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Rh-catalyzed reagent-free ring expansion of cyclobutenones and benzocyclobutenones†

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Here we report a reagent-free rhodium-catalyzed ring-expansion reaction *via* C–C cleavage of cyclobutenones. A variety of poly-substituted cyclopentenones and 1-indanones can be synthesized from simple cyclobutenones and benzocyclobutenones. The reaction condition is near pH neutral without additional oxidants or reductants. The potential for developing a dynamic kinetic asymmetric transformation of this reaction has also been demonstrated. Further study supports the proposed pathway involving Rh-insertion into the cyclobutenone C–C bond, followed by β-hydrogen elimination, olefin insertion and reductive elimination.

Introduction

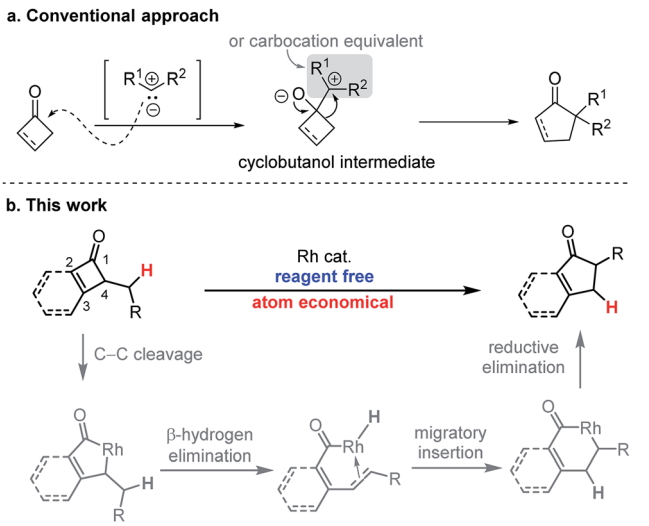
Ring expansion reactions, generally with cyclic ketones, are highly valuable transformations for constructing complex ring skeletons.[1] Conventional approaches for direct one-carbon homologation of cyclic ketones primarily rely on addition of a carbene reagent or its equivalent (Scheme 1a).[2] For example, diazoalkanes have been frequently employed for preparing cyclopentanones from cyclobutanones.[3] In contrast, the corresponding transformations with unsaturated enones (*e.g.* cyclobutenones) are much rarer largely due to the competing reactions with the olefin moiety (*e.g.* conjugate addition and cyclopropanation)[4] and lack of regioselectivity.[5] Moreover, most existing methods for one-carbon ring expansion of four-membered ring ketones[6] involve forming cyclobutanols[7] (or cyclobutenols[8]) as a transient or isolatable intermediate (Scheme 1a). Considering that, as important classes of organic compounds, cyclopentenones and 1-indanones are frequently employed as building blocks and widely found in a number of bioactive molecules (Fig. 1), herein we describe a unique, simple, and atom-economical strategy for the direct catalytic ring expansion of alkyl cyclobutenones and benzocyclobutenones to five-membered unsaturated ketones.[9]

Results and discussion

Research hypothesis

Our proposed strategy is described in Scheme 1b. Driven by strain release, cyclobutenones are known to undergo ring openings with transition metals (*e.g.* Rh^{I}) through cleavage of the C1–C4 bond.[10] We hypothesized that subsequent β-hydrogen elimination with the resulting acyl metallacycle would lead to a metal hydride–olefin complex, which can undergo hydride re-insertion followed by reductive elimination to furnish the ring expanded product.

While numerous elegant methods have been developed for synthesis of cyclopentenones and indanones,[11] such as Pauson–Khand (PK)[12] and Nazarov[13] reactions, this approach nevertheless exhibits a number of complementary features. First, poly-substituted cyclobutenones and benzocyclobutenones are readily available through many approaches,[14] including a [2 + 2] cycloaddition between an alkyne (or aryne) and a ketene equivalent (see ESI†). Second, it operates under near pH and



Scheme 1 One-carbon homologation of four-membered ring ketones.

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† Electronic supplementary information (ESI) available. CCDC 1059514 and 1059515. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5sc01875g

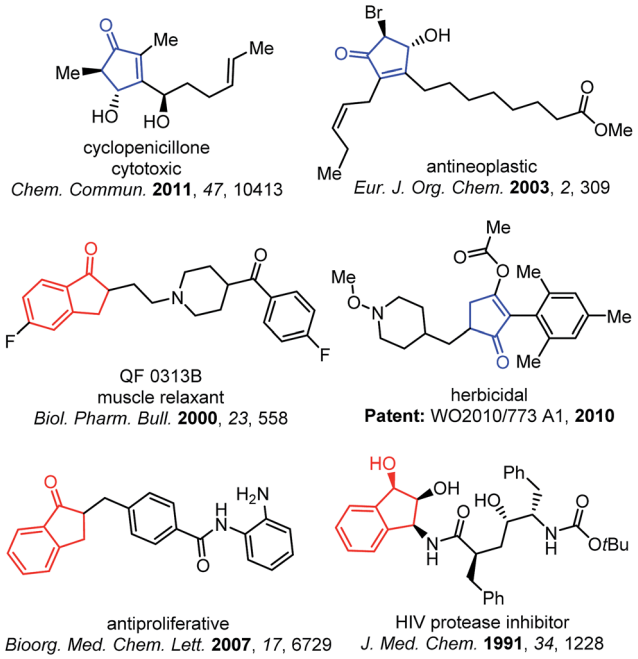


Fig. 1 Representative examples of related bioactive molecules.

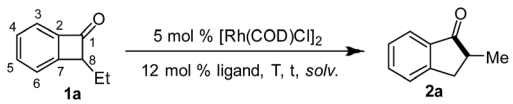
redox-neutral conditions, which would tolerate many functional groups (Nazarov reactions generally require use of a strong acid). Third, this transformation shows a complete regioselectivity when forming α-substituted cyclopentenones (*vide infra*, Table 4); in contrast, it is non-trivial to control the regioselectivity for intramolecular PK reactions.

Optimization studies and substrate scope

To test this hypothesis, benzocyclobutenone **1a** was employed as the model substrate, and the reaction was investigated by examining a number of parameters (Table 1). When Wilkinson's complex [$RhCl(PPh_3)_3$] was used as the catalyst, no desired product was observed (entry 1, Table 1), and **1a** remained intact. It is known that bidentate ligands can facilitate migratory insertion and reductive elimination.[15] Thus, a series of bisphosphine ligands were evaluated (entries 2–5, Table 1). To our delight, all these ligands provided the desired ring expansion product, whereas dppp proved to be the most efficient. Using dppp as the ligand, the reaction occurred smoothly at 80 °C albeit requiring a longer reaction time (entries 5–9, Table 1). When performed at 90 °C, the desired 1-indanone product was isolated in 93% yield (entry 9, Table 1). A survey of different solvents revealed that 1,4-dioxane was optimal, although THF and ethyl benzene worked almost equally well (entries 9–13, Table 1). Finally, control experiments showed that both the rhodium pre-catalyst and the phosphine ligand were essential for the success of this ring-expansion reaction (entries 14–15, Table 1).

With the optimal condition established, we next investigated the substrate scope of the reaction (Table 2). Benzocyclobutenones bearing different substituents at the C8 position all afforded the desired products (**2a–2d**, **2m**,[16] **2n**). Substituents at

Table 1 Selected optimization for ring expansion of 8-ethyl benzocyclobutenone



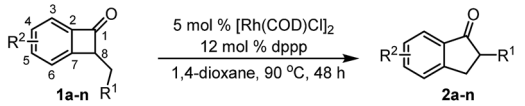
Entry	Ligand	T (°C)	Solvent	Time	Yield[a]
1	PPh_3[b]	110	Dioxane	24 h	0
2	dppe	110	Dioxane	24 h	75%
3	dppb	110	Dioxane	24 h	61%
4	dppf	110	Dioxane	24 h	64%
5	dppp	110	Dioxane	24 h	84%
6	dppp	120	Dioxane	24 h	68%
7	dppp	100	Dioxane	24 h	73%
8	dppp	80	Dioxane	48 h	77%
9	**dppp**	**90**	**Dioxane**	**48 h**	**93%**[c]
10	dppp	90	THF	48 h	90%
11	dppp	90	PhEt	48 h	89%
12	dppp	90	Benzene	48 h	81%
13	dppp	90	Toluene	48 h	76%
14	dppp w/o [Rh]	90	Dioxane	48 h	0
15	No ligand	90	Dioxane	48 h	0

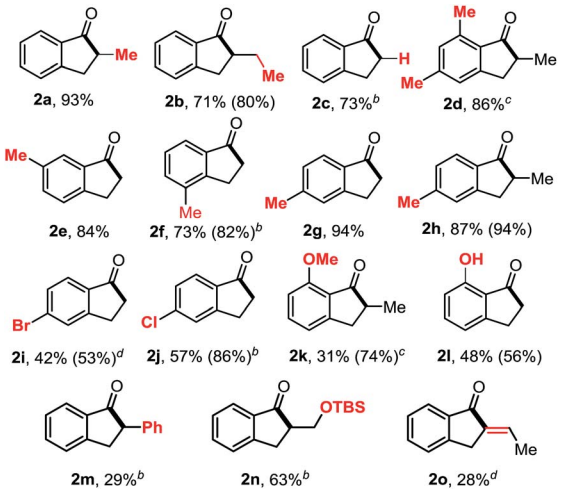
[a] Unless otherwise noted, all yields were determined by ^1H NMR using 1,1,2,2-tetrachloroethane as the internal standard. [b] Wilkinson's catalyst [$RhCl(PPh_3)_3$] was used. [c] Isolated yield.

all positions on the benzene ring can be tolerated (**2d–2h**). The 3,5-dimethyl substituted substrate required a higher temperature but still provided the desired product (**2d**) in a good yield. Functional groups, such as aryl bromides, chlorides, anisoles, free phenols and silyl ethers (**2i–2l** and **2n**) were compatible under the reaction conditions, albeit giving moderate yields. Interestingly, olefin migration was observed when 8-allyl-substituted substrate (**2o**) was used.

To explore whether the benzo-moiety is essential for the ring-expansion transformation, we next investigated simple cyclobutenone derivatives (Table 3). Compound **3a** was employed as the model substrate. It was surprising to note that when the optimal conditions for the benzocyclobutenones (*vide supra*) were applied, no desired ring-expansion product was found even at elevated temperatures (entry 1, Table 3), suggesting a significant difference in reactivity between the two closely related compounds. A survey of other ligands also remained unfruitful, and unlike benzocyclobutenones, compound **3a** remained inactive under these conditions (entries 2–4, Table 3). However, by switching the precatalyst from $[Rh(COD)Cl]_2$ to $[Rh(COD)OH]_2$ or $[Rh(COD)OMe]_2$,[17] cyclopentenone **4a** could be isolated in moderate to good yields (entries 5 and 6, Table 3). The analogous $[Ir(COD)OMe]_2$ failed to give any desired product (entry 7, Table 3). A number of bidentate phosphine ligands were subsequently evaluated (entries 8–11, Table 3), and dppb showed enhanced reactivity (entry 9, Table 3). Control experiments further revealed that both the metal and the ligand were required (entries 12–14, Table 3), and NaOH alone failed to catalyze the reaction, indicating that the transformation was not solely catalyzed by

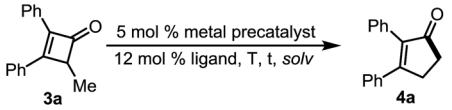
Table 2 Scope for the ring expansion of 8-alkyl benzocyclobutenones[a]





[a] All yields are isolated yields, and the numbers in parenthesis are yields based on recovered starting material. All reactions were carried out in a sealed vial under N_2 atmosphere. [b] The reaction was run at 110 °C for 48 h. [c] The reaction was run at 150 °C for 48 h. [d] The reaction was run at 130 °C for 48 h.

Table 3 Selected optimization for ring expansion of cyclobutenone 3a



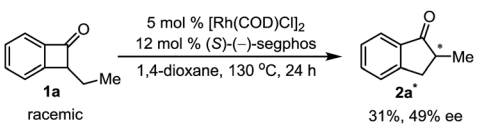
Entry	Ligand	Precatalyst	T (°C)	Solvent	Time	Yield[a]
1	dppp	$[Rh(COD)Cl]_2$	130	Dioxane	24 h	0%
2	dppb	$[Rh(COD)Cl]_2$	130	Dioxane	24 h	0%
3	PPh_3[b]	$[Rh(COD)Cl]_2$	150	Dioxane	24 h	0%
4	dppb	$[Rh(COD)Cl]_2$	150	Dioxane	24 h	0%
5	dppp	$[Rh(COD)OH]_2$	150	Dioxane	24 h	70%[c]
6	dppp	$[Rh(COD)OMe]_2$	150	Dioxane	24 h	56%[c]
7	dppp	$[Ir(COD)OMe]_2$	150	Dioxane	24 h	0%
8	dppe	$[Rh(COD)OH]_2$	150	Dioxane	24 h	50%
9	dppb	$[Rh(COD)OH]_2$	150	Dioxane	24 h	86%[c]
10	dpppent	$[Rh(COD)OH]_2$	150	Dioxane	24 h	76%
11	dppb	$[Rh(COD)OH]_2$	130	Dioxane	24 h	81%[c]
12	None	None	130	Dioxane	24 h	0%
13	None	$[Rh(COD)OH]_2$	130	Dioxane	24 h	37% (67%)
14	dppp	None	130	Dioxane	24 h	0%
15	None	none[d]	130	Dioxane	24 h	0%
18	dppb	$[Rh(COD)OH]_2$	110	Dioxane	48 h	92%
19	dppb	$[Rh(COD)OH]_2$	100	Dioxane	48 h	74% (80%)
20	dppb	$[Rh(COD)OH]_2$	90	Dioxane	48 h	65% (82%)
21	dppb	$[Rh(COD)OH]_2$	80	Dioxane	48 h	42% (77%)
22	dppb	$[Rh(COD)OH]_2$	110	THF	48 h	80% (93%)
23	dppb	$[Rh(COD)OH]_2$	110	Toluene	48 h	90%
24	dppb	$[Rh(COD)OH]_2$	110	CH_3CN	48 h	58% (73%)
25	dppb	$[Rh(COD)OH]_2$	110	nBu_2O	48 h	30% (79%)
26	**dppb**	**$[Rh(COD)OH]_2$**	**110**	**PhEt**	**48 h**	**95%[c]**

[a] Unless otherwise noted, all yields were determined by ^1H NMR using 1,1,2,2-tetrachloroethane as the internal standard. Values in the parentheses are yields based on recovered starting material. [b] 30 mol% of PPh_3 was used as the ligand. [c] Isolated yields. [d] 20 mol% of NaOH was used.

the hydroxy anion (entry 15, Table 3). It is worth noting that *the reaction can occur at 80 °C* (entry 21, Table 3). Considering the overall reaction efficiency, 110 °C was chosen as the temperature for further optimization (entry 18, Table 3). Finally, the solvent effect was investigated, and ethyl benzene gave the best results (95%, entry 26, Table 3).

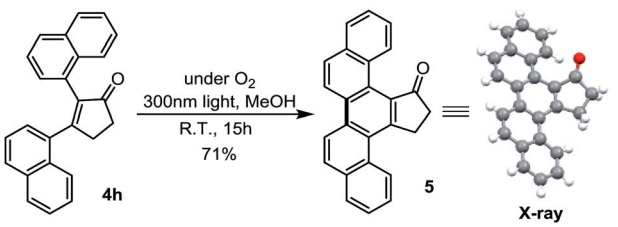
The substrate scope with simple cyclobutenones was then explored (Table 4). Substrates containing various aromatic or aliphatic substituents at the 2 and 3-positions all provided the desired cyclopentenones smoothly. Interestingly, simple α-methylated cyclopentenone **4b** has not been synthesized previously. The more sensitive thiophene (**4e**) and naphthalene rings (**4h**) can be tolerated. Although the 3,4-disubstituted cyclobutenones (no substitution at the C2 position) are known to be highly unstable and prone to undergo olefin isomerization,[18] the desired ring-expansion product (**4i**, Table 2) can still be obtained, suggesting the mildness of the reaction conditions.

Preliminary studies have revealed that chiral bidentate phosphine ligands, such as segphos, effect the dynamic kinetic asymmetric transformation (DYKAT) of benzocyclobutenone **1a** with a promising level of enantioselectivity (eqn (1), 49% ee).[19] This result suggests this reagent-free ring-expansion reaction is amenable to asymmetric catalysis, and work on this topic is ongoing.



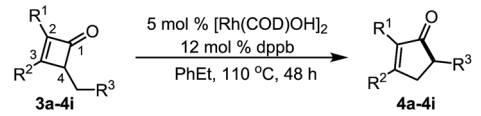
(1)

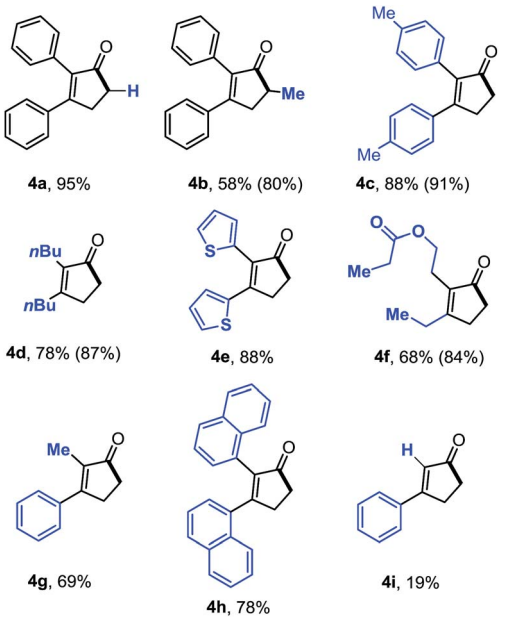
The utility of this method was demonstrated by converting ring-expansion product **4h** to an interesting picene-derived ketone (**5**) using a light-mediated dehydrogenative cyclization (eqn (2)).[20] Notably, picene **5** is nontrivial to prepare *via* a conventional approach. The application of picene **5** as an organic transistor material[21] is under exploration.



(2)

Table 4 Scope for the ring expansion of 4-alkyl cyclobutenones[a]



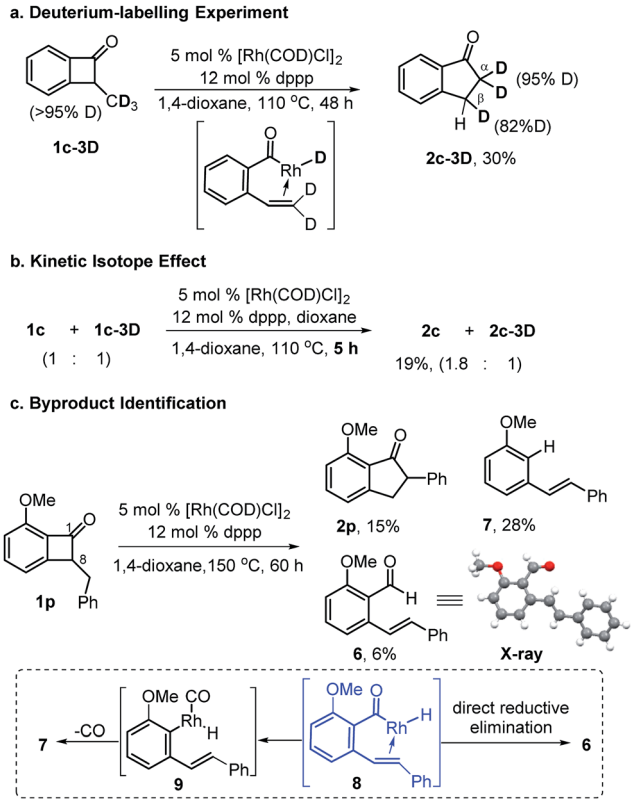


[a] All yields are isolated yields, and the numbers in parenthesis are yields based on recovered starting material. All reactions were carried out in a sealed vial under N_2 atmosphere.

Mechanistic studies

To explore the proposed mechanistic pathway in Scheme 1b, we first conducted a deuterium labelling experiment (Scheme 2a). When the $-CD_3$ substituted benzocyclobutenone (**1c-3D**) was used as the substrate, indeed, a near complete deuteration (95%) was found at the α-position of the 1-indanone product, and 82% deuterium incorporation was observed at one of the β-hydrogen. This result is consistent with the proposed β-hydrogen elimination and re-insertion pathway. Subsequently, a positive kinetic isotope effect (KIE) was observed when a 1 : 1 molar ratio of **1c** and **1c-3D** were mixed and reacted under the standard conditions (Scheme 2b). While only a moderate KIE (1.8) was observed, this intermolecular competition experiment suggested the β-hydrogen elimination either occurs before the rate-limiting step or is the rate-limiting step.[22]

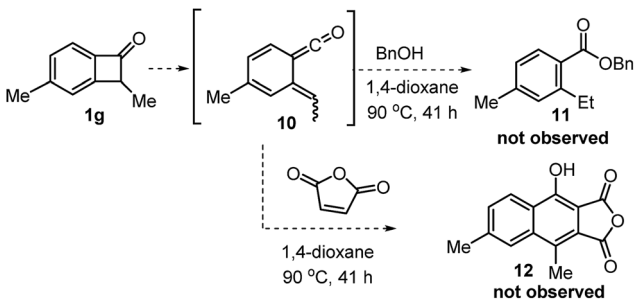
Byproducts from a catalytic reaction often provide useful information about the reaction intermediates. Consequently, the byproducts of this ring-expansion reaction were investigated. Benzocyclobutenone **1p** was subjected to the standard conditions at an elevated temperature. While the desired 2-phenyl-indanone product was afforded, two major byproducts, aldehyde **6** and stilbene **7**, were isolated and characterized (Scheme 2c). The presence of these two ring-opening products supports the pathway of C1–C8 bond cleavage of



Scheme 2 Mechanistic exploration.

benzocyclobutenone and Rh-hydride **8** as a possible intermediate. A direct acyl-hydrogen reductive elimination should lead to aldehyde **6**, while decarbonylation of intermediate **8** followed by aryl-hydrogen reductive elimination should result in stilbene **7**.[23] Compared to the standard substrate (**1a**), the presence of significant side reactions with substrate **1p** can be explained by an inefficient migratory insertion and/or reductive elimination with a *trans*-stilbene-like olefin (*vide supra*, Table 2, **2m**).[24]

Finally, we investigated whether the cleavage of benzocyclobutenone C1–C8 bond is catalyzed by the Rh catalyst or simply triggered by thermal heat (Scheme 3). If the C–C cleavage was caused by the thermal heat alone, a vinyl ketene intermediate would be generated. Vinyl ketenes are highly reactive species, and are known to react with various nucleophiles or dienophiles.[25] However, treatment of the benzocyclobutenone



Scheme 3 Capture of the vinyl ketene intermediate.

1g with benzyl alcohol or maleic anhydride at the same reaction temperature did not yield any coupling products, which suggested that the rhodium catalyst played an important role in assisting the C–C cleavage.[10]

Conclusion

In summary, we have developed a unique Rh-catalyzed ring expansion of cyclobutenones and benzocyclobutenones *via* C–C bond cleavage. A range of poly-substituted cyclopentenones and 1-indanones can be prepared. This approach is featured by: (1) the substrates are relatively simple and do not require pre-installation of an additional reacting group; (2) no additional stoichiometric reagents are needed for the ring expansion, and the transformation is atom-economical; and (3) the reaction conditions are near pH and redox neutral allowing for tolerance of many functional groups. Finally, the preliminary mechanistic study supports the proposed pathway involving Rh-oxidative addition into the C–C bond, followed by β-hydrogen elimination, olefin migratory insertion and reductive elimination. Efforts on developing a highly enantioselective DYKAT of this reaction for asymmetric synthesis is currently undertaken in our laboratories.

Acknowledgements

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