,[6] and resolution.[7] Although these approaches have been well developed and widely applied, in most cases preinstalled chiral auxiliaries and external stoichiometric chiral bases have been required.

Recently, Ogasawara and co-workers[8] reported an elegant method to prepare planar chiral ferrocenes through ring-closing metathesis reactions. We developed a facile introduction of planar chirality into the ferrocene backbone via enantioselective C−H functionalization.[9,10] Employing a similar strategy, Cui, Wu, and their co-workers[11] reported the synthesis of planar chiral ferrocenes via Pd-catalyzed oxidative Heck reaction. In both cases, the required oxidative conditions would cause the decomposition of ferrocene, leading to undesired side products. Aside from these studies, the catalytic enantioselective synthesis of planar chiral ferrocenes remains sporadic. In the light of their wide application in both academia and industry mentioned above, development of efficient syntheses of planar chiral ferrocenes under mild reaction conditions is extremely desirable. We envisioned that Pd(0)-catalyzed intramolecular C−H arylation may be an effective way to synthesize planar chiral ferrocenes (Figure 1). Particularly, eliminating external oxidant would avoid the side products due to the oxidation of ferrocene. In this Communication, we report such a direct access to enantiopure planar chiral ferrocene derivatives via Pd(0)-catalyzed intramolecular C−H arylation.

o-Bromobenzoylferrocene **2a**, readily prepared from ferrocene via Friedel−Crafts acylation, was chosen as the model substrate. In the presence of 5 mol % of $Pd(OAc)_2$ and 5.5 mol % of (R_a)-BINAP, gratifyingly, our preliminary attempt at 80 °C afforded the arylative product **3a** in 99% yield and 95% ee (Table 1, entry 1). Increasing the loading of ligand to 10 mol % gave even higher enantioselectivity (98% ee, Table 1, entry 2). By lowering the temperature to 60 °C, the enantioselectivity could be further improved to 99% ee without affecting the yield (99% yield, Table 1, entry 3). However, the reaction at room temperature did not afford any desired product, even after 24 h. Next, different chiral ligands were systematically examined. As shown in Table 1, the monophosphine ligand **L2** could also be used to catalyze the reaction with moderate ee but low conversion. The phosphoramidite ligands **L3**−**L5** had no catalytic activity (Table 1, entries 7−9). As expected, the reactions with the diphosphine ligands **L6** and **L7** also proceeded in excellent yields and enantioselectivity (>99% ee, Table 1, entries 10 and 11). Given its relatively low cost and ready availability, (R_a)-BINAP was chosen for further studies. Screening of bases, acids, and solvents led to the following optimal reaction conditions: 2.5 mol % of $Pd(OAc)_2$, 5.0 mol % of (R_a)-BINAP, 30 mol % of pivalic acid, and 1.5 equiv of Cs_2CO_3 in *p*-xylene at 60 °C (see the Supporting Information for details).

Under the above optimized reaction conditions, the substrate scope was then explored. As summarized in Table 2, various substituents on the different positions of the phenyl ring (4-Me, 5-Me, 6-Me, 7-Me, 6-MeO, 6-F, 6-Cl), regardless of their electronic nature, were well tolerated. Their corresponding

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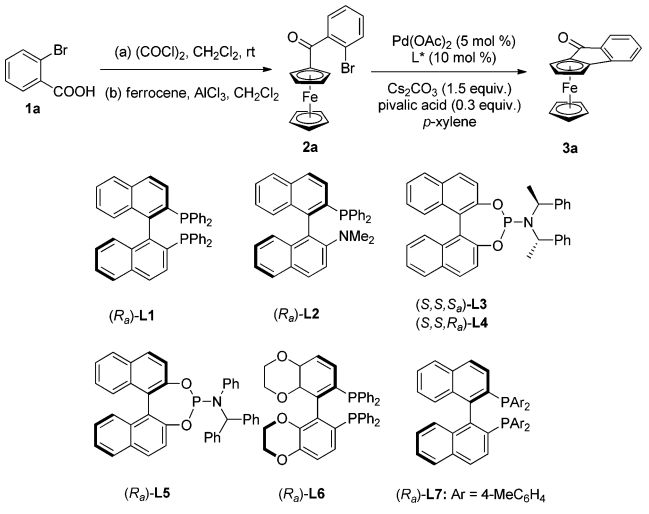
Table 1. Optimization of C−H Arylation[a]



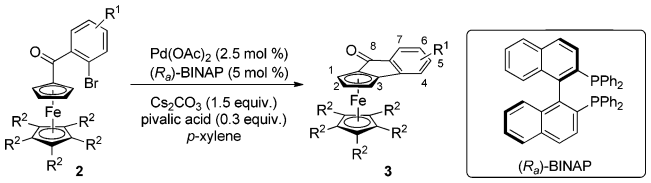
entry	ligand	temp (°C)	time (h)	yield (%)[b]	ee (%)[c]
1[d]	**L1**	80	10	99	95
2	**L1**	80	10	99	98
3	**L1**	60	18	99	99
4	**L1**	rt	24	tr	nd
5	**L2**	60	18	21	53
6[e]	**L2**	60	18	26	55
7	**L3**	60	18	tr	nd
8	**L4**	60	18	tr	nd
9	**L5**	60	18	tr	nd
10	**L6**	60	22	99	>99
11	**L7**	60	22	87	>99

[a]Reaction conditions: **2a** (0.2 mmol), $Pd(OAc)_2$ (5 mol %), ligand (10 mol %), Cs_2CO_3 (1.5 equiv), pivalic acid (0.3 equiv) in *p*-xylene (1.5 mL) unless noted otherwise. [b]Isolated yield (tr = trace). [c]Determined by HPLC analysis (nd = not detected). [d]5.5 mol % **L1** was used. [e]With 20 mol % of ligand.

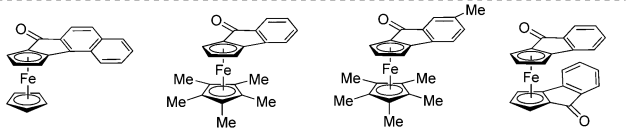
planar chiral ferrocenyl products were obtained in excellent yields and enantioselectivity (95−99% yield, 98−99% ee, Table 2). The reaction of substrate **2i**, bearing a naphthyl substituent, proceeded smoothly to afford the desired product **3i** in 82% yield and 98% ee. Notably, ferrocenes possessing a pentamethyl Cp ring, which could not be tolerated previously,[9a] were suitable substrates under the same conditions, giving the arylative products **3j** and **3k** in excellent yields and enantiocontrol (96% yield, 99% ee and 91% yield, 99% ee, respectively). Interestingly, introduction of an aryl bromide on each Cp ring was also tolerated for the double C−H arylation process: C_2-symmetric planar chiral ferrocene **3l** was obtained in 97% yield and >99% ee. The stereochemistry of the products was confirmed unambiguously by X-ray crystallographic analysis of a crystal of enantiopure **3a**. The absolute configuration was assigned as R_p (see the Supporting Information for details).

To test the practicality of the methodology, a gram-scale reaction was carried out. The intramolecular arylation of **2a** on a 4.0 mmol scale gave the desired product in 99% yield and 97% ee without any erosion on both yield and enantioselectivity (Scheme 1). Furthermore, when the catalyst loading was reduced to 0.5 mol %, the arylative product **3a** was obtained in a quantitative yield and excellent ee (99% yield, 96% ee).

Table 2. Pd(0)-Catalyzed Enantioselective Synthesis of Planar Chiral Ferrocenes[a]



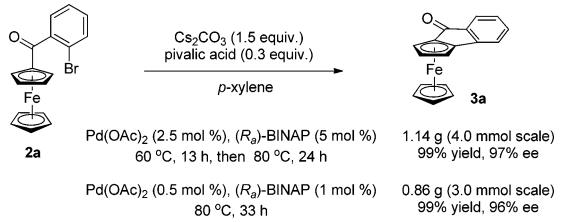
entry	R^1, R^2 (**3**)	temp (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	H, H (**3a**)	60	24	99	98
2	4-Me, H (**3b**)	80	35	95	98
3	5-Me, H (**3c**)	60	24	99	98
4	6-Me, H (**3d**)	60	24	99	99
5	7-Me, H (**3e**)	80	24	98	99
6	6-MeO, H (**3f**)	60	19	99	99
7	6-F, H (**3g**)	80	18	99	98
8	6-Cl, H (**3h**)	60	42	97	99



3i 35h, 60 °C, 82% yield, 98% ee
3j 65 h, 80 °C, 96% yield, 99% ee
3k 116 h, 80 °C, 91% yield, 99% ee
3l 53 h, 80 °C, 97% yield, >99% ee

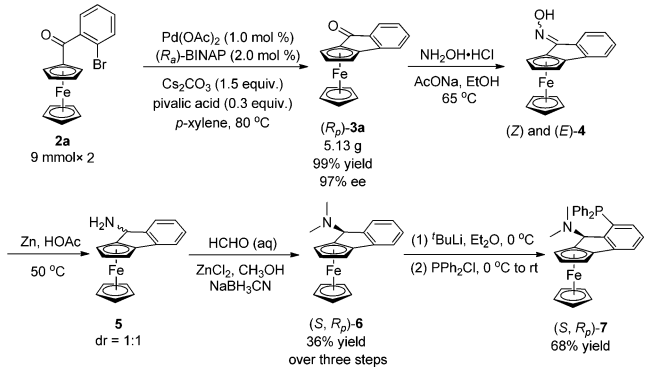
[a]Reaction conditions: **2a** (0.3 mmol), $Pd(OAc)_2$ (2.5 mol %), (R_a)-BINAP (5.0 mol %), Cs_2CO_3 (1.5 equiv), pivalic acid (0.3 equiv) in *p*-xylene (1.5 mL) at 60 or 80 °C. [b]Isolated yield. [c]Determined by HPLC analysis.

Scheme 1. Gram-Scale Synthesis of 3a



As a further demonstration of the utility of the current methodology, we developed an efficient synthesis of planar chiral *P,N* ligand **7**, in which planar chirality was previously introduced by the D*o*M strategy.[12] As shown in Scheme 2, ferrocene **6** was readily prepared from arylative product **3a** through oximation, reduction (dr = 1:1), and subsequent

Scheme 2. Synthesis of Planar Chiral *P,N* Ligand 7



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reductive amination in 36% yield over three steps. The two diastereoisomers of **6** could be easily separated by silica gel column chromatography. The chiral *P*,*N* ligand **7** was accomplished by lithiation of (S, R_p)-**6** and subsequent trapping with diphenylphosphanyl chloride in 68% yield. Ligand **7** has been demonstrated to be highly efficient in Pd-catalyzed asymmetric allylic alkylation and amination reactions.[12]

In summary, we have developed a highly efficient synthesis of planar chiral ferrocenes by enantioselective Pd(0)-catalyzed direct C−H arylation from readily available starting materials under mild reaction conditions. Compared with the previous oxidative C−H arylation,[9a] such an overall redox-neutral process (Pd^0/Pd^{II} catalysis) does not require an external stoichiometric oxidant, which avoids ferrocenium generation and is also crucial for compatibility with various commercially available chiral phosphine ligands. It is noteworthy that a straightforward transformation of the products provides a concise access to the highly efficient planar ferrocene ligands. Synthesis of ligands and catalysts from these enantiopure ferrocenes and development of new catalytic systems are currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analysis data for all new compounds. 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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