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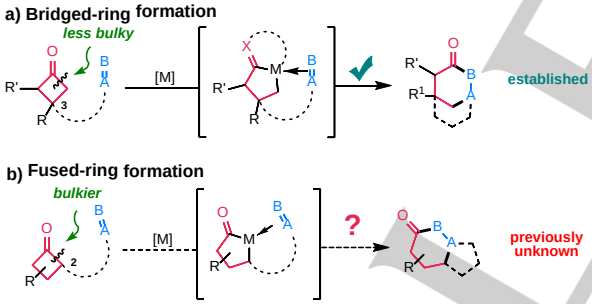
Fused-Ring Formation via an Intramolecular "Cut-and-Sew" Reaction between Cyclobutanones and Alkynes

Lin Deng, Likun Jin, and Guangbin Dong*

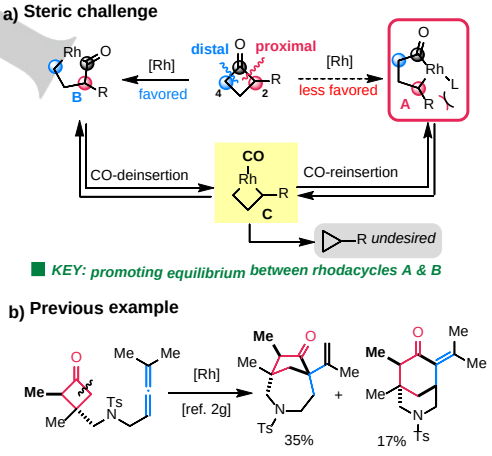
Abstract: Herein, we describe the development of a catalytic intramolecular "cut-and-sew" transformation between cyclobutanones and alkynes to construct cyclohexenone-fused rings. The challenge arises from the need for selective coupling at the more sterically hindered proximal position, which can be addressed using an electron-rich but less bulky phosphine ligand. The control experiment and ^{13}C-labelling study suggest that the reaction may start with cleavage of the less hindered distal C−C bond of cyclobutanones, followed by decarbonylation and CO reinsertion to enable Rh insertion at the more hindered proximal position.

Transition metal (TM)-catalyzed carbon−carbon bond (C−C) activation provides unique opportunities to develop various intriguing transformations.[1] In particular, oxidative addition of TM into C−C σ bonds followed by 2π-insertion, namely a "cut-and-sew" process, has been demonstrated to be effective for construction of complex ring scaffolds.[1r] Cyclobutanone derivatives are of special interest for this type of transformations due to their easy access from olefins and high reactivity towards C−C activation.[1i,n,o,q,r] To date, significant progress has been achieved for synthesis of bridged rings via intramolecular "cut-and-sew" reactions, in which cyclobutanones are coupled with an unsaturated unit tethered at the C3 position (Scheme 1a).[2] However, using such a strategy to assemble fused-ring systems remains an unmet challenge (Scheme 1b).[3]



Scheme 1. "Cut and sew" reactions with cyclobutanones

One main difficulty associated with the fused-ring formation arises from the need for C−C cleavage/coupling at the more sterically hindered C2 (proximal) position (Scheme 2a), as the selectivity typically favors the less bulky C4 (distal) position (Scheme 2b).[2g] In addition, decarbonylation of cyclobutanones to form the corresponding cyclopropane byproduct is always a *major competing pathway*.[2a,g,h] As illustrated in Scheme 2a, directly forming rhodacycle **A**, the reactive intermediate for subsequent 2π-insertion, is more difficult than rhodacycle **B**. One possible solution is to enable a facile and reversible decarbonylation/reinsertion pathway,[4] in which rhodacyclopentanone **B** can be converted first to a rhodacyclobutane intermediate **C** and then to rhodacycle **A** via CO-reinsertion. We anticipate that the choice of the ligand would be critical for this transformation, because it should allow efficient decarbonylation/CO-reinsertion without promoting further reductive elimination of **C** (an irreversible process to give cyclopropanes, *vide infra*, Scheme 5a), which represents *a main difference* from the prior benzocyclobutenone system.[5] Herein, we disclose the development of an effective catalytic system for fused-ring formation via an intramolecular "cut-and-sew" reaction between cyclobutanones and alkynes (Scheme 3a).[6] The transformation is enabled by use of an electron-rich, less bulky phosphine ligand and an electron-deficient Rh precatalyst, offering a rapid access to cyclohexenone-fused rings.



Scheme 2. Challenges for fused-ring formation with cyclobutanones

Of note, similar bicyclic structures could also be obtained through a (3+2+1) cycloaddition reactions[4e,7] involving C−C cleavage of cyclopropanes. The coupling of simple cyclopropanes, CO and alkynes was first reported by Narasaka,[8] albeit with low catalyst turnover and limited substrate scope (Scheme 3b). Use of more reactive vinyl cyclopropanes and cyclopropanes containing a directing group (DG) were recently developed by Yu[9] and Bower[10] respectively, both of which exhibit excellent reactivity and selectivity. Hence, methods that directly activate simple cyclobutanones should offer a complementary approach to the prior (3+2+1) reactions without the need for CO gas or auxiliary DGs.

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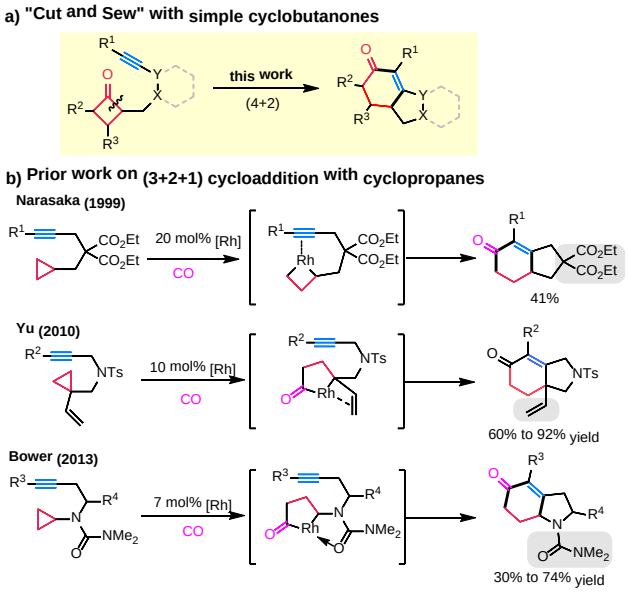
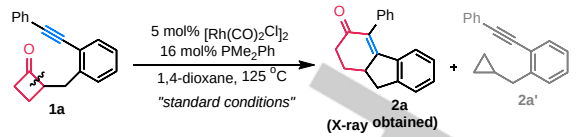


Scheme 3. Cyclohexenone-fused ring formation via C−C Activation of cyclopropanes and cyclobutanones.

To explore the proposed "cut-and-sew" reaction, cyclobutanone **1a** was employed as the initial substrate (Table 1). After careful optimization, the desired benzo-fused 6-5-6 tricycle product (**2a**) was ultimately obtained in 82% yield using $[Rh(CO)_2Cl]_2$ and PMe_2Ph as the metal-ligand combination (entry 1). First, control experiments showed that both the phosphine and Rh played pivotal roles in this reaction (entries 2 and 3). A range of monodentate phosphine ligands was found effective, and generally, higher conversion was obtained with more electron-rich ligands (entries 4-6). Surprisingly, one important factor was the ligand/metal ratio, with 1.6:1 being optimal (for detailed optimization, see SI). When less ligand was employed (P/Rh=1:1), the reaction still gave a complete conversion albeit with more cyclopropane side product (**2a'**); however, increasing the P/Rh ratio to 2:1 completely shut down the reactivity (entries 7 and 8), which could be attributed to the generation of inactive *trans*-$Rh(CO)(L)_2Cl$ species. We reason that the active catalytic species likely contains only one phosphine ligand, but it is relatively unstable in the absence of extra PMe_2Ph. In addition, use of the more π-acidic $[Rh(CO)_2Cl]_2$ as a precatalyst is also crucial to generate the active species; in contrast, use of more electron-rich Rh-olefin complexes gave almost no conversions of cyclobutanone **1a** (entries 9 and 10). A survey of solvent effect revealed 1,4-dioxane to be optimal (entries 11 and 12). At a lower temperature (115 °C), the reaction can still proceed to give 67% yield (entry 13). Finally, the temporary DG strategy was not effective likely due to the difficulty of cleaving the bulkier proximal C−C bond (entry 14).[2c]

Table 1. Selected optimization studies[a]



Entry	Variations from standard conditions	2a[b]	conversion[b]	2a'[b]
1	**none**	**82%**	>95%	13%
2	without $[Rh(CO)_2Cl]_2$	0%	<5%	0%
3	without PMe_2Ph	0%	>95%	0%
4	PPh_3 instead of PMe_2Ph	35%	50%	12%
5	$PMePh_2$ instead of PMe_2Ph	50%	78%	8%
6	PMe_3 instead of PMe_2Ph	57%	>95%	10%
7	10 mol% PMe_2Ph	64%	>95%	24%
8	20 mol% PMe_2Ph	<5%	8%	<5%
9	$[Rh(C_2H_4)_2Cl]_2$ instead of $[Rh(CO)_2Cl]_2$	trace	<5%	trace
10	$[Rh(cod)Cl]_2$ instead of $[Rh(CO)_2Cl]_2$	trace	<5%	trace
11	in THF	57%	90%	11%
12	in toluene	77%	>95%	14%
13	at 115 °C	67%	>95%	18%
14	with 100 mol% of 2-amino-3-picoline	0%	<5%	0%

[a] run on a 0.1 mmol scale at 125 °C for 60 h. [b] isolated yield.

With the optimized conditions in hand, the substrate scope was next investigated (Table 2). First, different aryl-substituted alkynes all underwent the "cut and sew" sequence to give the corresponding tricycle products (**2a**-**2e**). Alkyl-substituted alkynes are also competent coupling partners; primary, secondary and tertiary alkyl substituents are all tolerated. Unsurprisingly, increasing the bulkiness on the substituent from propyl (**2g**) to isopropyl (**2h**) to *t*-butyl (**2i**) groups reduced the yield. It is noteworthy that the reaction conditions are both *pH and redox neutral*. The acid-labile TBS ether is compatible and 89% yield of product **2j** was isolated. In addition, cycloalkyl-substituted alkynes can be effectively coupled; the generated vinyl cyclopropane moiety (**2m**) remained intact. Moreover, substitution on the arene (**2n**) or the methylene bridge (**2o**) (between the arene and cyclobutanone) is tolerated. The reduced yield for product **2o** is due to the increasing cyclopropane formation; it is likely that the substitution hindered the migratory insertion to certain extent. Interestingly, the aniline linkage provided an indoline scaffold (**2p**). On the other hand, the nitrogen linker was also found efficient.[11] With such a linker, coupling with aryl, alkyl and even silyl-substituted alkynes has been achieved, and the corresponding 6H-isoindole products can potentially serve as valuable synthetic building blocks.[10] Finally, both α and β substituted cyclobutanones can be employed albeit in moderate yields (eqs 1 and 2), probably caused by the increased steric hindrance in the substrates.

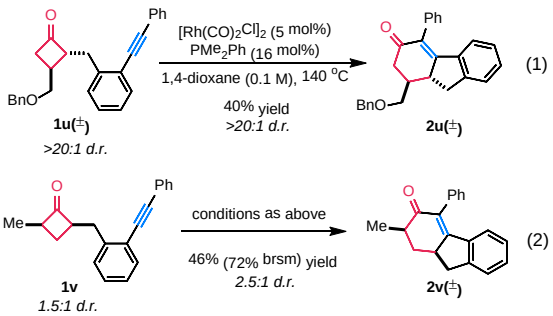


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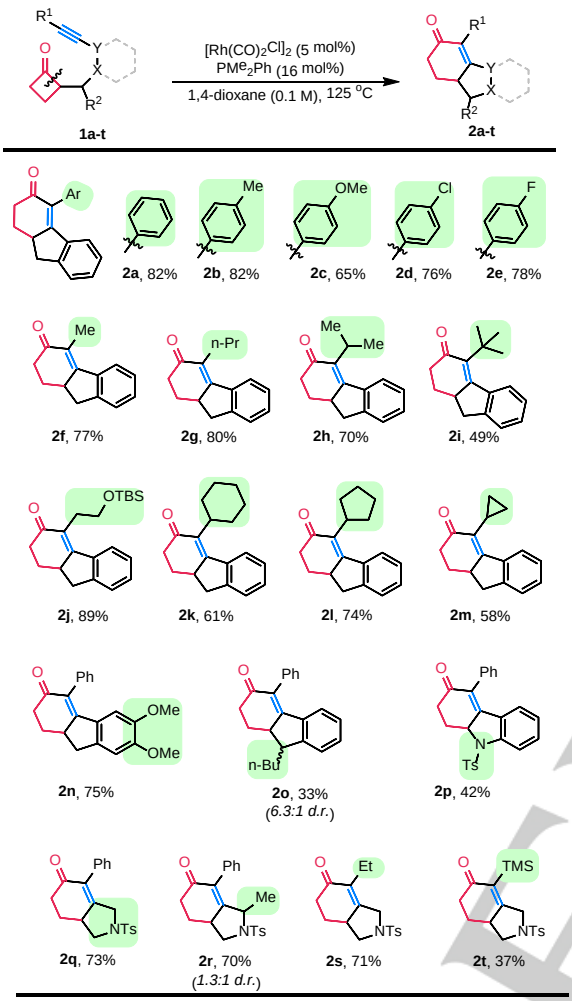
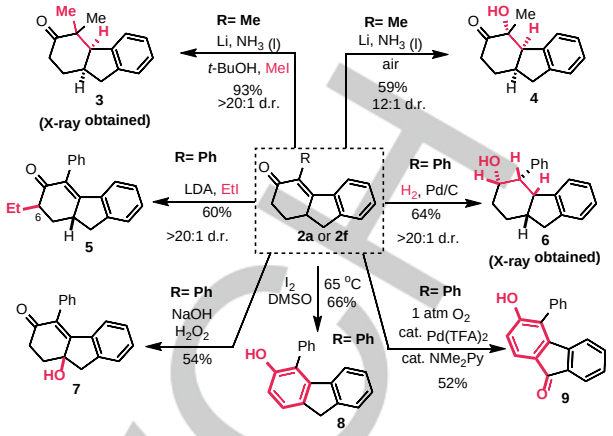
Table 2. Substrate Scope[a]



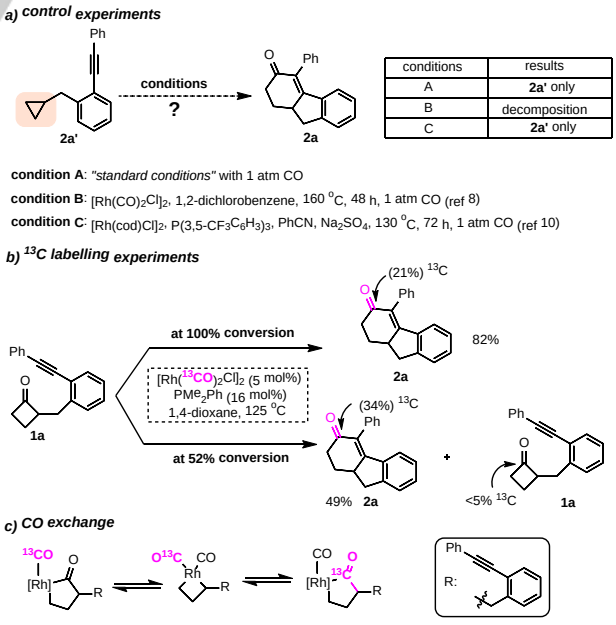
[a] isolated yields; [b] at 130 °C

The intriguing cyclohexanone-fused ring structures generated from this "cut-and-sew" reaction can be conveniently derivatized (Scheme 4). Excellent diastereoselectivity was obtained in most cases possibly driven by forming less strained 5-6 cis-fused rings. First, dissolving metal reduction, followed by alkylation or oxidation, afforded the α-disubstituted cyclohexanone products **3** (X-ray structure obtained) and **4** (stereochemistry tentatively assigned), respectively.[12,13] Moreover, enolate-based alkylation occurred site- and diastereoselectively at the C6-position of the cyclohexenone moiety. Pd/C-catalyzed hydrogenation took place at the *syn* side to the methine hydrogen and directly gave the corresponding saturated alcohol. Treatment of product **2a** with base and hydrogen peroxide unexpectedly led to a γ-hydroxylation product (**7**).[14] Finally, iodine/DMSO oxidation[15] converted the tricycle into a functionalized fluorene, and a Pd-catalyzed aerobic oxidation[16] surprisingly gave 9-fluorenone **9** as the dominant product.



Scheme 4. Synthetic applications

With regard to the plausible reaction mechanism, there are two major questions. One is whether this (4+2) cycloaddition shares the same catalytic pathway as the (3+2+1) reaction involving cyclopropane ring opening.[10] The other one is whether the reaction pathway involves the cleavage of the less hindered distal C–C bond. To address the first question, control experiments with cyclopropane side product **2a'** were conducted (Scheme 5a). Subjecting **2a'** to the standard (4+2) reaction conditions in the presence of CO gas or to the optimal conditions developed by Narasaka[8] or Bower[10] for the (3+2+1) reaction gave no desired **2a** product. This result suggests that cyclopropane formation during the (4+2) reaction is probably irreversible and **2a'** should not be an intermediate towards product formation. This observation is also consistent with the fact that coupling of unactivated cyclopropanes in the absence of DGs is rather difficult.[8]



Scheme 5. Preliminary Mechanistic Studies

To explore the second question, ^{13}C labeling study was conducted (Scheme 5b). We hypothesized that, if the reaction involved cleavage of the less hindered distal C−C bond, a CO de-insertion and re-insertion into the less hindered alkyl group would have to occur (*vide supra*, Scheme 2a). Thus, if this were the case, use of the Rh catalyst containing ^{13}CO ligands would introduce ^{13}C-labeled carbonyl moiety into the product. Indeed, replacement of $[Rh(CO)_2Cl]_2$ with $[Rh(\mathbf{^{13}CO})_2Cl]_2$ under the standard reaction conditions afforded product **2a** in 82% yield with 21% ^{13}C incorporation. Give that only 5 mol% $[Rh(^{13}CO)_2Cl]_2$ was used, 86% ^{13}CO from the Rh complex has been transferred into product. When the reaction was terminated at an earlier stage, higher ^{13}C incorporation (34%) was observed without significant ^{13}C incorporation in recovered starting material (for more details, see Supporting Information). These observations suggested that (i) decarbonylation/CO-reinsertion must have occurred (Scheme 5c), (ii) the exchange between the coordinated CO on Rh and the free CO is faster than the subsequent steps and (iii) reductive elimination of the rhodacyclopentanone intermediate to give back cyclobutanone **1a** is significantly slower than migratory insertion into the alkyne moiety. Hence, this observation is consistent with the hypothesis that the reaction may involve cleavage of the less hindered distal C−C bond, followed by a decarbonylation/CO reinsertion process, though the pathway initiated from direct activation of the bulkier proximal C−C bond cannot be completely ruled out at this stage.

In summary, we have developed the first intramolecular coupling between cyclobutanones and alkynes to construct versatile fused cyclohexenone scaffolds. In this reaction, 2π-insertion can selectively take place at the more sterically hindered proximal position, which significantly extends the "cut-and-sew" scope with cyclobutanones thereby opening the door for accessing other fused structures. Detailed mechanistic studies are ongoing in our laboratory.

Acknowledgements

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Keywords: rhodium catalysis • cyclobutanone • fused ring synthesis • C–C activation• cut-and-sew

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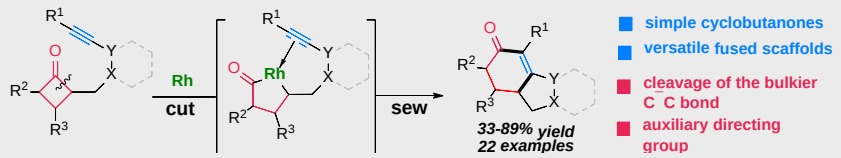

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