
Peer reviewed version

Link to published version (if available): 10.1002/anie.201811460

Link to publication record in Explore Bristol Research

PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via Wiley-VCH at https://onlinelibrary.wiley.com/doi/full/10.1002/anie.201811460. Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available: http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/
Carbonylative C-C Bond Activation of Electron-Poor Cyclopropanes: Rhodium-Catalyzed (3+1+2) Cycloadditions of Cyclopropylamides

Andrew G. Dalling,† Takayuki Yamauchi,‡ Niall G. McCreanor,† Lydia Cox‡ and John F. Bower*†

Abstract: Rh-catalyzed carbonylative C-C bond activation of cyclopropylamides generates configurationally stable rhodacyclopentanones that engage tethered alkenes in (3+1+2) cycloadditions. These studies provide the first examples of multicomponent cycloadditions that proceed via C-C bond activation of “simple” electron poor cyclopropanes.

Metal-catalyzed C-C bond activations of cyclopropane derivatives underpin a wide range of cycloadditions.1,2 Predominant methodologies require systems with internal or adjacent π-unsaturation (alkylidene cyclopropanes,3 cyclopropenes,4 vinyl cyclopropanes5,6) to enhance C-C oxidative addition and/or stabilize the ensuing transition metal intermediate (Scheme 1A). Although stoichiometric C-C bond activations of simpler (less-activated) cyclopropanes have been known for over 60 years,7 incorporation of such ring systems into cycloaddition processes is deceptively challenging.1,2,9,10,11† This is due to (a) the more demanding C-C bond activation step, (b) difficulties associated with achieving regiocontrol, and (c) the instability of the resulting metalacyclobutane, which is prone to β-hydride elimination (Scheme 1B).1c To address this, we have developed an N-directing group strategy where efficient and regioselective Rh-catalyzed carbonylative C-C bond activation of electron rich or neutral cyclopropanes (1a,b) provides tractable rhodacyclopentanones (2a,b) (Scheme 1C).11,12

A key feature of our methodologies is that reaction efficiency decreases as the cyclopropane becomes less nucleophilic, an observation consistent with a dominant HOMO-LUMO(M) interaction during C-C bond activation.1,12 This interpretation led us to question the limits of this step with respect to the electronics of the cyclopropane and, specifically, whether cyclopropylamides were suitable substrates for carbonylation. To address this, we have developed an N-directing group strategy where efficient and regioselective Rh-catalyzed carbonylative C-C bond activation of electron rich or neutral cyclopropanes (1a,b) provides tractable rhodacyclopentanones (2a,b) (Scheme 1C).11,12

We began by investigating C-C bond activation of cyclopropylamide system 4 (Scheme 2A). Exposure of this to a cationic Rh(I)-source modified with PPh3 provided acrylamide 6a in 47% yield and regioisomer 6b was not observed. This result indicates a substrate directed C-C bond activation pathway, which may proceed via 4-ring chelate 5. We have been unable to obtain direct crystallographic evidence for this but chelates related to 5 have been proposed in other contexts.15 Next, the facility of C-C bond activation of aminomethylcyclopropanes vs cyclopropylamides was probed by subjecting substrate 7 to the
COMMUNICATION

[Rh(cod)3]BF4/PPH3 system (Scheme 2B). This resulted in exclusive activation of the aminomethylcyclopropane unit to provide a 6:1 ratio of 8 and 8′; activation of the cyclopropylamide unit to give 9 was not observed. Accordingly, under Rh-catalyzed conditions, C-C bond activation of cyclopropylamides is harder than aminomethylcyclopropanes. This can be attributed to the less favorable electronics of the cyclopropane ring (electron poor vs neutral) and the less favorable chelate size (4- vs 6-ring) involved in the directed oxidative addition step.16

Scheme 2. Insertion and competition studies.

Having established the feasibility of Rh-catalyzed cyclopropylamide C-C bond activation, we examined the carbonylative (3+1+2) cycloaddition of N-benzyl protected alkenyl system 10h (Table 1). After extensive investigations, we found that a neutral Rh(I)-system modified with AsPh3 can deliver target 11h in 48% yield and with good selectivity for the trans-ring junction; this presumably reflects the inherent preference of alkene insertion into the rhodacyclopentanone. Further optimization by standard parameter variance or screening of commercially available ligands could not be achieved. Accordingly, we explored the effects of the N-substituent (R). Systems where R = H, Ph or OMe were not suitable (10a, d, e), but alkyl substituents were tolerated, albeit with varying degrees of efficiency (cf. 11b vs 11c vs 11h). An evaluation of different N-benzyl-like protecting groups revealed that systems containing methoxy-substituted aromatics are optimal, with 10j and 10k delivering targets 11j and 11k in 70% and 81% yield, respectively. Nitro-substituted systems 10l,g and bulky benzhydryl variant 10i offered no additional benefits vs 10h. These results indicate that the electronics of the N-substituent are key.17

Table 1. Prototype (3+1+2) cycloadditions.

(3+1+2) cycloaddition to form 11j/k was considered relatively facile; it was anticipated that substitution on the cyclopropane would render C-C bond activation more challenging. In this scenario, decomposition of the catalyst becomes problematic because its entry into the catalytic cycle is slower. Accordingly, ligand choice is of paramount importance in stabilizing the Rh-catalyst. Exposure of benzyl substituted system 10i to the conditions used in Table 1 provided target 11i/11l′ in only 12% yield (Table 2, Entry 1). Optimization of this process required the synthesis of a library of triarylarsine ligands L1-10. By switching to electron deficient As(4-CF3C6H4)3 (L1), 11l, which is derived from activation of more sterically accessible C-C bond a, was formed in 36% yield and 10:1 selectivity over 11l′ (Entry 2). In this process, multiple side products formed; however, when As(2-OMeC6H4)3 (L2) was used, 11l was generated in 30% yield and the mass balance consisted of starting material (Entry 3). Further optimization led to conditions where enantiopure 11l (99:1 e.r.) provided 11l in 65% yield, >15:1 d.r, 99:1 e.r. and 10:1 selectivity over 11l′ (Entry 4).18 This demonstrates that chemically efficient and highly regio-, diastereo- and enantiospecific cycloadditions of trans-disubstituted cyclopropylamides are achievable. Prior C-C bond activation methodologies that use electron poor cyclopropanes usually offer low diastereospecificity because of their propensity to generate oxo/azametallacyclohexenes 3 (Scheme 1D).3 By contrast, the present method appears to proceed via configurationally stable metalacycles (2c). The efficacy of L2 might stem from its hemilabile methoxy unit; interestingly, highest yields were obtained using a 2:1 ratio of Rh:L, suggesting that the ligand’s key role is to stabilize off-cycle species.19 The structural requirements of the arsine ligand are validated by results obtained using other variants (Entries 5-12), which confirmed that a single ortho-methoxy-substituent on each aryl ring is optimal.

Table 2. Ligand evaluation and optimization.
The conditions in Table 2, Entry 4 have been applied to trans-disubstituted systems 10m-o (Table 3A). In each case, highly selective activation of bond a occurred to give C7-substituted products (11m-o) with complete diasterecontrol, resulting from selective formation of the trans-ring junction and diastereospecific transfer of cyclopropane stereochemistry. The relative stereochemistry of the cyclopropane is also the critical factor in controlling C-C bond activation regioselectivity (bond a vs b). For cis-1,2-disubstituted cyclopropylamides 10p-t preferential activation of more hindered bond b occurred to afford C6-substituted products 11p-t, where the relative configuration of the C7a and C6 stereocenters is determined by the relative stereochemistry of the cyclopropane (Table 3B). Here, N-TMB systems offered higher efficiencies than PMB-protected variants. Even hindered tert-butyl system 10t underwent activation at bond b to provide 11t, albeit in diminished efficiency. The results in Table 3 are consistent with the generation of configurationally stable metallacycles, and this enables diastereospecific transfer of cyclopropane stereochemistry.

Further studies revealed that 1,1-disubstituted alkenes (10u-w) participate with good levels of diasterecontrol to provide products 11u-w containing quaternary stereocenters at C3a (Table 4). For cycloadditions involving 1,2-disubstituted alkenes stereospecific transfer of olefin geometry provided 11x and 11z. Systems with substituents at R1 (10aa-bb) cyclized to provide complex heterocyclic ring systems containing three contiguous stereocenters. Finally, cycloaddition of cyclic system 10cc generated tricyclic product 11cc in 66% yield. Overall, the results in Tables 3/4 show that the cycloaddition protocol offers exceptional flexibility for the provision of complex N-heterocyclic ring systems that can be manipulated further via either nitrogen or the ketone (see the SI). This is all enabled by the new initiation mode outlined in Scheme 1C (1c to 2c).

In summary, cyclopropylamides undergo Rh-catalyzed carboxylative C-C bond activation, and the ensuing multicomponent cycloadditions provide complex N-heterocycles with high levels of regio- and stereoccontrol. Our studies highlight the importance of both the N-protecting group and the ancillary ligand, which underlines the challenges in developing C-C bond activations with simple electron poor cyclopropanes. This is an underdeveloped area, and the present method is unique because it generates and harnesses configurationally stable metallacycles. Other aspects of novelty include the first examples of the efficient use of simple electron poor cyclopropanes in (a) multicomponent cycloadditions and (b) carboxylative processes. A wide range of methodologies now use the strategy outlined in Scheme 1C; consequently, application of the new initiation mode (1c to 2c) in other settings can be envisaged.

Table 3. Cycloadditions of disubstituted cyclopropanes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Rh source</th>
<th>Ligand</th>
<th>X</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Rh(cod)Cl]2</td>
<td>AsPh2</td>
<td>10</td>
<td>12% (n.d.)</td>
</tr>
<tr>
<td>2</td>
<td>[Rh(cod)Cl]2</td>
<td>L1</td>
<td>10</td>
<td>36% (10:1)</td>
</tr>
<tr>
<td>3</td>
<td>[Rh(cod)Cl]2</td>
<td>L2</td>
<td>10</td>
<td>30% (4:1)</td>
</tr>
<tr>
<td>4</td>
<td>[Rh(cod)Cl]2</td>
<td>L3</td>
<td>5</td>
<td>85% (10:1)</td>
</tr>
<tr>
<td>5</td>
<td>[Rh(cod)Cl]2</td>
<td>L3</td>
<td>5</td>
<td>42% (n.d.)</td>
</tr>
<tr>
<td>6</td>
<td>[Rh(cod)Cl]2</td>
<td>L4</td>
<td>5</td>
<td>27% (n.d.)</td>
</tr>
<tr>
<td>7</td>
<td>[Rh(cod)Cl]2</td>
<td>L5</td>
<td>5</td>
<td>17% (n.d.)</td>
</tr>
<tr>
<td>8</td>
<td>[Rh(cod)Cl]2</td>
<td>L5</td>
<td>5</td>
<td>30% (n.d.)</td>
</tr>
<tr>
<td>9</td>
<td>[Rh(cod)Cl]2</td>
<td>L6</td>
<td>5</td>
<td>53% (n.d.)</td>
</tr>
<tr>
<td>10</td>
<td>[Rh(cod)Cl]2</td>
<td>L7</td>
<td>5</td>
<td>30% (n.d.)</td>
</tr>
<tr>
<td>11</td>
<td>[Rh(cod)Cl]2</td>
<td>L8</td>
<td>5</td>
<td>30% (n.d.)</td>
</tr>
<tr>
<td>12</td>
<td>[Rh(cod)Cl]2</td>
<td>L9</td>
<td>5</td>
<td>0%</td>
</tr>
<tr>
<td>13</td>
<td>[Rh(cod)Cl]2</td>
<td>L10</td>
<td>5</td>
<td>40% (n.d.)</td>
</tr>
</tbody>
</table>

Ar of AsAr2:

**Note:** From enantioenriched 10l (99:1 e.r.).
**COMMUNICATION**

![Chemical structures](image-url)


[14] The intermediacy of species related to 3 has been exploited to re-establish and control a stereocenter during cycloaddition (see reference 9b). Reference 9g outlines an example where complete transfer of the stereocchemistry of a disubstituted cyclopropane occurs in a (3+2) cycloaddition.


[16] A similar competition experiment involving an aminocyclopropane vs a cyclopropanyl oxide resulted in an 84% yield of the product derived from insertion into the proximal C–C bond of the aminocyclopropane (see the SI). Reference 11e details an analogous experiment involving an aminocyclopropane vs an aminomethylcyclopropane. In these

**ACKNOWLEDGMENTS**

The Bristol Chemical Synthesis CDT, funded by EPSRC (ERC grant 639594 CatHet).

X-ray data is available under CCDC 1863328-1863331.

**Keywords:** rhodium, cyclopropane, C–C activation, cycloaddition.
insertion experiments, cationic Rh-sources mimic C-C bond activation selectivities observed for neutral Rh-systems under carbonylativ conditions.

[17] We propose electron rich N-protecting groups enhance π_{Ar}→σ^{*}_{C=N} interactions and thus amplify the amide directed C-C bond activation pathway proposed in Scheme 1C. Alternate rationalizations cannot be discounted.

[18] Enantiopure cyclopropyl carboxylic acid precursors are easily accessed (see the SI).

[19] We cannot discount a more involved role. For example, following cyclopropane coordination, the methoxy unit of L2 may facilitate C-C oxidative addition: A. G. Constable, C. R. Langrick, B. Shabanzadeh, B. L. Shaw, Inorg. Chim. Acta 1982, 65, L151. L2 also offers appreciable benefits for lower yielding processes reported in Table 1: 11f, 60% yield, >15:1 d.r.; 11g, 61% yield, >15:1 d.r.; 11h, 71% yield, >15:1 d.r. (see the SI).

[20] C-C bond activation selectivity (bond a vs b) is controlled by a balance of sterics and electronics. For cis-1,2-disubstituted systems, bond b is sufficiently accessible that activation at this more electron-rich site is preferred.

[21] A resubjection experiment suggests that erosion of diastereospecificity for 11x and 11z may occur by epimerization of the product (see the SI).

Carbonylative C-C Bond Activation of Electron-Poor Cyclopropanes: Rhodium-Catalyzed (3+1+2) Cycloadditions of Cyclopropylamides

Andrew G. Dalling, Takayuki Yamauchi, Niall G. McCreanor, Lydia Cox and John F. Bower*