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Carbon−Carbon Bond Formation through Double sp^2 C−H Activations: Synthesis of Ferrocenyl Oxazoline Derivatives

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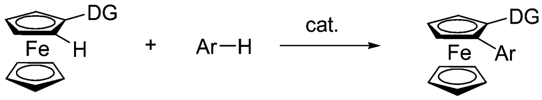
Summary: Direct arylation of simple arenes with ferrocenyl oxazolines was achieved in the presence of a stoichiometric amount of Pd(OAc)$_2$ or a catalytic amount of palladium with excess oxidant such as Cu(OAc)$_2$. This double sp^2 C−H activation process provides a unique access to the aryl-substituted ferrocene derivatives, even in the enantiopure form of planar chirality, in a few steps from readily available starting materials.

Synthesis of biaryl compounds and their heteroaromatic analogues represents one of the most intense research areas in chemistry due to their abundance among biologically active and functional molecules.[1] The classical coupling methods such as Suzuki coupling require stoichiometric amounts of organometallic aryl compounds and aryl halides.[2] The synthesis of these activated coupling precursors usually requires multistep syntheses, and a stoichiometric amount of undesired organometallic byproducts is also produced from the coupling reaction. Consequently, the direct arylation of C−H bonds via C−H activation for the biaryl synthesis, potentially the solution to the above problems, has received great attention and witnessed significant progress in the past decade.[3] However, most of the processes still use either stoichiometric amounts of organometallic aryl compounds or aryl halides.[4] Synthesis of the unsymmetrical biaryls through double sp^2 C−H activation remains rare but certainly extremely desirable.[5] In addition, ferrocene derivatives have been extensively applied in homogeneous catalysis, organic synthesis, materials science, etc., and facile syntheses of ferrocene derivatives, especially with intriguing planar chirality, are in great demand.[6]



(1)

We envisaged that a directing group introduced to the ferrocene would afford preferentially a proximal C−H activation on the Cp ring to initiate the coupling process and possibly reduce the homocoupling side product of the other arene (eq 1). An oxazoline is used for this purpose and also because of its potentially wide applications in asymmetric catalysis.[7,8] In this paper, we report the synthesis of aryl-substituted ferrocenyl oxazolines through double C−H activations with either stoichiometric or catalytic palladium catalyst.[9] This approach is also applicable to the highly diastereoselective synthesis of planar chiral ferrocenyl oxazoline derivatives.

We began our studies by using ferrocenyl oxazoline **1** and benzene as substrates in the presence of a stoichiometric amount of Pd(OAc)$_2$ to promote the coupling reaction. Refluxing **1** and Pd(OAc)$_2$ (1 equiv) in benzene without base did not lead to any observable coupling products. When the reaction was carried out by adding K$_3$PO$_4$ at the beginning, an 8% yield of **2a** was isolated. If the same base was added after refluxing **1** and Pd(OAc)$_2$ (1 equiv) in benzene for 3 h, forming the dimer **I**,[10]

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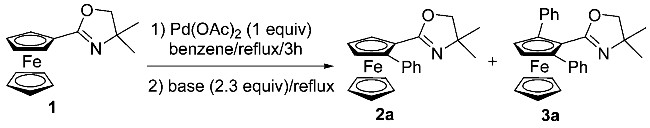
[10] For details, see the Supporting Information.

10.1021/om700806e CCC: $37.00

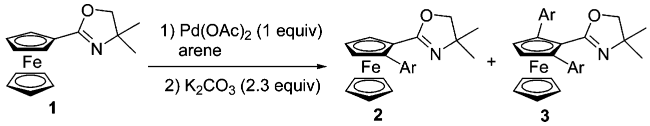
Table 1. Optimization of the Reaction Conditions[a]



entry	base	time (h)	yield (%)[b]
1		48	NR
2[c]	K_3PO_4	24	8
3	K_3PO_4	24	30(4)
4	Na_2CO_3	48	29(19)
5	KO^{t}Bu	30	36(7)
6	Cs_2CO_3	11	63(18)
7	K_2CO_3	11	70(16)
8	Et_3N	72	<5
9[c]	K_2CO_3	48	42(17)
10[d]	K_2CO_3	24	64(9)

[a] Reaction conditions: **1** (0.3 mmol) and Pd(OAc)$_2$ (0.3 mmol) in benzene (1.5 mL) were refluxed for 3 h, then base (0.69 mmol) was added. [b] Isolated yield of **2a** based on **1**. The number in parentheses indicates the yield of the recovered **1**. [c] Base was added at the beginning. [d] Isolated dimer **I** was used.

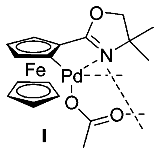
Table 2. Cross-Coupling Reactions of 1 with Arenes[a]



entry	arene	method	temp (°C)[b]	time (h)	yield (%)[c]
1	benzene	A	100	11	70 (**2a**)
2	toluene	A	100	24	44 (**2b**, *m*/*p*: 2.7:1):1 (**3b**)
3[d]	toluene		100	8	47 (**2b**, *m*/*p*: 2.6:1)
4	fluorobenzene	A	100	24	63 (**2c**, *o*/*m*/*p*: 13.3:9:1)
5	*tert*-butylbenzene	C	100	48	32 (**2d**, *m*/*p*: 1.7:1):3 (**3d**)
6	1,4-dimethoxybenzene	C	120	82	26 (**2e**)
7	2,3-benzofuran	B	100	51	37 (**2f**)
8	mesitylene	C	120	120	NR
9[e]	pentafluorobenzene	C	120	40	complicated

[a] Methods: A: **1** (0.3 mmol) and Pd(OAc)$_2$ (0.3 mmol) in arene (1.5 mL) were heated for 3 h, then K_2CO_3 (0.69 mmol) was added. B: **1** and Pd(OAc)$_2$ in CH_2Cl_2 were refluxed for 3 h; after removal of CH_2Cl_2, K_2CO_3 and arene was added and heated. C: **1**, Pd(OAc)$_2$, and K_2CO_3 were heated in arene. [b] The temperature of oil bath. [c] Isolated yield based on **1**. [d] Isolated dimer **I** was used. [e] A complex mixture was given.

the yield of **2a** was improved to 30% (entry 3, Table 1). Various bases were tested in the reaction, and all of them led to the formation of **2a** except organic base such as Et_3N. An optimal yield of 70% was obtained when K_2CO_3 was used (entry 7, Table 1). Noticeably, a 64% yield of **2a** was obtained when the isolated dimer **I** was used (entry 10, Table 1).

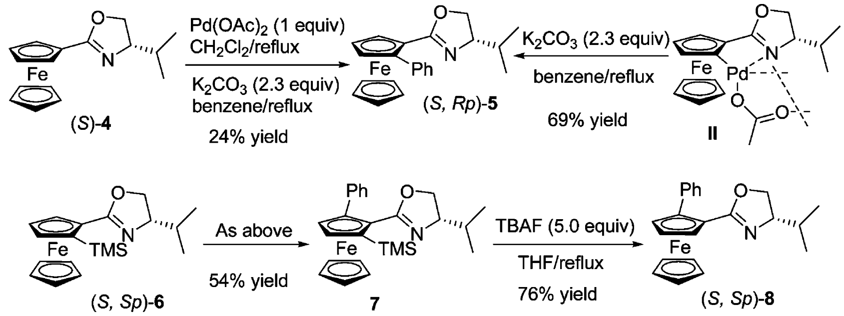


Under these optimized conditions, several other arenes have also been tested in the cross-coupling reaction with **1**. When toluene was used, **2b** was isolated in 44% yield (*m*/*p*: 2.7:1) together with 1% of **3b**. When the isolated palladium dimer was used, an identical result, isolation of **2b** in 47% yield (*m*/*p*: 2.6:1), was obtained. Fluorobenzene was also suitable for the cross-coupling reaction; **2c** was afforded in 63% yield as a mixture of three regioisomers (*o*/*m*/*p*: 13.3:9:1). When **1** was reacted with *tert*-butylbenzene, a 32% yield of **2d** (*m*/*p*: 1.7:1) and 3% of bis-coupled product **3d** were obtained. The lack of *ortho* product here, as well as in the case of toluene, is probably due to the steric bulkiness of the *tert*-butyl or methyl group. To avoid the regioisomer, symmetrical substrates such as 1,4-dimethoxybenzene were used, and 26% of **2e** was obtained. Interestingly, heterocyclic arenes such as 2,3-benzofuran could also undergo the cross-coupling reaction at the 2-position of 2,3-benzofuran to afford **2f** (37%). No reaction occurred when mesitylene was used, probably due to steric congestion. Cross-coupling of **1** with pentafluorobenzene led to a complex mixture.

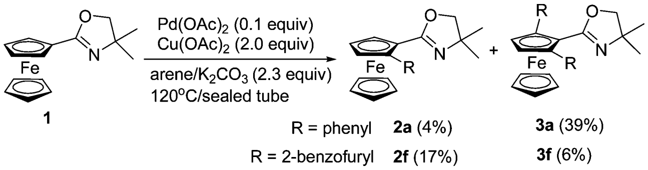
An intriguing feature of ferrocene derivatives is the introduction of planar chirality when two different groups are installed on the same Cp ring. Under the optimized reaction conditions, we have checked the possibility to synthesize planar chiral ferrocene derivatives by utilizing the enantiopure ferrocenyl oxazoline. As shown in Scheme 1, starting from ferrocenyl oxazoline **4**, **5** (24%) was obtained as a single diastereomer when the dimer was formed *in situ*. Interestingly, palladium dimer **II** was easily formed and the structure was confirmed by an X-ray analysis.[10,11] When the isolated dimer **II** was further refluxed in benzene in the presence of K_2CO_3 (2.3 equiv), a 69% yield of **5** resulted. To obtain the diastereomer of **5**, **6** was subjected to the coupling conditions, and cross-coupled product **7** was obtained in 54% yield. Removal of the trimethylsilyl group by refluxing **7** in a solution of TBAF in THF led to **8** (76%), a diastereomer of **5**. Therefore, compounds **5** and **8**, having the same central chirality but different planar chirality, could be synthesized conveniently with excellent diastereoselectivity.

The cross-coupling reactions with catalytic palladium acetate (10 mol %) and an extra oxidant have also been explored by using ferrocenyl oxazoline **1** as the substrate.[10] Several oxidants such as benzoquinone, Cu(OAc)$_2$, molecular oxygen, and different additives were tested, and Cu(OAc)$_2$ was found to be

Scheme 1. Synthesis of Planar Chiral Ferrocenyl Oxazolines



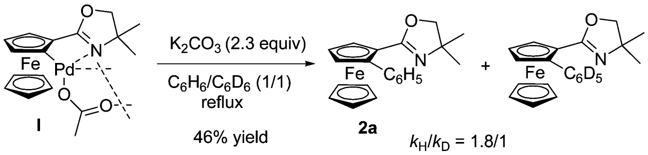
Scheme 2. Catalytic Cross-Coupling Reactions



optimal. In the presence of 10 mol % of $Pd(OAc)_2$, 2 equiv of $Cu(OAc)_2$, and 2.3 equiv of K_2CO_3, the reaction was carried out at 120 °C in a sealed tube to give a complete conversion of **1**; 4% of **2a** and 39% of **3a** were isolated (Scheme 2). However, further application of these catalytic conditions to other substrates proved less successful. For instance, coupling of **1** with 2,3-benzofuran under the catalytic conditions gave only 17% of **2f** and 6% of **3f**.

To determine the intermolecular isotope effects in this cross-coupling reaction, palladium dimer **I** was subjected to the reaction conditions utilizing equimolar benzene and benzene-d_6. As shown in Scheme 3, **2a** and the coupling product from benzene-d_6 were obtained in a ratio of 1.8:1 (k_H/k_D), suggesting the involvement of the C−H cleavage in the rate-limiting step.[4h,7a]

Scheme 3. Isotope Effects in the Cross-Coupling Reaction



In summary, we have found that ferrocenyl oxazoline, where the oxazoline was employed as a directing group, could react with simple arenes via double sp^2 C−H activations. Excellent diastereoselectivities were obtained in the cross-coupling reactions when chiral ferrocenyl oxazolines were used, providing a facile method to synthesize planar chiral aryl-substituted ferrocenyl oxazolines. A catalytic process has also been realized, but the catalytic efficiency needs further improvement. Further mechanistic investigations and development of a more efficient catalytic system are currently underway.

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Supporting Information Available: Experimental procedures and analysis data for new compounds, CIF file of **II** (CCDC 643978). This material is available free of charge via the Internet at http://pubs.acs.org.

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