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Bridged Cyclopentane Synthesis via Catalytic Decarbonylative Cycloaddition between Cyclobutanones and Olefins

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Abstract

Herein we report an intramolecular rhodium-catalyzed decarbonylative coupling between cyclobutanones and alkenes via C–C activation, which provides a distinct approach to access a diverse range of saturated bridged cyclopentanes. In this reaction, cyclobutanones serve as a cyclopropane surrogate, offering a formal (4+2-1) transformation. To demonstrate the efficacy of this method, a concise synthesis of antifungal-drug Tolciclate was achieved.

Graphical Abstract

Decarbonylative “cut and sew”: an intramolecular decarbonylative coupling between cyclobutanones and alkenes is developed via Rh-catalyzed C–C activation, which provides a distinct approach to access a diverse range of saturated bridged cyclopentanes. In this reaction, cyclobutanones serve as a cyclopropane surrogate, offering a formal (4+2-1) transformation.

Keywords

decarbonylation; rhodium catalysis; cyclobutanone; C–C activation; cycloaddition

Cyclopentanes are widely found in various bio-active natural products, agrochemicals and pharmaceuticals (Figure 1).^[1] To date, many robust methods, such as 1,3-zwitterion addition, ring-closing metathesis, Pauson-Khand or Nazarov reactions, have been developed for preparing unsaturated or oxygenated five-membered carbocycles.^[2] However, direct synthesis of *saturated non-oxidized cyclopentanes* has been challenging due to the lack of

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handles for ring closure. An ideal approach to construct saturated cyclopentane rings would be a (3+2) cycloaddition between simple cyclopropanes and olefins. While activated cyclopropanes, including vinyl, methylene^[3] and donor-acceptor cyclopropanes,^[4] can effectively participate in various (3+2) cycloadditions (Scheme 1a), the coupling between normal unactivated cyclopropanes and olefins remains an elusive transformation to date (Scheme 1b).^[5]

Stimulated by the aforementioned difficulties of directly forming saturated cyclopentane rings, we conceived the strategy of *using cyclobutanones as a cyclopropane surrogate through a catalytic decarbonylation process*. It is expected that oxidative addition of a transition metal into the cyclobutanone α C–C bond, followed by CO extrusion, should lead to a similar metalla-cyclobutane as the one from direct activation of a cyclopropane (Scheme 1c). Consequently, a decarbonylative “cut and sew” sequence^[6] between a cyclobutanone and an olefin can be imagined through olefin migratory insertion and reductive elimination, which would offer a rapid synthesis of saturated non-oxidized cyclopentanes (Figure 2a). Herein we describe the development of a catalytic intramolecular decarbonylative coupling between cyclobutanones and alkenes for construction of saturated bridged cyclopentanes.

The challenge of this decarbonylative “cut and sew” process is associated with two major side reactions: 1) decarbonylation of cyclobutanones to give cyclopropanes^[7] and 2) regular “cut and sew” reaction, which is a (4+2) process^[8] (Figure 2b). Direct CO extrusion from cyclobutanones is known to be fast and efficient with a rhodium catalyst.^[7] Thus, if the olefin insertion is slow, the cyclopropane formation would be dominating. On the other hand, if the decarbonylation is too slow, a regular non-decarbonylative olefin insertion would compete to give cyclohexanone byproducts.

Our study began with cyclobutanone **1a**^[8e] as a model substrate, and a range of mono- and bidentate phosphine ligands were investigated (Table 1). Using bidentate ligands only yielded cyclopropane **3a** as the observable product. However, when electron-deficient monodentate $\text{P}(\text{C}_6\text{F}_5)_3$ was used, the desired (4+2-1) product (**2a**) was isolated albeit with cyclopropane **3a** as the predominating product (entry 1). While changing to PPh_3 resulted in low conversion of the starting material (entry 2), a promising result was obtained when electron-rich bulky PCy_3 ligand was employed (entry 3). We hypothesized that bulky monodentate ligands would avoid more than one phosphine ligand coordinating, and the resulting unsaturated metal center should promote olefin coordination (Figure 3).^[9]

Encouraged by this discovery, more sterically hindered ligands were tested. While the bulkier P^tBu_3 only gave a complex mixture of unidentifiable products (entry 5), Buchwald’s SPhos ligand^[10] afforded the bridged cyclopentane product **2a** as the major product in 44% yield (entry 6). Further study revealed that using more thermally stable $[\text{Rh}(\text{coe})_2\text{Cl}]_2$ as a pre-catalyst along with bulkier XPhos ligand at 160°C , the conversion of **1a** reached to 95% and product **2a** was formed in 63% yield (entry 8). While it is challenging to completely avoid cyclopropane formation, fine tuning the metal/ligand ratio and adjusting the reaction temperature (for more details, see SI), 69% yield of the (4+2-1) bridged bicycle was obtained (entry 14), which can be easily separated and purified.^[11] The structure of **2a** was unambiguously characterized by X-ray crystallography.^[12]

The substrate scope of the decarbonylative alkene insertion was then examined (Table 2). First, various substituents at the cyclobutanone C3 position were found suitable for this reaction (entries 1–6). In particular, cyclobutanones bearing a hydrogen substituent at the C3 position (**1f**) are known to undergo facile β -hydrogen elimination upon C–C cleavage to give various ring-opening products;^[7,13] however, the desired 5–6 bicycle (**2f**) was still isolated in 48% yield. It is likely that the bulky XPhos ligand inhibited β -hydrogen elimination.^[14] Not surprisingly, increasing the steric hindrance of the olefin hampered the 2π -insertion, leading to more cyclopropane byproducts. Nevertheless, the substrate containing a 1,1-disubstituted alkene (**1g**) still gave the decarbonylative cycloaddition product in 58% yield.^[15] When spirocyclic compound **1h** reacted under the standard conditions, a novel 5–6–5 fused/bridged scaffold (**2h**) was isolated in 61% yield as a single diastereomer. Changing the *N*-protecting group from Ts to Ns (**1i**) did not significantly affect the reactivity (entry 9).^[16]

Apart from those with nitrogen linkers, substrates with an arene backbone (**1j–1q**) proved to be more reactive towards cycloaddition. Instead of cyclopropane formation, the (4+2) coupling (between the cyclobutanone and alkene) was found to be the major competing reaction pathway.^[8] For example, under the standard conditions, substrate **1j** produced an equal amount of (4+2-1) and (4+2) products in 90% total yield. We hypothesized that the CO pressure would play an important role on the product selectivity, and by reducing the CO concentration the decarbonylative pathway might be accelerated. Indeed, by choosing a reaction vessel with a significantly larger gas space (switching from an 8 mL to 40 mL vial), the desired benzo [2.2.1] bicycle (**2j**) was formed in 86% yield (entry 10). Gratifyingly, the reaction with a 1,1-disubstituted alkene (**1k**) also gave a high yield owing to the more reactive arene linkage (entry 11). In addition, many functional groups are tolerated (entries 12–17), which shows promise for applications into complex molecule synthesis.

As cyclopropane formation and regular (4+2) “cut and sew” were the major side reactions observed, it is reasonable to question if the (4+2-1) product comes from a (3+2) cycloaddition between cyclopropane and olefin, or from decarbonylation of the (4+2) cyclohexanone product. To gain more mechanistic insights, two control experiments were performed (Scheme 2). When cyclopropane **3a** and (4+2) product **4** were subjected to the standard decarbonylative coupling conditions respectively, neither reaction resulted in any product **2a**. These observations suggest that 1) the cyclopropane formation or the (4+2) cyclization unlikely stays in the catalytic cycle; 2) product **2a** should directly come from the cyclobutanone precursor through C–C cleavage, CO de-insertion, olefin migratory insertion and reductive elimination, although the timing of the decarbonylation step remains to be defined.

Further, the decarbonylative “cut and sew” products can be conveniently derivatized (Scheme 3). For example, the *N*-Ts group can be removed under mild conditions and converted to an acetyl group. In addition, lactam **6** or imide **7** could be obtained in high yields through C–H oxidation.^[17] Moreover, a photo-induced C–H cyanation protocol can be employed to afford α -amino nitriles efficiently.^[18]

Finally, to demonstrate the applicability of this (4+2-1) method, synthesis of Tolciclate, an antifungal drug (used in its racemic form),^[19] was achieved in two steps from bridged ring **13** through demethylation and thiocarbamate formation (Scheme 4).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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11. For substrate 1a with a nitrogen linker, the regular (4+2) product was not observed under these conditions.
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15. Formation of 39% cyclopropane product was observed.
16. Other nitrogen protecting groups, such as carbamate, acyl and benzyl groups, did not afford the desired product.
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Figure 1. Representative natural products or pharmaceutical compounds containing bridged cyclopentanes.

Figure 2.
Reactivity landscape of cyclobutanone activations.

Figure 3.
Ligand effect on the selectivity

a. activated cyclopropanes **b. (3+2) between regular cyclopropanes and olefins** **c. cyclobutanone as cyclopropane surrogate**

Scheme 1.
Cyclopentane formation via C–C activation.

Scheme 2.
Control experiments.

Scheme 3.

Synthetic applications. Brsm= based on recovered starting materials

Scheme 4.
Synthesis of Tolciclate.

Table 1

Selected optimization for the decarbonylative cycloaddition between cyclobutanones and olefins.

Entry	[Rh]	Ligand (mol%)	Temp (°C)	Conv.(%)	Yield (%) ^[a]
					2a 3a
1	[Rh(C ₂ H ₄) ₂ Cl] ₂	P(C ₆ F ₅) ₃ (24)	160	60	6 53
2	[Rh(C ₂ H ₄) ₂ Cl] ₂	PPh ₃ (24)	160	20	8 8
3	[Rh(C ₂ H ₄) ₂ Cl] ₂	PCy ₃ (24)	160	70	28 42
4	[Rh(C ₂ H ₄) ₂ Cl] ₂	PCy ₃ (12)	160	33	18 14
5	[Rh(C ₂ H ₄) ₂ Cl] ₂	(<i>n</i> -Bu) ₃ P (10)	160	100	0 0
6	[Rh(C ₂ H ₄) ₂ Cl] ₂	SPhos (12)	160	82	44 32
7	[Rh(C ₂ H ₄) ₂ Cl] ₂	XPhos (12)	160	76	48 27
8	[Rh(coe) ₂ Cl] ₂	XPhos (12)	160	95	63 30
9	[Rh(coe) ₂ Cl] ₂	XPhos (10)	160	99	65 32
10	[Rh(coe) ₂ Cl] ₂	RuPhos (10)	160	100	55 44
11	[Rh(coe) ₂ Cl] ₂	Davephos (10)	160	95	50 45
12	[Rh(coe) ₂ Cl] ₂	CyJohnPhos (10)	160	90	49 40
13	[Rh(coe) ₂ Cl] ₂	BrettPhos (10)	160	5	0 0
14	[Rh(coe)₂Cl]₂	XPhos (10)	170	100	69 29

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¹H NMR using mesitylene as the internal standard. PCy₃ = tricyclohexylphosphine, coe = cyclooctene.

Table 2

substrate scope ^[a]

Entry	Substrate	Product/Yield ^[b]
1	1a	2a 67%
2	1b	2b 68%
3	1c	2c 67%
4	1d	2d 65%
5	1e	2e 56%
6	1f	2f 48%
7 ^[c]	1g	2g 58%
8	1h	2h 61%
9 ^[d]	1i	2i 63%

^[a] Each reaction was run on a 0.1 mmol scale in a sealed 8 mL vial, using 5 mol% [Rh(coe)₂Cl]₂ and 10 mol% XPhos in 1,4-dioxane (1.4 mL) at 170 °C for 72 h.

^[b] Isolated yields. For the yields of the corresponding cyclopropane or (4+2) byproducts, see SI.

^[c] a 4 mL vial was used.

^[d] Ns: 2-nitrobenzenesulfonyl.

^[e] for entries 10–17, 40 mL vials were used.

^[f] NMR yield using mesitylene as the internal standard.

^[g] 2.5 mol% [Rh(coe)₂Cl]₂ and 5 mol% XPhos.

^[h] 0.7 mL of 1,4-dioxane.