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Reversible C−C Bond Activation Enables Stereocontrol in Rh-Catalyzed Carbonylative Cycloadditions of Aminocyclopropanes

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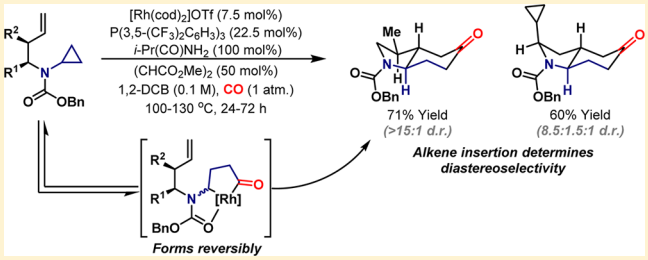
Supporting Information

ABSTRACT: Upon exposure to neutral or cationic Rh(I)-catalyst systems, amino-substituted cyclopropanes undergo carbonylative cycloaddition with tethered alkenes to provide stereochemically complex N-heterocyclic scaffolds. These processes rely upon the generation and trapping of rhodacyclopentanone intermediates, which arise by regioselective, Cbz-directed insertion of Rh and CO into one of the two proximal aminocyclopropane C−C bonds. For cyclizations using cationic Rh(I)-systems, synthetic and mechanistic studies indicate that rhodacyclopentanone formation is reversible and that the alkene insertion step determines product diastereoselectivity. This regime facilitates high levels of stereocontrol with respect to substituents on the alkene tether. The option of generating rhodacyclopentanones dynamically provides a new facet to a growing area of catalysis and may find use as a (stereo)control strategy in other processes.



INTRODUCTION

Methodologies that provide stereodefined, "sp^3-rich" scaffolds will underpin future advances in small molecule drug design.[1] This, in turn, requires the invention of catalysis platforms that (a) exploit readily available chiral precursors and (b) fulfill contemporary reaction ideals, such as high atom economy.[2] Recently, we outlined (3 + 1 + 2) cycloadditions of aminocyclopropanes, CO and alkynes to provide cyclohexenone products (Scheme 1A).[3a] These processes rely upon the regioselective generation of a new class of "sp^3-rich" organometallic intermediate **2** by urea directed insertion of Rh and CO into aminocyclopropanes **1** (R^3 = NMe_2).[3−8] C−C bond activation processes of this type can be viewed as progenitors to a wide range of cycloaddition reactions that are triggered by directed metal insertion into readily available cyclopropane derivatives.[9] Further development requires protocols that use synthetically flexible directing groups and provide increased "sp^3-content" in the product. In this report, we outline diastereoselective Cbz-directed (3 + 1 + 2) cycloadditions involving aminocyclopropanes, CO and alkenes to provide stereochemically complex heterocyclic scaffolds **5** (Scheme 1B). Key to these processes is a unique strategy that exploits reversible C−C bond activation to achieve stereocontrol. These studies provide important synthetic and mechanistic insights into the emerging area of catalysis based upon rhodacyclopentanones and related species.[3a−c,7,8]

RESULTS AND DISCUSSION

In our previous studies, competitive coordination of the Rh(I)-catalyst to the alkyne component mandated the use of strongly coordinating urea directing groups to effect efficient oxidative addition.[3a] To probe the relative properties of ureas vs more versatile carbamates, we prepared complexes **6a** and **6b**, which were characterized by X-ray diffraction (Scheme 2).[10] Here, analysis of the ν(CO) values, confirms that carbamates are weaker donor ligands than ureas (**6a**, R = OBn, ν(CO) = 2043.8 cm^{-1}; **6b**, R = NMe_2, ν(CO) = 2022.5 cm^{-1}). Because, in general, alkenes coordinate to late transition metals less strongly than alkynes,[11] we anticipated that carbamates would direct oxidative addition efficiently for the processes outlined in Scheme 1B. Additionally, because access to π-complex **4b** requires dissociation of the directing group from **4a**, the greater lability of carbamates should facilitate the formation of this intermediate and, in turn, enhance the rate of the alkene insertion step. Consequently, we elected to explore the development of Cbz-directed cycloadditions.

Initial synthetic studies focused upon the carbonylative cycloaddition of Cbz-protected derivative **3a** to generate adduct **5a** (Table 1). Using a catalyst system similar to that described in our earlier work, but with 1,2-dichlorobenzene (1,2-DCB) as solvent and dimethyl fumarate as an additive, target **5a** was isolated in 71% yield and as a single diastereomer, which was determined to be the *trans*-isomer by single crystal X-ray diffraction (see the Supporting Information). The role of dimethyl fumarate is unclear but, by analogy with other processes,[12] it may function as a labile electron-deficient ligand that accelerates alkene insertion and/or reductive elimination. In the absence of this additive, longer reaction times were required, and the yield of the process was lower.[13] Under

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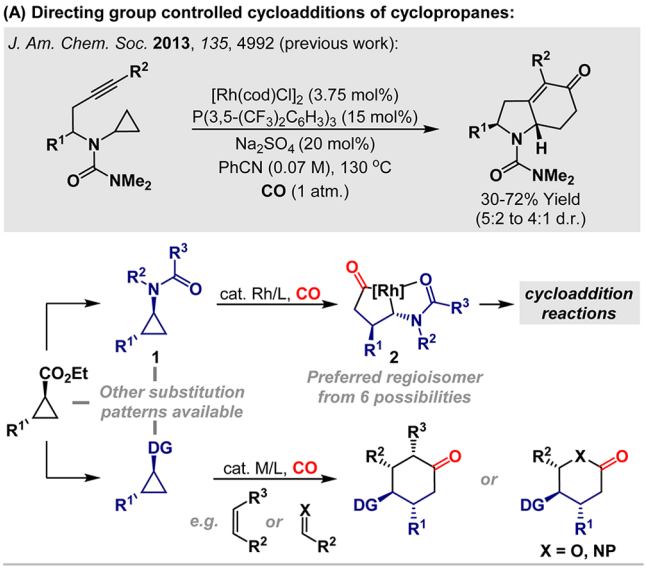
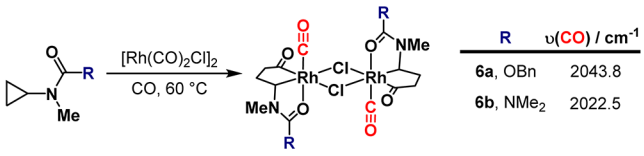
Scheme 1. Directing Group Controlled Cycloadditions of Cyclopropanes

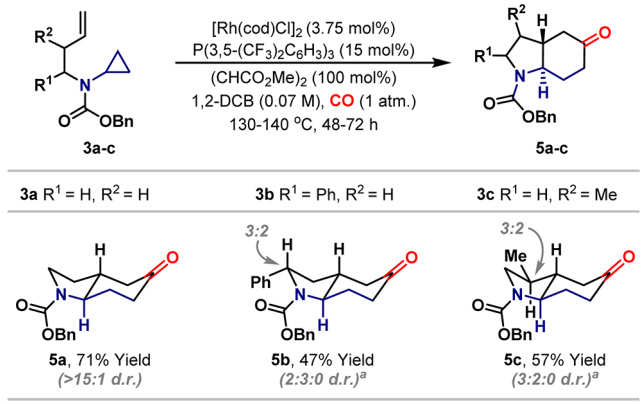


Scheme 2. Synthesis of Rhodacyclopentanone Complexes



R	ν(CO) / cm^{-1}
6a, OBn	2043.8
6b, NMe_2	2022.5

Table 1. (3 + 1 + 2) Cycloadditions Using a Neutral Rh(I)-System



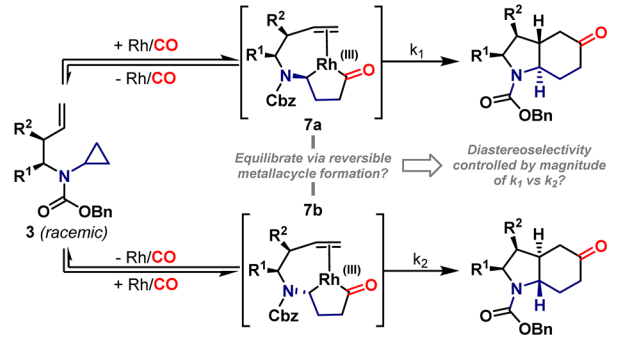
[a]Diastereoselectivities are quoted in a format that allows comparison with Table 3. Isolated diastereomer ratios were consistent with those determined by ^{1}H NMR of crude material.

optimized conditions, a more strongly coordinating dimethylurea directing group was not effective, presumably because access to the intermediate π-complex (cf. **4b**) is attenuated.

The *trans*-stereochemistry associated with the ring junction of **5a** reflects the inherent preference of the migratory insertion step from **4b**. We anticipated that this selectivity would be maintained for systems that possess substitution at R^1 or R^2. However, in these cases, an additional complication is how to control the stereorelationship between the R^1/R^2-substituted stereocenters and the ring junction. Indeed, although cyclizations of adducts **3b** and **3c** proceeded smoothly to afford targets **5b** and **5c**, diastereocontrol with respect to R^1 or R^2 could not be achieved (up to 3:2 d.r.).[13] If the carbonyl-directed C−C oxidative addition step is stereodetermining, then high diastereocontrol requires the R^1 or R^2 group to bias Rh-insertion into one of the two diastereotopic cyclopropane C−C bonds. For both **3b** and **3c** there is no obvious mechanism by which this can be achieved.

An alternate strategy that addresses this stereocontrol issue is outlined in Scheme 3. Following oxidative addition, two

Scheme 3. Diastereoselectivity via Reversible Rhodacycle Formation



diastereomeric rhodacyclic π-complexes (**7a** and **7b**) form en route to the two diastereomers of the target. Here, the bicyclic nature of these intermediates should amplify the steric effects of the R^1 and R^2 substituents. This, in turn, should lead to different rates of alkene insertion (k_1 and k_2) from **7a** and **7b**. Consequently, if a regime for reversible rhodacyclopentanone formation can be established then, in accord with the Curtin−Hammett principle, product selectivity should be dependent largely upon the relative magnitudes of k_1 and k_2. Murakami, Ito and co-workers have demonstrated that rhodacyclopentanones, derived from nondirected oxidative addition of Rh(I)-catalysts into the acyl-carbon bond of cyclobutanones, can undergo decarbonylation and reductive elimination to the corresponding cyclopropanes using specific catalyst systems.[7a,b,14] These studies indicate that conversion of **7a**/**b** to **3** may be feasible. However, a single catalyst system that effects reversible (i.e., dynamic) rhodacyclopentanone formation has not been reported. In the current scenario, this is especially challenging since equilibration (via **3**) must (a) occur under carbonylative conditions, which should disfavor the reverse process, (b) be fast with respect to k_1 and k_2, and (c) use a catalyst system that is also effective for directed oxidative addition, alkene insertion, and reductive elimination. Additionally, side reactions observed in Murakami and Ito's studies, such as decomposition of the metallacycle to alkene byproducts, must be minimized.[7a,b]

Based upon the idea that free coordination sites on the Rh-center should promote retro-carbonylation, and, in turn, provide reversibility, we opted to investigate the use of cationic Rh(I)-systems. After extensive investigation we established that replacement of $[Rh(cod)Cl]_2$ with $[Rh(cod)_2]OTf$ was

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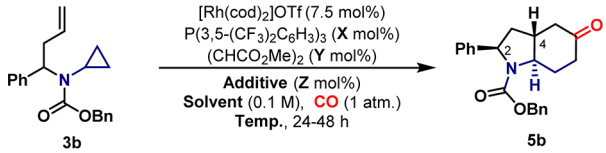
Table 2. Selected Optimization Results for the Cyclization of 3b to 5b Using a Cationic Rh(I)-System



entry	X	Y	additive	Z	solvent	temp., °C	Yield (d.r.)[a]
1	15	0	none	-	1,2-DCB	130	13% (n.d.)
2	15	0	none	-	PhCN	130	48% (3:1:0.5)
3	15	150	none	-	1,2-DCB	130	27% (14:1:1)
4	15	0	$Ph(CO)NH_2$	150	1,2-DCB	130	43% (8:1:1)
5	15	150	$Ph(CO)NH_2$	150	1,2-DCB	130	55% (8:1:1)
6	22.5	50	$Ph(CO)NH_2$	100	1,2-DCB	130	60% (8:1:1)
7	22.5	50	$Ph(CO)NH_2$	100	1,2-DCB	120	67% (8:1:1)
8	22.5	50	$Ph(CO)NH_2$	100	1,2-DCB	110	52% (6:1:1)
9	**22.5**	**50**	***i*-Pr(CO)NH_2**	**100**	**1,2-DCB**	**120**	**79% (8:1:1)**
10	22.5	50	Me(CO)NHMe	100	1,2-DCB	120	59% (15:1:1)
11	22.5	50	$Me(CO)NMe_2$	100	1,2-DCB	120	48% (>15:1:1)

[a]Yields and diastereoselectivities were determined by ^{1}H NMR using 1,4-dinitrobenzene as a standard. Diastereoselectivities are quoted in a format that allows comparison to Table 3: (A:B:C d.r.) = A (depicted): B (invert C-2 stereocenter): C (invert C-4 stereocenter).

possible, but only in the presence of coordinating solvents or additives.[15] Optimization was conducted on the cyclization of **3b** to **5b**, and key results are presented in Table 2. In the absence of additives, the use of 1,2-DCB as solvent resulted in low conversions, and accordingly, low yields of **5b** were obtained (Entry 1). PhCN, a coordinating solvent that was effective in our previous work,[3a] provided an increased yield of **5b**, albeit with modest diastereoselectivity (Entry 2). In this case, the formation of a third diastereomer of the product was observed for the first time (vide infra). Despite considerable effort, we were unable to further optimize processes conducted in PhCN. However, during these studies we had noted hydration to generate small quantities of $Ph(CO)NH_2$, and this led to the evaluation of amide additives in conjunction with 1,2-DCB as solvent. Gratifyingly, use of 150 mol% $Ph(CO)NH_2$ in 1,2-DCB had a beneficial effect on both yield and diastereoselectivity (Entry 1 vs 4). Parallel studies had shown that dimethyl fumarate also provided significant enhancements to yield and diastereoselectivity (Entry 3 vs Entry 1). When both the amide and fumarate additives were employed together, **5b** was isolated in 55% yield and 8:1:1 d.r. (Entry 5). Further optimization was achieved by the evaluation of a range of amides and the refinement of other reaction parameters (Entries 6−11). This resulted in the conditions outlined in Table 2, Entry 9, which use *i*-$Pr(CO)NH_2$ and deliver **5b** in 79% yield and 8:1:1 d.r.. Other amide additives generated **5b** with higher diastereoselectivity but in lower yield (e.g., Entries 10 and 11). The stereochemistry of the major diastereomer of **5b** was determined by single crystal X-ray diffraction (see Table 3). NMR studies (see the Supporting Information) indicated that the two minor diastereomers are related to the major component by inversion of the C-2 or C-4 stereocenter.

Application of the "cationic conditions" outlined in Table 2, Entry 9, to **3a** and **3c** provided adducts **5a** and **5c** in 80% and 71% yield and, importantly, with high levels of diastereocontrol for the ring junction and Me-substituted stereocenter (>15:1 diastereoselectivity in both cases) (Table 3). The conditions are generally applicable, and a range of systems with substitution at R^1 and/or R^2 cyclized smoothly to provide the products with good to excellent levels of stereocontrol. Notably, even substrate **3f**, which possesses a cyclopropane substituent, cyclized efficiently, thereby highlighting the C−C activation selectivity imparted by the directing group. The structure of **5i** was confirmed by single crystal X-ray diffraction, and, this, in conjunction with the X-ray structure of **5b**, served as the basis for the other stereochemical assignments. In all cases, further support was provided by detailed NMR analysis (see the Supporting Information). At the present stage of development, the catalytic protocol is applicable to monosubstituted alkenes only. For example, attempted cyclization of **3l**, which possesses a *trans*-disubstituted alkene, did not afford **5l**. Here, the issue appeared to be slow insertion of the alkene and byproducts derived from decomposition of the rhodacyclopentanone were observed (e.g., N-propenyl carbamate derivatives). Protocols that tolerate increased substitution on the alkene will be a focus of future investigations.

The idea that reversible rhodacycle formation provides diastereocontrol for the processes in Table 3 is supported by a series of stoichiometric experiments (Scheme 4A−C). Dimeric Rh-complexes **8a** and **8b** were prepared in a manner analogous to **6a**/**b** (Scheme 2).[10] Upon exposure to $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (400 mol%) and AgOTf (200 mol%), complexes **9a** and **9b** were formed quantitatively (as determined by ^{1}H and ^{31}P NMR) (Scheme 4A). ^{31}P NMR analysis of CD_2Cl_2 solutions of **9a**/**b** showed significant broadening of the "free" phosphine ligand at room temperature which suggests rapid exchange with the triflate ligand. The solid-state structures of **9a**/**b** were determined by X-ray diffraction; in the case of **9a**, substitution of the triflate ligand by adventitious water occurred during crystallization (see the Supporting Information). Exposure of a PhMe solution of rhodacycle **9a** to stoichiometric quantities of cyclopropane **10b** under a CO atmosphere resulted in partial exchange to generate **9b** and cyclopropane **10a** in 13% and 9% yield, respectively, along with 70% recovered rhodacycle **9a** (Scheme 4B). In the inverse experiment, rhodacycle **9a** and cyclopropane **10b** were both formed in 5% yield. When **9a** was subjected to 10 equiv of **10b**, increased yields of **9b** and cyclopropane **10a** were obtained, and rhodacycle **9a** was recovered in 76% yield. In all cases, some losses of aminocyclopropanes **10a**/**b** can be attributed to their relatively high volatility.[16] Overall, these experiments show that reversible

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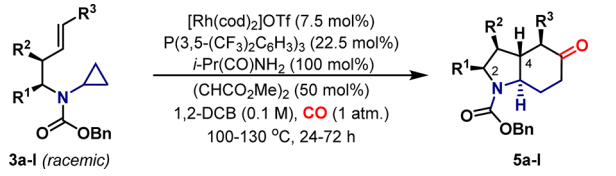
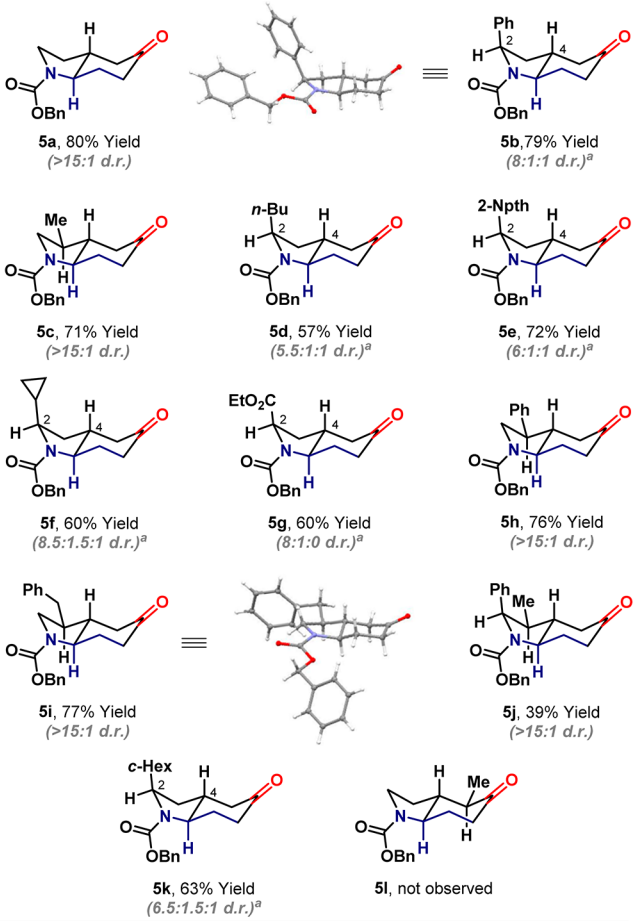
Table 3. Diastereoselective (3 + 1 + 2) Cycloadditions Using a Cationic Rh(I)-System



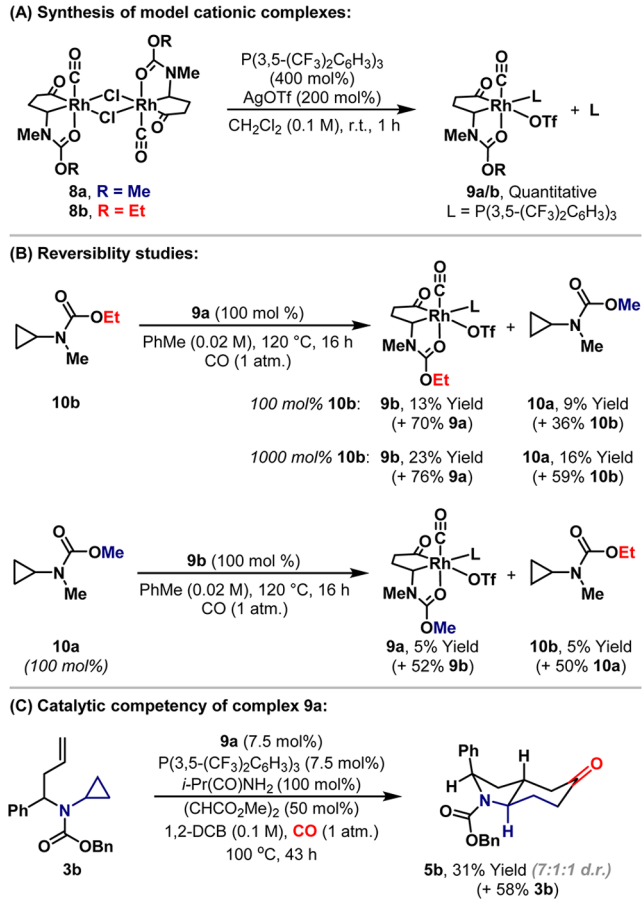
3d R^1 = *n*-Bu, R^2 = R^3 = H **3e** R^1 = 2-Npth, R^2 = R^3 = H **3f** R^1 = *c*-Pr, R^2 = R^3 = H
3g R^1 = CO_2Et, R^2 = R^3 = H **3h** R^1 = H, R^2 = Ph, R^3 = H **3i** R^1 = H, R^2 = Bn, R^3 = H
3j R^1 = Ph, R^2 = Me, R^3 = H **3k** R^1 = *c*-Hex, R^2 = R^3 = H **3l** R^1 = R^2 = H, R^3 = Me



[a](A:B:C d.r.) = A (depicted): B (invert C-2 stereocenter): C (invert C-4 stereocenter). Isolated diastereomer ratios were consistent with those determined by ^{1}H NMR of crude material.

rhodacycle formation can occur under carbonylative conditions using the catalyst components outlined in Table 3. To confirm catalytic competency, rhodacycle **9a** was employed as a precatalyst for the cyclization of **3b** (Scheme 4C). This generated **5b** in 31% yield and with similar diastereoselectivity to that observed earlier (cf. Table 3). It is notable that in this experiment the turnover frequency is lower than under the conditions used in Table 3 (31% vs 79% yield over the same time period) and that the exchange experiments in Scheme 4B do not provide an equilibrium composition of products. A plausible explanation that accounts for both of these observations is that the cyclopropane (**3**) does not dissociate readily from the Rh-center after retro-carbonylation and reductive elimination, and that interconversion between **7a**/**b** occurs at the metal center.[17] Another possibility is that

Scheme 4. Preliminary Mechanistic Studies



complexes **9a**/**b** are not exact analogues of the active catalytic species formed under the conditions outlined in Table 3.

We have explored the scope of the cationic Rh(I)-system outlined in Table 3 with respect to substitution on the cyclopropane. A series of *trans*-1,2-disubstituted systems **11a**−**c** cyclized to afford adducts **12a**−**c** in moderate to good yield (Scheme 5A). The structure of **12c** was confirmed by X-ray diffraction (see the Supporting Information). In these cases, complete transfer of cyclopropane stereochemistry is observed, which accounts for the high levels of diastereocontrol associated with the R^2-substituted stereocenter of **12a**−**c**. A further point to note is that the products are derived from highly selective Rh-insertion into the less hindered proximal C−C bond of the cyclopropane (bond a). This contrasts our earlier studies where more strongly directing urea groups gave significantly lower levels of regiocontrol.[3a] Extension to trisubstituted cyclopropane **11d** resulted in efficient cyclization to provide tricycle **12d** in 67% yield (Scheme 5B). Here, desymmetrization of the cyclopropane enables the introduction of four contiguous stereocenters with complete diastereocontrol.

We have not previously examined cyclizations involving *cis*-1,2-disubstituted systems, and so, in these cases, the regiochemical outcome was uncertain (Scheme 5C). Upon exposure to the cationic Rh(I)-system described in Table 3, *cis*-cyclopropane **11e** generated adduct **12e** in 42% yield and as a 4.5:1 mixture of diastereomers at C-6. Here, the product is derived from Rh-insertion into the more hindered proximal C−C bond (bond b) (cf. **12a**−**c**). The incomplete stereochemical

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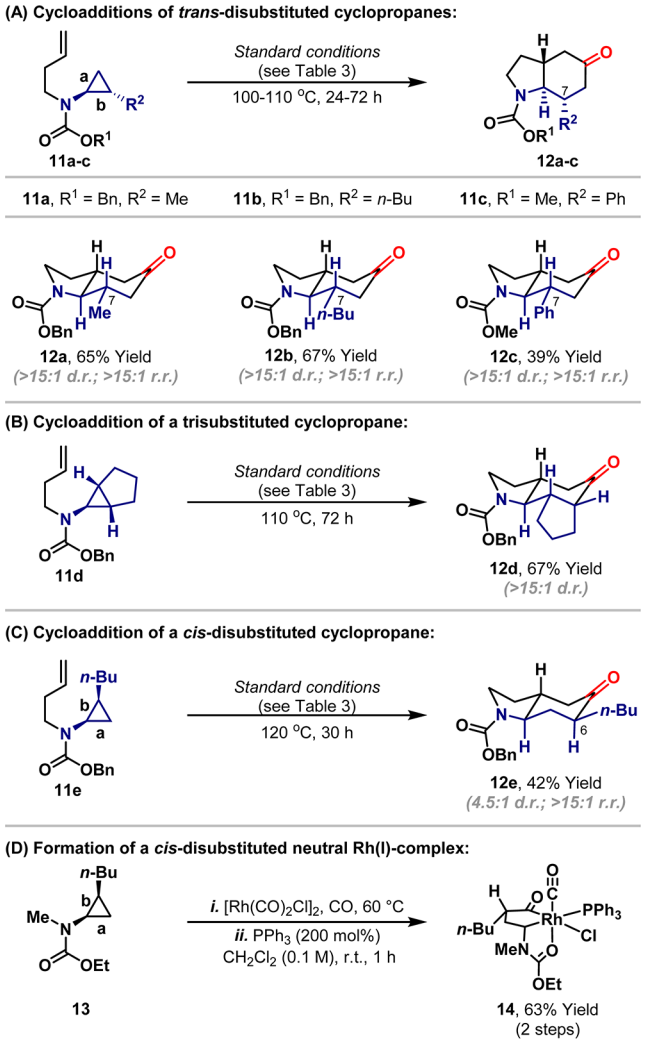
Scheme 5. (3 + 1 + 2) Cycloadditions of Substituted Aminocyclopropanes



transfer associated with the butyl moiety is tentatively attributed to epimerization of the labile C-6 stereocenter of **12e** under the reaction conditions.[18] The divergence in regiochemistry observed for **12e** vs **12a–c** is notable. By analogy with the stabilities of *cis*/*trans*-olefin complexes of rhodium,[19] *cis*-disubstituted cyclopropane C–C bonds might be expected to coordinate more strongly than *trans*-disubstituted variants, and this may facilitate electronically controlled and contrasteric Rh/CO insertion into bond b of **11e**, which would lead directly to **12e**. However, in light of the studies described in Scheme 4, an alternate possibility is that reversible Rh/CO insertion (into bond a or b) enables the relative rates of the two possible alkene insertion steps to determine the regioselectivity of the product (cf. Scheme 3).[20] Consequently, the regiochemical preference of rhodacyclopentanone formation may not be reflected in the structure of **12e**. To probe this issue, we have prepared a model complex derived from a *cis*-1,2-disubstituted cyclopropane (Scheme 5D). Sequential exposure of *cis*-cyclopropane **13** to $[Rh(CO)_2Cl]_2$ and PPh_3 afforded monomeric complex **14** in 63% yield (2 steps). The regiochemistry of **14** was assigned by detailed NMR analysis (^1H, ^{13}C, HSQC, COSY) and arises from insertion of Rh and CO into the more hindered bond b. This experiment supports a scenario where the regiochemistry of **12e** arises by regioselective generation of the requisite rhodacyclopentanone (i.e., preferential insertion of Rh/CO into bond b of **11e**).[21] The ability to program product regiochemistry by altering the stereochemistry of the starting material (cf. **11b** to **12b** vs **11e** to **12e**) may be important in target directed settings. Nevertheless, studies aimed at providing catalyst systems that deliver products derived from insertion into the less hindered proximal C–C bond (i.e., bond a) of *cis*-1,2-disubstituted cyclopropanes will be a focus of future investigations, as this would provide access to the alternate C-7 stereoisomers of **12a–c**.

CONCLUSIONS

In summary, we demonstrate that directing group controlled carbonylative insertion of Rh(I)-catalysts provides efficient (3 + 1 + 2) cycloadditions between amino-substituted cyclopropanes and tethered alkenes. Notable synthetic aspects of the current process include (a) the high levels of stereocontrol achieved, (b) the use of synthetically flexible carbamate directing groups, and (c) the high "sp^3-content" of the targets. Overall, this approach provides direct and versatile access to a family of complex heterocyclic scaffolds that are primed for further modification. From a mechanistic viewpoint, it is important to appreciate that two distinct catalyst systems have been developed. The neutral Rh(I)-system appears to promote kinetic diastereoselection, and this may be important for the eventual development of processes that rely upon ligand enforced stereocontrol. The cationic Rh(I)-system achieves high levels of, what is essentially, substrate controlled diastereoselectivity. Synthetic and mechanistic studies indicate that this is dependent upon reversible C–C bond activation. The option of generating rhodacyclopentanones dynamically provides a new facet to a growing area of catalysis[3a–c,7,8] and may find use as a stereocontrol strategy for other processes.[22]

ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization and crystallographic data. 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) (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) (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.

(3) (a) Shaw, M. H.; Melikhova, E. Y.; Kloer, D. P.; Whittingham, W. G.; Bower, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 4992. See also: (b) Wilkinson, G.; Roundhill, D. N.; Lawson, D. N. *J. Chem. Soc. A* **1968**, 845. (c) Narasaka, K.; Koga, Y. *Chem. Lett.* **1999**, *28*, 705. Leading references to other classes of Rh-catalyzed carbonylative (3 + 1 + 2) cycloaddition that use cyclopropanes or related species: (d) Jiao, L.; Lin, M.; Zhuo, L.-G.; Yu, Z.-X. *Org. Lett.* **2010**, *12*, 2528. (e) Lu, B.-L.; Wei, Y.; Shi, M. *Organometallics* **2012**, *31*, 4601. (f) Mazumder, S.; Shang, D.; Negru, D. E.; Baik, M.-H.; Evans, P. A. *J. Am. Chem. Soc.* **2012**, *134*, 20569. (g) Li, C.; Zhang, H.; Feng, J.; Zhang, Y.; Wang, J. *Org. Lett.* **2010**, *12*, 3082.

(4) For phosphinite directed insertion of rhodium into cyclopropane C−C bonds, see: Bart, S. C.; Chirik, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 886.

(5) For a review that encompasses cycloadditions involving aminocyclopropanes, see: de Nanteuil, F.; De Simone, F.; Frei, R.; Benfatti, F.; Serrano, E.; Waser, J. *Chem. Commun.* **2014**, *50*, 10912.

(6) Selected reviews on C−C activation processes: (a) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245. (b) Jennings, P. W.; Johnson, L. L. *Chem. Rev.* **1994**, *94*, 2241. (c) Murakami, M.; Ito, Y. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer: Berlin, 1999; p 97. (d) Rybtchinski, B.; Milstein, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 870. (e) Jun, C.-H. *Chem. Soc. Rev.* **2004**, *33*, 610. (f) Seiser, T.; Saget, T.; Tran, D. N.; Cramer, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 7740. (g) Murakami, M.; Matsuda, T. *Chem. Commun.* **2011**, *47*, 1100. (h) Aïssa, C. *Synthesis* **2011**, *21*, 3389. (i) Chen, F.; Wang, T.; Jiao, N. *Chem. Rev.* **2014**, *114*, 8613.

(7) Rhodacyclopentanones (and related intermediates) can also be generated by oxidative addition of Rh(I)-catalysts into the acyl-carbon bond of cyclobutanones. For pioneering studies, see: (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. (c) Murakami, M.; Itahashi, T.; Ito, Y. *J. Am. Chem. Soc.* **2002**, *124*, 13976. (d) Matsuda, T.; Tsuboi, T.; Murakami, M. *J. Am. Chem. Soc.* **2007**, *129*, 12596. For selected recent contributions in this area, see: (e) Liu, L.; Ishida, N.; Murakami, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 2485. (f) Masuda, Y.; Hasegawa, M.; Yamashita, M.; Nozaki, K.; Ishida, N.; Murakami, M. *J. Am. Chem. Soc.* **2013**, *135*, 7142. (g) Parker, E.; Cramer, N. *Organometallics* **2014**, *33*, 780. (h) Souillart, L.; Parker, E.; Cramer, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 3001. (i) Souillart, L.; Cramer, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 9640. (j) Ko, H. M.; Dong, G. *Nat. Chem.* **2014**, *6*, 739. See also citations within reference 3a. In the approach outlined here, carbonylative generation of the rhodacyclopentanone from a cyclopropane is a more appealing strategy for reasons discussed in reference 3a.

(8) For processes that involve the generation of rhodaindanones by oxidative addition of Rh(I)-catalysts into C(sp^2)-acyl bonds, see: (a) Xu, T.; Dong, G. *Angew. Chem., Int. Ed.* **2012**, *51*, 7567. (b) Xu, T.; Ko, H. M.; Savage, N. A.; Dong, G. *J. Am. Chem. Soc.* **2012**, *134*, 20005. (c) Chen, P.-h.; Xu, T.; Dong, G. *Angew. Chem., Int. Ed.* **2014**, *53*, 1674. (d) Xu, T.; Savage, N. A.; Dong, G. *Angew. Chem., Int. Ed.* **2014**, *53*, 1891. (e) Xu, T.; Dong, G. *Angew. Chem., Int. Ed.* **2014**, *53*, 10733.

(9) Representative asymmetric approaches to cyclopropane carboxylic acid derivatives: (a) Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 10270. (b) Lou, Y.; Remarchuk, T. P.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 14223. (c) Gao, L.; Hwang, G.-S.; Ryu, D. H. *J. Am. Chem. Soc.* **2011**, *133*, 20708. (d) Miyamura, S.; Araki, M.; Suzuki, T.; Yamaguchi, J.; Itami, K. *Angew. Chem., Int. Ed.*; DOI: 10.1002/anie.201409186.

(10) McQuillin, F. J.; Powell, K. C. *Dalton Trans.* **1972**, 2129.

(11) For discussions, see: Tatsumi, K.; Hoffmann, R.; Templeton, J. L. *Inorg. Chem.* **1982**, *21*, 466 and references cited therein.

(12) See: Huang, C.-Y.; Doyle, A. G. *J. Am. Chem. Soc.* **2012**, *134*, 9541 and references cited therein.

(13) In the absence of dimethyl fumarate, **5a** was isolated in 57% yield after 48 h (vs 71% yield after 48 h under the conditions in Table 1). **5b** was generated in 42% yield and 2:3 d.r. after 72 h when dimethyl fumarate was omitted.

(14) In Murakami and Ito's studies, both neutral and cationic systems were effective at generating cyclopropanes from cyclobutanones (see ref 7b). A major side reaction was competing β-hydride elimination from the rhodacyclopentanone which resulted in alkene byproducts. This competing pathway could be minimized by judicious choice of ligand.

(15) For beneficial effects of Lewis basic additives or solvents in other metal-catalyzed C−C activation processes, see: (a) Yasui, Y.; Kamisaki, H.; Takemoto, Y. *Org. Lett.* **2008**, *10*, 3303. (b) Rondla, N. R.; Levi, S. M.; Ryss, J. M.; Vanden Berg, R. A.; Douglas, C. J. *Org. Lett.* **2011**, *13*, 1940.

(16) Complexes **9a**/**b** are sparingly soluble in PhMe at room temperature, and this necessitated removal of the reaction solvent prior to NMR analysis in CD_2Cl_2.

(17) Another feasible method for obtaining stereocontrol involves the alkene directing Rh-insertion to access selectively **7a** or **7b**. Additional evidence disfavoring this selectivity mode includes: (a) less strongly donating directing groups, such as trifluoroacetamide, are completely ineffective under the conditions outlined in Table 3; (b) the processes appear to be insensitive to the steric demands of the R^2 substituent; and (c) for **5f**, an alkene directed process would likely favor Rh-insertion into the R^1 group (5-ring chelate) rather than the aminocyclopropane (6-ring chelate).

(18) When **12e** (4.5:1 d.r.) was resubjected to the cyclization conditions for 16 h, it was recovered in 75% yield and as a 3.5:1 mixture of diastereomers.

(19) Cramer, R. *J. Am. Chem. Soc.* **1967**, *89*, 4621.

(20) The neutral Rh(I)-system outlined in Table 1, which does not appear to provide high reversibility for the processes described here, *also* afforded selectively regioisomer **12e** (43% yield, >15:1 r.r., 6:1 d.r.).

(21) Whether rhodacyclopentanone formation is under kinetic or thermodynamic control in this case is unclear. For steric reasons, insertion into bond a may be kinetically favored, but the resulting rhodacyclopentanone is likely to be less stable than **14** due to steric interactions between the butyl moiety and the directing group. Consequently, reversible Rh/CO insertion may enable equilibration to the thermodynamically favored regioisomer **14**. Alternatively, **14** may form directly for reasons outlined in the main text. At the present time, evidence for reversible rhodacyclopentanone formation in cases involving *cis*-disubstituted aminocyclopropanes has not been obtained and products derived from Rh-insertion into the less hindered proximal C−C bond (i.e., bond a of **11e** and **13**) have not been observed.

(22) We note that related C−C bond activation/π-insertion processes have been described as "cut and sew" methodologies.[7j,8] In the present case, this terminology does not encompass the dynamic nature of the C−C activation process.

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