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Ru/Ag-Catalyzed Oxidative Alkenylation of Benzamides and Phenylazoles through Regioselective C–H Bond Cleavage

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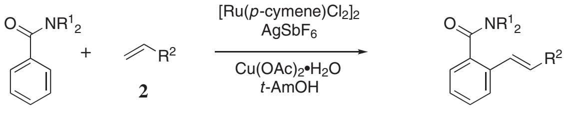
Oxidative alkenylation of *N*,*N*-disubstituted benzamides with alkenes accompanied by regioselective C–H bond cleavage proceeds efficiently in the presence of a Ru/Ag catalyst system together with a copper oxidant. The procedure is also applicable to phenylazoles.

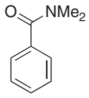
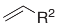
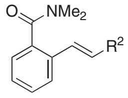
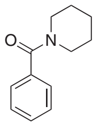
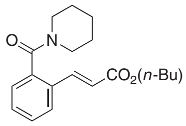
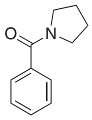
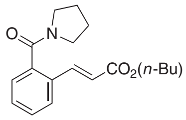
Direct C–C coupling reactions through regioselective C–H bond cleavage have attracted much attention as atom- and step-economic tools for precise synthesis, and various catalytic processes involving different modes to activate the ubiquitously available bond have been developed.[1] Among the most promising strategies is the chelate-assisted version with the aid of directing groups. Particularly, the transition-metal-catalyzed *ortho*-alkenylation of aromatic substrates through oxidative coupling with readily available alkenes[2] is a useful method to selectively construct π-conjugated alkenylarene frameworks, which can be widely seen in organic materials.[3] As early examples, we demonstrated that 2-phenylphenols,[4] *N*-(arylsulfonyl)-2-phenylanilines,[5] and benzoic acids[5,6] undergo directed alkenylation under Pd- or Rh-catalysis. Since then, a number of related oxidative alkenylation reactions have been disclosed by us[7] and others.[8] 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[9] and phenylazoles[10] undergo directed alkenylation under Ru-catalysis. Although the Ru-catalyzed alkenylation[11,12] seems to be attractive due to relatively lower catalyst cost compared to Pd and Rh, the effective substrates have so far been limited. Consequently, we have investigated retuning our Ru-catalyst system to improve the activity and to expand its applicability and found that addition of $AgSbF_6$ as a cocatalyst together with $[Ru(p\text{-cymene})Cl_2]_2$ enables *N*,*N*-disubstituted benzamides[13] to undergo the regioselective alkenylation smoothly. Actually, the reaction did not proceed at all without the cocatalyst. The catalyst system $[Ru(p\text{-cymene})Cl_2]_2$/$AgSbF_6$ was also found to be effective for the alkenylation of phenylazoles. These new findings are described herein.

In an initial attempt, *N*,*N*-dimethylbenzamide (**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 *t*-AmOH(*tert*-pentyl alcohol) at 100 °C for 4 h under N_2. Under such conditions similar to those previously employed for the reactions of 1-phenylpyrazoles,[10a] the starting materials were recovered almost completely (Entry 1 in Table 1). Addition of $AgSbF_6$ (0.05 mmol) promoted the reaction dramatically to quantitatively afford the corresponding alkenylated product, *N*,*N*-dimethyl-2-[(*E*)-(*n*-butoxycarbonyl)ethenyl]benzamide (**3a**) (Entry 2).[14] The reactions of **1a** with ethyl (**2b**) and cyclohexyl (**2c**) acrylates proceeded similarly to give the corresponding alkenylated products **3b** and **3c** in good yields (Entries 3 and 4). Styrene (**2d**) also underwent the reaction with **1a** smoothly to give a stilbene derivative **3d** (Entry 5). Besides **1a**, *N*-benzoylpiperidine (**1b**) and -pyrrolidine (**1c**) also reacted with **2a** to afford alkenylated products, **3e** and **3f**, respectively (Entries 6 and 7). Note that *ortho*-alkenylbenzamide derivatives are of interest due to their photochemical reactivity as well as applicabilities as photosensitizers and chiral auxiliaries.[15]

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

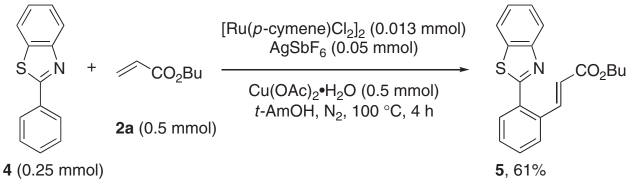


1 **2** **3**

Entry	1	2	Product, Yield/%
			
1[b]	**1a**	**2a**: $R^2 = CO_2(n\text{-Bu})$	**3a**: $R^2 = CO_2(n\text{-Bu})$, 0
2		**2a**: $R^2 = CO_2(n\text{-Bu})$	**3a**: $R^2 = CO_2(n\text{-Bu})$, 98
3		**2b**: $R^2 = CO_2Et$	**3b**: $R^2 = CO_2Et$, 92
4		**2c**: $R^2 = CO_2Cy$	**3c**: $R^2 = CO_2Cy$, 82
5		**2d**: $R^2 = Ph$	**3d**: $R^2 = Ph$, 62
			
6	**1b**	**2a**	**3e**, 82
			
7	**1c**	**2a**	**3f**, 75

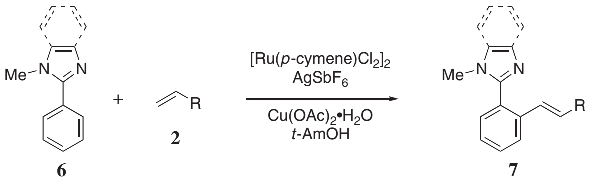
[a]Reaction conditions: **1** (0.25 mmol), **2** (0.5 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (0.013 mmol), $AgSbF_6$ (0.05 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.5 mmol), in *t*-AmOH (3 mL) at 100 °C for 4 h under N_2.
[b]Without $AgSbF_6$.

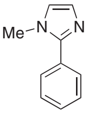
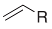
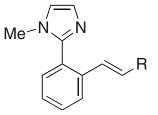
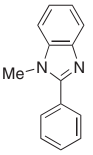
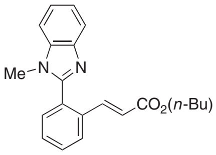
In the presence of the $[Ru(p\text{-cymene})Cl_2]_2$/$AgSbF_6$ catalyst system, the alkenylation of phenylazoles was also found to be promoted. Previously, we reported that the reaction of 2-phenylbenzothiazole (**4**) with **2a** using $[Ru(p\text{-cymene})Cl_2]_2$ gave the corresponding alkenylated product **5** in a low yield (ca. 20%).[10a] The reaction efficiency was considerably improved by the addition of $AgSbF_6$ cocatalyst to produce **5** in 61% yield (Scheme 1).



Scheme 1.

Table 2. Reaction of phenylazoles **6** with alkenes **2**[a]



Entry	6	2	Product, Yield/%
			
1	**6a**	**2a**: R = $CO_2(n\text{-Bu})$	**7a**: R = $CO_2(n\text{-Bu})$, 57
2[b]		**2a**: R = $CO_2(n\text{-Bu})$	**7a**: R = $CO_2(n\text{-Bu})$, 8[c]
3		**2b**: R = CO_2Et	**7b**: R = CO_2Et, 70
4		**2c**: R = CO_2Cy	**7c**: R = CO_2Cy, 61
5		**2d**: R = Ph	**7d**: R = Ph, 71[d]
			
6	**6b**	**2a**	**7e**, 82

[a] Reaction conditions: **6** (0.25 mmol), **2** (0.5 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (0.013 mmol), $AgSbF_6$ (0.05 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.5 mmol), in *t*-AmOH (3 mL) at 100 °C for 4 h under N_2. [b] Without $AgSbF_6$. [c] GC yield. [d] $E/Z = 9{:}1$.

With the result in hand, we reexamined the alkenylation of phenylazoles using [Ru(*p*-cymene)Cl_2]$_2$/$AgSbF_6$. As a result, 1-methyl-2-phenylimidazole (**6a**) was found to undergo the alkenylation with **2a** to produce **7a** selectively (Entry 1 in Table 2). In the absence of $AgSbF_6$, only a small amount of **7a** was formed (Entry 2). Other alkenes **2b**–**2d** also reacted with **6a** to afford the corresponding products **7b**–**7d** in 61–71% yields (Entries 3–5).[16] The reaction of 1-methyl-2-phenylbenzimidazole (**6b**) with **2a** also proceeded efficiently to give **7e** in 82% yield (Entry 6).

In summary, we have demonstrated that benzamides and phenylazoles efficiently undergo regioselective alkenylation in the presence of a Ru/Ag catalyst system and a copper oxidant.[17,18] The present catalyst system and related ones are expected to be applicable to other oxidative coupling reactions.[19] Work is underway toward further development of the catalysis.

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