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Ruthenium-Catalyzed Arylation of 2-Alkenylpyridines with Aryl Bromides: Alternative *E,Z*-Selectivity to Mizoroki–Heck Reaction

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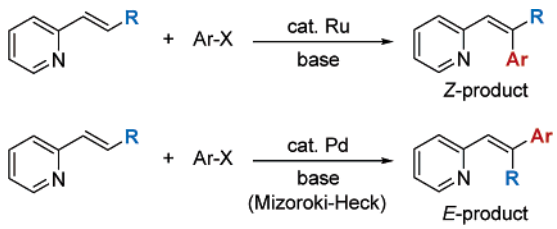
ABSTRACT

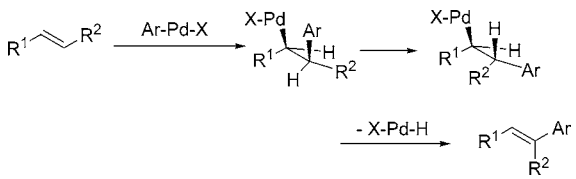


Regio- and stereoselective arylation of 2-alkenylpyridines with aryl bromides is catalyzed by specific Ru(II)–phosphine complexes affording *β*-arylated (*Z*)-2-alkenylpyridines, in which the aryl moiety is introduced cis to the pyridyl group. This geometrical selectivity is in sharp contrast to the Mizoroki–Heck reaction.

The palladium-catalyzed reaction of olefins with aryl halides, referred to as the Mizoroki−Heck reaction, has been recognized to be of great synthetic value for the substitution of olefinic hydrogen with aryl groups.[1,2] The Mizoroki−Heck reaction proceeds first via the formation of an arylpalladium intermediate, which then reacts with an olefinic compound via syn addition and then finally undergoes *syn*-*β*-hydride elimination of palladium hydride to afford the final product. This reaction pathway provides an excellent rationalization for the geometrical chemistry of reactions involving 1,2-disubstituted olefins, in which the geometry of the two functional groups R^1 and R^2 is reversed upon reaction with an aryl group introduced in the position trans to R^1 (Scheme 1).

We previously reported the direct ortho-arylation of pyridylarenes and aromatic imines using certain aryl halides in the presence of a catalytic amount of a ruthenium(II)−phosphine complex.[3] In these reactions, coordination of the pyridyl or imino group to a suitable ruthenium complex directs metalation to the ortho position of the aromatic ring. This ruthenium-catalyzed arylation has also been successfully applied to 2-alkenylpyridines affording *Z*-products exclusively (eq 1). It is noteworthy that the geometrical selectivity of this arylation reaction is in sharp

Scheme 1. Geometrical Chemistry of the Mizoroki−Heck Reaction



(1) (a) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581. (b) Heck, R. F.; Nolley, J. P., Jr. *J. Org. Chem.* **1972**, *37*, 2320.

(2) For reviews, see: (a) Heck, R. F. *Org. React.* **1982**, *27*, 345. (b) Heck, R. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 4. (c) Tsuji, J. *Palladium Reagents and Catalysts; InnoVations in Organic Synthesis*; Wiley: Chichester, 1996.

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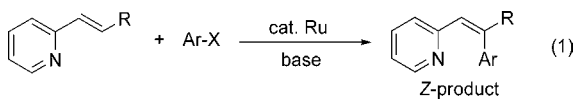
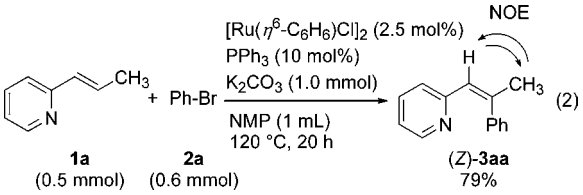
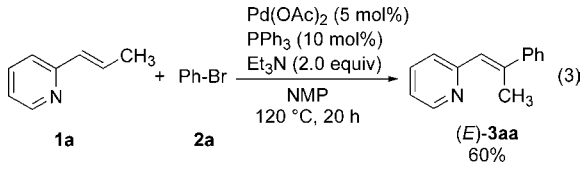
contrast to that observed for the above-mentioned Mizoroki−Heck reaction.[4,5]



Initially, the reaction of (*E*)-2-(1-propenyl)pyridine (**1a**) with bromobenzene (**2a**) was examined using a 2.5 mol % catalytic amount of $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$ in the presence of K_2CO_3 in NMP at 120 °C for 20 h. The reaction afforded the arylated product **3aa**, although the yield was as low as 10%. The addition of 2 equiv of PPh_3 to the ruthenium metal, however, dramatically increased the **3aa** yield to 79%. Here, arylation occurred exclusively at the β-position of **1a**, and the geometry of the olefinic part was determined to be *Z* through NOE experiments. Reactions involving divalent ruthenium complexes with coordinated triphenylphosphine, such as $RuCl_2(\eta^6\text{-}C_6H_6)(PPh_3)$ and $RuCl_2(PPh_3)_3$, were found to have lower catalytic activity than the combination of $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$ and PPh_3, while the cyclopentadienyl (Cp) complex $CpRuCl(PPh_3)_2$ showed no activity at all. With regard to other reaction conditions, Cs_2CO_3 was also found to act as a good base; however, organic bases such as Pr^i_2-NEt, and strong bases such as Bu^{t}OK, failed to afford **3aa**. Polar, aprotic solvents such as NMP and DMF were determined to be highly suited for this reaction, while the less polar solvents, such as xylene, afforded the product only in lower yields. The optimized reaction conditions are thus shown in eq 2.[6]

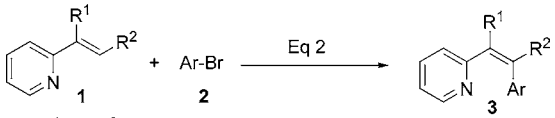


To compare the *E*,*Z*-selectivity of the present ruthenium-catalyzed reaction with that of the Mizoroki−Heck reaction, **1a** was reacted with **2a** using catalytic amounts of $Pd(OAc)_2$ (5 mol %) and PPh_3 (10 mol %) in the presence of Et_3N (2 equiv to **1a**) in NMP at 120 °C for 20 h (Mizoroki−Heck conditions). As expected, in direct contrast to the ruthenium-catalyzed reaction, the reaction under Mizoroki−Heck conditions resulted in the exclusive formation of (*E*)-**3aa** in 60% yield (eq 3).



The reactions between various 2-alkenylpyridines and aryl bromides were then examined under these optimized conditions (Scheme 2, Table 1). The reaction of (*E*)-2-styrylpyridine (**1b**) with bromobenzene (**2a**) gave the product **3ba** in quantitative yield (entry 1), while (*E*)-alkenylpyridines, bearing isopropyl **1c** and butyl **1d** groups in the β-position,

Scheme 2



1b: R^1=H, R^2=Ph
1c: R^1=H, R^2=Pr^i
1d: R^1=H, R^2=Bu^n
1e: R^1, R^2=$(CH_2)_4$
1f: R^1=R^2=H
1g: R^1=2-Me-C_6H_4, R^2=H

2a: Ar=Ph
2b: Ar=4-OMe-C_6H_4
2c: Ar=4-CF_3-C_6H_4
2d: Ar=2-Me-C_6H_4
2e: Ar=1-naphthyl
2f: Ar=2-styryl

Table 1. Ruthenium-Catalyzed Arylation of Alkenylpyridines **1** with Aryl Bromides **2**[a]

entry	1	2	product	yield (%)
1	**1b**	**2a**	**3ba**	100
2	**1c**	**2a**	(*Z*)-**3ca**	73
3	**1d**	**2a**	(*Z*)-**3da**	88
4	**1e**	**2a**	**3ea**	86
5	**1f**	**2a**		0
6	**1g**	**2a**	(*Z*)-**3ga**	59[b]
7	**1d**	**2b**	(*Z*)-**3db**	85
8	**1d**	**2c**	(*Z*)-**3dc**	86
9	**1d**	**2d**	(*Z*)-**3dd**	90
10	**1d**	**2e**	(*Z*)-**3de**	75
11	**1d**	**2f**	(*Z*,*E*)-**3df**[c]	33

[a] Reactions were carried out using 0.5 mmol of **1**, 0.6 mmol of **2**, 1.0 mmol of K_2CO_3, 0.0125 mmol of $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$, and 0.05 mmol of PPh_3 in 1 mL of NMP at 120 °C for 20 h under N_2 atmosphere. [b] 0.025 mmol of PPh_3 and 1.5 mmol of **2a** were used. [c] Containing 12% of the *E*,*E*-form.

also reacted well with **2a**, affording the products (*Z*)-**3ca** and (*Z*)-**3da**, in 73% and 88% yield, respectively (entries 2 and 3). The cycloalkenylpyridine, 2-(1-cyclohexenyl)pyridine (**1e**), was found to react with **2a**, affording the phenylated

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(4) Ruthenium catalyzed Mizoroki−Heck-type olefination and related reactions: (a) Na, Y.; Park, S.; Han, S.; Han, H.; Ko, S.; Chang, S. *J. Am. Chem. Soc.* **2004**, *126*, 250. (b) Chatterjee, A. K.; Toste, F. D.; Choi, T.; Grubbs, R. H. *Adv. Synth. Catal.* **2002**, *344*, 634.

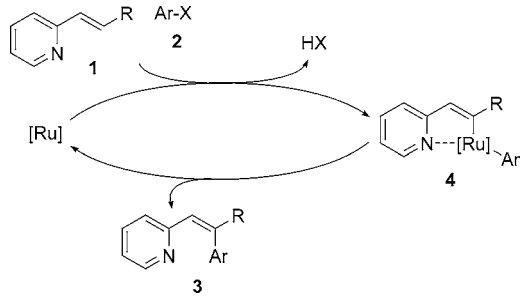
(5) Although the selectivity is not high, *Z*-selective Mizoroki−Heck reaction catalyzed by palladium has been reported. (a) Nilsson, P.; Larhed, M.; Hallberg, A. *J. Am. Chem. Soc.* **2001**, *123*, 8217. (b) Svennebring, A.; Nilsson, P.; Larhed, M. *J. Org. Chem.* **2004**, *69*, 3345.

(6) A mixture of **1a** (59.6 mg, 0.50 mmol), **2a** (94.2 mg, 0.60 mmol), K_2CO_3 (138.2 mg, 1.0 mmol), PPh_3 (13.1 mg, 0.05 mmol), and $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$ (6.3 mg, 0.0125 mmol) in 1 mL of dried and degassed NMP was stirred at 120 °C for 20 h. The reaction mixture was diluted with 10 mL of EtOAc, washed with water (10 mL × 2), and dried over Na_2SO_4. After the solvent was removed in vacuo, the residue was purified by silica gel flash chromatography (hexanes−EtOAc, 5:1) to give (*Z*)-**3aa** (77.1 mg, 0.395 mmol). All other reactions were performed using the same procedure.

product **3ea** with a yield of 86% (entry 4). Interestingly, the reaction between 2-vinylpyridine (**1f**) and **2a** failed to undergo arylation (entry 5), while the same reaction between 1.5 mmol of **2a** and the α-substituted 1-(2-tolyl)-2-vinylpyridine (**1g**), in the presence of a sufficient amount of PPh_3 (0.025 mmol, Ru/P = 1:1), afforded (*Z*)-**3ga** in 59% yield (entry 6). The reaction between **1d** and certain substituted bromobenzenes, bearing either electron-donating or -withdrawing groups in the para position (**2b** and **2c**), gave the corresponding products (*Z*)-**3db** and (*Z*)-**3dc** in good yield (entries 7 and 8). Moreover, **1d** also reacted well with sterically hindered 2-bromotoluene (**2d**) and 1-bromonaphthalene (**2e**), resulting in the formation of (*Z*)-**3dd** and (*Z*)-**3de**, respectively, in good yield (entries 9 and 10). Alkenyl bromides were also found to react under these conditions. The reaction between **1d** and (*E*)-*β*-bromostyrene (**2f**) produced 2-[(*Z*)-2-((*E*)-styryl)-1-hexenyl]pyridine ((*Z*,*E*)-**3df**), together with a small amount of *E*,*E*-form in this case, in 33% yield (entry 11).

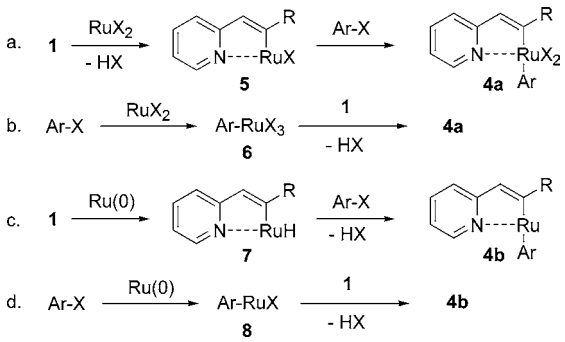
The reaction between (*E*)-stilbene and **2a** on the other hand, failed to occur, suggesting that the presence of the pyridyl group is necessary for the reaction to proceed. Although there is little experimental evidence at present to determine the exact reaction mechanism, the following two steps are believed to be involved in the catalytic pathway: (i) oxidative addition of the aryl halide to a ruthenium complex to give an arylruthenium intermediate and (ii) *β-cis*-ruthenation of the olefinic moiety, directed by coordination of the pyridyl group to the ruthenium atom. An outline of one possible reaction pathway is shown in Scheme 3. Here,

Scheme 3



the reaction between a ruthenium complex and an alkenylpyridine **1** and aryl halide **2** results in the formation of a nitrogen atom-coordinated ruthenacycle **4**. Reductive elimination of **4** affords the arylated product **3**, with the simultaneous regeneration of the initial ruthenium complex. We believe that the regioselectivity and *Z*-selectivity of the reaction is caused by the formation of the key intermediate **4**. Several pathways for the formation of **4** are envisaged (Scheme 4). For example, the *β-cis*-ruthenation of the olefinic moiety of **1** by a Ru(II) complex to form a divalent

Scheme 4



ruthenacycle **5**, followed by oxidative addition of the aryl halide, affords a tetravalent ruthenacycle **4a** (eq a). Alternatively, oxidative addition of the aryl halide to a Ru(II) complex to form a tetravalent arylruthenium complex **6**, followed by *β-cis*-ruthenation of **1** gives **4a** (eq b).[7] Moreover, pathways involving zerovalent ruthenium species present another possible route. The oxidative addition of a C−H bond at the *β*-position of **1** to a Ru(0) complex results in the formation of a ruthenium hydride complex **7**,[8,9] which after oxidative addition of the aryl halide, and subsequent elimination of HX, affords the divalent ruthenacycle **4b** (eq c). Alternatively, oxidative addition of the aryl halide to a Ru(0) complex to form a divalent arylruthenium complex **8**, followed by *β-cis*-ruthenation of **1**, is also expected to afford **4b** (eq d).

In conclusion, we have shown that the ruthenium-catalyzed arylation of alkenylpyridines with aryl bromides affords the normally less stable *β*-arylated (*Z*)-2-alkenylpyridines, selectively. The geometrical selectivity of this reaction is in stark contrast to that of the Mizoroki−Heck reaction, which we attribute to the unprecedented reaction pathway involving the nitrogen atom-coordinated ruthenacycle **4**. Further studies to expand the scope of the described reaction are now in progress.

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

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(7) Heteroatom directed cyclometalation, see: Omae, I. *Coord. Chem. Rev.* **2004**, *248*, 995.

(8) Review: Kakiuchi, F.; Murai, S. In *Topics in Organometallic Chemistry*; Murai, S., Ed.; Springer: Berlin, 1999; Vol. 3, pp 47−79.

(9) (a) Chatani, N.; Ishii, Y.; Ie, Y.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **1998**, *63*, 5129. (b) Trost, B. M.; Imi, K.; Davies, I. W. *J. Am. Chem. Soc.* **1995**, *117*, 5371. (c) Lim, Y.-G.; Kang, J.-B.; Kim, Y. H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 699.