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

Gang-Wei Wang,† Niall G. McCreanor,† Megan H. Shaw,† William G. Whittingham,‡ and John F. Bower*,†

†School of Chemistry, University of Bristol, Bristol, BS8 1TS, United Kingdom
‡Syngenta, Jealott’s Hill International Research Centre, Bracknell, Berkshire, RG42 6EY, United Kingdom

Supporting Information

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. 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 to provide highly regiocontrolled access to key rhodacyclopentanone intermediates. These can engage pendant alkynes or alkenes to generate stereochemically rich (3 + 1 + 2) or (7 + 1) cycloaddition products. Notable features of these methodologies include (a) the unusually high "sp³-character" of the metallacycle and (b) easy access to the aminocyclopropane unit by Curtius rearrangement of readily available and, where appropriate, enantiopure cyclopropane carboxylates.

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, which can be synthesized from cyclopropane carboxylates. We have developed a Rh-catalyzed cycloaddition platform that relies upon N-protecting group directed carbonylative ring expansion of aminocyclopropanes to provide highly regiocontrolled access to key rhodacyclopentanone intermediates. These can engage pendant alkynes or alkenes to generate stereochemically rich (3 + 1 + 2) or (7 + 1) cycloaddition products. Notable features of these methodologies include (a) the unusually high "sp³-character" of the metallacycle and (b) easy access to the aminocyclopropane unit by Curtius rearrangement of readily available and, where appropriate, enantiopure cyclopropane carboxylates.

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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)]_2/Cl/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. 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/Cl/PPh_3 at 140 °C for 1 h (Scheme 2B). This revealed high selectivity for activation of the 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. Indeed, we have already shown that (3 + 1 + 2) cycloadditions of aminocyclopropanes can be achieved with retention of an aminomethylcyclopropane unit.

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-(CF_3)_2)C_6H_3 as the ligand with the mass balance consisting of byproducts derived from β-hydride elimination triggered decomposition of metalacyclic 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-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 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 nolsy (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 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 6l, product 8l 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

### Table 1. Evaluation of Different Directing Groups

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Yield (%)</th>
<th>Directing Group</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>37%</td>
<td>P(3,5-(CF_3)_2)C_6H_3</td>
</tr>
<tr>
<td></td>
<td>84%</td>
<td>AsPh_3</td>
</tr>
<tr>
<td></td>
<td>89%</td>
<td>Ph_3</td>
</tr>
<tr>
<td></td>
<td>55%</td>
<td>Ph</td>
</tr>
<tr>
<td></td>
<td>64%</td>
<td>Ph_3</td>
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</table>

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

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Yield (%)</th>
<th>Directing Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>89%</td>
<td>6b</td>
</tr>
<tr>
<td></td>
<td>64%</td>
<td>6a</td>
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<tr>
<td></td>
<td>85%</td>
<td>8e</td>
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<tr>
<td></td>
<td>67%</td>
<td>6b</td>
</tr>
<tr>
<td></td>
<td>51%</td>
<td>6d</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>6g</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>6e</td>
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variance (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 thioethers 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 formed with good diastereorecontrol. 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). Trans-1,2-disubstituted cyclo-

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 diastero-specific 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 diastereocntrol 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 (kₐ vs kₓ) 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 diastereocntrol 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-derivable neutral rhodacyclopentanone complexes undergo retrocarbonylation and C=C reductive elimination to provide cyclopropanes. 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 aminomethycyclopropane 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 vinylcyclopropanes 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, carbonylative C=C bond activation of aminocyclopropanes now underpins (7 + 1) cycloadditions and capture—collapse heterocyclizations.

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, CIF, CIF)

Experimental details, characterization data (PDF)

AUTHOR INFORMATION

Corresponding Author
john.bower@bbris.ac.uk

The authors declare no competing financial interest.

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