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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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New Initiation Modes for Directed Carbonylative C−C Bond Activation: Rhodium-Catalyzed (3 + 1 + 2) Cycloadditions of Aminomethylcyclopropanes

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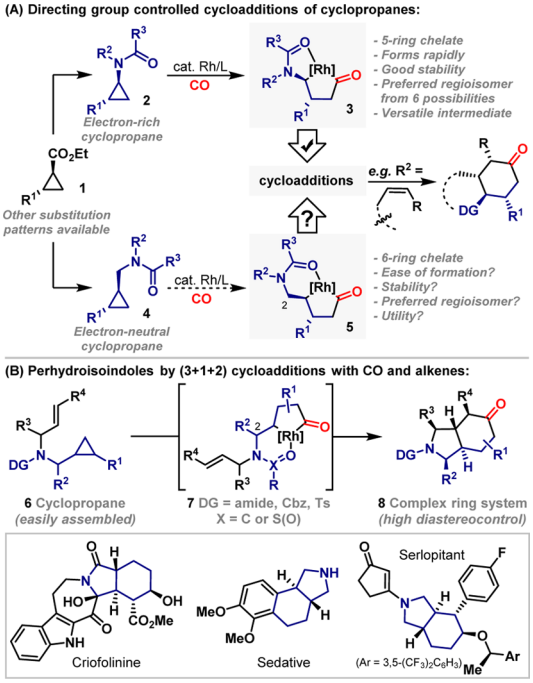
Supporting Information

ABSTRACT: Under carbonylative conditions, neutral Rh(I)-systems modified with weak donor ligands ($AsPh_3$ or 1,4-oxathiane) undergo N-Cbz, N-benzoyl, or N-Ts directed insertion into the proximal C−C bond of aminomethylcyclopropanes to generate rhodacyclopentanone intermediates. These are trapped by N-tethered alkenes to provide complex perhydroisoindoles.

Cycloaddition reactions are the most powerful approach for the construction of complex carbocycles. The emergence of methodologies mediated by redox metal catalysis (esp. Rh) has enabled access to ring systems that are inaccessible using classical organic reactivity.[1] Key to this is the identification of new oxidative initiation modes to provide reactive organometallic intermediates. We have developed a Rh-catalyzed cycloaddition platform that relies upon N-protecting group directed carbonylative ring expansion of aminocyclopropanes **2** to provide highly regiocontrolled access to key rhodacyclopentanone intermediates **3** (Scheme 1A).[2,3] These can engage pendant alkynes or alkenes to generate stereochemically rich (3 + 1 + 2)[2a,b,d] or (7 + 1)[2c] cycloaddition products. Notable features of these methodologies include (a) the unusually high "sp^3-character" of the metallacycle[4] and (b) easy access to the aminocyclopropane unit by Curtius rearrangement of readily available and, where appropriate, enantiopure cyclopropane carboxylates **1**.

The aminocyclopropane-based cycloadditions outlined in Scheme 1A are prototypes for a suite of related processes triggered by directed C−C bond activation. To broaden further the utility of this approach, expansion to other substrate classes that can be accessed from cyclopropane carboxylates is required. Thus, we considered the feasibility of processes based on aminomethylcyclopropanes **4**, which can be synthesized from **1** by an amide formation−reduction sequence. At the outset, this proposition was considered challenging because (a) 6-ring chelates form more slowly and are less stable than 5-ring variants (cf. **3** vs **5**);[5] (b) the cyclopropane unit of **4** is considerably less nucleophilic than that of **2**, such that C−C oxidative addition is more difficult;[6] and (c) whereas amino-rhodacyclopentanones **3** are relatively stable, homologues **5** can undergo facile exocyclic β-hydride elimination via C2−H upon dissociation of the directing group;[7] the latter is required for the Rh-center to engage an N-tethered π-unsaturate. Nevertheless, the prospect of establishing a new activation mode, which would enhance substantially the flexibility of any downstream catalytic protocols, motivated the exploration of aminomethylcyclopropane-based cycloadditions. The successful realization of this endeavor is described herein, with the resulting (3 + 1 + 2) cycloaddition methodology providing exceptionally flexible access to perhydroisoindoles, a core motif of numerous bioactive compounds (Scheme 1B).[8] *These studies provide rare examples of C−C activation triggered cycloadditions where a 3-carbon unit is provided by an electron neutral nonactivated cyclopropane.*[5,9] Existing C−C activation based cycloadditions using cyclopropane derivatives either require activated variants[9a−d] or rely on the incoming π-unsaturate to direct C−C activation,[9e] thereby limiting either the stereochemical complexity of the newly formed ring or further application of the initiation mode.

Scheme 1

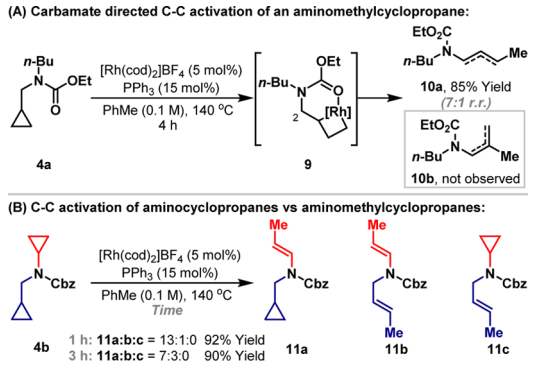


Received: August 17, 2016
Published: October 6, 2016

DOI: 10.1021/jacs.6b08608
J. Am. Chem. Soc. 2016, 138, 13501−13504

Preliminary experiments sought to confirm the feasibility of the new activation mode proposed in Scheme 1. Accordingly, carbamate **4a** was exposed to a cationic Rh(I)-system ($[Rh(cod)_2]BF_4/PPh_3$) in the absence of CO, which resulted in smooth conversion to **10a** (via rhodacyclobutane **9**) rather than regioisomer **10b**. This result supports the proposed directed C−C bond activation pathway because in the absence of directing groups the same catalyst system inserts into the less hindered C−C bond of monosubstituted cyclopropanes.[2a,10] As expected, a less Lewis acidic neutral Rh(I)-system derived from $[Rh(cod)Cl]_2/PPh_3$ did not promote directed oxidative addition, and branched product **10b** was generated in low yield (see the Supporting Information (SI)). Under carbonylative conditions, coordination of strongly π-accepting CO should enhance the Lewis acidity of neutral Rh(I)-centers such that carbonyl-directed C−C bond activation can occur.[2a] Thus, both cationic and neutral rhodium systems were deemed viable for the process outlined in Scheme 1B. To probe the facility of aminomethylcyclopropane vs aminocyclopropane C−C bond activation, we exposed competition substrate **4b** to $[Rh(cod)_2]BF_4/PPh_3$ at 140 °C for 1 h (Scheme 2B). This revealed high selectivity for activation of the

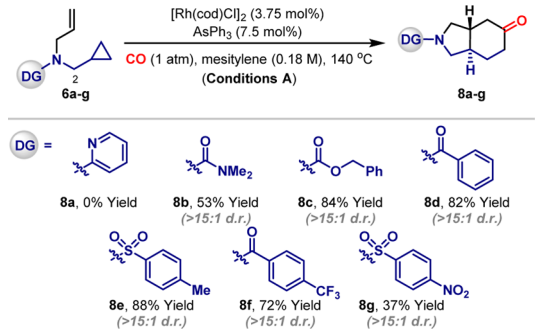
Scheme 2



aminocyclopropane unit, leading predominantly to *N*-vinyl carbamate **11a**; **11c** was not observed. Subsequent activation of the aminomethylcyclopropane moiety of **11a** (to afford **11b**) was much slower, demonstrating the relative difficulty of the 6-ring chelate driven C−C bond activation pathway.[11] Indeed, we have already shown that (3 + 1 + 2) cycloadditions of aminocyclopropanes can be achieved with retention of an aminomethylcyclopropane unit.[2b]

Having established the feasibility of the proposed C−C bond activation mode, its incorporation into a cycloaddition process was explored. This required the identification of conditions to suppress β-hydride elimination via C2−H at the stage of either the rhodacyclobutane (cf. **9**) or rhodacyclopentanone (**7**) intermediate. Indeed, carbonylative (3 + 1 + 2) cycloaddition of carbamate **6c** to **8c** was not efficient using neutral Rh(I)-precatalysts modified with a wide range of P-based ligand systems (Table 1 and the SI). At best, **8c** was formed in 37% yield using $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ as the ligand with the mass balance consisting of byproducts derived from β-hydride elimination triggered decomposition of metallacyclic intermediates. Cationic Rh(I)-systems were completely ineffective, presumably because the additional vacant coordination site facilitates β-hydride elimination at the stage of **7**. After extensive investigation, we found that **8c** could be formed in 84% yield and >15:1 d.r. using $AsPh_3$ as the ligand ("Conditions A"); note that the *trans*-

Table 1. Evaluation of Different Directing Groups

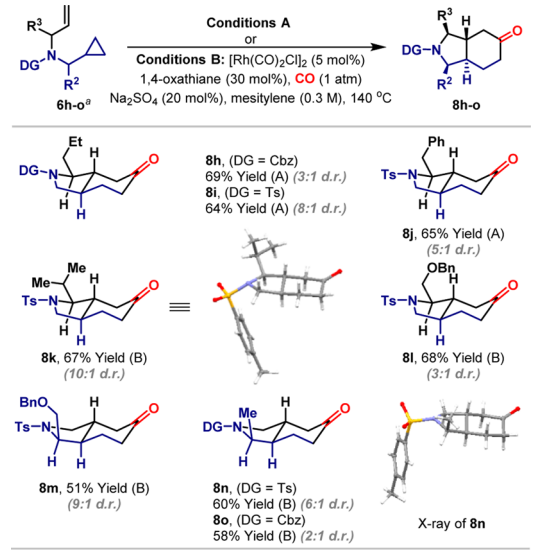


stereochemistry of the ring junction reflects the inherent preference of the alkene migratory insertion step.

The choice of directing group for the process in Scheme 1B is critical, as it must be not only sufficiently Lewis basic to promote C−C oxidative addition but also sufficiently labile to dissociate from **7** prior to alkene coordination. Accordingly, a range of potential directing groups were examined under optimized conditions. Amide **6d** and sulfonamide **6e**[12] delivered targets **8d** and **8e** in excellent yield. Strongly coordinating urea (**6b**) and 2-pyridyl (**6a**) directing groups were less efficient or provided no cycloaddition product, presumably because of slow dissociation at the stage of **7**. More weakly coordinating *p*-trifluorobenzamide (**6f**) and nosyl (**6g**) directing groups were less effective than their parent systems (**6d** and **6e**), likely due to less efficient directed C−C bond activation. These results highlight the importance of selecting an appropriately Lewis basic directing group.

Extension of the protocol to systems with substitution at R^2 or R^3 raised the issue of whether high diastereocontrol could be achieved for these substituents with respect to the ring junction (vide infra) (Table 2). Cyclization of N-Cbz substrate **6h**

Table 2. Diastereoselective (3 + 1 + 2) Cycloadditions



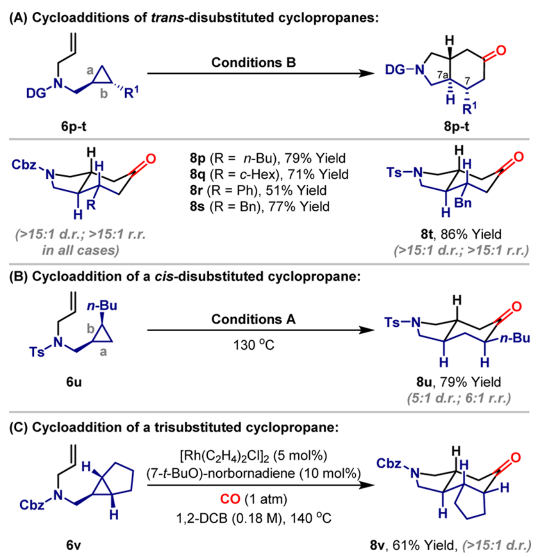
delivered **8h** in 69% yield but only 3:1 d.r. Here, the ability to use different directing groups was beneficial, and by switching to N-Ts variant **6i**, product **8i** was generated in 8:1 d.r. and 64% yield. A similar result was obtained for benzyl substituted system **8j**. For **6k**, which possesses a bulky isopropyl group, "Conditions A" were not overly effective, generating **8k** in only 45% yield and 14:2:1 d.r.[13] Efforts to improve conversion by standard parameter

DOI: 10.1021/jacs.6b08608
J. Am. Chem. Soc. 2016, 138, 13501−13504

variance (concentration, temperature, etc.) were not fruitful, so further ligand systems were investigated. For this hindered substrate, we hypothesized that ligands less bulky than $AsPh_3$ might provide enhanced efficiencies. In seeking other classes of weak donor ligand, but with decreased steric demands, we were drawn to sulfides.[14] The coordination chemistry of certain thioethers to Rh has been studied,[15] but they are rarely used as monodentate ligands in catalysis.[16] From a broad screen of commericial sulfides, we discovered that 1,4-oxathiane, which is readily available at low cost,[17] could deliver adduct **8k** in 67% yield and 10:1 d.r. ("Conditions B"). Extension to N-Ts systems **6l−n** proceeded smoothly, and targets **8l−n** were formed with good diastereocontrol. The results for **8n** (6:1 d.r.) vs Cbz-variant **8o** (2:1 d.r.) highlight once again the benefits of an N-Ts group to diastereoselectivity.

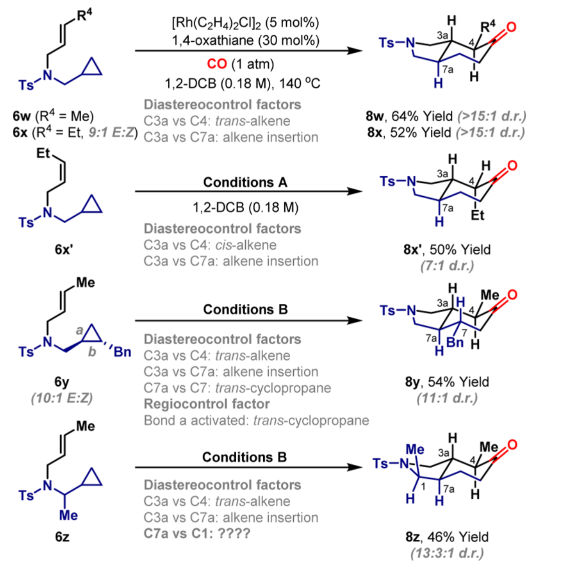
We have investigated the scope of the system with respect to substitution on the cyclopropane unit, and these studies revealed similar regioselectivity trends to aminocyclopropane-based processes (Scheme 3).[2a−c] *Trans*-1,2-disubstituted cyclopropanes **6p−t** underwent preferential activation of less hindered proximal C−C **bond a** to deliver targets **8p−t** with exquisite levels of regio- and diastereocontrol. Here, the relative stereochemistry of the cyclopropane is transferred to the C7−C7a stereochemical relationship of the products. For these processes the use of 1,4-oxathiane as the ligand conferred substantial advantages; for example, cyclohexyl system **8q** was generated in only 38% yield under "Conditions A" vs 71% yield with 1,4-oxathiane ("Conditions B").[13] *Cis*-1,2-disubstituted system **6u** delivered **8u**, which is the pseudoregioisomer of **8p**, via cleavage of more hindered but more electron-rich **bond b**. Again, this result mirrors the preferred site of activation for aminocyclopropane-based systems.[2b] Thus, the relative stereochemistry of the cyclopropane unit (*cis* vs *trans*) controls both C−C bond activation selectivity (**bond a** vs **b**) and the relative stereochemistry of the product. Bicyclic system **6v** was smoothly desymmetrized to deliver tricyclic system **8v** with complete diastereocontrol; unique to this example, a diene ligand [(7-*t*-BuO)-norbornadiene] was found to be most effective.[13]

Scheme 3



All of the processes described so far involve insertion of a monosubstituted alkene into the incipient rhodacyclopentanone (**7**). Extension to 1,2-disubstituted alkenes offers the option of exploiting alkene geometry for diastereocontrol; however, processes of this type are sterically challenging and have not been realized for aminocyclopropane-based cycloadditions.[2b] Gratifyingly, cycloaddition of *trans*-alkenes **6w** and **6x** delivered products **8w** and **8x** with high diastereocontrol for the three new adjacent stereocenters, wherein the R^4-substituent resides in a pseudoequatorial position (Scheme 4). *Cis*-substituted alkene **6x′**

Scheme 4. (3 + 1 + 2) Cycloadditions Involving 1,2-Disubstituted Alkenes and Key Control Factors

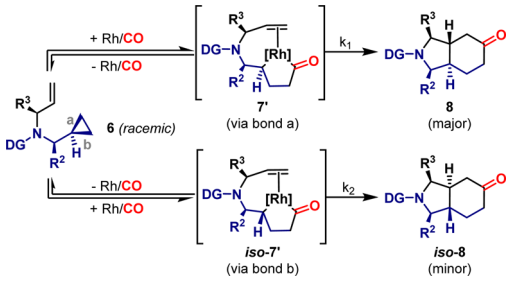


provided **8x′**, the diastereomer of **8x**, in 7:1 d.r. favoring a pseudoaxial ethyl substituent. Thus, the processes are diastereospecific with respect to alkene geometry. By combining this feature with stereochemically defined cyclopropanes, ring systems of even higher complexity can be constructed. For example, cycloaddition of **6y** provided **8y** in 11:1 d.r. favoring the indicated (and expected) diastereomer; here, four contiguous stereocenters are controlled. Systems with α-substitution can also be exploited: cycloaddition of **6z** provided **8z** in 13:3:1 d.r., with good diastereocontrol for the C1-methyl group.

It is pertinent at this stage to clarify key diastereo- and regiocontrol factors (also highlighted in Scheme 4). For **6y** to **8y**, the C3a−C4 stereorelationship is controlled by the *trans*-geometry of the alkene, the C3a−C7a stereorelationship reflects the preference of alkene migratory insertion, and the C7a−C7 stereorelationship is determined by the *trans*-stereochemistry of the cyclopropane; the latter also controls C−C bond activation regioselectivity such that **bond a** is cleaved and the C7-substituted product is generated (cf. Scheme 3A vs 3B). An additional and more intriguing consideration is what controls the C1−C7a stereorelationship established during conversion of **6z** to **8z** and the high diastereoselectivities obtained in Table 2. A plausible explanation is that rhodacyclopentanone formation is reversible, such that the relative rate of alkene insertion (k_1 vs k_2) from π-complexes **7′** and ***iso*-7′** controls product diastereoselectivity (Scheme 5). A similar Curtin−Hammett selectivity model is operative for aminocyclopropane-based processes catalyzed by cationic Rh(I)-complexes; neutral Rh(I)-systems provided low diastereocontrol in those cases, likely because they lack the free coordination site required for retrocarbonylation from **3** (see Scheme 1A).[2b] In the cycloadditions described here, which use

DOI: 10.1021/jacs.6b08608
J. Am. Chem. Soc. 2016, 138, 13501−13504

Scheme 5. Possible Diastereocontrol Model for Systems with R^2/R^3 Substituents



neutral Rh(I)-complexes, the requisite free coordination site may be provided by relatively facile dissociation of the directing group of the weaker 6-ring chelate. Indeed, in the absence of directing groups, Murakami and Ito have shown that cyclobutanone-derived neutral rhodacyclopentanone complexes undergo retrocarbonylation and C−C reductive elimination to provide cyclopropanes.[18] The enhanced diastereoselectivities observed in Table 2 for N-Ts vs N-Cbz protected systems may reflect increased reversibility for rhodacyclopentanone formation and/or enhanced conformational preferences for alkene insertion due to the greater sp^3 character at nitrogen.

In summary, we show that directed carbonylative C−C bond activation can be extended beyond aminocyclopropane-based systems to readily available aminomethylcyclopropane derivatives. The resulting (3 + 1 + 2) cycloaddition methodology provides exceptionally flexible and controlled access to stereochemically complex perhydroisoindoles. This study represents a significant extension to the cycloaddition strategy outlined in Scheme 1A, validating for the first time electronically distinct cyclopropanes and 6-ring chelate driven processes. Applications of the new initiation mode described here to other diverse processes can easily be envisaged. Indeed, in addition to (3 + 1 + 2) cycloadditions,[2a,b,d] carbonylative C−C bond activation of aminocyclopropanes now underpins (7 + 1) cycloadditions[2c] and capture−collapse heterocyclizations.[2e]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b08608.

Crystallographic data (CIF, CIF, CIF, CIF, CIF, CIF, CIF, CIF, CIF, CIF)

Experimental details, characterization data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Bristol Chemical Synthesis CDT, funded by EPSRC (EP/G036764/1), and Syngenta for studentships (M.H.S. and N.G.M.), the Royal Society for a URF (J.F.B.) and a K. C. Wong Postdoctoral Fellowship (G.-W.W.), and the European Research Council for financial support (ERC grant 639594 CatHet). We also thank Emma Blackham (Bristol) for preliminary studies.

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(10) For the processes described later we cannot definitively rule out an alkene directed pathway. In addition to the results in Scheme 2A/Table 1, further evidence against this activation mode includes the following: (a) under optimized conditions, the cycloadditions in Table 2 are insensitive to the sterics of the R^3-substituent (e.g., under Conditions B, **8i** (Pr): 61% yield vs **8k** (*i*-Pr): 67% yield), but sensitive to the sterics of the R^2-substituent, and (b) systems where DG = benzyl (cf. Table 1) are ineffective.

(11) We have been unable to isolate rhodacyclopentanones related to **5**; analogous 5-ring chelates (**3**) are easily isolated (see refs 2a−c).

(12) Directed insertion into *N*-cyclopropylsulfonamides has been achieved previously (see ref 2d).

(13) Representative product derivatizations and results for alternate cycloaddition conditions are given in the SI.

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(17) Approximately $3.60/g from Sigma-Aldrich. Binding competition studies for $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ vs $AsPh_3$ vs 1,4-oxathiane are in the SI.

(18) Here, neutral Rh(I) systems modified with $AsPh_3$ were especially effective (cf. Conditions A). (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.

DOI: 10.1021/jacs.6b08608
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