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Rh^I-Catalyzed Decarbonylative Spirocyclization via C–C Cleavage of Benzocyclobutenones: An Efficient Approach to Access Functionalized Spirocycles

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Abstract

We describe a rhodium-catalyzed all-carbon spirocenter formation through a decarbonylative coupling of trisubstituted cyclic olefins and benzocyclobutenones via C–C activation. A [Rh(CO)₂Cl]₂/P(C₆F₅)₃ metal-ligand combination was found to catalyze this transformation most efficiently. A range of diverse spirocyclic rings were synthesized in good to excellent yields and many sensitive functional groups were tolerated. Mechanistic study supports the hydrogen-transfer process that occurs via a β-H elimination/decarbonylation pathway.

Keywords

C–C activation; homogeneous catalysis; rhodium; spirocycle; decarbonylation

Catalytic carbon–carbon bond (C–C) activation/functionalization provides a unique platform to develop novel transformations that are otherwise challenging using conventional approaches.^[1] In particular, C–C activation that involves a decarbonylation process is of significant synthetic value because it allows for the preparation of compounds that lack a carbonyl moiety from a more readily available ketone precursor.^[2] Given the ubiquity of carbonyl compounds, the decarbonylative C–C activation followed by new C–C formation process would potentially offer a distinct synthetic strategy using carbonyl groups as a “traceless handle”.

(1)

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Supporting information for this article is available on the WWW under <http://www.angewandte.org>

Although highly attractive, the decarbonylative C–C activation strategy has been largely limited to its reaction scope. Previous efforts primarily involved a direct CO extrusion to give the corresponding hydrocarbon products (eq 1).^[3,4] Only a few examples are known to engage the addition of simple olefins (eq 2).^[5] To advance the scope and applicability of the decarbonylative C–C activation/functionalization strategy, new classes of synthetically useful transformations are highly sought. Herein we describe our development of a rhodium-catalyzed decarbonylative spirocyclization reaction through an intramolecular coupling between olefins and benzocyclobutenones (Figure 1), in which the reaction course can be controlled by the choice of the ligand on the metal catalyst.

Recently, we developed a Rh-catalyzed intramolecular carboacylation between benzocyclobutenones and olefins.^[6] This “cut and sew” transformation begins with the oxidative addition of Rh^I into the benzocyclobutenone C₁–C₂ bond, which is followed by migratory insertion into the olefin to give a seven-membered metallocycle (**C**), and subsequent reductive elimination to afford fused-ring systems (**D**). However, if a β-H elimination/decarbonylation process can be promoted instead of direct C–C reductive elimination, spirocycles containing all-carbon quaternary centers would be rapidly constructed when cyclic trisubstituted olefins were employed as the coupling partner (Figure 1). Given that spirocycles are important structural motifs often found in bioactive natural products whereas efficient synthesis of functionalized spirocycles has heretofore been challenging,^[7] this decarbonylative C–C activation strategy would provide a complementary approach to the previous spirocyclization methods.^[8] However, the challenge here is how can one promote the β-H elimination and decarbonylation instead of direct reductive elimination?

(3)

Previously, we discovered that bidentate phosphine ligands bearing a large bite-angle promoted direct reductive elimination; however, a Lewis acid is needed to enhance the electrophilicity of the substrate to permit coupling with poly-substituted olefins (eq 3).^[6a] We hypothesized that the use of monodentate π-acidic ligands (inspired by a recent work of Tang^[9]) would benefit spirocycle formation in two different aspects: 1) the faster ligand exchange (compared to bidentate ligands) would facilitate forming open coordination sites on the Rh, which in turn could favor both β-H elimination and CO deinsertion; 2) the more electron-deficient catalyst would coordinate more strongly with the trisubstituted olefins thus enhancing subsequent migratory insertion.^[10]

To test our hypothesis, compound **1a** that previously gave the tetracyclic “cut and sew” product (**2a**, eq 3) was employed as the model substrate for the spirocycle formation. A number of Rh^I precatalysts and phosphine ligands were examined. Indeed, when electron-rich or bidentate ligands, such as PCy₃, dppb and dppf, were employed, no desired decarbonylative spirocyclization product was obtained; in contrast, use of the more electron-poor [Rh(CO)₂Cl]₂ alone produced the 2*H*-benzofuran-[4.5]-spirocycle (**3a**) in ca 3% yield (entry 1, Table 1). Use of an acac ligand on the Rh *versus* Cl was found to be detrimental to the catalyst reactivity, leading to slight decomposition of **1a** (entry 2, Table 1). The *in situ* generated cationic Rh^I led to the dealkylation of **1a** to give 3-OH-benzocyclobutenone (entry 3, Table 1). Use of the more electron-rich PPh₃ or highly electron-deficient phosphites as the ligands completely shut down the catalyst reactivity (entries 4–6, Table 1).

However, we found that employment of the π -acidic triarylphosphine ligands significantly promoted formation of the desired spirocycle **3a** (entries 7–11, Table 1), among which the $P(C_6F_5)_3$ ligand proved to be most efficient. Finally, simply by lowering the ligand/metal ratio to 1:1, formation of the undesired reductive-elimination product (**2a**) was significantly inhibited; spirocycle **3a** was isolated as the major product in a 72% yield (entry 10, Table 1). Presumably, when less ligand is present, the metal tends to provide open coordination sites for β -H elimination.^[10] It is interesting to note that under these reaction conditions the C_3 -olefin isomer (after one chain-walk^[11]) of the spirocycle product was selectively afforded (for a mechanistic study, *vide infra*).^[12,13] Further lowering the ligand/metal ratio to 0.5:1 gave a similar result (entry 11, Table 1).

The scope of this decarbonylative spirocyclization was investigated (Table 2). First, cyclic olefins with different ring sizes were examined. To our delight, 5, 6, 7, 8 and 12-membered ring substrates all underwent this transformation smoothly (entries 1–5, Table 2); a single olefin isomer was observed except for the 5-membered ring substrate (entry 2, Table 2). Intriguingly, spirocyclization of the 12-membered ring substrate (**1e**) proceeded to give a *trans*-olefin in 90% yield without further alkene isomerization (entry 5, Table 2). The enhanced reactivity of substrate **1e** is likely attributed to a transannular interaction caused by the 12-membered cycle.^[14] The structures of spirocycles **3a**, **3c** and **3d** were unambiguously confirmed by X-ray crystallography. Electron-deficient olefins, such as an enone, also reacted, albeit with a lower conversion (entry 6, Table 2). It is noteworthy that this spirocycle formation method is highly chemoselective and a variety of sensitive functional groups, including dienes, ketones, enamides, esters, benzyl and vinyl ethers, and unprotected tertiary alcohols are tolerated (entries 6–10, 15, 16, Table 2), which is likely attributed to the near neutral reaction conditions. For example, when dihydrobenzopyran **1h** was employed as the substrate, the vinyl ether-based spirocycle was isolated in 71% yield (entry 8, Table 2).

In addition, when the C_8 -methoxy substituted benzocyclobutenone **1j** was utilized, the spirocycle containing a benzyl ether moiety (**3j**) was isolated in 59% yield as a single isomer (Table 2, entry 10). While the exact reason is still unclear, the presence of the C_8 -methoxy group likely promotes a faster C–H reductive elimination rather than olefin migration.^[10] Interestingly, the demethoxy spirocycle (**3b**) was also isolated in 18% yield.^[15] Furthermore, we discovered that, besides forming benzofuran-based products, other classes of spirocycles can also be efficiently synthesized: first, this transformation works well with substrates lacking an ether linkage (entry 11, Table 2); second, the 6-membered ring forming cyclization proceeded equally well to give benzopyrane-based spirocycle **3l** in 79% yield (entry 12, Table 2). Note that, except for substrates **1a**, **1i** and **1m**,^[16] no direct reductive elimination (the “cut and sew”) product was observed for other substrates depicted in Table 2. In addition, substrates with different substitutions at the C_4 and C_5 positions of the benzocyclobutenone also proceeded the spirocyclization smoothly (entries 13–16, Table 2).^[17] It is encouraging to note that substitutes with different steric and electronic properties, including methyl, 1-butyl-1-hydroxypentyl and methyl ester groups, all provided good yields of the desired spirocycles.^[17b]

(4)

To provide mechanistic insights for this transformation, a deuterium-labeling experiment (eq 4) was designed. Substrate **1n** was readily synthesized from propargyl alcohol and D₂-paraformaldehyde in five steps with an overall yield of 44% (for details, see supporting information). Subjecting **1n** to the standard decarbonylative spirocyclization conditions, spirocycle **3n** with >95% deuterium-incorporation at the methyl group was isolated in 79% yield. This experiment strongly supports our hypothesis that this transformation underwent a β -H elimination, decarbonylation and then C–H reductive elimination pathway (*vide supra*, Figure 1).

Another mechanistic puzzle regards the selective olefin chain-walk with most substrates. It was postulated that two reaction pathways are possible for the olefin migration: 1) alkene isomerization **after** the decarbonylative spirocyclization [i.e. the C₃-isomer comes from the C₂-isomer]; 2) alkene isomerization **during** the decarbonylative spirocyclization [i.e. the C₃- and C₂-isomers are formed independently]. Compounds **3i** and **3i'** were chosen as the model compounds because they can be readily separated through column chromatography. When pure **3i** and **3i'** were subjected to the standard reaction condition (shown in Table 2) respectively, no isomerization for either product was observed after 36 h (eq 5), which indicates the [Rh(CO)₂Cl]₂/P(C₆F₅)₃ system cannot isomerize the alkenes in the products.

(5)

(6)

(7)

(8)

A cross-over experiment was also carried out to examine whether the intermediates generated in the catalytic cycle, e.g. a Rh^{III}-H species, can isomerize the alkenes. Subjection

of compounds **1b** and **3i** under the standard reaction conditions provided **3b** in 80% yield but no isomerization of **3i** was found (eq 6). When the reactions of **1i** and **1b** were monitored separately over time, the ratio between the C₂ and C₃ isomers remained largely unchanged (eqs 7 and 8), which is consistent with our earlier observation for substrate **1a**.^[13] Combining with the deuterium-labeling experiment (eq 4), these studies suggest that the olefin chain-walk likely occurs **during** (instead of **after**) the process of the spirocycle formation, thus the C₂ and C₃ isomers are expected to form independently (not shown in Figure 1).

(9)

Furthermore, we found this transformation is not limited to cyclic trisubstituted olefins, as the linear disubstituted olefins also underwent the decarbonylative cyclization to provide the cyclization products. While coupling of linear tri-substituted alkenes proved challenging,^[18] reactions with the 1,2-disubstituted olefins proceeded smoothly (eq 9).^[19] It is interesting to note that the olefin geometry does not significantly affect the reactivity.

In conclusion, we have developed a Rh-catalyzed decarbonylative spirocyclization of olefins and benzocyclobutenones via C–C activation, which provides a complementary but distinct way to generate all-carbon spirocenters. This reaction exhibits several key features. First, it operates at near neutral reaction conditions, and therefore tolerates many acid or base-sensitive functional groups, which represents a major advantage over classical spirocycle syntheses. Second, it has a broad substrate scope (both electron-rich and -poor olefins react) providing a range of structurally diversified spirocycles, which indicates great potential for application in complex molecule synthesis. Furthermore, to the best of our knowledge, this represents the only report that couples C–C activation, olefin insertion, β-H elimination and decarbonylation into a one-reaction sequence. The unique mode of reactivity described here may provide broad implications for designing new tandem transformations. Further expansion of the substrate/reaction scope and the development of an enantioselective version of this reaction^[20] are ongoing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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- [15]. The mechanism for the formation of **3b** is unclear.

- [16]. For substrate **1i**, the corresponding “cut and sew” product (**2i**) was isolated in a 14% yield. For substrate **1m**, the corresponding “cut and sew” product (**2m**) was isolated in a 12% yield.
- [17]. a) The C₆-substituted substrate was found challenging to prepare; b) The C₅-ester-substituted substrate **1s** has been attempted twice under the decarbonylative spirocyclization conditions (eq 10). The desired spirocycle was obtained albeit in a lower yield with decomposition of the starting material (the exact reason is unclear).

(10)

- [18]. A linear trisubstituted olefin substrate (**1t**) was also synthesized and tested under the reaction conditions (eq 11). The desired decarbonylative cyclization product **3t** was obtained, albeit in a low yield (low conversion), which is likely due to the steric hindrance of the alkene group.

(11)

- [19]. The cyclization product from eq 9 contains several olefin isomers.
- [20]. Not surprisingly, when monophos was employed as the chiral ligand for this transformation, no desired spirocyclization product was observed (*vide supra*, entries 5 and 6, Table 1). Chiral monodentate electron-deficient triarylphosphines will be developed and investigated for the asymmetric transformation in due course.
- [21]. CCDC 962877 (**3a**), 962878 (**3c**), and 962879 (**3d**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Figure 1. Rh^{I} -catalyzed decarbonylative coupling between olefins and benzocyclobutenones via C–C activation.

Table 1

Selected optimization conditions

Entry	Precatalyst	Ligand/Additive	Yield ^[a]	
			3a/4a	2a
1	$[\text{Rh}(\text{CO})_2\text{Cl}]_2$	none	3% / <1%	2%
2 ^[b]	$\text{Rh}(\text{CO})_2\text{acac}$	none	0%	0%
3 ^[c]	$[\text{Rh}(\text{CO})_2\text{Cl}]_2$	10 mol % AgSbF_6	0%	0%
4	$[\text{Rh}(\text{CO})_2\text{Cl}]_2$	PPh_3	0%	0%
5	$[\text{Rh}(\text{CO})_2\text{Cl}]_2$	$\text{P}(\text{OCH}_2\text{CF}_3)_3$	0%	0%
6	$[\text{Rh}(\text{CO})_2\text{Cl}]_2$	$\text{P}[\text{OCH}(\text{CF}_3)_2]_3$	0%	0%
7	$[\text{Rh}(\text{CO})_2\text{Cl}]_2$	$\text{P}(2\text{-furyl})_3$	7% / 4%	22%
8	$[\text{Rh}(\text{CO})_2\text{Cl}]_2$	$\text{P}[3,5\text{-(CF}_3)_2\text{C}_6\text{H}_3]_3$	14% / 14%	39%
9 ^[d]	$[\text{Rh}(\text{CO})_2\text{Cl}]_2$	$\text{P}(\text{C}_6\text{F}_5)_3$	30% / 7%	60%
10 ^{[d],[e]}	$[\text{Rh}(\text{CO})_2\text{Cl}]_2$	$\text{P}(\text{C}_6\text{F}_5)_3$	72% ^[f] / 4%	22% ^[f]
11 ^{[d],[g]}	$[\text{Rh}(\text{CO})_2\text{Cl}]_2$	$\text{P}(\text{C}_6\text{F}_5)_3$	66% / 5%	15%

^[a] Yields were determined by $^1\text{H-NMR}$ using mesitylene as the internal standard.

^[b] 10 mol % $\text{Rh}(\text{CO})_2\text{acac}$ was used.

^[c] 3-OH-benzocyclobutenone was isolated in 53% yield.

^[d] The reaction time was 36 h.

^[e] 10 mol % $\text{P}(\text{C}_6\text{F}_5)_3$ ligand was used.

^[f] Isolated yield.

^[g] 5 mol % $\text{P}(\text{C}_6\text{F}_5)_3$ was used. Acac=acetylacetonates.

Table 2

Substrate scope ^[a]

Entry	Substrate	Product ^{Yield} [b]	Entry	Substrate	Product ^{Yield} [b]
1		 X-ray structure (3a) 72% C ₂ : C ₃ isomer = 1:1.7 ^{ff}	9 ^{ff}		 67% C ₂ : C ₃ isomer = 3.2:1 (separable)
2 ^{ff}		 78% C ₂ : C ₃ isomer = 1:1.7 ^{ff}	10		 59% + 3b (18%) C ₂ : C ₃ isomer = 1:1.7 ^{ff}
3		 X-ray structure (3c) 86% C ₂ : C ₃ isomer = 1:1.7 ^{ff}	11 ^{ff}		 57% C ₂ : C ₃ isomer = 1:1.7 ^{ff}
4		 X-ray structure (3d) 50%	12		 79%
5		 90%	13		 84%
6 ^{ff}		 59% (82%) C ₂ : C ₃ isomer = 1:1.4 (separable)	14		 67%
7 ^{ff}		 45% (2.5 : 1) ^{ff}	15		 99%
8		 71%	16		 77% C ₂ : C ₃ isomer = 1:6.3 ^{ff}

^[a] Each reaction was run on a 0.2 mmol scale in a sealed vial, using 5 mol % [Rh(CO)₂Cl]₂ and 10 mol % P(C₆F₅)₃, in THF, 130 °C, 36 h.^[b] Isolated yields.^[c] Ratio of the olefin regioisomers were determined by ¹H-NMR or based on their isolated yields (see supporting information for more details).^[d] Numbers in the parenthesis are brsm yields.^[e] Compound **3k** was characterized via a subsequent olefin hydrogenation (see supporting information for more details). brsm=based on recovered starting material.^[f] Isolated as inseparable isomers.