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Nitrogen-Directed Ortho-Selective Homocoupling of Aromatic Compounds Catalyzed by Ruthenium Complexes

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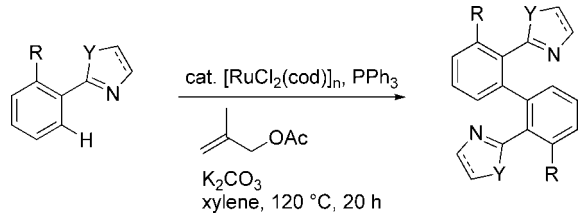
ABSTRACT



A nitrogen-directed regioselective homocoupling reaction of aromatic compounds has been found to be catalyzed by a ruthenium complex in the presence of methallyl acetate as a hydrogen scavenger.

Recently, C−H bond cleavage and C−C bond formation between aromatic rings have gained significant attention.[1] Among the several combinations of the aromatic compounds for such direct coupling reactions, the coupling reaction between two aromatic C−H bonds is the most desirable transformation from the standpoint of simplicity, substrate availability, and reduction of byproducts. However, intermolecular versions of such reactions are often limited due to low conversions and/or lack of regioselectivity.[2] A few examples on the regioselective oxidative coupling reaction have been reported, involving Cu-catalyzed coupling of naphthols,[3] Pd-catalyzed C−H homocoupling of thiophenes,[4] and Pd-catalyzed C−H cross-coupling of naphthalene,[5] benzofuranes,[6] and indoles[7] with simple arenes. The directing group-assisted ortho-metalation of aromatic compounds is one of the powerful solutions to the regioselectivity,[8] resulting in ortho-selective C−C bond formation. Elegant examples of such transformations were recently reported by Sanford and co-workers, featuring a regioselective oxidative homocoupling reaction of 2-arylpyridines[9] and a cross-coupling reaction of 2-arylpyridines with simple arenes[10] using Pd catalysts. Our research, in contrast, focuses on Ru-catalyzed ortho-selective direct coupling reactions of aromatic compounds using substrates that possess coordinating functional groups.[11,12] In relation to our previous report on Ru-catalyzed ortho-allylation of 2-arylpyridines with allyl ac-

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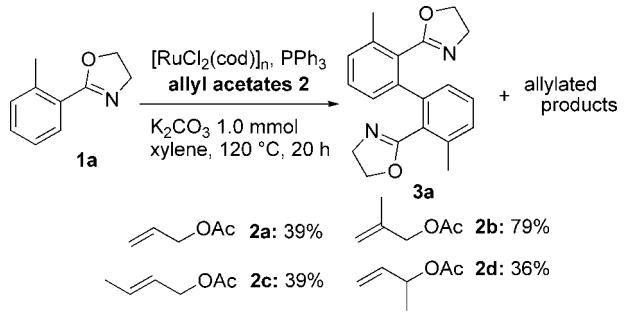
etates,[13] we have found that, when 2-aryloxazolines were employed as the substrates, substantial amounts of homocoupling products were formed along with the expected allylated products. Herein, we report that the homocoupling reaction of 2-aryloxazilines predominantly proceeded by choosing an appropriate allyl acetate, in the presence of Ru catalyst. In addition to 2-aryloxazolines, our reaction was applicable to substrates that possess nitrogen-containing functional groups, such as 2-arylimidazoles, -oxazoles, and -thiazoles and 1-arylpyrazoles and -indazoles. Furthermore, insights into the reaction mechanism involving a ruthenium(IV) intermediate are also presented.

As shown in Scheme 1, 2-tolyl-2-oxazoline (**1a**) was treated with allyl acetates **2a**−**d** in the presence of a base (K_2CO_3) and a catalytic amount of $[RuCl_2(cod)]_n$ (5 mol % based on Ru) with PPh_3 (10 mol %) in xylene at 120 °C for 20 h. In the case of **2a**, homocoupling (ortho position) product **3a** was obtained in 39% yield together with a mixture of isomers of allylated products. Consequently, the conditions that promote the formation of the homocoupling products were explored. Our results show that the structure of the allyl acetates greatly affected the yield of **3a**; methallyl acetate (**2b**) resulted in the predominant formation of **3a** in 79% yield, whereas crotyl acetate (**2c**) and 3-buten-2-yl acetate (**2d**) resulted in moderate formation of **3a**.

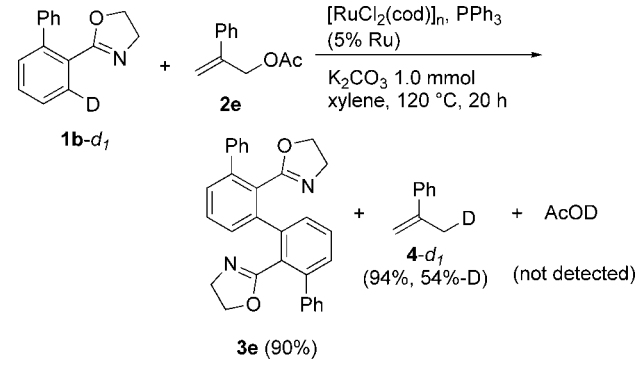
Scheme 1



The homocoupling of various substrates, in the presence of **2b**, was examined (Table 1). The yield of **3a** increased to 83% by adding powdered molecular sieves 4 Å (entry 1). Reactions of 2-aryl-2-oxazolines having an ortho substituent (**1a**−**g**) proceeded smoothly to afford the corresponding homocoupling products (**3a**−**g**) in good to excellent yields (entries 1–7). Reactions of 2-aryl-2-oxazolines having a meta substituent (**1h** and **i**) selectively underwent the coupling reaction at the 6-position to avoid the steric hindrance of the meta substituent (entries 8 and 9). 2-(1-Naphthyl)-2-oxazoline (**1j**) also underwent the coupling reaction to afford the product **3j** in a good yield of 82% (entry 10). On the other hand, the reaction of 2-phenyl-2-oxazoline (**1k**), despite the complete consumption of the substrate, did not form the expected coupling product (entry 11). In this case, the absence of the desired product can be attributed to the formation of oligomers due to the extended coupling reactions at both ortho positions. A series of reactions were then carried out to examine the effect of the directing group. In contrast to the unsuccessful reaction of 2-phenyl-2-oxazoline (**1k**), the reaction of *N*-methyl-2-phenylimidazole (**1l**) selectively gave homocoupling product **3l** in 74% yield (entry 12). In this case, the methyl group of the imidazole ring prevented the second coupling reaction at the alternate ortho position. Similarly, *N*-methyl-(3-methylphenyl)imidazole (**1m**), which corresponds to **1 h** (entry 8), selectively afforded coupling (6-position) product **3m** in 76% yield (entry 13). Other directing groups such as 2-thiazolyl (**1n**, entry 14), 2-oxazolyl (**1o**, entry 15), 1-pirazolyl (**1p**, entry 16), and 1-indazolyl groups (**1q**, entry 17) were also effective in the present homocoupling reaction.

Several experiments were carried out to gain insight into the reaction mechanism. As shown in Scheme 2, to confirm the role of allyl acetate, the reaction was carried out using ortho-deuterated **1b**-d_1 and 2-phenylallyl acetate (**2e**), resulting in a nearly quantitative yield of coupling product **3e** and deuterated α-methylstyrene (**4**-d_1). Deuteration of the methyl group of **4**-d_1 indicates that the C−O bond of **2e** was cleaved through the reaction, and two deuterium atoms of **1b**-d_1 were introduced to the cleaved C−O bond.

Scheme 2



Next, as shown in Scheme 3, ruthenacycle complex **5**, which was prepared by the reaction between **1b** and $[(\eta^6\text{-}C_6H_6)RuCl_2]_2$,[14] was utilized as an intermediate in the stoichiometric coupling reaction with **1a**. Although the re-

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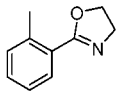
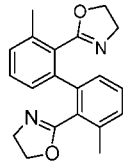
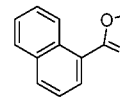
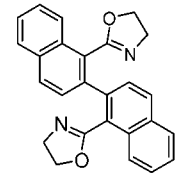
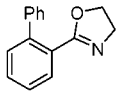
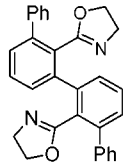
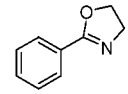
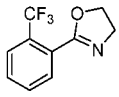
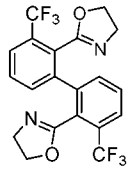
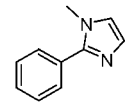
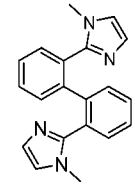
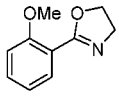
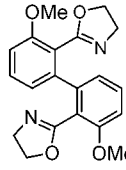
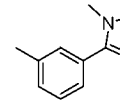
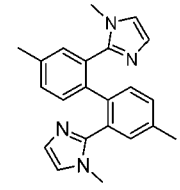
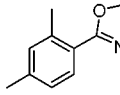
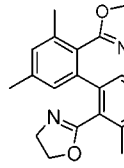
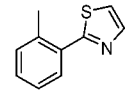
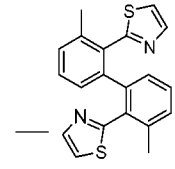
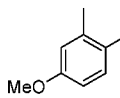
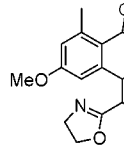
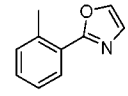
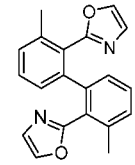
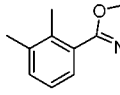
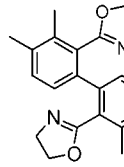
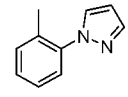
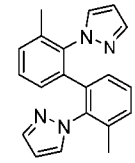
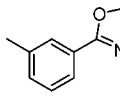
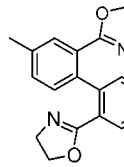
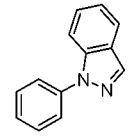
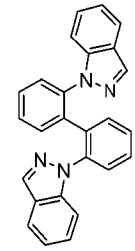
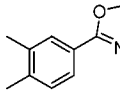
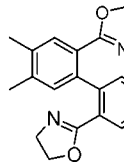
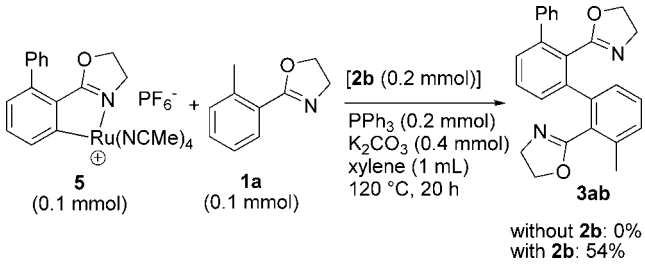
Table 1. Nitrogen-Directed Homocoupling of Aromatic Compounds **1** Catalyzed by a Ruthenium Complex[a]

entry	substrate **1**	product **3**	% yield	entry	substrate **1**	product **3**	% yield
1	 (**1a**)	 (**3a**)	83	10	 (**1j**)	 (**3j**)	82
2	 (**1b**)	 (**3b**)	93	11	 (1k)		0
3	 (**1c**)	 (**3c**)	63	12	 (**1l**)	 (**3l**)	74
4	 (**1d**)	 (**3d**)	67	13	 (**1m**)	 (**3m**)	76
5	 (**1e**)	 (**3e**)	85	14	 (**1n**)	 (**3n**)	75
6	 (**1f**)	 (**3f**)	96	15	 (**1o**)	 (**3o**)	40
7	 (**1g**)	 (**3g**)	83	16	 (**1p**)	 (**3p**)	41
8	 (**1h**)	 (**3h**)	33	17	 (**1q**)	 (**3q**)	68
9	 (**1i**)	 (**3i**)	30				

[a] Reactions were carried out using 0.5 mmol of **1**, 1.5 mmol of **2b**, 1.0 mmol of K_2CO_3, 50 mg of powdered molecular sieves 4 Å, 0.025 mmol (based on Ru) of $[RuCl_2(cod)]_n$, and 0.05 mmol of PPh_3 in 1 mL of xylene at 120 °C for 20 h.

action between **5** (0.1 mmol) and **1a** (0.1 mmol) in the presence of PPh_3 and K_2CO_3 in xylene at 120 °C for 20 h did not afford any coupling products, addition of methallyl acetate (**2b**, 0.2 mmol) to the reaction mixture afforded the

Scheme 3

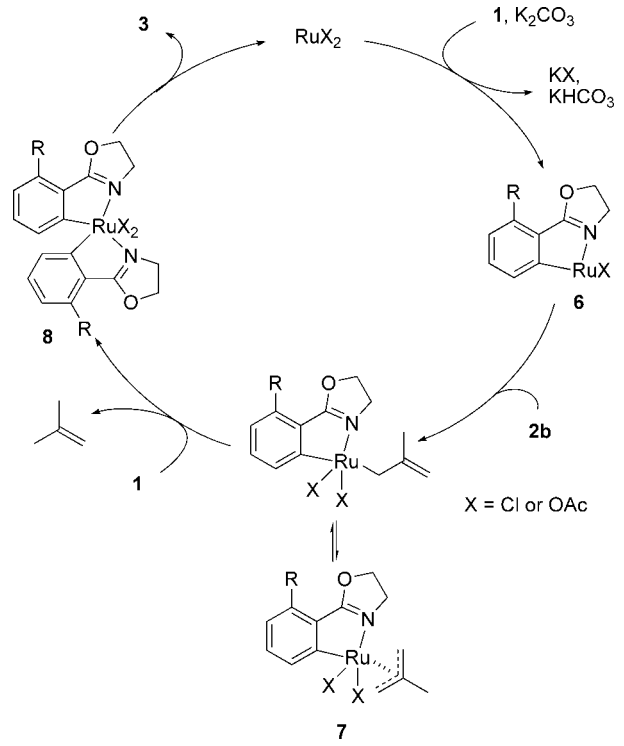


cross-coupling product **3ab** in 54% yield, clearly indicating that **5** first reacted with **2b** and then with **1a** to give the coupling product. We also examined the stoichiometric reaction of complex **5** with **2b** in the absence of **1a**, which resulted in the formation of an allylated product of **1b**. It can be assumed that a η^1- or η^3-allyl complex would be formed by oxidative addition of methallyl acetate to complex **5** and then reductive elimination would give the allylated product.

Based on these results, a reaction mechanism as shown in Scheme 4 can be proposed. The nitrogen-directed ruthenation of **1** with a ruthenium(II) complex gives a ruthenacycle complex **6**. For this step, a proton abstraction mechanism was proposed by Dixneuf and Maseras from DFT calculations.[12e] The ruthenacycle complex **6** would then undergo oxidative addition with **2** to give an η^1- or η^3-allylruthenium(IV) intermediate **7**. A second ruthenation of **1** with **7**, while releasing isobutene, would give a diarylruthenium intermediate **8**. Although details are not clear at present, the ortho hydrogen atom of **1** would be transferred to methallyl group on the ruthenium center in this step. The formation of **4**-d_1 in the deuterium label experiment (Scheme 2) also supports such transformations. The homocoupling product **3** is then formed through reductive elimination from **8**, with the simultaneous regeneration of the initial ruthenium(II) complex.

In conclusion, we have successfully demonstrated the nitrogen-directed oxidative coupling reaction of aromatic compounds catalyzed by ruthenium complexes, which shows complete regioselectivity and wide applicability. As the oxazolinyl group can be derived to a variety of functional

Scheme 4



groups, the present reaction provides a useful and powerful method for the synthesis of 2,2′-disubstituted-1,1′-biaryls. Further investigations to expand the scope of the reaction are currently underway.

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Supporting Information Available: Experimental details and analytical and spectral data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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