C–C Activation

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Synthesis of Bridged Cyclopentane Derivatives by Catalytic Decarbonylative Cycloaddition of Cyclobutanones and Olefins

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Abstract: *Herein, we report an intramolecular rhodium-catalyzed decarbonylative coupling between cyclobutanones and alkenes that proceeds by C–C activation and provides a distinct approach to a diverse range of saturated bridged cyclopentane derivatives. In this reaction, cyclobutanones serve as cyclopropane surrogates, reacting in a formal (4+2−1) transformation. To demonstrate the efficacy of this method, it was applied in a concise synthesis of the antifungal drug Tolciclate.*

Cyclopentanes are widely found in various bioactive natural products, agrochemicals, and pharmaceuticals (Figure 1).[1] To date, many robust methods, such as 1,3-zwitterion addition, ring-closing metathesis, Pauson–Khand, and Nazarov reactions, have been developed for preparing unsaturated or oxygenated five-membered carbocycles.[2] However, the direct synthesis of saturated, non-oxygenated cyclopentanes has been challenging owing to the lack of synthetic handles for ring closure. An ideal approach to construct saturated cyclopentane rings would be a (3+2) cycloaddition between simple cyclopropanes and olefins. Whereas 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 has remained elusive (Scheme 1b).[5]

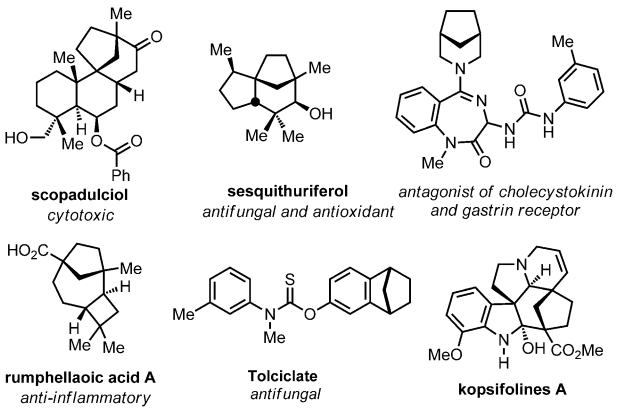
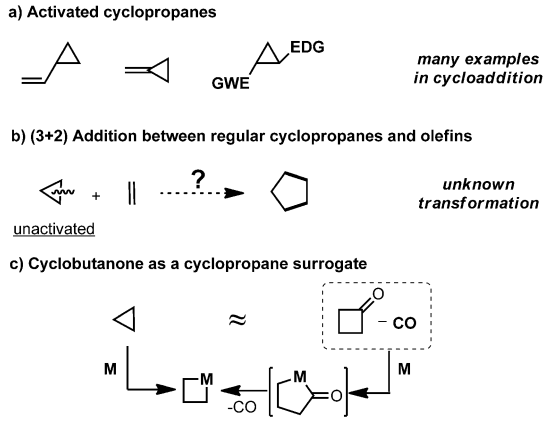


Figure 1. Representative natural products and pharmaceuticals containing bridged cyclopentanes.



Scheme 1. Cyclopentane formation by C–C activation. EDG = electron-donating group, EWG = electron-withdrawing group.

Stimulated by the aforementioned difficulties of directly forming saturated cyclopentane rings, we considered using cyclobutanones as cyclopropane surrogates in a catalytic decarbonylation process. It was expected that the oxidative addition of a transition metal into the cyclobutanone α-C–C bond followed by CO extrusion should lead to a similar metallacyclobutane as the one that is obtained by direct activation of a cyclopropane (Scheme 1c). Consequently, a decarbonylative "cut and sew" sequence[6] between a cyclobutanone and an olefin can be imagined that proceeds through olefin migratory insertion and reductive elimination, and would enable the rapid synthesis of saturated non-oxygenated cyclopentanes (Figure 2a). Herein, we describe the development of a catalytic intramolecular decarbonylative coupling between cyclobutanones and alkenes for the construction of saturated bridged cyclopentanes.

The challenges of this decarbonylative cut-and-sew process are associated with two major side reactions: 1) decarbonylation of the cyclobutanone to give a cyclopropane,[7] and 2) the regular (4+2) cut-and-sew process[8] (Figure 2b). Direct CO extrusion from cyclobutanones is known to be

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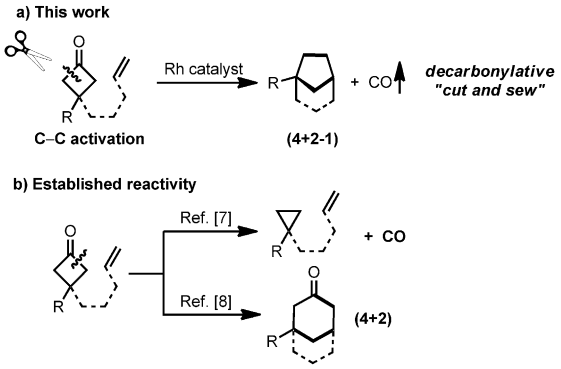


Figure 2. Reactivity landscape of cyclobutanone activation.

fast and efficient with rhodium catalysts.[7] Thus, if olefin insertion is slow, cyclopropane formation will dominate. On the other hand, if the decarbonylation step is too slow, regular, non-decarbonylative olefin insertion would compete to give cyclohexanone side products.

Our study began with cyclobutanone **1a**[8e] as a model substrate, and a range of mono- and bidentate phosphine ligands were investigated (Table 1). The use of bidentate ligands yielded cyclopropane **3a** as the only observable product. However, when electron-deficient monodentate $P(C_6F_5)_3$ was used, the desired (4+2−1) product (**2a**) was isolated, albeit with cyclopropane **3a** as the dominating product (entry 1). Whereas 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 was employed as the ligand (entry 3). We hypothesized that bulky monodentate ligands prevent the coordination of more than one phosphine ligand, and that the resulting unsaturation of the metal center should promote olefin coordination (Figure 3).[9]

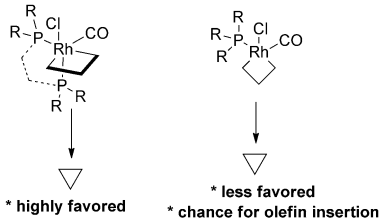
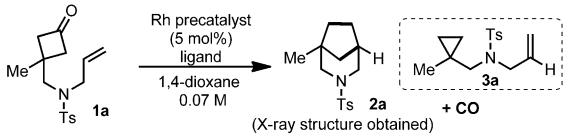


Figure 3. Ligand effect on the selectivity.

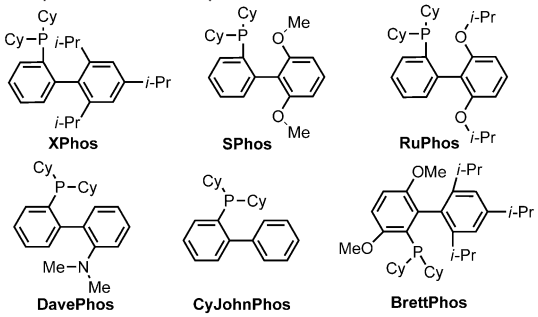
Encouraged by this discovery, more sterically hindered ligands were tested. Whereas bulkier $P(t\text{-Bu})_3$ gave a complex mixture of unidentifiable products (entry 5), Buchwald's SPhos ligand[10] afforded bridged cyclopentane **2a** as the major product in 44% yield (entry 6). Further investigations revealed that when more thermally stable $[Rh(coe)_2Cl]_2$ was used as the precatalyst along with bulkier XPhos at 160 °C, the conversion of **1a** reached 95%, and product **2a** was formed in 63% yield (entry 8). Whereas it is challenging to completely avoid cyclopropane formation, upon fine-tuning the metal/ligand ratio and adjusting the reaction temperature (for more details, see the Supporting Information), we were able to obtain the (4+2−1) bridged bicycle in 69% yield (entry 14), which could be easily separated and purified.[11] The structure of **2a** was unambiguously determined by X-ray crystallography.[12]

Table 1: Optimization of the decarbonylative cycloaddition between cyclobutanones and olefins (selected results).



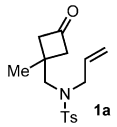
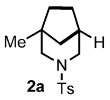
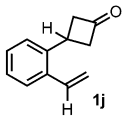
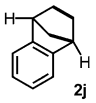
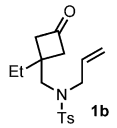
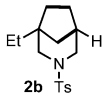
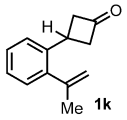
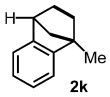
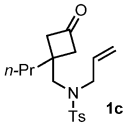
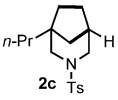
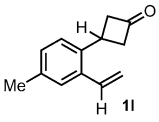
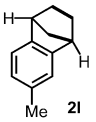
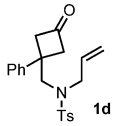
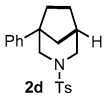
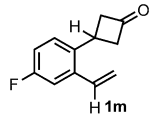
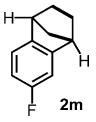
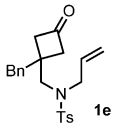
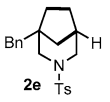
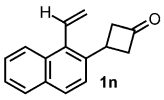
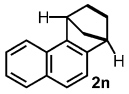
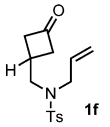
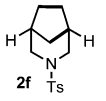
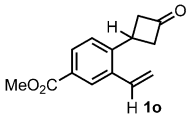
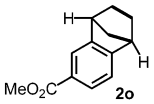
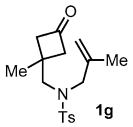
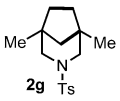
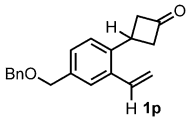
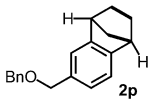
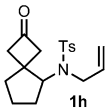
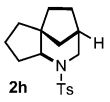
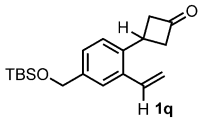
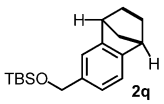
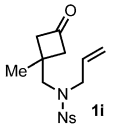
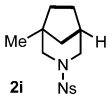
Entry	[Rh]	Ligand (mol%)	*T* [°C]	Conv. [%]	Yield[a] [%] **2a**	**3a**
1	$[Rh(C_2H_4)_2Cl]_2$	$P(C_6F_5)_3$ (24)	160	60	6	53
2	$[Rh(C_2H_4)_2Cl]_2$	PPh_3 (24)	160	20	8	8
3	$[Rh(C_2H_4)_2Cl]_2$	PCy_3 (24)	160	70	28	42
4	$[Rh(C_2H_4)_2Cl]_2$	PCy_3 (12)	160	33	18	14
5	$[Rh(C_2H_4)_2Cl]_2$	$(t\text{-Bu})_3P$ (10)	160	100	0	0
6	$[Rh(C_2H_4)_2Cl]_2$	SPhos (12)	160	82	44	32
7	$[Rh(C_2H_4)_2Cl]_2$	XPhos (12)	160	76	48	27
8	$[Rh(coe)_2Cl]_2$	XPhos (12)	160	95	63	30
9	$[Rh(coe)_2Cl]_2$	XPhos (10)	160	99	65	32
10	$[Rh(coe)_2Cl]_2$	RuPhos (10)	160	100	55	44
11	$[Rh(coe)_2Cl]_2$	DavePhos (10)	160	95	50	45
12	$[Rh(coe)_2Cl]_2$	CyJohnPhos (10)	160	90	49	40
13	$[Rh(coe)_2Cl]_2$	BrettPhos (10)	160	5	0	0
14	**$[Rh(coe)_2Cl]_2$**	**XPhos (10)**	**170**	**100**	**69**	29

[a] Yields determined by ^1H NMR analysis using mesitylene as the internal standard. coe = cyclooctene, PCy_3 = tricyclohexylphosphine, Ts = *para*-toluenesulfonyl.



Cyclobutanones with various substituents at the C3 position were found to be suitable substrates 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 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 larger quantities of the cyclopropane side products. Nevertheless, a 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, the novel 5-6-5 fused/bridged scaffold (**2h**) was isolated in 61% yield as a single diastereomer. Changing the nitrogen protecting group from

Table 2: Substrate scope.[a]

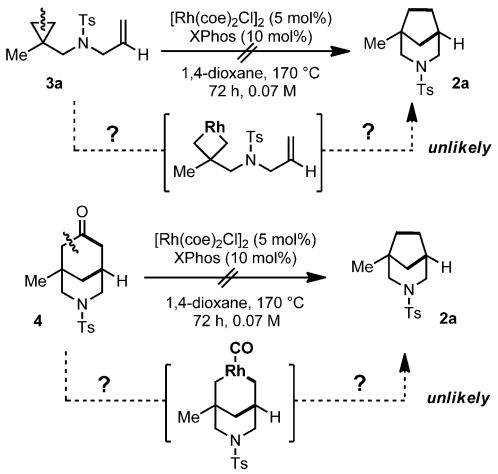
Entry	Substrate	Product	Yield [%][b]	Entry	Substrate	Product	Yield [%][b]
1	 **1a**	 **2a**	67	10[e]	 **1j**	 **2j**	86[f] 70[f,g]
2	 **1b**	 **2b**	68	11[e]	 **1k**	 **2k**	80
3	 **1c**	 **2c**	67	12[e]	 **1l**	 **2l**	83
4	 **1d**	 **2d**	65	13[e]	 **1m**	 **2m**	80
5	 **1e**	 **2e**	56	14[e]	 **1n**	 **2n**	82
6	 **1f**	 **2f**	48	15[e,h]	 **1o**	 **2o**	58
7[c]	 **1g**	 **2g**	58	16[e,h]	 **1p**	 **2p**	78
8	 **1h**	 **2h**	61	17[e,h]	 **1q**	 **2q**	76
9[d]	 **1i**	 **2i**	63				

[a] Each reaction was run on 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] Yields of isolated products. For the yields of the corresponding cyclopropane and (4+2) side products, see the Supporting Information. [c] A 4 mL vial was used. [d] Ns = 2-nitrobenzenesulfonyl. [e] For entries 10–17, 40 mL vials were used. [f] Yield determined by ^{1}H NMR spectroscopy using mesitylene as the internal standard. [g] $[Rh(coe)_2Cl]_2$ (2.5 mol%) and XPhos (5 mol%). [h] 1,4-Dioxane (0.7 mL). Bn = benzyl, TBS = *tert*-butyldimethylsilyl.

Ts to Ns (**1i**) did not significantly affect the reactivity (entry 9).[16]

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

As cyclopropane formation and regular (4+2) cut-and-sew addition were the major side reactions, we asked ourselves whether the (4+2−1) product originates from a (3+2) cycloaddition between cyclopropane and olefin or from decarbonylation of the (4+2) cyclohexanone product. To gain more mechanistic insight, two control experiments were conducted (Scheme 2). When cyclopropane **3a** or (4+2) product **4** was subjected to the standard decarbonylative coupling conditions, product **2a** was not formed. These

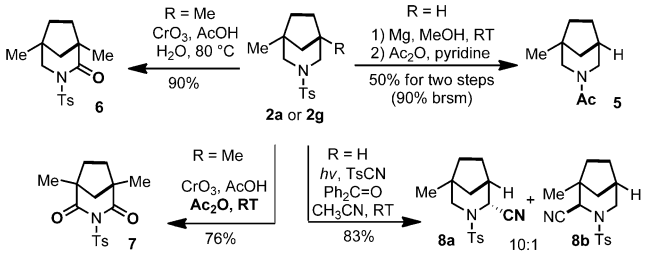


Scheme 2. Control experiments.

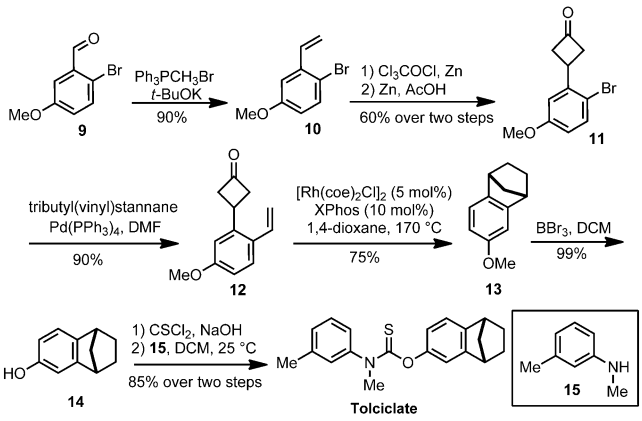
observations suggest that 1) the cyclopropane formation and the (4+2) cyclization are unlikely part of the catalytic cycle, and that 2) product **2a** should be directly formed from the cyclobutanone precursor through C−C cleavage, CO de-insertion, olefin migratory insertion, and reductive elimination, although the timing of the decarbonylation step remains to be defined.

Furthermore, the decarbonylative cut-and-sew products can be conveniently derivatized (Scheme 3). For example, the *N*-tosyl group can be removed under mild conditions and converted into an acetyl group. In addition, lactam **6** and imide **7** were obtained in high yields through C−H oxidation.[17] Moreover, a photoinduced C−H cyanation reaction afforded α-amino nitriles in an efficient process.[18]

Finally, to demonstrate the applicability of this (4+2−1) method, we employed it for the synthesis of Tolciclate, an antifungal drug (used in its racemic form).[19] This compound



Scheme 3. Synthetic applications. brsm = based on recovered starting material.



Scheme 4. Synthesis of Tolciclate.

was obtained in two steps from bridged intermediate **13** through demethylation and thiocarbamate formation (Scheme 4).

Acknowledgements

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Keywords: C−C activation · cycloaddition · cyclobutanones · decarbonylation · rhodium catalysis

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[15] The cyclopropane product was formed in 39% yield.

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