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Synthesis

A Versatile Enantioselective Catalytic Cyclopropanation-Rearrangement Approach to the Divergent Construction of Chiral Spiroaminals and Fused Bicyclic Acetals

Li Zhou[+], Wen-Guang Yan[+], Xiu-Li Sun, Lijia Wang, and Yong Tang**

Dedicated to Shanghai Institute of Organic Chemistry on the occasion of its 70th anniversary

Abstract: *A highly enantioselective synthesis of various chiral heterobicyclic molecules including spiroaminals and fused bicyclic acetals has been developed via a chiral copper catalyzed cyclopropanation-rearrangement (CP-RA) approach under mild reaction conditions. Remarkably, the asymmetric CP-RA for exocyclic vinyl substrates without a pro-stereogenic carbon at the β-position has been realized for the first time and a broad substrate scope with excellent results (33 examples; 34–99 % yields; > 95/5 dr and 91–99 % ee) has been achieved. An application of a successive enantioselective CP-RA approach was also described, providing a concise access to complex chiral heteropolycycles.*

Chiral heterobicyclic molecules, such as spiroketals, spiroaminals, bicyclic acetals and their analogues, are found as the prevalent substructures occurring frequently in a number of biologically active compounds,[1a,c–f] privileged chiral ligands[1g–j] as well as important frameworks in functional materials.[1b] For examples, the marine natural products Xyloketal B that exhibited potential application for the treatment of Parkinson's disease[1f] and Azaspiracid-1 was found as a new potent biotoxin[1a,c–d] (Figure 1). Since the first highly enantioselective catalytic intramolecular spiroacetalization reactions of hydroxyenol ether as well as bis(2-hydroxyarylidene) ketones have been realized by List et al.[2a] and Ding et al. independently.[2b] in 2012, many effective methods have been developed in the construction of chiral spiroketals.[2] Compared with the documented achievements towards spiroketals, however, few direct methods are available to elaborate chiral spiroaminals to date.[3] In 2016, Feng and co-workers developed an elegant Au^{I}/Ni^{II} bimetallic relay asymmetric catalysis to provide both the chiral spiroketals and spiroaminals based on a dihydropyran subunit via a formal [4+2] cycloaddition.[2f] Kang and co-workers reported an efficient Au^{I}/Rh^{III} bimetallic relay chemistry to furnish these structures in a similar strategy.[2h] Remarkably, although spiroaminals containing an oxygenated five membered ring widely appear in a good number of biologically active molecules, to the best of our knowledge, these attractive motifs have barely been achieved in a catalytic enantioselective manner. Meanwhile, asymmetric synthesis of chiral bicyclic acetals has always been an area of interest, but known methods that are both general and efficient are still in scarce.[4,5] The increasing demand on the diversity-oriented asymmetric synthesis of chiral heterobicyclic molecules appeals to chemists developing new versatile method to build diverse types of such molecules.

α-Diazoketones are considered as useful building blocks in organic synthesis and have received a steadily interest due to its distinct reactivity.[6] Significant progresses in catalytic asymmetric reaction with α-diazoketones have been made, such as asymmetric X-H insertion reactions,[6b,c,e] asymmetric cyclopropanations,[6a] tandem reactions[6d,f] and others.[6g] Pioneered in 1990s, the CP-RA (cyclopropanation-rearrangement) strategy has been developed to synthesize racemic bicyclic acetals with diazo-1,3-dione and dihydrofuran in a rhodium carbene chemistry.[7] Since then, studies on the asymmetric version of this strategy have been explored and proved to be difficult to achieve excellent enantioselectivity for the direct method (Scheme 1 a).[8] In 2005, Müller and co-

[*] L. Zhou,[+] W.-G. Yan,[+] Prof. Dr. X.-L. Sun, Prof. Dr. Y. Tang
The State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, CAS, University of Chinese Academy of Sciences
345 Lingling Lu, Shanghai 200032 (China)
E-mail: tangy@sioc.ac.cn
Prof. Dr. L. Wang
Shanghai Engineering Research Center of Molecular Therapeutics and New Drug Development, Department of Chemistry, East China Normal University
3663 North Zhongshan Road, Shanghai 200062 (China)
E-mail: ljwang@chem.ecnu.edu.cn
[+] These authors contributed equally to this work.
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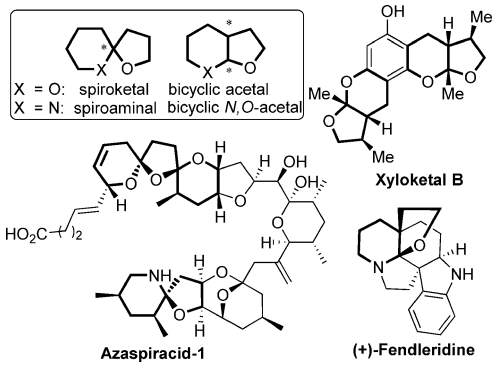
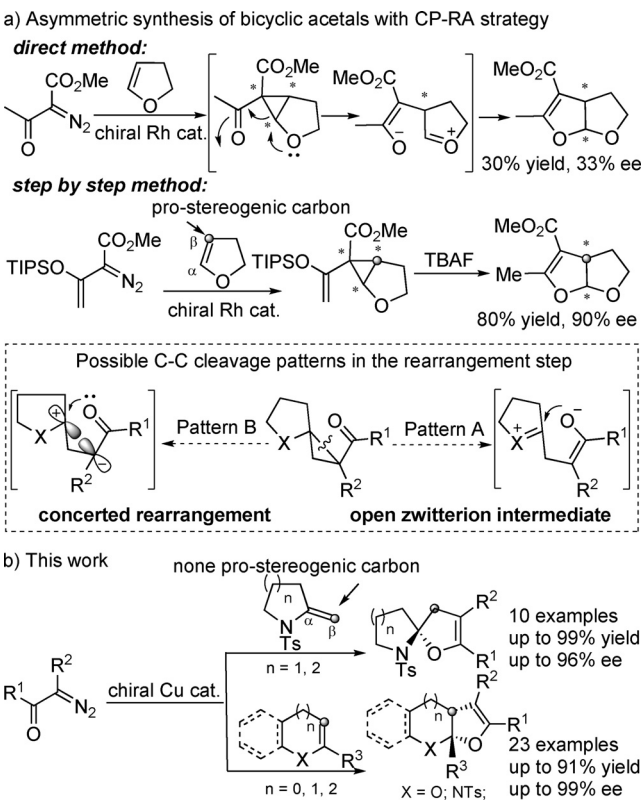


Figure 1. The spiroketal and bicyclic acetal subunits in natural products.

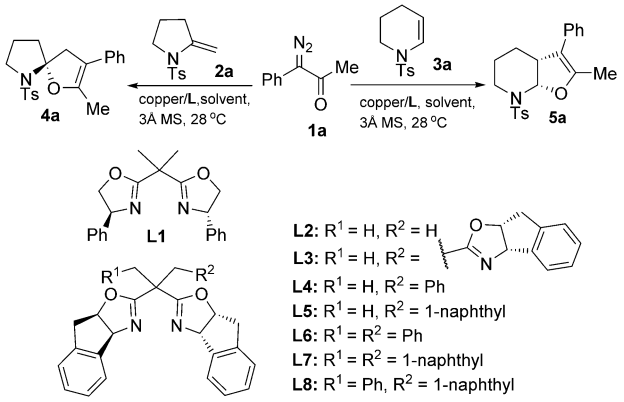


Scheme 1. CP-RA approaches for the asymmetric synthesis of heterobicycles.

workers reported a step by step solution that a stable chiral cyclopropane bearing a silyl enol ether subunit was firstly generated, followed by the rearrangement step triggered by adding TBAF (tetrabutylammonium fluoride) to form the chiral bicyclic acetal, in which a pro-stereogenic carbon at the β-position of the enol ether substrate is quite essential (Scheme 1 a).[10] Although it could achieve excellent *ee* values, only limited substrates are reported. The direct synthesis of chiral bicyclic acetals employing CP-RA strategy has not been realized in high efficiency. In fact, there are two possible C–C bond cleavage patterns in the ring opening of donor-acceptor cyclopropanes,[9] including forming an open zwitterion intermediate as pattern A, as well as undergoing a S_N2 nucleophilic concerted substitution as pattern B. In the case of the asymmetric CP-RA for exocyclic vinyl substrates without a pro-stereogenic carbon at the β-position, it is even harder to control the enantioselectivity, which has not been realized to date, due to the fact that the in situ generated chiral cyclopropane is likely to suffer from complete racemization in the RA step through a zwitterion intermediate (Pattern A) as shown in Scheme 1.[10a] Herein, we report a copper catalyzed direct asymmetric CP-RA reaction[11] of exocyclic vinyl substrates, which could also be extended to internal cyclic olefin substrates, providing divergent synthesis of chiral heterobicycles including both spiroaminals and fused bicyclic acetals in high yields with excellent levels of enantioselectivity.

Initially, the exocyclic *N*-sulfonyl enamide **2a** without pro-stereogenic carbon at the β-position was employed as starting material. By employing 10 mol% of chiral copper(II) as catalyst, α-aryl-α-diazoketone **1a** and **2a** were reacted at room temperature (Table 1). With the catalyst $Cu(OTf)_2$ and chiral phenyl-BOX ligand **L1**, very poor enantioselectivity was obtained (Table 1, entry 1). When indanyl-BOX ligand **L2** was employed, both the yield and the enantioselectivity were disappointed (Table 1, entry 2). Unexpectedly, with indanyl-TOX ligand **L3**, [12] 66% yield and 65% *ee* was obtained (Table 1, entry 3). Next, through a range of copper catalyst, $[Cu(CH_3CN)_4]PF_6$ emerged as the optimal catalyst, providing the desired product **4a** in 73% yield with 79% *ee* (Table 1, entries 4–5). The enantioselectivity slightly improved when the solvent was changed from DCM (dichloromethane) to DCE (1,2-dichloroethane) (Table 1, entry 6). Chiral ligands including mono-side-armed SaBOX ligand[13] **L4** and **L5** as well as the bi-side-armed SaBOX ligands[14] **L6** and **L7** were studied, which resulted in a range of 74–86% *ee* (Table 1, entry 7–10). To our delight, the best result was achieved in 99% yield with 91% *ee* by using a newly-developed unsymmetrical bi-side-armed SaBOX ligands **L8** (Table 1, entry 11). Interestingly, in the case of *N*-sulfonyl 1,2,3,4-tetrahydropyridine **3a** with **L8**, $[Cu(CH_3CN)_4]PF_6$ in DCE only lead to 46% of cyclopropanation product[15] without any expected bicyclic N,O-acetals, but

Table 1: Optimization of the reaction conditions.



Entry[a]	Copper	L	Solvent	Yield [%][b]	*ee* [%][c]
1	$Cu(OTf)_2$	**L1**	DCM	53	2
2	$Cu(OTf)_2$	**L2**	DCM	38	53
3	$Cu(OTf)_2$	**L3**	DCM	66	65
4	$CuOTf{\cdot}(toluene)_{0.5}$	**L3**	DCM	99	71
5	$[Cu(CH_3CN)_4]PF_6$	**L3**	DCM	73	79
6	$[Cu(CH_3CN)_4]PF_6$	**L3**	DCE	83	81
7	$[Cu(CH_3CN)_4]PF_6$	**L4**	DCE	83	72
8	$[Cu(CH_3CN)_4]PF_6$	**L5**	DCE	73	86
9	$[Cu(CH_3CN)_4]PF_6$	**L6**	DCE	99	84
10	$[Cu(CH_3CN)_4]PF_6$	**L7**	DCE	68	85
11	$[Cu(CH_3CN)_4]PF_6$	**L8**	DCE	99	91
12	$[Cu(CH_3CN)_4]PF_6$	**L8**	DCE	0[e]	–
13[d]	$Cu(OTf)_2$	**L8**	DCM	51[e]	98
14[d]	$Cu(OTf)_2$	**L7**	DCM	78[e]	99

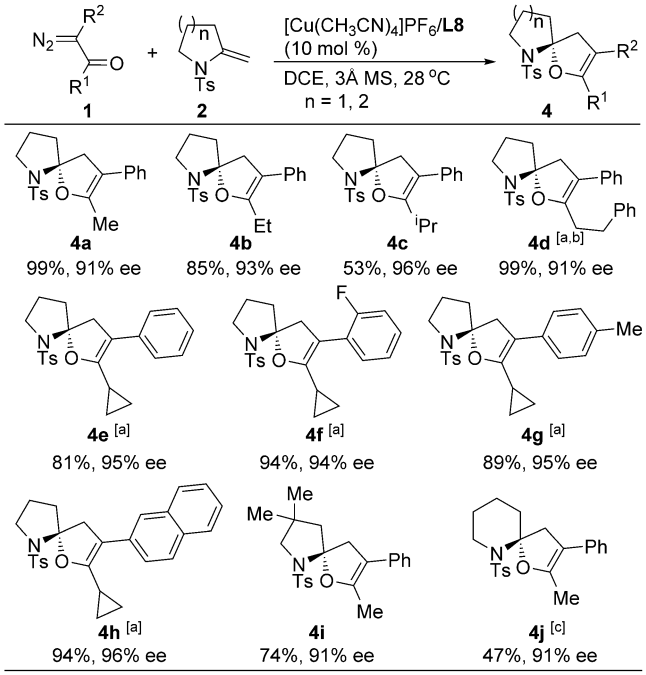
[a] Reaction conditions: copper (0.01 mmol), **L** (0.012 mmol), **1a** (0.1 mmol); **2a** (0.2 mmol), 3 Å MS (50 mg) in solvent (2.5 mL) at 28 °C, under Ar atmosphere. [b] ^1H NMR yield of **4a**. [c] Determined by Chiral HPLC. [d] With **1a** (0.2 mmol) and **3a** (0.1 mmol). [e] Isolated yield of **5a**.

$Cu(OTf)_2$ in DCM could result in the desired **5a** in 51% yield with 98% *ee* (Table 1, entries 12–13). Further investigation on the chiral ligand effect showed that, with **L7** as ligand, both the yield and the enantioselectivity could be further improved. The best result for **5a** was 78% yield with 99% *ee* (Table 1, entry 14).

Under the optimized conditions (Table 1, entry 11), the substrate scope of spiroaminals was explored (Scheme 2). α-Diazoketones bearing different carbonyl substituents, such as acetyl, propionyl and isopropyl acyl groups were suitable reaction candidates, delivering the corresponding products **4a–c** in 53–99% yields with 91–96% *ee*. Furthermore, α-diazoketone **1d** with the long chain phenyl substituent could also work well in this reaction (99% yield, 91% *ee*).[16] Remarkably, cyclopropyl group, which is often employed in the design of drug molecules owing to its superiorities over linear and cyclic aliphatic hydrocarbons in drug efficacy and metabolic stability,[17] could be introduced to give corresponding spiroaminals **4e–h** in 81–94% yields with 94–96% *ee*. For example, α-diazoketone **1f**, containing the crucial frame of the antiplatelet durg Prasugrel, proceeded smoothly to provide **4f** in 94% yield with 94% *ee*. Meanwhile, this reaction could tolerate different exocyclic *N*-sulfonyl enamides, such as **2i** with bulky substituents, and **2j** with six-membered ring, affording the corresponding spiroaminals **4i** and **4j** with excellent enantioselectivity.

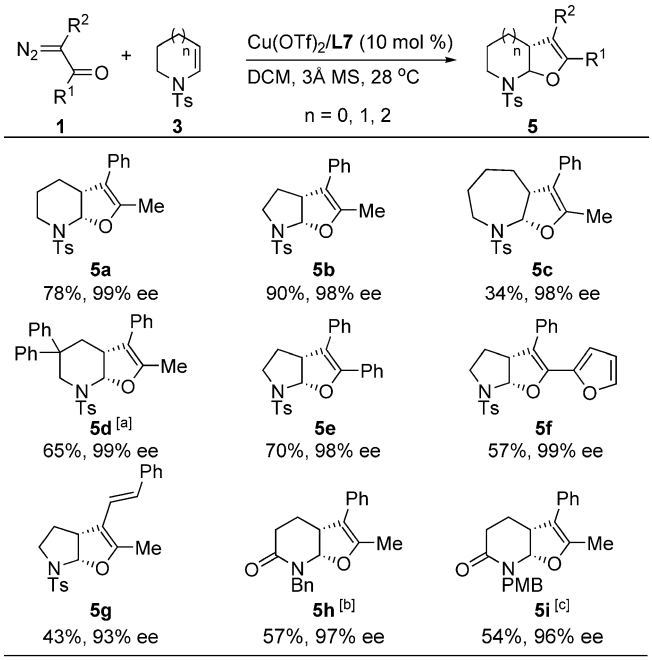
Subsequently, we explored the substrate scope of the fused bicyclic *N,O*-acetals (Scheme 3). A series of fused bicyclic *N,O*-acetals (**5a–c**) containing five- to seven-membered ring systems could be obtained with excellent enantioselectivities (98–99% *ee*). Sterically hindered cyclic *N*-sulfonyl enamides (**3d**) also could deliver 99% *ee*.[16] Importantly, α-diazoketones with an aryl or a heterocyclic aryl subunit were found as suitable substrates, affording **5e** and **5f** in good yields with 98–99% *ee*. Cinnamyl group substituted α-diazoketone **3g** was tolerated in the current catalytic system to give the desired product **5g** with excellent *ee* value. Moreover, lactam substrates, such as **3h** and **3i** could also work well, providing the corresponding chiral heterobicycles **5h** and **5i** in moderate yields with 96–97% *ee*.

The current catalytic system was applicable in a wide range that a series of cyclic enol ethers, which proved very good reaction candidates (Scheme 4). Fused bicyclic acetals (**7a**) were obtained in 84% yield with 93% *ee* under the optimized reaction conditions (Table 1, entry 14).[18] Enol ethers with bulky substituents were also employed, giving excellent ees. For example, 2,2-dimethyl and 2,2-diphenyl substituted products **7b–e** were obtained in 78–85% yields with 95–97% *ee*. Enol ether with an ester group was found as suitable substrate, and delivered **7f** in 90% yield with 73/17 dr and excellent *ee* values. Products **7g–i** bearing a *spiro*-quaternary carbon moiety were also successfully built in good to high yields (75–91%) with excellent *ee* values (95–97% *ee*). It was worth to mention that substrates bearing benzyl or alkyl substituents at 2-position of the cyclic enol ethers could result in the fused bicyclic ketals **7j–m** with a quaternary carbon in good yields with excellent enantioselectivity (52–60% yield, 98–99% *ee*). Furthermore, when 4H-chromene was employed as the substrate, the aromatic bicyclic acetal product **7n** was obtained in 53% yield with 99% *ee*.



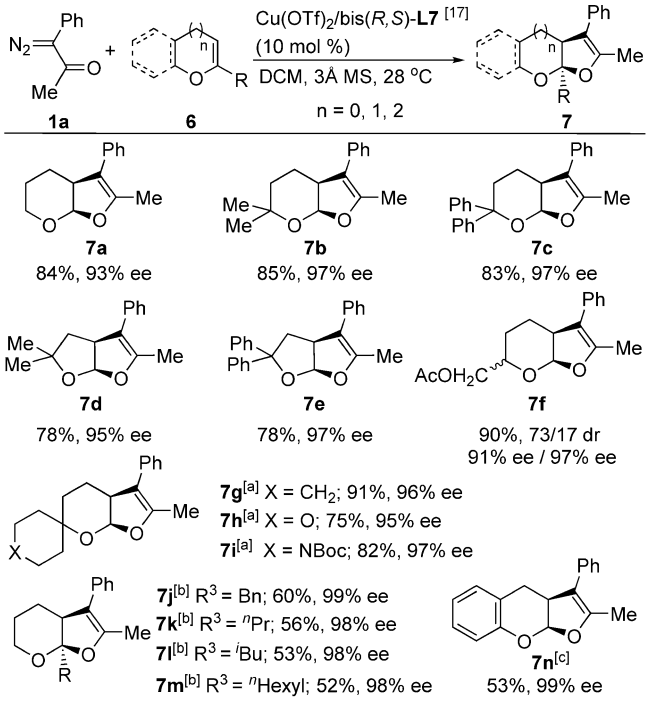
Reaction condition: **1** (0.1 mmol), **2** (0.2 mmol), $[Cu(CH_3CN)_4]PF_6$ (0.01 mmol), **L8** (0.012 mmol), 3Å S (50 mg) in DCE (2.5 mL), at 28 °C under Ar; isolated yields; the ee values were determined by Chiral HPLC. [a] **1** (0.11 mmol), **2a** (0.1 mmol). [b] The absolute configuration of **4d** was determined by X-ray diffraction. [c] **1** (0.3 mmol), **2** (0.1 mmol).

Scheme 2. Substrate scope of the spiroaminal products.



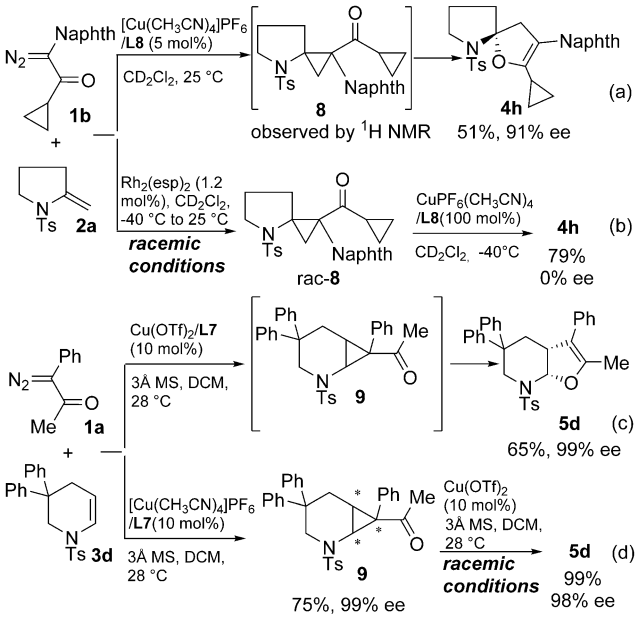
Reaction condition: **1** (0.2 mmol), **3** (0.1 mmol), $Cu(OTf)_2$ (0.01 mmol), **L7** (0.012 mmol) and 3Å MS (50 mg) in DCM (2.5 mL) at 28 °C under Ar; isolated yields, the ee values were determined by Chiral HPLC. [a] The absolute configuration of **5d** was determined by X-ray diffraction. [b] **1a** (0.3 mol) with 20 mol% of catalyst. [c] **1a** (0.3 mmol) in DCE at 60 °C.

Scheme 3. Substrate scope of the fused bicyclic *N,O*-acetals.



Reaction condition: **1a** (0.2 mmol), **6** (0.1 mmol), $Cu(OTf)_2$ (0.01 mmol), bis(*R,S*)-**L7** (0.012 mmol) and 3Å MS (50 mg) in DCM (2.5 mL) at 28 °C under Ar; isolated yields, the ee values were determined by Chiral HPLC. [a] **1a** (0.4 mmol), **6** (2.0 mmol) and 3Å MS (300 mg) in DCM (6 mL). [b] **1a** (0.4 mmol), **6** (4.0 mmol) and 3Å MS (300 mg) in DCE (6 mL). [c] $Cu(NTf_2)_2$, was used instead of $Cu(OTf)_2$ with 20 mol% catalyst loading.

Scheme 4. Substrate scope of the fused bicyclic acetals.

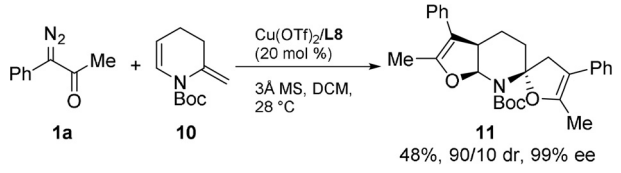


Scheme 5. Control experiments.

The current study showed that the exocyclic vinyl sulfamide substrates without a pro-stereogenic carbon at the β-position could achieve excellent enantioselectivity, which is different from the previous report on the CP-RA process of vinyl ethers.[10] To understand the insights, we initially tried to obtain both racemic and optically active intermediate **8** with and without **L8** but failed. Then several control experiments were carried out (Scheme 5). Further study showed ***rac*-8** could be prepared in situ as a main product in an NMR tube with 1.2 mol% of $Rh_2(esp)_2$ via cyclopropanation of exocyclic *N*-sulfonyl enamide **2a** with **1b** (Scheme 5b),[19] which was unstable and would rearrange to the spiroaminal. The similar results were observed in the enantioselective reaction of **2a** and **1b** in the presence of the $[Cu(CH_3CN)_4]PF_6$/**L8** by in situ ^1H NMR monitoring in CD_2Cl_2 at 25 °C, in which the RA step was found faster than the one in the racemic version and trace amount of **8** was observed accompany with the formation of the RA product **4h**. (Scheme 5a).[19] These experiments suggests the exocyclic vinyl sulfamide substrates achieved excellent enantio-induction via a CP-RA process. Next, we turn to investigate the step to control the enantioselectivity. When the ***rac*-8** was treated with 1.0 equiv of chiral copper catalyst at −40 °C, 79% yield of **4h** was obtained with 0% *ee* (Scheme 5b), suggesting that the rearrangement step might undergo through Pattern B (Scheme 1).[20] As **5d** could be obtained in 65% yield with 99% *ee* from the reaction of **1a** with **3d** in the presence of $Cu(OTf)_2$/**L7** as catalyst, we also tried to isolate the corresponding intermediate **9** but failed (Scheme 5c). To our delight, when $[Cu(CH_3CN)_4]PF_6$ was employed instead of $Cu(OTf)_2$, the intermediate aminocyclopropane[21] **9** could be isolated in 75% yield with 99% *ee*. Noticeably, the chiral aminocyclopropane **9** could be further transformed into **5d** in the presence of a racemic copper catalyst without loss of stereochemical purity (Scheme 5d, 98% *ee*). These experiments suggest that the enantioselectivity in both cases is likely to be determined in the cyclopropanation step.

Interestingly, the CP-RA approach could be applied successfully to the construction of a complex chiral heteropolycycle in a successive manner with a nitrogenous heterocyclic substrate bearing both internal olefin and *exo*-olefin moieties. The corresponding product **11** was obtained in 48% yield with 90/10 dr and 99% *ee* (Scheme 6).

In summary, we have successfully developed an asymmetric copper-catalyzed cyclization reaction of α-diazoketones with various enamides/enol ethers via a cyclopropanation-rearrangement (CP-RA) approach. Importantly, both exocyclic vinyl substrates and internal cyclic olefin substrates, no matter with or without a pro-stereogenic carbon at the β-position, proved very efficient for the non-stepwise asymmetric CP-RA reaction for the first time (to our knowledge). Thus, this method has extremely broad substrate scopes to provide a new access to diverse chiral spiroaminals (10



Scheme 6. An application of successive CP-RA approaches to chiral heteropolycycles.

examples, in up to 99% yield with up to 96% *ee*) and fused bicyclic acetals (23 examples, in up to 91% yield with up to 99% *ee*). ^{1}H NMR experiment confirmed that the exocyclic vinyl sulfamide substrates achieved excellent enantio-induction via a CP-RA process. The CP-RA approach could also be applied to the synthesis of a fused bicyclic acetal with a spiroaminal subunit in a successive manner with excellent enantioselectivity (99% *ee*), which provided a concise access to complex chiral heteropolycycles. Further studies on the application of the enantioselective CP-RA approach are underway.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: bicyclic acetal · copper catalyst · cyclopropanation · enantioselective · spiroaminal

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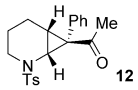

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[16] Deposition Numbers 1997551 (for **4d**), 1997552 (for **5d**) and 1997553 (for **12**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

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