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Rhodium-Catalyzed Alkylation of C−H Bonds in Aromatic Amides with Styrenes via Bidentate−Chelation Assistance

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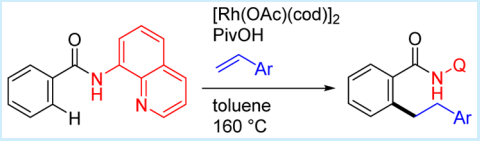
Supporting Information

ABSTRACT: Rhodium-catalyzed alkylation reactions of aromatic C−H bonds in aromatic amides with styrene derivatives have been developed by using an 8-aminoquinoline as a bidentate directing group. C−C bond formation selectively occurred between the *ortho* C−H bonds in aromatic amides and the terminal carbon of the styrene derivatives. The presence of an 8-aminoquinoline moiety is essential for the success of the reaction.



Carbon−hydrogen bond functionalization has become one of the most reliable methods for introducing a variety of functional groups into organic compounds. In recent years, C−H bond functionalization has been used in the synthesis of complex naturally occurring molecules, medicinally relevant structures, or useful materials.[1] In most cases, the regioselective functionalization of the C−H bond involves the use of a directing group, such as pyridine, oxazole, amide, ester, ketone, or a related structure.[2] In 1993, Murai and co-workers reported on the ruthenium-catalyzed alkylation of *ortho*-C−H bonds of aromatic ketone with vinylsilane.[3] The regioselective alkylation at the ortho position was achieved via the coordination of the ketone to a ruthenium center. Since this pioneering work, a variety of regioselective C−H bond functionalization reactions have been developed. C−H bond alkylation with alkenes is the most atom-economical reaction compared to the use of alkyl halides or alkyl metal species as a coupling partner, because all atoms are incorporated into the desired products through this transformation. Recently, not only vinylsilanes but also other alkenes, including acrylic esters, styrenes, and even unreactive normal olefins, were used as coupling partners.[4] In the case of styrene, significant achievements have been made by Darses,[5] Nakamura,[6] Yoshikai,[7] Shibata,[8] and others.[9] Herein, we report on the rhodium-catalyzed alkylation of aromatic C−H bond of aromatic amides with styrene derivatives by using a bidentate directing group. The resulting 2-phenethylbenzoic acid moiety is a common structure in natural products and displays various bioactivities (Figure 1).[10] To the best of our knowledge, this reaction is the first synthetically useful application of the use of an amide directing group into the rhodium-catalyzed alkylation reactions with styrene derivatives.

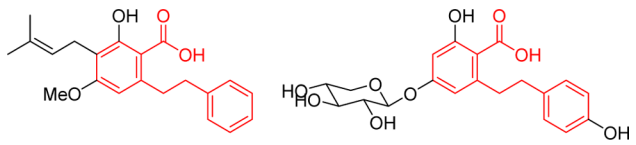
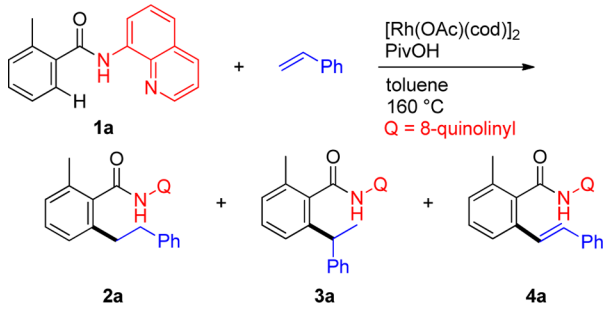


Figure 1. Examples of 2-phenethylbenzoic acid moiety containing naturally occurring compounds.

The reaction of amide **1a** (0.3 mmol) with styrene (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 produced the linear alkylation product **2a** in 47% NMR yield with a small amount of branched type product **3a** and the alkenylation product **4a** (Scheme 1).[11] The product

Scheme 1. Rh-Catalyzed Alkylation of C−H Bonds in Aromatic Amides with Styrene



yield could be significantly improved by using $[Rh(OAc)(cod)]_2$ as a catalyst. To our delight, the addition of pivalic acid suppressed the formation of the alkenylation product **4a**.[12] The reaction occurred predominantly at the *β*-position of styrene predominant to produce the desired linear product **2a**.

Inspired by transition-metal-catalyzed C−H bond functionalization reactions that involve the use of a bidentate chelation system,[13] the effect of directing groups was examined (Figure 2). When an *N*-methyl substituent was introduced in the directing group, the desired product was not obtained. No reaction occurred when other directing groups similar to 8-aminoquinoline were used in the reaction. These results show that the presence of both of an amide NH and a quinoline nitrogen is indispensable for the success of this reaction.

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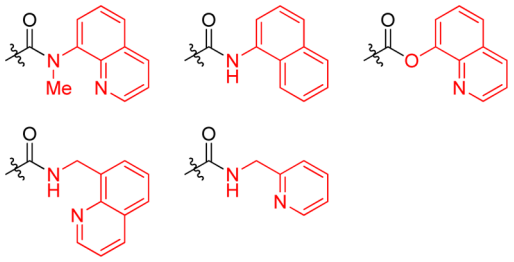
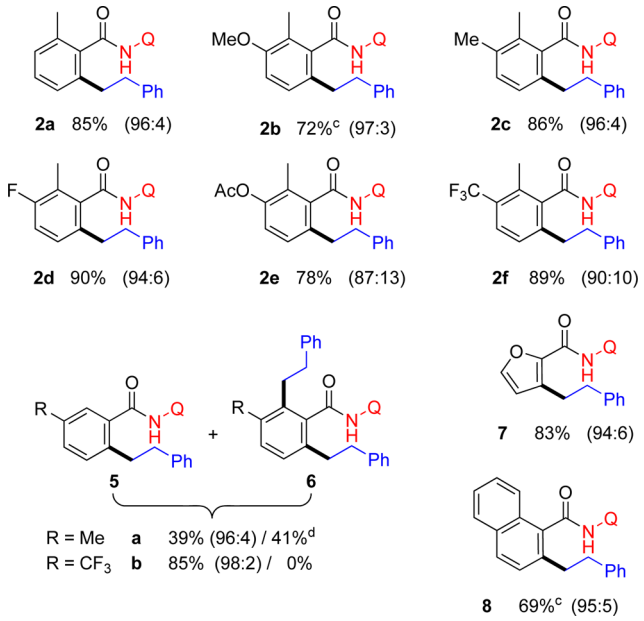


Figure 2. Screening of directing groups.

The substrate scope for a variety of functional group substituted aromatic amides was examined under the standard reaction conditions (Scheme 2). In all cases, a small amount of

Scheme 2. Rh-Catalyzed Reaction of Aromatic Amides with Styrene[a,b]

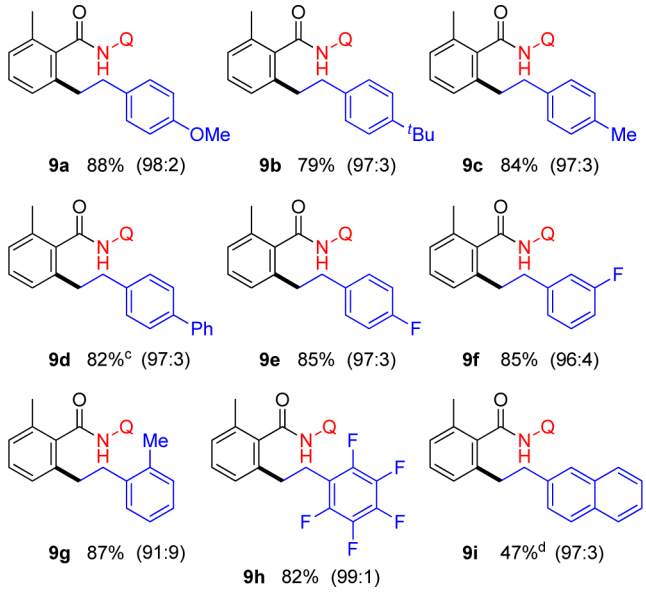


[a]Reaction conditions: amide (0.3 mmol), styrene (0.6 mmol), $[Rh(OAc)(cod)]_2$ (0.0075 mmol), PivOH (0.3 mmol), toluene (1 mL), at 160 °C for 12 h. [b]Isolated yields. Values in parentheses are the ratio of linear and branched alkylation products. [c]$[Rh(OAc)(cod)]_2$ (0.015 mmol) was used for 24 h. [d]Styrene (1.2 mmol) was used.

the corresponding alkenylation product (equivalent to **4a**) was formed. Some functional groups, such as OMe, F, OAc, and CF_3, were tolerated under the standard reaction conditions (**2a**–**f**). The number in parentheses denotes the ratio of linear- and branched-type products. When a *m*-methyl-substituted amide was used, the monoalkylation product **5a** and the dialkylation product **6a** were formed. However, only the monoalkylation product **5b** was obtained when a *m*-CF_3 substituted amide was used. These results indicate that an electron-donating group accelerates the reaction. We further investigated the compatibility of this reaction for heterocycle and fused ring systems. Gratifyingly, the reaction is also applicable to furan ring **7** and naphthalene ring-containing compound **8**.

The scope of the reaction with respect to styrene derivatives was next examined (Scheme 3). Overall, the desired products were produced from a wide range of styrene derivatives in excellent yields with a high linear selectivity. Various functional

Scheme 3. Rh-Catalyzed Reaction of Aromatic Amides with Styrene Derivatives[a,b]



[a]Reaction conditions: amide (0.3 mmol), styrene (0.6 mmol), $[Rh(OAc)(cod)]_2$ (0.0075 mmol), PivOH (0.3 mmol), toluene (1 mL), at 160 °C for 12 h. [b]Isolated yields. Values in parentheses are the ratio of linear and branched alkylation products. [c]$[Rh(OAc)(cod)]_2$ (0.015 mmol) was used for 24 h. [d]$[Rh(OAc)(cod)]_2$ (0.0225 mmol) was used for 24 h.

groups substituted at the 4-position of the styrene derivative were tolerated under the standard reaction conditions and gave the corresponding alkylation products in good yields (**9a**–**e**). The more sterically hindered 2-methylstyrene **9g** was also applicable in this reaction. To our delight, a strong electron-withdrawing pentafluorophenylethene **9h** did not hamper the reactivity. We were pleased to find that 2-vinylnaphthalene **9i** was also applicable in this reaction. However, α-methylstyrene failed to give the corresponding alkylation products.

To collect additional mechanistic information regarding the reactions, deuterium-labeling experiments were carried out (Scheme 4). When **1a**-d_7 was subjected to the standard reaction conditions for 2 h, but in the absence of styrene, H/D exchange was observed only at the *ortho*-position on the benzene ring, and no exchange was observed at the *meta*- and *para*-positions. In addition, H/D exchange took place even at the methyl C–H bond, although alkylation did not occur at the methyl group. A small amount of H/D exchange was also observed at the quinoline ring probably because of acidic conditions.[11] These results indicate that the cleavage of the *ortho* C–H bond is reversible. In the reaction of naphthalenecarboxamide with styrene-d_8, nearly two proton atoms were incorporated into the product **8** (1.01H + 0.91H = 1.92H). Most importantly, proton atoms were incorporated into both the α and β positions of the methylene carbon in a nearly comparable ratio.

Although we do not currently fully understand the reaction mechanism, on the basis of the deuterium-labeling experiments summarized in Scheme 4 and our previous work,[14] a proposed mechanism for the reaction is shown in Scheme 5. The coordination of a quinoline nitrogen to the rhodium center followed by a ligand exchange between the amide nitrogen and Rh-OAc generates intermediate **A**. The subsequent oxidative addition of the *ortho* C–H bond to the rhodium center gives

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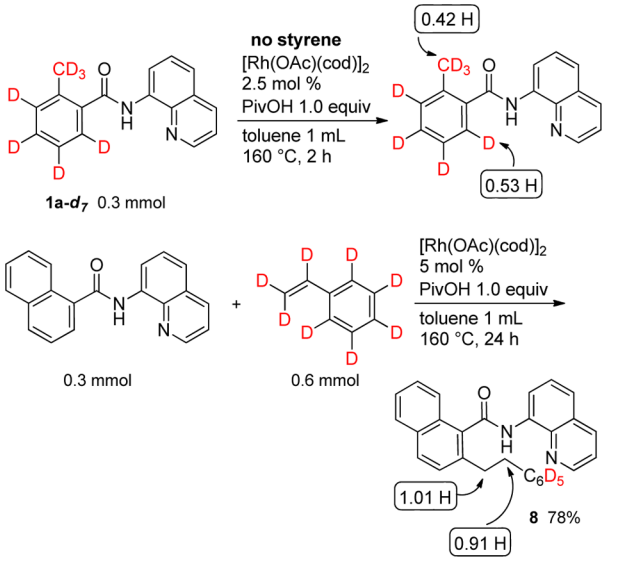
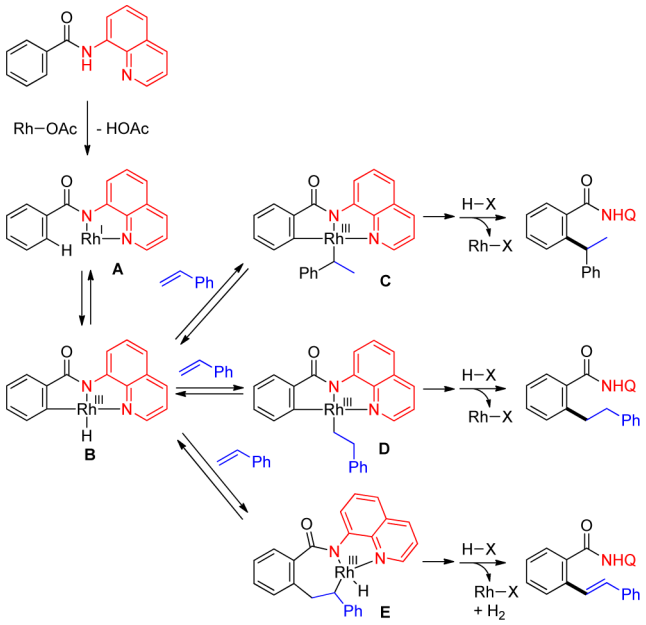
Scheme 4. Deuterium-Labeling Experiments



Scheme 5. Proposed Mechanism



the five-membered Rh−H species **B**.[15] The facile coordination of styrene to the rhodium center followed by the insertion of styrene into the Rh−H bond generates a Rh alkyl species **D**, and reductive elimination and protonation produce the desired product with the regeneration of a rhodium(I) species. The H/D scrambling shown in Scheme 4 suggests that the insertion of styrene is reversible and that another pathway in which insertion occurs in the reverse direction is also operative to give complex **C**. However, reductive elimination from complex **C** would be unfavorable because of steric congestion. The alkenylation byproduct is produced via the seven-membered complex **E**.[16]

N,N′-Bidentate directing groups have recently been widely used in many types of C−H functionalization reactions in which various types of transition-metal catalysts have been used.[13] However, in these reactions, the C−H bond cleavage step proceeds via σ-bond metathesis or by a concerted metalation−deprotonation mechanism. In sharp contrast, the C−H bond-cleavage step in the case of this reaction likely proceeds through oxidative addition.[13b] This result suggests that the *N,N′*-chelation system has the potential to be employed in a variety of new types of reactions. Although a variety of functionalization reactions utilizing the *N,N′*-bidentate directing group have been developed, only a limited number of C−H alkylation reactions with alkenes have been reported.[14,17] Daugulis recently reported on the cobalt-catalyzed reaction of aromatic amides consisting of an 8-aminoquinoline directing group with styrene, but the products obtained were not alkylation products but cyclized products.[18]

In summary, we report the development of the direct, rhodium-catalyzed *ortho*-alkylation of C(sp^2)−H bonds in aromatic amides with styrene derivatives by using a bidentate chelation system. The presence of an 8-aminoquinoline moiety as the directing group is crucial for the success of the reaction. Multiple bond insertion reactions via the use of an *N,N′*-bidentate directing group are currently being pursued in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure and characterization of new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01682.

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Notes

The authors declare no competing financial interest.

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