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Nickel-Catalyzed Chelation-Assisted Transformations Involving Ortho C−H Bond Activation: Regioselective Oxidative Cycloaddition of Aromatic Amides to Alkynes

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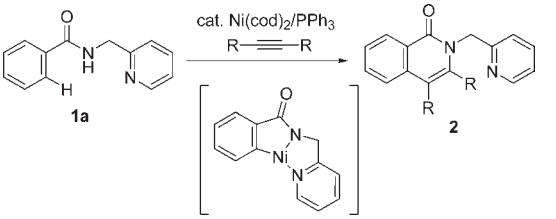
Supporting Information

ABSTRACT: Although the pioneering example of ortho metalation involving cleavage of C−H bonds was achieved using a nickel complex (Kleiman, J. P.; Dubeck, M. *J. Am. Chem. Soc.* **1963**, *85*, 1544), no examples of catalysis using nickel complexes have been reported. In this work, the Ni-catalyzed transformation of ortho C−H bonds utilizing chelation assistance, such as oxidative cycloaddition of aromatic amides with alkynes, has been achieved.

The development of methods for the direct conversion of C−H bonds into C−C, C−O, C−N, and C−halogen bonds remains a critical challenge in organic chemistry. Chelation-assisted C−H bond activation is currently in widespread use in such transformations of C−H bonds.[1] Various transition-metal complexes, in particular those of Ru, Rh, Pd, and Ir, have been used as catalysts in chelation-assisted transformations of ortho C−H bonds. The use of Ni, an abundant and low-cost transition metal, to catalyze the transformation of C−H bonds has recently been reported.[2] However, to the best of our knowledge, there are still no examples of Ni-catalyzed transformations of ortho C−H bonds utilizing chelation assistance,[3] although chelation-assisted ortho C−H bond activation was achieved by the cyclometalation of azobenzene with Cp_2Ni in a pioneering study.[4] We recently reported the Ru-catalyzed carbonylation of ortho C−H bonds of aromatic amides that contain a 2-pyridinylmethylamine moiety, in which coordination of the 2-pyridinylmethylamine moiety to the ruthenium center in an N,N fashion is involved as a key step and a cyclometalated complex was proposed as a key intermediate.[5a] It would be expected that newly designed directing groups could have the potential for applications to new catalytic reactions that cannot be achieved using a conventional directing group.[5b] Encouraged by the previous results, we proceeded to explore new types of catalytic reactions involving activation of the ortho C−H bonds of aromatic amides containing a 2-pyridinylmethylamine structure. We report herein the Ni-catalyzed transformation of such ortho C−H bonds utilizing chelation assistance (Scheme 1).

The reaction of amide **1a** with 4-octyne in the presence of $Ni(cod)_2/PPh_3$ as the catalyst in toluene at 130 °C for 18 h gave isoquinolone derivative **2a** in 28% isolated yield as a single product. A longer reaction time (3 days) resulted in an increase in the product yield to 66%. After optimization of the reaction conditions, the following conditions were selected as the standard ones: amide **1a** (0.5 mmol), 4-octyne (1.5 mmol), $Ni(cod)_2$ (0.05 mmol), and PPh_3 (0.2 mmol) in toluene (2 mL) at a temperature of 160 °C for 6 h. Matsubara[6] and Murakami[7] recently independently reported the Ni-catalyzed synthesis of isoquinolones with the extraction of CO or N_2. Cheng also reported the Ni-catalyzed reaction of 2-halobenzamides with alkynes leading to the synthesis of isoquinolones.[8] These reactions involve cleavage of reactive chemical bonds that are already present on the aromatic ring, such as C(O)−N, C−(N=N), and C−halogen. The reactions described in this report, however, involve cleavage of ortho C−H bonds.

Scheme 1



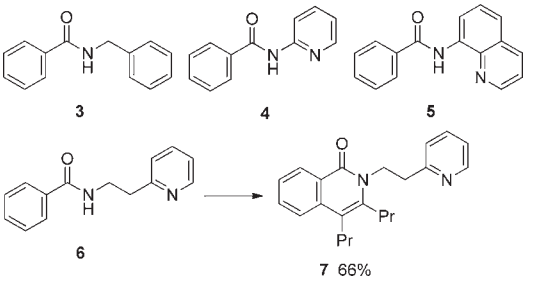


Figure 1. Effect of the directing group.

We next examined the effect of the directing group on the efficiency of the reaction (Figure 1). The corresponding benzyl amide **3** and the one-carbon-shorter amide **4** did not react with 4-octyne under the standard conditions. However, the reaction of the one-carbon-longer amide **6** with 4-octyne under the standard conditions gave isoquinolone derivative **7** in 66% yield along with 15% recovery of **6**. Among the directing groups examined, 2-pyridinylmethylamine gave the best results.

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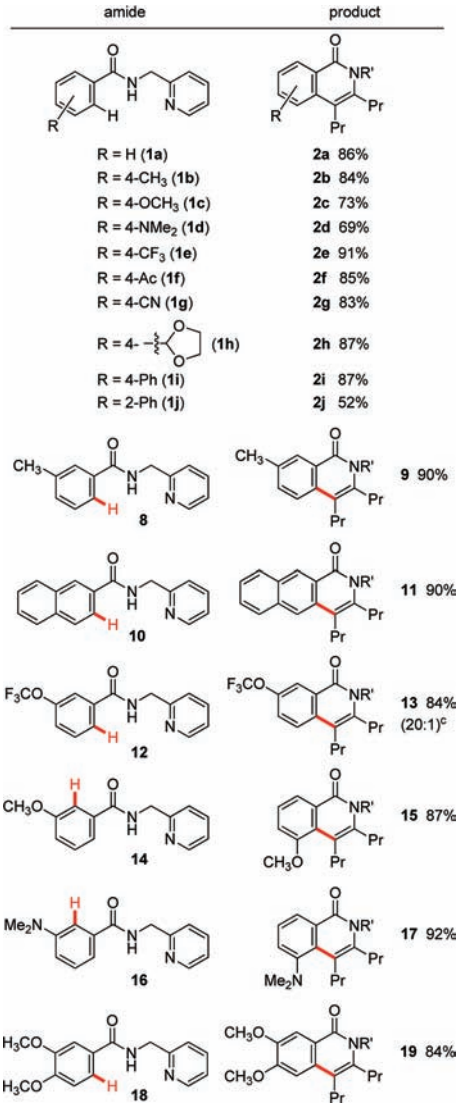
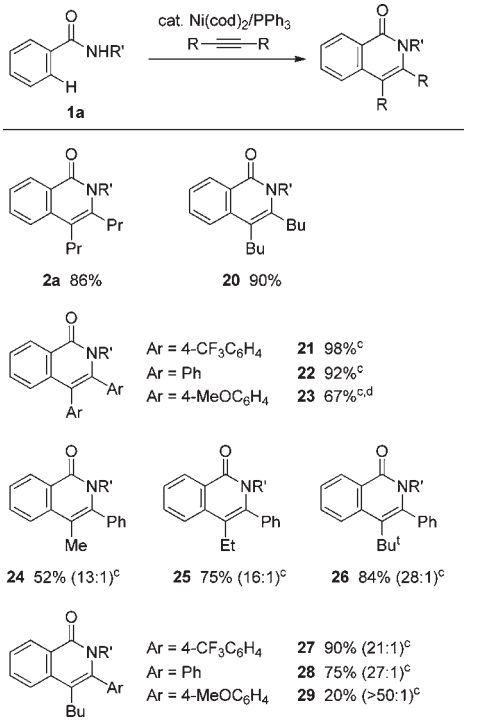
Table 1. Ni-Catalyzed Reactions of Aromatic Amides with 4-Octyne[a,b]



[a] Reaction conditions: amide (0.5 mmol), 4-octyne (1.5 mmol), $Ni(cod)_2$ (0.05 mmol), and PPh_3 (0.2 mmol) in toluene (2 mL) at 160 °C for 6 h. [b] Isolated yields are shown. [c] The ratio of regioisomers is shown in parentheses.

Some representative results of Ni-catalyzed reactions of aromatic amides with 4-octyne are shown in Table 1. Various functional groups, such as methoxy, amino, trifluoromethyl, acetyl, cyano, and acetal groups, were tolerated under the reaction conditions. Substrates with an electron-donating group were slightly less reactive than those with an electron-withdrawing group. Thus, the reaction of **1c** and **1d** did not proceed to completion (**1c** and **1d** were recovered in 26 and 28% yield, respectively), but substrates with an electron-withdrawing group, such as **1e** and **1f**, reacted completely. We next examined the regioselectivity of the annulation using meta-substituted aromatic amides. The reaction of *m*-methyl-substituted aromatic amide **8** gave **9** as a single regioisomer through selective cleavage of the less-hindered C−H bond. The same selectivity was observed in the cases of **10** and **12**. In sharp contrast, in the case of *m*-methoxy- and *m*-dimethylamino-substituted substrates **14** and **16**, the more-hindered

Table 2. Ni-Catalyzed Reactions of Amide 1a with Internal Alkynes[a,b]



[a] Reaction conditions: amide (0.5 mmol), alkyne (1.5 mmol), $Ni(cod)_2$ (0.05 mmol), and PPh_3 (0.2 mmol) in toluene (2 mL) at 160 °C for 6 h. [b] Isolated yields are shown. Ratios of regioisomers as determined by NMR analysis are shown in parentheses. [c] Alkyne (2.5 mmol) was used. [d] The reaction was run using $Ni(cod)_2$ (0.075 mmol) for 2 days.

C−H bond was cleaved to afford **15** and **17**, respectively. However, the reaction took place at the less-hindered C−H bond in the reaction of 3,4-dimethoxy-substituted substrate **18**. These results suggest that steric effects are a dominant factor for this type of reaction but that the electronic nature of the substituents also can have a significant effect on the regioselectivity of the reaction if they have a lone pair of electrons.

Table 2 shows the results of reactions of **1a** with internal alkynes. Dialkylacetylenes gave the corresponding isoquinolones in high yields. It was found that diarylacetylenes also participate in the oxidative cycloaddition. The reaction of **1a** with diphenylacetylene gave **22** in 71% yield under the reaction conditions used. The use of 5 equiv of alkyne resulted in an increase in the product yield to 92%. Unsymmetrical alkynes regioselectively gave the corresponding isoquinolones **24**−**26** having the aryl group attached at the carbon adjacent to the nitrogen atom. The conversion of **1a** to an isoquinolone requires the release of two hydrogen atoms, suggesting that the reaction requires a hydrogen acceptor or an oxidizing agent for a high conversion to be achieved. We expected that the alkyne would also function as a hydrogen acceptor as well as a two-component coupling partner. In fact, stilbene was produced in a yield (81%) comparable to that for **22** (92%) in the reaction of **1a** with diphenylacetylene, providing evidence that the alkyne functions as a hydrogen acceptor.

The reaction with unsymmetrical alkynes was highly regioselective. In the case of phenyl alkyl alkynes, the phenyl group in the product was attached at the carbon next to the nitrogen atom. As the size of the alkyl group was increased, the regioselectivity

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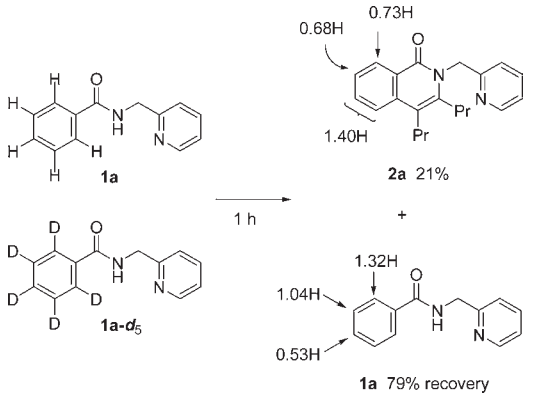
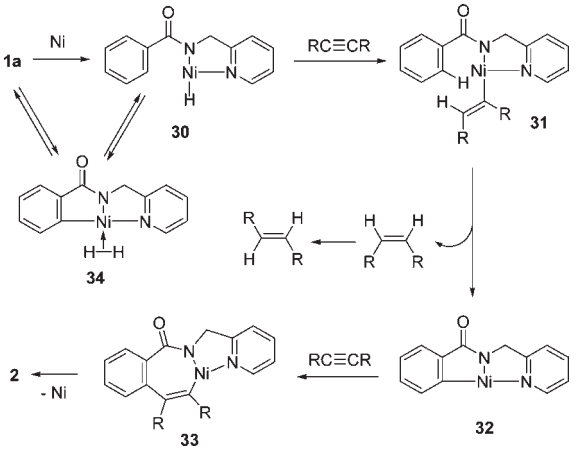
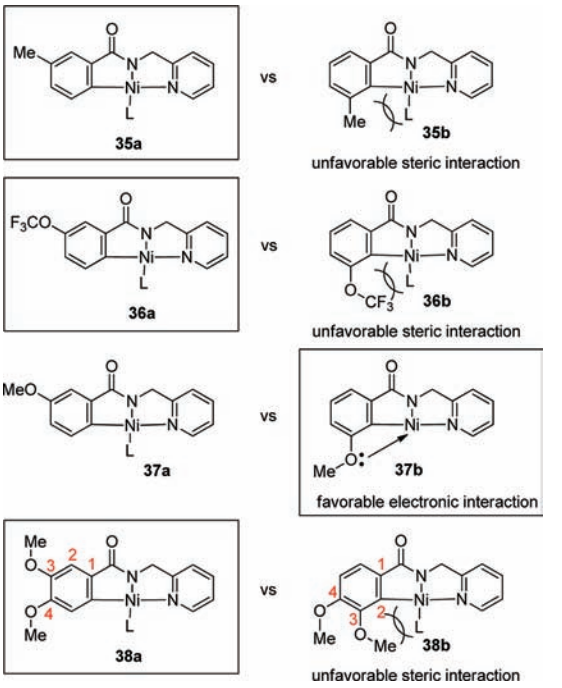
Scheme 2



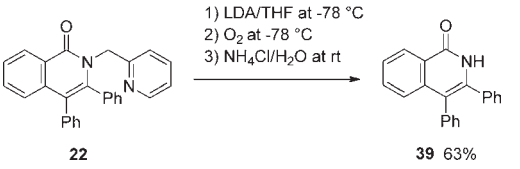
Scheme 3. Proposed Mechanism



Scheme 4. Rationale for the Regioselectivity of C−H Bond Activation Based on Steic and Electronic Factors



Scheme 5. Removal of the 2-Pyridinylmethylamine Moiety



also increased (Me < Et < ^{t}Bu = 13:1 < 16:1 < 28:1). The electronic effects of a substituent on the aromatic ring also had a slight effect on the regioselectivity. Thus, the presence of an electron-donating group resulted in a slightly increased regioselectivity (CF_3 < H < OMe = 21:1 < 27:1 < 50:1).

We conducted a series of experiments to probe the mechanism of the reaction. The reaction of a 1:1 ratio of **1a** and **1a-d_5** was run for 1 h under otherwise standard reaction conditions (Scheme 2). ^{1}H NMR analysis of the product **2a** showed that the **1a** reacted more than 2 times faster than **1a-d_5** (0.7/0.3 = 2.3).

In both the product and the recovered starting amide, the ratios of the protons of the ortho C−H bonds were slightly higher than those of the other positions. To determine the proton source, the reaction of **1a-d_5** was conducted in the absence of 4-octyne. When the reaction was carried out in toluene, **1a-d_5** was recovered in 95% yield and H/D exchange occurred only at the ortho position. The same result was obtained when the reaction was run in toluene-d_8, indicating that the source of the proton is not the solvent but that H/D exchange between the ortho C−H bond and the N−H bonds probably occurs.

A proposed mechanism is shown in Scheme 3. Coordination of amide **1a** to the nickel center as an N,N-donor followed by activation of the N−H bond gives nickel hydride complex **30**, and the insertion of the alkyne into the H−Ni bond of **30** affords vinylnickel complex **31**. Cleavage of the ortho C−H bond with concomitant formation of an alkene gives ortho-metalated complex **32**. Insertion of the alkyne into complex **32**[9] followed by reductive elimination results in the formation of an isoquinolone, with nickel being regenerated. Similar transformations of aromatic amides to isoquinolone derivatives using $[Cp^*RhCl_2]_2$ or $[RuCl_2(p\text{-cymene})]_2$ as the catalyst have been independently reported by four different groups.[10,11] Unlike these reported examples, the present reaction does not require either an expensive catalyst such as $[Cp^*RhCl_2]_2$ or $[RuCl_2(p\text{-cymene})]_2$ or a stoichiometric amount of a metal oxidant such as a silver or copper salt.[10a,c,d,11] While the regioselectivity of the reaction has not been examined extensively in the $[Cp^*RhCl_2]_2$- and $[RuCl_2(p\text{-cymene})]_2$-catalyzed reactions reported to date, the reaction occurred at the less-hindered C−H bond or a mixture in all cases examined. In sharp contrast to the present reaction, even the substitution of a methoxy group at the meta position resulted in the cleavage of the less-hindered C−H bond.[10c] On the basis of the result that H/D exchange occurs between the ortho C−H bond and the N−H bonds, it is likely that H/D exchange between **1a** and **30** occurs through σ-hydrogen complex **34**.

The findings reported herein indicate that the regioselectivity of reactions using meta-substituted aromatic amides is highly dependent on the nature of substituent. The substitution of a methyl or trifluoromethoxy group at the meta position resulted in the selective cleavage of the less-hindered C−H bond to give **9**

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or **13**, respectively, as shown in Table 1. This can be attributed to unfavorable steric interactions between a meta substituent and a ligand on the nickel center, as in **35b** and **36b** (Scheme 4). In sharp contrast, the substitution of a methoxy or dimethylamino group at the meta position favors the cleavage of the hindered C−H bond to give **15** or **17**, respectively. This reverse selectivity can be rationalized by the coordination of an oxygen or nitrogen atom to the nickel center. Thus, the coordination of a heteroatom stabilizes the cyclometalated complex, as in **37b**. In contrast to the 3-methoxy substrate **14**, in the reaction of the 3,4-dimethoxy substrate **18**, the less-hindered C−H bond underwent cleavage, probably because of the buttressing effect of the methoxy group.[12] A methoxy group at the 4-position pushes the other methoxy group at the 3-position away toward the nickel center, thus creating an unfavorable steric interaction, as in **38b**.

The directing group, a 2-pyridinylmethylamine, can be easily removed by treatment of **22** with lithium diisopropylamide (LDA) and then bubbling O_2 followed by hydrolysis to give NH-isoquinolone **39** in good yield (Scheme 5).

In summary, we have reported the development of a new catalytic system that takes advantage of chelation assistance by a 2-pyridinylmethylamine moiety.[5,13] As a result, the first example of the Ni-catalyzed transformation of ortho C−H bonds utilizing chelation assistance has been achieved. Although the pioneering example of ortho metalation involving cleavage of C−H bonds was achieved using a nickel complex,[4] no examples of catalysis using nickel complexes have been reported even more than 45 years after the pioneering work appeared in the literature. Although similar types of transformations using a $[Cp^*RhCl]_2$ or $[RuCl_2(p\text{-cymene})]_2$ complex as the catalyst have been reported,[10,11] it is significant that even less expensive nickel complexes can be used as catalysts for the reaction. To examine the potential of the newly designed directing group for exploring new reactions that have not been achieved using a conventional chelation-assisted system, we are currently testing the system for its potential for use in a variety of catalytic reactions.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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