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Rhodium-Catalyzed Alkylation of C−H Bonds in Aromatic Amides with α,β-Unsaturated Esters

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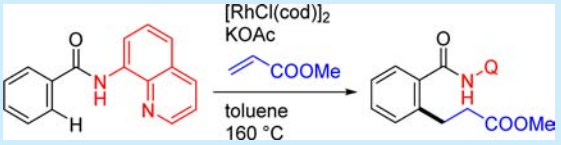
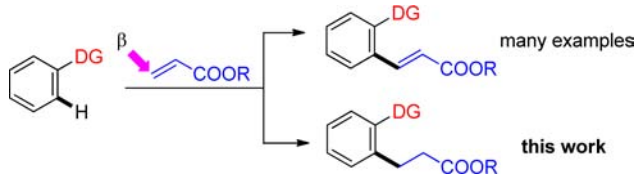
Supporting Information

ABSTRACT: The alkylation of C−H bonds with α,β-unsaturated carbonyl compounds by a rhodium-catalyzed reaction of aromatic amides containing an 8-aminoquinoline moiety is reported. The reaction is highly regioselective. The formation of C−C bonds occurs between the *ortho* C−H bonds in aromatic amides and the β-position of the acyclic α,β-unsaturated carbonyl compounds. The reaction is applicable to various acyclic α,β-unsaturated carbonyl compounds, such as acrylic esters, acrylamide, fumarate, maleate, and phenyl vinyl sulfone.

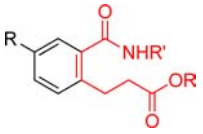


The introduction of functional groups via catalytic C−H bond activation is now well recognized to have significant potential owing to the ubiquitous nature of such bonds in organic substances.[1] A wide variety of functionalizations of C−H bonds have been developed to date. Among them, the arylation of C−H bonds with aryl electrophiles or aryl nucleophiles has been the most widely studied because of its alternative method of conventional Ar−Ar cross-coupling reactions, such as Suzuki coupling. In sharp contrast, examples of the alkylation of C−H bonds with alkyl halides are limited because of the resistance of alkyl halides to oxidative addition and the tendency for the resulting alkyl metal species to undergo β-hydride elimination.[2] The alkylation of C−H bonds with alkenes is one of the alternative methods for introducing alkyl groups in conjunction with the cleavage of C−H bonds. Although the Ru-catalyzed alkylation of C−H bonds in aromatic ketones with alkenes has opened new ground in the field of catalytic activation of C−H bonds,[3] the range of alkenes that are applicable still remain limited. Jun et al. reported that the first effective example of C−H bond alkylation with acrylic esters was achieved using Rh(I) complexes as the catalyst, with aromatic imines as the substrates.[4] Later, the groups of Kuninobu and Takai,[5] Li,[6] Huang,[7] Shibata,[8] and Ramana[9] and our group[10] made some additional contributions to this field. However, only a limited number of studies on the use of α,β-unsaturated carbonyl compounds as the coupling partner in the catalytic alkylation of C−H bonds have appeared in the literature, compared to the extensively studied oxidative alkenylation of C−H bonds with α,β-unsaturated esters (Scheme 1).[11] Because 3-(2-carbamoylphenyl)propanoic acid is a key structural component found in many biologically active and pharmaceutically important molecules, the construction of such a structure would be synthetically important (Scheme 2).[12] To construct such a structure, alkylation of C−H bonds in aromatic amides with α,β-unsaturated esters, in which an amide functions as the directing group, would be an attractive and straightforward method. However, to the best of our knowledge, there are no examples of the alkylation of C−H bonds in amides with α,β-unsaturated esters.[13] We wish to report here on the use of

Scheme 1. Oxidative Alkenylation and Alkylation of C(sp²)−H Bonds with α,β-Unsaturated Esters



Scheme 2. 3-(2-Carbamoylphenyl)propanoic Acid Analogues as Biologically Active and Pharmaceutically Important Molecules



rhodium complexes as catalysts in conjunction with an 8-aminoqunolinyl group as the directing group[14] resulting in regioselective alkylation of C−H bonds in aromatic amides with α,β-unsaturated carbonyl compounds (Scheme 1). The formation of C−C bonds occurs between the *ortho* C−H bonds in aromatic amides and the β-position of α,β-unsaturated carbonyl compounds.

The reaction of amide **1a** (0.3 mmol) with methyl acrylate (0.6 mmol) in the presence of $[RhCl(cod)]_2$ (0.0075 mmol) as the catalyst and KOAc (0.075 mmol) as the base in toluene (1 mL) at 160 °C for 12 h gave the alkylation product **2a** in 86% isolated yield along with the cyclized product **3a** in 8% yield (Scheme 3). The byproduct **3a** appears to be formed by the oxidative alkenylation of C−H bonds followed by cyclization.[15] Various attempts were made to avoid the formation of **3a**, but none were successful. However, the products **2a** and **3a** were easily

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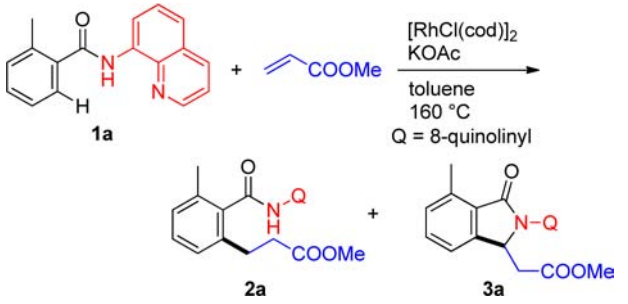
Scheme 3. Rh-Catalyzed Alkylation of C−H Bonds in Aromatic Amides with α,β-Unsaturated Esters

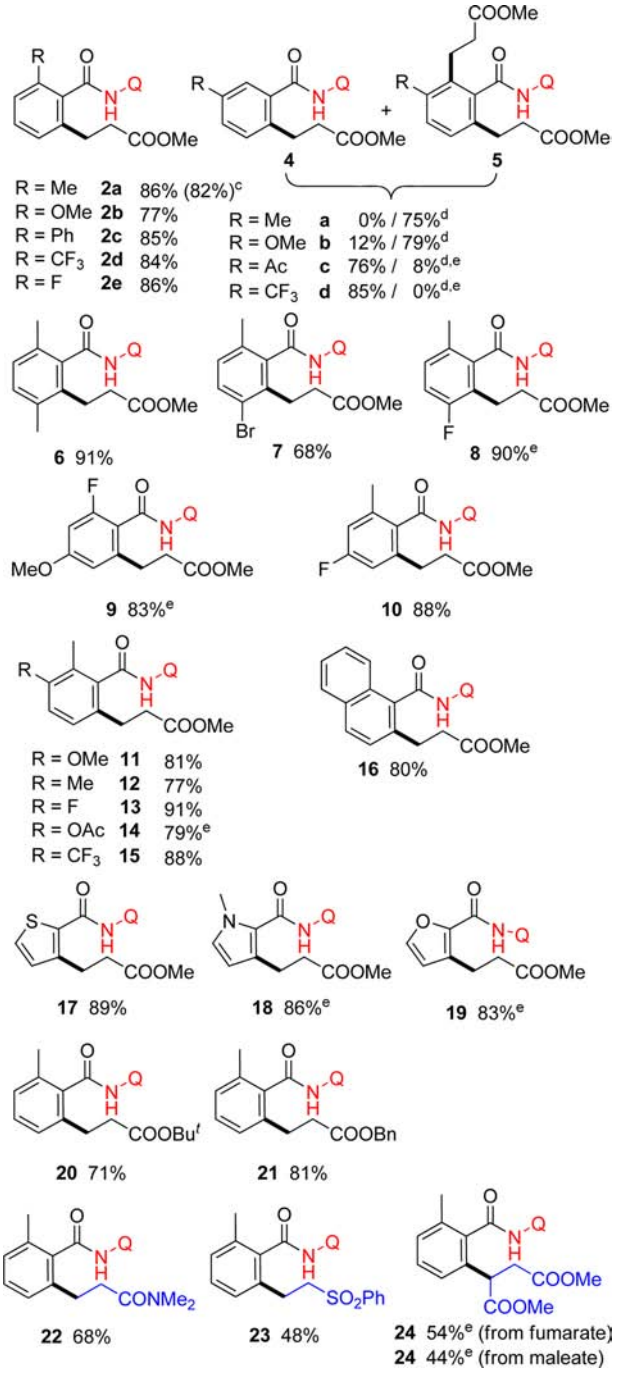


separated by column chromatography. Curiously, Rh(0), Rh(I), Rh(II), and even Rh(III) rhodium complexes, such as $Rh_4(CO)_{12}$, $RhCl(PPh_3)_3$, $Rh_2(OAc)_4$, and $[Cp^*RhCl_2]_2$, also show catalytic activity. Among the rhodium complexes, $[RhCl(cod)]_2$ and $[Rh(OAc)(cod)]_2$ were found to be the most active catalysts.[16]

Scheme 4 shows representative results for some reactions of aromatic amides with acyclic esters, acrylamide, and phenyl vinyl sulfone under standard reaction conditions. In all cases, the corresponding cyclization products (equivalent to **3a**) were formed in less than 10% yield, and alkylation products were easily separated from the mixture by column chromatography. The reactions were highly regioselective, exclusively producing alkylation products, in which C−C bond formation occurred between the ortho C−H bonds and the β-position of the olefins. A variety of functional groups are tolerated in the reaction. In the case of meta-substituted aromatic amides, a mixture of monoalkylation products **4** and dialkylation products **5** are formed. When 4 equiv of an ester was used, the dialkylation products **5a** and **5b** were the major isomers in the case of an electron-rich system, as in R = Me and R = OMe. In contrast, monoalkylation products **4c** and **4d** were obtained as the major isomer in the case of an electron-deficient system (R = Ac and CF_3), although an excess amount of acrylic ester was used. This suggests that the less hindered C−H bonds are initially alkylated and the hindered C−H bonds then react when the substituents on the aromatic ring are electron-donating groups. In fact, a Hammett study indicated that electron-donating groups facilitate the reaction (discussed latter). The reaction was also applicable to heteroaromatic systems, such as thiophene **17**, pyrrole **18**, and furan rings **19**. Subsitituted acrylic esters, such as methyl crotonate and methacrylate were unreactive, with **1a** being recovered. Some electron-deficient olefins, such as *N*,*N*-dimethylacrylamide and phenyl vinyl sulfone, also gave the corresponding alkylation products, such as **22** and **23**. Dimethyl fumarate and maleate also participate in the reaction to give **24**.

Deuterium-labeling experiments using **1a**-d_7 were carried out in an attempt to gain insights into the mechanism for the reaction (eq 1 in Scheme 5). Unexpectedly, deuterium atom was incorporated into both the methylene carbon of the product **25**, and the total number of deuterium atoms incorporated into **25** was nearly one atom (1.33H + 1.54H = 2.87H). In addition, no deuterium was incorporated into the recovered acrylic ester. Deuterium-labeling experiments were also carried out in the absence of acrylate. When $[RhCl(cod)]_2$ was used as the catalyst in the absence of KOAc, the H/D exchange was very slow (eq 2 in Scheme 5). No H/D exchange was detected after a 15 min reaction, but the exchange was rapid when KOAc was present. In contrast, the presence of KOAc did not affect the efficiency of H/D exchange when $[Rh(OAc)(cod)]_2$ was used as the catalyst (eq 3 in Scheme 5). These results suggest that the role of KOAc is to generate the Rh-OAc species, a key catalytic species, by reaction with $[RhCl(cod)]_2$.

Scheme 4. Rh-Catalyzed Reaction of Aromatic Amides with Acrylic Esters[a,b]



[a]Reaction conditions: amide (0.3 mmol), acrylic ester (0.6 mmol), $[RhCl(cod)]_2$ (0.0075 mmol), KOAc (0.075 mmol), toluene (1 mL), at 160 °C for 12 h. [b]Isolated yields. [c]The reaction was carried out using 1.31 g of **1a** (5 mmol) to give 1.43 g (82% yield). [d]Acrylic ester (1.2 mmol) was used. [e]K_2HPO_4 was used in place of KOAc.

A proposed mechanism for the reaction is shown in Scheme 6. A Rh−Cl species is converted to Rh−OAc species by reaction with $[RhCl(cod)]_2$ with KOAc. The coordination of a quinoline

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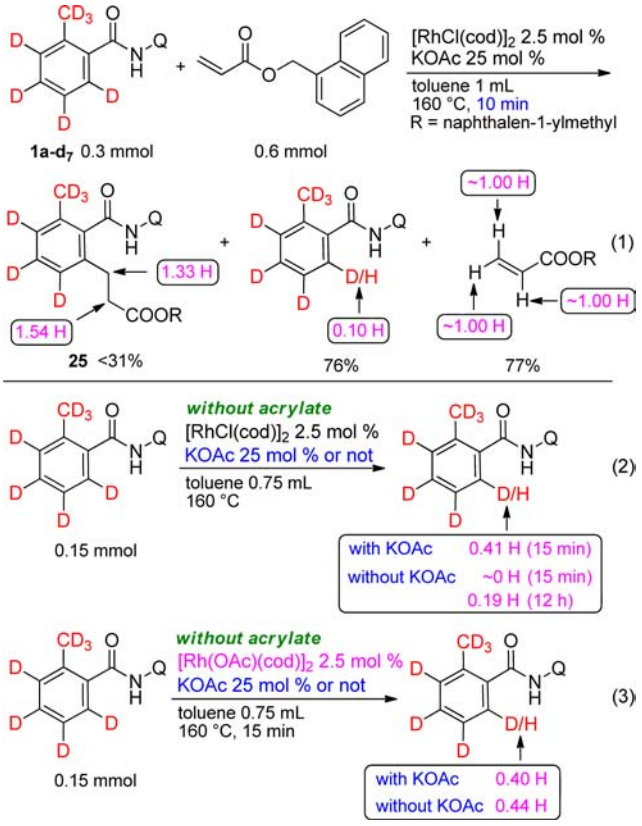
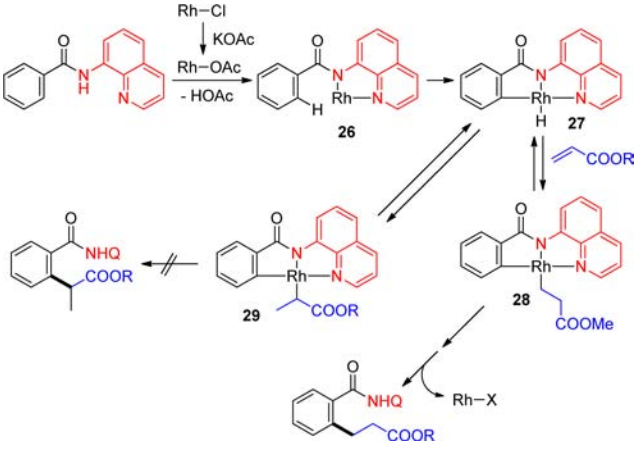
Scheme 5. Deuterium-Labeling Experiments



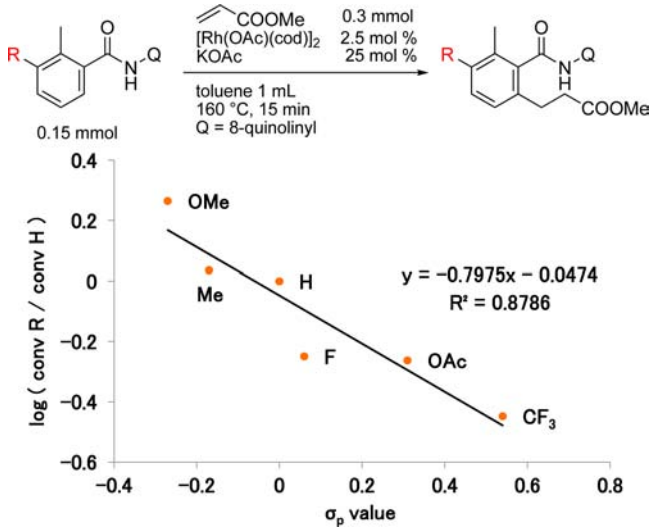
Scheme 6. Proposed Mechanism



nitrogen to the rhodium center followed by ligand exchange on the amide nitrogen generates complex **26**. The oxidative addition of the ortho C–H bond to the rhodium center gives the cyclometalated Rh–H complex **27**,[17] which reacts with the acrylic ester to give **28**.[18] The reductive elimination from **28** followed by protonation gives the alkylation product with the regeneration of rhodium. When **27** reacts with the acrylic ester in the reverse direction, the complex **29** would be formed. However, complex **29** is prevented from participating in reductive elimination because of steric congestion. When a deuterated substrate was used, deuterium was incorporated into both the methylene carbon of the product **25**, and the total of number of deuterium atoms incorporated into **25** was nearly one atom, as shown in eq 1 of Scheme 5, suggesting that the interconversion between **28** and **29** via the complex **27** is very fast and that the alkene never dissociates from the rhodium center.

In order to gain additional information on the mechanism, the Hammett plot was constructed (Scheme 7). The result shows

Scheme 7. Hammett Plots



that electron-donating groups accelerate the reaction, suggesting that reductive elimination is a rate-determining step and it proceeds via a concerted mechanism.

We previously reported that the reaction of amides consisting an 8-aminoquinoline directing group proceeds through two different mechanisms depending on the oxidation state of the catalysts used.[14b] When low-valent transition-metal complexes, such as Ru(0) and Ni(0) are used as the catalyst,[19] C–H bond cleavage appears to proceed through σ-bond metathesis. In contrast, C–H bonds are activated via a concerted metalation–deprotonation mechanism (CMD) when Pd(II), Ru(II), and Ni(II) are used as the catalyst.[20] In the alkylation of C–H bonds reported here, the cleavage of C–H bonds is proposed to proceed through the oxidative addition of C–H bonds. These results suggest a diversity of possibilities in the present bidentate–chelation system.

In summary, the direct *ortho*-alkylation of C(sp^2)–H bonds in aromatic amides with α,β-unsaturated carbonyl compounds was achieved by catalysis by rhodium species. The presence of an 8-aminoquinoline moiety as the directing group is crucial for the reaction to proceed.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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