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Rh(I)-Catalyzed Alkylation of *ortho*-C−H Bonds in Aromatic Amides with Maleimides

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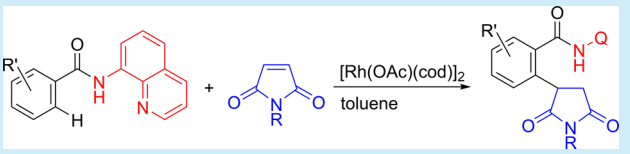
Supporting Information

ABSTRACT: An alkylation of C−H bonds with maleimides by a rhodium-catalyzed reaction of aromatic amides containing an 8-aminoquinoline moiety as the directing group is reported. Various *N*-substituents in the maleimide, including methyl, ethyl, cyclohexyl, benzyl, and phenyl groups and even H, are applicable to the reaction. The reaction is highly regioselective at the less hindered *ortho*-C−H bond when *meta*-substituted aromatic amides are used as substrates.



Catalytic C−H functionalization has proven to be a powerful tool for producing C−C and C−heteroatom bonds.[1] A wide variety of functionalization reactions of C−H bonds, including arylation, alkenylation, alkynylation, alkylation, carbonylation, silylation, borylation, hydroxylation, amination, and halogenation have been reported to date. Among them, C−H alkylation (hydroarylation) with alkenes is the most straightforward and atom- and step-economical route known for preparing alkyl-substituted aromatic compounds because all of the atoms of the substrates and alkenes are incorporated into the desired products.[2] Maleimides have frequently been used as alkenes in C−H alkylations because the resulting succinimide derivatives contain structures that are relevant to the fields of medicine and biological cycles and in modifying RNA.[3] In addition, maleimides have been reported to be reactive toward C−H alkylation reactions with various catalysts, such as Cu(II),[4] Ru(II),[5] Rh(III),[6] Co(III),[7] and Mn(0)[8] complexes.

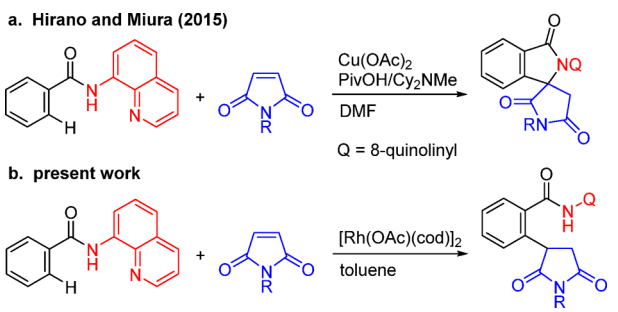
Hirano and Miura recently reported that the Cu(II)-catalyzed reaction of aromatic amides containing an 8-aminoquinoline directing group with maleimides resulted in oxidative cyclization to give spirocyclic products (Scheme 1a).[4] The reaction involved two steps: oxidative C−H alkenylation and intramolecular cyclization of the resulting alkenylation products. Herein we report a rhodium-catalyzed reaction of aromatic amides containing an 8-aminoquinoline directing group with maleimides, leading to the production of alkylation products.

We previously reported on a series of Rh(I)-catalyzed reactions of aromatic amides containing an 8-aminoquinoline directing group with various alkenes.[9,10] Although the mechanism for this reaction is presently unclear, these reactions do not appear to proceed via the generally accepted mechanisms for C−H alkylation or alkenylation, such as hydrometalation or carbometalation, on the basis of the results of deuterium-labeling experiments. To expand the substrate scope for this reaction, we screened a variety of alkenes, and maleimides were also found to participate in the Rh(I)-catalyzed C−H alkylation (Scheme 1b).

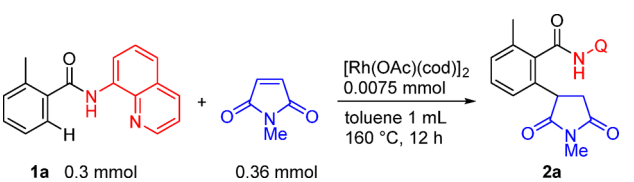
The reaction of amide **1a** (0.3 mmol) with *N*-methylmaleimide (0.36 mmol) in the presence of $[Rh(OAc)(cod)]_2$ (0.0075 mmol) as the catalyst in toluene (1 mL) at 160 °C for 12 h produced the alkylation product **2a** in 97% NMR yield (Scheme 2). The addition of a carboxylic acid had only a marginal effect on the efficiency of the reaction (2-MeC_6H_4COOH: 97% NMR yield).

The effect of the directing group was examined (Figure 1). No reaction occurred when other directing groups were used in the reaction. These results show that the presence of both an amide NH and a quinoline nitrogen is indispensable for the success of this reaction.

Scheme 1. C−H Functionalization with Maleimides



Scheme 2. Rh-Catalyzed C−H Alkylation of an Aromatic Amide (1a) with *N*-Methylmaleimide



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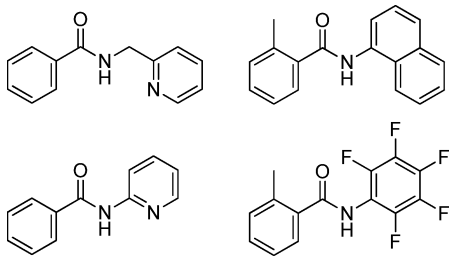
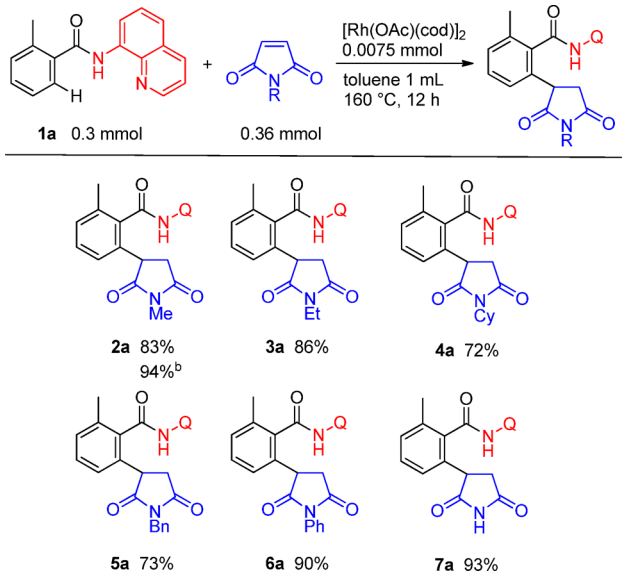


Figure 1. Ineffective directing groups.

The effect of the *N*-substituent on the maleimide molecule was examined next (Scheme 3). Methyl, ethyl, cyclohexyl, benzyl, and phenyl groups all gave the corresponding products in high yields. Even when simple maleimide was used, the corresponding alkylation product **7a** was produced in high yield. The reaction of **1a** can be conducted on a gram scale (4 mmol) in excellent yield (94%).

Scheme 3. Effect of the *N*-Substituent[a]

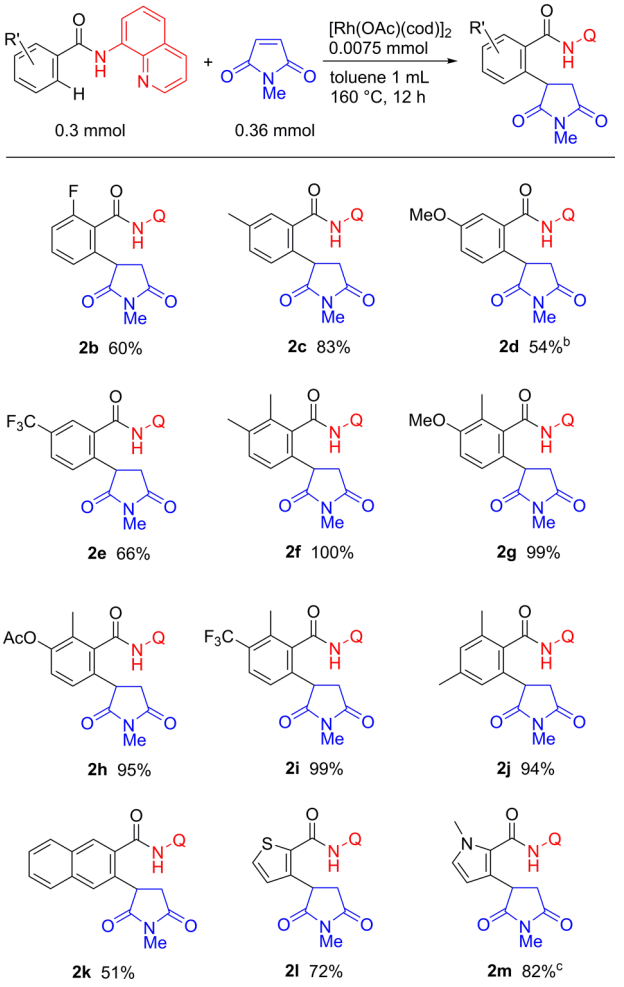


[a]Isolated yields by column chromatography are shown. [b]4 mmol of **1a** was used.

The substrate scope of aromatic amides containing a variety of functional groups was examined under the standard reaction conditions (Scheme 4). In the case of *meta*-substituted aromatic amides containing methyl, methoxy, and trifluoromethyl substituents, the less hindered C−H bonds reacted selectively irrespective of the electronic nature of the substituents, as in **2c**, **2d**, and **2e**. Heteroaromatic amides such as thiophenes and pyrroles also participated in the reaction.

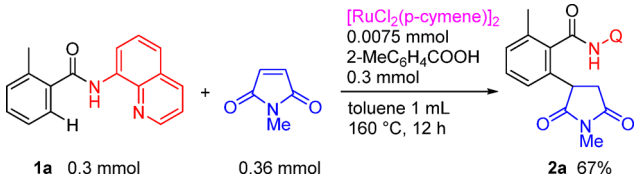
After screening a series of catalysts, we found that a Ru(II) catalyst also showed high catalytic activity. Prabhu previously reported on the Ru(II)-catalyzed reaction of aromatic amides with maleimides.[5c] In that case, no specific directing groups were needed, but 20 mol % $AgBF_4$, 1.5 equiv of $Cu(OAc)_2$, and an excess amount (10 equiv) of acetic acid were required, although the role of $Cu(OAc)_2$ was not discussed. In our Ru(II) catalyst/8-aminoquinoline chelation system, the presence of 1 equiv of carboxylic acid in the reaction solution was essential for the reaction to proceed, but neither $AgBF_4$ nor $Cu(OAc)_2$ was required (Scheme 5).[11]

Scheme 4. Rh-Catalyzed Reaction of Aromatic Amides with *N*-Methylmaleimide[a]



[a]Isolated yields by column chromatography are shown. [b]Isolated by GPC. [c][Rh(OAc)(cod)]$_2$ (0.015 mmol) was used as the catalyst for 24 h.

Scheme 5. Ru(II)-Catalyzed C−H Alkylation of Aromatic Amides with Maleimides



To understand the difference between the reaction mechanisms for the two catalytic systems, deuterium-labeling experiments using **1a**-d_7 were carried out (Scheme 6). In the Rh(I)-catalyzed reaction, H/D exchange took place at the *ortho* position of **1a**-d_7 even within a short reaction time (15 min), indicating that C−H bond cleavage is reversible. In the product **2a**, no deuterium atom was incorporated at the α-position of **2a**, which is different from the reaction with styrene and α,β-unsaturated lactones.[9] However, 0.6D was observed at the β-position (Scheme 6a). In the case of the Ru(II) system, a significant amount of H/D exchange also took place at the *ortho* position of the recovered **1a**-d_7 (0.7H) because the Ru(II) system requires the use of a carboxylic acid as an

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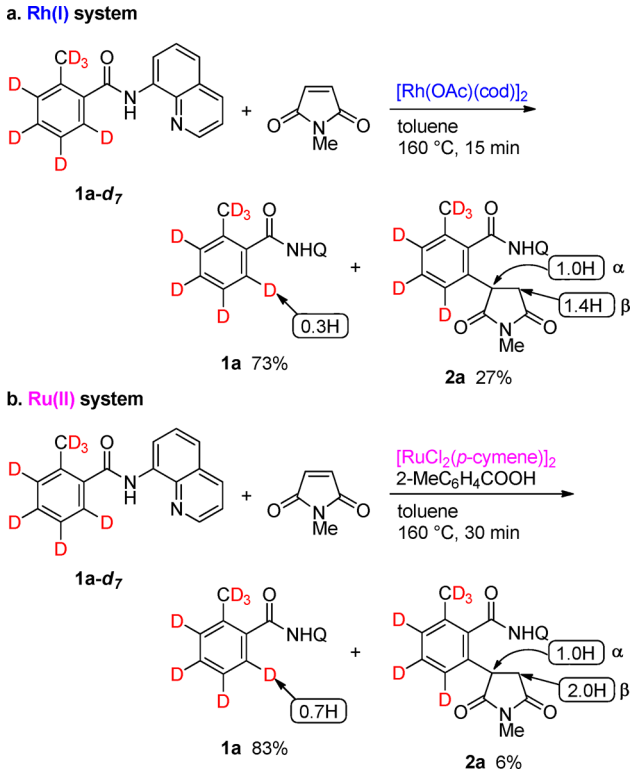
Scheme 6. Deuterium-Labeling Experiments: Rh(I) versus Ru(II)



additive (Scheme 6b). No deuterium atom was incorporated at either the α- or β-position of the product **2a**, suggesting that a different mechanism is operative in this systems. As proposed by Prabhu,[5c] the mechanism of the Ru(II)-catalyzed system involves the insertion of maleimide into the C−Ru bond in a ruthenacycle (carboruthenation) followed by protonation of the resulting C−Ru bond by a carboxylic acid. This mechanism explains the deuterium-labeling results in which no deuterium atom was incorporated into the product **2a** (Scheme 6b). In contrast, in the mechanism responsible for the Rh(I)-catalyzed reaction, more complicated paths appear to be involved.

In summary, we have reported the development of a direct rhodium-catalyzed alkylation of C(sp^2)−H bonds in aromatic amides with maleimides using an 8-aminoquinoline bidentate chelation system. In the case of the Cu(II) catalyst in an 8-aminoquinoline bidentate chelation system reported by Hirano and Miura,[4] oxidative cyclization took place to give spriocyclic products. In addition, the use of a Ru(II) catalyst gave the same products as the Rh(I) system, but the mechanism was clearly different. The reaction is highly regioselective at the less hindered *ortho*-C−H bonds in the case of *meta*-substituted aromatic amides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02135.

Experimental procedures and characterizations of new compounds (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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