Published in final edited form as:

Nature. 2015 November 5; 527(7576): 86–90. doi:10.1038/nature15691.

Rh-Catalyzed Intermolecular *Syn*-Carboamination of Alkenes via a Transient Directing Group

Tiffany Piou[1] and **Tomislav Rovis**[1,*]

[1]Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523, USA

Abstract

Alkenes are the most ubiquitous pro-chiral functional groups accessible to synthetic chemists. For this reason, difunctionalization reactions of alkenes are particularly important, as they can be used to access highly complex molecular architectures.[1,2] Stereoselective oxidation reactions, including dihydroxylation, aminohydroxylation and halogenation reactions,[3,4,5,6] are well-established methods for functionalizing alkenes. However, the intermolecular incorporation of both carbon- and nitrogen-based functionalities stereoselectively across an alkene has not been reported. In this manuscript, we describe the Rh(III)-catalyzed *syn* carboamination of alkenes initiated by a C–H activation event that uses enoxyphthalimides as the source of the carbon and the nitrogen functionalities. The reaction methodology allows for the stereospecific formation of one C–C and one C–N bond across an alkene in a fully intermolecular sense, which is unprecedented. The reaction design involves the *in situ* generation of a bidentate directing group and the use of a novel cyclopentadienyl ligand to control the reactivity of Rh(III). The results provide a new route to functionalized alkenes and are expected to lead to the more convergent and stereoselective assembly of amine-containing acyclic molecules.

The prominence and importance of nitrogen functionality in biologically relevant molecules is undeniable,[7] and stereoselective methods for introducing nitrogen atoms into organic molecules remain a subject of intense interest. Alkene hydroamination is an emerging technology for the introduction of nitrogen functionality (Fig. 1a).[8,9,10] On the other hand, incorporation of carbon-based coupling partners is more limited, in spite of the crucial role of C-C bond forming reactions in synthesis. Among these, Heck-type approaches are noteworthy for their ability to introduce a carbon fragment in a stereoselective manner under typically mild conditions.[11,12] Both the hydroamination and Heck-type reactions have the same strategic drawback: only one end of the alkene is functionalized. Simultaneous

Correspondence and requests for materials should be addressed to T.R. (rovis@colostate.edu).

Supplementary Information is available in the online version of the paper.

Author Contributions

T. P. and T. R. conceived this concept and prepared the manuscript. T. R. directed the investigations. T. P. developed and studied the reaction.

Author Information

The authors declare no competing financial interests.

incorporation of both carbon- and nitrogen-based functionalities across an alkene would address this deficiency.

Established stereoselective carboamination reactions are currently limited and fall into three categories (Fig. 1b). Annulative reactions are well-entrenched and powerful strategies but deliver a cyclic product which inherently limits their impact.[13,14] A handful of intramolecular approaches have been developed wherein one of the reacting partners is tethered to the alkene.[15,16,17] Lastly, there is a growing subset of radical-based reactions which functionalize both ends of the alkene in a carboamination process.[18,19] However, the involvement of radicals in the mechanism means that stereochemistry present in the alkene starting material is typically lost in the course of the reaction. Herein we describe the first stereoselective intermolecular carboamination reaction of alkenes, using enoxyphthalimides as the source of both carbon and nitrogen atoms (Fig. 1c). In the presence of a Rh(III) catalyst, these precursors undergo *syn*-addition across a variety of disubstituted alkenes in a stereospecific manner, delivering acyclic products containing two contiguous stereocenters in an intermolecular fashion.

We have previously described that enoxyphthalimides undergo Rh(III)-catalyzed reactions with electron-deficient alkenes to deliver cyclopropane adducts (Fig. 2).[20] The proposed mechanism involves the generation of intermediate **A**, the product of carborhodation of the alkene partner. We hypothesized that the Rh atom is coordinatively unsaturated and thus ligates the enol alkene fragment, which subsequently undergoes migratory insertion to form the C–C bond in the cyclopropane product. Should the Rh atom be coordinatively saturated, intramolecular alkene coordination should be disfavored and we may favor reductive elimination to form the carboamination product. Coordinative saturation of the Rh atom could conceivably occur by intramolecular coordination to a bidentate directing group.

Efforts to install requisite bidentate directing groups[21] on the enoxyamine were frustrated by the instability of the product. We succeeded in overcoming this instability by generating it *in situ* through the use of a more nucleophilic solvent such as methanol, which we hypothesized would open the phthalimide to form the phthalimide-derived amido ester. Under these conditions, the formation of the carboamination product **3aa** is favored over the cyclopropane **4aa** in 2.8:1 ratio (Table 1, entry 2). We also observed the formation of **5aa** derived from opening of the phthalimide ring. Fortunately, the product **5aa** could be converted back to **3aa** without erosion of diastereoselectivity by simply heating the crude reaction mixture at 60 °C in toluene after consumption of the starting material **1a** (entry 3). Furthermore, it was established that **3aa** was formed as a single diastereoisomer, the relative configuration being unambiguously assigned by X-ray crystallography and consistent with a *syn*-addition process, thereby confirming our initial hypothesis. Selectivity between **3aa** and **4aa**, however, remained sub-optimal.

Building on our previous work on cyclopentadienyl ligands, we speculated that control of the chemoselectivity could be achieved through ligand design. Disappointingly, however, when using the monosubtituted Cp^{iPr} ligand, which performed well in the cyclopropanation reaction, the carboamination product **3aa** is not formed (entry 4). Sterically hindered (Cp^{t})[22] or electron-deficient (Cp^{CF3})[23] ligands furnish compound **3aa** in poor yields (entries 5 and

6). To our delight, the pentasubstituted Cp^{*Cy} ligand gives the desired product **3aa** in 69% yield and good chemoselectivity (**3aa:4aa** = 8.0:1, entry 7). Further increasing the steric hindrance of the cyclopentadienyl ligand (Cp^{*tBu}) allows the formation of **3aa** in an increased yield (72%) with slightly better chemoselectivity (**3aa:4aa** = 8.4:1, entry 8). Finally, replacing CsOAc with cesium adamantylcarboxylate (1-$AdCO_2Cs$) significantly improves the chemoselectivity (**3aa:4aa** = 14.8:1) producing the desired product **3aa** in 82% yield (entry 9). Importantly, decreasing the catalyst loading from 10 to 5 mol % and using an equimolar amount of base did not affect the efficiency of the reaction (entry 10).

With the optimized reaction conditions in hand, we investigated the generality of the title transformation (Fig. 3a). Structural variations on the N-enoxyphthalimide **1** were examined first (Fig. 3b). The presence of a phenyl ring on substrate **1** proved to be essential. Electron-donating and -withdrawing substituents located at the *para*, *meta*, or *ortho* positions of the phenyl ring are all well tolerated in the reaction, providing the corresponding carboamination adducts **3ba-ka** in good to high yields (30–76%). A small handful of products were formed in low yields, which we believe correlates with the relative insolubility of their derived starting materials (specifically N-enoxyphthalimides **1e**, **1j** and **1k**).

In order to probe the stereochemical outcome of the reaction, we subjected fumarate and maleate esters to the optimized reaction conditions (**2a** and **2b**, Fig. 3c). The reaction delivered isomeric products **3aa** and **3ab** in high diastereoselectivity, suggesting that the insertion event is a stereospecific *syn* addition across the alkene. We next tested a variety of alkenes in our carboamination reaction (Fig. 3d), and were pleased to find that the reaction conditions are mild enough to tolerate sensitive functional groups such as silyl ethers, chloro- and fluoro-alkyls. The corresponding adducts **3ac-ae** were isolated in high yields (85–89%) with excellent chemoselectivity. The reaction also proceeds with hindered alkenes leading to **3af** and **3ag** in excellent yields. Interestingly, in the case of unsymmetrical *trans*-1,2-disubstituted alkenes, the carboamination reaction takes place with a high control of regioselectivity, leading to products **3ah-aj** as the major regioisomers (53–86% yield). In all cases, the most bulky substituent is placed away from the phthalimide group. Additionally, N-phenylmaleimide **2k** is a suitable substrate giving the desired product **3ak** in 74% yield. Electron-rich alkenes such as 1,2-dihydrofuran **2l** and 1,2-dihydropyrrole **2m** are also reactive and furnish disubstituted tetrahydrofuran **3al** and pyrrolidine **3am** in 69% and 25% yield, respectively. Gratifyingly, both heterocycles were obtained as single regio- and diastereoisomers in accordance with a previous report.[24] Finally, by switching to $[Cp^{*Cy}Rh(CH_3CN)_3](SbF_6)_2$ as catalyst, the scope of the carboamination reaction was expanded to monosubstituted alkenes. Accordingly, when employing ethyl acrylate **2n** as coupling partner, the unnatural α-aminoacid derivative **3an** is isolated in 53% yield (Fig. 3e).

The carboamination products **3** are versatile entities. Besides their obvious similarity to novel unnatural α-amino acids, they may also be converted into pyrrolidines **7** (Fig. 3f). Deprotection of the phthalimide group followed by cyclization affords the 1,2-

dihydropyrrole **6** (*dr* = 10:1, 85% yield). The latter can be reduced under heterogeneous conditions to yield pyrrolidine **7** in high diastereoselectivity (*dr* >20:1).

In order to interrogate our mechanistic hypothesis, we probed whether the delivery of the phthalimide moiety occurs via an intra- or intermolecular process. To this end, we performed a crossover experiment by submitting an equimolar mixture of N-enoxyphthalimides **1f** and **1l** to our optimized reaction conditions (Fig. 4a). No crossover adduct **8** is formed suggesting that, in accordance with our initial proposal (Fig. 2b), delivery of the phthalimide moiety takes place in an intramolecular fashion. Moreover, when subjecting product **3aa** back to the reaction, the formation of **5aa** was not observed (Fig. 4b). This result suggests that the opening of the phthalimide group occurs prior to formation of the final product **3aa**. Thus, the adduct **5aa** might be formed first and cyclizes back in the course of the reaction to give **3aa**. This assumption was further confirmed by monitoring the reaction progress by ^{1}H NMR (see Supporting Information for details). To further elaborate on this idea, we investigated the reactivity of a bidentate substrate. Attempts to open the phthalimide group with MeOH were unsuccessful due to the instability of the product. However, the parent substrate **1m** proves to be relatively more stable and was subjected in the carboamination reaction (Fig. 4c). The expected product **3ma** is indeed formed, albeit in moderate yield (35%). A control experiment demonstrates that the carboamination product **3ma** does not open in presence of exogeneous pyrrolidine under our standard reaction conditions (see Supporting Information for details). Taken together, these results support our hypothesis that the directing group might be bidentate and emerge from *in situ* opening of the phthalimide moiety.

Based on these mechanistic experiments, we propose the following catalytic cycle (Fig. 4d). First, in presence of MeOH and a base, the N-enoxyphthalimide **1a** can reversibly open to form intermediate **II** (route a, Fig. 4d). The active Rh(III) catalyst then undergoes an irreversible C-H activation at the vinylic position leading to the five-membered rhodacycle **III**. Alternatively, we cannot rule out the possibility that the C-H activation event precedes the opening of the phthalimide group (**IV** to **III**, route b). Subsequent migratory insertion of alkene **2** generates the coordinatively saturated Rh(III) complex **V** with coordination of the ester group to the metal. We postulate that the bidentate directing group formed *in situ* stabilizes intermediate **V** inhibiting both competitive migratory insertion into the enol alkene and β-H-elimination,[25,26] and instead favoring reductive elimination. An oxidative addition of the N-O bond into Rh(I) followed by protonation/tautomerization of the enol liberates the opened product **5a** with concomitant regeneration of the active Rh(III) catalyst. Finally, in the course of the reaction, the phthalimide group is reformed to afford product **3a**. Contemplating the proposed mechanism, the origin of the chemoselectivity could be rationalized by the solvent effect (entry 1 vs 2). When using MeOH as solvent the initial opening of the phthalimide moiety prevails favoring the formation of intermediate **III** and therefore the carboamination pathway. Conversely, less nucleophilic trifluoroethanol tends to preserve the integrity of the phthalimide, and thus the cyclopropanation pathway is preferred.

In conclusion, we have developed a *syn*-carboamination of disubstituted alkenes. The reaction utilizes enoxyphthalimides and a Rh(III) catalyst. Ligand development has revealed

a new bulky cyclopentadienyl group that alters the inherent chemoselectivity of a reaction. The use of methanol as a solvent is key as was the observation that the phthalimide group undergoes in situ ring opening. Mechanistic experiments suggest that the basicity of the pendant carbonyl stabilizes a Rh(III) intermediate by coordinative saturation which leads to reductive elimination rather than cyclopropanation. Efforts are underway to broaden this reaction and develop an asymmetric version of the transformation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank NIGMS (GM80442) for support. We thank Johnson Matthey for a generous loan of Rh salts, and John Chu and Dr. Brian Newell (CSU) for solving X-ray structures.

References

1. McDonald RI, Liu G, Stahl SS. Palladium(II)-catalyzed alkene functionalization via nucleopalladation: stereochemical pathways and enantioselective catalytic applications. Chem Rev. 2011; 111:2981–3019. [PubMed: 21428440]
2. Chemler SR, Bovino MT. Catalytic Aminohalogenation of Alkenes and Alkynes. ACS Catal. 2013; 3:1076–1091. [PubMed: 23828735]
3. Berkesell, A.; Gröger, H. Asymmetric Organocatalysis. Wiley-VCH; Weinheim: 2005.
4. Jacobsen, EN.; Wu, MH. Comprehensive Asymmetric Catalysis. Jacobsen, EN.; Pfaltz, A.; Yamamoto, H., editors. Springer; Berlin: 1999.
5. Hennecke U. New Catalytic Approaches towards the Enantioselective Halogenation of Alkenes. Chem Asian J. 2012; 7:456–465. [PubMed: 22315237]
6. Tan CK, Yu WZ, Yeung YY. Stereoselective Bromofunctionalization of Alkenes. Chirality. 2014; 26:328–343. [PubMed: 24339201]
7. Vitaku E, Smith DT, Njardarson JT. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. J Med Chem. 2014; 57:10257–10274. [PubMed: 25255204]
8. Zhou J, Hartwig JF. Intermolecular, Catalytic Asymmetric Hydroamination of Bicyclic Alkenes and Dienes in High Yield and Enantioselectivity. J Am Chem Soc. 2008; 130:12220–12221. [PubMed: 18715004]
9. Shen X, Buchwald SL. Rhodium-Catalyzed Asymmetric Intramolecular Hydroamination of Unactivated Alkenes. Angew Chem Int Ed. 2010; 49:564–567.
10. Beller M, Seayad J, Tillack A, Jiao H. Catalytic Markovnikov and anti-Markovnikov Functionalization of Alkenes and Alkynes: Recent Developments and Trends. Angew Chem Int Ed. 2004; 43:3368–3398.
11. Beletskaya IP, Cheprakov AV. The Heck Reaction as a Sharpening Stone of Palladium Catalysis. Chem Rev. 2000; 8:3009–3066. [PubMed: 11749313]
12. Werner EW, Mei TS, Burckle AJ, Sigman MS. Enantioselective Heck Arylations of Acyclic Alkenyl Alcohols Using a Redox-Relay Strategy. Science. 2012; 338:1455–1458. [PubMed: 23239733]
13. Coldham I, Hufton R. Intramolecular Dipolar Cycloaddition Reactions of Azomethine Ylides. Chem Rev. 2005; 105:2765–2810. [PubMed: 16011324]
14. Nakamura I, Yamamoto Y. Transition-Metal-Catalyzed Reactions in Heterocyclic Synthesis. Chem Rev. 2004; 104:2127–2198. [PubMed: 15137788]

15. Mai DN, Wolfe JP. Asymmetric Palladium-Catalyzed Carboamination Reactions for the Synthesis of Enantiomerically Enriched 2-(Arylmethyl)- and 2-(Alkenylmethyl)pyrrolidines. J Am Chem Soc. 2010; 132:12157–12159. [PubMed: 20718417]
16. Wolfe JP. Synthesis of Saturated Heterocycles via Metal-Catalyzed Alkene Carboamination or Carboalkoxylation Reactions. Top Heterocycl Chem. 2013; 32:1–38.
17. Zeng W, Chemler SR. Copper(II)-Catalyzed Enantioselective Intramolecular Carboamination of Alkenes. J Am Chem Soc. 2007; 129:12948–12949. [PubMed: 17918850]
18. Weidner K, Giroult A, Panchaud P, Renaud P. Efficient Carboazidation of Alkenes Using a Radical Desulfonylative Azide Transfer Process. J Am Chem Soc. 2010; 132:17511–17515. [PubMed: 21082832]
19. Zhang H, Pu W, Xiong T, Li Y, Zhou X, Sun K, Liu Q, Zhang Q. Copper-Catalyzed Intermolecular Aminocyanation and Diamination of Alkenes. Angew Chem Int Ed. 2013; 52:2529–2533.
20. Piou T, Rovis T. Rh(III)-Catalyzed Cyclopropanation Initiated by C H Activation: Ligand Development Enables a Diastereoselective [2 + 1] Annulation of N-Enoxyphthalimides and Alkenes. J Am Chem Soc. 2014; 136:11292–11295. [PubMed: 25093811]
21. Mo J, Wang L, Liu Y, Cui X. Transition-Metal-Catalyzed Direct C H Functionalization under External-Oxidant-Free Conditions. Synthesis. 2015:439–459.
22. Neely JM, Rovis T. Rh(III)-Catalyzed Regioselective Synthesis of Pyridines from Alkenes and α,β-Unsaturated Oxime Esters. J Am Chem Soc. 2013; 135:66–69. [PubMed: 23244023]
23. Hyster TK, Rovis T. An improved catalyst architecture for rhodium(III) catalyzed C H activation and its application to pyridone synthesis. Chem Sci. 2011; 2:1606–1610. [PubMed: 25580208]
24. Webb NJ, Marsden SP, Raw SA. Rhodium(III)-Catalyzed C H Activation/Annulation with Vinyl Esters as an Acetylene Equivalent. Org Lett. 2014; 16:4718–4721. [PubMed: 25165993]
25. Guimond N, Gorelsky SI, Fagnou K. Rhodium(III)-Catalyzed Heterocycle Synthesis Using an Internal Oxidant: Improved Reactivity and Mechanistic Studies. J Am Chem Soc. 2011; 133:6449–6457. [PubMed: 21452842]
26. Rakshit S, Grohmann C, Besset T, Glorius F. Rh(III)-Catalyzed Directed C H Olefination Using an Oxidizing Directing Group: Mild, Efficient, and Versatile. J Am Chem Soc. 2011; 133:2350–2353. [PubMed: 21275421]

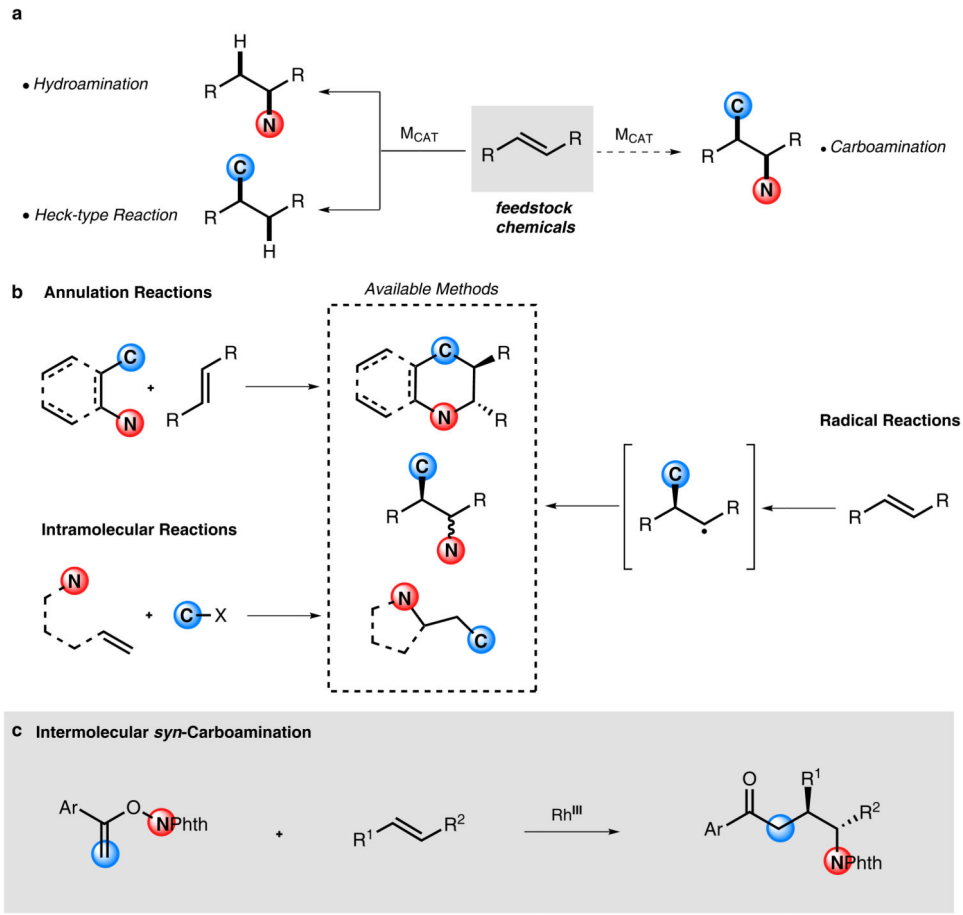


Figure 1. Carboamination Reactions

a, Transition metal catalyzed difunctionalization of alkenes. **b**, Available carboamination reactions in organic synthesis. **c**, Rh(III)-catalyzed intermolecular *syn*-carboamination of alkenes. Ar, aromatic; M_{CAT}, metal based catalyst; Ph, phenyl; Phth, phthalimide.

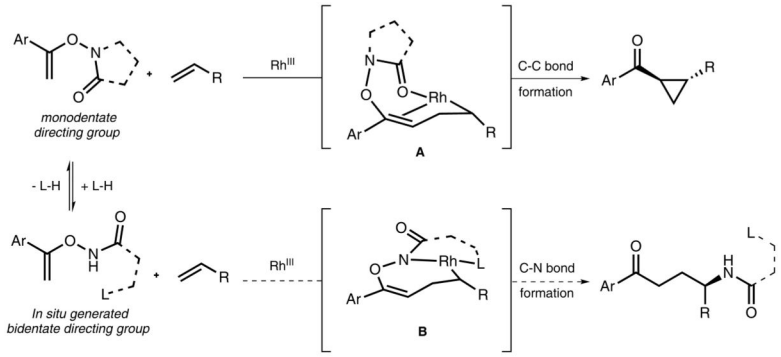


Figure 2. Working hypothesis: Tuning of the directing group to influence reactivity
Ligands on Rh omitted for clarity. Ar, aromatic; L, exogenous nucleophile.

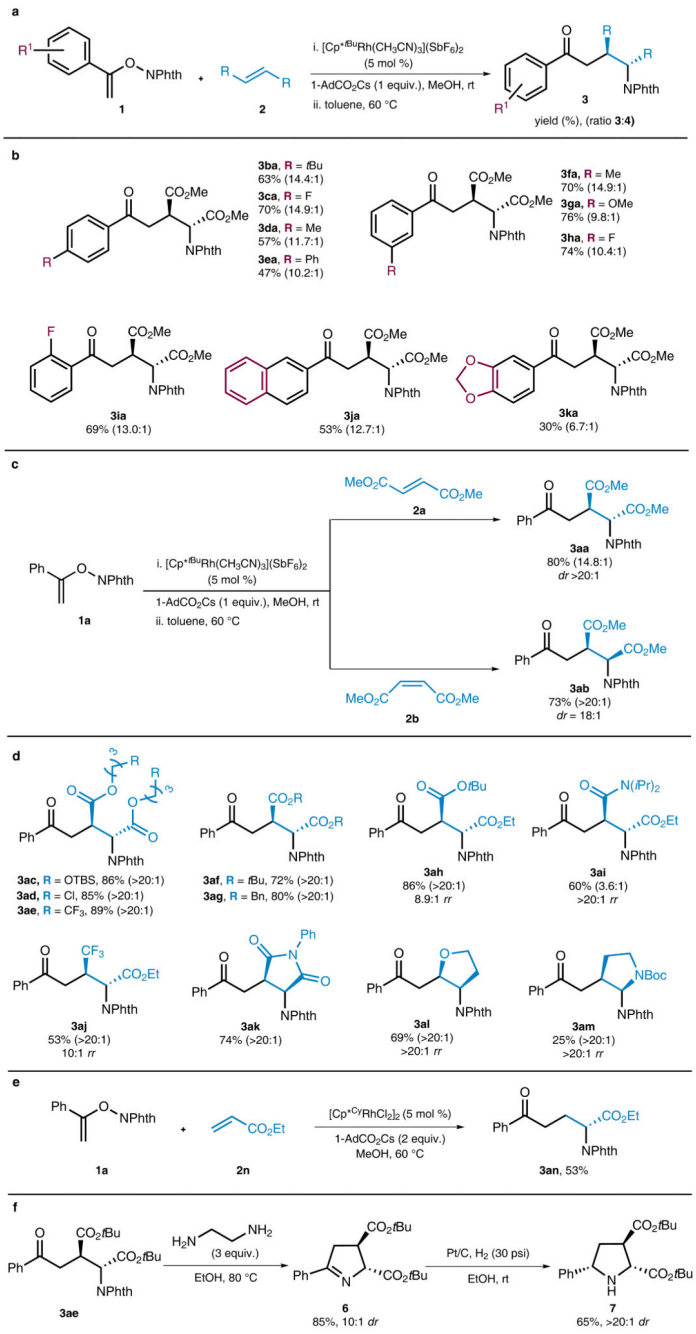


Figure 3. Applications of the carboamination reaction

a, General conditions for carboamination of 1,2-disubstituted alkenes. **b**, Effect of substituents on the N-Enoxyphthalimide. **c**, Probe of reaction stereospecificity. **d**, Functionalization of 1,2-disubstituted alkenes. **e**, Functionalization of mono-substituted alkene. **f**, Derivatization of the carboamination adduct: Formation of pyrrolidine. Ac, acetyl; Ad, adamantyl; Bn, benzyl; Boc, *tert*-butoxycarbonyl; Cy, cyclohexyl; Cp, cyclopentadienyl, Et, ethyl; *i*Pr, isopropyl; Me, methyl; Phth, phthalimide; Ph, phenyl; rt, room temperature; *t*Bu, *tert*-butyl; TBS, *tert*-butylsilyl.

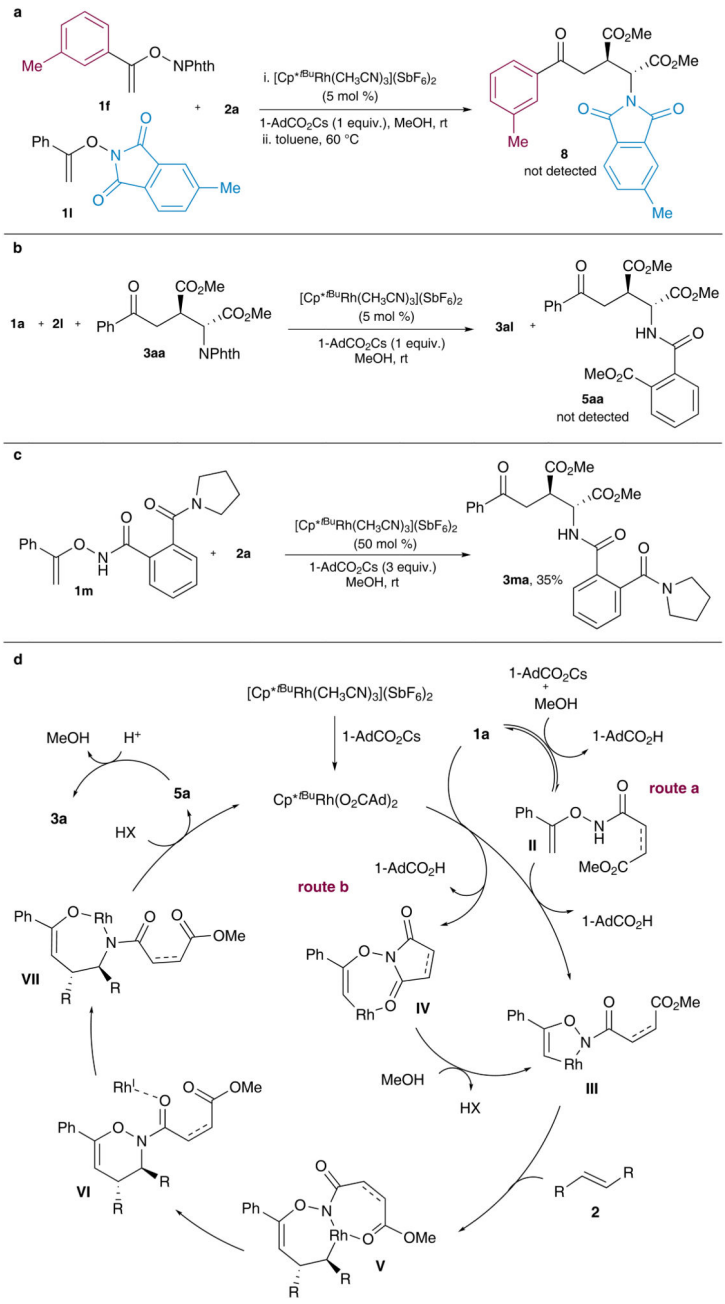
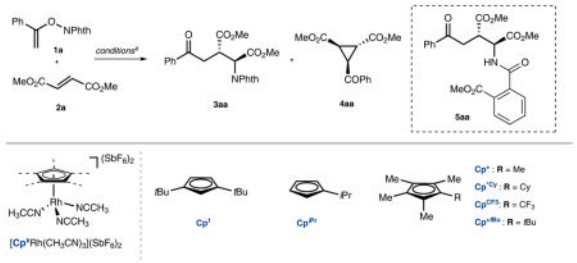


Figure 4. Reaction mechanism: study and proposal

a, Crossover experiment. **b**, Probe of the formation of **5aa. c**, Reactivity of a secondary amide in the carboamination reaction. **d,** Proposed mechanism for the carboamination reaction. Ligands on Rh and phthalimide substituents omitted for clarity. Ad, adamantyl; Cp, cyclopentadienyl, Me, methyl; Ph, phenyl; Phth, phthalimide; *t*Bu, *tert*-butyl; rt, room temperature.

Table 1

Optimization of reaction conditions.



entry	Method	Cp^{x}	solvent	ratio 3aa:4aa[b]	Yield 3aa (%)[c]
1	A	Cp*	trifluoroethanol	1:2.3	30%[d]
2	A	Cp*	MeOH	2.8:1	49%[e]
3	B	Cp*	MeOH	3.5:1	60%
4	B	Cp^{iPr}	MeOH	-	0%
5	B	Cp^{t}	MeOH	-	<10%
6	B	Cp^{CF3}	MeOH	-	<10%
7	B	Cp^{*Cy}	MeOH	8.0:1	69%
8	B	Cp^{*tBu}	MeOH	8.4:1	72%
9	B[f]	Cp^{*tBu}	MeOH	14.8:1	82%
10	C	Cp^{*tBu}	MeOH	14.8:1	80% [d]

[a] *Method A:* **1a** (1 equiv.), **2a** (1.2 equiv.), [Rh^{III}] (10 mol %), CsOAc (2 equiv.) in solvent (0.2 M), at rt for 16 h. *Method B:* **1a** (1 equiv.), **2a** (1.2 equiv.), [Rh^{III}] (10 mol %), CsOAc (2 equiv.) in solvent (0.2 M), at rt for 16 h then stirred in toluene (0.2 M) at 60 °C for 4 h. *Method C:* **1a** (1 equiv.), **2a** (1.2 equiv.), [Rh^{III}] (5 mol %), 1-AdCO$_2$Cs (1 equiv.) in MeOH (0.2 M), at rt for 16 h then stirred in toluene (0.2 M) at 60 °C for 4 h.

[b] Determined by analysis of the unpurified mixture by ^{1}H NMR.

[c] NMR yield.

[d] Isolated yield.

[e] ratio **3aa:5aa:4aa** = 2.8:1:1.

[f] 1-AdCO2Cs was used as base instead of CsOAc. Ac, acetyl; Ad, adamantyl; Cy, cyclohexyl; Cp, cyclopentadienyl, *i*Pr, isopropyl; Me, methyl; *t*Bu, *tert*-butyl; Phth, phthalimide; Ph, phenyl; rt, room temperature.