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Directing Group Enhanced Carbonylative Ring Expansions of Amino-Substituted Cyclopropanes: Rhodium-Catalyzed Multicomponent Synthesis of N-Heterobicyclic Enones

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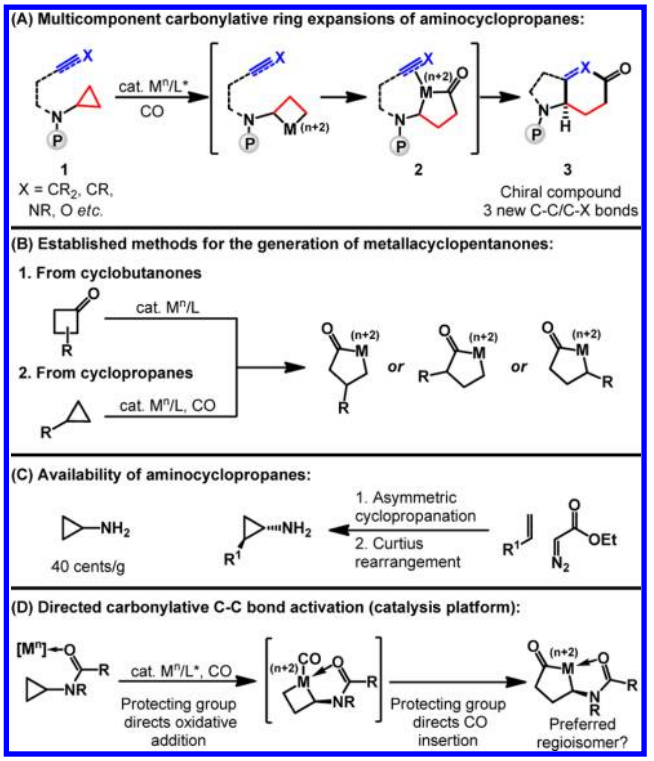
Supporting Information

ABSTRACT: Aminocyclopropanes equipped with suitable N-directing groups undergo efficient and regioselective Rh-catalyzed carbonylative C−C bond activation. Trapping of the resultant metallacycles with tethered alkynes provides an atom-economic entry to diverse N-heterobicyclic enones. These studies provide a blueprint for myriad N-heterocyclic methodologies.

Modern medicinal chemistry requires more efficient and diverse methods for the synthesis of chiral scaffolds.[1] Cognizant of both this goal and the ideals of green chemistry,[2] we recently initiated a program aimed at the generation and trapping of amino-substituted metallacyclopentanones. Here, we envisaged that exposure of CO and aminocyclopropanes **1** to an appropriate catalyst would afford metallacyclic intermediates **2** (Scheme 1A). Intra- or intermolecular trapping of these species with various π-unsaturates then potentially delivers heterocyclic products **3**. In this scenario, diverse and readily available building blocks are converted to medicinally valuable chiral heterocycles with complete atom economy. Moreover, modification of the catalyst system with appropriate chiral ligands potentially provides asymmetric processes. In a broader context, this approach requires the development of a new family of (3+2+1) cycloadditions involving aminocyclopropanes. Cyclopropane-based carbonylative (3+2+1) cycloadditions have been developed previously under Rh-catalyzed conditions by Narasaka[3] and Yu,[4] but examples involving amino-substituted variants have not been reported.

Key to achieving the goal outlined in Scheme 1A is the realization of strategies that facilitate selective generation of the requisite aminometallacyclopentanone **2**. In principle, this is achievable by either (a) the oxidative addition of a metal catalyst into a cyclobutanone acyl−carbon bond[5,6] or (b) the carbonylative insertion of a metal into a cyclopropane C−C bond (Scheme 1B).[3,7−10] This latter approach is more attractive because parent aminocyclopropane is commercially available and substituted variants are readily accessed using established asymmetric technologies (Scheme 1C).[11] However, the key issue of *regioselective* metallacycle formation remains, and a strategy to promote selective insertion of the metal and CO into the *more hindered* aminocyclopropane C−C bond is required. Existing strategies for regioselective metallacyclopentanone formation are not applicable to aminocyclopropanes, especially within the wider context of the general methodology outlined in Scheme 1A.[12] Of particular relevance to this study is the work of Chirik, who demonstrated phosphinite-directed Rh insertion into the more hindered C−C bond of alkyl-substituted cyclopropanes in the absence of CO.[13] Based upon this, we envisaged selective metallacycle formation by employing N-protecting groups that can serve a dual role of pre-coordinating the metal catalyst (Scheme 1D).[14] Herein, we report the successful realization of this strategy in the context of processes involving tethered alkynes. This provides a direct entry to complex N-heterobicyclic enones and also validates a unique

Scheme 1. Aminometallacyclopentanones as a Catalysis Platform for N-Heterocycle Synthesis



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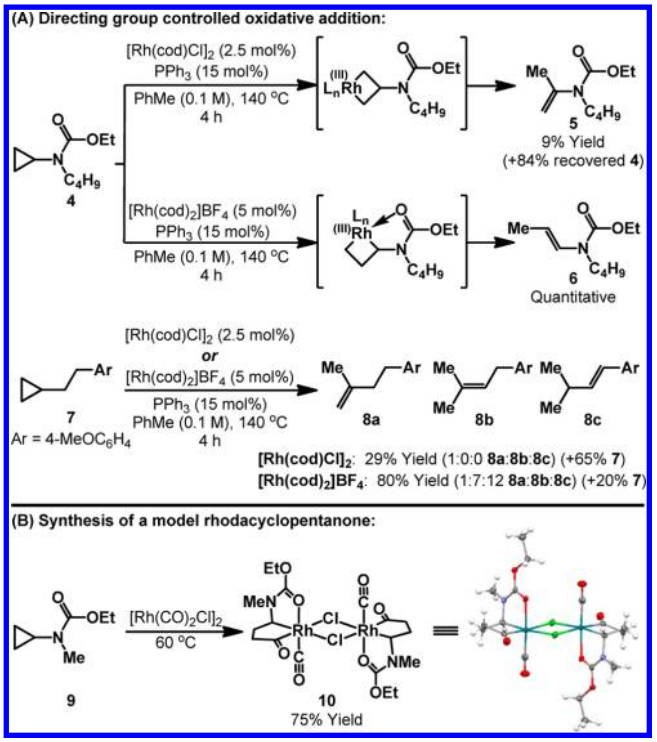
approach to the carbonylative C−C bond activation of aminocyclopropanes.

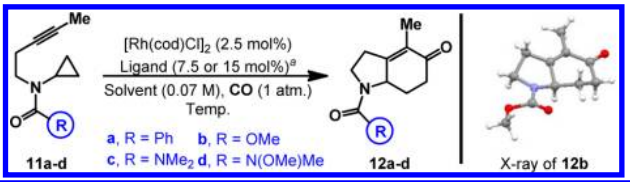
Our initial studies established that directing group controlled oxidative addition is feasible under the conditions of Rh catalysis. Accordingly, carbamate-protected aminocyclopropane **4** was exposed to various Rh(I) catalysts in the absence of CO (Scheme 2A). Here, we found that neutral Rh(I) salts (e.g., $[Rh(cod)Cl]_2$/PPh_3) slowly delivered *branched* enamine **5**, thereby indicating (slow) insertion into the less hindered cyclopropane C−C bond. On the other hand, cationic Rh(I) systems (e.g., $[Rh(cod)_2]BF_4$/PPh_3), which are more Lewis acidic, efficiently delivered *linear* product **6**.[15] To confirm the importance of the carbamate moiety, we performed analogous experiments on alkyl-substituted cyclopropane **7**. Here, both neutral and cationic Rh(I) systems delivered branched products that result from exclusive insertion into the less hindered cyclopropane C−C bond. In the case of $[Rh(cod)Cl]_2$, only the direct product of β-hydride elimination and reductive elimination, **8a**, was observed. $[Rh(cod)_2]BF_4$ afforded a mixture of alkene products **8a**−**c** (1:7:12); **8b,c** likely arise by Rh-catalyzed isomerization of the initial adduct **8a**.[16] Taken together, these results confirm that carbamate-directed oxidative addition is possible if the Rh catalyst is sufficiently Lewis acidic. Under carbonylative conditions, we anticipated that neutral systems may also be effective because CO is a strong π-acceptor ligand; consequently, carbonyl-ligated neutral Rh(I) catalysts may possess sufficient Lewis acidity to promote directed oxidative addition. Probing this possibility was challenging because treatment of carbamate **4** with neutral Rh(I) systems under a CO atmosphere did not lead to appreciable quantities of enamines **5** or **6**, presumably because rhodacyclopentanones formed instead. We therefore undertook studies to isolate and characterize a model metallacyclic intermediate (Scheme 2B). Heating carbamate **9** with stoichiometric $[Rh(CO)_2Cl]_2$ at 60 °C generated dimeric rhodacyclopentanone **10**, which was characterized by X-ray diffraction.[17] In support of our catalysis design, the structure of complex **10** reveals axial coordination of the carbamate directing group and the desired regioselectivity for both the oxidative addition and CO insertion steps.[18] This establishes that neutral carbonyl-ligated Rh(I) catalysts are effective for directed rhodacyclopentanone formation.

Scheme 2. Studies on Controlling the Regioselectivity of Metallacyclopentanone Formation



With these preliminary studies in hand, we sought to incorporate our directing-group-based strategy into a prototypical multicomponent carbonylative coupling process involving a tethered alkyne (Table 1). Seminal work by Narasaka has demonstrated the feasibility of a related process to provide *carbocyclic* systems; in these cases, the alkyne moiety was proposed to direct Rh insertion.[3a] Relatively high temperatures and catalyst loadings and elevated CO pressures, in conjunction with a favorable Thorpe−Ingold effect, were required to provide acceptable yields of the targets. In our case, judicious choice of N-directing group is critical as it must (a) compete for the catalyst with the alkyne moiety of the starting material but (b) also be labile enough to then allow alkyne coordination at the stage of the metallacyclopentanone (see Scheme 1A). Accordingly, we evaluated the conversion of a range of differentially protected aminocyclopropanes **11a**−**d** to the corresponding enones **12a**−**d**.

Table 1. Development of a Prototypical Process



Entry	Substrate	Ligand	Temp./°C	Solvent	Time/h	Yield (12a-d)[b]
1	**11a**	*rac.* BINAP	160 °C	1,2-DCB	48	27% (26)
2	**11b**	*rac.* BINAP	160 °C	1,2-DCB	48	35% (33)
3	**11c**	*rac.* BINAP	160 °C	1,2-DCB	24	43% (42)
4	**11d**	*rac.* BINAP	160 °C	1,2-DCB	48	<5%
5[c]	**11c**	$P(3,5\text{-}(CF_3)_2C_6H_3)_3$	130 °C	1,2-DCB	72	56% (53)
6[c,d]	**11c**	**$P(3,5\text{-}(CF_3)_2C_6H_3)_3$**	**130 °C**	**PhCN**	**72**	**74% (72)**

[a]7.5 mol% for bidentate ligands and 15 mol% for monodentate ligands. [b]Yields were determined by ^1H NMR using 1,4-dinitrobenzene as a standard. Isolated yields are given in parentheses. [c]Na_2SO_4 (20 mol%) was employed as desiccant. [d]$[Rh(cod)Cl]_2$ (3.75 mol%) and $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (15 mol%) were used. [1,2-DCB = 1,2-dichlorobenzene]

Exposure of amide **11a** to a BINAP-ligated neutral Rh(I)-catalyst system at 160 °C under an atmospheric pressure of CO generated **12a**, but in only 26% yield (Table 1, entry 1). Anticipating that the amide directing group was not sufficiently Lewis basic, we evaluated carbamate **11b** and observed the more efficient formation of **12b** in 33% yield (Table 1, entry 2); the structure of **12b** was confirmed by single-crystal X-ray diffraction. Increasing the directing group Lewis basicity further was beneficial, and urea **11c** afforded **12c** in 42% yield (Table 1, entry 3). Importantly, this directing group also conferred a *significant* rate enhancement (24 vs 48 h for **12a,b**) and, ultimately, this allowed lower reaction temperatures (see below).[19] However, the more Lewis basic methoxy-urea **11d** was inefficient, and only traces of **12d** were formed (Table 1, entry 4). Throughout these initial studies, we found that cationic Rh(I) sources (e.g., $[Rh(cod)_2]BF_4$) were less effective due to competitive formation of enamine byproducts (cf. Scheme

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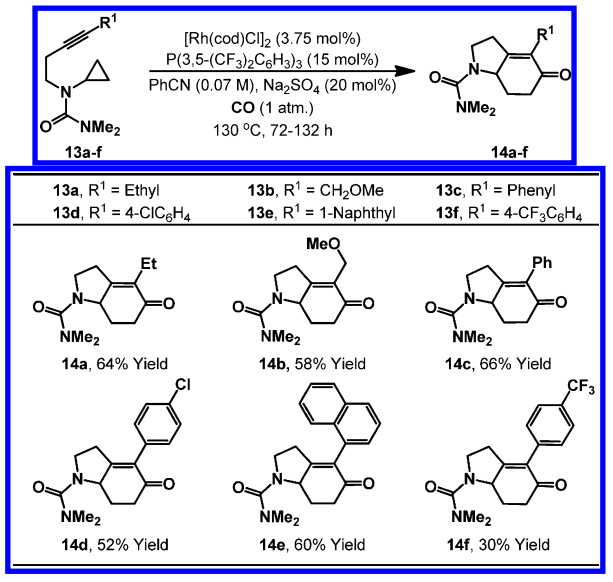
2A).[15] Further studies involving $[Rh(cod)Cl]_2$ and **11c** identified $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ as an effective ligand and PhCN as a suitable solvent. Under these conditions, and using 7.5 mol% Rh catalyst, full conversion of **11c** occurs at 130 °C to afford **12c** in 72% isolated yield (Table 1, entry 6).[20] Notably, carbonyl-based directing groups are critical to the process; other classes of N-protecting group (e.g., R = SO_2Ar) did not afford appreciable amounts of product. These results highlight the key role of the N-directing group and show that, in these cases, the alkyne moiety is not effective at orchestrating catalysis.

Our prototypical catalytic process is tolerant of a wide range of electron-neutral and electron-rich alkynes (Table 2). Sterically distinct alkyl- and aryl-substituted systems **13a−e** are tolerated, and the target heterocycles **14a−e** were obtained in good yield. Electron-deficient alkynes also participate but provide the products with diminished efficiency. For example, cyclization of **13f**, which possesses an electron-deficient aryl-substituted alkyne, provided **14f** in 30% yield. The lower yield here possibly reflects decreased alkyne coordination at the stage of the metallacyclic intermediate **2** (see Scheme 1A). Terminal alkynes (R^1 = H) are not tolerated using this first-generation protocol, and only traces (≤15%) of product are observed.[21] These results demonstrate the current scope and limitations of the process with respect to the alkyne.

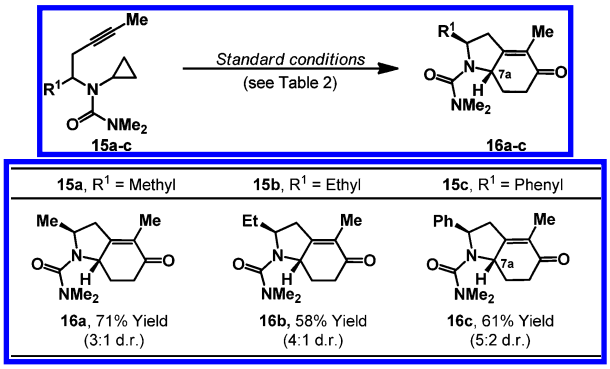
Table 2. Scope of the Alkyne Component



Heterocyclic products of greater stereochemical complexity are generated by increasing the substitution of the starting material. For example, elaboration of the alkyne tether (e.g., **15a−c**) provides diastereoselective access to adducts **16a−c** (Table 3).[22] Here, substitution on the tether results in shorter reaction times compared to the examples shown in Table 2 (36−60 vs 72−132 h). This is presumably reflective of a conformationally enhanced rate of alkyne insertion into the metallacyclopentanone. To probe the origins of diastereoselectivity, the two diastereomers of **16c** were separated and independently re-subjected to the catalysis conditions. No equilibration between these diastereomers was observed, which supports diastereoselection during cyclization rather than by epimerization of the C(7a) stereocenter of the product.

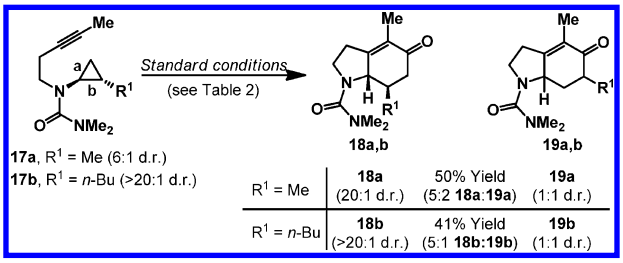
Substitution of the cyclopropane moiety is also possible (Scheme 3). In these cases, the steric demands of the R^1

Table 3. Substitution of the Alkyne Tether



substituent control product selection by influencing the site of oxidative addition (bond a vs b). Carbonylative cyclization of **17a** (R^1 = Me) generated **18a** (20:1 dr),[22] which is derived from metal insertion into the less hindered bond a. However, this product was accompanied by appreciable levels of the alternate regioisomer **19a**, which is derived from insertion into the more hindered bond b (5:2 **18a**:**19a**). In the case of **17b** (R^1 = *n*-Bu), the more pronounced steric demands of the butyl moiety result in higher regioselectivity for the formation of **18b** (5:1 **18b**:**19b**; **18b** >20:1 dr).[22]

Scheme 3. Substitution of the Aminocyclopropane



In summary, we present protecting group directed carbonylative C−C bond activation of aminocyclopropanes as the basis of a flexible entry to N-heterobicyclic systems. The present work demonstrates proof-of-principle for the underlying catalysis platform and outlines the preliminary scope of an approach that potentially enables entries to a wide range of chiral scaffolds. Future work will concentrate on expanding the methodologies available, including the provision of asymmetric variants.[23] We will also target the development of enhanced catalyst systems that are tolerant of a suite of synthetically useful directing groups.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For insightful discussions, see: (a) Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752. (b) Walters, W. P.; Green, J.; Weiss, J. R.; Murcko, M. A. *J. Med. Chem.* **2011**, *54*, 6405. (c) Nadin, A.; Hattotuwagama, C.; Churcher, I. *Angew. Chem., Int. Ed.* **2012**, *51*, 1114.

(2) Atom-economic processes are a key ideal of green chemistry, see: (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.

(3) (a) Narasaka, K.; Koga, Y. *Chem. Lett.* **1999**, *28*, 705. This process is postulated to proceed via a rhodacyclopentanone intermediate. For a related process that employs cyclopropenes, see: (b) Li, C.; Zhang, H.; Feng, J.; Zhang, Y.; Wang, J. *Org. Lett.* **2010**, *12*, 3082.

(4) (a) Jiao, L.; Lin, M.; Zhuo, L.-G.; Yu, Z.-X. *Org. Lett.* **2010**, *12*, 2528. This process requires vinyl-substituted cyclopropanes and does not proceed via a metallacyclopentanone. Alkenylidenecyclopropanes undergo carbonylative (3+2+1) cycloadditions where the alkenylidene moiety is incorporated into the carbocyclic ring of the product: (b) Lu, B.-L.; Wei, Y.; Shi, M. *Organometallics* **2012**, *31*, 4601. (c) Mazumder, S.; Shang, D.; Negru, D. E.; Baik, M.-H.; Evans, P. A. *J. Am. Chem. Soc.* **2012**, *134*, 20569.

(5) Leading references — Rh-catalyzed cyclobutanone C−C reduction and decarbonylation: (a) Murakami, M.; Amii, H.; Ito, Y. *Nature* **1994**, *370*, 540. (b) Murakami, M.; Amii, H.; Shigeto, K.; Ito, Y. *J. Am. Chem. Soc.* **1996**, *118*, 8285. These studies indicate that, under appropriate conditions, carbonylative rhodacyclopentanone formation is reversible. Rh-catalyzed intramolecular alkene insertions into cyclobutanones: (c) Murakami, M.; Itahashi, T.; Ito, Y. *J. Am. Chem. Soc.* **2002**, *124*, 13976. (d) Xu, T.; Dong, G. *Angew. Chem., Int. Ed.* **2012**, *51*, 7567. In both cases, the alkene may direct insertion. For an asymmetric variant, see: (e) Xu, T.; Ko, H. M.; Savage, N. A.; Dong, G. *J. Am. Chem. Soc.* **2012**, *134*, 20005. Directed Pd-catalyzed insertions into cyclobutanones: (f) Ishida, N.; Ikemoto, W.; Murakami, M. *Org. Lett.* **2012**, *14*, 3230.

(6) Related processes that *do not* proceed via metallacyclopentanones — Ni-catalyzed alkyne and alkene insertion into cyclobutanones: (a) Murakami, M.; Ashida, S.; Matsuda, T. *J. Am. Chem. Soc.* **2005**, *127*, 6932. (b) Liu, L.; Ishida, N.; Murakami, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 2485. Rh-catalyzed ring expansion of vinyl cyclobutanones: (c) Wender, P. A.; Correa, A. G.; Sato, Y.; Sun, R. *J. Am. Chem. Soc.* **2000**, *122*, 7815.

(7) Leading references — Rh-catalyzed carbonylation of cyclopropane to form cyclobutanone: (a) Hidai, M.; Orisaku, M.; Uchida, Y. *Chem. Lett.* **1980**, *9*, 753. Rh-catalyzed carbonylation of spiropentanes to form cyclopentenones: (b) Matsuda, T.; Tsuboi, T.; Murakami, M. *J. Am. Chem. Soc.* **2007**, *129*, 12596. Co-catalyzed carbonylation of alkylidenecyclopropanes: (c) Kurahashi, T.; de Meijere, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7881. Cyclopropylamine undergoes Rh-catalyzed carbonylation to γ-lactams: (d) Iqbal, A. F. M. *Tetrahedron Lett.* **1971**, *37*, 3381. Polarized cyclopropanes undergo regioselective oxidative addition, for example: (e) Tamaki, T.; Ohashi, M.; Ogoshi, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 12067.

(8) Vinylcyclopropanes readily undergo Rh-catalyzed ring expansion, but carbonylative variants *do not* proceed via metallacyclopentanones: Liu, P.; Sirois, L. E.; Cheong, P. H.-Y.; Yu, Z.-X.; Hartung, I. V.; Rieck, H.; Wender, P. A.; Houk, K. N. *J. Am. Chem. Soc.* **2010**, *132*, 10127.

(9) Metallacyclopentanones have been characterized — Rhodium: (a) Wilkinson, G.; Roundhill, D. N.; Lawson, D. N. *J. Chem. Soc. (A)* **1968**, 845. (b) McQuillin, F. J.; Powell, K. C. *Dalton Trans.* **1972**, 2129. Cobalt: (c) Theopold, K. H.; Bergman, R. G. *J. Am. Chem. Soc.* **1980**, *102*, 5694.

(10) For a recent review on C−C bond activation of cyclobutane derivatives, see: (a) Seiser, T.; Saget, T.; Tran, D. N.; Cramer, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 7740. For a review detailing transition metal insertion into cyclopropanes, see: (b) Jennings, P. W.; Johnson, L. L. *Chem. Rev.* **1994**, *94*, 2241. Selected reviews on metal insertion into C−C bonds: (c) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245. (d) Murakami, M.; Ito, Y. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer: Berlin, 1999; p 97. (e) Rybtchinski, B.; Milstein, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 870. (f) Murakami, M.; Matsuda, T. *Chem. Commun.* **2011**, *47*, 1100. (g) Aïssa, C. *Synthesis* **2011**, *21*, 3389.

(11) For a review covering asymmetric alkene cyclopropanation with diazo compounds, see: Pellissier, H. *Tetrahedron* **2008**, *64*, 7041.

(12) Previous strategies for controlling metallacyclopentanone formation rely upon either the inherent electronic or steric bias of the substrate or the use of a π-unsaturated directing group (e.g., alkene or alkyne) (see refs 3, 5, and 7). In the case of aminocyclopropanes, the requirement to protect nitrogen engenders a significant steric impediment for metal insertion into the more hindered cyclopropane C−C bond. The use of the π-unsaturate to direct metallacycle formation would necessarily limit the scope of the strategy outlined in Scheme 1A.

(13) Bart, S. C.; Chirik, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 886. Here, Pd-, Ir-, and Pt-based systems were also effective.

(14) For a review on substrate-directed reactions, see: (a) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307. For a recent review on removable or catalytic directing groups, see: (b) Rousseau, G.; Breit, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 2450.

(15) For $[Rh(cod)_2]BF_4$, significant conversion to **6** was observed even at 60 °C; this indicates that oxidative addition is reasonably facile. The faster rate of formation of enamine vs $[Rh(cod)Cl]_2$ may be due to an additional vacant coordination site facilitating β-hydride elimination. Longer reaction times provide higher conversions of **4** to **5**.

(16) Cationic Rh(I) systems are particularly effective for alkene isomerization: Tanaka, K. In *Comprehensive Organometallic Chemistry III*; Crabtree, R. H., Mingos, D. M. P., Ojima, I., Eds.; Elsevier: Oxford, U.K., 2007; Vol. *10*, p 71.

(17) The procedure for the formation of **10** was adapted from earlier work by McQuillin (see ref 9b). Attempts to isolate complexes related to **10** by exposure of **9** to phosphine-ligated Rh(I) systems under a CO atmosphere have so far been unsuccessful.

(18) To the best of our knowledge this is the first X-ray structure of a dimeric rhodacyclopentanone and the first X-ray structure of a metallacyclopentanone formed by carbonylation of a cyclopropane. For an X-ray structure of a bimetallic rhodacyclopentanone derived from insertion of an allene into a carbonyl-ligated Rh−Ru complex, see: Chokshi, A.; Rowsell, B. D.; Trepanier, S. J.; Ferguson, M. J.; Cowie, M. *Organometallics* **2004**, *23*, 4759.

(19) **11a,b** reached approximately 80−90% conversion after 48 h. Full conversion of **11c** occurred within 24 h.

(20) Under optimized conditions, elevated pressures of CO are detrimental to reaction efficiency. The use of Na_2SO_4 as desiccant was found to have a small but reproducible benefit. Carbamate **11b** affords enone **12b** in 20% yield under the conditions outlined in Table 2. In the absence of CO, enamine formation is observed (cf. Scheme 2A). PPh_3 is not an effective ligand for these carbonylative cyclizations, even though it is suitable for the processes in Scheme 2A.

(21) Inefficiencies here may be due to competing Rh-vinylidene formation. For a review, see: Bruce, M. I. *Chem. Rev.* **1991**, *91*, 197.

(22) The relative stereochemistry of the major diastereomers was assigned using NOE experiments (see the Supporting Information). The lack of stereocontrol in the formation of **19a,b** may reflect the lability of the R^1-substituted stereocenter.

(23) At the present stage of reaction development, elongation of the alkyne linker is not tolerated (e.g., quinoline-based scaffolds are not accessible). Processes that involve replacement of the alkyne component with an alkene are currently being optimized, and these studies will be reported in due course.