Rhodium Catalysis

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Rhodium(III)-Catalyzed Intramolecular Hydroarylation, Amidoarylation, and Heck-type Reaction: Three Distinct Pathways Determined by an Amide Directing Group**

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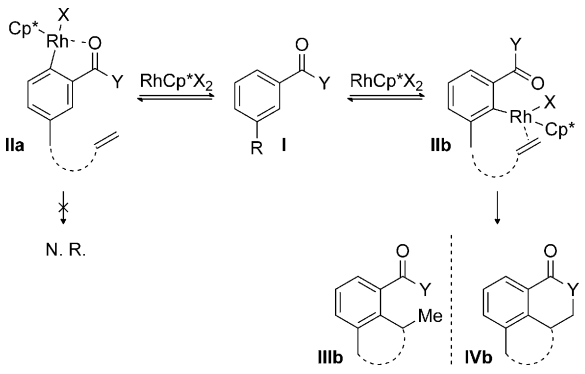
Rh^{III} catalysis has enabled a vast number of transformations through C–H activation. Many examples exist of functionalization of arenes at the *ortho* position to a directing group, thus eliminating the need for prior activation at that position. This is a powerful emerging strategy for forming C_{sp^2}–C_{sp^3} bonds from aryl and alkenyl C–H bonds.[1]

The use of simple alkenes as partners in the C–H/N–H activation of benzamides has been demonstrated previously,[2] and in a few cases has been rendered enantioselective.[3] Nevertheless, most cases are limited to functionalized alkenes: styrenes and acrylates undergo regioselective insertion (5:1 to 20:1) whereas terminal alkenes perform poorly (ca. 1:1 to 2:1).[4] The situation is further exacerbated by the use of unsymmetrical benzamide partners: 3-substituted benzamides have two distinct C–H bonds *ortho* to the directing group, thus leading to a pair of potential rhodacycles (**IIa** and **IIb**, Scheme 1), and these benzamides give mixtures of products sometimes dominated by steric effects and other times by electronic effects.[5]

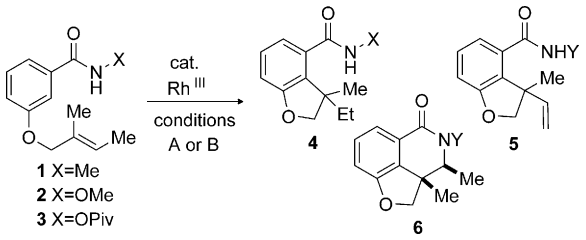
To understand these issues of regioselectivity, we sought to use simple alkenes tethered to the benzamide system through the *meta* position.[6] While this has the obvious disadvantage of being a tethering strategy, we hoped to gain insights into the reaction and use more complex stereochemically defined internal alkenes to arrive at products **IIIb** and **IVb** (Scheme 1). In particular, the ability to use 1,1-disubstituted and trisubstituted alkenes could lead to synthetically challenging compounds containing all-carbon quaternary stereocenters that have not been accessed through previous methods.[7] We have previously demonstrated that {Cp^*Rh^{III}} undergoes reversible C–H activation in the absence of alkyne[8] and we thus felt that even if the more sterically accessible C–H bond was first to be activated (**IIa**, Scheme 1), it should not undergo reaction because of the lack of an appropriate coupling partner.

Subjection of a simple *E*-trisubstituted alkene tethered to the 3-position of methylbenzamide to a cationic Rh^{III} catalyst (condition A, entry 1, Table 1) and stoichiometric pivalic acid in DCE at 80 °C led to full conversion into the hydroarylation product **4**.[9] The subjection of the corresponding *N*-OMe amide (entry 2, Table 1) to the same reaction conditions provided a 71:29 mixture of the hydroarylation product **4** and the dehydrogenative Heck-type (DH) product **5**.[10] Reaction of the *N*-OPiv amide resulted in the amidoarylation product **6** along with hydrolysis of the starting material (entry 3, Table 1). Finally, conducting the reaction of amides **2** and **3**



Scheme 1. Regioselective C–H activation. Cp* = pentamethylcyclopentadienyl.

Table 1: Initial optimization of hydroarylation conditions.[a]



Entry	X	Y	Condition	4/5/6	Conv. [%][b]
1	Me	Me	A, 17 h	100:0:0	100
2	OMe	H	A, 17 h	71:29:0	53
3	OPiv	H	A, 17 h	0:0:100	61[c]
4	OMe	H	B, 2 h	0:100:0	100
5	OPiv	H	B, 12 h	0:22:78	100

[a] Reactions conducted on 0.1 mmol scale. A: $[RhCp^*(MeCN)_3](SbF_6)_2$ (1 mol%), $tBuCO_2H$ (1 equiv), 1,2-dichloroethane (0.2 M), 80 °C; B: $[RhCp^*Cl_2]_2$ (2.5 mol%), CsOAc (2 equiv), MeOH (0.2 M), RT. [b] Conversion determined by ^1H NMR. [c] Hydrolysis of the starting material was also observed. OPiv = pivalate.

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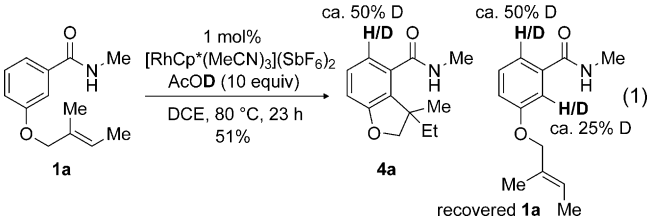
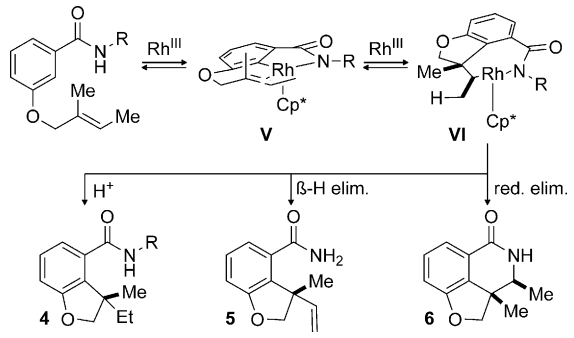
under basic conditions resulted in products **5** and **6** selectively at ambient temperature (entries 4,5, Table 1).

Mechanistically, this reaction may proceed through a C–H activation event and addition of the aryl rhodium species across the alkene to provide the seven-membered metallacycle **VI** (Scheme 2). Protonation could then lead to the hydroarylation product **4**. This common metallacycle could also proceed to a reductive elimination pathway (**6**) or a β-hydride elimination pathway (**5**) with reduction of the metal. Validation of our hypothesis that the Rh catalyst samples both *ortho* positions on the benzamide came from a deuterium labeling experiment. Subjection of **1a** to the hydroarylation conditions in the presence of AcOD resulted in deuterium incorporation at the *ortho* position in product **4a** as well as at both *ortho* positions in the recovered starting material [Eq. (1)].



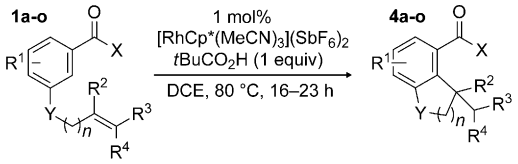
(1)

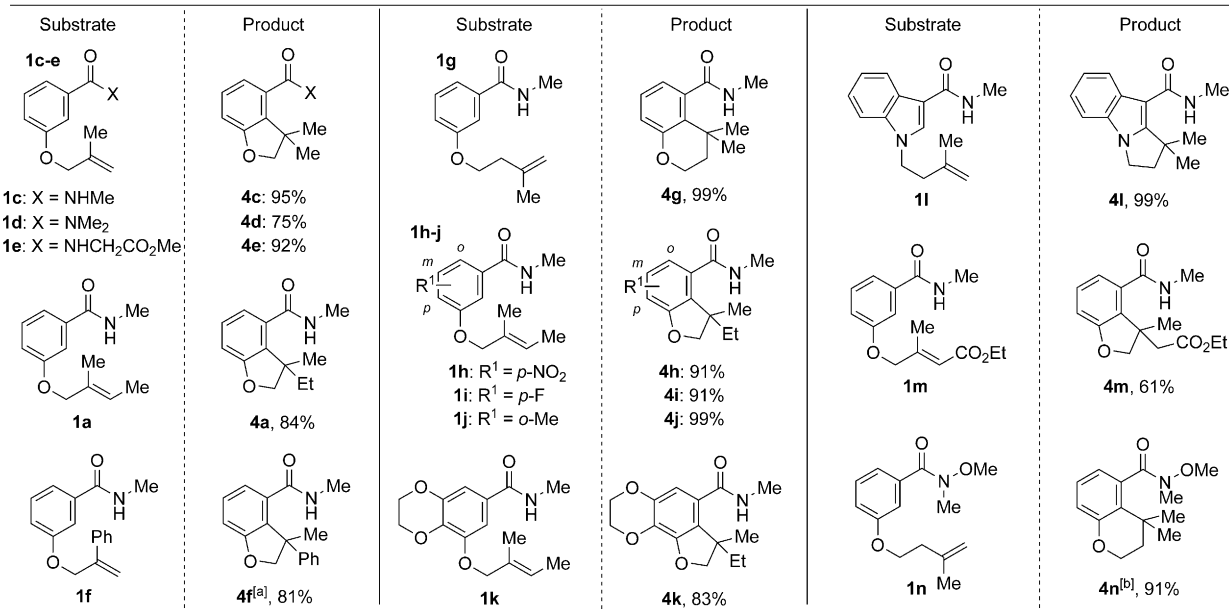


Scheme 2. Plausible mechanistic pathways.

We were intrigued by the ability to deliver three distinct products simply by choice of amide substituent and sought to delineate the scope of each transformation. Using the optimal conditions for hydroarylation,[11,12] the amide portion of the tethered alkene was varied to investigate its impact (Scheme 3). An *N*,*N*-dimethylamide was used to provide cyclized product **4d** in 75% yield. A glycine amide led to product **4e** in excellent yield (92%). Changing the directing group to an ester was detrimental since only a small amount of conversion into product was observed by NMR spectroscopy under the standard conditions.

A wide variety of tethered alkenes were found to undergo the desired cyclization. Modification of the alkene was tolerated since several 1,1-di- and trisubstituted alkenes[13] were converted into the cyclized products. In addition to five-membered rings, six-membered rings (**4g**, **4n**) could be





Scheme 3. Rh^{III}-catalyzed intramolecular hydroarylation. Reaction conditions: $[RhCp^*(MeCN)_3](SbF_6)_2$ (1 mol%), $tBuCO_2H$ (1 equiv), 1,2-dichloroethane (0.2 M), 80°C, 16–23 h. [a] 5 mol% $[RhCp^*(MeCN)_3](SbF_6)_2$ used. [b] 2.5 mol% $[RhCp^*(MeCN)_3](SbF_6)_2$ used.

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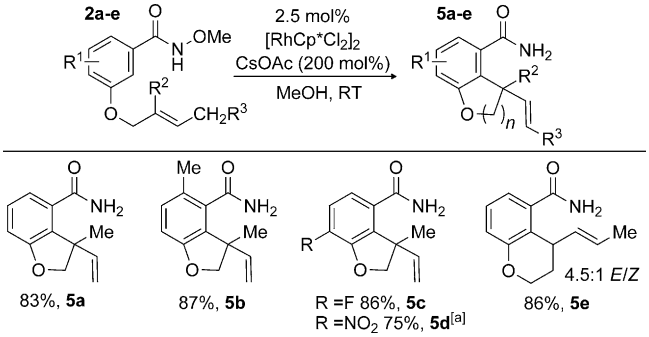
formed. Electronic and steric modification of the aryl group was also tolerated. Electron-deficient *p*-nitro and *p*-flouro substrates each gave the corresponding bicyclic systems (**4h** and **4i**, respectively) in 91% yield. *Ortho* substitution of a methyl group also led to good yield of product **4j** (99%). An electron-rich dioxanyl substrate was converted into product **4k** in 83% yield. An alkene tethered to an indole cleanly converted to product **4l** (99%). An acrylate system reacted to give the resulting ester **4m** in 61% yield. A Weinreb amide was also tolerated and delivered the hydroarylation product **4n** in 91% yield.[14]

The β-H elimination/DH pathway produces another useful product with an all-carbon quarternary stereocenter. Direct intermolecular C–H allylations have been demonstrated with a variety of metals but are limited by the necessity to use electron-deficient arenes or harsh conditions. More recently, allenes (Ir[15] and Rh^{III}-catalyzed[16]) and allyl carbonates (Rh^{III}-catalyzed[17]) have been used in directed C–H allylations. In contrast to the previous examples that use a variety of leaving groups on the allyl fragment, this pathway provides the allylated product from an allyl substrate by an oxidative pathway.

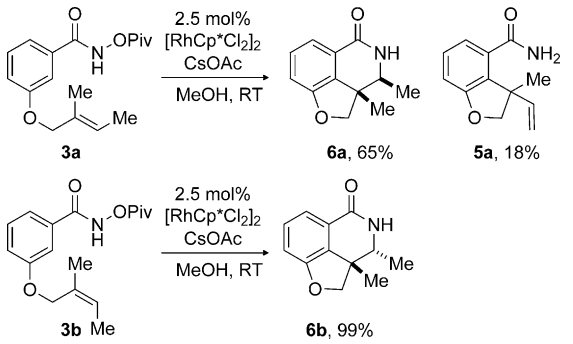
We briefly explored the scope of this transformation (Scheme 4). With the necessity to use an alkene with an available β-hydride, we modified the aryl portion with trisubstituted alkenes. Three additional substrates were shown



Scheme 4. Rh^{III}-catalyzed intramolecular DH-type reactions. Reaction conditions: $[RhCp^*Cl_2]_2$ (2.5 mol%), CsOAc (2 equiv), MeOH (0.2 M), 1–2 h. [a] 20 h reaction time.

to undergo the DH reaction in good yield (75–86%). An *E*-1,1-disubstituted alkene also underwent the DH reaction to form the dihydrobenzopyran product **5e** in good yield and moderate *E*/*Z* selectivity (86%, 4.5:1).

The third pathway identified in this work, the amidoarylation reaction, allowed us to examine the impact of olefin geometry on the reaction. When the *E* olefin **3a** was subjected to the reaction conditions shown in Scheme 5, a single isomer of desired insertion product was isolated in 65% yield with a small amount of byproduct **5a** (resulting from β-H elimination) isolated in 18% yield. Subjection of the *Z* alkene **3b** to the same reaction conditions provided the opposite diastereomer of the insertion product (**6b**) exclusively (99% yield). Importantly, starting olefin geometry is faithfully relayed into product stereochemistry.



Scheme 5. Amidoarylations of *E* and *Z* olefins. Reaction conditions: $[RhCp^*Cl_2]_2$ (2.5 mol%), CsOAc (2 equiv), MeOH (0.2 M).

An extensive scope was demonstrated for this reaction as shown in Scheme 6. This reaction tolerated mono-, 1,1-di-, and trisubstituted olefins. An all-carbon-tethered alkene and a phenyl-substituted alkene provided product in good yield (**6f**, 81% and **6g**, 99%, respectively). Electron-poor (**6h** and **6j**), electron-rich (**6i**), and *ortho*-substituted (**6k**) aryl products were prepared. *E* and *Z* tethered α,β-unsaturated esters each successfully inserted to give a single diastereomer (*E* giving **6l**, 87%; *Z* giving **6m**, 50%). An *E*-1,1-disubstituted alkene cyclized to solely give the *trans* product **6n** in good yield.

In an attempt to provide access to a broader range of products, an ester-tethered substrate was subjected to the optimal reaction conditions. Cyclization of *N*-methoxy amide **2f** (Scheme 7) proceeded smoothly to provide the cleavable lactone product **5f** in 72% yield. By contrast, reaction of the corresponding *N*-pivaloxy amide **3o** resulted in the formation of methanolysis product **7**. This mild lactone cleavage is likely an indication of considerable strain within this tricyclic system and other similar systems shown in Scheme 6. Alternatively, the use of a non-nucleophilic solvent (1,2-dichloroethane) allowed the desired lactone **6o** to be synthesized and isolated in modest yield (45%).

To further demonstrate the utility of this reaction, we explored the effect of a pre-existing stereocenter on these transformations. It seemed likely that reactivity could be directed to one face of the olefin based on the steric constraints provided by a stereocenter. This would potentially lead to a product with three contiguous stereocenters in a highly controlled fashion. An alkyl substituent α to the tethered alkene was well tolerated under the standard conditions since the product **6p** was obtained in 98% yield (Scheme 8). Furthermore, this reaction was found to be highly diastereoselective since the compound was isolated with a d.r. > 20:1 as determined by ^1H NMR and 72:1 by GC–MS. A series of NOESY experiments[18] indicated a *syn*,*syn* relationship between the three alkyl groups.

In summary, we have found three distinct Rh^{III}-catalyzed reaction pathways of tethered olefin-containing benzamides. Hydroarylation, amidoarylation, and dehydrogenative Heck-type products can be accessed based on the type of amide substrate used. A wide variety of tethered alkenes can cyclize to make the five- or six-membered products in good to excellent yields. Furthermore, high diastereoselectivity has

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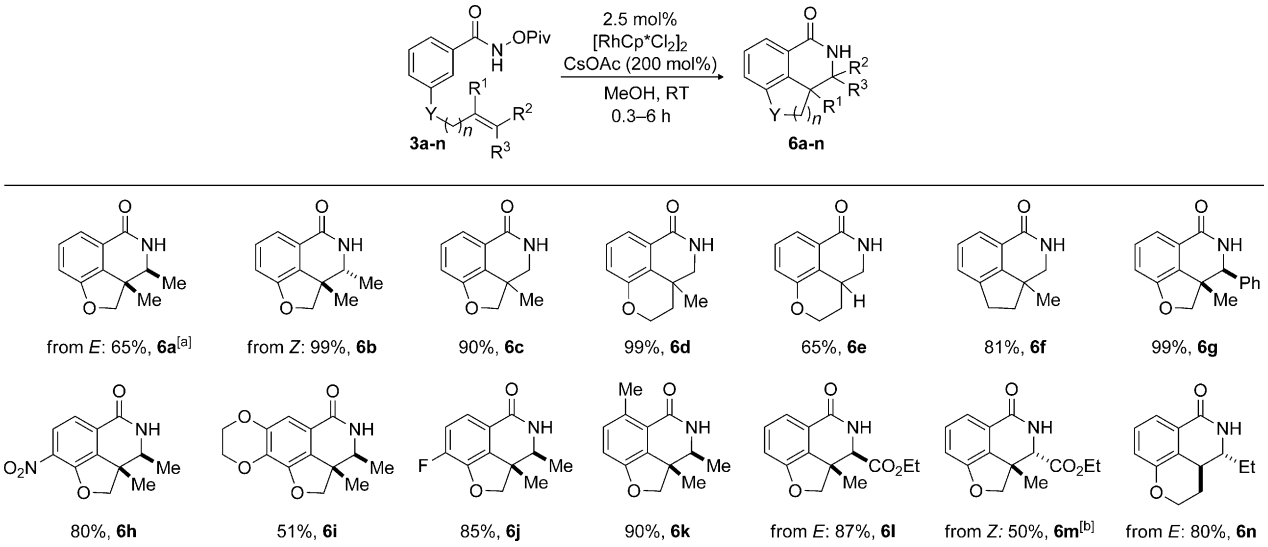
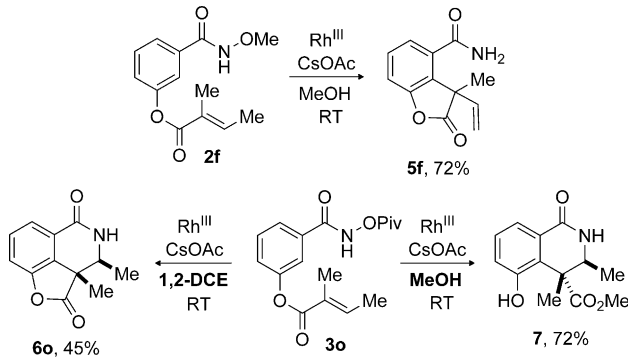
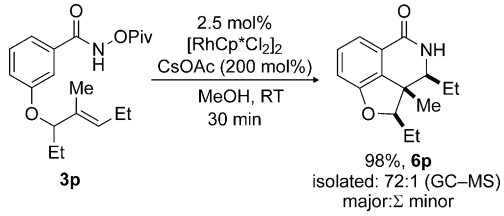


Scheme 6. Rh^{III}-catalyzed intramolecular amidoarylations. Reaction conditions: see Scheme 5, 0.3–6 h reaction time. [a] 18 h reaction time. [b] 48 h reaction time.



Scheme 7. DH and amidoarylation of a cleavable ester tether. Reaction conditions: $[RhCp^*Cl_2]_2$ (2.5 mol%), CsOAc (2 equiv), MeOH or 1,2-dichloroethane (0.2 M), 0.5–18 h.



Scheme 8. Diastereoselective cyclization. Reaction conditions: see Scheme 5.

been observed in the amidoarylation reaction of a substrate containing a pre-existing stereocenter. Efforts to further expand the scope and impart enantioselectivity to this reaction are underway.

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