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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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ABSTRACT: Under carbonylative conditions, neutral Rh(I)-systems modified with weak donor ligands (AsPh₃ 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 "sp³-character" of the metallacycle⁴ 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);³ (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;⁶ 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

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Scheme 1

Supporting Information

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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)Cl]_2/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. 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 Scheme 1B). To probe the facility of aminomethylcyclopropane vs rhodium systems were deemed viable for the process outlined in Scheme 1B. To probe the facility of aminomethylcyclopropane vs methylcyclopropane unit.2b

aminocyclopropane unit, leading predominantly to aminocarbamate 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. 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 Supporting Information (SI)). At best, 8c was formed in 37% yield using P(3,5-(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-stereocchemistry 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 delivered targets 8d and 8e in excellent yield. Strongly coordinating urea (6f) 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-trifluorobenzoamide (6f) and nosyl (6g) directing groups were less efficient 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 diasterecontrol could be achieved for these substrates with respect to the ring junction (vide infra) (Table 2). Cyclization of N-Cbz substrate 6h 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. Efforts to improve conversion by standard parameter.

![Scheme 2](image)

**Table 1. Evaluation of Different Directing Groups**

![Table 2. Diastereoselective (3 + 1 + 2) Cycloadditions](image)
variability of concentration, temperature, etc.) were not fruitful, so further ligand systems were investigated. For this hindered substrate, we hypothesized that ligands less bulky than AsPh₃ might provide enhanced efficiencies. In seeking other classes of weak donor ligand, but with decreased steric demands, we were drawn to sulfides. The coordination chemistry of certain thiocarbonyls to Rh has been studied, but they are rarely used as monodentate ligands in catalysis. From a broad screen of commercial sulfides, we discovered that 1,4-oxathiane, which is readily available at low cost, 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 diastereoselection. 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 diastereoselection.

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). Thus, the relative stereochemistry of the cyclopropane is transferred to the C⁻7 substituent to deliver targets 8n−o with good diastereocontrol for the C¹-methyl group.

Scheme 3

(A) Cycloadditions of trans-disubstituted cyclopropanes:

(B) Cycloaddition of a cis-disubstituted cyclopropane:

(C) Cycloaddition of a trisubstituted cyclopropane:

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 diastereoselection 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 selectivity 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 (k₅ vs k₆) from π-complexes 7’ and iso-7’ controls product diastereoselection (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 diastereoselection in those cases, likely because they lack the free coordination site required for retrocarbonylation from 3 (see Scheme 1A). In the cycloadditions described here, which use
neutral Rh(1)-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 sp2 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 chemically complex perhydroisoindoles. This study represents a

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**ASSOCIATED CONTENT**

Supporting Information

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

Experimental details, characterization data (PDF)

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The authors declare no competing financial interest.

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**Communication**