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Asymmetric Synthesis of Planar Chiral Ferrocenes by Enantioselective Intramolecular C−H Arylation of *N*-(2-Haloaryl)ferrocenecarboxamides

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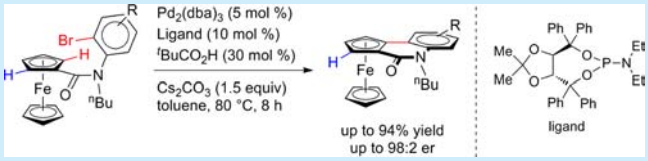
Supporting Information

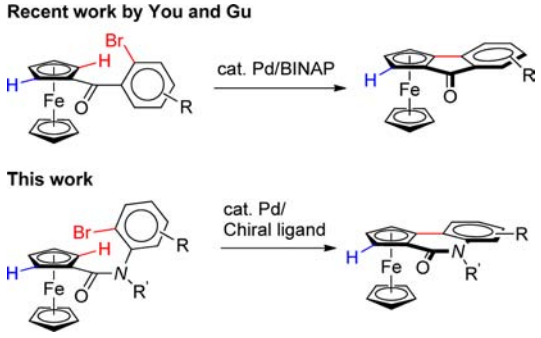
ABSTRACT: The palladium-catalyzed intramolecular C−H arylation reaction of *N*-(2-bromoaryl)ferrocenecarboxamides furnishes planar chiral ferrocene derivatives. TADDOL-derived phosphoramide ligands induce enantioselectivities ranging from 91:9 to 98:2 er.



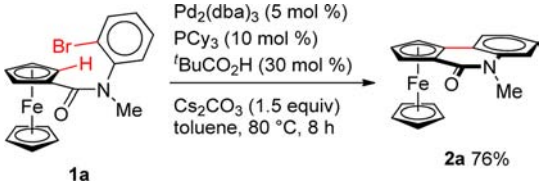
Ferrocene possesses unique structural and electronic characters, and its derivatives have found a broad range of applications in organic synthesis,[1] materials science,[2] and medicinal chemistry.[3] Particularly attractive are those having a planar chirality, which is the core structural element contained in a number of chiral ligands and catalysts inducing high enantioselectivities. The usefulness of planar chiral ferrocene derivatives has made their stereoselective synthesis the subject of intensive research.[4]

Stereoselective metalation of enantiotopic[5] or diastereotopic[6] C−H bonds on the cyclopentadienyl ring with a stoichiometric amount of organolithium agents followed by a reaction with electrophiles is one of the typical methods to fix planar chirality in the ferrocene skeletons. More step- and atom-economical pathways became accessible with the advent of transition metal-based methods including asymmetric C−H activation chemistry[7,8] like the direct arylation of ferrocenylmethylamines with a chiral palladium complex[9] and the alkylation of pyridine-containing ferrocenes with a chiral iridium complex.[10] Palladium-catalyzed intramolecular C−H arylation reactions have been recently applied to the asymmetric synthesis of planar chiral indenone-fused ferrocenes (Scheme 1, top).[11]

Scheme 1. Intramolecular Asymmetric C−H Arylation Forming Planar Chiral Ferrocenes



Scheme 2. Intramolecular C−H Arylation Reaction of 1a



Scheme 3. Proposed Mechanism

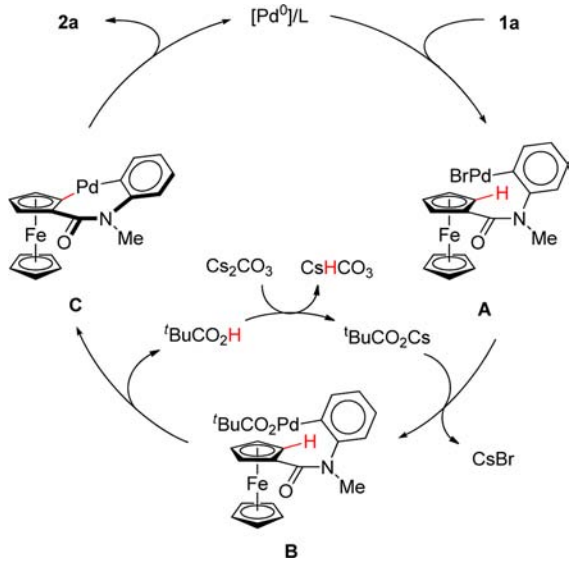


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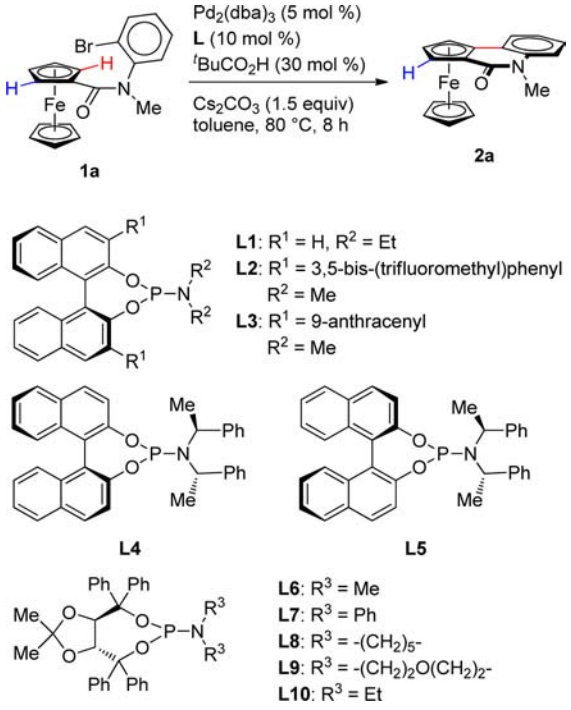
Table 1. Screening of Ligands[a]



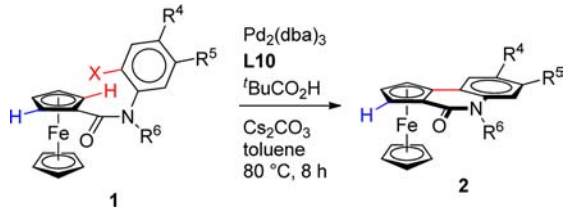
entry	ligand	yield[b] (%)	er[c] (%)
1	(*R*)-BINAP	44	53:47
2	(*R*)-SEGPHOS	36	50:50
3	(*R*)-H_8-BINAP	78	76:24
4	(*R,R*)-DIOP	56	60:40
5	(*R,S*)-PPFA	53	53:47
6	**L1**	54	58:42
7	**L2**	73	55:45
8	**L3**	51	53:47
9	**L4**	45	55:45
10	**L5**	34	52:48
11	**L6**	81	91:9
12	**L7**	34	62:38
13	**L8**	76	87:13
14	**L9**	52	80:20
15	**L10**	84	92:8

[a]Reaction conditions: amide **1a** (0.05 mmol, 1.0 equiv), $Pd_2(dba)_3$ (5 mol %), **L** (10 mol %), Cs_2CO_3 (1.5 equiv), toluene (1 mL), 80 °C, 8 h. [b]Isolated yield. [c]Determined by chiral HPLC.

Preparation of optically active *N*-heterocycle-fused ferrocenes, however, necessitates a stoichiometric amount of a chiral auxiliary[12] or resolution of racemic compounds.[13] Herein, we report asymmetric construction of quinolin-2(1*H*)-one-fused ferrocenes by the palladium-catalyzed enantioselective intramolecular C−H arylation reaction of *N*-(2-haloaryl)-ferrocenecarboxamides (Scheme 1, bottom).[14] TADDOL-derived phosphoramidite ligands induced the enantioselectivity ranging from 91:9 to 98:2 er.

The achiral substrate *N*-(2-bromophenyl)-*N*-methylferrocenecarboxamide **1a** was readily prepared by acylation of 2-bromoaniline with ferrocenoyl chloride and subsequent *N*-methylation. When **1a** was treated with $Pd_2(dba)_3$ (5 mol %), PCy_3 (10 mol %), Cs_2CO_3 (1.5 equiv), and pivalic acid (30 mol %) in toluene at 80 °C, the C−H bond of the cyclopentadienyl ring was cleaved and arylated intramolecularly to afford quinolinone-fused ferrocene **2a** in 76% yield (Scheme 2).[15]

Table 2. Substrate Scope[a]



entry	R^4	R^5	R^6	X	product	yield[b] (%)	er[c] (%)
1	H	H	Me	I	**2a**	80	91:9
2	H	H	Et	Br	**2b**	84	95:5
3	H	H	^{n}Bu	Br	**2c**	80	95:5
4	H	H	Bn	Br	**2d**	83	93:7
5	H	Me	^{n}Bu	Br	**2e**	81	95:5
6	^{t}Bu	H	^{n}Bu	Br	**2f**	70	91:9
7	Me	H	^{n}Bu	Br	**2g**	87	96:4
8	Ph	H	^{n}Bu	Br	**2h**	79	95:5
9	OMe	H	^{n}Bu	Br	**2i**	82	95:5
10	F	H	^{n}Bu	Br	**2j**	85	98:2
11	Cl	H	^{n}Bu	Br	**2k**	91	97:3

[a]Reaction conditions: amide **1** (0.05 mmol, 1.0 equiv), $Pd_2(dba)_3$ (5 mol %), **L10** (10 mol %), Cs_2CO_3 (1.5 equiv), PivOH (30 mol %), toluene (1 mL), 80 °C, 8 h. [b]Isolated yield. [c]Determined by chiral HPLC.

A plausible mechanistic pathway for the formation of **2a** is depicted in Scheme 3. Initially, oxidative addition of the C(sp^2)−Br bond onto palladium(0) affords arylpalladium bromide **A**. A pivalate anion replaces the bromide ligand on palladium to furnish palladium pivalate **B**. Then, a C−H bond on the cyclopentadienyl ring is cleaved to generate the di(organyl)palladium species **C**.[16] Reductive elimination ensues to produce quinolin-2(1*H*)-one **2a** possessing planar chirality along with regeneration of the palladium(0) species.

Next examined were various types of chiral ligands to induce enantioselectivity (Table 1). (*R*)-BINAP, which is the best ligand for the enantioselective synthesis of indenone-fused ferrocenes,[11] gave **2a** in 44% yield with 53:47 er (entry 1). Although H_8-BINAP showed better selectivity (78% yield with 76:24 er), no improvement was observed with other bidentate ligands like (*R,R*)-DIOP, (*R*)-SEGPHOS, and (*R,S*)-PPFA (entries 2−5). Monodentate phosphoramidite ligands were also examined. BINOL-derived phosphoamidites **L1**−**5** showed low enantioselectivities (entries 6−10). TADDOL-derived ones (**L6**−**10**) generally afforded better results in terms of both yield and enantioselectivity. Whereas **2a** was obtained in 81% yield with 91:9 er with **L6** (R^3 = Me) (entry 11), the optimal result (84% yield with 92:8 er) was obtained with **L10** (R^3 = Et) (entry 15).

The substrate scope was studied under the optimized reaction conditions (Table 2). Although aryl chloride (X = Cl) failed to participate in the reaction, aryl iodide (X = I) gave a result similar to that obtained with aryl bromide (entry 1). Whereas no reaction occurred with unprotected amide (R^6 = H), the use of bulkier *N*-protecting groups improved the enantioselectivity (entries 2 and 3). A removable *N*-benzyl group was also suitable (entry 4). The substrates derived from substituted 2-bromoanilines including 2-bromo-4-chloroaniline successfully took part in the reaction with the enantioselectivities ranging from 91:9 to 98:2 er (entries 5−11).[17,18] The

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absolute configuration of **2j** was assigned as S_p by X-ray crystallographic analysis.[19]

In conclusion, we have developed a concise way to synthesize quinolin-2(1*H*)-ones equipped with a planar chiral ferrocene moiety in an enantioselective manner, providing an example of asymmetric synthesis of ferrocene derivatives fused with nitrogen-containing heterocycles via enantioselective C−H activation.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data for new compounds, and details of X-ray crystallographic analysis for **2j**. 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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(14) During preparation of this manuscript, an analogous palladium-catalyzed intramolecular C−H arylation reaction producing planar chiral ferrocenes with moderate enantioselectivity (up to 67% ee) has appeared: Ma, X.; Gu, Z. *RSC Adv.* **2014**, *4*, 36241−36244.

(15) The reaction failed when other bases including K_2CO_3, Na_2CO_3, $NaHCO_3$, ^tBuONa, and Et_3N were employed instead of Cs_2CO_3. No reaction took place in the absence of pivalic acid.

(16) The pivalate ligand would facilitate C−H activation via concerted metalation−deprotonation mechanism: (a) Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066−1067. (b) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496−16497.

(17) It is reported that an *N*-unsubstituted quinolinone-fused ferrocene racemizes in solution (ref 12). However, the erosion of the enantiomeric excess of *N*-butyl derivative **2e** was not observed in toluene even at refluxing temperature.

(18) Low enantioselectivities were observed when pyridine-containing substrates were subjected to the optimized reaction conditions. See the Supporting Information for details.

(19) CCDC1002966 (**2j**) contains the supplementary crystallographic data for this paper.