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Ruthenium-Catalyzed Regioselective C−H Alkenylation Directed by a Free Amino Group

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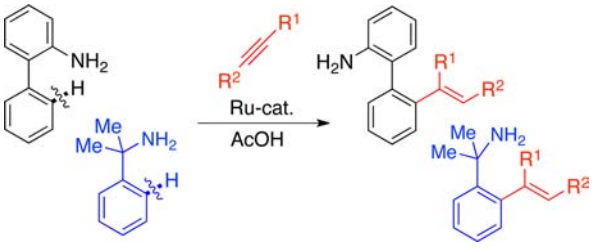
ABSTRACT



The ruthenium-catalyzed alkenylation reactions of 2-aminobiphenyls and cumylamine proceed smoothly to produce the corresponding regioselectively alkenylated products. These reactions involve a C−H bond cleavage directed by their free amino groups.

Transition-metal-mediated or -catalyzed C−H functionalization has recently gained significant attention because of their utility as atom- and step-economical tools in organic synthesis.[1] Especially, a chelation-assisted version with the aid of directing groups is of importance, since they lead to a regioselective C−H bond cleavage through *ortho*-metalation. In most precedent examples, carbonyl (ketones, aldehydes, esters, and amides), hydroxy, carboxy, imino, and pyridyl, and azolyl groups have been employed as directing groups. Meanwhile, amino groups, which are more simple and ubiquitously available in a wide range of organic molecules, have also been utilized for stoichiometric *ortho*-functionalization.[2] However, interaction between transition metals and amino groups, especially *N*-unsubstituted ones, has been regarded to be too strong to be involved in catalytic processes.[3,4]

On the other hand, we have reported that benzamides and phenylazoles undergo *ortho*-alkenylation with internal

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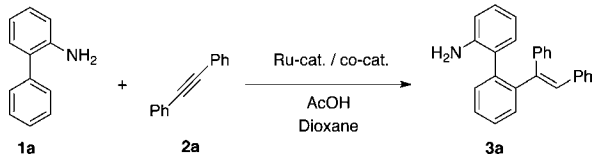
alkynes in the presence of a ruthenium/silver catalyst system and acetic acid.[5,6] Under such weakly acidic conditions, the coordination ability of amino groups to a ruthenium center seems to be weakened. Indeed, under similar conditions using acetic acid, the alkenylation of 2-aminobiphenyls was found to take place smoothly via a C−H bond cleavage at the 2′-position with the aid of their free-amino group to produce the corresponding 2-amino-2′-alkenylbiphenyls selectively. It should be noted that 2-aminobiphenyl frameworks are included in a wide range of functional molecules such as bioactive reagents,[7] fluorescent probes for bioimaging,[8] conductive polymers,[9] inclusion compounds,[10] porous materials,[11] and ligands.[12] Therefore, various methods for their precise synthesis and modification are desired in such broad fields. By using a similar reaction system, the amino-directed *ortho* alkenylation of cumylamine could also be conducted efficiently. α,α-Dialkylbenzylamine derivatives including cumylamines are also of interest because of their biological activities.[13] These new findings are described herein.

In an initial attempt, 2-aminobiphenyl (**1a**) (0.25 mmol) was treated with diphenylacetylene (**2a**) (0.25 mmol) in the presence of $[Ru(p\text{-cymene})Cl_2]_2$ (0.0125 mmol, 5 mol %), $AgSbF_6$ (0.05 mmol), and AcOH (1 mmol) in dioxane at 100 °C for 3 h under N_2. As a result, the alkenylation product, (*E*)-2′-(1,2-diphenylethenyl)-[1,1′-biphenyl]-2-amine (**3a**), was formed stereoselectively in 52% yield (entry 1 in Table 1).[14] Increasing the amount of **2a** to 0.5 mmol significantly enhanced the product yield to 70% (entry 2). Even with excess **2a**, no overreaction was observed. It was confirmed that the reaction did not proceed at all in the absence of AcOH (entry 3). Other silver salts such as $AgBF_4$ and AgOTf could also be used as cocatalysts in place of $AgSbF_6$ (entries 4 and 5). Without any silver salt, **3a** could not be obtained at all (entry 6). The use of $[Ru(benzene)Cl_2]_2$ in place of $[Ru(p\text{-cymene})Cl_2]_2$ slightly improved the yield of **3a** (entry 7). A comparable result was obtained in the case using 1-AdCO_2H (Ad = adamantyl) in place of AcOH (entry 8). Finally, the best result was obtained at 80 °C: under such mild conditions, **3a** was produced in 85% yield (entry 9). Decreasing the reaction temperature further reduced the yield of **3a** (entries 10 and 11).

Table 1. Reaction of **2**-Aminobiphenyl (**1a**) with Diphenylacetylene (**2a**)[a]



entry	Ru-cat.	cocat.	temp (°C)	time (h)	yield of **3a** (%)[b]
1[c]	$[Ru(p\text{-cymene})Cl_2]_2$	$AgSbF_6$	100	3	52
2	$[Ru(p\text{-cymene})Cl_2]_2$	$AgSbF_6$	100	3	70
3[d]	$[Ru(p\text{-cymene})Cl_2]_2$	$AgSbF_6$	100	5	0
4	$[Ru(p\text{-cymene})Cl_2]_2$	$AgBF_4$	100	5	67
5	$[Ru(p\text{-cymene})Cl_2]_2$	AgOTf	100	5	71
6	$[Ru(p\text{-cymene})Cl_2]_2$	–	100	5	0
7	$[Ru(benzene)Cl_2]_2$	$AgSbF_6$	100	5	80
8[e]	$[Ru(benzene)Cl_2]_2$	$AgSbF_6$	100	5	82
9	$[Ru(benzene)Cl_2]_2$	$AgSbF_6$	80	5	85(61)
10	$[Ru(benzene)Cl_2]_2$	$AgSbF_6$	60	7	81
11	$[Ru(benzene)Cl_2]_2$	$AgSbF_6$	rt	24	3

[a] Reaction conditions: [**1a**]:[**2a**]:[Ru-cat.]:[cocat.]:[AcOH] = 0.25:0.5:0.0125:0.05:1 (in mmol), in dioxane (3 mL) under N_2. [b] GC yield based on the amount of **1a** used. Value in parentheses indicates yield after purification. [c] [**2a**] = 0.25 mmol. [d] Without AcOH. [e] 1-AdCO_2H (1 mmol) was employed in place of AcOH.

Next, the alkenylation of substituted 2-aminobiphenyls was examined under the optimized conditions (entry 8 in Table 1). 4′-Methyl (**1b**), -methoxy (**1c**), -chloro (**1d**), and -trifluoromethyl (**1e**) substituted 2-aminobiphenyls

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reacted with **2a** smoothly to produce the corresponding alkenylated products **3b**–**e** in 75–82% yields (entries 1–4 in Table 2). The reactions of 3′-substituted substrates **1f** and **1g** with **2a** took place at the sterically less hindered position exclusively to produce **3f** and **3g** (entries 5 and 6). A series of 5-substituted 2-aminobiphenyls **1h**–**k** also underwent the alkenylation to afford **3h**–**k** (entries 7–10).

Table 2. Reaction of **2**-Aminobiphenyls **1** with Diphenylacetylene (**2a**)[a]

entry	1	time (h)	product, % yield[b]
1	**1b**: R = Me	5	**3b**: R = Me, 82
2	**1c**: R = OMe	8	**3c**: R = OMe, 75
3	**1d**: R = Cl	1	**3d**: R = Cl, 78
4	**1e**: R = CF_3	1	**3e**: R = CF_3, 75
5	**1f**: R = OMe	5	**3f**: R = OMe, 50
6	**1g**: R = CF_3	5	**3g**: R = CF_3, 74
7	**1h**: R = Me	5	**3h**: R = Me, 65
8	**1i**: R = OMe	5	**3i**: R = OMe, 62
9	**1j**: R = Cl	5	**3j**: R = Cl, 70
10	**1k**: R = CF_3	5	**3k**: R = CF_3, 71

[a] Reaction conditions: [**1**]:[**2a**]:[{Ru(benzene)Cl_2}$_2$]:[$AgSbF_6$]:[AcOH] = 0.25:0.5:0.0125:0.05:1 (in mmol), in dioxane (3 mL) at 80 °C under N_2. [b] Isolated yield based on the amount of **1** used.

The reactions of **1a** with various alkynes **2** were next examined. *para*-Substituted diphenylacetylenes **2b**–**e** coupled with **1a** to form **3l**–**o** (entries 1–5 in Table 3). Among them, the reaction with **2c** was somewhat sluggish under the standard conditions (entry 2). Increasing the amount of [Ru(benzene)Cl_2]$_2$ slightly improved the yield of **3m** (entry 3). The reactions of unsymmerical alkynes **2f** and **2g** gave the corresponding 2′-alkenyl[1,1′-biphenyl]-2-amines as mixtures of regioisomers **3** and **3′** (entries 6 and 7). The reaction of **1a** with 2-methyl-4-phenylbut-3-yn-2-ol (**2h**) proceeded through alkenylation and cyclization to produce **4**, albeit with low efficiency (entry 8). The structure of **4** was determined by X-ray crystallography (see the Supporting Information).

A plausible mechanism for the reaction of **1a** with **2** is illustrated in Scheme 1. Coordination of the amino nitrogen in **1a** seems to be the key for the regioselective C–H bond

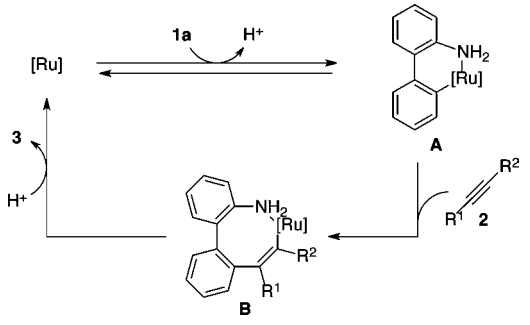
Table 3. Reaction of **2**-Aminobiphenyl (**1a**) with Alkynes **2**[a]

entry	2	time (h)	product, % yield[b]
1	**2b**: X = Me	5	**3l**: X = Me, 60
2	**2c**: X = OMe	5	**3m**: X = OMe, 25
3[c]	**2c**: X = OMe	7	**3m**: X = OMe, 39
4	**2d**: X = Cl	5	**3n**: X = Cl, 67
5	**2e**: X = CF_3	24	**3o**: X = CF_3, 68
6	**2f**: R = Me	5	**3p** + **3p′**: R = Me, 51 (61:39)[d]
7	**2g**: R = Bu	5	**3q** + **3q′**: R = Bu, 64 (71:29)[d]
8	**2h**	5	**4**, 20

[a] Reaction conditions: [**1a**]:[**2**]:[{Ru(benzene)Cl_2}$_2$]:[$AgSbF_6$]:[AcOH] = 0.25:0.5:0.0125:0.05:1 (in mmol), in dioxane (3 mL) at 80 °C under N_2. [b] Isolated yield based on the amount of **1a** used. [c] [{Ru(benzene)Cl_2}$_2$] = 0.025. [d] Determined by ^{1}H NMR.

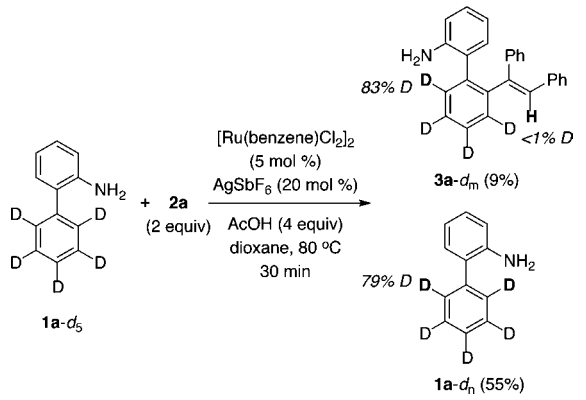
cleavage at the 2′-position to form a ruthenacycle intermediate **A**. Then, alkyne insertion into the resulting aryl–Ru bond to form an intermediate **B** and subsequent protonolysis may take place to produce **3**. The last step appears to be promoted by added AcOH.[15]

Scheme 1



(15) It is possible that AcOH promotes the C–H bond activation step: (a) Flegeau, E. F.; Bruneau, C.; Dixneuf, P. H.; Jutand, A. *J. Am. Chem. Soc.* **2011**, *133*, 10161and references therein. See also: (b) Boutadla, Y.; Davies, D. L.; Macgregor, S. A.; Poblador-Bahamonde, A. I. *Dalton Trans.* **2009**, 5820. (c) Davies, D. L.; Al-Duaij, O.; Fawcett, J.; Giardiello, M.; Hilton, S. T.; Russell, D. R. *Dalton Trans.* **2003**, 4132. In contrast, the exact role of a silver cocatalyst is obscure at the present stage.

Scheme 2

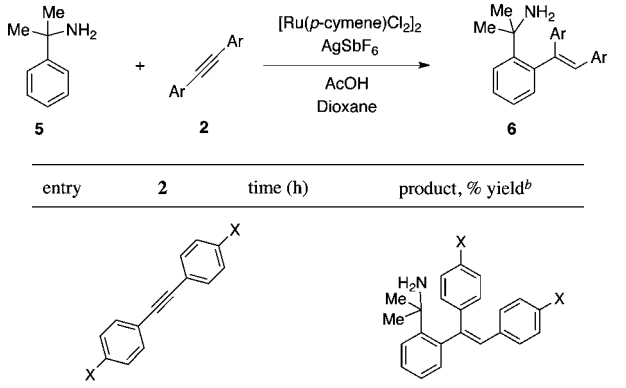


In the early stage (30 min) of the reaction of a deuterated 2-aminobiphenyl **1a**-d_5 with **2a**, considerable contamination by protons at the 6′-position of 2′-alkenylated product **3a**-d_m and at the 2′- and 6′-positions of recovered **1a**-d_n occurred (Scheme 2). These facts indicate that the C−H bond cleavage step to form **A** appears to be reversible. In addition, deuterium incorporation in the alkenyl position of the product could not be detected by ^{1}H NMR. Therefore, the reaction pathway involving oxidative addition of a C−H bond at the 2′-position, which should bring about deuterium incorporation at the alkenyl position, can be excluded.

The alkenylation procedure could be applied to the reactions of cumylamine (**5**). Thus, treatment of **5** with **2a** under the standard conditions gave *ortho*-alkenylated product **6a** in 64% yield (entry 1 in Table 4). Using 1 equiv of **2a** at 100 °C, **6a** was obtained in 74% yield (entry 3). Under similar conditions, **5** reacted with **2b**, **2d**, and **2e** to form **6b**−**d**, respectively (entries 4−6).

In summary, we have demonstrated that the ruthenium-catalyzed alkenylation of 2-aminobiphenyls with alkynes takes place efficiently via amino-group-directed C−H bond cleavage. The procedure is also applicable to cumylamine. Catalytic processes utilizing a free amino group as a directing group have been less explored, and this represents a new, effective protocol for achieving chelation control. Further work for developing related reactions at the proximal positions of common and ubiquitous function is underway.

Table 4. Reaction of Cumylamine (**5**) with Alkynes **2**[a]



entry	2	time (h)	product, % yield[b]
1[c,d]	**2a**: X = H	0.5	**6a**: X = H, 64
2[c]	**2a**: X = H	1	**6a**: X = H, 73
3	**2a**: X = H	0.5	**6a**: X = H, 74 (67)
4	**2b**: X = Me	2	**6b**: X = Me, (46)
5	**2d**: X = Cl	1	**6c**: X = Cl, (41)
6	**2e**: X = CF_3	1	**6d**: X = CF_3, (45)

[a] Reaction conditions: [**5**]:[**2**]:[{Ru(*p*-cymene)Cl_2}$_2$]:[$AgSbF_6$]:[AcOH] = 0.25:0.25:0.0125:0.05:1 (in mmol), in dioxane (3 mL) at 100 °C under N_2. [b] GC yield based on the amount of **5** used. Value in parentheses indicates yield after purification. [c] [**2a**] = 0.5. [d] At 80 °C.

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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.