Chemical Science

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DOI: 10.1039/C7SC04784C

Journal Name

COMMUNICATION

Rhodium(I)-Catalyzed Asymmetric [4+2] Cycloaddition Reactions of 2-Alkylenecyclobutanols with Cyclic Enones through C-C Bond Cleavage: Efficient Access to *trans*-Bicyclic Compounds

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Xinxin Zheng[a], Rui Guo[b], Guozhu Zhang*[b] and Dayong Zhang*[a]

We report a rhodium-catalyzed asymmetric formal intermolecular [4+2] cycloaddition reaction of 2-alkylenecyclobutanols with α,β-unsaturated cyclic ketones leading to synthetically useful *trans*-bicyclic molecules. Three consecutive stereogenic centers are formed in a highly enantio- and diastereoselective manner. Stepwise C-C bond cleavage and annulation are likely involved in the reaction pathway. Here, *i*Pr-Duphos is the viable chiral ligand that promotes excellent enantio-control.

Introduction

Bicyclic rings are found in the skeletons of many terpenoids natural products such as (-)-corallidictyals, fatimanone, and diosbulbin E (Figure 1).[1] Terpenoids and synthetic small molecules containing bicyclic ring structures exhibit a broad range of important bioactivities.[2] Intermolecular [4+2] cycloaddition to the C2-C3 positions of α,β-unsaturated cyclic ketones has the high synthetic potential for the synthesis of structurally diverse and complex bicyclic systems.[3] Among those, the Diels-Alder (DA) reaction constitutes one of the most widely used and efficient approaches.[4] However, DA adducts generally possess *cis* configurations that are less common in natural products; meanwhile, asymmetric catalysis has had only limited success.[5]

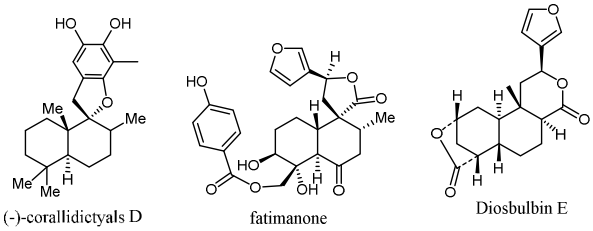
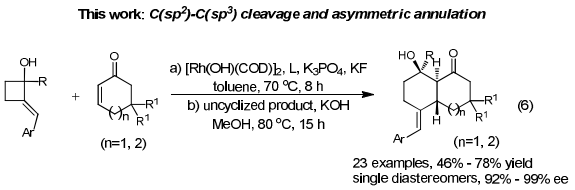


Figure 1. Representative natural products.

Therefore, new catalytic methods for the expedient synthesis of bicyclic motifs in a trans- and enantioselective fashion are highly desirable.

Studies of transition-metal-catalyzed selective cleavage of carbon–carbon single bonds as the initiation for further functionalizations have been booming in recent years due to the high potential of this strategy in synthesis.[6] Cyclobutenols and cyclobutanols are privileged building blocks in this field.[7] Murakami pioneered a series of studies on the rhodium-catalyzed tandem C-C single bond cleavage/formal cycloaddition of benzocyclobutenols with various functionalities including alkynes,[7q,f] vinyl ketones,[7j] carbene precursors,[7l] and allenes[7e]. As a special surrogate to benzocylobutenols, 2-alkylenecyclobutanols have attracted much less attention in C-C bond cleavage research field.[8] Therefore, the means to render 2-alkyledene cyclobutanols with similar reactivities of selective C-C bond cleavage and annulation would offer a new avenue to this rapidly expanding synthetic tool box.



Stimulated by the Murakami's work on successful cycloaddition of benzolcyclobutenol with acyclic alkyl vinyl ketones leading to tetralin skeletons,[7j] we envision here the feasibility of combining cyclic enones with 2-alkylenecyclobutanols and possible enantioinductions enabled by a proper chiral ligand. Thus, we report the highly efficient rhodium(I)-catalyzed formal [4+2] cycloaddition of 2-alkylene cyclobutanols with α,β-unsaturated cyclic ketones via a tandem C(sp2)–C(sp3) bond cleavage and cycloaddition leading to complex *trans*-bicyclic ring systems. Here, *i*Pr-Duphos is the most effective chiral ligand to enable enantioselective transformation.

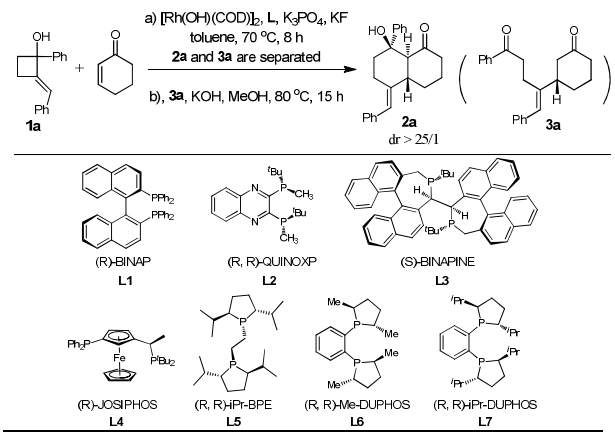
We started our studies by exploring the reaction of cyclohex-2-enone with (*E*)-2-benzylidene-1-phenylcyclobutanol. After numerous trials, the use of $[Rh(COD)OH]_2$ catalyst and K_3PO_4 as the base produced the desired product **2a** as a single diatereromer plus

[a] *Institute of Pharmaceutical Science, China Pharmaceutical University, Nanjing, P. R. China, E-mail: cpuzdy@163.com*
[b] *State Key Laboratory of Organometallic Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, P. R. China, Email:guozhuzhang@sioc.ac.cn*
Electronic Supplementary Information (ESI) available:

View Article Online
DOI: 10.1039/C7SC04784C

uncyclized **3a** in a ratio of 1/1. Interestingly, **3a** could be separated and converted to **2a** by treatment with KOH in MeOH at 80°C in 70% isolated yield as a single diastereomer indicating that cyclization is highly stereospecific (Table 1, entry 1).[9]

Table 1. Optimization of the reaction conditions for the rhodium (I)-catalyzed tandem ring opening and cyclization.



Entry[a]	L	2a/3a	Yield (2a)[%][b]	ee [%][c]
1[d]	-	1.0/1.0	30	-
2	-	2.1/1.0	60	-
3[e]	-	0/1.0	49	-
4	L1	-	-	-
5	L2	1.0/1.0	30	0
6	L3	1.0/2.0	43	27
7	L4	-	-	-
8	L5	1.2/1.0	28	87
9	L6	1.2/1.0	27	96
10[d]	L7	1.9/1.0	60	96

[a]Unless otherwise noted, two-step reactions were carried out: step a, **1a** (0.2 mmol), cyclohexenone (2 equiv), $[Rh(COD)OH]_2$ (2.5 mol %), **L** (10 mol %), K_3PO_4 (2 equiv), KF (2 equiv) heated in toluene (0.2 M) at 70°C for 8 h; step b, **3a** (isolated from the step a), KOH (1.1 equiv), heated in MeOH (0.1 M) at 80°C for 15 h. [b]Combined yield of two steps.[c]The absolute configuration of product was assigned by single crystal X-Ray analysis of **2a**.[d]Without KF. [e]The reaction conditions for step a were **1a** (0.2 mmol), cyclohexenone (2 equiv), $[Rh(COD)OH]_2$ (2.5 mol %), K_2CO_3 (1.1 equiv), and 10% H_2O in toluene (0.2 M) heated at 70°C for 8 h.

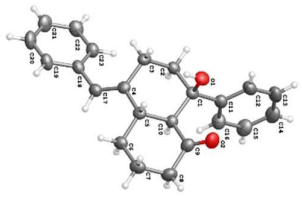
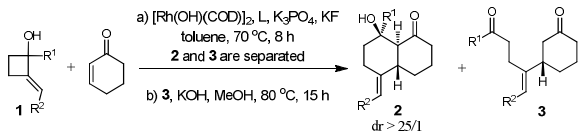


Figure 2. X-ray crystal structure of ***ent*-2**

To improve the yield of **2a**, a range of additives were tested, and to our delight, a 60% yield of **2a** was attained in the presence of KF which likely facilitates the formation of enolate and the next Aldol cyclization (Table 1, entry 2).[10] However, no further improvement in the yield of **2a** or the ratio of **2a** over **3a** was obtained after many experiments. We emphasized the use of commercial chiral ligands for asymmetric carbon-carbon bond formation. Several representative phosphine ligands such as BINAP, QuinoxP*, Binapine, and Josiphos were ineffective at catalyzing the reaction. They resulted in either low yields or negligible enantiomer ratios of **2a** (Table 1, entries 4 to 7). To our delight, a much improved enantioselectivity of 87% ee was obtained for **2a** with **L5** as the ligand (Table 1, entry 8). Further studies identified **L7** as the most effective ligand of those tested—they resulted in **2a** in 96% ee (Table 1, entry 10). Notably, the ee values of **3a** and **2a** are almost identical under the reaction conditions. The absolute configuration of the product was then determined with single crystal X-ray analysis of *ent*-**2a** (Figure 2). Thus, the optimal conditions were identified as a two-step procedure with **L7** as the ligand.

Table 2. Scope studies: enantioselective cycloadditions.[a, b]



Entry[a]	product	R^1	R^2	2/3	Yield (2)[%][b]	ee [%][c]
1	**2b**	*p*-MeC_6H_4	Ph	1.1/1.0	55	98
2	**2c**	*p*-$MeOC_6H_4$	Ph	1.3/1.0	58	97
3	**2d**	*p*-FC_6H_4	Ph	1.9/1.0	62	97
4	**2e**	*m*-^{i}PrC_6H_4	Ph	2.1/1.0	57	96
5	**2f**	*p*-^{n}BuC_6H_4	Ph	1.7/1.0	56	94
6	**2g**	Me	Ph	2.0/1.0	58	97
7	**2h**	Et	Ph	2.7/1.0	58	97
8[d]	**2i**	Ph	*p*-MeC_6H_4	2.8/1.0	57	95
9	**2j**	*p*-MeC_6H_4	*p*-MeC_6H_4	1.4/1.0	57	99
10	**2k**	*m*-ClC_6H_4	*p*-MeC_6H_4	2.6/1.0	66	96
11	**2l**	*p*-FC_6H_4	*p*-MeC_6H_4	3.8/1.0	77	92
12	**2m**	Ph	*o*-MeC_6H_4	2.1/1.0	57	98
13	**2n**	*p*-^{n}BuC_6H_4	*o*-MeC_6H_4	4.4/1.0	56	99
14	**2o**	*m*-ClC_6H_4	*o*-MeC_6H_4	3.0/1.0	68	>99
15	**2p**	Ph	*p*-$MeOC_6H_4$	1.4/1.0	54	97
16	**2q**	*p*-MeC_6H_4	*p*-$MeOC_6H_4$	4.2/1.0	78	99
17	**2r**	*p*-MeC_6H_4	*p*-ClC_6H_4	3.6/1.0	78	99
18	**2r**	Ph	2-fural	2.5/1.0	59	>99

[a]Unless otherwise noted, the two-step reactions were carried out under these optimized conditions (Table 1, entry 10). [b]Combined yield of two steps. [c]The absolute configuration was assigned by analogy.

We found a broad substrate scope with respect to the R^1 and R^2 of cyclobutanol (Table 2). With R^2 as a phenyl, various cyclobutanols bearing *para*- and *meta*-substituted phenyl groups (R^1) reacted smoothly to give the desired products in moderate to satisfactory yields and high enantioselectivities (ee = 94 – 98%); the substitutions could be alkyl, methoxy, and fluoro groups (Table 2, entries 1-5). The 1-alkylated 2-alkylenecyclobutanols are suitable substrates as well, and the desired bicyclic products were obtained in moderate yields with excellent ee (Table 2, entries 6, 7). The variations of substitutions on the alkylene were then briefly

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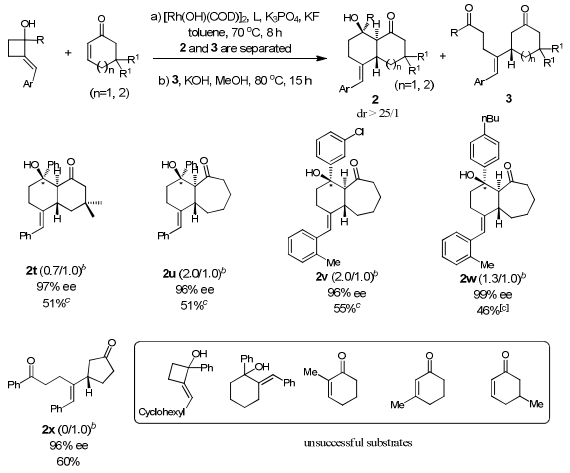
DOI: 10.1039/C7SC04784C

investigated, and to our delight arenes bearing electron-donating methyl and methoxy at the either *para*, or *ortho* positions with various combinations of benzene substitutions (R^1) are compatible with the reaction conditions (Table 2, entries 8 - 16). A chloro group on the *para* position of the R^2 was well tolerated (Table 2, entry 17). The reaction also proceeded well when a furyl group was employed (Table 2, entry 18).

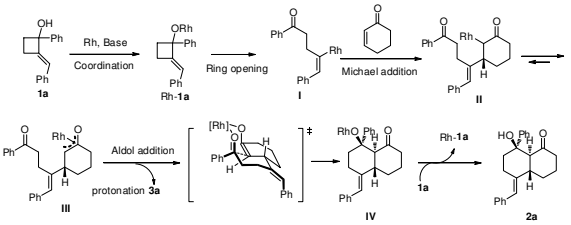
We then turned our attention to the variations on the α,β-unsaturated cyclic ketones. With **1a** as the substrate, a variety of cyclohex-2-enones were tested under optimal conditions. The reaction seemed very sensitive to the electronic and steric properties of the substitutions. Substrates with a methyl substituent either on the double bond or at the β position to the carbonyl group did not give the desired products. To our delight, 5,5-dimethylcyclohex-2-enone reacted under standard conditions to provide the desired product in moderate yield and with excellent ee as usual. We then surveyed other cyclic enones with different ring sizes. For cyclopent-2-enone, the diketone could be obtained in good yield with excellent ee; however, no cyclized product was observed under various conditions. The cyclohept-2-enone underwent annulation with **1a** under optimal conditions leading to [4.5.0] bicyclic products in moderate yield with excellent ee. This represents another type of important molecular scaffold that is difficult to access using other methods.[11]

Table 3. Scope studies: enantioselective cycloaddition[a]



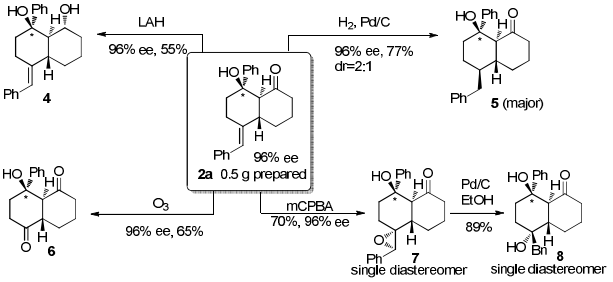
[a]Two-step reactions were carried out under the optimized conditions (Table 1, entry 10). The absolute configuration was assigned by analogy. [b]Ratio of **2**/**3** in step a. [c] Combined yield of **2** from two steps.

According to previous studies and our observations,[7f,j] a stepwise reaction mechanism is proposed (Scheme 1). At the beginning, a well-established rhodium(I) cyclobutanolate formation and β-carbon elimination occur to afford the vinylrhodium species **I**. A highly enantioselective Michael addition to the cyclohexanone occurs to form intermediate II that undergoes isomerization to give the enolate **III**.[12] The intramolecular aldol type cyclization proceeds in a highly stereoselective manner. Hydrolysis would afford the final bicyclic product with regeneration of the catalyst. Concurrently, protonation of **III** is another pathway to yield the uncyclized product **3a**.



Scheme 1. Proposed catalytic cycle.

This series of bicyclic products are synthetically versatile building blocks due to the presence of several different functional groups for further elaborations (Scheme 2). For example, reduction of the ketone in **2a** using LiAlH4 produced the corresponding diol **4** in 55% yield as a single diastereomer. Reductive hydrogenation of the *exo* alkene gave rise to **5** as two inseparable diastereomers (2/1 ratio) both with four consecutive stereogenic centers. The double bond could be cleaved by ozonolysis leading to diketone **6** with slightly decreased ee. Epoxidation and the ring opening sequence proceeded effectively to afford both **7** and **8** as single diastereomer.



Scheme 2. Synthetic utilities of *trans*-bicyclic products.

Conclusions

In summary, we developed a rhodium(I)-catalyzed cycloaddition reaction of 2-alkyledene cyclobutanols with α,β-unsaturated cyclic ketones to form *trans*-bicyclic ketones containing three contiguous stereogenic centers in moderate yields with excellent enantioselectivities. Both [4.4.0] and [4.5.0] bicyclic systems are readily accessible in an optically pure form. The synthetic potential of products was demonstrated via several easy derivatizations.

Conflicts of interest

There are no conflicts to declare.

Acknowlegements

We are grateful to NSFC-21421091, 21772218, 30973607, 81172934, XDB20000000, the "Thousand Plan" Youth program, State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, and the Chinese Academy of Sciences.

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DOI: 10.1039/C7SC04784C

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