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Asymmetric Annulation of Donor–Acceptor Cyclopropanes with Dienes

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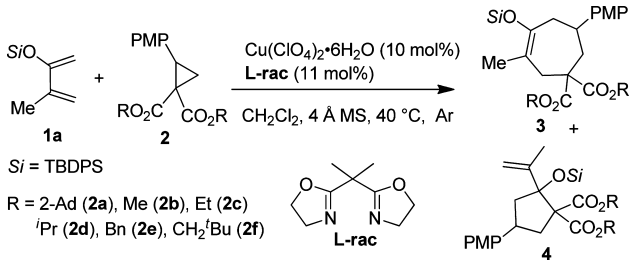
Supporting Information

ABSTRACT: An efficient [4 + 3] cycloaddition reaction of D–A cyclopropanes with dienes has been successfully developed. The reaction proceeds well with various dienolsilyl ethers in the presence of Lewis acid, delivering a variety of cycloheptenes and [*n*,5,0]carbobicycles with excellent stereoselectivity. The asymmetric version of this reaction is also realized using a newly designed chiral Cy-TOX ligand, providing a new approach to access optically active cycloheptenes and [*n*,5,0]carbobicycles. Mechanisic study reveals that the reaction involves a stepwise pathway, which undergoes an unusual ring opening of five-membered [3 + 2] intermediate and sequential intramolecular cyclization to afford the thermodynamically stable [4 + 3] annulation product.

Cycloheptenes and [*n*,5,0]carbobicycles are widely present as key structures in a large number of natural products and biologically active molecules such as salvicnol, palustrol, and dolastanes.[1] Accordingly, the establishment of efficient and reliable methodologies for the highly enantioselective construction of this structural motif from simple materials is highly desirable.[2] Herein, we envision that a [4 + 3] annulation protocol of donor–acceptor (D–A) cyclopropanes with dienolsilyl ethers may serve as a new approach for the aforementioned subunits. However, reactions of D–A cyclopropanes with common dienolsilyl ethers usually result in ring-opening products or [3 + 2] cycloaddition products, which suggests this transformation to be challenging.[3−7] In our continuing effort on studies of D–A cyclopropanes in organic synthesis, we developed a novel and efficient [4 + 3] reaction of cyclopropane 1,1-dicarboxylates with both acyclic and cyclic dienolsilyl ethers, which provided a new and concise approach to the synthesis of cycloheptenes and [*n*,5,0]carbobicycles. Importantly, the catalytic asymmetric version of this transformation is also realized with high enantioselectivity by employing a newly designed chiral trisoxazoline (Cy-TOX).[8,9] Herein, we report the preliminary results.

Initially, the reaction of dienolsilyl ether **1a** with both dimethyl and diethyl cyclopropane 1,1-dicarboxylate (**2b**, **2c**) were tried by employing 10 mol % of bisoxazoline (BOX) **L-rac**/$Cu(ClO_4)_2·6H_2O$. There are two possible cycloadducts, [4 + 3] cycloadduct **3** and [3 + 2] cycloadduct **4**. However, no product was observed due to the decomposition of the cyclopropanes and side reactions (Table 1, entries 1–2). In the initial exploration, the ester group[10] was found to significantly influence the reaction. When the isopropyl ester was used, 38% yield of the desired product was achieved with a 60/40 ratio of **3**/**4** (entry 3). To our delight, the [4 + 3] cycloadduct could be highly selectively obtained albeit in moderate yield when using benzyl ester (entry 4). Further study showed that 87% yield of **3** was obtained when di-2-adamantyl (2-Ad) cyclopropane 1,1-dicarboxylate **2a** was employed (entry 6). Further screening[11] of Lewis acids and solvents led to the optimal reaction condition under which the [4 + 3] product **rac-3a** was furnished exclusively in 95% yield in dicloromethane in the presence of 10 mol % **L-rac**/$Cu(SbF_6)_2$ (Table 1, entry 7).

Table 1. Reaction Optimization[a]



entry	2	time (h)	conv. (%)[b]	3/4[b]	yield (%)[c]
1	**2b**	1	>99	–	<5
2	**2c**	1	>99	–	<5
3	**2d**	53	91	60/40	38
4	**2e**	1	>99	>99/1	56
5	**2f**	31	92	>99/1	77
6	**2a**	64	>99	95/5	87
7[d]	**2a**	8	>99	>99/1	95

[a]**1a** (0.30 mmol), **2** (0.20 mmol), $Cu(ClO_4)_2·6H_2O$ (0.020 mmol), **L-rac** (0.022 mmol), CH_2Cl_2 (2.0 mL), 40 °C, 4 Å MS (100 mg), argon. [b]Conversion and the ratio of **3**/**4** were determined by ^1H NMR spectroscopy. [c]Isolated yield. [d]$Cu(SbF_6)_2$ was used. Ad = 2-adamantyl. PMP = *para*-methoxyphenyl

The substrate scope of this process was examined next. A variety of electron-rich phenyl cyclopropanes **2** reacted smoothly with conjugated enol silyl ethers **1** to afford the [4 + 3] cycloadducts in good to excellent yields (Table 2, entries 1–3). Cyclopropanes with heteroaryl or alkenyl substituents

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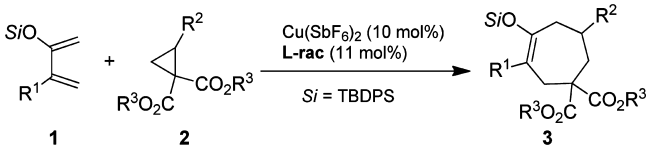
Table 2. Generality of the Reaction[a]



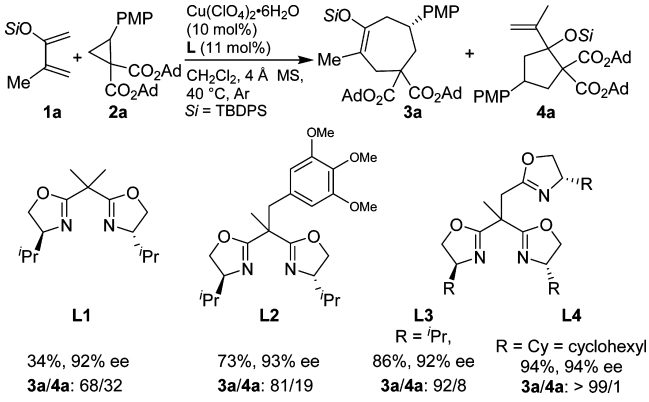
entry	R^1	R^2	R^3	time (h)	product	yield (%)[b]
1	Me(**1a**)	4-MeOC$_6$H$_4$ (**2a**)	2-Ad	8	**rac-3a**	95
2	Me(**1a**)	4-BnOC$_6$H$_4$ (**2g**)	2-Ad	56	**rac-3b**	88
3	Me(**1a**)	(3,4-MeO)2C$_6$H$_3$ (**2h**)	2-Ad	34	**rac-3c**	68
4	Me(**1a**)	*N*-Boc-Indolyl (**2i**)	2-Ad	30	**rac-3d**	80
5	Me(**1a**)	CH═CHPh (**2j**)	2-Ad	15	**rac-3e**	80
6[c]	Me(**1a**)	2-thiophenyl (**2k**)	2-Ad	7	**rac-3f**	72
7[c]	Me(**1a**)	5-Me-2-thiophenyl (**2l**)	2-Ad	12	**rac-3g**	84
8[d]	Me(**1a**)	Ph (**2m**)	Bn	14	**rac-3h**	79
9[d]	Me(**1a**)	2-MeC$_6$H$_4$ (**2n**)	Bn	24	**rac-3i**	90
10[d]	Me(**1a**)	3-MeC$_6$H$_4$ (**2o**)	Bn	10	**rac-3j**	84
11[d]	Me(**1a**)	4-MeC$_6$H$_4$ (**2p**)	Bn	8	**rac-3k**	94
12[d]	Me(**1a**)	4-F-C$_6$H$_4$ (**2q**)	Bn	10	**rac-3l**	86
13[d]	Me(**1a**)	4-Cl-C$_6$H$_4$ (**2r**)	Bn	14	**rac-3m**	75
14[d]	Me(**1a**)	4-Br-C$_6$H$_4$ (**2s**)	Bn	13	**rac-3n**	73
15[d]	Me(**1a**)	4-I-C$_6$H$_4$ (**2t**)	Bn	10	**rac-3o**	75
16[d]	Me(**1a**)	4-^{t}Bu-C$_6$H$_4$ (**2u**)	Bn	10	**rac-3p**	93
17[d]	Me(**1a**)	vinyl (**2v**)	Bn	10	**rac-3q**	52
18	Et (**1b**)	4-MeOC$_6$H$_4$ (**2a**)	2-Ad	32	**rac-3r**	96
19	Ph (**1c**)	4-MeOC$_6$H$_4$ (**2a**)	2-Ad	24	**rac-3s**	94
20[e]	H (**1d**)	4-MeOC$_6$H$_4$ (**2a**)	2-Ad	12	**rac-3t**	75

[a]**1** (0.30 mmol), **2** (0.20 mmol), Cu(SbF$_6$)$_2$ (0.020 mmol), **L-rac** (0.022 mmol), CH_2Cl_2 (2.0 mL), 40 °C, 4 Å MS (100 mg), argon. No [3 + 2] cycloadducts were observed. [b]Isolated yield. [c]DCE (2.0 mL), at 60 °C. [d]With 20 mol % of catalyst. [e]DCE (1.0 mL), at 80 °C.

delivered high yields of the desired products. (entries 4−7). For less active cyclopropanes, the benzyl ester group was demonstrated to be more favored to ensure a high yield (entries 8−17). The reaction was found to be insensitive to the ortho-, meta-, or para-substituents at the aromatic rings (entries 9−11). Notably, reactions of vinyl-substituted cyclopropane also proceeded smoothly to give the desired product in 52% yield (entry 17). Furthermore, enol silyl ethers with different substituents (R^1 = Me, Et, Ph, H) were all suitable substrates (entries 1, 18−20).

The presence of the scaffold in enantiopure form in many natural products encouraged us to develop the asymmetric version of this reaction. As BOX **L-rac** is highly efficient for the racemic reaction, we first tried the asymmetric reaction with chiral BOX **L1** instead of **L-rac** (Scheme 1). Unfortunately, we found that BOX **L1** slowed down the reaction dramatically, resulting in 34% yield of **3a** due to poor regioselectivity and incomplete conversion. SaBOX **L2** was also employed, which proved to be very efficient in the asymmetric [3 + 2] annulation reaction of D−A cyclopropanes with enol silyl ether.[3c] The yield of **3a** was improved to 73% in 93% ee with a 81/19 ratio of **3a**/**4a**. Further examination[11] of Lewis acids, solvents, ester groups, SaBOX, and TOX ligands as well as reaction temperature showed that a mixture of [4 + 3] and [3 + 2] annulation products were obtained. The best result was achieved by employing TOX **L3** which gave 86% yield of **3a** in 92% ee, with a 92/8 ratio of **3a**/**4a**.

Scheme 1. Ligand Effects on Asymmetric [4 + 3] Annulations



To further improve the selectivity and gain a deeper understanding of the inter-relationship between [4 + 3] and [3 + 2] products, ^{1}H NMR was used to monitor the reaction. As shown in Figure 1, at the initial stage of the reaction (1 h),

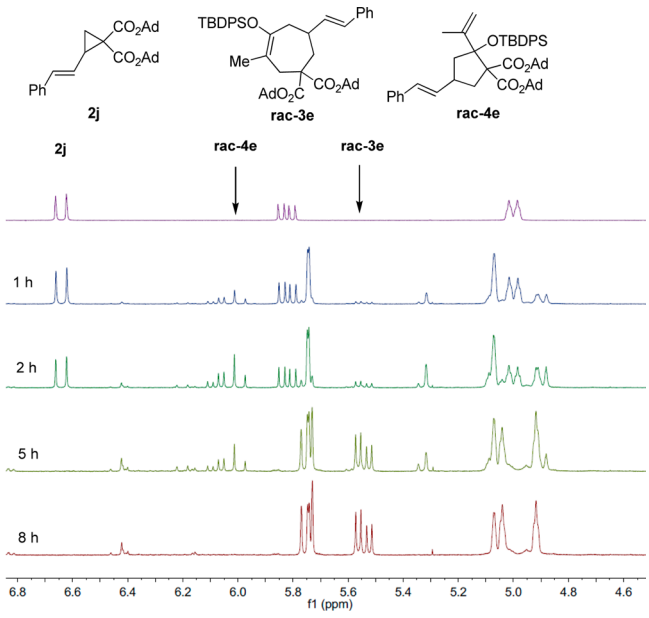


Figure 1. Monitoring the Cu(SbF$_6$)$_2$/**L-rac**-catalyzed reaction between **1a** and **2e** in CH_2Cl_2 by ^{1}H NMR.

the [3 + 2] annulation product **rac-4e** (unique peaks at 6.0 ppm) was produced as the major products with a 35/65 ratio of **rac-3e**/**rac-4e**. After 5 h, the peaks of cyclopropane **2j** disappeared, and the [4 + 3] product **rac-3e** became predominant. Eight hours later, **rac-4e** was converted into **rac-3e** completely. This observation suggests the [3 + 2] annulation is a kinetically controlled process, and the [4 + 3] product **rac-3e** is thermodynamically favored. In addition, the intermediate cyclopetane **rac-4e** was isolated and was subjected to the optimized reaction conditions (Scheme 2). Significantly, it was found that **rac-4e** was readily converted to the corresponding cycloheptene **rac-3e** in 82% yield after 10 h. Moreover, the optically active **4e** (88% ee) could also be transformed into **3e** (88% ee) in the presence of 10 mol % BOX **L-rac**/Cu(SbF$_6$)$_2$ without loss of enantiomeric excess.[11] These results clearly demonstrate that the reaction mainly

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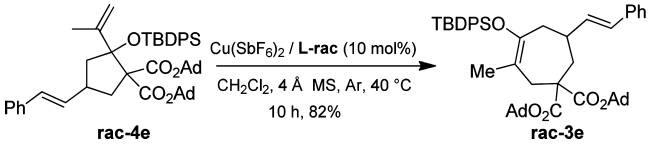
Scheme 2. Conversion of [3 + 2] Cycloadduct to [4 + 3] Product



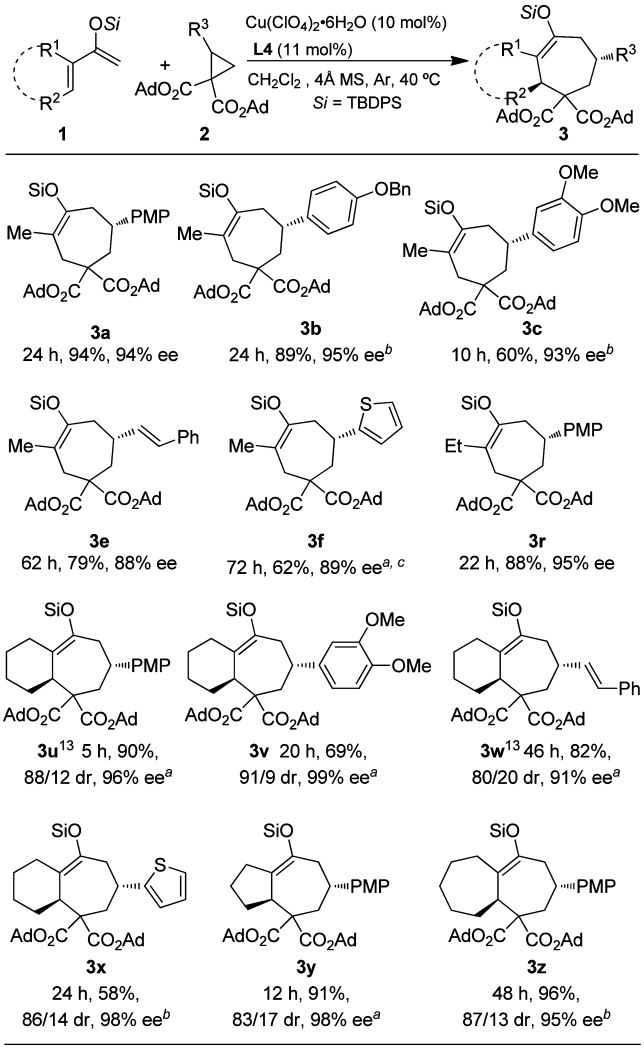
undergoes a stepwise mechanism in which the [3 + 2] annulation first takes place kinetically, followed by the ring opening of the [3 + 2] intermediate and intramolecular cyclization to afford the thermodynamically stable [4 + 3] annulation product. The stepwise mechanism of our methodology distinguishes it from the concerted cycloaddition reaction of 1,3-diphenylisobenzofuran with cyclopropanes.[12]

Based on these observations, we continued to optimize the reaction conditions by means of several typical methods that would favor a thermodynamically controlled process, including elevating the reaction temperature and prolonging the reaction time. However, no further improvement on increasing the ratio of **3a**/**4a** was made. In order to minimize the undesired [3 + 2] products and to increase the catalytic efficiency, we designed new ligands that can speed up this transformation. Since ^{i}Pr-TOX **L3** was found to favor the [4 + 3] product, we envisioned that TOX ligands possessing a similar chiral environment, but bearing sterically rigid cyclohexyl backbones, might be beneficial for the transformation of **4a** to **3a**. As expected, we found that Cy-TOX **L4** could promote the reaction very efficiently, affording **3a** exclusively in 94% yield with 94% ee (Scheme 1).

Under the optimized conditions, **1a** reacted with **2a** in the presence of $Cu(ClO_4)_2{\cdot}6H_2O$ and **L4** in dichloromethane providing **3a** in 94% yield with 94% ee (Table 3). Good to excellent levels of enantioselectivity were obtained in the reaction of electron-rich phenyl-substituted cyclopropanes with 88−95% ee (**3a**−**3c**, **3r**). Moreover, cyclopropanes with heteroaryl and alkenyl substitutents were also compatible for the reaction with high enantioselectivity (**3e**, **3f**). Of note is the cyclic enol silyl ethers, bearing five-, six- and seven-membered rings, could also react with electron-rich phenyl- and aryl-substituted cyclopropanes smoothly in good yields with excellent enantioselectivities, even under an elevated temperature in DCE (**3u**−**3w**, **3y**).[13] The obtained optically active [*n*,5,0]carbobicyclic structural motif is a key intermediate in a plenty of biologically active and natural products.[1]

In conclusion, an efficient Cu(II)/TOX catalyzed [4 + 3] annulation of D−A cyclopropanes with dienes has been developed. By employing a newly designed chiral Cy-TOX instead of BOX ligand, asymmetric version of the current reaction can be realized with excellent enantioselectivity, providing an efficient and new access to a variety of optically active cycloheptenes and [*n*,5,0]carbobicycles. To the best of our knowledge, these reactions represent the first examples of catalytic asymmetric [4 + 3] annulation reactions of enol silyl ethers with D−A cyclopropanes. Preliminary study reveals that a stepwise mechanism is mainly involved in the reaction, which undergoes an unusual five-membered ring opening of the [3 + 2] intermediate, followed by an intramolecular cyclization to afford the thermodynamically stable [4 + 3] annulation product.

Table 3. Asymmetric [4 + 3] Annulation of 1 with 2



Reaction conditions: $Cu(ClO_4)_2{\cdot}6H_2O$ (0.020 mmol), **L4** (0.022 mmol), **1** (0.30 mmol) and **2** (0.20 mmol) in 2.0 mL of CH_2Cl_2, 40 °C, the ratio of [4 + 3] and [3 + 2] cycloadducts is >99/1. [a]60 °C, in DCE. [b]Using $Cu(SbF_6)_2$. [c]20 mol % $Cu(ClO_4)_2{\cdot}6H_2O$ was used.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterizations, and analytical data of products, spectra of NMR, and HPLC. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b04429.

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Notes

The authors declare no competing financial interest.

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