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# Rhodium-catalyzed Oxidative Coupling/Cyclization of Benzamides with Alkynes via C–H Bond Cleavage

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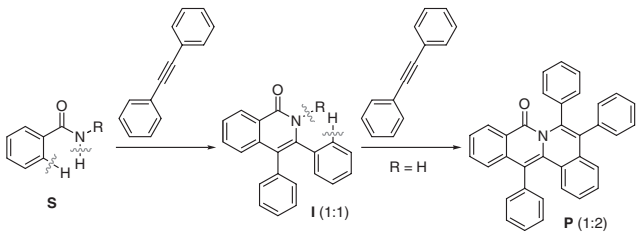
Oxidative coupling of primary, secondary, and tertiary benzamides with internal alkynes proceeds efficiently under rhodium catalysis to selectively give the corresponding 1:1 and 1:2 coupling products, accompanied by C–H and/or N–H bond cleavages. Some of the products exhibit intense fluorescence in the solid state.

The transition-metal-catalyzed C–C bond formation reactions via C–H bond cleavage have attracted much attention from the atom- and step-economical point of view, and have been significantly developed in recent years.[1] Particularly, the reactions of aromatic substrates possessing a directing group such as carbonyl and imino functions are powerful synthetic tools, because they allow regioselective C–H activation and functionalization at the *ortho*-positions. Besides the directing groups containing a neutral heteroatom, an amide group can also act as a good anchor to exhibit the proximate effect.[2,3] Thus, we previously reported the palladium-catalyzed arylation[2a–2c] and vinylation reactions[2d] of aromatic amides with aryl halides and alkenes, respectively. In the context of our further study of regioselective C–H functionalization,[4] we have undertaken the coupling of amides with alkynes. As a result, the oxidative coupling of *N*-free benzamide with diphenylacetylene has been found to proceed smoothly accompanied by regioselective C–H bond cleavage by using a rhodium catalyst and a copper oxidant. In this case, to our surprise, not their 1:1 but unexpected 1:2 coupling product was obtained predominantly (R = H in Scheme 1). The tetracyclic structure, constructed via the 1:2 coupling, can be seen in various naturally occurring and synthetic compounds that exhibit a broad range of interesting biological and optoelectronic properties.[5] Its construction usually needs complicated multisteps with huge effort.[5,6]

In the reaction of *N*-monosubstituted benzamides (R ≠ H in Scheme 1) with alkynes under similar conditions, on the other hand, the expected 1:1 coupling products, isoquinolin-1(2*H*)-one derivatives, could be obtained selectively.[7] Such a fused heteroaromatic skeleton is also of interest because it is found in various natural products such as dorianine and ruprechstyril[8] and has been utilized in versatile building blocks for the total synthesis of more complex molecules.[9] Recently, transition-metal-catalyzed coupling reactions of *o*-substituted benzamides have been shown to be applicable to the simple construction of isoquinolinone frameworks.[10] Our protocol provides a more straightforward approach from readily available parent benzamides.




**Scheme 1.**

In addition to such primary and secondary benzamides, tertiary compounds also underwent the rhodium-catalyzed oxidative coupling with alkynes via two C–H bond cleavages. These new findings are described herein.

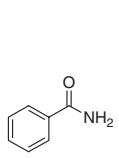
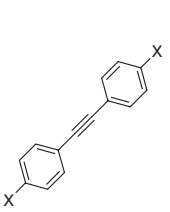
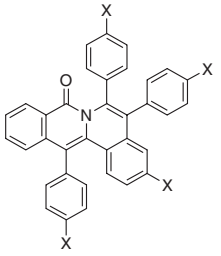
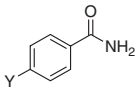
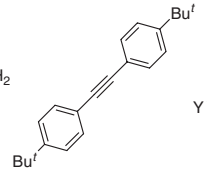
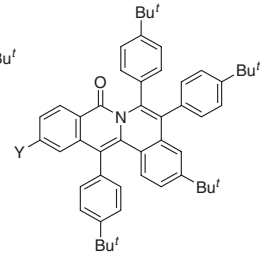
In an initial attempt, benzamide (**1a**) (0.5 mmol) was treated with diphenylacetylene (**2a**) (0.5 mmol) in the presence of $[Cp^*RhCl_2]_2$ (0.005 mmol, $Cp^*$ = pentamethylcyclopentadienyl) and $Cu(OAc)_2 \cdot H_2O$ (1 mmol) as catalyst and oxidant, respectively, in *o*-xylene at 100 °C for 10 h under $N_2$. As described above, the 1:2 coupling product, 5,6,13-triphenyl-8*H*-dibenzo[*a*,*g*]quinolizin-8-one (**3a**), was obtained in 39% isolated yield (Entry 1 in Table 1). It was confirmed by GC-MS analysis of the resulting mixture that the corresponding 1:1 coupling product, *N*-free isoquinolinone [**I** (R = H) in Scheme 1], was also formed (ca. 30%). The latter was sparingly soluble in organic solvents. Therefore, it is possible that part of this intermediate precipitated during the reaction to result in the moderate yield of **3a**. Expectedly, the reactions using alkyl-substituted diphenylacetylenes **2b** and **2c** in place of **2a** gave more soluble products **3b** and **3c**, respectively, in enhanced yields (Entries 2 and 3). Methoxy-substituted product **3d** was also obtained under similar conditions (Entry 4). Similarly, 4-substituted benzamides **1b**–**1d** also coupled with **2c** in the ratio of 1:2 to produce the corresponding product **3e**–**3g** (Entries 5–7).

A plausible mechanism for the 1:2 coupling of **1a** with **2a** via directed metalation involving intermediates **A**–**E** is illustrated in Scheme 2, in which neutral ligands are omitted. In the cyclorhodation steps from **A** and **D**, coordination of the nitrogen atom to a $Rh^{III}$ species appears to be the key for the regioselective C–H bond cleavage.

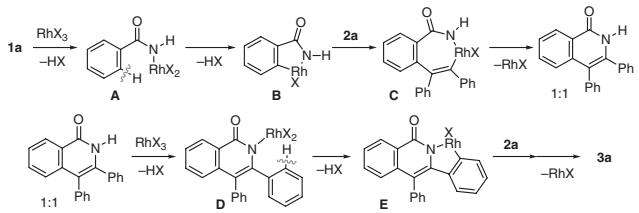
We next examined the reaction of a secondary amide, benzanilide (**4a**) with **2a** under similar conditions to those for the reaction of **1**. Thus, in the presence of the $[Cp^*RhCl_2]_2$/$Cu(OAc)_2 \cdot H_2O$ catalyst system, the 1:1 coupling efficiently took place to afford 2,3,4-triphenylisoquinolin-1(2*H*)-one (**5a**) in 75% yield (Entry 1 in Table 2). The reaction of **4a** with diarylacetylenes **2c**–**2e** also proceeded smoothly to produce the corresponding 3,4-diaryl-2-phenylisoquinolin-1(2*H*)-one **5b**–**5d** in good yields (Entries 2–4). 1-Phenyl-1-propyne (**2f**) reacted with **4a** to give 4-methyl-2,3-diphenylisoquinolin-1(2*H*)-one (**5e**) predominantly, along with a minor amount of a regioisomer (Entry 5). Similarly, from the reaction of 1-phenyl-1-hexyne (**2g**) with **4a**, 4-butyl-2,3-diphenylisoquinolin-1(2*H*)-one (**5f**) was obtained along with its regioisomer (Entry 6).[11] *N*-Aryl (**4b** and **4c**) as well as *N*-butylbenzamides (**4d**) underwent the

**Table 1.** Reaction of *N*-unsubstituted benzamides **1a–1d** with alkynes **2a–2d**[a]

| Entry | 1 | 2 | Product, yield[b]/% |
|---|---|---|---|
| |  |  |  |
| 1 | **1a** | **2a**: X = H | **3a**: X = H, 39 |
| 2 | | **2b**: X = Me | **3b**: X = Me, 60 |
| 3 | | **2c**: X = Bu$^t$ | **3c**: X = Bu$^t$, 73 |
| 4 | | **2d**: X = OMe | **3d**: X = OMe, 40 |
| |  |  |  |
| 5 | **1b**: Y = Me | **2c** | **3e**: Y = Me, 62 |
| 6 | **1c**: Y = OMe | | **3f**: Y = OMe, 25 |
| 7 | **1d**: Y = Cl | | **3g**: Y = Cl, 59 |

[a]Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), $[Cp^*RhCl_2]_2$ (0.005 mmol), $Cu(OAc)_2 \cdot H_2O$ (1 mmol) in *o*-xylene (2.5 mL) at 120 °C for 6 h under $N_2$. [b]Isolated yield based on the amount of **2** used.



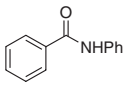
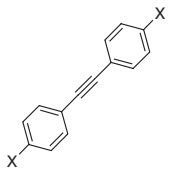
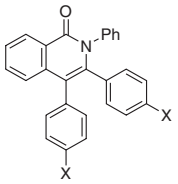
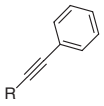
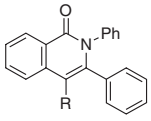
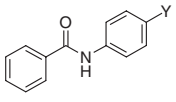
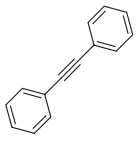
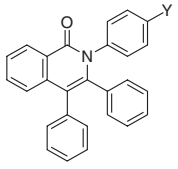
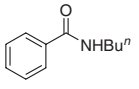
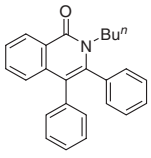
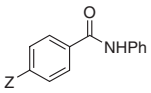
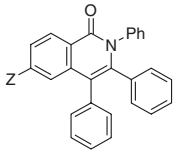
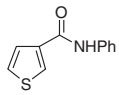
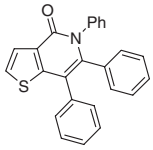
**Scheme 2.**

coupling with **2a** to produce the corresponding isoquinolin-1(2*H*)-ones **5g-i** in 65–84% yields (Entries 7–9). *N*-(4-Substituted benzoyl)- (**4e** and **4f**) and *N*-(3-thenoyl)anilines (**4g**) also coupled with **2a** to afford isoquinolin-1(2*H*)-ones **5j** and **5k** and thieno[3,2-*c*]pyridin-4(5*H*)-one **5l** (Entries 10–12).

Most of isoquinolin-1(2*H*)-ones **5** obtained above showed solid-state fluorescence in a range of 370–420 nm (see the Supporting Information). Notably, **5a** exhibited a relatively strong emission compared to anthracene by a factor of 1.4 ($\lambda_{emis} = 414$ nm). In contrast, tetracyclic **3** did not show fluorescence in the solid state.

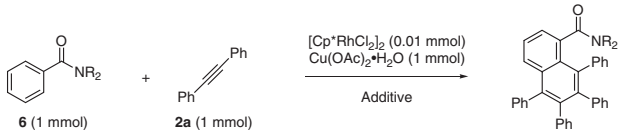
In contrast to primary and secondary amides, tertiary amides were found to undergo the oxidative coupling with **2a** via two C–H bond cleavages in a 1:2 manner.[4e] Thus, the reaction of *N*,*N*-dimethylbenzamide (**6a**) (1 mmol) with **2a** (1 mmol) gave *N*,*N*-dimethyl-5,6,7,8-tetraphenyl-1-naphthalenecarboxamide (**7a**) in 61% yield (Scheme 3). The addition of $Na_2CO_3$ (3 mmol) and $AgSbF_6$ (0.08 mmol)[3e] was needed in addition to the $[Cp^*RhCl_2]_2/Cu(OAc)_2 \cdot H_2O$ system to conduct the reaction effectively. *N*-Benzoylpyrrolidine (**6b**) also underwent the 1:2

**Table 2.** Reaction of *N*-monosubstituted benzamides **4a–4f** with alkynes **2a–2d**[a]

| Entry | 4 | 2 | Product, yield[b]/% |
|---|---|---|---|
| |  |  |  |
| 1 | **4a** | **2a**: X = H | **5a**: X = H, 75 (66) |
| 2 | | **2c**: X = Bu$^t$ | **5b**: X = Bu$^t$, 68 (63) |
| 3 | | **2d**: X = OMe | **5c**: X = OMe, 73 (70) |
| 4 | | **2e**: X = Cl | **5d**: X = Cl, 72 (69) |
| | |  |  |
| 5 | **4a** | **2f**: R = Me | **5e**: R = Me, 60 (42)[c] |
| 6 | | **2g**: R = Bu$^n$ | **5f**: R = Bu$^n$, 58 (54)[d] |
| |  |  |  |
| 7 | **4b**: Y = OMe | **2a** | **5g**: Y = OMe, 69 (60) |
| 8 | **4c**: Y = Cl | | **5h**: Y = Cl, 84 (80) |
| |  | |  |
| 9 | **4d** | **2a** | **5i**, 65 (55) |
| |  | |  |
| 10 | **4e**: Z = OMe | **2a** | **5j**: Z = OMe, 55 (45) |
| 11 | **4f**: Z = Cl | | **5k**: Z = Cl, 40 (36) |
| |  | |  |
| 12 | **4g** | **2a** | **5l**, 75 (67) |

[a]Reaction conditions: **4** (1 mmol), **2** (0.5 mmol), $[Cp^*RhCl_2]_2$ (0.005 mmol), $Cu(OAc)_2 \cdot H_2O$ (1 mmol) in *o*-xylene (2.5 mL) at 100 °C for 10 h under $N_2$. [b]GC yield based on the amount of **2** used. Value in parentheses indicates yield after purification. [c]Contaminated with a regioisomer (**5e**:isomer = 78:22). [d]Contaminated with a regioisomer (**5f**:isomer = 84:16).




**6** (1 mmol) **2a** (1 mmol)

| **6** | Additive (mmol) | Solvent/Temp/°C/Time/h | Product, yield/% |
|---|---|---|---|
| **6a**: R = Me<br>**6b**: $R_2$ = -$(CH_2)_4$- | $AgSbF_6$ (0.04)/$Na_2CO_3$ (3)<br>2,6-$Me_2C_6H_3CO_2H$ (0.5) | *o*-xylene/150/2<br>DMF/100/10 | **7a**: R = Me, 61<br>**7b**: $R_2$ = -$(CH_2)_4$-, 72 |

**Scheme 3.**

coupling with **2a** in the presence of 2,6-dimethylbenzoic acid[12] as well as the Rh/Cu catalyst system to selectively produce *N*-(5,6,7,8-tetraphenyl-1-naphthoyl)pyrrolidine (**7b**) in 72% yield.

In summary, we have demonstrated that various benzamides undergo oxidative coupling with alkynes under rhodium catalysis accompanied by C–H and/or N–H bond cleavages to afford their 1:1 or 1:2 coupling product selectively.[13] Some of the products exhibit intense fluorescence in the solid state.

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*Note added in proof*: A report of the synthesis of isoquinolinone via the $Rh^{III}$-catalyzed non-oxidative coupling of benzhydroxamic acids with alkynes appeared after submission of this manuscript.[14]

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