C–C Activation

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Rhodium-Catalyzed Regioselective Carboacylation of Olefins: A C–C Bond Activation Approach for Accessing Fused-Ring Systems**

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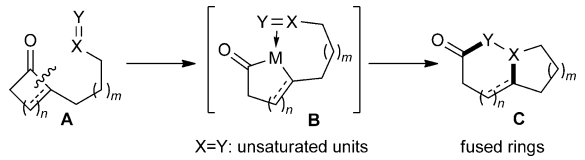
Dedicated to Professor Robert H. Grubbs on the occasion of his 70th birthday

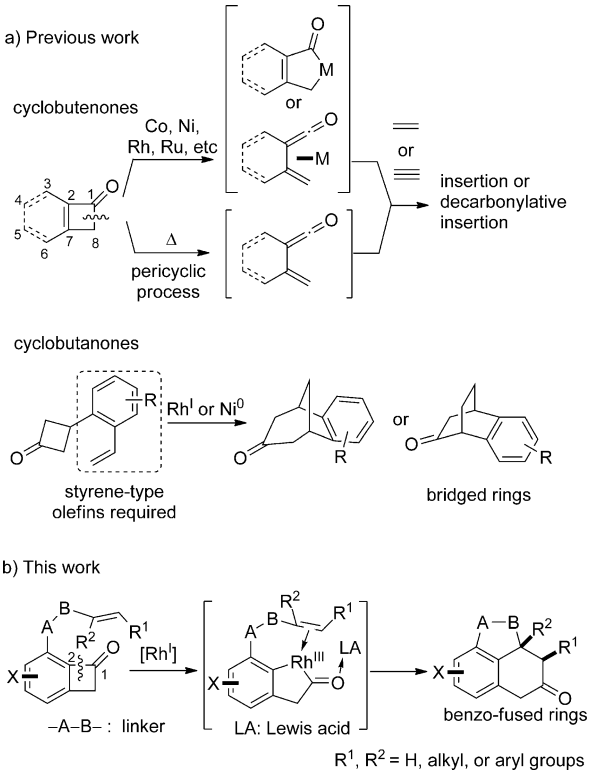
Efficiency in the synthesis of a complex molecular target is greatly dictated by the strategy used for building the key skeletal structure. In particular, fused rings are extremely common structural motifs in natural products and drug molecules, and thus access to these motifs through selective and atom-economic methods is of significant importance.[1] Despite the existence of various elegant stepwise cycloaddition methods for building fused-ring systems,[2] we were particularly intrigued by a catalytic "cut-and-sew" reaction, which involves the oxidative addition of a transition metal to a C–C bond (Scheme 1).[3] In this type of reaction, a key intermediate, for example, metallocycle **B**, is formed when



Scheme 1. Cut-and-sew approach involving oxidative addition.

a relatively inert C–C bond is replaced by two reactive M–C bonds, thus representing an unusual strategy for accessing complex structures that are difficult to access using conventional methods. For example, for substrates such as ketone **A**, regioselective cleavage of a C–C bond followed by intramolecular migratory insertion of an unsaturated moiety, such as an olefin, and reductive elimination would lead to fused-bicyclic structure **C**.[4]

Four-membered ring compounds,[5] in particular, cyclobutanones and cyclobutenones,[6] are privileged substrates for reactions involving the activation and subsequent functionalization of C–C bonds.[7,8] Not only are they readily accessible from simple starting materials, such as ketones, olefins, and alkynes,[5] their activation, which is driven by strain relief, often does not require temporary[9] or permanent directing groups.[10] Regioselective cleavage of the C1–C8 σ bond in benzocyclobutenones with insertion of alkenes and alkynes has been achieved using either thermal methods or transition metals (Scheme 2a).[6a] For example, cyclobutenones are often considered as vinyl-ketene equivalents: the research group of Danheiser has developed an efficient strategy for the bringing together of cyclobutenones and electron-rich alkynes to give polysubstituted phenols through thermal retro-4π cyclization;[11] Schiess et al. reported addition reactions with benzocyclobutenones that proceeded via vinyl-ketene intermediates.[12] The transition metal mediated insertion of alkynes into cyclobutenones and cyclobutendiones was first



Scheme 2. C–C bond cleavage in cyclobutenones and cyclobutanones.

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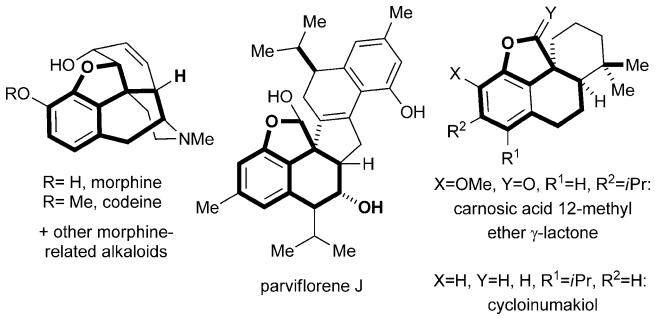
reported by the research group of Liebeskind and represents a practical method for accessing various phenols and quinones.[13,14] Later, the research groups of Kondo and Mitsudo successfully extended the scope of the reaction to electron-deficient olefins, norbornene, and ethylene by using rhodium and ruthenium catalysts.[15] Recently, the insertion of alkynylboronates into cyclobutenones was reported by Auvinet and Harrity.[16] The activation of cyclobutanones was first reported by the research group of Murakami (Scheme 2a).[17] Murakami et al. subsequently reported a catalyzed intramolecular insertion of styrene-type olefins into cyclobutanones to give [3.1.2] bicycles.[18,19] More recently, the research group of Murakami reported a nickel-catalyzed addition of alkynes and alkenes to cyclobutanones through oxidative cyclization and β-carbon elimination.[20]

We wanted to explore the feasibility of using such a cut-and-sew approach to access fused rings by investigating benzocyclobutenones. The intramolecular insertion of olefins into the C1–C2 σ bond of benzocyclobutenones would lead to benzofused tricycles (Scheme 2b), which are key motifs in a number of biologically important natural products (Scheme 3).[21] However, there are a number of challenges:

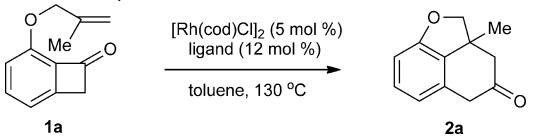


Scheme 3. Representative natural products.

1) achieving the desired regioselectivity is not trivial, because, in general, cleavage of the C1–C8 bond of benzocyclobutenones is kinetically favored and therefore catalyzed transformations that involve the cleavage of the C1–C2 bond remain elusive; 2) the scope of olefins that can undergo carboacylation is often limited.[22] Herein, we describe the development of a rhodium-catalyzed regioselective olefin carboacylation reaction of benzocyclobutenones for rapid access to polyfused rings.[23]

To convert benzocyclobutenone **1a**[24] into tricyclic ketone **2a**, Wilkinson's catalyst was investigated initially (Table 1, entry 1). To our delight, the desired product was isolated albeit with low conversion, thus showing that activation had occurred at the unusual C1–C2 bond. The yield was slightly higher when Wilkinson's catalyst was generated in situ by mixing $[Rh(cod)Cl]_2$ and PPh_3 (Table 1, entry 3). When $[Rh(cod)Cl]_2$ was used in the absence of additional ligand, 58% conversion was observed and the product was isolated in 11% yield, thus indicating that the intermediate, that is, the diene–metal complex, is still reactive although it does not react very selectively. The discrepancy between the conversion of substrate and the yield of product, as in Table 1,

Table 1: Reaction optimization.



1a **2a**

Entry	Ligand	Bite angle [°][a]	Conversion [%][b]	Yield [%][b]
1	PPh_3[c]	N/A	24	7
2	none	N/A	58	11
3	PPh_3[d]	N/A	40	14
4	dppm	72	23	5
5	dppe	85	62	5
6	dppp	91	77	46
7	dppb	98	>99	88
8	dppb[e]	98	>99	84

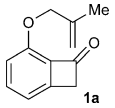
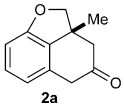
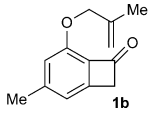
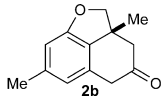
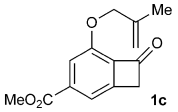
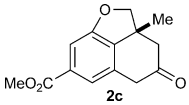
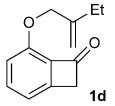
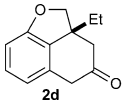
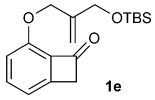
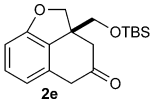
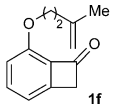
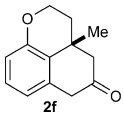
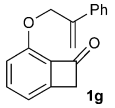
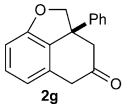
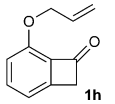
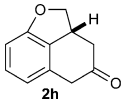
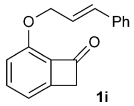
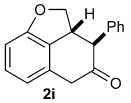
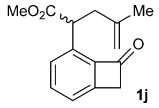
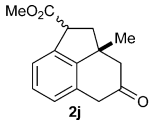
[a] The bite angle was obtained from Ref. [26]. [b] Determined by ^1H NMR spectroscopy using mesitylene as the internal standard. [c] Wilkinson's catalyst was used. [d] 24 mol% of PPh_3 was used. [e] $ZnCl_2$ (20 mol%) was added and THF was used as solvent. cod = 1,5-cyclooctadiene, dppm = 1,1-bis(diphenylphosphino)methane, dppe = 1,1-bis(diphenylphosphino)ethane, dppp = 1,1-bis(diphenylphosphino)propane, dppb = 1,1-bis(diphenylphosphino)butane, N/A = not applicable.

entries 2 and 3, is attributed to decomposition of **1a**, presumably in the form of undesired decarbonylation.[18] A series of bidentate phosphine ligands were examined. Interestingly, the yields and conversions correlate well with the bite angle of these ligands (dppb > dppp > dppe > dppm; Table 1, entries 4–7), and the highest yield (88%) was obtained using dppb (Table 1, entry 7).[25]

The efficacy of dppb can be tentatively attributed to its large bite angle because it then engenders a metal complex that is unsuitable for promoting the undesired decarbonylation pathway, owing to the blockage of potential coordination sites on the rhodium atom; this feature also promotes both migratory insertion and reductive elimination.[27] In contrast, the use of the combination of $[Rh(cod)Cl]_2$ and dppm gave a conversion and yield that was similar to those obtained when Wilkinson's catalyst was used (Table 1, entry 4); starting material decomposition was observed when dppe was used (Table 1, entry 5). In addition, the presence of the Lewis acid, $ZnCl_2$, is compatible with the carboacylation reaction[28] and a high yield was obtained (Table 1, entry 8). Furthermore, control experiments indicated that no desired product **2a** was formed in the absence of a rhodium catalyst either in the presence or in the absence of $ZnCl_2$. The tricyclic product **2a** was unambiguously identified by ^1H, ^{13}C NMR, and IR spectroscopy, as well as HRMS and X-ray crystallography (see the Supporting Information).

With optimized reaction conditions established, we next investigated the scope of this reaction (Table 2). As expected, 1,1-disubstituted olefins were converted into the corresponding fused-ring products, which contained all-carbon quaternary carbon centers, in good to excellent yield (Table 2, entries 1–7). The presence of both electron-donating and electron-withdrawing substituents on the benzocyclobutenones were tolerated (Table 2, entries 2 and 3). Moreover, the presence of esters, TBS silyl ethers, and styrene moieties were

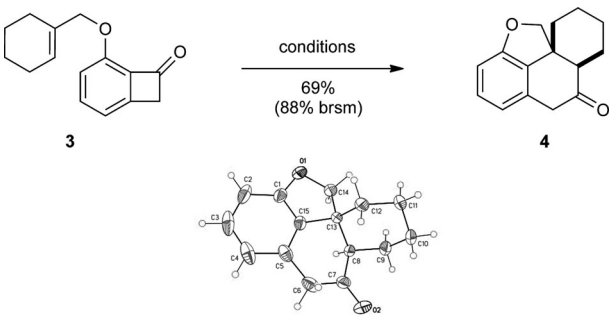
Table 2: Substrate scope.

Entry	Substrate	Product	Condition[a]	Yield [%][b]
1	 1a	 2a	A	83
2	 1b	 2b	A	74
3	 1c	 2c	A	94
4	 1d	 2d	A	92
5	 1e	 2e	A	93
6	 1f	 2f	B	91 (95)
7	 1g	 2g	B	65 (83)
8	 1h	 2h	A[c]	35 (67)
9	 1i	 2i	B	10 (47)
10	 1j	 2j	B	61 (92)[d]

[a] Conditions A: $[Rh(cod)Cl]_2$ (5 mol%), dppb (12 mol%), toluene, 130°C, 24 h; condition B: $[Rh(cod)Cl]_2$ (2.5 mol%), dppb (6 mol%), $ZnCl_2$ (10 mol%), THF, 130°C, another portion of the same catalysts was added after 12 h. [b] Yield upon isolation; the number in parentheses represents the yield based on recovered starting material (brsm). [c] THF was used as solvent. [d] The product was obtained as a mixture of diastereomers (d.r. = 1.3:1). TBS = *tert*-butyldimethylsilyl.

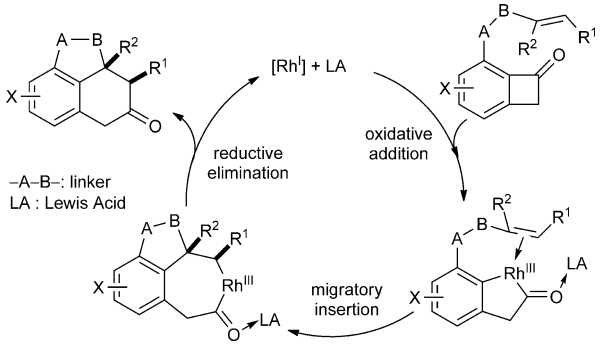
compatible (Table 2, entries 3, 5, and 7). The conversion of compound **1f** into the tricycle **2f**, which contains three fused six-membered rings, was also efficient when the reaction was conducted in the presence of $ZnCl_2$ (Table 2, entry 6); in contrast, when the same reaction was conducted in the absence of $ZnCl_2$ in either toluene or THF as solvent, the product was obtained in only 10% and 4% yield, respectively.[29] It has been observed previously that alkyl monosubstituted olefins are challenging substrates for carboacylation.[10c,22] Indeed, under the original reaction conditions with toluene as the solvent (condition A), the product was obtained in less than 5% yield; however, when the solvent was switched to THF, the yield was significantly higher (35% and 67% brsm; Table 2, entry 8). The carboacylation of 1,2-disubstituted olefins has only been reported in the context of strained substrates such as norbornene.[10d,15,22] We were pleased to find that 1,2-disubstituted olefin **1i** gave the desired insertion product (**2i**) as a single diastereomer when $ZnCl_2$ was used as a cocatalyst (Table 2, entry 9).[30] In addition, the linking of the olefin to the benzocyclobutenones through an ether moiety is not essential for the reaction, because when they were linked through a C–C bond, as in substrate **1j**, the corresponding tricyclic carbocycle **2k** was obtained in good yield (Table 2, entry 10).

To the best of our knowledge, carboacylation of trisubstituted olefins through C–C bond activation has not been reported.[31] Gratifyingly, the subjection of trisubstituted olefin **3** to the reaction conditions with $ZnCl_2$ as a cocatalyst gave the complex tetracycle **4** as a single diastereomer in 69% yield (88% brsm; Scheme 4).



Scheme 4. The transformation of trisubstituted olefin **3** into **4.** Reactions conditions: $[Rh(cod)Cl]_2$ (5 mol%), dppb (12 mol%), $ZnCl_2$ (10 mol%), THF, 130°C; a second portion of the same catalysts was added after 12 h. For the X-ray crystal structure of **4**, thermal ellipsoids are shown at 50% probability and hydrogen atoms are omitted for clarity.

A proposed catalytic cycle is depicted in Scheme 5. It is likely that the olefin serves as a strong directing group[32] and guides the rhodium catalyst to activate, through oxidative addition, the proximal C1–C2 bond rather than the distal C1–C8 bond. Subsequent migratory insertion would lead to



Scheme 5. Proposed catalytic cycle.

a seven-membered rhodacycle, which would then undergo reductive elimination to give the desired fused-ring product. The operation of a pathway involving *syn* migratory insertion and reductive elimination is supported by the relative stereochemistry in product **4**, the structure of which was confirmed by X-ray crystallography (Scheme 4). We postulate that the role of the Lewis acid, $ZnCl_2$, in this catalytic cycle is twofold:[33] it promotes both oxidative addition[34] and reductive elimination[35] through coordination with the carbonyl group of the substrate and the rhodacycle intermediate, respectively, an interaction, which makes both the substrate and the rhodacycle intermediate electron deficient.

In conclusion, we have developed an intramolecular rhodium-catalyzed olefin-carboacylation reaction of benzocyclobutenones. This method involves the selective cleavage of the usually-less-reactive C1–C2 bond, thus providing a facile means for accessing polyfused ring systems, the access to which may be challenging through conventional methods. Although still in its infancy stage, this cut-and-sew strategy that employs simple cyclic ketones as substrates should have broad applications in synthesis. Efforts toward developing highly enantioselective variants together with detailed mechanistic study of the reaction to broaden the reaction scope and facilitate application of this method in the total synthesis of bioactive natural products are in progress.[36,37]

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