An unusual endo-selective C-H hydroarylation of norbornene by the Rh(I)-catalyzed reaction of benzamides

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Hydroarylation is an environmentally attractive strategy which incorporates all of the atoms contained in the substrates into the desired products. Almost all the hydroarylations of norbornene reported to date involve an exo-selective reaction. Here we show the endo-selective hydroarylation of norbornene in the Rh(I)-catalyzed reaction of aromatic amides. The addition of sterically bulky carboxylic acids enhances the endo-selectivity of the reaction. The results of deuterium-labeling experiments show that both the ortho-carbon and the ortho-hydrogen atoms of aromatic amides were attached to the same carbon atom of the norbornane skeleton in the hydroarylation product. These results clearly suggest that hydrometalation or carbometalation, which are commonly accepted mechanisms for the catalytic hydroarylation of C-H bonds, are not involved as the key step in the present reaction, and suggest that the reaction involves a rhodium carbene complex generated from norbornene as the key intermediate.
Catalytic addition reactions of X–Y species to alkenes are one of fundamental transformations in organic synthesis. Among the various alkenes that are used in such addition reactions, bicyclo[2.2.1]hept-2-ene (norbornene) has been extensively used in a variety of addition reactions, including hydroboration, hydrosilylation, hydroamination, carbometallation, carboesterification, and silylmetalation, because of the high reactivity of its C–C double bond due to ring strain. In most cases, addition reactions of norbornene have been reported to be exo-selective, irrespective of the reaction mechanism, and numerous attempts have been made to explain the origin of this selectivity.

Numerous advances in the catalytic activation of C–H bonds have been made in the past decades. While a wide variety of functionalizations of C–H bonds has been reported to date, the hydroarylation of alkenes is the most direct and atom-economical.

**Fig. 1** Conventional key steps in catalytic addition reactions to norbornene. Irrespective of the mechanism, the addition reactions of X–Y species to norbornene proceed in an exo-manner.

![Fig. 1](image)

**Fig. 2** Endo-selective hydroarylation of C–H bonds with norbornene. There are many examples of the exo-selective hydroarylation of C–H bonds with norbornene, but none of an endo-selective hydroarylation. An acetate ligand on the rhodium catalyst has a significant effect on the efficiency of the reaction.
reaction for preparing alkylarenes, because all of the atoms of the substrates and reagents are incorporated into the desired products. There are many reports on the reaction of C(sp^2)-H bonds with norbornene. Although the hydroarylation of norbornene has been extensively studied, almost all of the examples reported to date have involved an exo-selective reaction or the stereoselectivity of the reaction products was not clearly demonstrated, irrespective of the mechanism including hydroetathelation, carbenolation, heteroatom-carbenolation, and Friedel–Crafts type reactions. To the best of our knowledge, only a single, specific example of the endo-selective hydroarylation of norbornene has been reported. In that report, the reaction of mesitylene with norbornene in the presence of a W(II) carbonyl complex gave the endo product exclusively, however curiously, benzene, toluene, and p-xylene gave only exo-products as a single isomer, but the details of the reaction were not discussed.

Herein, we report on an unusual, endo-selective hydroarylation of norbornene that proceeds via the Rh(I)-catalyzed reaction of aromatic amides by taking advantage of an 8-aminoquinoline directing group. The available evidence, based on deuterium-labeling experiments, suggests that a carbone mechanism is involved.

Results

Reaction development and optimization. We initiated our study by investigating the reaction of the aromatic amide 1a with norbornene under our previously reported hydroarylation conditions (Fig. 2). The reaction of amide 1a (0.3 mmol) with norbornene (0.6 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 gave an 8.0:1 mixture of the hydroarylation product 2a in an isolated yield of 89%. Fortunately, the major isomer was obtained in crystalline form and was recrystallized from hexane/EtOAc. Unexpectedly, an X-ray crystallographic analysis clearly showed that the major isomer of 2a was the endo-isomer. Encouraged by this unusual but promising result, the effect of directing groups was examined. No reaction occurred when 2-methyl-N-(naphthalen-1-yl)benzamide (3) was used as the substrate. Furthermore, when quinolin-8-yl 2-methylbenzoate (4) and N_2-dimethyl-N-(quinolin-8-yl)benzamide (5) were used in place of 1a as the substrate, no reaction took place. These results indicate that the presence of both a quinoline N(sp^2) atom and a proton on the amide nitrogen is essential for the reaction to proceed. The use of 2-pyridinylmethylamine, as in the case where 6 was used as the substrate did not give the expected hydroarylation product, but, rather, a complex mixture was obtained. The reaction of N-pentafluorophenyl benzamide 7 resulted in no reaction. Thus, the presence of an 8-aminoquinoline directing group is crucial for the success of the reaction.

The nature of the catalyst was next examined. Curiously, when [RhCl(cod)]_2 was used as the catalyst in place of [Rh(OAc)(cod)]_2, no hydroarylation product 2a was produced (Fig. 2, entry 2). However, when KOAc was used as an additive, 2a was produced in good yield (Fig. 2, entries 3 and 4), suggesting that an acetate ligand on the rhodium catalyst has a significant effect on the efficiency of the reaction. Among the rhodium complexes examined, [Rh(OAc)(cod)]_2 gave the best results. A shorter reaction time, lower reaction temperature, and low catalyst loading all resulted in a decreased conversion of 1a (Fig. 2, entries 7–9).

To increase the yield of the hydroarylation product and to increase the endo-selectivity of the reaction, various parameters were investigated. The use of bulky carboxylic acids as additives dramatically improved the endo-selectivity of the reaction. A shorter reaction time, lower reaction temperature, and low catalyst loading all resulted in a decreased conversion of 1a (Fig. 2, entries 7–9).

**Fig. 3** Endo-selective hydroarylation of C-H bonds with norbornene. The use of bulky carboxylic acids as additives dramatically improved the endo-selectivity of the reaction.
were examined in the reaction of meta-phenyl-substituted amide 1b (Fig. 3). The solvent had no significant effect on product yield (Fig. 3, entries 1–6). None of the hydrocarbon solvents examined resulted in an improved endo-selectivity. However, the use of 4-methyltetrahydropyran as a solvent gave a low ratio of endo/exo (Fig. 3, entry 6). The addition of a carboxylic acid as an additive dramatically improved the endo-selectivity. It is noteworthy that the use of bulky carboxylic acids as additives dramatically improved the endo-selectivity: 4.5:1 for no acid, 10.3:1 for pivalic acid, 13.4:1 for 2,6-Me2C6H3COOH (Fig. 3, entries 1, 7, and 10). Finally, the use of 3 equivalents of pivalic acid or 2,6-dimethylbenzoic acid gave the best results in terms of both conversion and endo-selectivity. However, trace amounts of unidentified byproducts were produced when carboxylic acids were used as additives, the formation of which frequently caused some difficulties in isolating the main products in pure form.

**Substrate scope.** The scope of amides was investigated by carrying out the reaction in the presence of 3 equivalents of pivalic acid or 2,6-dimethylbenzoic acid (Fig. 4). A number of functional groups, including dimethylamino, methoxy, acetoxy, fluoro, bromo, and trifluoromethyl groups, were tolerated in the reaction. It was worth noting that meta-substituted aromatic amides exhibited excellent regioselectivity to give the corresponding hydroarylation products at the less-hindered C–H bonds, irrespective of the electronic nature of the substituent. Curiously, the electronic nature of the substituent also affected the endo-selectivity of the reaction. Thus, an electron-donating substituent tended to result in a higher endo-selectivity. In sharp contrast, five-membered heteroaromatic amides gave a significant amount of the exo-isomer, the absolute structure of which was confirmed by X-ray crystallographic analysis. The other heteroaromatic amides gave a nearly 1:1 ratio of the hydroarylation products.

Norbornene derivatives, such as benzene-fused norbornene, naphthalene-fused norbornene, and 2,3-diazabicyclo[2.2.1]hept-5-ene were also found to participate in the present reaction to give the corresponding hydroarylation products 8–10. The stereochemistry of the major isomer of 10a was confirmed to be the endo form by X-ray crystallographic analysis.
In competition experiments (Supplementary Table 1), an electron-donating group facilitated the reaction when it was carried out in the absence of a carboxylic acid. In contrast, the electronic nature of the substituent had no effect on the efficiency of the reaction in the presence of a carboxylic acid as the additive.

Mechanistic insights. If hydrometalation or carbometalation, commonly accepted mechanisms for catalytic hydroarylation reactions were to be involved as the key step, exo-selective hydroarylation would be expected to occur, as has been observed in most reported examples. However, a high degree of endo-selectivity was observed in the present system, which suggests that neither hydrometalation nor carbometalation are involved as the key step in this reaction. In an attempt to gain more insights into the mechanism of the reaction, deuterium-labeling experiments were carried out (Fig. 5). In the reaction of 1a with norbornene, a significant amount of H/D exchange occurred in the recovered amide, and both the ortho-carbon and the ortho-H of aromatic amides were attached to the 2-position of the norbornane ring in the product. In sharp contrast to 1a, no deuterium incorporation was observed at the 2-position in the norbornane ring in the hydroarylation product obtained from 1r. One of the deuterium atoms migrates to the adjacent carbon.
quinoline ring was also detected by 1H NMR, indicating that drofuran 39. This kind of the bond connection has never observed, but again only at the ortho-position (Fig. 5b). The proton source of the H/D exchange appears to be an NH bond. This H/D exchange between the ortho-C–H bond and the NH bond in 1a–d 39, was very rapid, making the result complicated. Because of the fast H/D exchange of the starting amide, the ratio of the deuterium atom incorporated at the 2-position of the norbornane ring increased to 80% (0.20 H), and the ratio of deuterium incorporation at the 2-position decreased to 19% (0.19 H) and the ratio of deuterium incorporation at the N(sp 2) atom of the quinoline ring was also detected by 1H NMR, indicating that protons in the quinoline ring can also serve as a proton source for the H/D exchange. It should be noted that deuterium atoms were again detected only at the 2-position in the norbornane skeleton of the hydroarylation product. In sharp contrast, different results were obtained when five-membered heterocyclic substrates were used. Thus, exo-products were selectively produced (Fig. 4) and no deuterium incorporation was observed in the norbornane ring of the product obtained from 1r (Fig. 5d), suggesting that two different mechanisms are operating, depending on the structure of the substrate. Because a rapid H/D exchange in the starting amides was observed, the results obtained from deuterium-labeling experiments were complicated. To avoid such complicated results, a deuterium-labeled benzene-fused norbornene was used in attempt to develop a better understanding of the reaction mechanism (Fig. 4). The reaction of 1a with the deuterium-labeled benzene-fused norbornene gave the hydroarylation product 8 in which 0.93 H was observed at the 2-position of the norbornane ring, indicating that one of the deuterium atoms migrates to the adjacent carbon.

A plausible mechanism for the endo-selective hydroarylation is shown in Fig. 6. The coordination of the N(sp 2) atom in the quinoline ring and the NH in amide 1 to a rhodium center gives the Rh(I)X species A. The electrophilic addition of norbornene to the rhodium complex A gives complex B, which undergoes a hydride shift to give the rhodium carbene complex C 41. The oxidative addition of the ortho-C–H bond to the rhodium center followed by hydride migration from the rhodium center to the carbene carbon gives E 42, which undergoes reductive elimination to give the hydroarylation product 2 with the regeneration of the Rh(I) species. The stereo-determining step is the hydride migration from the rhodium center to the carbene carbon in D (D → E), which proceeds from the exo-face because it is more accessible. As the alternative mechanism, the concerted oxidative addition of C–H bonds directly from C to E or the elimination of HX form D followed by re-addition of HX to F cannot be excluded. Irrespective of the mechanism, the reaction, which involves the generation of a rhodium carbene complex from an alkene, is a rare occurrence. As shown in Fig. 5a and c, when the reaction is conducted using a deuterium-labeled substrate, a deuterium atom is incorporated exclusively at the 2-position of the norbornane ring of the hydroarylation product and no deuterium atoms were detected at any other positions in the norbornane skeleton. The proposed mechanism, which involves the formation of the rhodium carbene complex C, is consistent with the deuterium-labeling data, although we currently have no direct experimental evidence for the generation of the rhodium carbene C. While diazo compounds are commonly used for the generation of metal carbenes, a metal carbene complex can also be generated from tosylhydrazones, triazoles, alkynes and cyclopropanes and these methods have been extensively used in...
Methods

**General procedure for the Rh(I)-catalyzed hydroarylation of aromatic amides with norbornene.** To an oven-dried 5 mL screw-capped vial, 3-fluoro-2-methyl-N-(quinolin-8-yl)benzamide (1n) (84 mg, 0.3 mmol), 2-norbornene (57 mg, 0.6 mmol), [Rh(OAc)2(cod)] (4.1 mg, 0.0075 mmol), pivalic acid (92 mg, 0.9 mmol) and toluene (0.5 mL) were added. The mixture was stirred for 12 h at 160 °C and then allowed to cool. The resulting mixture was filtered through a celite pad, the filtrate was washed with saturated aqueous NaHCO3 (10 mL) and the organic phase concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc = 50/1) to afford the alkylation product 2n (104.4 mg, 93%, \(endo,exo = 16.3:1\)) as a colorless oil.

**Data availability.** The authors declare that the data supporting the findings of this study are available within the paper and its Supplementary Information files, and also are available from the corresponding author upon reasonable request.

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Author contributions

N.C. conceived the project and wrote the manuscript. K.S. and S.N. planned and carried out the experiments. All authors participate in the discussion of the results and commented on the manuscript.

Additional information

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