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Ruthenium-catalyzed Oxidative Alkenylation of Arenes via Regioselective C–H Bond Cleavage Directed by a Nitrogen-containing Group

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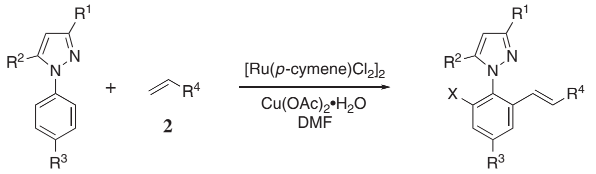
Direct alkenylation of 1-phenylpyrazoles with alkenes such as acrylates accompanied by regioselective C–H bond cleavage proceeds efficiently under ruthenium catalysis in the presence of a copper oxidant. The procedure is also applicable to 2-phenylbenzothiazole and benzanilide.

Transition-metal-catalyzed regioselective C–H functionalization reactions with the aid of directing groups have been recognized as synthetically attractive tools from atom- and step-economic points of view.[1] Particularly, the palladium- and rhodium-catalyzed *ortho*-alkenylation of aromatic substrates with readily available alkenes seems to be a useful method to selectively construct π-conjugated vinylarene frameworks, which can be widely seen in organic materials.[2] As early examples, we demonstrated that 2-phenylphenols,[3] *N*-(arylsulfonyl)-2-phenylanilines,[4] and benzoic acids[4,5] undergo directed alkenylation under Pd- or Rh-catalysis. Since then, a number of related oxidative alkenylation reactions have been disclosed by us[6] and others.[7] Compared to well-developed Pd- and Rh-catalyzed reactions, the ruthenium-catalyzed version has been less explored. Recently, we succeeded in finding that heteroarene carboxylic acids undergo directed alkenylation under Ru-catalysis.[8a] Although the Ru-catalyzed alkenylation[9,10] seems to be attractive due to relatively lower catalyst cost compared to Pd and Rh, the substrates have so far been limited to carboxylic acids.[8] Therefore, we have investigated the applicability of our Ru-catalyst system to other substrates and found that phenylazoles and benzanilide are capable of undergoing the regioselective alkenylation directed by their nitrogen-containing groups. In most cases, monoalkenylated products can be obtained selectively. The results obtained for the reactions are described herein.

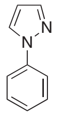
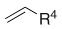
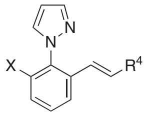
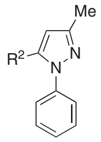
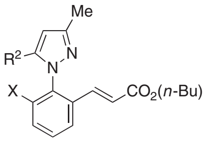
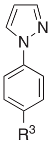
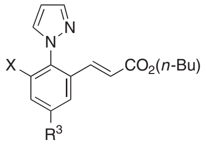
In an initial attempt, 1-phenylpyrazole (**1a**) (0.25 mmol) was treated with butyl acrylate (**2a**) (0.5 mmol) in the presence of $[Ru(p\text{-cymene})Cl_2]_2$ (0.013 mmol) and $Cu(OAc)_2\cdot H_2O$ (0.5 mmol) as catalyst and oxidant, respectively, in DMF at 100 °C for 4 h under N_2. As a result, a monoalkenylated product, 1-{2-[(*E*)-2-(*n*-butoxycarbonyl)ethenyl]phenyl}pyrazole (**3a**), was obtained in 67% yield (Entry 1 in Table 1). Note that even under conditions using excess **2a**, only a minor amount of dialkenylated product was detected by GC-MS. This is in contrast to the fact that the selective monoalkenylation could be achieved by using excess **1a** under Rh catalysis.[6a] The catalyst loading could be reduced up to 2 mol % to afford **3a** in a comparable yield (Entry 2). The reaction of **1a** with ethyl acrylate (**2b**) proceeded similarly to give monoalkenylated product **3b** in 62% yield (Entry 3). In the case using cyclohexyl acrylate (**2c**), in contrast, a separable mixture of mono- (**3c**) and dialkenylated (**4c**) products was formed and isolated in 46% and 16% yields, respectively (Entry 4). Acrylonitrile (**2d**) and styrene (**2e**) also underwent alkenylation with **1a** to afford **3d** and **3e** albeit in lower yields (Entries 5 and 6). Under the present conditions, the reaction with *N*,*N*-dimethylacrylamide was sluggish.

Table 1. Reaction of 1-phenylpyrazoles **1** with alkenes **2**[a]



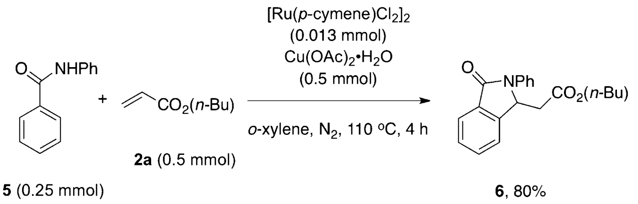
1

3: X = H
4: X = CH=CHR^4

Entry	1	2	Product(s), Yield[b]/%
			
1	**1a**	**2a**: $R^4 = CO_2(n\text{-Bu})$	**3a**: $R^4 = CO_2(n\text{-Bu})$, 67
2[c]		**2a**: $R^4 = CO_2(n\text{-Bu})$	**3a**: $R^4 = CO_2(n\text{-Bu})$, 65
3		**2b**: $R^4 = CO_2Et$	**3b**: $R^4 = CO_2Et$, 62
4		**2c**: $R^4 = CO_2Cy$	**3c**: $R^4 = CO_2Cy$, 42 **4c**: $R^4 = CO_2Cy$, 16
5		**2d**: $R^4 = CN$	**3d**: $R^4 = CN$, 43[d]
6		**2e**: $R^4 = Ph$	**3e**: $R^4 = Ph$, 18
			
7	**1b**: $R^2 = H$	**2a**	**3f**: $R^2 = H$, 41 **4f**: $R^2 = H$, 19
8	**1c**: $R^2 = Me$		**3g**: $R^2 = Me$, 78
			
9	**1d**: $R^3 = Me$	**2a**	**3h**: $R^3 = Me$, 74 **4h**: $R^3 = Me$, 20
10	**1e**: $R^3 = Cl$		**3i**: $R^3 = Cl$, 53 **4i**: $R^3 = Cl$, 11

[a] Reaction conditions: **1** (0.25 mmol), **2** (0.5 mmol), $[(Ru(p\text{-cymene})Cl_2)_2]$ (0.013 mmol), $Cu(OAc)_2\cdot H_2O$ (0.5 mmol) in DMF (3 mL) at 100 °C for 4 h under N_2. [b] Isolated yield based on the amount of **1** used. [c] $[(Ru(p\text{-cymene})Cl_2)_2]$ (0.005 mmol) was used. [d] $E/Z = 4{:}1$.

The reactions of substituted 1-phenylpyrazoles with **2a** were next examined. 3-Methyl-1-phenylpyrazole (**1b**) underwent the



Scheme 1.

alkenylation to afford a separable mixture of mono- and dialkenylated products, **3f** and **4f** (Entry 7). The reaction of 3,5-dimethyl-1-phenylpyrazole (**1c**) gave monoalkenylated **3g** exclusively (Entry 8). 1-(4-Methylphenyl)pyrazole (**1d**) and 1-(4-chlorophenyl)pyrazole (**1e**) also underwent the reaction to produce the corresponding **3** and **4** (Entries 9 and 10).

Besides pyrazoles, 2-phenylbenzothiazole also reacted with **2a** in the presence of the [Ru(*p*-cymene)Cl$_2$]$_2$/Cu(OAc)$_2$•H$_2$O catalyst system to form the corresponding monoalkenylated product, albeit in a low yield (ca. 20%). The reactions of 1-methyl-2-phenylimidazole and 2-phenylpyridine were more sluggish to afford only trace amounts of alkenylated products under similar conditions.

In addition, benzanilide (**5**) was found to undergo the coupling with **2a** under Ru catalysis (Scheme 1).[11] In this case, the reaction proceeded smoothly in *o*-xylene rather than in DMF to afford lactam **6**, an alkenylation/nucleophilic cyclization product, in 80% yield.

In summary, we have demonstrated that phenylpyrazoles and benzanilide efficiently undergo regioselective alkenylation in the presence of a ruthenium catalyst and a copper oxidant.[12] The present Ru catalyst system and related ones are expected to be applicable to other oxidative coupling reactions. Work is underway toward further development of the catalysis.

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