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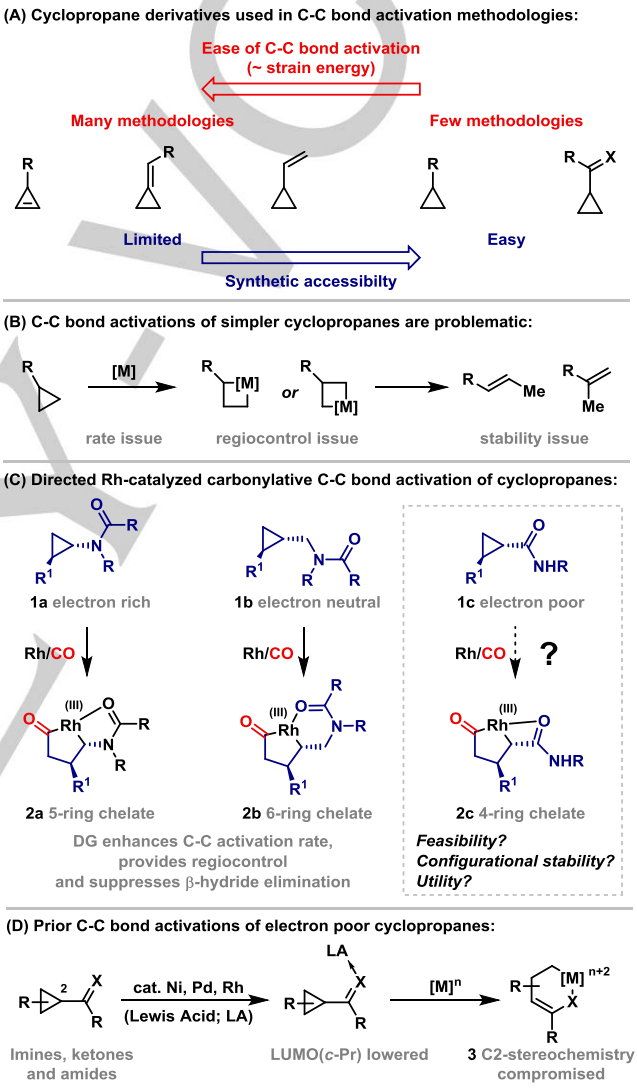
Carbonylative C-C Bond Activation of Electron-Poor Cyclopropanes: Rhodium-Catalyzed (3+1+2) Cycloadditions of Cyclopropylamides

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 cyclopropanes)[5,6] to enhance C-C oxidative addition and/or stabilize the ensuing organometallic 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.[1,2,8,9,10,11e] 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 metallacyclobutane, 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]

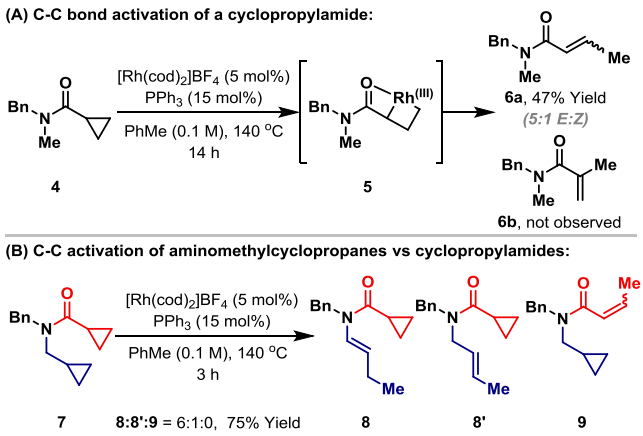
A key feature of our methodologies is that reaction efficiency decreases as the cyclopropane becomes less nucleophilic, an observation consistent with a dominant HOMO(*c*-Pr)-LUMO(Rh) interaction during C-C bond activation.[11,12] This interpretation led us to question the limits of this step with respect to the electronics of the cyclopropane and, specifically, whether cyclopropylamide-based processes might be feasible (**1c** to **2c**, Scheme 1C). The significance of this is evidenced by the scarcity of reports on C-C bond activation methodologies that harness simple electron poor cyclopropanes.[6,9,10,13] This type of initiation mode has not been used previously either for carbonylative processes or for multicomponent cycloadditions. Two component cycloadditions of cyclopropyl ketones, imines and amides have been reported using Rh-, Ni- or Pd-systems and are most effective in the presence of Lewis acid activators (Scheme 1D).[9] Such conditions are indicative of a dominant (1,4-addition-like) HOMO(M)-LUMO(*c*-Pr) interaction during C-C bond activation, a trait that commonly leads to oxa/azametallacyclohexenes **3**.[9] Accordingly, stereospecific transfer of cyclopropane stereochemistry is not easily achieved.[14] In this report, we describe Rh-catalyzed carbonylative C-C bond activations of cyclopropylamides within the context of powerful (3+1+2) cycloadditions. In contrast to the prior art,[9] these processes proceed via *configurationally stable* metallacycles (cf. **2c** vs **3**). *To our knowledge, these studies encompass the first examples of the efficient use of simple electron poor cyclopropanes in (a) multicomponent cycloadditions and (b) carbonylative processes.*[1a-c]



Scheme 1. Introduction.

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 PPh_3 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

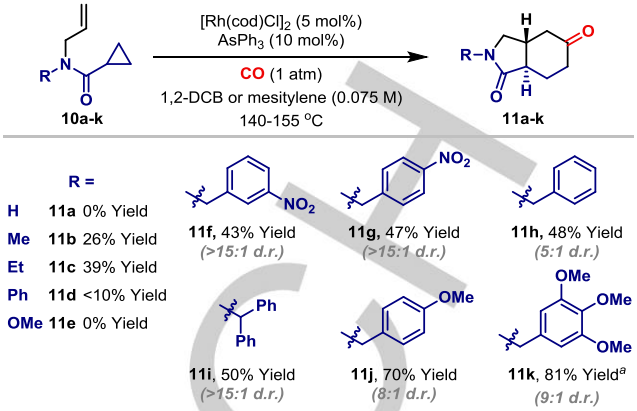
$[Rh(cod)_2]BF_4/PPh_3$ system (Scheme 2B). This resulted in exclusive activation of the aminomethylcyclopropane unit to provide a 6:1 ratio of **8** and **8'**; activation of the cyclopropylamide unit to give **9** was not observed. Accordingly, under Rh-catalyzed conditions, C-C bond activation of 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 $AsPh_3$ 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 **10f,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]

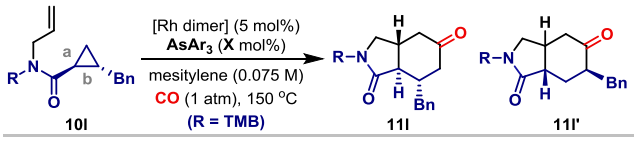
Table 1. Prototype (3+1+2) cycloadditions.



[a] $[Rh(coe)_2Cl]_2$ was used.

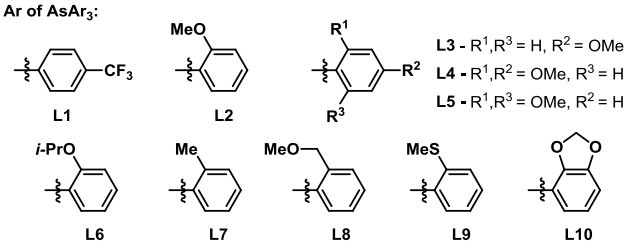
(3+1+2) cycloaddition to form **11j/k** was considered relatively facile; it was anticipated that substitution on the cyclopropane would render C-C bond activation more challenging. In this scenario, decomposition of the catalyst becomes problematic because its entry into the catalytic cycle is slower. Accordingly, ligand choice is of paramount importance in stabilizing the Rh-catalyst. Exposure of benzyl substituted system **10l** to the conditions used in Table 1 provided target **11l/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 $As(4\text{-}CF_3C_6H_4)_3$ (**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 $As(2\text{-}OMeC_6H_4)_3$ (**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 **10l** (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 oxa/azametallacyclohexenes **3** (Scheme 1D).[9] By contrast, the present method appears to proceed via configurationally stable metallacycles (**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.



Entry	Rh source	Ligand	X	Yield (11l:11l')
1	$[Rh(cod)Cl]_2$	$AsPh_3$	10	12% (n.d.)
2	$[Rh(cod)Cl]_2$	**L1**	10	36% (10:1)
3	$[Rh(cod)Cl]_2$	**L2**	10	30% (4:1) + 68% **10l**
4	$[Rh(coe)_2Cl]_2$	**L2**	5	65% (10:1) ***(99:1 e.r.)***[a]
5	$[Rh(coe)_2Cl]_2$	**L3**	5	42% (n.d.)
6	$[Rh(coe)_2Cl]_2$	**L4**	5	27% (n.d.)
7	$[Rh(coe)_2Cl]_2$	**L5**	5	17% (n.d.)
8	$[Rh(coe)_2Cl]_2$	**L6**	5	53% (n.d.)
9	$[Rh(coe)_2Cl]_2$	**L7**	5	30% (n.d.)
10	$[Rh(coe)_2Cl]_2$	**L8**	5	30% (n.d.)
11	$[Rh(coe)_2Cl]_2$	**L9**	5	0%
12	$[Rh(coe)_2Cl]_2$	**L10**	5	40% (n.d.)

Ar of $AsAr_3$:



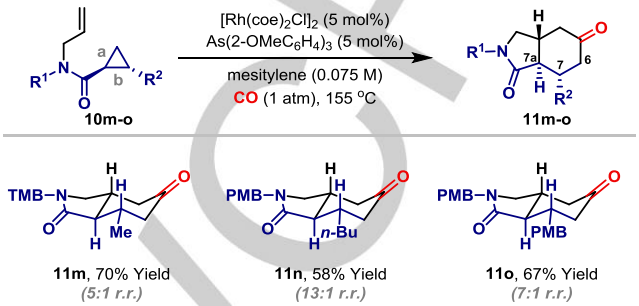
[a] From enantioenriched **10l** (99:1 e.r.).

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 diastereocontrol, 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).[20] Here, N-TMB systems offered higher efficiencies than PMB-protected variants. Even hindered *t*-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.

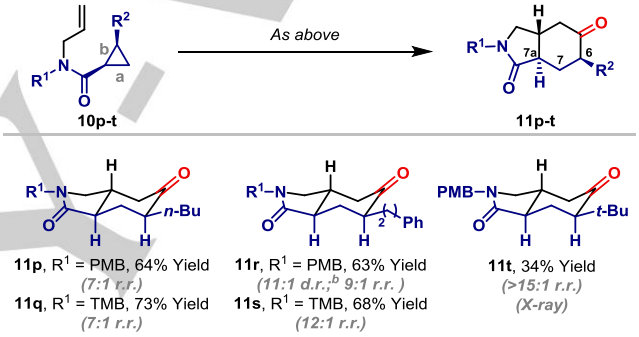
Further studies revealed that 1,1-disubstituted alkenes (**10u-w**) participate with good levels of diastereocontrol to provide products **11u-w** containing quaternary stereocenters at C3a (Table 4). For cycloadditions involving 1,2-disubstituted alkenes stereospecific transfer of olefin geometry provided **11x** and **11z**.[21] Systems with substituents at R^1 (**10aa-bb**) cyclized to provide complex heterocyclic ring systems **11aa-bb** 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**).

Table 3. Cycloadditions of disubstituted cyclopropanes.[a]

(A) (3+1+2) cycloadditions of *trans*-disubstituted cyclopropanes:



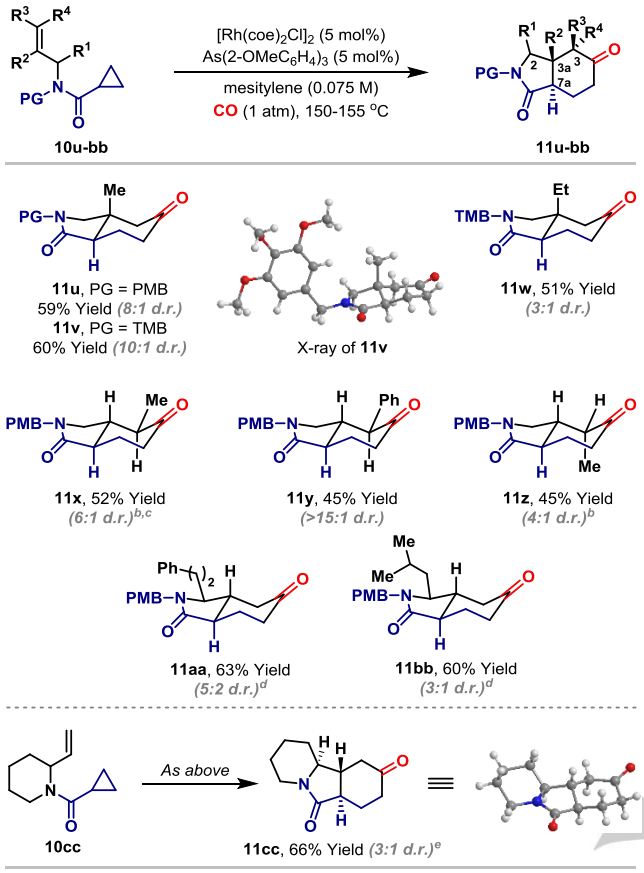
(B) (3+1+2) cycloadditions of *cis*-disubstituted cyclopropanes:



[a] Diastereomer ratios (>15:1 unless stated) of isolated material were consistent with those of crude material. Regioisomer ratios (r.r.) refer to C7 vs C6 substituted products (major product depicted). [b] (A:B d.r.) = A (depicted): B (invert C7a).

In summary, cyclopropylamides undergo Rh-catalyzed carbonylative C-C bond activation, and the ensuing multicomponent cycloadditions provide complex N-heterocycles with high levels of regio- and stereocontrol.[22] 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.[9] Other aspects of novelty include the first examples of the efficient use of simple electron poor cyclopropanes in (a) multicomponent cycloadditions and (b) carbonylative processes. A wide range of methodologies now use the strategy outlined in Scheme 1C;[11,12] consequently, application of the new initiation mode (**1c** to **2c**) in other settings can be envisaged.

Table 4. Substitution at other positions.[a]



[a] Diastereomer ratios of isolated material were consistent with those of crude material. [b] (A:B d.r.) = A (depicted): B (invert C3); [c] Run at 0.20 M; [d] (A:B d.r.) = A (depicted): B (invert C2); [e] (A:B d.r.) = A (depicted): B (invert C7a).

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

Keywords: rhodium, cyclopropane, C-C activation, cycloaddition

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[13] "Simple electron poor cyclopropane" describes an EWG-group substituted cyclopropane lacking additional activating units. For a radical-based enantioselective (3+2) cycloaddition of electron poor cyclopropanes, see: W. Hao, J. H. Harenberg, X. Wu, S. N. MacMillan, S. Lin, *J. Am. Chem. Soc.* **2018**, *140*, 3514.

[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 stereochemistry of a disubstituted cyclopropane occurs in a (3+2) cycloaddition.

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[16] A similar competition experiment involving an aminocyclopropane vs a cyclopropylamide 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

insertion experiments, cationic Rh-sources mimic C-C bond activation selectivities observed for neutral Rh-systems under carbonylative conditions.

[17] We propose electron rich N-protecting groups enhance $\pi_{Ar} \rightarrow \sigma^*_{(C\text{-}N)}$ 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).

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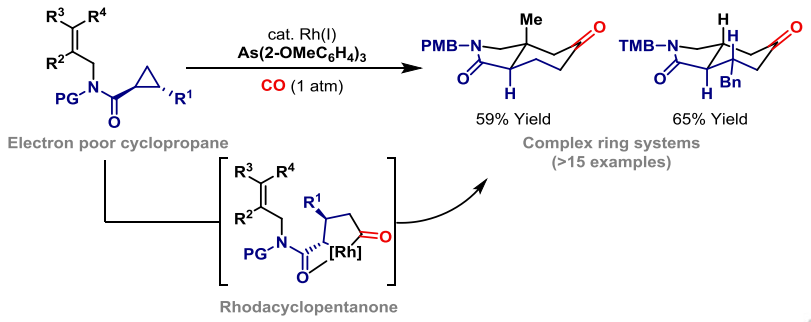

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