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Three-Component 1,2-Carboamidation of Bridged Bicyclic Alkenes *via* Rh^{III}-Catalyzed Addition of C–H Bonds and Amidating Reagents

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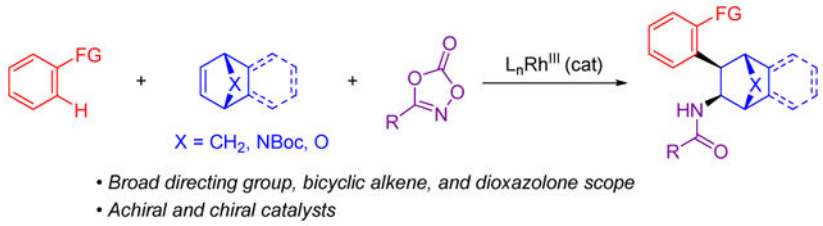
Abstract

A three-component method is described for the preparation of *syn*-1,2-disubstituted bridged bicyclic compounds. The reaction was demonstrated for readily available aromatic and heteroaromatic C–H bond substrates with tertiary and secondary amide, lactam, pyrazole and triazole directing groups, and a variety of bridged bicyclic alkenes, including norbornene, benzonorbornadiene, oxygen and nitrogen-bridged analogs, and an unsaturated tropinone. Broad dioxazolone scope was also observed. The use of a chiral Cp-derived Rh^{III} catalyst enables asymmetric synthesis of products.

Graphical Abstract



Bridged bicyclic systems are an important chemical motif due to their prevalence in approved drugs and drug candidates. For example, [2.2.1]-bridged bicycles are present in molecules such as Ifetroban, which is currently in Phase II Clinical Trials for Duchenne muscular dystrophy.[1] Similarly, the [3.2.1] tropane framework is present in important drugs such as the asthma and COPD medication Spiriva and the HIV drug Selzentry.[1] Development of new methodologies for the elaboration of these structures thus has value in the discovery of pharmaceutical agents.

Bridged bicyclic alkenes have also served as versatile reactants for transition-metal catalysis. For example, Lautens carried out seminal work on Rh^{I} catalyzed asymmetric ring opening

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SUPPORTING INFORMATION.

The Supporting Information is available free of charge via the Internet at http://pubs.acs.org.

Procedure details and NMR spectra (PDF)

Crystallographic data for **7** (CIF)

The authors declare no competing financial interest.

reactions [Scheme 1, (eq 1)],[2] and related approaches for transition-metal catalyzed C–H bond addition and ring-opening have subsequently been reported.[3] Of the C–H functionalization methods that leave the strained bicycle intact, most proceed with monofunctionalization,[4] with relatively few bifunctionalizations having been reported.[5] The carboamidation of bridged bicyclic alkenes using N-aryloxy aliphatic amides as internal redox C–H bond substrates is a notable example of bifunctionalization as recently disclosed by the Zhao and Cramer groups to provide ortho-substituted phenolic products (eq 2).[6] In 2019, our lab reported a modular, functional group compatible three-component reaction for the synthesis of α-branched amines (eq 3).[7,8] Because three different components were used, C–H bond substrates with various directing groups and different amidating reagents could be employed to generate different classes of 1,1-disubstituted α-branched amine derivatives.

Herein, we describe a modular three-component reaction to access 1,2-disubstituted [2.2.1]-bridged bicycles via Rh^{III}-catalyzed 1,2-addition of C–H bonds and amidating reagents to bridged bicyclic alkenes (eq 4). Different types of C–H bond substrates, both aliphatic and aromatic amidating reagents, and a variety of bridged bicyclic alkenes, including norbornene, benzonorbornadiene, oxygen and nitrogen-bridged analogs, and an unsaturated tropinone, led to a broad range of 1,2-disubstituted products. Additionally, asymmetric catalysis was achieved using a chiral Rh^{III} catalyst employing a chiral ligand designed by Cramer.[9,10] A reaction mechanism is proposed that provides a rationale for exclusive 1,2-disubstitution for bridged bicyclic alkenes in contrast to the 1,1-disubstitution that had been observed for three-component carboamidation of terminal alkenes.[7]

Extensive reaction optimization was conducted for the three-component coupling of pyrrolidine benzamide **1a**, isopropyl dioxazolone **2a**,[11] and azabenzonorbornadiene **3a** (Table 1). The cationic Rh^{III} catalyst $[Cp^*Rh(MeCN)_3](SbF_6)_2$ was critical to the reaction (entry 2), and the combination of the $[Cp^*RhCl_2]_2$ dimer and $AgSbF_6$, which forms the active catalyst *in situ*, was found to be a comparable system to the chosen catalyst (entry 3). Other d^6 metal catalyst systems such as $[Cp^*Co(CO)I_2]$, $[Cp^*IrCl_2]_2$, and $[RuCl_2(p\text{-cymene})]_2$, paired with $AgSbF_6$, did not provide any product (entries 4–6). The addition of sodium acetate as an additive was found to be important in facilitating the initial C–H activation step, leading to enhanced conversion to product (entry 7). In contrast, acidic additives such as HOAc led primarily to two-component alkylation products. No reaction occurred with $Cp^*Rh(OAc)_2$ in the absence of NaOAc, but when $AgSbF_6$ was included in the reaction mixture, 86% conversion to product was observed (entries 8–9). The optimal solvent for this transformation was 1,4-dioxane, although 1,2-dichloroethane (DCE) resulted in only a modest reduction in yield (entry 10). The reaction concentration could be increased from 0.2 to 0.5 M with minimal effect on the reaction yield (entry 11). In addition, lowering the temperature from 70 to 50 °C gave a modest drop to 85% yield (entry 12). For some substrates, lowering the temperature to 50 °C and/or reducing the reaction time to 2 h was necessary to avoid the formation of overalkylation products (*vide infra*). Finally, when the alkene was employed as the limiting reagent, product was obtained, but with a reduction in the yield (entry 13).

After determining optimal reaction conditions, we explored the scope of the bridged bicyclic alkene (Scheme 2). We evaluated a variety of [2.2.1]-bridged bicyclic systems with nitrogen,

oxygen and carbon at the bridge position. The reaction proceeded in good yields for bicyclic systems containing nitrogen (**4a-4b**) and oxygen bridges (**4c**), even though these bridges might have been expected to act as leaving groups through a strain-relieving elimination. It is notable that the transformation was effective for a [3.2.1]-nitrogen-bridged bicyclic alkene (**4b**), thereby providing a promising new method for the elaboration of the tropinone core, which is present in a wide variety of natural products, approved drugs and drug candidates, including Selzentry and Spiriva.[1] When the alkene contained a methylene bridge, the reaction also proceeded in good to excellent yields for commercially available norbornene (**4d**) and the more strain-activated benzonorbornadiene (**4e**), respectively. With norbornadiene no conversion of starting material was observed, likely due to non-productive complexation to the catalyst. The scalability of this method was demonstrated by the preparation of **4e** in 71% yield on the 1.0 mmol scale with a catalyst loading of 5 mol %.

A variety of C–H bond substrates were successfully employed (Scheme 2). Commonly encountered motifs such as tertiary (**4a, 4f-4g**) and secondary (**4h**) amides, pyrazoles (**4i**), and triazoles (**4j**) were effective directing groups for this transformation. Product **4f** is of interest due to the presence of a fused bicyclic lactam motif. Product **4g** is also of interest, as it requires activation of a heteroaromatic C–H bond. For the sterically unencumbered secondary amide in product **4h**, the reaction time was reduced to 2 h in order to prevent the addition of a second alkene.

This reaction demonstrated a wide scope for dioxazolone amidating reagents (Scheme 3), with both aliphatic (**4a**, **4k-4m**), aromatic (**4n-4r**) and heteroaraomatic (**4s**) dioxazolones coupling in moderate to high yields. Aliphatic dioxazolones were particularly effective, including for both an unhindered acetamide (**4k**) and a sterically encumbered pivalamide (**4l**). For some of the aromatic amide products, **4o-4r**, it was necessary to reduce the reaction time to 2 h and the temperature to 50 °C to prevent overalkylation by C–H functionalization at the ortho position of the newly formed aromatic or heteroaromatic amide in the product.

We were interested in exploring asymmetric catalysis for this system, given the recent impressive advances in asymmetric Rh^{III}-catalyzed C–H functionalization methodology.[9,10] The Rh complex **6** employing Cramer's chiral ligand led to promising enantioselectivity (Scheme 4).[9c] Optimization of the asymmetric reaction showed that increasing the $AgSbF_6$ loading beyond what was necessary to abstract the Rh-bound iodides increased the yield.[9e] In addition, for products **5a** and **5b**, use of DCE instead of dioxane led to higher yields while maintaining similar enantioselectivities. The scope of this enantioselective reaction was constrained to norbornene and benzonorbornadiene as the bridged bicyclic alkene substrate. Oxygen and nitrogen-bridged alkenes did not provide the desired products, possibly due to elimination of the heteroatomic bridge and non-productive anionic coordination to the metal center.[3] Both pyrrolidine carboxamide (**5a**) and pyrazole (**5b-5e**) were effective directing groups. In addition, 3,5-dimethylphenyl (**5a, 5b, 5d**) and phenyl (**5c, 5e**) dioxazolone coupling partners provided comparable yields and enantioselectivity. The absolute configuration of **5d** was rigorously determined by amide hydrolysis and X-ray structural characterization of the resulting amine **7** (see Supporting Information). The sense of induction for these enantioenriched products is opposite that of previously reported additions

to *N*-tosyl-azabenzonorbornadienes using Cramer's chiral ligand, presumably due to the decreased steric bulk of the methylene bridge in our bridged bicyclic alkenes.[3j,k]

The three-component addition to the bicyclic alkenes reported here proceeds exclusively with *syn*-1,2-carboamidation, while the previously reported three-component addition to terminal alkenes proceeded solely with 1,1-addition (see eq 3, Scheme 1).[7] As supported by a number of mechanistic experiments,[7] the reaction first proceeds by concerted metallation deprotonation to generate rhodacycle **I** (Scheme 5). Then, migratory insertion of the bridged bicyclic alkene into the Rh–C bond of rhodacycle **I** forms the 7-membered rhodacycle **II**. In contrast to the previously reported work with terminal alkenes, *syn*-β-hydride elimination and reinsertion is not possible due to the lack of an appropriately oriented *syn* hydride. Additionally, the bridgehead hydrogens cannot undergo elimination because this would result in the formation of a high-energy anti-Bredt alkene. Nitrene insertion of the 7-membered rhodacycle **II** with retention of configuration then forms the amidated species **III**, which upon protodemetallation produces the observed 1,2-disubstituted product **IV**. The $AgSbF_6$ additive was found to be necessary in order to enable formation of product when using $Cp^*Rh(OAc)_2$ (see entries 8–9, Table 1). The $AgSbF_6$ might facilitate anion exchange with $Cp^*Rh(OAc)_2$ to provide the cationic $Cp^*Rh(OAc)^+$ which is necessary for coordination to the C–H bond substrate. Alternatively, based upon literature reports, it could facilitate breakdown of the 7-membered rhodacycle **III** to release the product **IV**.[12]

In summary, we have developed a modular, three-component Rh^{III}-catalyzed 1,2-carboamidation of bridged bicyclic alkenes. This methodology shows potential for elaborating the common [2.2.1]- and [3.2.1]-bridged bicyclic frameworks found in a variety of approved drugs and drug candidates. In addition, we showed that the use of a chiral Rh^{III} catalyst enables the asymmetric synthesis of the three-component products.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

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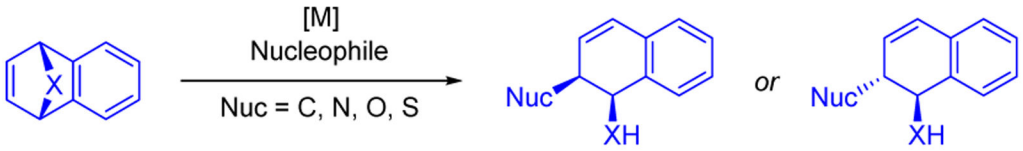
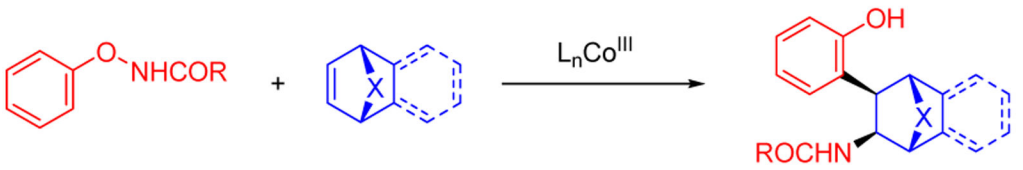
Previous work:

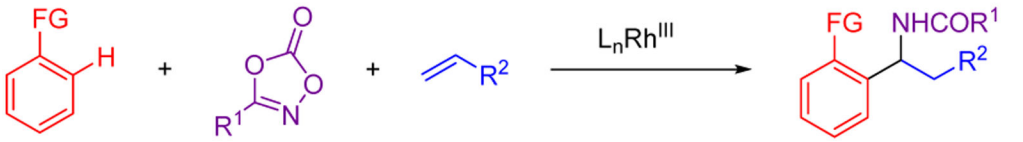
Asymmetric ring opening of bridged bicyclic alkenes[2]



Two-component carboamidation of bridged bicyclic alkenes[6]

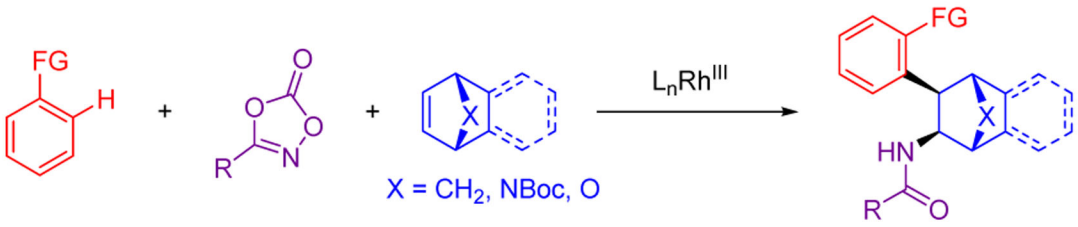


Three-component 1,1-carboamidation of terminal alkenes[7]

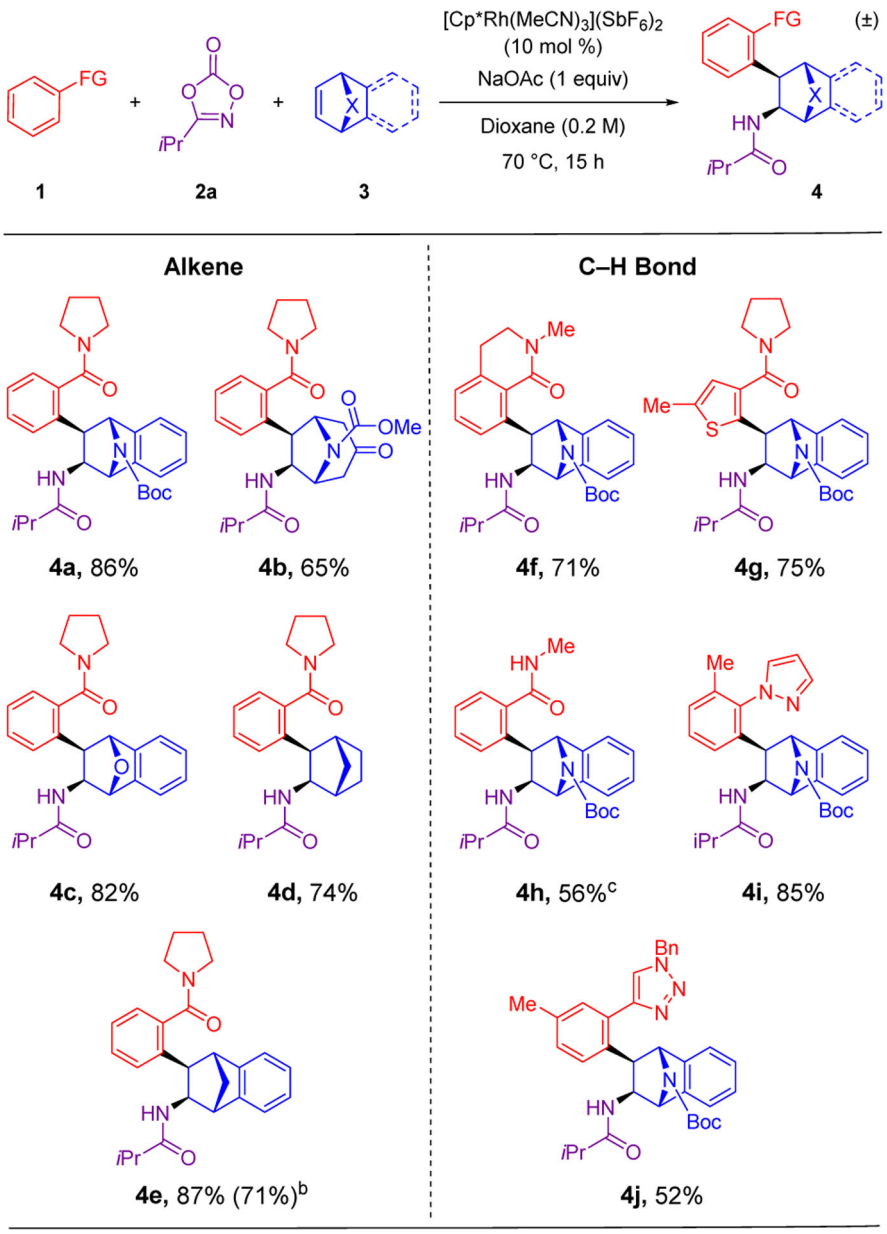


This work:

Three-component 1,2-carboamidation of bridged bicyclic alkenes

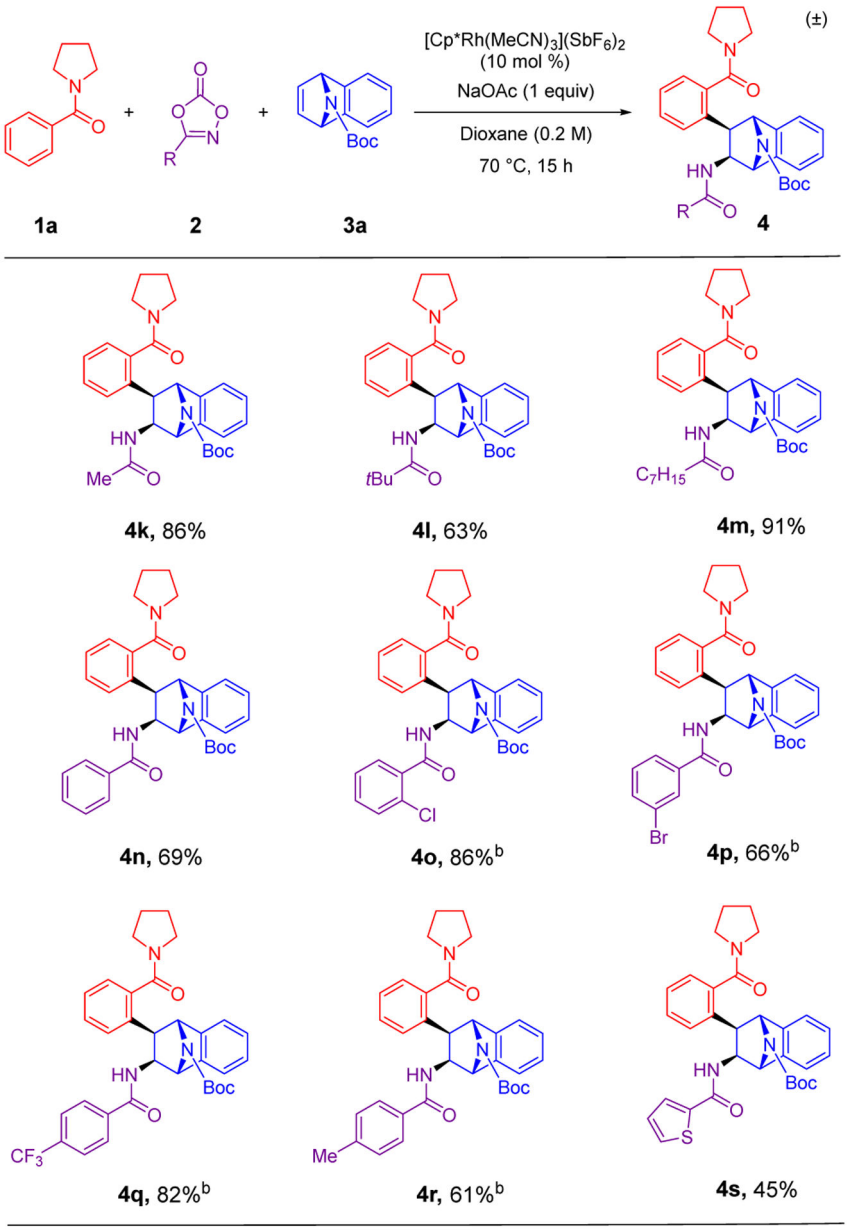


Scheme 1.
Background for Three-Component 1,2-Carboamidation of Bridged Bicyclic Alkenes



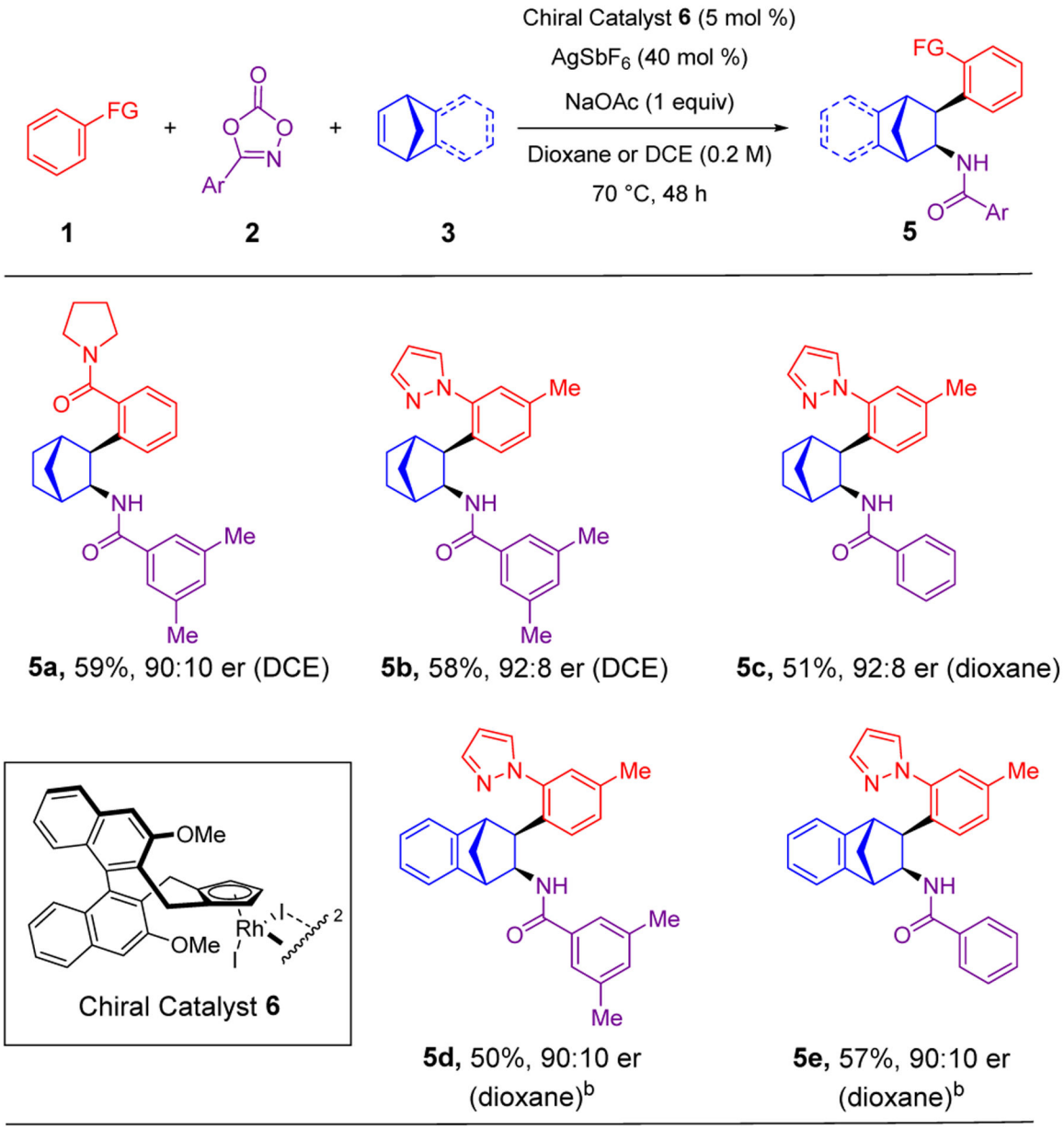
Scheme 2. Alkene and C–H Bond Scope[a]

[a]Conditions: 0.20 mmol of **1**, 0.60 mmol of **2a**, 0.40 mmol of **3**. Isolated yields of products after purification by chromatography are reported. [b]Reaction performed on a 1.0 mmol scale in the C–H bond substrate with 5 mol % catalyst. [c]Reaction performed at 70 °C for 2 h.



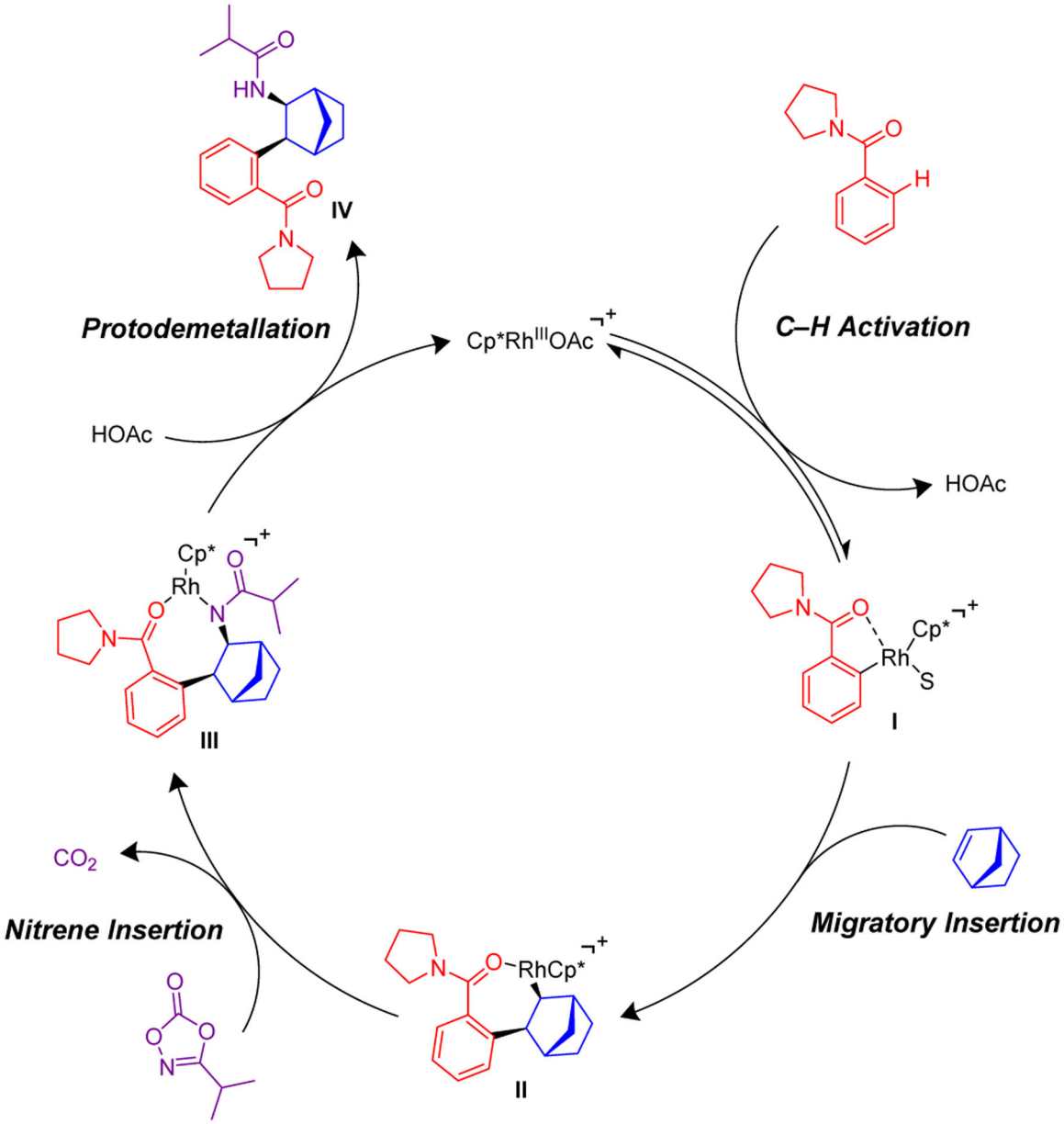
Scheme 3. Dioxazolone Scope[a]

[a]Conditions: 0.20 mmol of **1a**, 0.60 mmol of **2**, 0.40 mmol of **3a**. Isolated yields of products after purification by chromatography are reported. [b]Reactions performed at 50 °C for 2 h.



Scheme 4. Asymmetric Synthesis with Chiral Catalyst[a]

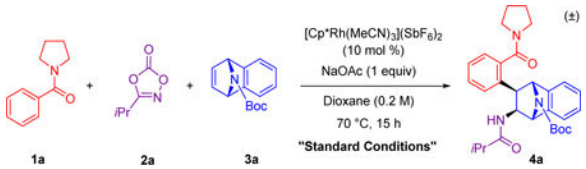
[a]Conditions: 0.05 mmol of **1**, 0.15 mmol of **2**, 0.20 mmol of **3**. Isolated yields of products after purification by chromatography are reported. bReaction performed with 0.05 mmol of 1-[3-methylphenyl]pyrazole, 0.15 mmol of aryl dioxazolone, 0.10 mmol of benzonorbornadiene.



Scheme 5.
Proposed Mechanism for the Three-Component Transformation

Table 1.

Reaction Condition Deoptimization



Entry[a]	Variation from the standard conditions	Yield 4a[b]
1	None	97%[c]
2	No $[Cp^*Rh(MeCN)_3](SbF_6)_2$	0%
3	$[Cp^*RhCl_2]_2$ (5%) / $AgSbF_6$ (20%)	91%
4	$[Cp^*IrCl_2]_2$ (5%) / $AgSbF_6$ (20%)	0%
5	$[Cp^*Co(CO)I_2]$ (10%) / $AgSbF_6$ (20%)	0%
6	$[RuCl_2(p\text{-cymene})]_2$ (5%) / $AgSbF_6$ (20%)	0%
7	No NaOAc	87%
8	$Cp^*Rh(OAc)_2$ (10%)[d]	0%
9	$Cp^*Rh(OAc)_2$ (10%) / $AgSbF_6$ (20%)[d]	86%
10	DCE as solvent	77%
11	0.5 M	91%
12	50 °C	85%
13	2:3:1 ratio **1a:2a:3a**	63%

[a]Conditions: 0.10 mmol of **1a**, 0.30 mmol of **2a**, 0.20 mmol of **3a**

[b]Yields determined by ^1H NMR relative to trimethylphenylsilane as an external standard.

[c]Isolated yield of the pure material was 86%.

[d]No NaOAc was added.