Concise Report

Donor-acceptor cyclopropane, Cyclic ketones, [3+2] annulation, Asymmetric catalysis, Copper

CJC Chinese Journal of Chemistry 中国化学 An International Journal

Asymmetric Catalytic [3+2] Annulation of Donor-Acceptor Cyclopropane with Cyclic Ketones: Facile Access to Enantioenriched 1-Oxaspiro[4.5]decanes†

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Cite this paper: *Chin. J. Chem.* **2020**, *38*, 1629—1634. **DOI: 10.1002/cjoc.202000277**

Summary of main observation and conclusion A copper catalyzed enantioselective [3+2] annulation of donor-acceptor cyclopropanes with cyclic ketones has been developed, providing a concise protocol to enantioenriched 1-oxaspiro[4.5]decanes in up to 98% yield with up to >99/1 dr and up to 92% ee. In addition, this method also provides a facile access to the enantioselective desymmetrisation of various 4-substituted cyclohexanones. The resulting products were easily converted to the core structures of two natural products Heliespirones A and halogenated sesquiterpene isolated from *L. saitoi.*

Background and Originality Content

1-Oxaspiro[4.5]decane skeleton bearing a stereogenic spiro carbon usually appears as core structure in a good number of biologically active natural products (Figure 1).[1] For examples, Cyclopamine was found as an inhibitor of Hh signaling, and the inhibition of Hh signaling has been considered as a novel route to anticancer therapies;[1d] Heliespirones A showed potential allelopathic activity in the coleoptiles bioassay;[1f] Theaspirone and Dactyloxene-B are important natural perfume and widely applied in flavoring industry.[1a,1c] Owing to its important bioactivity and unique oxa-spirocyclic structure, 1-oxaspiro[4.5]decane attracts continuing interest to organic synthetic chemists. Aiming to this interesting skeleton, various synthetic strategies have been developed, such as intramolecular oxygen-nucleophilic cyclization of alcohol,[2] 1,5-transfer/cyclization,[3] [3+2] cycloaddition of spiro oxiran with olefin[4] and so on. However, for a long time, enantioselective construction of optically active 1-oxaspiro[4.5]decanes has been rare.[5] In 2012, Tu and co-workers developed an elegant organocatalytic asymmetric 1,5-transfer/cyclization reaction, leading to an efficient approach to chiral spiroether compounds in 62%—87% yields, up to 94/6 dr and up to 96% ee (Scheme 1a).[5a] In 2006, Yadav and co-workers demonstrated that Lewis acid catalyzed [3+2] annulation of silylmethylcyclopropanes with cyclohexanone could provide a facile access to the racemic 1-oxaspiro[4.5]decane (Scheme 1a).[6a] In 2012, Waser and co-workers reported a catalytic enantiospecific [3+2] annulation of aminocyclopropanes with cyclohexanone, where enantioenriched cyclo-

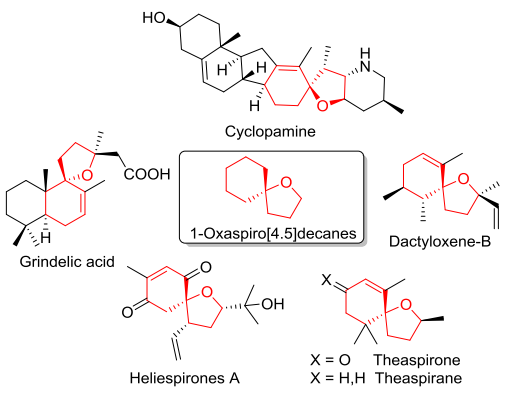
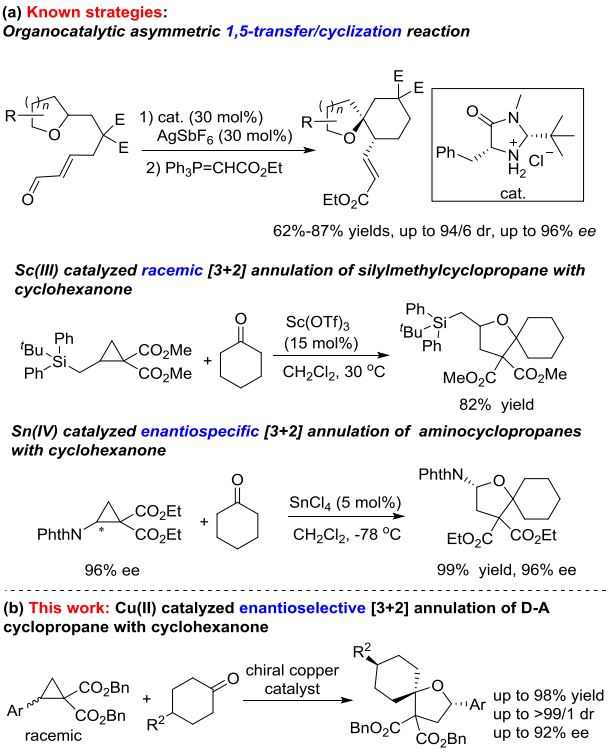


Figure 1 Natural products containing 1-oxaspiro[4.5]decane skeleton.

Scheme 1 Enantioselective construction of optically active 1-oxaspiro[4.5]-decanes



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† Dedicated to the 70th Anniversary of Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences.

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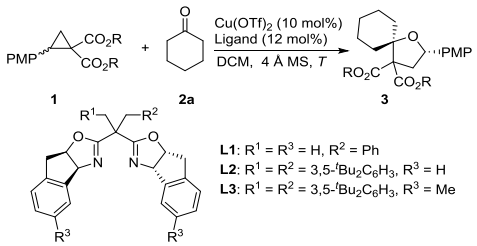
propanes were converted to enantioenriched 1-oxaspiro[4.5]decanes in high efficiency (Scheme 1a).[7] Donor-acceptor (D-A) cyclopropanes are very useful organic synthons, which have been widely employed in various asymmetric [3+*n*] annulation reactions for the rapid construction of chiral cyclic compounds.[8-10] However, the highly enantioselective reaction of D-A cyclopropanes with ketones has not been realized to the best of our knowledge. Herein, we developed a chiral copper catalyzed asymmetric [3+2] annulation of D-A cyclopropane with cyclic ketones, delivering a wide range of optically active 1-oxaspiro[4.5]decanes in high yields with good to excellent enantioselectivity (Scheme 1b). Meanwhile, this method also provided an efficient approach to the enantioselective desymmetrisation of 4-substituted cyclohexanones.[11]

Results and Discussion

Initially, dimethyl 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (**1**) was reacted with cyclohexanone **2a** in the presence of catalytic amount of $Cu(OTf)_2$ as metal salt and **L1** as chiral ligand and in DCM (dichloromethane) at room temperature. Only 38% yield of the desired 1-oxaspiro[4.5]decane product was obtained with 44% ee, accompanied with the decomposition of the cyclopropane methyl diester substrate in the current catalyst system (Table 1, entry 1). When a more stable 1,1-cyclopropane ethyl diester was employed as starting material, both the yield and the enantioselectivity were improved (Table 1, entry 2). Thus, cyclopropane bearing two benzyl ester groups was used, which was found to be more suitable in the asymmetric [3+2] annulation reaction with cyclohexanone, affording the 1-oxaspiro[4.5]decane **3a** in 83% yield with 48% ee (Table 1, entry 3). Lowering the reaction temperature could dramatically increase the enantioselectivity of this reaction. When the reaction was carried out at 0 °C, 70% ee could be obtained and 93% yield was achieved by prolonging the reaction time (Table 1, entry 4). By employing SaBOX ligand[12-13] **L2** containing two bulky side arms, the enantioselectivity was further improved to 76% ee (Table 1, entry 5). Continuing to lower the reaction temperature to –20 °C could slightly increase the ee value (Table 1, entry 6). When two methyl groups were installed on the indanyl skeletons of **L2** to furnish **L3**,[14] a dramatic increase of the enantioselectivity of this [3+2] annulation was observed, leading to the 1-oxaspiro[4.5]decane **3a** in 95% yield with 90% ee (Table 1, entry 7). In addition, both the yield and the enantioselectivity could be further improved by employing a mix-solvent system with the ratio of DCM to THF (tetrahydrofuran) as 9 : 1, which afforded **3a** in 98% yield with 91% ee (Table 1, entry 8).

Table 1 Optimization of reaction conditions

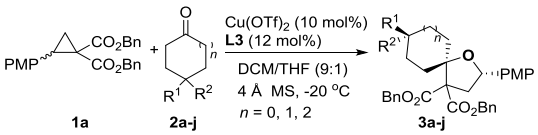


Entry[a]	R	*T*/°C	Ligand	Yield[b]/%	ee[c]/%
1	Me	r.t.	**L1**	38	44
2	Et	r.t.	**L1**	52	49
3	Bn	r.t.	**L1**	83	48
4	Bn	0	**L1**	93	70
5	Bn	0	**L2**	90	76
6	Bn	-20	**L2**	91	83
7	Bn	-20	**L3**	95	90
8[d]	Bn	-20	**L3**	98	91

[a] Conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $Cu(OTf)_2$ (0.02 mmol), ligand (0.024 mmol), [**1**] = 0.1 M in DCM, 4 Å MS (100 mg). [b] Isolated yields. [c] Determined by chiral HPLC analysis. [d] DCM/THF = 9/1.

With the optimized reaction conditions in hand (Table 1, entry 8), we next evaluated the reaction scope of this catalyst system. As shown in Table 2, the reaction proceeded smoothly with a range of mono-substituted cyclohexanons by using $Cu(OTf)_2$/**L3** as catalyst, including various groups such as –Me, –Et, –^{i}Pr, –^{t}Bu and *t*-amyl, leading to the desymmetrization products **3b–f** in 83%—97% yields, up to > 99/1 dr and 91%—92% ee (Table 2, entries 2—6). The current catalytic system is also compatible with 4,4-disubstituted cyclohexanone (**2g**) and 4-methylene cyclohexanone (**2h**), furnishing the corresponding products **3g–h** in 71%—95% yields with 85%—88% ee (Table 2, entries 7—8). In addition, both cyclopentanone (**2i**) and cycloheptanone (**2j**) were compatible, giving the corresponding products **3i** and **3j** in 53%—92% yields with 37%—65% ee, respectively(entries 9—10).

Table 2 Substrate scope of cyclic ketones



Entry[a]	R^1, R^2	**3**	Yield[b]/%	dr[c]	ee[d]/%
1	H, H	**3a**	98	—	91
2	Me, H	**3b**	88	86/14	92
3	Et, H	**3c**	97	88/12	92
4	^{n}Pr, H	**3d**	90	95/5	92
5	^{i}Pr, H	**3e**	90	> 99/1	92
6	*t*-amyl, H	**3f**	83	> 99/1	91
7	Me, Me	**3g**	95	—	85
8	(**2h**)	**3h**	71	—	88
9	(**2i**)	**3i**	92	—	65
10	(**2j**)	**3j**	53	—	37

[a] Conditions: **1a** (0.2 mmol), **2** (0.4 mmol), $Cu(OTf)_2$ (0.02 mmol), **L3** (0.024 mmol), [**1a**] = 0.1 M in DCM/THF, 4 Å MS (100 mg). [b] Isolated yields. [c] Determined by crude ^{1}H NMR. [d] Determined by chiral HPLC analysis.

Further investigation on the substrate scope of cyclopropanes was summarized in Table 3. We were pleased to find that cyclopropanes **1b** and **1c** bearing cinnamyl or α-methyl cinnamyl substituents were suitable reaction candidates, and provided the corresponding products **3k** and **3l** in 82%—90% yields with 80%—86% ee (Table 3, entries 1—2). Cyclopropanes containing heterocyclic substituents such as thienyl and indolyl groups were also tolerated in the current chiral copper catalyst system, delivering various 1-oxaspiro[4.5]decanes **3m–n** in up to 98% yield with up to 87% ee (Table 3, entries 3—4).

Since the resulting 1-oxaspiro[4.5]decanes were liquid, in order to determine the absolute configuration of the product, **3f** was transformed to the solid product **3f'** by an ester aminolysis reaction with 4-bromoaniline in a basic condition. The absolute configuration of **3f'** was determined by X-Ray diffraction analysis as 2*S*, 5*S*, 8*R*, as shown in Scheme 2.[15]

The current method provided a facile access to important chiral oxaspiro[4.5]decane scaffolds. By simple functional group transformations, the core structures of two natural products were synthesized as shown in Scheme 3. Firstly, the cinnamyl group of

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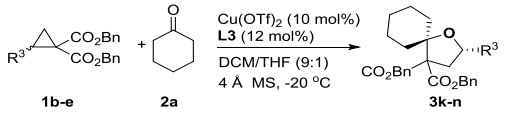
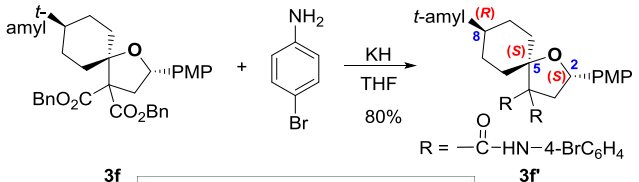
Table 3 Substrate scope of cyclopropane

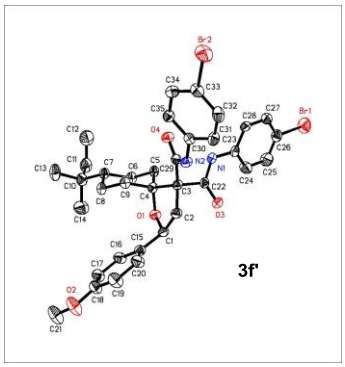


Entry[a]	R^3	3	Yield[b]/%	ee[c]/%
1	PhCH=CH	**3k**	90	86
2	PhCH=CMe	**3l**	82	80
3	2-thienyl	**3m**	87	87
4	*N*-Boc-2-indolyl	**3n**	98	75

[a] Conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $Cu(OTf)_2$ (0.02 mmol), **L3** (0.024 mmol), [**1**] = 0.1 M in DCM/THF, 4 Å MS (100 mg). [b] Isolated yields. [c] Determined by chiral HPLC analysis.

Scheme 2 Determination the absolute configuration of **3f**



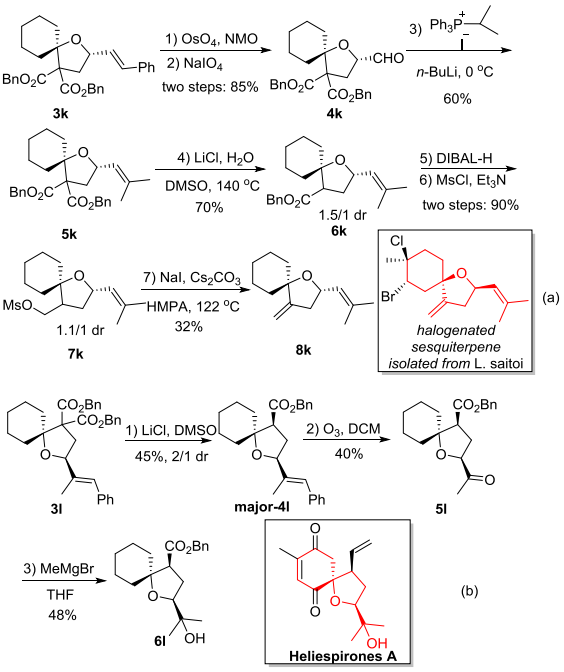


3k was oxidized to formyl group to afford **4k** in 85% yield by two steps. Introducing an olefin to **4k** by a Wittig reaction, **5k** was obtained in 60% yield. Then the decarboxylation was conducted in order to remove one of the ester group with a yield of 70% to give **6k**, and the remaining ester group of **6k** was reduced to hydroxyl group, followed by being treated with MsCl to furnish **7k** in 90% yield by two steps. At last, after elimination of the MsO-group, **8k** was yielded in 32% yield to produce the core structure of a halogenated sesquiterpene isolated from *L. saitoi*[1e] (Scheme 3a). Meanwhile, **3l** was easily transformed to **4l** by decarboxylation reaction with LiCl in DMSO, and **4l** was then converted to **5l** by an ozonization reaction. The carbonyl group of **5l** was able to transform to tertiary alcohol via Grignard reaction to give **6l** as the core structure of Heliespirones A[1f] (Scheme 3b).

A catalytic cycle was proposed in Figure 2. The catalysis would be initiated by the chiral copper complex A generated via coordination of the copper salt with chiral ligand followed by the activation of cyclopropane **1** to form species **B**. Then, an *O*-nucleophilic attack of ketone **2** to species **B** would generate species **C** followed by the ring closure to deliver species **D**. Finally, species **D** give product **3** and release the copper catalyst **A**, thus accomplishing the catalytic cycle.

Based on our previous study on the crystal structure of **L2**/$CuBr_2$ complex,[9g] an enantio-induction model was proposed to explain the observed enantioselectivity. As shown in Figure 3, the approach of the *Si* face of ketone to the transient (*R*)-cyclopropane (left) should be more favored, which suffers less steric interactions with the ligand indanyl substituent. This induction model

Scheme 3 Transformations of products **3i** and **3j**



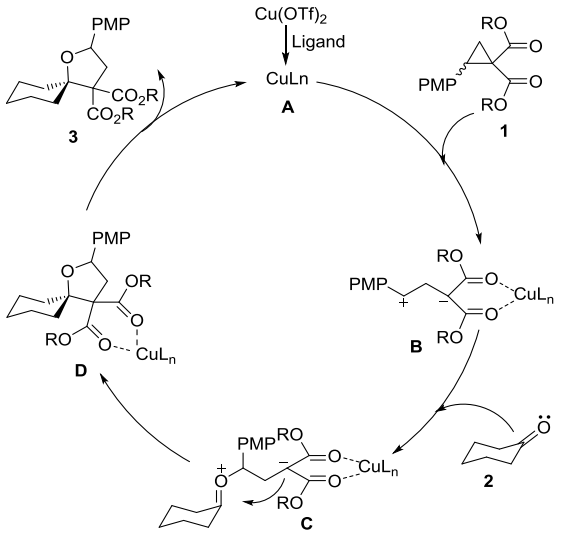


Figure 2 Proposed catalytic cycle

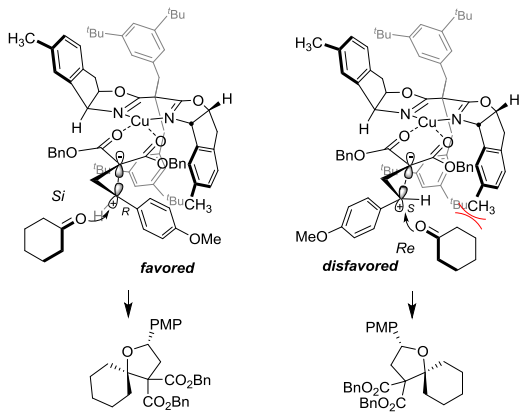


Figure 3 Proposed stereoinduction model.

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is in accordance with the experimental results as listed in Tables 2 and 3.

Conclusions

In summary, we have developed an enantioselective catalytic asymmetric [3+2] annulation of D-A cyclopropanes with cyclic ketones. In the presence of copper(II)/SaBOX complex as catalyst, various cyclopropanes, as well as many different cyclohexanones with substituents at 4-position reacted smoothly, providing a facile approach to the construction of optically active 1-oxaspiro-[4.5]decanes in up to 98% yield with up to 99/1 dr and up to 92% ee. Furthermore, this method also furnished an efficient access to the enantioselective desymmetrisation of 4-substituted cyclohexanones. In the application of this method, the core structures of Heliespirones A and a halogenated sesquiterpene isolated from *L. saitoi* were synthesized by simple functional group transformations. Further application of the useful method to the construction of biologically active molecules is ongoing in our laboratory.

Experimental

Typical procedure for the [3+2] annulation (**3a** as an example): A mixture of $Cu(OTf)_2$ (0.02 mmol), **L3** (0.024 mmol) and 100 mg 4 Å molecular sieve in the mixture of DCM (1.8 mL) and THF (0.2 mL) was stirred at room temperature for 2 h under the atmosphere of nitrogen. Substrate **1a** (0.2 mmol) was added, and the mixture was stirred for 10 min at room temperature. Then the reaction system was cooled to –20 °C and substrate **2a** (0.4 mmol) was added at –20 °C. After the reaction was completed (monitored by TLC), the reaction was filtered through a glass funnel with thin layer (30 mm) of silica gel (100—200 mesh) and eluted with DCM. The filtrate was concentrated under reduced pressure, purified by flash chromatography (petroleum ether/ethyl acetate = 50/1) to afford the product **3a** as a colorless oil, in 98% yield with 91% ee (Chiralpak AD-H, *n*-hexane/*i*PrOH = 90/10, 0.7 mL/min, λ = 280 nm: t_R(minor) = 14.3 min, t_R(major) = 16.9 min); $[\alpha]_D^{27}$= –4.1° (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.32—7.22 (m, 12H), 6.83 (d, *J* = 8.1 Hz, 2H), 5.24—5.05 (m, 5H), 3.76 (s, 3H), 2.92 (dd, *J* = 13.7, 7.6 Hz, 1H), 2.55 (dd, *J* = 13.7, 8.7 Hz, 1H), 1.88—1.53 (m, 9H), 1.12—1.08 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.2, 169.1, 158.7, 135.2, 135.1, 134.8, 128.5, 128.4, 128.2, 128.0, 127.1, 113.5, 85.6, 76.9, 67.5, 67.1, 67.0, 55.1, 41.2, 33.1, 31.4, 25.3, 22.3, 22.1. IR (neat) *v*: 3033, 2932, 2852, 1730, 1612, 1586, 1513, 1454, 1372, 1286, 1243, 1171, 1066, 1035, 984, 910, 827, 735, 696 cm^{-1}; HRMS-ESI $[M+NH_4]^+$: Calculated for $C_{32}H_{38}NO_6^+$, 532.2694; Found: 532.2700.

Supporting Information

Experimental procedures and characterization data for all products and crystallographic data are included. The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.202000277.

Acknowledgement

We thank the NSFC (Nos. 91956103, 21772224), the CAS (Nos. QYZDY-SSW-SLH016, XDB20000000), and the STCSM (No. 17JC1401200) for the financial support.

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[15] CCDC 2004633 (**3f'**) contains the supplementary crystallographic data, which can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Manuscript received: May 25, 2020
Manuscript revised: July 13, 2020
Manuscript accepted: July 20, 2020
Accepted manuscript online: July 22, 2020
Version of record online: XXXX, 2020

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