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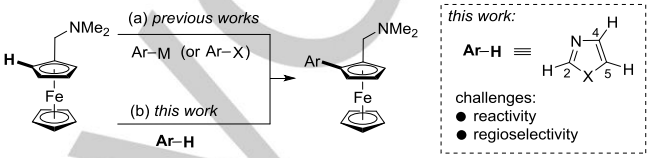
Pd(II)-Catalyzed Regio- and Enantioselective Oxidative C-H/C-H Cross-Coupling Reaction between Ferrocenes and Azoles

Zhong-Jian Cai,[†] Chen-Xu Liu,[†] Qing Gu*,[†] Chao Zheng,[†] and Shu-Li You*,[†,‡]

Abstract: Asymmetric C-H bond functionalization reaction is one of the most efficient and straightforward methods for the synthesis of optically active molecules. Herein we disclose an asymmetric C-H/C-H cross-coupling reaction of ferrocenes with azoles such as oxazoles and thiazoles. Palladium(II)/monoprotected amino acid (MPAA) catalytic system exhibits excellent reactivity and regioselectivity for oxazoles and thiazoles. This method offers a powerful strategy for constructing planar chiral ferrocenes. Mechanistic studies suggest that the C-H bond cleavage of azoles is likely proceeding *via* a S_EAr process and may not be a turnover limiting step.

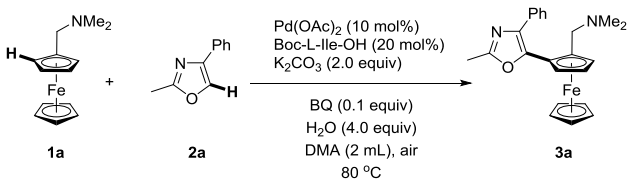
Transition-metal-catalyzed C-H functionalization reaction has tremendously contributed to the improvement of molecular complexity from simple and readily available chemical feedstocks.[1,2] In recent years, extensive efforts have been made on the enantioselective C-H bond functionalization reaction, which offers a highly atom- and step-economic method towards the facile synthesis of high-value-added optically active molecules.[3,4] From the viewpoint of atom and step economy, the direct asymmetric cross-coupling reaction of two unfunctionalized arenes (Ar-H) would undoubtedly be an attractive pathway to construct chiral compounds.[5] Our group has been interested in developing asymmetric C-H bond functionalization reaction to construct different types of stereogenic elements.[6] For instance, we and others[7] have developed several asymmetric C-H functionalization reactions of ferrocenes to introduce planar chirality. In general, the asymmetric C-H arylation reactions utilize functionalized arenes such as aryl halides and aryl organometallic reagents (Scheme 1, a). We next turn our attention to develop enantioselective oxidative C-H/C-H cross-coupling reaction of arenes (Scheme 1, b).[8] Notably, oxazoles and thiazoles are fundamental ring systems widely utilized in organic synthesis,[9] agrochemicals,[10] pharmaceuticals[11] and organic functional materials such as fluorescent dyes,[12] light emitting and liquid crystalline materials[13]. The importance of oxazoles and thiazoles in biologically active compounds and advanced materials continues to inspire the development of synthetic application to introduce them into novel frameworks. Inspired by the rapidly growing area of transition-metal-catalyzed direct arylation reaction of oxazoles and thiazoles with functionalized arenes,[14] we began to explore the capability of enantioselective C-H/C-H cross-coupling reaction of ferrocenes with oxazoles and thiazoles. Although this approach was conceptually attractive, the reactivity and the regioselectivity between C2-, C4- and C5-H bonds of azoles remain challenging. More importantly, experimental studies will be crucial to gain insights into the mechanisms and important elementary steps of such enantioselective dual C-H bond functionalization reactions. Herein, we report our results from this study.



Scheme 1. Asymmetric C-H Arylation of Ferrocene.

We initially hypothesized that the more electrophilic C5-H of oxazole might be a plausible reactive position that participates in the cross-coupling reaction. Based on this proposal, we started our attempt by allowing a model substrate 2-methyl-4-phenyloxazole **2a** to react with dimethylaminomethylferrocene **1a**.[15] To our delight, the desired product **3a** was obtained in 83% yield and 98% ee in the presence of 10 mol% $Pd(OAc)_2$, 20 mol% Boc-L-Ile-OH,[16] 2.0 equiv. K_2CO_3, 0.1 equiv. BQ, 4.0 equiv. H_2O in DMA at 80 °C (Table 1). We then sought to employ an O_2 balloon to improve the reaction efficiency; however, no obvious improvement was observed (entry 2). In the absence of excessive H_2O, the reaction proceeded smoothly to give **3a** in 81% yield without decreasing the ee value (entry 3). However, in the absence of BQ, this operation gave **3a** in a diminished yield, and an enhanced yield of 72% was resulted in combination with an O_2 balloon (entries 4-5). These results

Table 1. Optimization of the reaction conditions. [a]



entry	deviation from standard conditions	yield (%)[b]	ee (%)[c]
1	none	83	98
2	O_2	80	99
3	no H_2O	81	99
4	no BQ	51	99
5	No BQ, under O_2 atmosphere, no H_2O	72	99
6	**$Pd(OAc)_2$ (5 mol%), no H_2O**	**80**	**99**
7	$Pd(OAc)_2$ (2.5 mol%), no H_2O	75	99
8	$Pd(OAc)_2$ (1 mol%), no H_2O	42	97

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), $Pd(OAc)_2$ (10 mol%), Boc-L-Ile-OH (20 mol%), K_2CO_3 (0.6 mmol), H_2O (1.2 mmol) and BQ (10 mol%) in DMA (2 mL) at 80 °C. [b] Yield of isolated product. [c] Determined by HPLC analysis.

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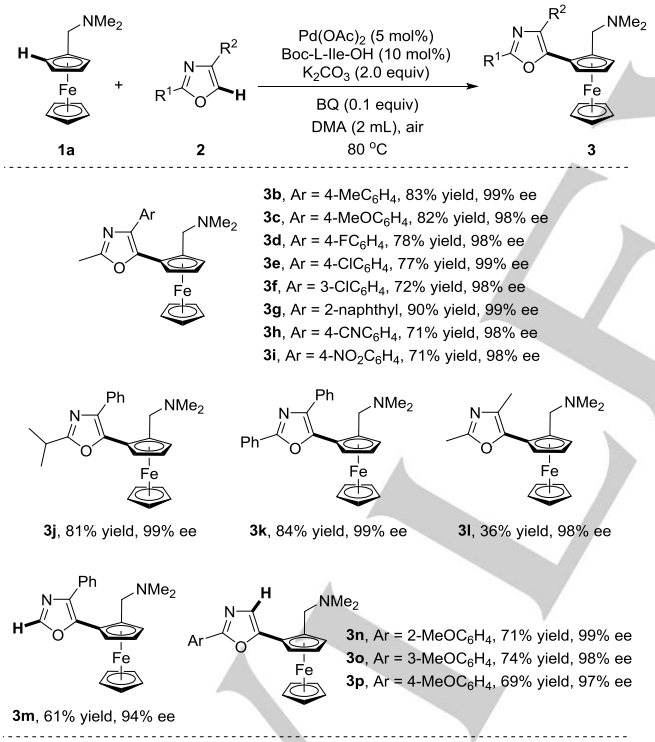
highlight the critical role of BQ in promoting the enantioselective cross-coupling reaction. Reducing $Pd(OAc)_2$ to 5 mol% had minimal deleterious effects (entry 6), whereas further lowering the loading of palladium catalyst to 2.5 mol% decreased the yield slightly (entry 7). A switch of the loading to 1 mol% further reduced the yield of product **3a** to 42%.

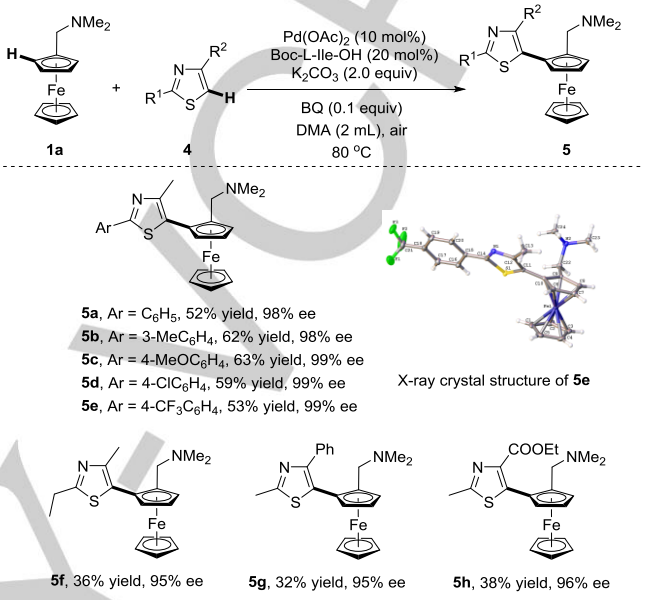
Then, we investigated the scope of oxazole substrates (Scheme 2). The introduction of electron-donating groups (Me, MeO), halogen substituents (F, Cl) and electron-withdrawing groups (CN, NO_2) on the phenyl ring of 4-aryloxazole proved acceptable, providing planar chiral ferrocenes in good to excellent yields and excellent enantioselectivity (**3b**-**i**, 71-90% yields, 98-99% ee). The 2-isopropyl and phenyl substituted oxazoles reacted smoothly, generating the desired products **3j** and **3k** respectively, in 81% and 84% yield with excellent ee. Notably, this protocol was also applicable to 2,4-dimethyloxazole, although the corresponding product **3l** was obtained in a lower yield (36% yield, 98% ee). In order to study the regioselectivity of oxazoles, 4-phenyloxazole **2m** was used as the cross-coupling partner in our catalytic system. Interestingly, the reaction proceeded smoothly to product (**3m**) with exclusive C5 regioselectivity in 61% yield and 94% ee. The moderate yield was caused by the relatively low conversion of **2m**. Furthermore, 2-aryloxazoles **2n**-**p** are also suitable substrates for this process, leading to the C5-oxazole products **3n**-**p** regioselectivity in 69-71% yields with excellent ee values (97-99%).



Reaction conditions: **1a** (0.3 mmol), **2** (0.6 mmol), $Pd(OAc)_2$ (5 mol%), Boc-L-Ile-OH (10mol%), K_2CO_3 (0.6 mmol), and BQ (10 mol%) in DMA (2 mL) at 80 °C for 14 h. Isolated yield is reported. Ee was determined by HPLC analysis.

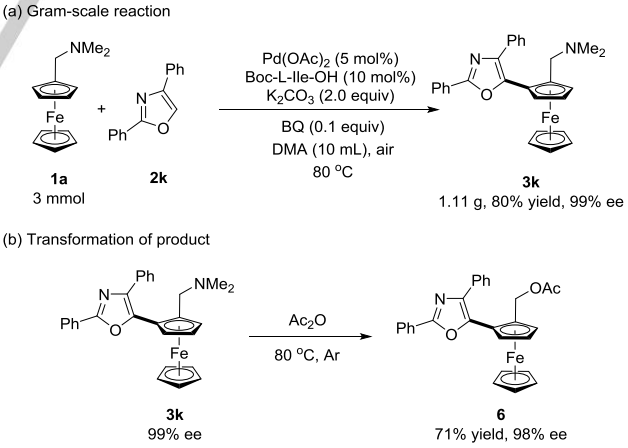
Scheme 2. Scope of the oxazoles.

We next examined the suitability of thiazoles as substrates in the asymmetric cross-coupling reaction. Gratifyingly, a range of thiazoles could be converted into the corresponding planar chiral ferrocenes smoothly, although an increased catalyst loading and a longer reaction time were necessary. In these cases, a variety of 2-aryl-substituted thiazoles proved to be good coupling partners, yielding the desired products **5a**-**e** in moderate yields with excellent ee. Meanwhile, the absolute configuration of product **5e** was confirmed by X-ray crystallographic diffraction and found to be R_p (see the SI for details). 2-Ethyl-4-methylthiazole, 2-ethyl-4-phenylthiazole and ethyl 2-ethylthiazole-4-carboxylate are also suitable substrates. Products **5f**-**h** were isolated in 32-38% yields with excellent level of enantioselectivity (95-96% ee).



Reaction conditions: **1a** (0.3 mmol), **4** (0.6 mmol), $Pd(OAc)_2$ (10 mol%), Boc-L-Ile-OH (20 mol%), K_2CO_3 (0.6 mmol), and BQ (10 mol%) in DMA (2 mL) at 80 °C for 24 h. Isolated yield is reported. Ee was determined by HPLC analysis.

Scheme 3. Scope of the thiazoles.



Scheme 4. Gram-scale reaction and transformation.

To further investigate the potential application of this asymmetric dual C-H bonds functionalization, we conducted a gram-scale reaction of **1a** with **2k**. To our delight, the cross-coupling product **3k** was obtained in 1.11 grams in 80% yield and 99% ee (Scheme 4, a). In addition, the dimethylamino group could be easily converted into an acetoxy group by a simple nucleophilic substitution (Scheme 4, b).

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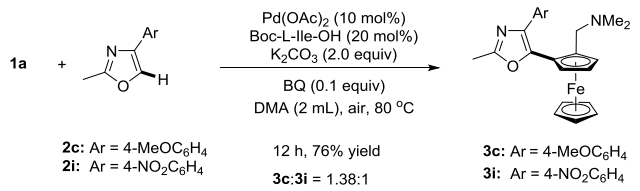
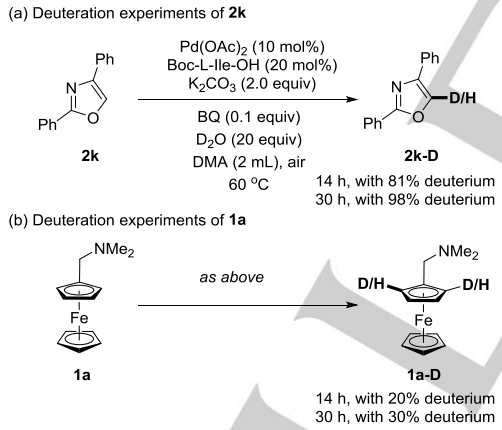
To shed lights on the mechanism of this cross-coupling reaction, we conducted a competitive experiment of **2c** and **2i**, and it was found that products **3c** and **3i** were obtained in a 1.38:1 ratio (Scheme 5). This indicated that the relative rate of C-H functionalization is slightly larger for electron-rich oxazole.



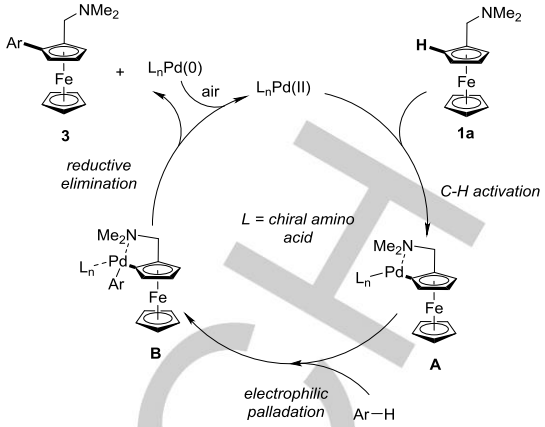
Scheme 5. Competitive experiment.

Next, we carried out the H/D exchange experiments of oxazole and dimethylaminomethylferrocene under the standard conditions. It was found that oxazole **2k** could be deuterated easily and **2k-[D]** was obtained with high deuterium incorporation in a short time (Scheme 6, a). However, product **1a-[D]** was obtained in only 30% deuterium although the reaction time was extended to 30 h (Scheme 6, b). In addition, the kinetic isotope effect of the dual C-H bond functionalization reaction was studied. It was found that the kinetic isotope effect of oxazole was only 1.17 and a significant intermolecular kinetic isotope effect (3.33) was obtained for ferrocene (Supporting Information, S25-26). These above results suggested that the C-H bond cleavage of oxazole likely proceeds *via* a S_EAr process and may not be a turnover limiting step. The C-H bond cleavage of dimethylaminomethylferrocene **1a** likely proceeds via a concerted metalation deprotonation (CMD) pathway which may be the rate-limiting step.



Scheme 6. Deuteration experiments.

Based on the above experiments and computational studies[17], a plausible catalytic cycle was proposed for this enantioselective dual C-H/C-H bond cross-coupling reaction. As illustrated in Scheme 7, initially, Pd(II) intermediate **A** is generated by an enantioselective C-H bond cleavage with the assistance of chiral amino acid. Then, **A** is converted into the intermediate **B** by an electrophilic palladation of azole. Finally, the reductive elimination of **B** affords planar chiral product **3**. Meanwhile, the released Pd(0) is oxidized by air to generate Pd(II) species for the next catalytic cycle.



Scheme 7. Proposed catalytic cycle.

In summary, we have developed an efficient and straightforward asymmetric C-H/C-H cross-coupling reaction of ferrocenes with azoles such as oxazoles and thiazoles. The reaction shows excellent regioselectivity toward C5-H bond of various oxazoles and thiazoles and offers a powerful tool to synthesize planar chiral ferrocenes. The excellent enantioselectivity and regioselectivity of this methodology are derived from the combination of palladium acetate and a monoprotected amino acid (MPAA) ligand. Competitive experiments, H/D scrambling experiments, and kinetic studies gave further insights into the mechanism. It is indicated that the C-H bond cleavage of heteroarenes proceeds likely *via* a S_EAr process and may not be a turnover limiting step, and the C-H bond cleavage of dimethylaminomethylferrocene **1a** proceeds likely via a concerted metalation deprotonation (CMD) pathway which may be the rate-limiting step.

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Keywords: azole • asymmetric catalysis • C-H activation • ferrocene • regioselectivity

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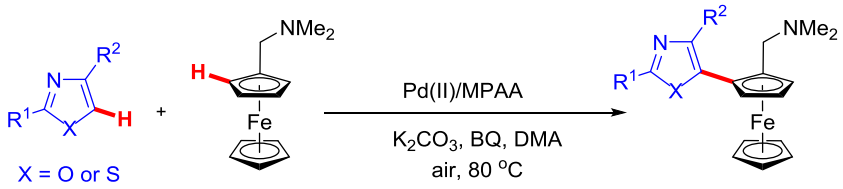

- **up to 90% yield, 99% ee**
- **palladium(II)/monoprotected amino acid (MPAA) catalytic system**
- **unnecessity of excess amount of either coupling partner**
- **excellent regioselectivity**

Asymmetric C-H bond functionalization reaction is one of the most efficient and straightforward methods for the synthesis of optically active molecules. Herein we disclose an asymmetric C-H/C-H cross-coupling reaction of ferrocenes with azoles such as oxazoles and thiazoles. Palladium(II)/monoprotected amino acid (MPAA) catalytic system exhibits excellent reactivity and regioselectivity for oxazoles and thiazoles. This method offers a powerful strategy for constructing planar chiral ferrocenes. Mechanistic studies suggest that the C-H bond cleavage of azoles is likely proceeding *via* a S_EAr process and may not be a turnover limiting step.

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Pd(II)-Catalyzed Regio- and Enantioselective Oxidative C-H/C-H Cross-Coupling Reaction between Ferrocenes and Azoles