An Enantioselective Oxidative C−H/C−H Cross-Coupling Reaction: Highly Efficient Method To Prepare Planar Chiral Ferrocenes

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S *Supporting Information*

ABSTRACT: A Pd-catalyzed, asymmetric oxidative cross-coupling reaction between ferrocenes and heteroarenes is described. The process, which takes place via a twofold C−H bond activation pathway, proceeds with modest to high efficiencies (36−86%) and high levels of regio- and enantioselectivity (95−99% ee). In the reaction, air oxygen serves as a green oxidant and excess amounts of the coupling partners are not required. The process is the first example of a catalytic asymmetric biaryl coupling reaction that occurs via double C−H bond activation. Finally, the generated coupling products can be readily transformed into chiral ligands and catalysts.

Asymmetric C−H bond functionalization has attracted the attention of chemists[1] owing to its unprecedented applications in organic synthesis.[2] In the past few years, a number of coupling reactions between unfunctionalized arenes (Ar−H) and aryl halides or aryl organometallics have been uncovered. Although the processes produce a variety of chiral compounds, prefunctionalization of at least one of the coupling partners is required (Figure 1a).[1] From the viewpoint of atom and step economy, an enantioselective cross-coupling reaction of two unfunctionalized arenes (Ar−H) via a double C−H

Previous works:

Ar—H + FG—Ar → (a) → Ar—*—Ar

Ar—H + H—Ar → (b) → Ar—Ar

This work:

Fc—H + H—Ar → (c) → Fc—*—Ar

- double C-H bond activation
- atom & step economy
- air as an oxidant
- H₂O as the sole byproduct
- no requirement of excess substrate
- exclusive regioselectivity
- excellent enantioselectivity

Figure 1. Asymmetric cross-coupling for C−C bond formation. (a) Asymmetric cross-coupling reaction involving one C−H bond activation. (b) Twofold oxidative C−H cross-coupling reaction in a racemic manner. (c) Asymmetric oxidative C−H/C−H cross-coupling reaction. FG = functional group. * = symbol of chirality. Ar = arene. Fc = ferrocene.
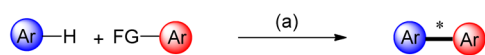
bond activation pathway would undoubtedly be an extremely attractive process for construction of enantio-enriched compounds. A strategy of this type would have numerous advantages such as low cost and minimized manipulations as well as waste. To the best of our knowledge, only racemic versions of these types of coupling reactions have been described owing to the fact that chiral recognition of inert C−H bonds of arene has not been well addressed (Figure 1b).[3] Additionally, the processes are typically limited by poor regioselectivities and by the required use of large excesses of coupling partners and stoichiometric amounts of metal oxidants. Therefore, the development of a method for carrying out asymmetric, twofold oxidative C−H cross-coupling reactions, although extremely challenging, is highly desirable.[4]

Since the time of the serendipitous discovery and later structural determination of ferrocene, related "sandwich" compounds have been subjected to extensive studies.[5] Ferrocenes, possessing planar chirality, have been used in the synthesis of industrial, pharmaceutical, and agrochemical commodities.[6] As a result, considerable effort has been devoted to the development of procedures to prepare planar chiral members of the ferrocene family.[7] There is little doubt that methods employing catalytic asymmetric C−H functionalization would be ideal for introducing substituents on the ferrocene backbone.[8]
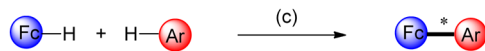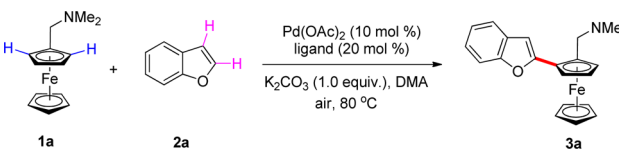
A major breakthrough in the area of catalytic asymmetric C−H bond activation was made recently by Yu and his co-workers. This group demonstrated that monoprotected amino acids can be utilized as chiral ligands in these processes.[9] Recently, a few remarkable Pd(II)-catalyzed asymmetric C−H functionalization reactions of ferrocene derivatives have been described, as exemplified by processes developed in our recent studies of asymmetric C−H arylations with aryl boronic acids.[8a] Removal of the need for preactivation of arene substrates would simplify this process. For this purpose, we envisioned that planar chiral ferrocenes could be synthesized directly from ferrocene and unfunctionalized arenes via a twofold C−H activation process (Figure 1c).

To test the validity of this proposal, an initial investigation was carried out exploring the enantioselective cross-coupling reaction of dimethylaminomethylferrocene (**1a**) and 1.5 equiv of benzofuran (**2a**). In this case, dimethylamino group acts as a directing group for the first palladation, and the electron-rich benzofuran facilitates subsequent electrophilic regioselective

palladation. It should be noted that **1a** was used earlier in a stoichiometric asymmetric cyclopalladation reaction developed by Sokolov.[10] The cross-coupling process between **1a** and **2a** takes place in the presence of 10 mol % of Pd(OAc)$_2$ and 20 mol % of Boc-L-Val-OH at 70 °C with air as an oxidant to generate product **3a** in a highly C2-regioselective manner and a 44% yield and with 99% ee (Table 1, entry 1).

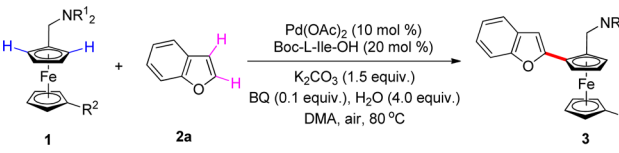**Table 1. Enantioselective C−H Oxidative Cross-Coupling**[a]

entry	2a (equiv)	ligand	yield (%)[b]	ee (%)[c]
1[d]	1.5	Boc-L-Val-OH	44	99
2	1.5	Boc-L-Val-OH	48	98
3	1.5	Boc-L-Ile-OH	53	98
4	1.5	Boc-L-Phe-OH	45	94
5	1.5	Boc-L-Nva-OH	48	94
6	1.5	Boc-L-Pro-OH	15	0
7[e]	2.0	Boc-L-Ile-OH	60	99
8[f]	2.0	Boc-L-Ile-OH	65	99
9[g]	2.0	Boc-L-Ile-OH	69	99
10[h]	2.0	Boc-L-Ile-OH	71	99

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.45 mmol), Pd(OAc)$_2$ (10 mol %), ligand (20 mol %), K$_2$CO$_3$ (0.3 mmol) in DMA under air at 80 °C unless noted otherwise. [b]Isolated yield. [c]Determined by HPLC analysis. [d]At 70 °C. [e]With K$_2$CO$_3$ (1.5 equiv). [f]With K$_2$CO$_3$ (1.5 equiv) and benzoquinone (10 mol %). [g]With K$_2$CO$_3$ (1.5 equiv), benzoquinone (10 mol %), and water (1.0 equiv). [h]With K$_2$CO$_3$ (1.5 equiv), benzoquinone (10 mol %), and water (4.0 equiv).

Encouraged by this result, the conditions for this reaction were optimized. The efficiency of the reaction was found to be only slightly enhanced by raising the temperature to 80 °C (entry 2). The results of screening commercially available chiral amino acid derivatives revealed that the use of Boc-L-Ile-OH leads to an improved yield of **3a** without lowering the level of enantioselectivity (entry 3). Notably, racemic **3a** is generated when Boc-L-Pro-OH is employed as a chiral ligand, a likely result of the fact that this ligand does not have a NH moiety that is required for formation of a bidentate complex with Pd (entry 6). Interestingly, an increase in the loading of benzofuran causes an increase in the yield of the process (entry 7). Moreover, the use of 10 mol % of benzoquinone and 4 equiv of water leads to improvement of the efficiency of this process (71% yield, 99% ee; entry 10).

Having identified optimized conditions (entry 10, Table 1), an exploration of asymmetric C−H oxidative cross-coupling reactions of ferrocene derivatives, containing a variety of electronically different substituents, was carried out. The results of this effort (Table 2) show that regardless of the nature of the N-directing group (e.g., pyrrolidinyl, piperidinyl, or methyl-propylamino group) the ferrocenes (**1b−d**) participate in this process to generate products in high yields and nearly enantiopure forms. The reaction displays an excellent functional group tolerance that is reflected by the fact that sensitive functionality, such as an aldehyde (**1e**), unprotected 3° alcohol (**1f−g**), and silyl group (**1h**), can be present on the Cp ring. A particularly interesting observation is that asymmetric C−H functionalization takes place exclusively at the position *ortho* to

Table 2. Regio- and Enantioselective Cross-Coupling Reactions of Ferrocene Derivatives[a,b,c]

$R^1 = R^{1'} = Me$ (**3a**)	10 h, 71% yield, 99% ee	
$R^1 = R^{1'} = -(CH_2)_4-$ (**3b**)	10 h, 74% yield, 98% ee	
$R^1 = R^{1'} = -(CH_2)_5-$ (**3c**)	13 h, 70% yield, 98% ee	
$R^1 = Me, R^{1'} = {}^nPr$ (**3d**)	13 h, 68% yield, 99% ee	

$R^2 =$		
CHO (**3e**)	13 h, 40% yield, 97% ee	
(**3f**)	16 h, 73% yield, 98% ee	
(**3g**)	13 h, 55% yield, 99% ee	
TMS (**3h**)	12 h, 82% yield, 97% ee	
PPh$_2$ (**3i**)	13 h, 69% yield, 99% ee	

[a]Reaction conditions: **1** (0.3 mmol), **2a** (0.6 mmol) Pd(OAc)$_2$ (10 mol %), Boc-L-Ile-OH (20 mol %), K$_2$CO$_3$ (0.45 mmol), benzoquinone (10 mol %) and water (4.0 equiv) in DMA under air at 80 °C unless noted otherwise. [b]Isolated yield. [c]Determined by HPLC analysis.
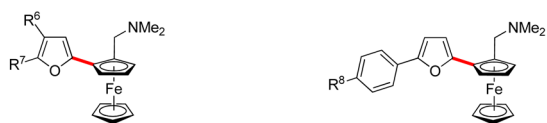
the N-directing group (**1i** to **3i**, 69% yield, 99% ee) even when a phosphoryl-directing group is present on the ferrocene ring. Finally, the pathway involving regioselective formation of 2-ferrocenyl-benzofurans is followed in all cases.

The generality of the direct coupling reaction was explored using ferrocene (**1a**) and a variety of heteroarenes (Table 3). The results show that benzofurans bearing electronically different substituents (5-Me, 5-OMe, 5-^{i}Pr, 5-Ph, 5-F, 5-Cl, 5,7-Me$_2$, 7-^{t}Bu, 7-Cl) react with **1a** to produce the corresponding products (**3j−r**) in satisfactory yields (49−77%) and with excellent levels of enantioselectivity (97−99% ee). It is worth noting that reactions of furans bearing various substituents, regardless of their electronic nature and position, take place with exclusive C2 regioselectivity, and in high yields and levels of enantioselectivity (**3s−y**). Both C2 and C3 substituted thiophenes also serve as substrates for the oxidative cross-coupling reaction that form products (**3z−zh**) in moderate to high yields and with near-perfect levels of enantiocontrol. Furthermore, reactions occur smoothly using ketone, ester, aldehyde, and acrylate functionalized pyrroles to form the corresponding products (**3zi−zl**). In addition, 1-methylindole bearing an electron-withdrawing group (5-Cl) is a substrate for this process, which forms the C2-indole product **3zm** regioselectively in a 51% yield and with 98% ee. Interestingly, 5-methylbenzothiophene undergoes an efficient coupling reaction with **1a** to generate **3zn²** and **3zn³** in a 9.4:1 ratio and a 74% combined yield. However, pentafluorobenzene, imidazole, and oxazole are not suitable substrates for the coupling reaction. Finally, the configurations of the stereogenic centers in the products of these reactions is assumed to be R_p based on X-ray crystallographic analysis of single crystals of representative enantiopure products **3zh** and **3zk** (see the Supporting Information for details).

To further demonstrate the utility of the new methodology developed in this effort, various straightforward transformations

Table 3. Regio- and Enantioselective Cross-Coupling Reactions of Heteroarenes[a,b,c]


A. (benzo)furan

R[3] = Me (**3j**)   13 h, 66% yield, 97% ee
R[3] = OMe (**3k**) 13 h, 72% yield, 99% ee
R[3] = *i*Pr (**3l**) 11 h, 68% yield, 99% ee
R[3] = Ph (**3m**)   13 h, 77% yield, 99% ee
R[3] = F (**3n**)   12 h, 49% yield, 99% ee
R[3] = Cl (**3o**)   12 h, 51% yield, 99% ee

R[4] = Me, R[5] = Me (**3p**) 13 h, 67% yield, 99% ee
R[4] = H, R[5] = *t*Bu (**3q**) 18 h, 64% yield, 98% ee
R[4] = H, R[5] = Cl (**3r**)   16 h, 57% yield, 99% ee[d]

R[6] = H, R[7] = Me (**3s**)   13 h, 36% yield, 95% ee
R[6] = Me, R[7] = Me (**3t**)   12 h, 50% yield, 97% ee
R[6] = H, R[7] = Ac (**3u**)   19 h, 63% yield, 99% ee
R[6] = H, R[7] = COOMe (**3v**) 13 h, 76% yield, 99% ee

R[8] = H (**3w**)   10 h, 71% yield, 99% ee
R[8] = OMe (**3x**) 7 h, 76% yield, 99% ee
R[8] = Ac (**3y**)   6 h, 82% yield, 99% ee

B. (benzo)thiophene, pyrrole & indole
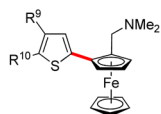
R[9] = H, R[10] = Me (**3z**),   16 h, 58% yield, 97% ee[d]
R[9] = H, R[10] = CHO (**3za**), 18 h, 64% yield, 98% ee
R[9] = H, R[10] = Ac (**3zb**),   16 h, 60% yield, 97% ee
R[9] = H, R[10] = COOMe (**3zc**), 22 h, 74% yield, 99% ee
R[9] = H, R[10] = Ph (**3zd**),   10 h, 86% yield, 98% ee
R[9] = Ph, R[10] = H (**3ze**),   17 h, 44% yield, 98% ee
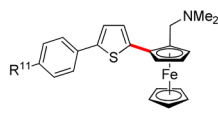
R[11] = OMe (**3zf**) 19 h, 80% yield, 99% ee
R[11] = F (**3zg**)   12 h, 76% yield, 97% ee
R[11] = Cl (**3zh**)   6 h, 76% yield, 99% ee

3zm: 18 h, 51% yield, 98% ee
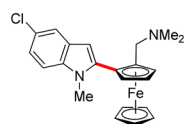
R[12] = Ac (**3zi**)   17 h, 82% yield, 98% ee
R[12] = COOMe (**3zj**)   12 h, 47% yield, 98% ee
R[12] = CHO (**3zk**)   22 h, 76% yield, 99% ee[d]
R[12] = (E)-CH=CHCO₂Et (**3zl**) 22 h, 48% yield, 95% ee
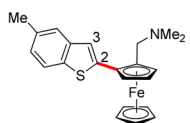
3zn: 21 h, 74% yield, **3zn²**/**3zn³** = 9.4:1[e]

[a]Reaction conditions: **1a** (0.3 mmol), **2** (0.6 mmol), Pd(OAc)₂ (10 mol %), Boc-L-Ile-OH (20 mol %), K₂CO₃ (0.45 mmol), benzoquinone (10 mol %), and water (4.0 equiv) in DMA under air at 80 °C unless noted otherwise. [b]Isolated yield. [c]Determined by HPLC analysis. [d]With heteroarenes (4 equiv). [e]Enantioselectivity was not determined.

of the coupling product **3a** were carried out to produce planar chiral ligands, which are difficult to prepare by using existing methods. As illustrated in Figure 2A, **3a** was converted through *ortho*-lithiation and subsequent reactions with electrophiles to an array of planar chiral bidentate type, ferrocene ligands (**4a**–**d**). Planar chiral ferrocenes bearing similar privileged scaffolds have been demonstrated to serve as efficient asymmetric catalysts.[6] For example, **4a** is an efficient catalyst in asymmetric diethylzinc addition of benzaldehyde and 1-naphthaldehyde (90% yield, 86% ee and 86% yield, 87% ee, Figure 2B). In spite
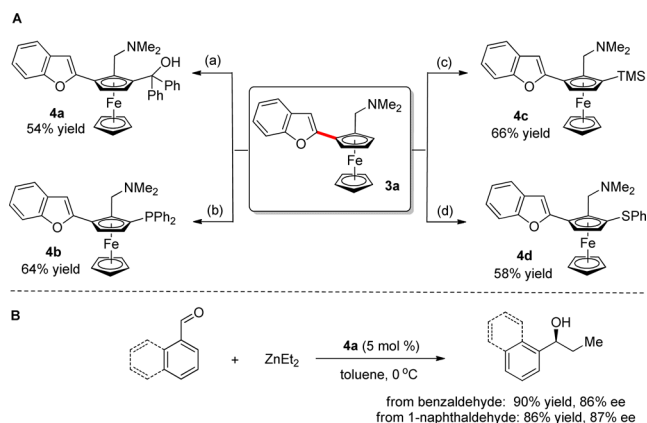

Figure 2. Transformations of **3a** and an asymmetric diethylzinc addition reaction. (A) Transformations of **3a**. (B) The application of **4a** in asymmetric diethylzinc addition reaction. See the Supporting Information for details.

of the fact that the enantioselectivity of this process is not as high as other state-of-art reactions described in the literature,[11] the new method serves as a useful platform for the design of new ligands and catalysts for asymmetric transformations.

In the investigation described above, we developed a new asymmetric twofold C−H oxidative cross-coupling reaction of ferrocenes with heteroarenes. These processes take place with excellent levels of regio- and enantioselectivity and high efficiencies. Consequently, a strategy now exists for carrying out enantioselective C−H bond activation reactions without the need for preactivation of either coupling substrate. Additionally, the employment of air oxygen as a green oxidant and the absence of the need to use significant excesses of either coupling partner serve as further advantageous features of the new methodology. Finally, the new protocol can be incorporated into routes for the synthesis of a variety of new enantiopure ligands or catalysts for asymmetric transformations.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b00127.

Experimental procedures and analytical data for all new compounds (PDF)
Crystallographic data for **3zk** (CIF)
Crystallographic data for **3zh** (CIF)

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Notes
The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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