

Enantioselective Catalytic Cyclopropanation–Rearrangement Approach to Chiral Spiroketal

Kuioyng Dong, Raj Gurung, Xinfang Xu,* and Michael P. Doyle*



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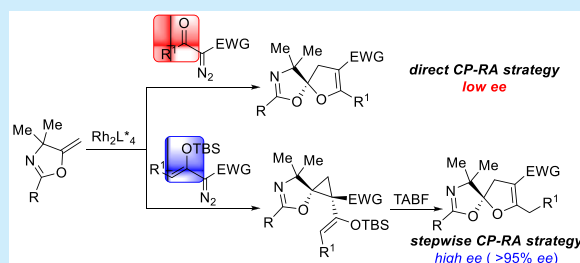


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ABSTRACT: A highly enantioselective synthesis of chiral heterobicyclic spiroketals is reported via a “one-pot” cyclopropanation–rearrangement (CP-RA) cascade reaction that is sequentially catalyzed by a chiral Rh(II) catalyst and tetrabutylammonium 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*).

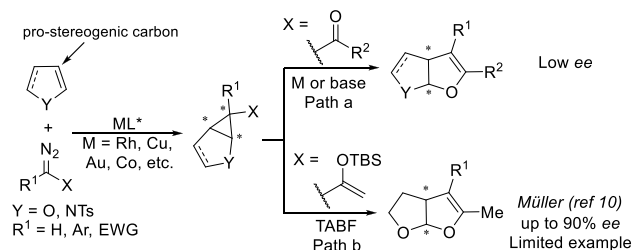


Diazo compounds are versatile building blocks in synthetic organic chemistry that have received increasing interest due to their diverse transformations.¹ Significant catalytic asymmetric reactions have been made in cyclopropanation,² C(X)–H insertion,³ cycloaddition,⁴ tandem reactions,⁵ and other transformations.⁶ 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

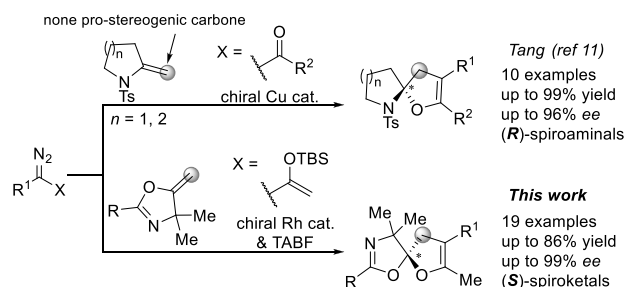
An important application of heteroatom-embodied cyclopropanes is their subsequent rearrangement to 2,3-dihydrofurans using a metal catalyst or a strong base; however, chiral cyclopropanes that undergo this Cloke–Wilson-type rearrangement into 2,3-dihydrofurans generally do so with a loss of enantiopurity (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 pro-stereogenic 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

a) Asymmetric synthesis of bicyclic acetals with endocyclic olefin via CP-RA strategy



b) Asymmetric synthesis of spiroketals with exocyclic olefin via CP-RA strategy



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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 ketodials 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

conditions were achieved with Rh₂(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 enolizable diazoacetate (**5a**) when reacted under the same conditions without further treatment with TBAF (eq 1); spiroketal **3aa** was directly obtained in

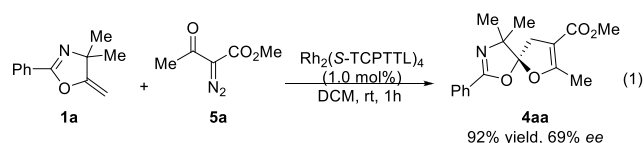
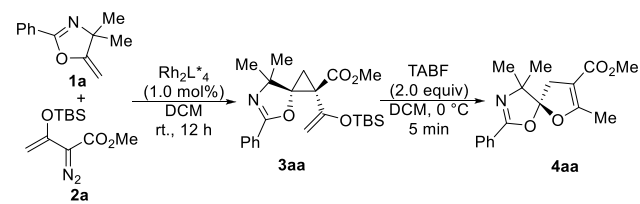


Table 1. Optimization of Reaction Conditions for the Cyclopropanation–Rearrangement Reaction^a



entry	Rh(II)	3aa		4aa	
		yield (%)	<i>ee</i> (%)	yield (%)	<i>ee</i> (%)
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

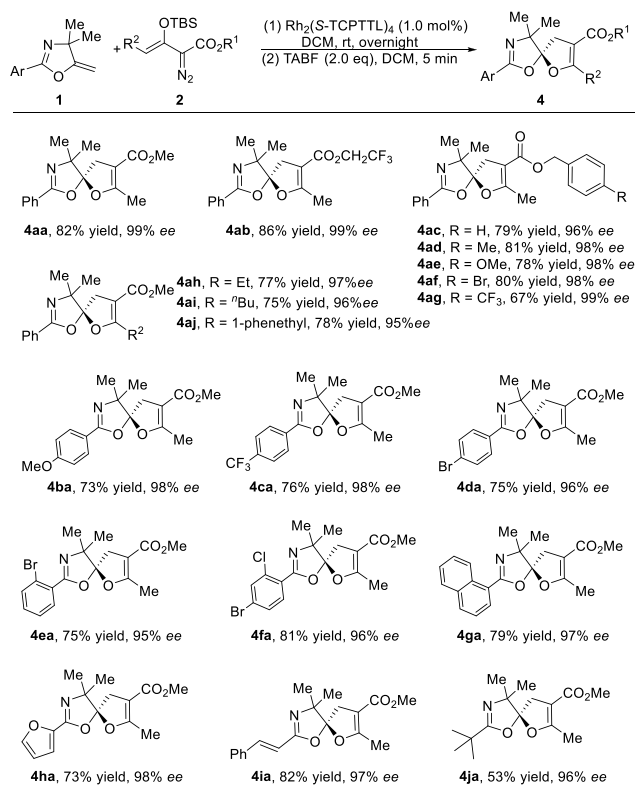
^aReactions were carried out on a 0.2 mmol scale: To the dirhodium catalyst (1.0 mol %) and **1a** (0.2 mmol) in DCM (2.0 mL) was added **2a** (0.3 mmol) in the DCM (2.0 mL) via a syringe pump over 1 h under an argon atmosphere at room temperature. Desilylation with TBAF occurred at 0 °C. Isolated yields after flash chromatography.

^bOne-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 proline-ligated catalyst Rh₂(S-DOSP)₄ (entry 8), possibly because of its coordination with the basic imine of reactant **1a**. However, the chiral phthalimide-carboxylate-ligated catalyst Rh₂(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

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) catalysts and solvents. (See the SI for details.) The scope of spiroketal syntheses was explored with Rh₂(S-TCPTTL)₄ catalysis under the optimum conditions. A variety of 4,4-dimethyl-methylenedihydrooxazoles **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



^aReactions 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.

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 ^tBu 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* = C₆H₅) 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).

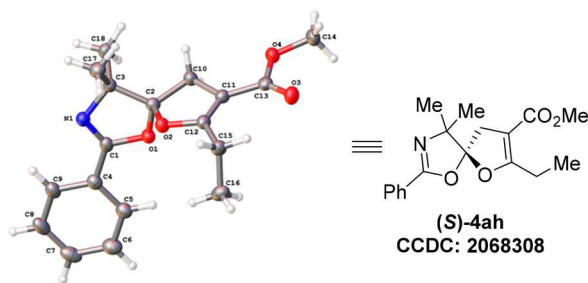
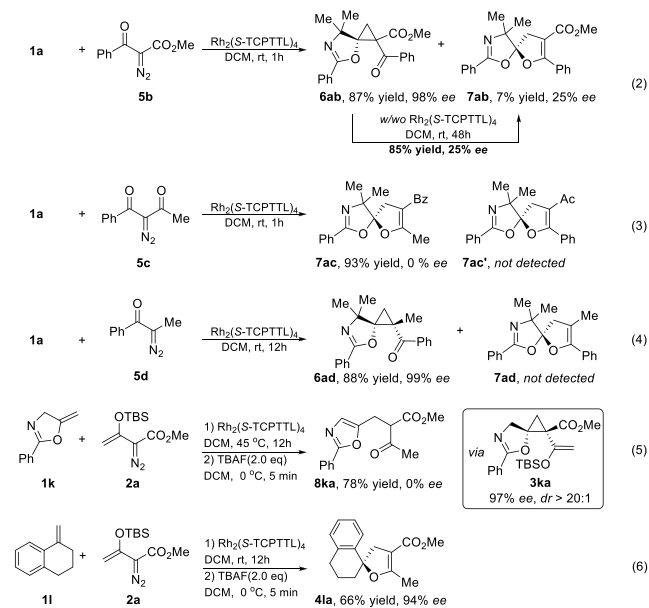


Figure 1. ORTEP diagram of the X-ray crystal structure of (*S*)-methyl-7-ethyl-4,4-dimethyl-2-phenyl-1,6-dioxo-3-azaspiro[4.4]nona-2,7-diene-8-carboxylate **3a**.

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

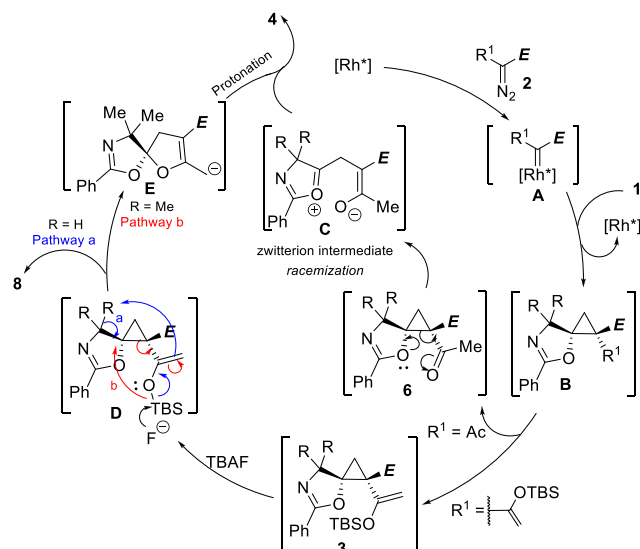


the low% *ee* is due to the rearrangement step rather than cyclopropanation. The functional group is not stable,¹⁰ and it undergoes spontaneous ring-opening to the zwitterion intermediate with subsequent recyclization with 0% *ee* (eq 3). Furthermore, only the acetyl group provides this rearrangement (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*

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.

■ AUTHOR INFORMATION

Corresponding Authors

Michael P. Doyle – Department of Chemistry, University of Texas at San Antonio, San Antonio, Texas 78249, United States; orcid.org/0000-0003-1386-3780; Email: michael.doyle@utsa.edu

Xinfang Xu – Guangdong Key Laboratory of Chiral Molecule and Drug Discovery, School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, China; orcid.org/0000-0002-8706-5151; Email: xuxinfang@mail.sysu.edu.cn

Authors

Kuiyong Dong – Department of Chemistry, University of Texas at San Antonio, San Antonio, Texas 78249, United States

Raj Gurung – Department of Chemistry, University of Texas at San Antonio, San Antonio, Texas 78249, United States

Complete contact information is available at:

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) (a) Nawrat, C.; Moody, C. J. Natural Products Containing A Diazo Group. *Nat. Prod. Rep.* **2011**, *28*, 1426–1444. (b) Davies, H. M. L.; Lian, Y. The Combined C-H Functionalization/Cope Rearrangement: Discovery and Applications in Organic Synthesis. *Acc. Chem. Res.* **2012**, *45*, 923–935. (c) Davies, H. M. L.; Itami, K.; Stoltz, B. M. New Directions in Natural Product Synthesis. *Chem. Soc. Rev.* **2018**, *47*, 7828–7829. (d) Doyle, M. P.; Ratnikov, M.; Liu, Y. Intramolecular Catalytic Asymmetric Carbon-Hydrogen Insertion reactions. Synthetic Advantages in Total Synthesis in Comparison with Alternative Approaches. *Org. Biomol. Chem.* **2011**, *9*, 4007–4016. (e) Ford, A.; Miel, H.; Ring, A.; Slatery, C. N.; Maguire, A. R.; McKervey, M. A. Modern Organic Synthesis with α -Diazocarbonyl Compounds. *Chem. Rev.* **2015**, *115*, 9981–10080. (f) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, 1998; Chapters 8.3 and 8.4.
- (2) (a) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. Stereoselective Cyclopropanation Reactions. *Chem. Rev.* **2003**, *103*, 977–1050. (b) Pellissier, H. Recent Developments in Asymmetric Cyclopropanation. *Tetrahedron* **2008**, *64*, 7041–7095. (c) Denton, J. R.; Davies, H. M. L. Enantioselective Reactions of Donor/Acceptor Carbenoids Derived from α -Aryl- α -Diazoketones. *Org. Lett.* **2009**, *11*, 787–790. (d) Qian, D.; Zhang, J. Gold-Catalyzed Cyclopropanation Reactions Using A Carbenoid Precursor Toolbox. *Chem. Soc. Rev.* **2015**, *44*, 677–698. (e) Chanthamath, S.; Iwasa, S. Enantioselective Cyclopropanation of A Wide Variety of Olefins Catalyzed by Ru(II)-Pheox Complexes. *Acc. Chem. Res.* **2016**, *49* (10), 2080–2090.
- (3) (a) Zhu, S.; Zhou, Q. Transition-Metal-Catalyzed Enantioselective Heteroatom-Hydrogen Bond Insertion Reactions. *Acc. Chem. Res.* **2012**, *45*, 1365–1377. (b) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. Catalytic Carbene Insertion into C-H Bonds. *Chem. Rev.* **2010**, *110*, 704–724. (c) Davies, H. M. L.; Manning, J. R. Catalytic C-H Functionalization by Metal Carbenoid and Nitrenoid Insertion. *Nature* **2008**, *451*, 417–424. (d) Liao, K. B.; Davies, H. M. L. Dirhodium Tetracarboxylates as Catalysts for Selective Intermolecular C-H Functionalization. *Nature Reviews Chemistry* **2019**, *3*, 347–360. (e) Davies, H. M. L.; Morton, D. Guiding Principles for Site Selective and Stereoselective Intermolecular C-H Functionalization by Donor/Acceptor Rhodium Carbenes. *Chem. Soc. Rev.* **2011**, *40*, 1857–1869.
- (4) (a) Cheng, Q.; Deng, Y.; Lankelma, M.; Doyle, M. P. Cycloaddition Reactions of Enol-diazo Compounds. *Chem. Soc. Rev.* **2017**, *46*, 5425–5443. (b) Xu, X.; Doyle, M. P. The [3 + 3]-Cycloaddition Alternative for Heterocycle Syntheses: Catalytically Generated Metallo-enolcarbenes as Dipolar Adducts. *Acc. Chem. Res.* **2014**, *47*, 1396–1405. (c) Padwa, A. Domino Reactions of Rhodium(II) Carbenoids for Alkaloid Synthesis. *Chem. Soc. Rev.* **2009**, *38*, 3072–3081. (d) Davies, H. M. L.; Alford, J. S. Reactions of Metallo-carbenes Derived from N-sulfonyl-1,2,3-triazoles. *Chem. Soc. Rev.* **2014**, *43*, 5151–5162.
- (5) (a) Dong, K.; Pei, C.; Zeng, Q.; Wei, H.; Doyle, M. P.; Xu, X. Selective C(sp³)-H Bond Insertion in Carbene/Alkyne Metathesis reactions. Enantioselective Construction of Dihydroindoles. *ACS Catal.* **2018**, *8*, 9543–9549. (b) Padwa, A.; Blacklock, T. J.; Loza, R. Silver-Promoted Isomerizations of Some Cyclopropene Derivatives. *J. Am. Chem. Soc.* **1981**, *103*, 2404–2405. (c) Hoye, T. R.; Dinsmore, C. J. Rhodium(II) Acetate Catalyzed Alkyne Insertion Reactions of α -Diazo Ketones: Mechanistic Inferences. *J. Am. Chem. Soc.* **1991**, *113*, 4343–4345. (d) Jansone-Popova, S.; May, J. A. Synthesis of Bridged

Polycyclic Ring Systems via Carbene Cascades Terminating in C-H Bond Insertion. *J. Am. Chem. Soc.* **2012**, *134*, 17877–17880. (e) Dong, K.; Fan, X.; Pei, C.; Zheng, Y.; Chang, S.; Cai, J.; Qiu, L.; Yu, Z.; Xu, X. Transient-Axial-Chirality Controlled Asymmetric Rhodium-Carbene C(sp²)-H Functionalization for the Synthesis of Chiral Fluorenes. *Nat. Commun.* **2020**, *11*, 2363–2372. (f) Qian, Yu; Shanahan, C. S.; Doyle, M. P. Templated Carbene Metathesis Reactions from the Modular Assembly of Enol-diazo Compounds and Propargyl Acetates. *Eur. J. Org. Chem.* **2013**, *2013*, 6032–6037.

(6) (a) Xia, Y.; Qiu, D.; Wang, J. Transition-Metal-Catalyzed Cross-Couplings through Carbene Migratory Insertion. *Chem. Rev.* **2017**, *117*, 13810–13889. (b) Nunewar, S.; Kumar, S.; Talakola, S.; Nanduri, S.; Kanchupalli, V. Co(III), Rh(III) & Ir(III)-Catalyzed Direct C-H Alkylation/Alkenylation/Arylation with Carbene Precursors. *Chem. - Asian J.* **2021**, *16*, 443–459. (c) Chen, L.; Chen, K.; Zhu, S. Transition-Metal-Catalyzed Intramolecular Nucleophilic Addition of Carbonyl Groups to Alkynes. *Chem.* **2018**, *4*, 1208–1262. (d) Guo, X.; Hu, W. Novel Multicomponent Reactions via Trapping of Protic Onium Ylides with Electrophiles. *Acc. Chem. Res.* **2013**, *46*, 2427–2440. (e) Suleman, M.; Lu, P.; Wang, Y. Recent Advances in the Synthesis of Indole Embedded Heterocycles with 3-Diazoindolin-2-imines. *Org. Chem. Front.* **2021**, *8*, 2059.

(7) Nozaki, H.; Takaya, H.; Moriuti, S.; Noyori, R. Homogeneous Catalysis in the Decomposition of Diazo Compounds by Copper Chelates: Asymmetric Carbenoid Reactions. *Tetrahedron* **1968**, *24*, 3655–3669.

(8) (a) Cohen, Y.; Cohen, A.; Marek, I. Creating Stereocenters within Acyclic Systems by C-C Bond Cleavage of Cyclopropanes. *Chem. Rev.* **2021**, *121*, 140–161. (b) Breckenridge, R. J.; Suckling, C. J. Enzyme Inhibition by Electrophilic Cyclopropane Derivatives. *Tetrahedron* **1986**, *42*, 5665–5677. (c) Salaün, J. Cyclopropane Derivatives and Their Diverse Biological Activities. *Top. Curr. Chem.* **2000**, *207*, 1–67. (d) Faust, R. Fascinating Natural and Artificial Cyclopropane Architectures. *Angew. Chem., Int. Ed.* **2001**, *40*, 2251–2253. (e) Wessjohann, L. A.; Brandt, W.; Thiemann, T. Biosynthesis and Metabolism of Cyclopropane Rings in Natural Compounds. *Chem. Rev.* **2003**, *103*, 1625–1648. (f) Chen, D. Y.; Pouwer, H.; Richard, J. A. Recent Advances in the Total Synthesis of Cyclopropane-Containing Natural Products. *Chem. Soc. Rev.* **2012**, *41*, 4631–4642.

(9) (a) Ahmed, G.; Calvo, R. L.; Churchill, M. R.; Churchill, D. G.; Davies, H. M. L. Asymmetric Synthesis of 2,3-Dihydrofurans by Reaction of Rhodium-Stabilized Vinylcarbenoids with Vinyl Ethers. *J. Org. Chem.* **1998**, *63*, 2641–2645. (b) Lin, C.-H.; Pursley, D.; Klein, J. E. M. N.; Teske, J.; Allen, J. A.; Rami, F.; Kohn, A.; Plietker, B. Plietker, B. Non-decarbonylative Photochemical versus Thermal Activation of Bu₄N[Fe(CO)₃(NO)]-the Fe-catalyzed Cloke-Wilson Rearrangement of Vinyl and Arylcyclopropanes. *Chem. Sci.* **2015**, *6*, 7034–7043. (c) Zhang, J.; Tang, Y.; Wei, W.; Wu, Y.; Li, Y.; Zhang, J.; Zheng, Y.; Xu, S. Organocatalytic Cloke-Wilson Rearrangement: DABCO-Catalyzed Ring Expansion of Cyclopropyl Ketones to 2,3-Dihydrofurans. *Org. Lett.* **2017**, *19*, 3043–3046. (d) Piotrowski, M. L.; Kerr, M. A. Tandem Cyclopropanation/Vinyllogous Cloke-Wilson Rearrangement for the Synthesis of Heterocyclic Scaffolds. *Org. Lett.* **2018**, *20*, 7624–7627.

(10) (a) Müller, P.; Bernardinelli, G.; Allenbach, Y.; Ferri, F.; Grass, M. S. Asymmetric Synthesis of Dihydrofurans via Rh(II)-Catalyzed Cyclopropanation-Rearrangement of Enol Ethers with 1-(Silanyloxy)-vinyl Diazoacetates. *Synlett* **2005**, 1397–1400. (b) Müller, P.; Chappellet, S. Asymmetric 1,3-Dipolar Cycloadditions of 2-Diazo-cyclohexane-1,3-diones and Alkyl Diazopyruvates. *Helv. Chim. Acta* **2005**, *88*, 1010–1021.

(11) Zhou, L.; Yan, W. G.; Sun, X. L.; Wang, L.; Tang, Y. A Versatile Enantioselective Catalytic Cyclopropanation-Rearrangement Approach to the Divergent Construction of Chiral Spiroaminals and Fused Bicyclic Acetals. *Angew. Chem., Int. Ed.* **2020**, *59*, 18964–18969.

(12) For examples, see: (a) Cheng, X. C.; Kihara, T.; Kusakabe, H.; Magae, J.; Kobayashi, Y.; Fang, R. P.; Ni, Z. F.; Shent, Y. C.; Ko, K.;

Yamaguchi, I.; Isono, K. A New Antibiotic, Tautomycin. *J. Antibiot.* **1987**, *40*, 907–909. (b) Tachibana, K.; Scheuer, P. J.; Tsukitani, Y.; Kikuchi, H.; Van Engen, D.; Clardy, J.; Gopichand, Y.; Schmitz, F. J. Okadaic Acid, A Cytotoxic Polyether from Two Marine Sponges of the Genus Halichondria. *J. Am. Chem. Soc.* **1981**, *103*, 2469–2471. (c) Pettit, G. R.; Chicacz, Z. A.; Gao, F.; Herald, C. L.; Boyd, M. R.; Schmidt, J. M.; Hooper, J. N. A. Antineoplastic Agents. 257. Isolation and Structure of Spongistatin 1. *J. Org. Chem.* **1993**, *58*, 1302–1304. (d) Bai, R.; Cichacz, Z. A.; Herald, C. L.; Pettit, G. R.; Hamel, E. Spongistatin 1, A Highly Cytotoxic, Sponge-Derived, Marine Natural Product that Inhibits Mitosis, Microtubule Assembly, and the Binding of Vinblastine to Tubulin. *Mol. Pharmacol.* **1993**, *44*, 757–766. (e) Banerjee, A.; Sergienko, E.; Vasile, S.; Gupta, V.; Vuori, K.; Wipf, P. Triple hybrids of steroids, spiroketals, and oligopeptides as new biomolecular chimeras. *Org. Lett.* **2009**, *11*, 65–68.

(13) (a) Perron, F.; Albizzati, K. F. Chemistry of spiroketals. *Chem. Rev.* **1989**, *89*, 1617–1661. (b) Jacobs, M. F.; Kitching, W. B. Spiroacetals of Marine Origin. *Curr. Org. Chem.* **1998**, *2*, 395–436. (c) Mead, K. T.; Brewer, B. N. Strategies in Spiroketal Synthesis Revisited: Recent Applications and Advances. *Curr. Org. Chem.* **2003**, *7*, 227–256. (d) Aho, J. E.; Pihko, P. M.; Rissa, T. K. Nonanomeric Spiroketals in Natural Products: Structures, Sources, and Synthetic Strategies. *Chem. Rev.* **2005**, *105*, 4406–4440. (e) Ley, S. V.; Milroy, L. G.; Myers, R. M. *Science of Synthesis* **2007**, *29*, 613.

(14) (a) Palmes, J. A.; Aponick, A. Strategies for Spiroketal Synthesis Based on Transition-Metal Catalysis. *Synthesis* **2012**, *44*, 3699–3721. (b) Quach, R.; Chorley, D. F.; Brimble, M. A. Recent Developments in Transition Metal-Catalysed Spiroketalisation. *Org. Biomol. Chem.* **2014**, *12*, 7423–7432. (c) Gai, S.; Hennevel, J. S.; Cording, A. P.; Badart, M. P.; Lucas, N. T.; Hawkins, B. C. The Synthesis of Benzannulated Spiroketals from 1,1-Diacyl-2-phenylcyclopropanes. *Tetrahedron Lett.* **2021**, *69*, 152984. (d) Liang, M.; Zhang, S.; Jia, J.; Tung, C.; Wang, J.; Xu, Z. Synthesis of Spiroketals by Synergistic Gold and Scandium Catalysis. *Org. Lett.* **2017**, *19*, 2526–2529.

(15) (a) Li, J.; Lin, L.; Hu, B.; Lian, X.; Wang, G.; Liu, X. H.; Feng, X. Bimetallic Gold(I)/Chiral N, N'-dioxide Nickel(II) Asymmetric Relay Catalysis: Chemo- and Enantioselective Synthesis of Spiroketals and Spiroaminals. *Angew. Chem., Int. Ed.* **2016**, *55*, 6075–6078. (b) Gong, J.; Wan, Q.; Kang, Q. Gold(I)/Chiral Rh(III) Lewis Acid Relay Catalysis Enables Asymmetric Synthesis of Spiroketals and Spiroaminals. *Adv. Synth. Catal.* **2018**, *360*, 4031–4036. (c) Moilanen, S. B.; Potuzak, J. S.; Tan, D. S. Stereocontrolled Synthesis of Spiroketals via Ti(Oi-Pr)₄-Mediated Kinetic Spirocyclization of Glycol Epoxides with Retention of Configuration. *J. Am. Chem. Soc.* **2006**, *128*, 1792–1793. (d) Wang, X.; Han, Z.; Wang, Z.; Ding, K. Catalytic Asymmetric Synthesis of Aromatic Spiroketals by SpinPhox/Iridium(I)-Catalyzed Hydrogenation and Spiroketalization of α,α' -Bis(2-hydroxyarylidene) Ketones. *Angew. Chem., Int. Ed.* **2012**, *51*, 936–940. (e) Ćorić, I.; List, B. Asymmetric spiroacetalization catalysed by confined Brønsted acids. *Nature* **2012**, *483*, 315–319. (f) Sun, Z.; Winschel, G. A.; Borovika, A.; Nagorny, P. Chiral Phosphoric Acid-Catalyzed Enantioselective and Diastereoselective Spiroketalizations. *J. Am. Chem. Soc.* **2012**, *134*, 8074–8077. (g) Wu, H.; He, Y.-P.; Gong, L.-Z. Direct Access to Enantioenriched Spiroacetals through Asymmetric Relay Catalytic Three-Component Reaction. *Org. Lett.* **2013**, *15*, 460–463.