Rhodium-catalysed syn-carboamination of alkenes via a transient directing group

Tiffany Piou1 & Tomislav Rovis1

Alkenes are the most ubiquitous prochiral functional groups—that can be converted from achiral to chiral in a single step—that are accessible to synthetic chemists. For this reason, difunctionalization reactions of alkenes (whereby two functional groups are added to the same double bond) are particularly important, as they can be used to produce highly complex molecular architectures.1,2 Stereoselective oxidation reactions, including dihydroxylation, aminohydroxylation and halogenation,3–6 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. Here we describe the rhodium-catalysed carboamination of alkenes at the same (syn) face of a double bond, initiated by a carbon–hydrogen activation event that uses enoxyphthalimides as the source of both the carbon and the nitrogen functionalities. The reaction methodology allows for the intermolecular, stereoselective formation of one carbon–carbon and one carbon–nitrogen bond across an alkene, which is, to our knowledge, unprecedented. The reaction design involves the in situ generation of a bidentate directing group and the use of a new cyclopentadienyl ligand to control the reactivity of rhodium. The results provide a new way of synthesizing functionalized alkenes, and should lead to the convergent and stereoselective assembly of amine-containing acyclic molecules.

Functional groups that are based on nitrogen are prominent in biologically relevant molecules, and stereoselective chemical methods for introducing nitrogen atoms into organic molecules are the subject of intense interest. Alkene hydroamination—the addition of a nitrogen and hydrogen across a carbon–carbon double bond—is an emerging technology for introducing nitrogen functionality (Fig. 1a)6–10. However, the incorporation of carbon-based coupling partners is more limited, despite the crucial role of reactions that form carbon–carbon bonds in chemical 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. But both the hydroamination and the Heck-type reactions have the same strategic drawback: only one end of the alkene is functionalized. Simultaneous incorporation of both carbon- and nitrogen-based functionalities (carboamination) across an alkene would address this deficiency.

Established stereoselective carboamination reactions are limited and fall into three categories (Fig. 1b). Of these, annulative reactions are popular and powerful but deliver a cyclic product, which limits the reactivity of the double bond.13,14 A handful of intramolecular approaches have also been developed, wherein one of the reacting partners is tethered to the alkene.15–17. Finally, 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 means that the stereoselectivity present in the alkene starting material is typically lost. Here, we describe the stereoselective intermolecular carboamination of alkenes, using enoxyphthalimides as the source of both the carbon and the nitrogen atoms (Fig. 1c). In the presence of an Rh(III) catalyst, these precursors undergo stereospecific syn addition (addition to the same face of a double bond) to a variety of disubstituted alkenes, delivering acyclic products containing two contiguous stereocentres in an intermolecular fashion.

We have previously shown that enoxyphthalimides undergo Rh(III)-catalysed reactions with electron-deficient alkenes to deliver cyclopropane adducts (Fig. 2).20 The mechanism proposed 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 carbon–carbon bond in the cyclopropane product. Should the Rh atom instead be coordinatively saturated, intramolecular alkene coordination should be disfavoured, and reductive elimination to form the carboamination product might be favoured. Coordinative saturation of the Rh atom could conceivably occur by intramolecular coordination to a bidentate directing group.

Our past efforts to install requisite bidentate directing groups on the enoxyamine were frustrated by the instability of the product. We overcame this instability by generating a bidentate directing group

---

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

---

Figure 1 | Carboamination reactions. a, Transition-metal-catalysed difunctionalization of alkenes. Previously, such reactions could reliably achieve the introduction of either nitrogen-based or carbon-based functional groups (left-hand reaction); known reactions that introduce both groups across a single alkene (carboamination reactions, right, dotted arrow) have drawbacks. Mₘₐₜ, metal-based catalyst; R, functional group. b, The previously known carboamination reactions in organic synthesis: annulation reactions, intramolecular reactions and radical reactions, all of which have limitations. c, Our proposed Rh(III)-catalysed intermolecular syn-carboamination of alkenes. Ar, aromatic groups; Ph, phenyl; Phth, phthalimide.
in situ using 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 favoured over the cyclopropane 4aa in a 2.8/1 ratio (Table 1, entry 2). We also observed the formation of the product 5aa, derived from the opening of the phthalimide ring. Fortunately, the product 5aa could be converted back to 3aa without erosion of diastereoselectivity, simply by heating the crude reaction mixture at 60 °C in toluene after consumption of the starting material 1a (entry 3). Furthermore, we 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 less than 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 monosubstituted cyclopentadienyl isopropyl (CpPr) ligand, which performed well in the cyclopropanation reaction, the carboamination product 3aa is not formed (Table 1, entry 4). Sterically hindered (1,3-di-tert-cyclopentadienyl, Cp3) (ref. 22) or electron-deficient (trifluoromethyl-tetra-methyl-cyclopentadienyl, CpCF3) (ref. 23) ligands furnish compound 3aa in poor yields (entries 5 and 6). But the pen-tasubstituted ligand cyclohexyl-tetra-methyl-cyclopentadienyl (CpICy) gives the desired product 3aa with 69% yield and good chemoselectivity (3aa/4aa = 8.0/1; Table 1, entry 7). Further increasing the steric hindrance of the cyclopentadienyl ligand (tert-butyl-tetra-methyl-cyclopentadienyl, CpPr3) allows the formation of 3aa with an increased yield (72%) and slightly better chemoselectivity (3aa/4aa = 8.4/1; entry 8). Finally, replacing the base caesium acetate with caesium adamantly-carboxylate significantly improves the chemoselectivity (3aa/4aa = 14.8/1), producing the desired product 3aa with an 82% yield (entry 9). Notably, decreasing the catalyst loading from 10 mol% to 5 mol% and using an equimolar amount of base did not affect the efficiency of the reaction (entry 10).

Having optimized the reaction conditions, we investigated the generality of the syn-carboamination (Fig. 3a). We first examined structural variations in the N-exoxyphthalimide (substrate 1; Fig. 3b). The presence of a phenyl ring on substrate 1 proved essential. Electron-donating and electron-withdrawing substituents located at the para,
In order to probe the stereochemical outcome of the reaction, we subjected fumarate and maleate esters (2a and 2b, Fig. 3c) to the optimized reaction conditions. 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); we found that the reaction conditions are mild enough to tolerate sensitive functional groups such as silyl ethers, chloro-alkyls and fluoro-alkyls. The corresponding adducts 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–3aj as the major regioisomers (53–86% yield). In all cases, the most bulky substituent is placed away from the phthalimide group. Also, N-phenylmaleimide 2k is a suitable substrate, giving the desired product 3ak with a 74% yield. Electron-rich alkenes such as 1,2-dihydrofuran (2l) and 1,2-dihydropyrrrole (2m) are also reactive, and produce disubstituted tetrahydrofuran (3al) and pyrrolidine (3am) with a 69% and a 25% yield, respectively. Gratifyingly, both heterocycles were obtained as single regioisomers and diastereoisomers, as found previously. Finally, by switching to [Cp*Rh(CH3CN)3]SbF6 as the catalyst, the scope of the carboamination reaction was expanded to include monosubstituted alkenes. Thus, when using ethyl acrylate (2n) as a coupling partner, the unnatural z-aminoacid derivative 3an is isolated with a 53% yield (Fig. 3e).

The carboamination products, 3, are versatile entities. In addition to showing similarity to unnatural z-amino acids, they may also be converted into pyrrolidines (7; Fig. 3f). Deprotection of the phthalimide group followed by cyclization affords the 1,2-dihydropyrrrole 6 (diastereomeric ratio, d.r. = 10/1, 85% yield), which can be reduced under heterogeneous conditions to yield pyrrolidine 7 in high diastereoselectivity (d.r. > 20/1).

In order to investigate the mechanism underlying the carboamination reaction, we probed whether delivery of the phthalimide moiety occurs through an intramolecular or intermolecular process. We carried out a crossover experiment by submitting an equimolar mixture of N-enoxphthalimides Iff and Ii to our optimized reaction conditions (Fig. 4a). No crossover adduct 8 is formed, suggesting that, in agreement with our initial proposal (Fig. 2b), delivery of the phthalimide...
moire takes place intramolecularly. Moreover, when product 3aa was subjected back to the reaction, product 5aa did not form (Fig. 4b), suggesting that the phthalimide group opens before the final product 3aa is formed. Thus, the adduct 5aa might be formed first, and cyclizing back during the reaction to give 3aa. We confirmed this assumption by monitoring the reaction progress using nuclear magnetic resonance (see Supplementary Information). To elaborate further on this idea, we investigated the reactivity of a bidentate substrate. Attempts to open the phthalimide group with methanol were unsuccessful owing to the instability of the product. However, the parent substrate 1m proved more stable, and was subjected to the carboamination reaction (Fig. 4c). The expected product 3ma was indeed formed, albeit with a moderate yield (35%). A control experiment demonstrates that the carboamination product 3ma does not open in the presence of exogenous pyrrolidine under our standard reaction conditions (see Supplementary Information). Taken together, these results support our hypothesis that the directing group might be bidentate and emerge from in situ opening of the phthalimide moiety.

On the basis of these experiments, we propose the following catalytic cycle (Fig. 4d). First, in the presence of methanol and a base, the N-enoxophthalimide 1a can reversibly open to form intermediate II (Fig. 4d, route a). The active Rh(III) catalyst then undergoes an irreversible carbon–hydrogen activation at the alkene position, leading to the five-membered rhodacycle III. Alternatively, we cannot rule out the possibility that the carbon–hydrogen activation event precedes the opening of the phthalimide group (IV to III, Fig. 4d, route b). In either case, migratory insertion of alkene, 2, then 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 the β-H-elimination that forms the corresponding diene by a Heck-type process.25,26 Instead, intermediate V undergoes reductive elimination to form intermediate VI. An oxidative addition of the nitrogen–oxygen 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, during the reaction, the phthalimide group is re-formed to afford product 3a. The origin of the chemoselectivity might be produced by the solvent effect (Table 1, entry 1 versus entry 2). When using methanol as the solvent, the initial opening of the phthalimide moiety prevails, favoring the formation of intermediates III and therefore the carboamination pathway. Conversely, the less-nucleophilic solvent trifluoroethanol tends to preserve the integrity of the phthalimide, and thus the cyclopropanation pathway is preferred.

We have developed a reaction that achieves syn-carboamination of disubstituted alkenes. The reaction uses enoxophthalimides 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 crucial, as is 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, leading to reductive elimination rather than to cyclopropanation. We are now investigating ways to broaden this reaction and to develop an asymmetric version of the transformation.

Received 2 June; accepted 4 September 2015.
Published online 21 October 2015.

1. McDonald, R. L., Liu, G. & Stahl, S. S. Palladium(II)-catalyzed alkene functionalization via nucleopalladation: stereochemical pathways and enantioselective catalytic applications. Chem. Rev. 111, 2981–3019 (2011).

2. Chemler, S. R. & Bovino, M. T. Catalytic aminohalogenation of alkenes and alkenes. Am. Chem. Soc. Catal. 3, 1076–1091 (2013).

3. Berkessel, A. & Gröger, H. Asymmetric Organo-catalysis (Wiley-VCH, 2005).

4. Jacobsen, E. N. & Wu, M.-H. in Comprehensive Asymmetric Catalysis (eds Jacobsen, E. N., Pfaltz, A. & Yamamoto, H.) 1309–1326 (Springer, 1999).

5. Hennecke, U. New catalytic approaches towards the enantioselective halogenation of alkenes. Chem. Asian J. 7, 456–465 (2012).

6. Tan, C.-K., Yu, W. & Yeung, Y. Y. Stereoselective bromo-functionalization of alkenes. Chem. Commun. 26, 328–334 (2014).

7. Vitaku, E., Smith, D. T. & Njardarson, J. T. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals. J. Med. Chem. 57, 10257–10274 (2014).

8. Zhou, J. & Hartwig, J. F. Intermolecular, catalytic asymmetric hydroamination of bicyclic alkenes and dienes in high yield and enantioselectivity. J. Am. Chem. Soc. 130, 12220–12221 (2008).

9. Shen, X. & Buchwald, S. L. Rhodium-catalyzed asymmetric intramolecular hydroamination of unactivated alkenes. Angew. Chem. Int. Edn 49, 564–567 (2010).

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. Edn 45, 3366–3396 (2006).

11. Belletskaya, I. P. & Cheprakov, A. V. The Heck reaction as a sharpening stone of palladium catalysis. Chem. Rev. 100, 3009–3066 (2000).

12. Werner, E. W., Mei, T.-S., Burckle, A. J. & Signam, M. S. Enantioselective Heck arylation of acyclic alkyl alcohol catalysts using a redox-relay strategy. Science 338, 1455–1458 (2012).

13. Coldham, I. & Hutton, R. Intramolecular diquat cyclodaddition reactions of azomethine ylides. Chem. Rev. 105, 2765–2810 (2005).

14. Nakamura, I. & Yamamoto, Y. Transition-metal-catalyzed reactions in heterocyclic synthesis. Chem. Rev. 104, 2127–2198 (2004).

15. Mäi, O. N. & Wolfe, J. P. Asymmetric palladium-catalyzed carboamination reactions for the synthesis of enantioenriched 2-(arylmethyl)- and 2-(alkenylmethyl)pyrrolidines. J. Am. Chem. Soc. 132, 12157–12159 (2010).

16. Wolfe, J. P. Synthesis of saturated heterocycles via metal-catalyzed alkenic carboamination or carboxalcoholization reactions. Top. Heterocycl. Chem. 32, 1–37 (2013).

17. Zeng, W. & Chemler, S. R. Copper(II)-catalyzed enantioselective intramolecular carboamination of alkenes. J. Am. Chem. Soc. 129, 12948–12949 (2007).

18. Wiedner, K., Giroult, A., Panchaud, P. & Renaud, P. Efficient carboazidation of alkenes using a radical desulfonylative azide transfer process. J. Am. Chem. Soc. 132, 17511–17515 (2010).

19. Zhang, H. et al. Copper-catalyzed intermolecular aminocyanation and diamination of alkenes. Angew. Chem. Int. Ed. 52, 2529–2533 (2013).

20. Piou, T. & Rovis, T. Rh(III)-catalyzed cyclopropanation initiated by C-H activation: ligand development enables a diastereoselective [2 + 1] annulation of N-enoxophthalimides and alkenes. J. Am. Chem. Soc. 136, 11292–11295 (2014).

21. Mo, J., Wang, L., Liu, Y. & Cui, X. Transition-metal-catalyzed direct C-H functionalization under external-oxidant-free conditions. Synthesis 439–459 (2015).

22. Neely, J. M. & Rovis, T. Rh(III)-catalyzed regioselective synthesis of pyridines from alkenes and α,β-unsaturated oxime esters. J. Am. Chem. Soc. 135, 66–69 (2013).

23. Hyster, T. K. & Rovis, T. An improved catalyst architecture for rhodium(III) catalyzed C-H activation and its application to pyridine synthesis. Chem. Sci. (Camb.) 2, 1606–1610 (2011).

24. Webb, N. J., Marsden, S. P. & Raw, S. A. Rhodium(III)-catalyzed C-H activation/ annihilation with vinyl esters as an acetylene equivalent. Org. Lett. 16, 4718–4721 (2014).

25. Guimond, N., Gorelsky, S. I. & Fagnou, K. Rhodium(II)-catalyzed heterocycle synthesis using an internal oxidant: improved reactivity and mechanistic studies. J. Am. Chem. Soc. 133, 6449–6457 (2011).

26. Rakshit, S., Grohmann, C., Besset, T. & Glorius, F. Rh(II)-catalyzed direct C–H olefination using an oxidizing directing group: mild, efficient, and versatile. J. Am. Chem. Soc. 133, 2350–2353 (2011).

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

Acknowledgements We thank the National Institute of General Medical Sciences (grant no. GM04842) for support. We thank Johnson Matthey for rhodium salts, and J. Chu and B. Newell (at Colorado State University) for solving X-ray structures.

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

Author Information Reprints and permissions information is available at www.nature.com/reprints. The authors declare no competing financial interests. Readers are welcome to comment on the online version of the paper. Correspondence and requests for materials should be addressed to T.R. (rovis@colostate.edu).