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Rh-Catalyzed Oxidative Coupling between Primary and Secondary Benzamides and Alkynes: Synthesis of Polycyclic Amides

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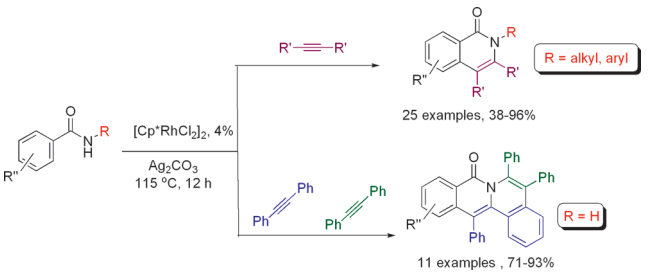

A methodology for the high yield and facile synthesis of isoquinolones from benzamides and alkynes via the oxidative ortho C−H activation of benzamides has been developed. Ag_2CO_3 proved to be an optimal oxidant when MeCN was used as a solvent, and $[RhCp^*Cl_2]_2$ was utilized as an efficient catalyst. Both N-alkyl and N-aryl secondary benzamides can be applied as effective substrates. Furthermore, primary benzamides react with two alkyne units, leading to tricyclic products via double C−H activation and oxidative coupling. The reactivity of the structurally related 1-hydroxyisoquinoline was also demonstrated, where both N- and O-containing rhodacyclic intermediates can be generated, leading to the construction of different O- or N-containing heterocycles.

In the past decade, catalytic activation of C−H bonds has become an increasingly important strategy for the elaboration of readily available simple substrates to complex products in an atom-economic fashion.[1] In this context, the construction of nitrogen-containing heterocycles via (directed) C−H cleavage is very important due to their wide biological and photo- and electrochemical applications.[2] Among them, isoquinolones are important structural motifs in various natural products.[3] Recent seminal work on the synthesis of isoquinolones by the group of Murakami[4] and the group of Kurahashi and Matsubara[5] focused on nickel-catalyzed denitrogenative insertion of alkynes into benzotriazin-4(3*H*)-ones and the decarbonylative insertion of alkynes into phthalimides, respectively. In these systems, five-membered metalacycles have been proposed as key intermediates. We envision that an atom-economic synthesis of isoquinolones from simple benzamides and alkynes can be advantageous by way of chelation-assisted C−H activation under rhodium-catalyzed oxidative conditions. Recently, Fagnou,[6] Satoh and Miura,[7] Jones,[8] and Glorius[9] have independently reported the important and useful Rh-catalyzed oxidative coupling reactions between arenes or heteroarenes and alkynes or alkenes, wherein the active five- or six-membered organorhodium species were generated with the assistance of directing groups such as amides,[6b,9a] carboxyls,[7e] hydroxyls,[7g,i] imines,[7a] and other N atoms.[7b,f,h] Considering that amides are readily available, the ortho C_{aryl}−H activation of secondary acetanilides has been well documented in oxidative coupling with alkenes or alkynes catalyzed by Pd(II)[10] and Rh(III).[6b,9a] In the case of benzamides bearing *N*-aryl groups such as **1**, complication of selectivity of C−H activation can arise as to which arene undergoes C−H activation. To the best of our knowledge, no such selectivity has been examined,[11]

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SCHEME 1. Metal-Mediated Synthesis of Isoquinolones

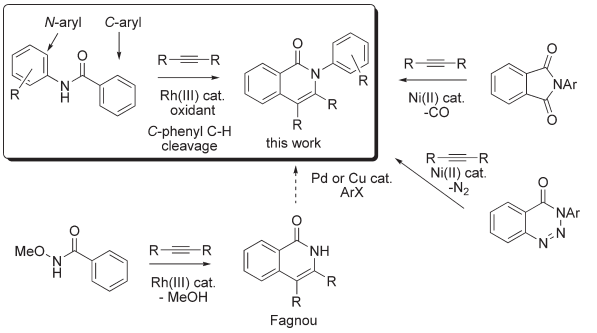
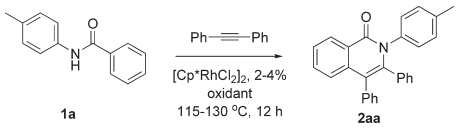


TABLE 1. Screening of Rh-Catalyzed Oxidative Coupling[a]



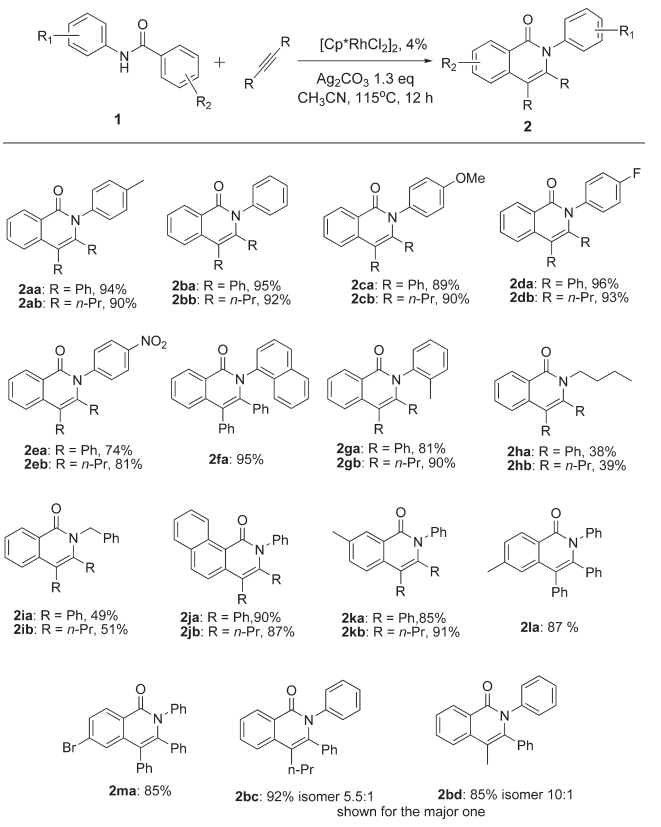
entry	oxidant+	cat. loading (mol %)	solvent (temp)	yield (%)[b]
1	Ag_2CO_3	4	toluene (130 °C)	45
2	Ag_2O	4	toluene (130 °C)	34
3	$Cu(OAc)_2$	4	toluene (130 °C)	< 5
4	Ag_2CO_3	4	$ClCH_2CH_2Cl$ (115 °C)	64
5	Ag_2CO_3	4	CH_3CN (115 °C)	97 (94[c])
6	Ag_2CO_3	2	CH_3CN (115 °C)	77
7	Ag_2CO_3	2	CH_3CN (115 °C)	88

[a]Reaction conditions: **1a** (50.0 mg, 0.237 mmol), diphenylacetylene (55.0 mg, 0.308 mmol, 1.3 equiv), oxidant (1.5 equiv of Ag_2X or 2.2 equiv of $Cu(OAc)_2$, catalyst, solvent (3 mL) in a 25 mL sealed tube under nitrogen, 12 h. [b]^{1}H NMR yields with 1,3,5-trimethoxybenzene as an internal standard. [c]Isolated yield. [d]1,2,3,4-Tetraphenyl-1,3-cyclopentadiene (5 mol % based on **1a**) was added.

although the ortho C−H activation of PhC(O)NHMe has been reported by Fagnou (Scheme 1).[12] We now report the facile synthesis of a variety of *N*-alkyl and *N*-aryl isoquinolones via the selective activation of ortho C−H bonds of the benzyl ring (*C*-phenyl) in *N*-alkyl and *N*-aryl benzamides (Scheme 1). More importantly and unexpectedly, we successfully achieved the double oxidative insertion of alkyne into primary benzamides to give unreported tricyclic amides.

We initiated our investigation on the coupling between **1a** and PhC≡CPh using $[Cp^*RhCl_2]_2$ (4 mol %) as the catalyst. During the survey of the reaction conditions, essentially no appreciable formation of isoquinolone **2aa** was observed when $Cu(OAc)_2$ was used as the oxidant in the presence or absence of air in several common aprotic solvents such as 1,4-dioxane, toluene, or $ClCH_2CH_2Cl$ (115 to 130 °C, 12 h, Table 1). Thus we felt that Ag(I) might be an appropriate oxidant. Indeed, when this reaction was conducted with Ag_2CO_3 as the oxidant (1.3 equiv) in MeCN or acetone, product **2aa** was obtained in nearly quantitative yield after 12 h (condition A, Table 1), which was characterized by X-ray crystallography (see the Supporting Information). Strong solvent effect was observed in that switching MeCN or acetone to DMF, 1,4-dioxane, or dichloroethane all resulted in significantly lower yield. Decreasing the loading of the $[Cp^*RhCl_2]_2$ is possible with the introduction of tetraphenylcyclopentadiene ($(CpH)Ph_4$) as an additive. However, a slightly lower isolated yield of **2aa** was obtained with the $(Cp^*RhCl_2)_2$ (2%)/$(CpH)Ph_4$ (5%) catalyst system (condition B).

TABLE 2. Rh(III)-Catalyzed Oxidative Coupling between Secondary Benzamides and Alkynes



Following the screening, the scope of this reaction was investigated. As given in Table 2, secondary benzamides bearing electron-donating or -withdrawing groups at both the *N*-phenyl and the *C*-phenyl rings all react to give high yield under condition A. Halogenated benzamides can also be tolerated (**2ma**), and high selectivity was obtained when ortho and meta substituents were introduced into the *C*-phenyl ring (**2ja**, **2jb** and **2ka**, **2kb**), and this high selectivity is likely caused by efficient steric shielding of such groups, consistent with those previously reported for coupling reactions that involve ortho C−H activation of arenes.[13] Interestingly, introduction of an ortho substituent into the N-phenyl ring has no detrimental effect on this reaction (**2fa** and **2ga**, **2gb**). Since this reaction involves no cleavage of any C−H bond in the *N*-substituent, benzamides bearing both *N*-alkyl (**2ha**, **2hb**) and *N*-benzyl (**2ia**, **2ib**) groups are applicable, and they successfully undergo oxidative coupling with alkynes although lower yields were observed, together with the recovery of nearly all the starting benzamides. In contrast to the high yield and insensitivity to steric perturbation caused by ortho substitutents of the *N*-aryls of benzamides, essentially no reaction proceeds

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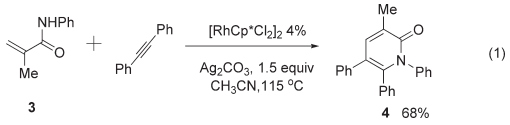
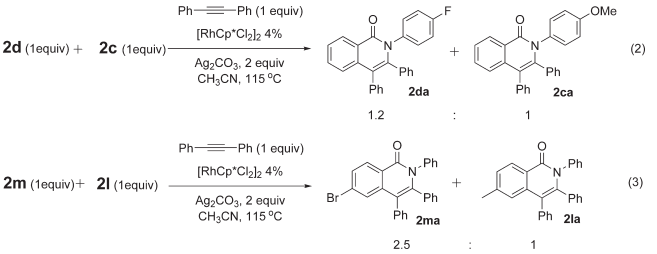
for PhC(O)NHCy. In addition, the scope of the alkyne can be extended to a dialkyl-substituted alkyne (PrC≡CPr) and unsymmetrical alkynes which give high yield and moderate to high regioselectivity (**2bc** and **2bd** for unsymmetrical alkynes), and the major isomer of **2bd** was unambiguously identified by X-ray crystallography (see the Supporting Information). The preferred regioselectivity agrees with that reported in related rhodium-catalyzed oxidative coupling reactions.[6] In addition to benzamides, the structurally related methylmethacramide reacts with PhC≡CPh under the same conditions to give pyridinone **4** in 68% yield (eq 1).



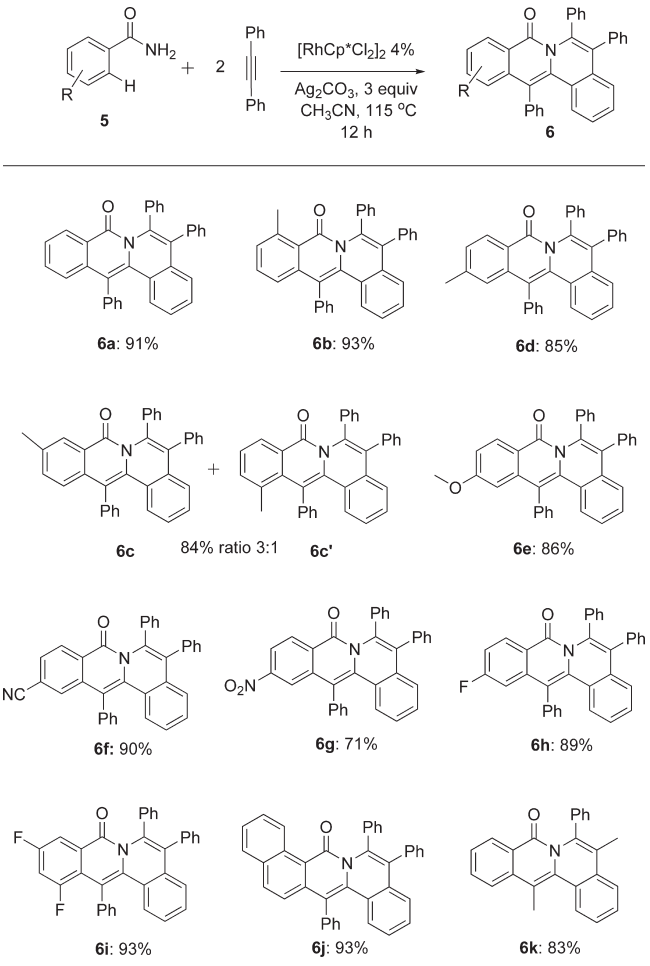
(1)

Since this reaction involves the cleavage of both C−H and N−H bonds, we carried out competitive reactions to explore the electronic effects of both aryl groups in *N*-aryl benzamides. An equimolar amount of **2c**, **2d**, and PhC≡CPh was allowed to react under the standard conditions. Benzamides with electron-poor groups in the *N*-aryl ring react with the alkyne in slight preference (eq 2). Likewise, the competitive reaction between benzamides **2*l*** and **2m** also leads to the conclusion that coupling reaction is favored for benzaimdes with electron-withdrawing groups in the *C*-aryl ring (eq 3). Ideally, useful information on the cleavage of the ortho C−H bond may be obtained from kinetic isotope effect experiments. However, KIE obtained from inter- or intramolecular competitive reaction is not applicable since heating protonated and deuterated benzamide ($C_6D_5C(O)NHPh$) in equimolar ratio in the absence of PhC≡CPh resulted in scrambling of deuterium into the ortho sites of both benzamides, which indicates that the ortho C−H activation here should be a reversible process under these conditions (see the Supporting Information), consistent with the results obtained for PhC(O)NHOMe.[12]



Noting the somewhat "spectating" behavior of the *N*-alkyl and *N*-aryl groups in benzamides, we moved to the extreme case by using simple primary benzamides as substrates. Surprisingly, the expected *N*-H isoquinolone was not observed under the standard conditions. Instead, a tricyclic product was obtained and fully characterized by NMR spectroscopy (and X-ray crystallography for **6a**, see the Supporting Information) as a result of double oxidative coupling with the incorporation of two alkyne units, a process that theoretically requires 2 equiv of Ag_2CO_3 (Table 3). Additional optimization of the conditions by simply providing an excess of PhC≡CPh and Ag_2CO_3 leads to the nearly quantitative formation of the product (91% isolated

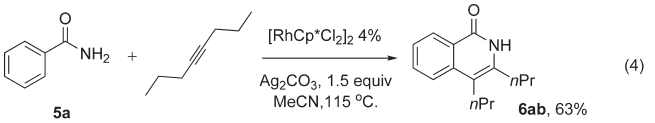
TABLE 3. Rh(III)-Catalyzed Double Oxidative Coupling between Primary Benzamides and Alkynes



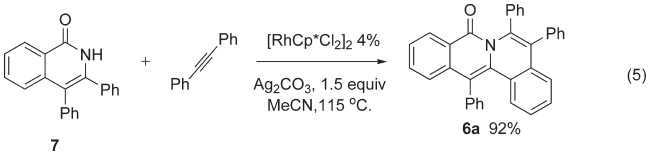
yield). Further exploration of the scope of primary benzamides reveals that substrates bearing both electron-donating (**6b**−**e**) and -withdrawing groups (**6f**−**i**) at different positions react with PhC≡CPh to give the corresponding products in high isolated yields (71−93%). In contrast to the high selectivity of C−H activation for a secondary benzamide bearing *m*-methyl groups (**2ka**, **2kb**, Table 2), the regioselectivity for *m*-$CH_3(C_6H_4)C(O)NH_2$ is not significant, and isomeric products **6c** and **6c′** were obtained in 3:1 ratio. This diminished selectivity is likely caused by the reduced steric hindrance of the NH_2 group, which makes the cleavage of the two ortho C−H bonds less discriminating. Interesting results were obtained in the oxidative coupling between $PhC(O)NH_2$ and Me—C≡C—Ph. Although four regioisomeric products can be possible, only product **6k** was obtained (83%).

When 4-octyne was used as diphenylacetylene substitute to react with **5a**, the first oxidative coupling product isoquinolone **6ab** was obtained in 63% yield (eq 4). This result suggests that double oxidative insertion of alkynes is a stepwise process, wherein the isoquinolone acts as an intermediate. To further explore this likelyhood, isoquinolone **7** was independently synthesized[12] and was allowed to react with Ph—C≡C—Ph under the same conditions (eq 5). Indeed product **6a** was isolated in 92% yield, and this result supports the hypothesis that **7** is a

likely intermediate during the course of this double oxidative coupling reaction.

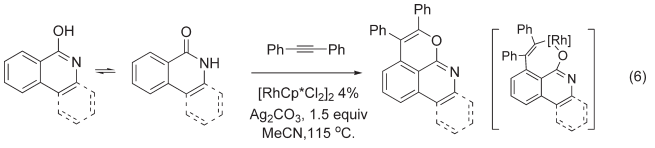


(4)



(5)

The scope of this reaction was further explored by using commercially available 1-hydroxyisoquinoline (**8a**). Here the absence of the two phenyl groups renders unlikely the formation of N-containing rhodacycle. Instead, oxidative insertion into the tautomeric O−H bond was observed, and product **9a** was isolated in high yield with the construction of a new six-membered heterocycle (eq 6). A question may arise when both N and O atoms are accessible in substituted 2-hydroxyisoquinolines, a scenario similar to the selectivity of C−H activation in the two aryl groups in *N*-aryl benzamides. In this context, we carried out the oxidative coupling reaction between **8b** and PhC≡CPh under the standard conditions (eq 6). Although low yield of the analogous product **9b** (29%) was isolated due to the rather poor solubility of **8b** in most common organic solvents (**8b** was recovered in 65% yield), no other coupling product was detected on the basis of NMR and LC analysis. Amide groups are well-known in facilitating the activation of ortho C−H bonds as in acetanilides. However, it remains a question whether the chelation assistance was offered by the N or the O atom. Our results strongly support that both N- and O-containing rhodacyclic intermediates can be generated from C−H activation of 1-hydroxyisoquinoline (eqs 5 and 6). These results also reveal that 1-hydroxyisoquinolines may deliver versatile reactivity in their oxidative coupling with internal alkynes.



(6)

In summary, we have developed a methodology to achieve the catalytic ortho C−H activation of benzamides in the *C*-phenyl ring under oxidative coupling conditions to give isoquinolones. Both *N*-alkyl and *N*-aryl secondary benzamides can be applied as effective substrates, while primary benzamides react differently in that two alkyne units are oxidatively incorporated to give tricyclic products. The reactivity of the structurally related 2-hydroxyisoquinolines was also demonstrated, where both N- and O-containing rhodacyclic intermediates can be generated, leading to the construction of different O- or N-containing heterocycles.

Experimental Section

Synthesis of compound 2aa: 1a (106.0 mg, 0.502 mmol), diphenylacetylene (116.3 mg, 0.653 mmol, 1.3 equiv), Ag_2CO_3 (208 mg, 0.752 mmol, 1.5 equiv), and $[RhCp^*Cl_2]_2$ (12.4 mg, 4 mol %) were weighted into a pressure tube, and degassed acetonitrile (5 mL) was added. After being purged by nitrogen, the mixture was stirred at 115 °C for 12 h. The mixture was then diluted with CH_2Cl_2 and filtered through Celite. All volatiles were removed under reduced pressure. The crude product was purified by column chromatography on silica gel to afford **2aa** as white microcrystals (182 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, J = 8.0 Hz, 1H), 7.54 (t, J = 6.8 Hz, 1H), 7.48 (t, J = 6.8 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.11−7.18 (m, 5H), 6.98 (s, 4H), 6.89 (s, 5H), 2.20 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 141.3, 137.6, 137.3, 136.8, 136.5, 134.9, 132.5, 131.6, 131.0, 129.3, 129.1, 128.3, 128.0, 127.2, 127.0, 126.8 (two overlapping signals), 125.5 (two overlapping signals), 118.7, 21.1. IR 1660, 1605, 1590, 1509, 1489, 1329, 700. HRMS (ESI) calcd for $[C_{28}H_{21}NO + H]^+$ 388.1696, found 388.1694. Anal. Calcd for $C_{28}H_{21}NO$ (387.47): C, 86.79; H, 5.46; N, 3.61. Found: C, 86.67; H, 5.60; N, 3.70.

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Supporting Information Available: Detailed experimental procedures, characterization of new compounds, X-ray crystallographic data for **2aa**, **2bc**, and **6a**, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.