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Enantioselective Catalytic Cyclopropanation–Rearrangement Approach to Chiral Spiroketals

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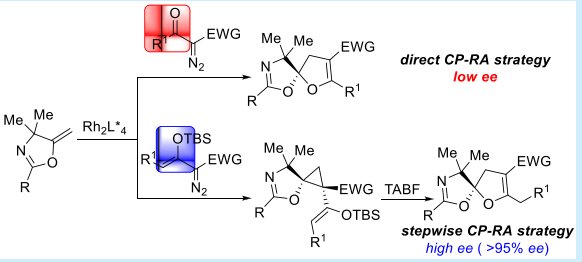
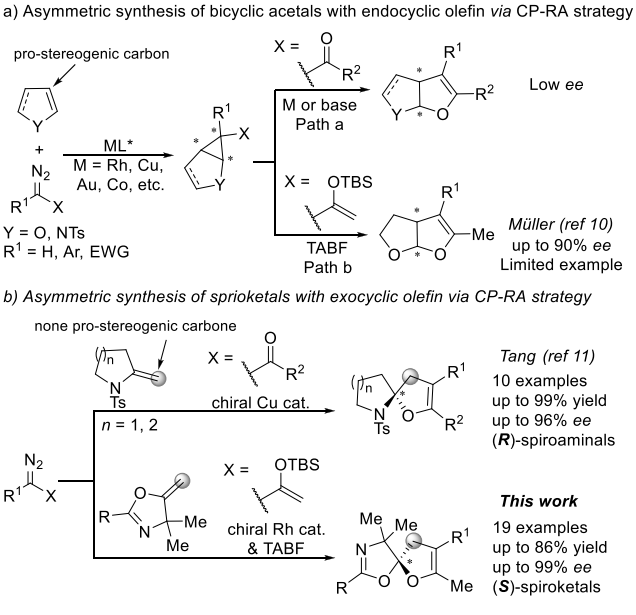
ABSTRACT: A highly enantioselective synthesis of chiral heterobicyclic spiroketals is reported via a "one-pot" cyclopropanation–rearrangement (CP-RA) cascade reaction that is sequentially catalyzed by a chiral Rh(II) catalyst and tetrabutylammonium fluoride (TBAF). Exocyclic vinyl substrates form spirocyclopropanes with *tert*-butyldimethylsilyl-protected enoldiazoacetates in excellent yields and with excellent enantioselectivities when catalyzed by chiral dirhodium(II) carboxylates, and following desilylation with simultaneous rearrangement in the presence of TBAF, they give (*S*)-spiroketals in high yields with excellent chirality retention (>95% *ee*).



Diazo compounds are versatile building blocks in synthetic organic chemistry that have received increasing interest due to their diverse transformations.[1] Significant catalytic asymmetric reactions have been made in cyclopropanation,[2] C(X)–H insertion,[3] cycloaddition,[4] tandem reactions,[5] and other transformations.[6] Reactions of diazoacetate esters in the formation of cyclopropane derivatives were among the first demonstrations of catalytic asymmetric induction,[7] and cyclopropane derivatives now serve as versatile building blocks for a variety of bioactive compounds.[8]

An important application of heteroatom-embodied cyclopropanes is their subsequent rearrangement to 2,3-dihydrofurans using a metal catalyst or a strong base; however, chiral cyclopropanes that undergo this Cloke–Wilson-type rearrangement into 2,3-dihydrofurans generally do so with a loss of enantiopurity (Scheme 1a, path a).[9] A stepwise solution was initially reported by Müller and coworkers. With internal olefin substrates producing stable chiral donor–acceptor cyclopropanes tethered to a silyl enol ether, they were able to force rearrangement. An intermediate enolate was formed by treating the donor–acceptor cyclopropane with TBAF (tetrabutylammonium fluoride), which generated chiral bicyclic acetals with high *ee* values. In these cases, a prostereogenic carbon of the enol ether is critical to stereocontrol in the rearrangement step (Scheme 1a, path b).[10] However, for exocyclic olefins, stereocontrol is more difficult because of its rapid racemization during the rearrangement step. Recently, Tang's group reported a chiral copper/SaBOX complex-catalyzed asymmetric cyclopropanation–rearrangement (CP-RA) reaction of exocyclic vinyl enamines that directly provided (*R*)-spiroaminals in high yields with excellent enantioselectivity.[11] Encouraged by these results and our continued interest in rhodium(II)-catalyzed asymmetric reactions, we have investigated a more challenging transformation with a vinyl ether

Scheme 1. Synthetic Asymmetric Heterobicycles via CP-RA Strategies



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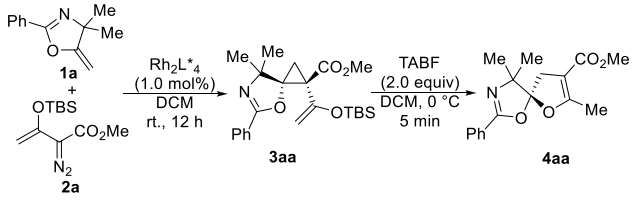
and now report a dirhodium(II)-catalyzed stepwise asymmetric CP-RA reaction, providing (*S*)-spiroketals with a high level of enantioselectivity in a "one-pot" reaction.

Spiroketals are widely found in natural products, and they have diverse biological activities.[12] Consequently, their synthetic chemistry has been promoted in recent years. Among the methods employed, the acid-catalyzed dehydration of ketodiols is the classical strategy,[13] but a variety of transition-metal-catalyzed strategies have also been developed.[14] However, synthetic access to chiral spiroketals is rarely reported.[15]

Our initial exploration was carried out using 4,4-dimethyl-5-methylene-2-phenyl-4,5-dihydrooxazole **1a** and *tert*-butyldimethylsilyl (TBS)-protected enoldiazoacetate **2a** as model substrates in dichloromethane (DCM) at room temperature (Table 1). A variety of copper, silver, rhodium, and gold

Table 1. Optimization of Reaction Conditions for the Cyclopropanation−Rearrangement Reaction[a]

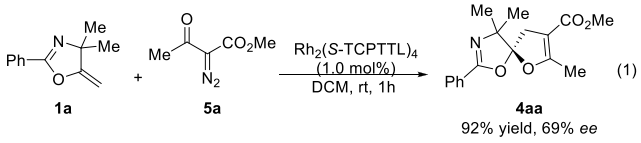


		3aa		4aa	
entry	Rh(II)	yield (%)	*ee* (%)	yield (%)	*ee* (%)
1	$Rh_2(OAc)_4$	67		92	
2	$Rh_2(esp)_2$	88		90	
3	Rh_2(*S*-PTTL)$_4$	90	96	90	95
4	Rh_2(*S*-TFPTTL)$_4$	85	96	93	96
5	Rh_2(*S*-TCPTTL)$_4$	92	99	91	99
6	Rh_2(*S*-TBPTTL)$_4$	89	97	90	97
7	Rh_2(*S*-PTAD)$_4$	67	88	88	85
8	Rh_2(*S*-DOSP)$_4$	NR			
9[b]	Rh_2(*S*-TCPTTL)$_4$			82	99

[a]Reactions were carried out on a 0.2 mmol scale: To the dirhodium catalyst (1.0 mol %) and **1a** (0.2 mmol) in DCM (2.0 mL) was added **2a** (0.3 mmol) in the DCM (2.0 mL) via a syringe pump over 1 h under an argon atmosphere at room temperature. Desilylation with TBAF occurred at 0 °C. Isolated yields after flash chromatography. [b]One-pot reaction without separating **3aa**. NR, no reaction occurred over 48 h, and most of **1a** and **2a** was recovered.

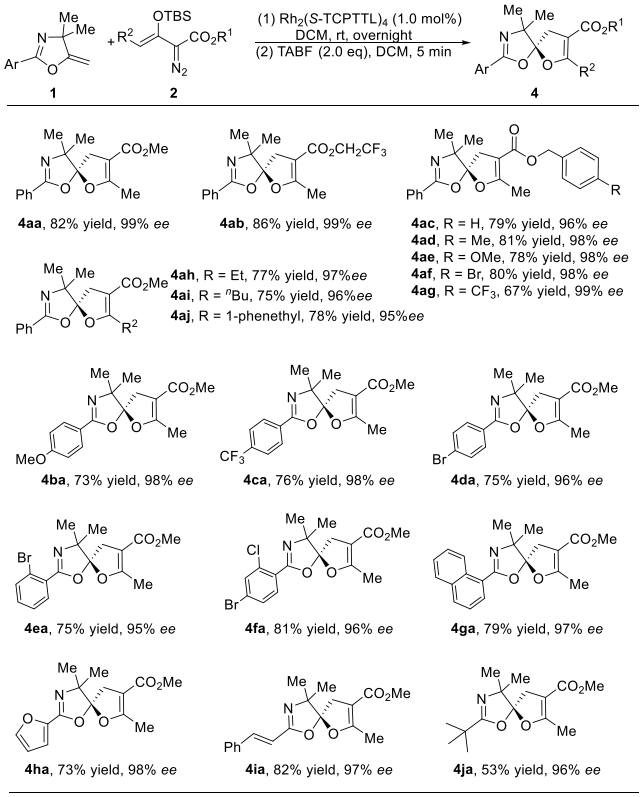
catalysts were surveyed, but only dirhodium(II) carboxylates gave the desired product. Spiro-cyclopropane **3aa** was generated as the sole outcome with complete diastereocontrol using dirhodium(II) carboxylate catalysis and easily underwent desilylation to generate the spiroketal product **4aa** (entries 1 and 2). Further improvement of reactivity and selectivity was investigated by evaluating an array of chiral dirhodium(II) carboxylate catalysts (entries 3−9). (Structure details are presented in the SI.) Product formation failed when the reaction was performed using the chiral prolinate-ligated catalyst Rh_2(*S*-DOSP)$_4$ (entry 8), possibly because of its coordination with the basic imine of reactant **1a**. However, the chiral phthalimide-carboxylate-ligated catalyst Rh_2(*S*-PTTL)$_4$ produced **3aa** in excellent yield (90%) with excellent enantioselectivity (entry 3, 96% *ee*). Remarkably, the spiroketal product **4aa** was formed in high yield with excellent chirality retention from desilylation (90% yield, 95% *ee*). Optimized conditions were achieved with Rh_2(*S*-TCPTTL)$_4$ (91% yield, 99% *ee*) as the catalyst. Notably, in a one-pot reaction performed without separating **3aa**, direct desilylation occurred, giving an overall good yield with excellent enantiocontrol (82% yield, 99% *ee*).

Notably, the observed high enantioselectivity determined from the catalytic CP-RA reaction of **2a** was not observed with the corresponding enolizeable diazoacetoacetate (**5a**) when reacted under the same conditions without further treatment with TBAF (eq 1); spiroketal **3aa** was directly obtained in



higher yield (92 vs 82%) but with only 69% *ee*. In addition, no significant improvements were detected from the results of other chiral dirhodium(II) catalyses and solvents. (See the SI for details.)The scope of spiroketal syntheses was explored with Rh_2(*S*-TCPTTL)$_4$ catalysis under the optimum conditions. A variety of 4,4-dimethyl-methlenedihydrooxazoles **1** and enoldiazoacetates **2** were investigated. As presented in Scheme 2, the reactions proceeded smoothly with different ester groups of enoldiazoacetates **2**. In particular, the

Scheme 2. Substrate Scope in Asymmetric Catalytic Cyclopropanation−Rearrangement[a]



[a]Reactions were carried out at room temperature on a 0.20 mmol scale of **1** with 0.3 mmol of enoldiazoacetate **2**. Isolated yields after flash chromatography for the two-step procedure. The *ee* values were determined by high-performance liquid chromatography (HPLC) analyses with chiral columns.

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trifluoroethyl ester of **2** gave **4ab** in high yield (up 86%) with excellent enantioselectivity (99% *ee*). Further exploration revealed that the reactions exhibited little electronic or steric influence on the reactivity or selectivity. Comparable yields (**4ac**−**4ag**, up to 81%) with excellent enantioselectivities (>96% *ee*) were obtained from different benzyl esters. Furthermore, enoldiazoacetates containing a γ-substituent showed a slight effect on the reactivity. Substituents including methyl (**2h**), ethyl (**2i**), and benzyl (**2j**) produced the target products in high yields (75−78%) with excellent enantioselectivities (95−97% *ee*). Modest product yields (**4ba**−**4da**, 63−75%) but high enantioselectivities (95−98% *ee*) were observed when **1** bearing electron-neutral, electron-rich, or electron-deficient substituents on the aryl group was tested in this reaction. The ortho-substituted congeners were also tolerated under the current conditions (**1e** and **1f**), delivering the desired products in good yields with excellent enantioselectivities (**4ea** in 71% yield with 95% *ee* and **4fa** in 81% yield with 96% *ee*, respectively). In addition to aryl-substituted dihydrooxazoles, the desired products (**4ga** and **4ha**) were smoothly generated in isolated yields above 73% with enantioselectivities up to 98% *ee* when 1-naphthyl and heterocyclic 2-furyl-substituted dihydrooxazoles (**1g** and **1h**) were employed. The introduction of *E*-cinnamyl-substituted dihydrooxazole (**1i**) resulted in a high yield (**4ia**, 82%) with excellent enantioselectivity (**4ia**, 99% *ee*) without detecting any reaction at the cinnamyl group. Changing the substitution at the 2-position of the dihydrooxazole from an aryl to an aliphatic ^{t}Bu group was also compatible with this catalytic process in somewhat lower yield but with excellent enantioselectivity (**4ja**, 53% yield and 99% *ee*). However, an internal 5-(*R*)-methylenedihydrooxazole (R = C_6H_5) without 4,4-dimethyl substitution failed to deliver the target spiroketal product due to its low reactivity, and decomposition of the diazo compound **2a** was detected only in this reaction. The structure and absolute configuration of spiroketal (*S*)-**4ai** were established by X-ray diffraction (Figure 1).

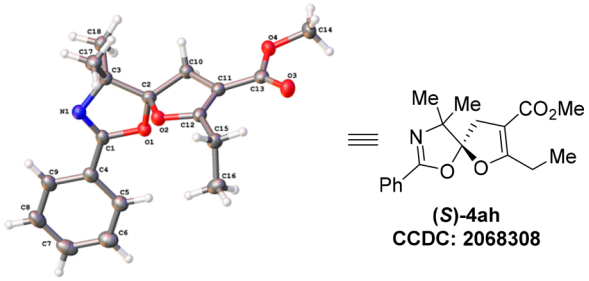
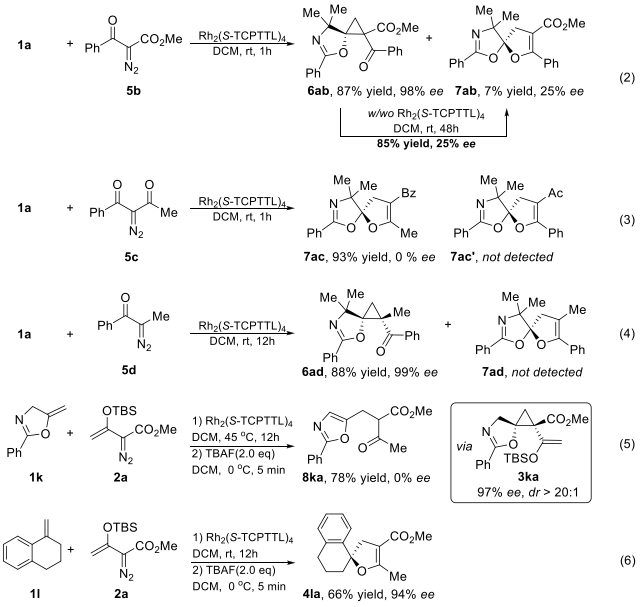


Figure 1. ORTEP diagram of the X-ray crystal structure of (*S*)-methyl-7-ethyl-4,4-dimethyl-2-phenyl-1,6-dioxa-3-azaspiro-[4.4]nona-2,7-diene-8-carboxylate **3a**.

To gain insight into the reaction mechanism, we carried out control experiments (Scheme 3). α-Benzoyldiazoacetate **5b** was reacted with **1a** under standard conditions. Unlike α-acetyldiazoacetate **5a**, which directly generated the spiroketal product **3aa**, this diazoacetate formed cyclopropane **6ab** as the major product in 87% yield with 98% *ee* along with a minor amount of spiroketal product **7ab** in 7% yield with a poor 25% *ee*. Further treatment of **6ab** at room temperature with or without Rh(II) catalyst resulted in the same outcome: 85% yield with 25% *ee* after 48 h (eq 2). This result indicated that

Scheme 3. Control Experiments



the low% *ee* is due to the rearrangement step rather than cyclopropanation. The functional group is not stable,[10] and it undergoes spontaneous ring-opening to the zwitterion intermediate with subsequent recyclization with 0% *ee* (eq 3). Furthermore, only the acetyl group provides this rearrangement (eq 3). As predicted, when the donor−acceptor diazo compound **5d** was employed in this reaction, the stable cyclopropane **6ad** was generated in high yield with high enantioselectivity (88% yield, 99% *ee*) (eq 4), which further supports our hypothesis that the reaction involves a concerted and subsequent asynchronous annulation process. However, to our disappointment, dihydrooxazole **1k** without the geminal dimethyl group failed to give the corresponding spiroketal product, even though cyclopropane **3ka** having a high % *ee* value was detected. Because of the driving force to achieve aromaticity, the racemic proton-transfer product **8ka** was isolated in 78% yield (eq 5). To our surprise, when 1-methylenetetrahydronaphthalene **1l** without a heteroatom was employed, the desired product **4la** was obtained with excellent enantioselectivity in moderate yield (eq 6, 66% yield, 94% *ee*), which has potential implication for similar transformations with other methylene substrates.

A tentative reaction mechanism is proposed in Scheme 4. Initially, the carbene complex **A** is formed from diazo compound **2** in the presence of the Rh(II) catalyst, followed by cyclopropanation to form **B**. When R^1 is an acetyl group, **B** undergoes spontaneous ring-opening to the zwitterion intermediate **C** with subsequent recyclization to furnish **4** with low enantiomeric excess. However, when R^1 is a silyl enol ether group, intramolecular C−C bond displacement, triggered by fluoride-promoted removal of the TBS group, occurs to generate intermediate **E** from **D**, and subsequent protonation completes the transformation. The aromatic product **8** is obtained through direct proton transfer of the intermediate **D**.

In summary, a highly efficient asymmetric CP-RA approach of enoldiazoacetates with methylenedihydrooxazoles has been achieved by a one-pot cascade reaction catalyzed by a chiral Rh(II) catalyst and promoted by TBAF sequentially. Chiral spiroketals were generated in up to 86% yield with >95% *ee*

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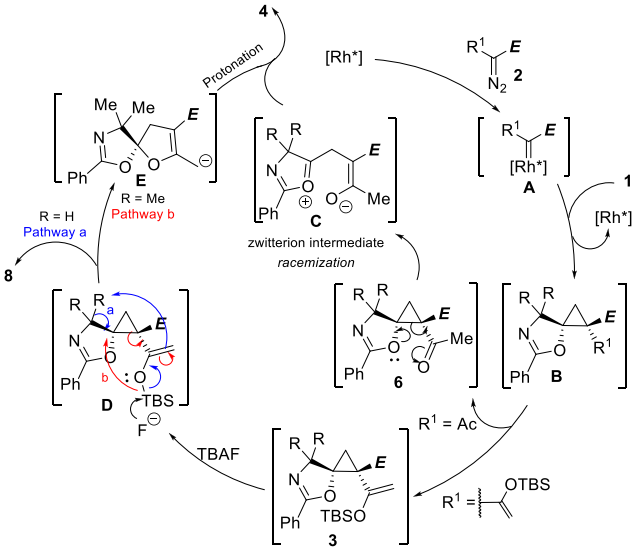
Scheme 4. Proposed Reaction Mechanism



with a broad selection of substrates. Further exploration of this asymmetric CP-RA approach is under way in our lab.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01113.

Experimental procedure and spectroscopic data for all new compounds (PDF)

Accession Codes

CCDC 2068308 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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