Communication

Enantioselective Synthesis of Planar Chiral Ferrocenes via Palladium-catalyzed Direct Coupling with Aryl Boronic Acids

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Enantioselective Synthesis of Planar Chiral Ferrocenes via Palladium-catalyzed Direct Coupling with Aryl Boronic Acids

De-Wei Gao, Yan-Chao Shi, Qing Gu,* Zheng-Le Zhao, and Shu-Li You*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, P. R. of China

Supporting Information Placeholder

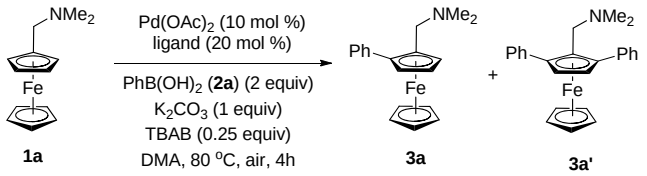
ABSTRACT: Enantioselective Pd(II)-catalyzed direct coupling of aminomethyl ferrocene derivatives with boronic acids was realized. With commercially available Boc-L-Val-OH as a ligand, planar chiral ferrocenes could be synthesized in 14-81% yields with up to 99% ee under mild conditions.

Chiral ferrocenes are of great interest in the fields of asymmetric catalysis, materials science, biomedical research, etc.[1] Particularly, ferrocenes bearing planar chirality, in some cases with additional central chirality, have been demonstrated highly efficient ligands or catalysts in asymmetric catalysis.[2] Consequently, the development of methods to introduce planar chirality into ferrocene backbone has attracted intense attention. To date, the most widely used strategy is diastereoselective directed *ortho*-metalation (DoM) induced by various chiral auxiliaries (or chiral directing groups), and in this approach a central chirality in general is required to be pre-installed.[3] Notably, Snieckus et al developed an enantioselective DoM of ferrocene derivatives with an external chiral base such as (-)-sparteine, which provides a straightforward route to ferrocenes with only planar chirality.[4] Recently, Ogasawara et al reported an elegant method to synthesize planar chiral ferrocenes through ring-closing metathesis reactions.[5] However, the catalytic enantioselective synthesis of planar chiral ferrocenes remains rare.[6] Developing such a process with readily available starting materials and catalysts is challenging but highly desirable.

Palladium-catalyzed direct functionalization of inert C-H bonds has witnessed significant progress during the past decade.[7] Despite the continuous efforts, catalytic enantioselective C-H activation as a highly challenging topic progressed rather slowly.[8] Breakthroughs recently have been achieved by Yu and coworkers[9] who discovered chiral monoprotected amino acids as efficient ligands to enable enantioselective C-H activation of series of prochiral substrates. Inspired by these results, we recently explored the enantioselective synthesis of planar chiral ferrocenes as our ongoing program towards direct functionalization of ferrocenes.[10-11] The commercially available amino acid derivatives were found to be highly efficient ligands for Pd-catalyzed direct functionalization of ferrocene with boronic acids. The conditions developed tend to be mild, general and practical for the synthesis of enantiopure planar chiral ferrocenes. In this paper, we report such a highly enantioselective synthesis of planar chiral ferrocenes *via* Pd-catalyzed C-H bond activation process.

We began our studies by using dimethylaminomethyl ferrocene (**1a**) as a model substrate. Pd-catalyzed direct arylation of **1a** with phenylboronic acid[12] was then carried out in the presence of 10 mol % $Pd(OAc)_2$, 20 mol % Boc-L-Val-OH and 1 equiv K_2CO_3 in DMA at 80 ℃ under air. To our great delight, the reaction proceeded smoothly to afford the desired product **3a** in 58% yield and 97% ee along with trace amount of diarylation product **3a'** (entry 1, Table 1). By adding 25 mol % TBAB (tetrabutyl ammonium bromide) as an additive, the yield of product **3a** could be further improved to 74% without affecting the enantioselectivity (98% ee, entry 2, Table 1). Next, commercially available *N*-Boc protected L-amino acids as ligands were systematically examined. The results are summarized in Table 1. The reactions all gave the desired product in yields ranging from 48% to 75% and excellent ee values ranging from 81% to 98% (entries 2-10, Table 1). Boc-L-Val-OH and Boc-L-Tle-OH proved to be the most efficient chiral ligands in terms of enantioselectivity and reactivity, giving the desired product in 74-75% yield and 98% ee (entries 2 and 8, Table 1). Boc-L-Val-OH was chosen for further studies given its cheapness. The protecting groups on the nitrogen of L-valine were found to have dramatic impact on the reactivity and enantioselectivity (Ac: 60% yield, 88% ee; Cbz: 52% yield, 96% ee; Fmoc: 19% yield; entries 11-13, Table 1). Lowering the reaction temperature to 60 ℃ improved the yield slightly (79% yield, entry 14, Table 1). Notably, there is a moderate kinetic resolution for the formation of bisphenylation product **3a'**. Along with the reaction time, both the ratio of bisphenylation byproduct **3a'** and the ee of **3a** increased slightly (for details, see the SI). Further screening other reaction parameters including oxidant, base, solvent, catalyst loading and the amount of phenyl boronic acid did not improve the results (for details, see the SI). Thus the optimized conditions were obtained as the following: 10 mol % $Pd(OAc)_2$, 20 mol % Boc-L-Val-OH, 2 equiv of boronic acid, 1 equiv of K_2CO_3 and 25 mol % TBAB in DMA at 60 ℃ under air (entry 14, Table 1).

Table 1. Screening protected amino acids [a]

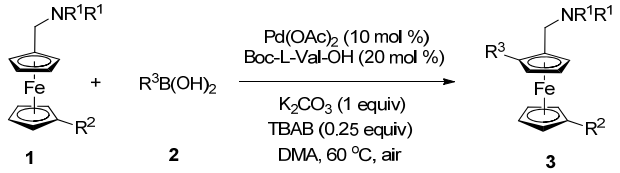


Entry	Ligand	3a:3a'[b]	Yield (%)[c]	Ee (%)[d]
1[e]	Boc-L-Val-OH	42:1	58	97
2	Boc-L-Val-OH	8.3:1	74	98
3	Boc-L-Phe-OH	8.7:1	71	98
4	Boc-L-Abu-OH	10:1	64	94
5	Boc-L-Ala-OH	4.2:1	61	92
6	Boc-L-Leu-OH	20:1	51	96
7	Boc-L-Ile-OH	9.5:1	70	97
8	Boc-L-Tle-OH	9:1	75	98
9	Boc-L-Nva-OH	6.4:1	69	96
10	Boc-L-Phg-OH	6.5:1	48	81
11	Ac-L-Val-OH	10:1	60	88
12	Cbz-L-Val-OH	25:1	52	96
13	Fmoc-L-Val-OH	-	19[b]	-
14[f]	**Boc-L-Val-OH**	**20:1**	**79**	**98**
15[g]	Boc-L-Val-OH	50:1	59	97

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $Pd(OAc)_2$ (10 mol %), ligand (20 mol %), K_2CO_3 (1 equiv), TBAB (0.25 equiv) in DMA at 80 ℃ under air. [b] Determined by ^1H NMR with CH_2Br_2 as an internal standard. [c] Isolated yield. [d] Determined by HPLC analysis. [e] Without TBAB. [f] At 60 ℃. [g] At 40 ℃.

Under the above optimized reaction conditions, various aminomethyl ferrocene derivatives and boronic acids were examined to test the generality of the current reaction. The results are summarized in Table 2. Various substituted aryl boronic acids bearing either an electron-donating group or an electron-withdrawing group were well tolerated and led to their corresponding products in good yields and excellent ee values (55-81% yields, 94-99% ee, entries 2-3, 5, 7-10, Table 1) except for *ortho*-methyl phenylboronic acid **2b** (33% yield, 94% ee, entry 4, Table 2). Notably, the reaction with 2-naphthyl boronic acid also led to product **3f** in 75% yield and 96% ee (entry 6, Table 2). The reaction of alkyl boronic acid required higher temperature in prolonged reaction time, giving the desired product in a moderate yield (entry 11). In addition, the reaction was general for ferrocenes with different alkyl group on nitrogen atom (NEt_2, 67% yield, 90% ee; N-$(CH_2)_4$-, 71% yield, 98% ee; entries 12-13, Table 2). Introduction of a substituent on another Cp ring could also be tolerated. For instance, when 1-aminomethyl 1'-bromo ferrocene (**1d**) was used, the arylation product **3n** was obtained in 69% yield and 97% ee (entry 14, Table 2). The wide tolerance of substituents provided the opportunity for further transformation of the products into useful ligands or catalysts.

Table 2. Enantioselective synthesis of planar chiral ferrocene *via* C-H activation [a]

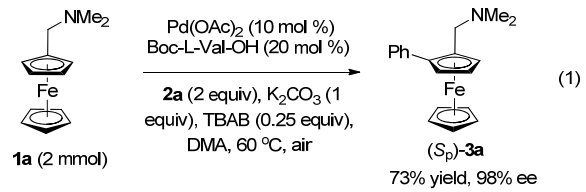


1a R^1 = Me, R^2 = H; **1b** R^1 = Et, R^2 = H
1c R^1 = -$(CH_2)_4$-, R^2 = H; **1d** R^1 = Me, R^2 = Br

Entry	1	R^3 (2)	Time (h)	Yield (%)[b]	Ee(%)[c]
1	**1a**	C_6H_5 (**2a**)	10	79 (**3a**)	98
2	**1a**	4-MeC_6H_4 (**2b**)	10	70 (**3b**)	97
3	**1a**	3-MeC_6H_4 (**2c**)	10	81 (**3c**)	99
4	**1a**	2-MeC_6H_4 (**2d**)	75	33 (**3d**)	94
5	**1a**	4-$MeOC_6H_4$ (**2e**)	10	59 (**3e**)	96
6	**1a**	2-naphthyl (**2f**)	3.5	75 (**3f**)	96
7	**1a**	4-ClC_6H_4 (**2g**)	10	72 (**3g**)	97
8	**1a**	4-FC_6H_4 (**2h**)	10	55 (**3h**)	97
9	**1a**	4-$CF_3C_6H_4$ (**2i**)	10	61 (**3i**)	94
10	**1a**	4-$EtOCOC_6H_4$ (**2j**)	8	72 (**3j**)	95
11[d]	**1a**	Me (**2k**)	24	14 (**3k**)	ND
12	**1b**	C_6H_5 (**2a**)	22	67 (**3l**)	90
13	**1c**	C_6H_5 (**2a**)	10	71 (**3m**)	98
14	**1d**	C_6H_5 (**2a**)	16	69 (**3n**)	97

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), $Pd(OAc)_2$ (10 mol %), Boc-L-valine (20 mol %), K_2CO_3 (1 equiv), TBAB (0.25 equiv) in DMA at 60 ℃ under air. [b] Isolated yield. [c] Determined by HPLC analysis. [d] At 90 ℃.

The absolute configuration of the product **3a** was assigned as (S_p) by comparing the optical rotation of the same compound, which was transformed from either **3a** or a compound reported in the literature with known absolute configuration (for details, see the SI).

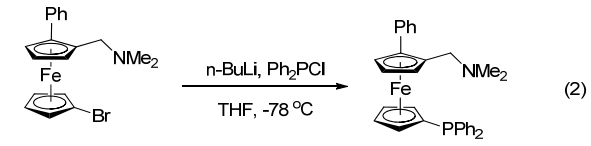


(1)

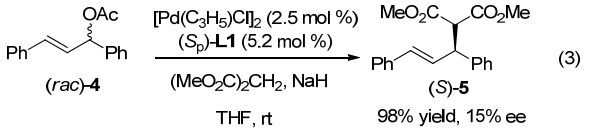
To test the practicality of the methodology, a relatively large scale reaction was carried out. The arylation of ferrocene **1a** in a 2 mmol scale with phenylboronic acid (**2a**) afforded the desired product [(S_p)-**3a**] without notable erosions in both yield and enantioselectiv-

ity (73% yield, 98% ee, eq 1). However, addition of phenylboronic acid in five times (every two hours) has a beneficial effect for achieving a higher yield comparing with one-time addition.

As a further demonstration of the utility of our methodology, planar chiral *P*, *N*-ligand **L1** was prepared from product **3n** obtained in the current study. Starting from **3n** (96% ee), lithiation with n-BuLi followed by quenching with Ph_2PCl afforded **L1** in 68% yield and 92% ee (eq 2). A preliminary examination of **L1** (92% ee) in palladium-catalyzed allylic alkylation reaction disclosed that this type of *P*, *N*-ligand is highly efficient although the enantioselectivity needs further improvement (98% yield, 15% ee, eq 3).



(S_p)-**3n**, 96% ee (S_p)-**L1**, 68% yield, 92% ee (2)



(*rac*)-**4** (S)-**5** 98% yield, 15% ee (3)

In summary, we have developed an asymmetric Pd-catalyzed direct functionalization of aminomethyl ferrocene derivatives with boronic acids. The new methodology provides a highly enantioselective synthesis of planar chiral ferrocenes from readily available starting materials under mild reaction conditions. The requirement of commercially available and cheap *N*-Boc-protected amino acids as efficient ligands and air as oxidant makes the current access to enantiopure ferrocene compounds potentially practical. Further mechanistic investigations, application of these enantiopure ferrocenes and development of more efficient catalytic system are currently underway 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.

AUTHOR INFORMATION

Corresponding Author

qinggu@sioc.ac.cn or slyou@sioc.ac.cn

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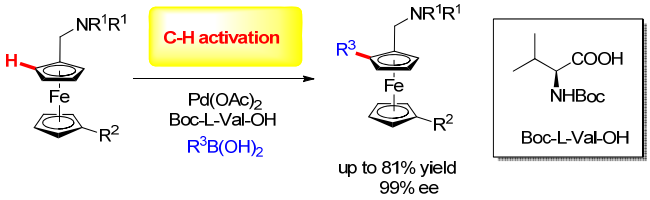
NR1R1
H
Fe
R2
C-H activation
Pd(OAc)2
Boc-L-Val-OH
R3B(OH)2
NR1R1
R3
Fe
R2
up to 81% yield
99% ee
COOH
NHBoc
Boc-L-Val-OH