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Ruthenium(II)-Catalyzed Regio- and Stereoselective Hydroarylation of Alkynes via Directed C–H Functionalization

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ABSTRACT

The ruthenium-catalyzed hydroarylation of alkynes with benzamides proceeds regio- and stereoselectively through a directed C–H bond cleavage. Preliminary mechanistic investigations indicate that the reaction involves amide-directed *ortho*-metalation, carbometalation of alkyne, and protonolysis. Similarly, phenylazoles also add to alkynes regioselectively.

Catalytic aryl–vinyl and aryl–aryl coupling reactions have been recognized to be one of the most important tools for constructing π-conjugated molecules. Compared to conventional cross-coupling reactions of halogenated or metalated aromatic reagents, the direct couplings of unactivated aromatic substrates through C–H bond cleavage have attracted significant attention as atom- and step-economical synthetic methods.[1] To activate the ubiquitously available C–H bond regioselectively and efficiently, a directing group is usually utilized. As pioneering work on such catalytic reactions, Murai and co-workers reported carbonyl-directed alkylation of aromatic ketones under ruthenium catalysis, involving *ortho* C–H bond activation and subsequent insertion of alkenes.[2] Related reactions with internal alkynes in place of alkenes have also been developed as synthetic tools for *ortho*-olefination,[3] although products are usually obtained as regio- and

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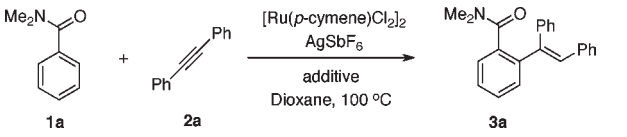
stereoisomeric mixtures. Recently, similar hydroarylation reactions of alkynes using rhodium,[4,5] iridium,[6] palladium,[7] rhenium,[8] nickel,[9] and cobalt[10] catalysts have also been reported,[11] but the substrate scope remains limited. Consequently, development of new catalyst systems with high selectivity and wide applicability is strongly desired. In the context of our study of ruthenium-catalyzed C−H olefination,[3a−c,12] we have succeeded in finding that the regio- and stereoselective hydroarylation of various alkynes with benzamides involving amide-directed C−H bond cleavage can be realized by using a ruthenium/silver catalyst system.[13] The catalyst was also found to be effective for the hydroarylation with phenylazoles. These new findings are described herein.

In an initial attempt, the reaction of *N*,*N*-dimethylbenzamide (**1a**) (0.25 mmol) with diphenylacetylene (**2a**) (0.5 mmol) was conducted in the presence of [Ru(*p*-cymene)Cl_2]$_2$ (0.0125 mmol, 5 mol %) and $AgSbF_6$ (0.05 mmol) in dioxane at 100 °C for 5 h under N_2. As a result, the hydroarylation product **3a** was obtained in 43% yield (entry 1 in Table 1). The product yield was remarkably improved to 96% by addition of AcOH (1 mmol) (entry 2). Decreasing the amount of AcOH to 0.1 mmol reduced the yield (entry 3). Under conditions using H_2O or KOAc in place of AcOH, **3a** could not be obtained at all (entries 4 and 5). Even with a slight excess (0.3 mmol) of **2a**, **3a** was formed in 82% yield (entry 6).

Table 1. Reaction of *N*,*N*-Dimethylbenzamide (**1a**) with Diphenylacetylene (**2a**)[a]



1a 2a 3a

entry	additive (mmol)	yield of **3a** (%)[b]
1	–	43
2	AcOH (1)	96 (81)
3	AcOH (0.1)	55
4	H_2O (1)	0
5	KOAc (1)	0
6[c]	AcOH (1)	82

[a] Reaction conditions: [**1a**]/[**2a**]/[{Ru(*p*-cymene)Cl_2}$_2$]/[$AgSbF_6$] = 0.25:0.5:0.0125:0.05 (in mmol), in dioxane (3 mL) at 100 °C for 5 h under N_2. [b] GC yield based on the amount of **1a** used. Value in parentheses indicates yield after purification. [c] [**2a**] = 0.3 mmol.

Next, the hydroarylation of various alkynes with amides was examined under similar reaction conditions in the presence of AcOH. Unsymmetrical alkylphenylacetylenes, 1-phenylpropyne (**2b**) and -hexyne (**2c**), reacted with **1a** to smoothly produce **3b** and **3c**, respectively (entries 1 and 2 in Table 2). It should be noted that no regio- and stereoisomers could be detected at all. Bis(4-chlorophenyl)acetylene (**2d**) coupled with **1a** to form **3d** (entry 3). The reaction of 1-phenyl-2-(trimethylsilyl)acetylene (**2e**) proceeded efficiently through hydroarylation and subsequent desilylation to produce a 1,1-diarylethene derivative **3e** in 63% yield, along with a minor amount of normal product **3e′** (entry 4). From a terminal alkyne, tris(isopropyl)silylacetylene (**2f**), the corresponding hydroarylation product **3f** was obtained, albeit with a low yield (entry 5). A series of *N*,*N*-disubstituted benzamides having a cyclic- or diphenylamino group, **1b**−**d**, reacted with **2a** to form products **3g**−**i**, respectively, in 47−79% yields (entries 6−8).

A plausible mechanism for the reaction of **1** with **2** is illustrated in Scheme 1. First, *ortho*-metalation of **1** takes

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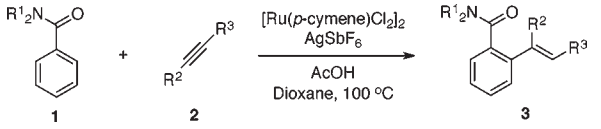
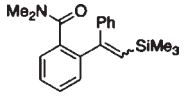
Table 2. Reaction of Benzamides **1** with Alkynes **2**[a]



1 2 3

entry	1	2	3, yield[b]
1	**1a**	**2b**, R = Me	**3b**, R = Me (77%)
2		**2c**, R = Bu	**3c**, R = Bu (68%)
3	**1a**	**2d**	**3d** (42%)
4	**1a**	**2e**	**3e** (63%)[c]
5	**1a**	**2f**	**3f** (19%)
6	**1b**, $R_2 = (CH_2)_4$	**2a**	**3g**, $R_2 = (CH_2)_4$ (79%)
7	**1c**, $R_2 = (CH_2)_5$		**3h**, $R_2 = (CH_2)_5$ (56%)
8	**1d**, R = Ph		**3i**, R = Ph (47%)

[a] Reaction conditions: [**1**]/[**2**]/[{Ru(*p*-cymene)Cl_2}$_2$]/[$AgSbF_6$]/[AcOH] = 0.25:0.5:0.0125:0.05:1 (in mmol), in dioxane (3 mL) at 100 °C for 5 h under N_2. [b] Isolated yield based on the amount of **1** used. [c] A separable byproduct, *N*,*N*-dimethyl-2-(1-phenyl-2-(trimethylsilyl)vinyl)benzamide (**3e′**), was also formed in 17% yield.

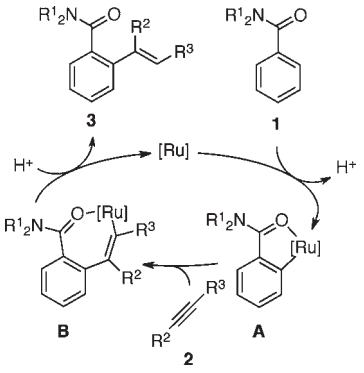


3e′

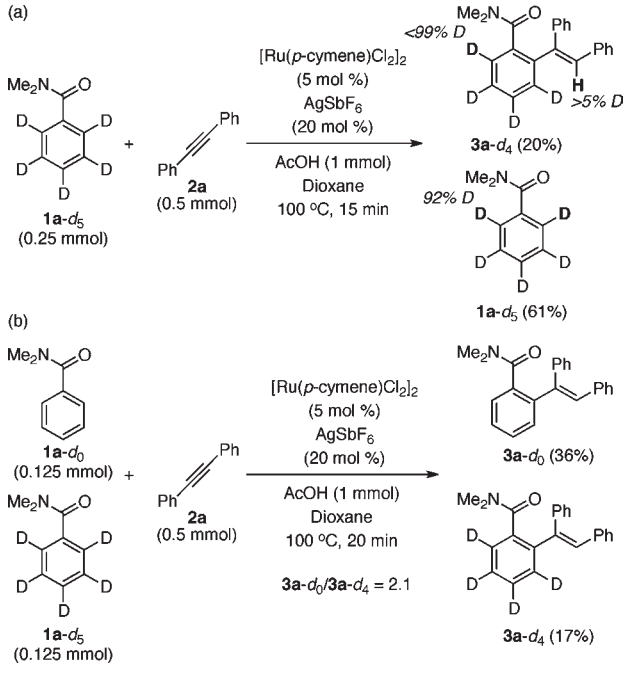
place to give a five-membered ruthenacycle intermediate **A** accompanied by loss of a proton.[14] Subsequently, alkyne insertion into the resulting Ru−C bond to form an intermediate **B** and protonolysis may occur to produce **3**.

(14) It was recently reported that AcOH promotes the C−H bond activation of 2-phenylpyridine: Flegeau, E. F.; Bruneau, C.; Dixneuf, P. H.; Jutand, A. *J. Am. Chem. Soc.* **2011**, *133*, 10161 and references therein.

Scheme 1

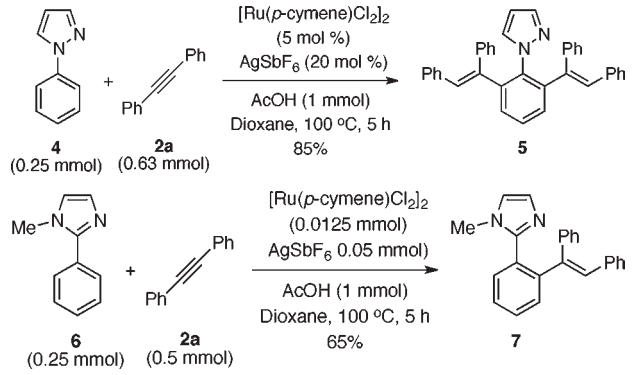


Scheme 2



For further mechanistic information, deuterated *N*,*N*-dimethylbenzamide (**1a**-d_5) was subjected to the reaction conditions (Scheme 2a). In the early stage, deuterium incorporation in the olefinic position of the product could not be detected by ^{1}H NMR. The fact excludes the possibility of a reaction pathway via oxidative addition of an *ortho* C−H bond, which should lead to deuterium incorporation at the position.[10a,d] In addition, no significant deuterium loss at the *ortho* positions of recovered **1a**-d_5 as well as at the 6-position of product **3a**-d_4 was observed. This result indicates that the *ortho*-metalation step to form **A** is likely irreversible. Next, an intermolecular competition reaction of **1a**-d_0/**1a**-d_5 with **2a** was conducted. As shown in Scheme 2b, a considerable primary isotope effect of 2.1 was observed, which suggests that the rate-determining step involves C−H(D) bond cleavage.

Scheme 3



The catalyst system was found to be applicable to the reactions of phenylazoles. Thus, 1-phenylpyrazole (**4**) underwent 2-fold coupling with **2a** via C−H bond cleavage at the 2′- and 6′-positions to afford **5** in 85% yield (Scheme 3). In contrast, *N*-methyl-2-phenylimidazole (**6**) coupled with **2a** in a 1:1 manner to produce **7** selectively.

In summary, we have demonstrated that the ruthenium-catalyzed hydroarylation of alkynes with benzamides takes place efficiently. The procedure is also applicable to phenylazoles. The present catalyst system and related ones are expected to be applicable to other hydroarylation reactions. Work is underway toward further development of the catalysis.

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Supporting Information Available. Standard experimental procedure and characterization data of products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.