A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

Accepted Article

Title: Catalytic Desymmetric Cycloaddition of Diaziridines with Metalloenolcarbenes: the Special Role of Donor-Acceptor Cyclopropenes

Authors: Haifeng Zheng and Michael P. Doyle

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201906754
Angew. Chem. 10.1002/ange.201906754

Link to VoR: http://dx.doi.org/10.1002/anie.201906754
http://dx.doi.org/10.1002/ange.201906754

WILEY-VCH

10.1002/anie.201906754

WILEY-VCH

COMMUNICATION

Catalytic Desymmetric Cycloaddition of Diaziridines with Metalloenolcarbenes: the Role of Donor-Acceptor Cyclopropenes

Haifeng Zheng, Michael P. Doyle*

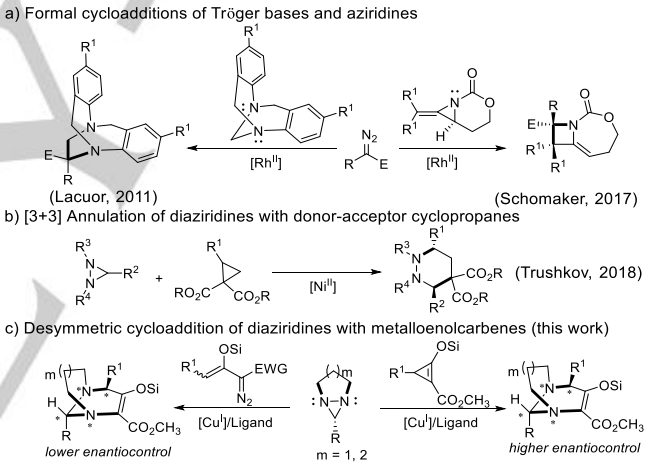
Dedication to Professor Xiaoming Feng on the occasion of his 55th birthday

Abstract: Chiral copper(I) catalysed reactions of symmetrical diaziridines with enoldiazo compounds undergo novel N-N bond ring opening with formal [3+3] cycloaddition to form four chiral centers with high stereocontrol. A broad spectrum of highly enantioenriched bridged bis-nitrogen heterocyclic compounds were obtained in high yield and diastereoselectivity using γ-substituted enoldiazoacetates, but their geometrical isomers gave different enantioselectivities. Donor-acceptor cyclopropenes formed from the geometrical isomers of γ-substituted enoldiazoacetates underwent catalytic ring opening to give only the more selective *Z*-isomer of the metallo-enolcarbene intermediate provided optimum yields and selectivities for the 1,5-diazabicyclo[*n*.3.1]non-2-ene derivatives.

Diazo compounds are versatile reagents that are easily accessible and have provided an attractive platform for various transformations.[1] Their metal-catalyzed carbene transfer strategies have enabled diverse cycloadditions,[2] rearrangements,[3] insertions,[4] and ylide transformations.[5] Except in ylide-forming reactions, basic nitrogen heterocycles, which can be synthetic building blocks in metal-catalytic carbene transfer reactions, have rarely been used even though many compounds produced by these methodologies are biologically relevant.[6] However, Lacuor and co-workers developed a dirhodium(II)-catalyzed 1,2-Stevens-like rearrangement of aryl diazoacetate with Tröger bases (Scheme 1a, left).[7] In addition, Schomaker and coworkers found an elegant stereoselective [3+1]-ring expansion for the synthesis of highly substituted methyl azetidines from methylene aziridines (Scheme 1a, right).[8] Each transformation is initiated by nitrogen ylide formation followed by C-N bond breakage and migration or rearrangement.

Diaziridines are saturated three-membered ring heterocyclic compounds with two nucleophilic nitrogen atoms. Prior work has shown that they can be used as the precursors of stabilized azomethine imines for thermal and Lewis acid catalysed reactions with unsaturated compounds.[9] Trushkov and co-workers recently reported the first Lewis acid catalyzed [3+3] annulation of donor-acceptor cyclopropanes with diaziridines, which resulted in the formation of perhydropyridazine derivatives in moderate yields and diastereocontrol (Scheme 1b),[10] indicating the suitability of diaziridines for nitrogen ylide formation and C-N ring opening. However, the strong coordinating ability of diaziridines could also deactivate an electrophilic catalyst employed to generate the essential metal carbene intermediate.

We report here the highly stereoselective formal [3+3] desymmetrization cycloaddition of diaziridines with enoldiazo compounds that occur with nitrogen ylide formation followed by a novel N-N bond ring opening. Using a chiral copper(I)/Box complex catalyst, high enantioselectivities could be obtained with γ-substituted enoldiazoacetates, and even higher enantiocontrol (up to 97% ee) was achieved with their derivative donor-acceptor cyclopropenes that produced only *Z*-metalloenolcarbene isomer (Scheme 1c).



Scheme 1. Background and this work.

Enoldiazoacetate **1a** and diaziridine **2a** were selected as model substrates to evaluate the title reaction. Commercially available dirhodium(II) complexes were initially employed as catalysts, but no cross-coupled products were obtained (Table 1, entries 1 and 2). ^{1}H NMR spectral analysis showed only the formation of the corresponding donor-acceptor cyclopropene that did not undergo further reaction over the extended reaction time. Strong coordination between the diaziridine and dirhodium(II) carboxylate was evident by colorimetric assay, indicating deactivation of the catalyst for ring opening of the donor-acceptor cyclopropene.[11] Gold complexes (Table 1, entries 3 and 4), which were efficient catalysts in previous transformations of vinyldiazo compounds,[12] also failed to afford any coupling product, and a similar lack of reactivity was found with catalytic $AgSbF_6$ (Table 1, entry 5). However, when the reaction was performed in the presence of copper(I) complexes, formal [3+3] cycloaddition occurred, affording 1,5-diazabicyclo[3.3.1]non-2-ene product **3a** in good yields (Table 1, entries 6-8). This outcome

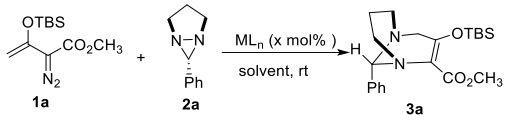
[a] Dr. H. F. Zheng, Prof. Dr. M. P. Doyel
Department of Chemistry, The University of Texas at San Antonio
One UTSA Circle, San Antonio, TX 78249 (USA)
E-mail: michael.doyle@utsa.edu

Supporting information for this article is given via a link at the end of the document.

10.1002/anie.201906754

involved cleavage of the N-N bond of the diaziridine rather than the expected C-N bond cleavage.[10] The most effective catalyst was found to be $[Cu(CH_3CN)_4][BF_4]$, producing the desired product **3a** in 81% yield at room temperature (Table 1, entry 8). Attempts to optimize the yield of **3a** by changing the solvent were unsuccessful (Table 1, entries 9-11).

Table 1. Optimization of reaction conditions for [3+3] annulation of **1a** and **2a**.[a]



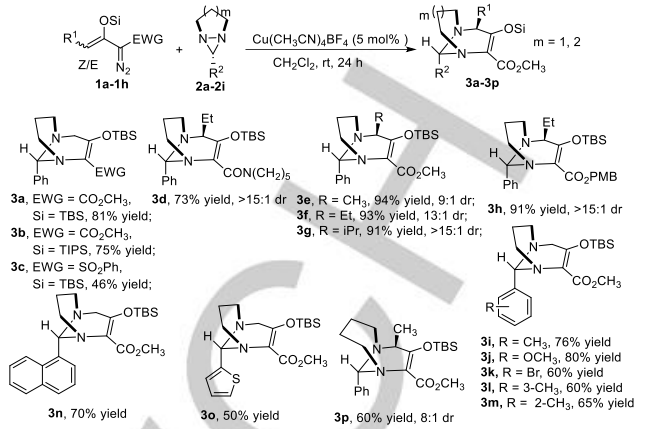
Entry	ML_n	x (mol %)	Solvent	Yield **3a** (%)[b]
1	$Rh_2(OAc)_4$	2	CH_2Cl_2	-
2	Rh_2(S-DOSP)$_4$	2	CH_2Cl_2	-
3	IPrAu$(CH_3CN)BF_4$	5	CH_2Cl_2	-
4	JohnPhosAuCl	5	CH_2Cl_2	-
5	$AgSbF_6$	5	CH_2Cl_2	-
6	$[Cu(OTf)]_2{\cdot}C_6H_6$	5	CH_2Cl_2	40
7	$Cu(CH_3CN)_4PF_6$	5	CH_2Cl_2	73
8	$Cu(CH_3CN)_4BF_4$	5	CH_2Cl_2	81
9	$Cu(CH_3CN)_4BF_4$	5	$CHCl_3$	20
10	$Cu(CH_3CN)_4BF_4$	5	CH_2ClCH_2Cl	45
11	$Cu(CH_3CN)_4BF_4$	5	toluene	24

[a] Reactions were performed with **1a** (0.24 mmol) and **2a** (0.2 mmol) in solvent (4 mL). [b] Yields of isolated product.

With optimized conditions in hand, we examined the scope of reactions with enoldiazo compounds **1** (**1d**-**1h** were mixtures of geometrical isomers) with diaziridine **2** (Scheme 2). The *tert*-butyldimethylsilyl (TBS) protected enoldiazoacetate (**1a**) gave the corresponding 1,5-diazabicyclo[3.3.1]non-2-ene product in higher yield than did the triisopropylsilyl (TIPS) protected enoldiazo compound (**1b**). In addition, enoldiazosulfone **1c**[13d] and enoldiazoacetamide **1d**[13a] gave the corresponding [3+3]-cycloaddition products, albeit in lower yields. Furthermore, the terminal alkyl-substituted enoldiazo compounds (**1e**-**1g,** *Z*/*E* = 1.5:1-5:1) showed excellent reactivity, from which products **3e**-**3g** were obtained in 91-94% yields with diastereoselectivities that were good to excellent (9:1 to >15:1 dr). The ester substituent had little impact on the reaction outcome.

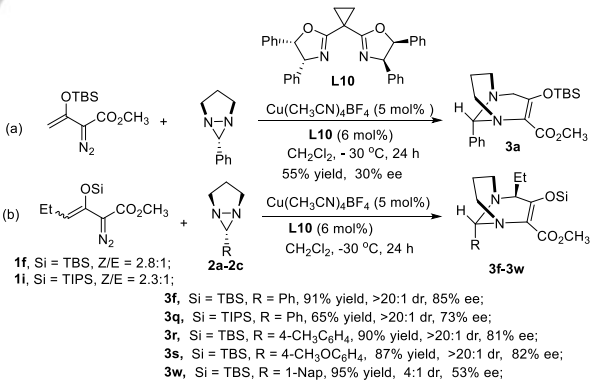
The substrate scope of diaziridines **2** was also explored (Scheme 2). Both electron-withdrawing and electron-donating substituents on the 4-position of phenyl ring of diaziridine produced the corresponding products (**3i**-**3k**) in good yields, and substituents at different positions of the phenyl ring had little effect on the reaction (**3l** and **3m**). Diaziridines bearing electron-donating substituents provided higher yields than those with electron-withdrawing groups (EWG) (**3i** and **3j** versus **3k**), and 1-naphthyl (**2f**) and 2-thienyl (**2g**) substituted diaziridines were suitable substrates (70% and 50% product yields). The [6,3]-bicyclic diaziridine substrate **2i** also underwent [3+3]-cycloaddition with **1e** in good yield and diastereoselectivity.

Recent progress with enantioselective cycloaddition reactions of enoldiazo compounds[13] prompted us to examine enantiocontrol in [3+3]-cycloaddition with diaziridines catalysed by copper(I) complexes with chiral ligands. Our objective was to prepare [*n*.3.1]-bridged nitrogen heterocyclic compounds in good yields with both high diastereo- and enantio-selectivities. However, the terminal hydrogen substituted enoldiazo compound



Scheme 2. Scope of the copper(I)-promoted [3+3] annulation reaction

1a reacted with **2a** to produce **3a** in only 55% yield with 30% ee (Scheme 3a). Expecting that γ-substituted enoldiazoacetates could enhance enantiocontrol, enoldiazoacetate **1f** and diaziridine **2a** were selected as model substrates to determine optimum conditions (for details, see SI). A systematic inspection of tridentate (pybox), bidentate (bis-oxazoline), and double-side arm bisoxazoline (sabox) ligands (see Supplementary Information) revealed that the optimum results were obtained with $Cu(CH_3CN)_4BF_4$/**L10** in CH_2Cl_2 at -30 °C. The desired bridged nitrogen heterocyclic derivative **3f** was isolated in 91% yield with >20:1 dr and 85% ee (Scheme 3a). Variation of the silicon protecting group (**1i**) and substituents of diaziridines (**2b**, **2c**, and **2h**) generally provided 1,5-diazabicyclo[3.3.1]non-2-ene derivatives (**3q**-**3w**) in high yields with good diastereocontrol, but with only modest enantioselectivities (Scheme 3b).



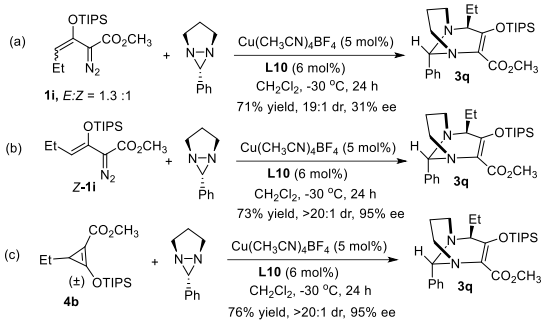
Scheme 3. Catalytic enantioselective [3+3] cycloaddition reaction.

Although product yields were good and diastereocontrol was high, we were disappointed with enantioselectivity. Our extensive survey of catalysts and ligands had left us with $Cu(CH_3CN)_4BF_4$/**L10** as optimum, but different *E*/*Z*-ratios **1f** showed inconsistencies in product %ee values. Considering that the *Z*/*E*-mixture may influence enantioselectivity, we prepared the *Z*-isomer of **1i** (*Z*/*E* > 20:1) and **1i** whose isomeric

10.1002/anie.201906754

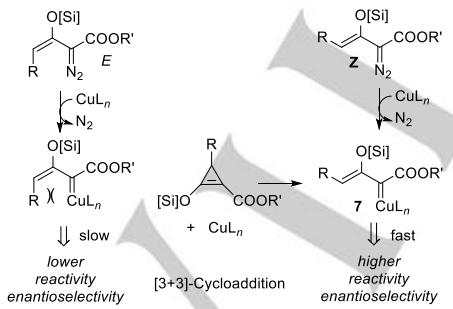
WILEY-VCH

COMMUNICATION



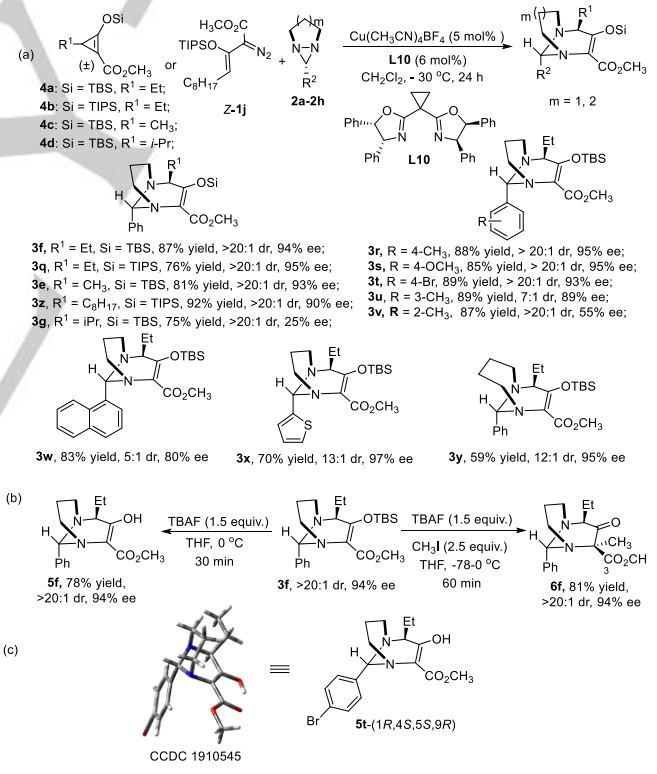
Scheme 4. Control experiments.

ratio was predominantly the *E*-isomer (*E*/*Z* = 1.3:1). In addition, the donor–acceptor-substituted cyclopropene **4b**, that had proven to be efficient metallo-vinylcarbene precursors,[14c] was used in place of the diazo compound for the asymmetric [3+3] cycloaddition reaction. For reactions forming **3q** (Scheme 4)**,** enantioselectivity was significantly higher using *Z*-**1i** or **4b** than with the *E*/*Z*-mixtures of **1i**. Stereoselectivities obtained with *Z*-**1i** matched those with **4b,** and **3q** was obtained with >20:1 dr and 95% ee (Scheme 4b and 4c). Monitoring the reaction of diaziridine **2a** with *Z*/*E*-**1f** showed that (a) both *Z* and *E* isomer underwent cycloaddition, but the *Z*-isomer exhibited higher reactivity, and (b) cyclopropene 4**a** was not observed under the reaction conditions, which indicated that the reaction rate for [3+3]-cycloaddition with the metallo-enolcarbene was faster than that for the formation of the donor-acceptor cyclopropene. As described in Scheme 5, these experiments suggested that the *Z*-metallo-enolcarbene **7** showed high reactivity and enantioselectivity for cycloaddition, and that cyclopropenes underwent catalytic ring opening to give only the *Z*-isomer of the metallo-enolcarbene intermediate that provided excellent results. As a consequence, the donor-acceptor cyclopropene, conveniently formed either thermally or catalytically from its parent enoldiazo-*E*/*Z*-mixture,[14] is preferred over the enoldiazo-*E*/*Z*-mixture as the reactant for [3+3]-cycloaddition with diaziridines.



Scheme 5. [3+3]-Cycloaddition of enoldiazo compounds and cyclopropenes.

Under the optimized reaction conditions the cycloaddition reactions between a wide range of donor–acceptor substituted cyclopropenes **6** and diaziridines **2** were investigated (Scheme 6a). The TIPS protected **4b**, methyl-substituted cyclopropenes **4c,** and enoldiazo compound *Z*-**1j** gave the desired products in good yields and excellent stereoselectivities (**3q**, **3e** and **3z**). The more sterically encumbered isopropyl-substituted cyclopropene **4d** afforded **3g** in only 25% ee, but the *n*-octyl substituent did not diminish stereocontrol from selectivities found with methyl and ethyl substituents. For reactions with *para*-substituted phenyl substituents of diaziridines **2,** both electron-withdrawing and electron-donating groups provided good product yields and excellent dr with er greater than 96:4 (**3r**-**3t**). O*rtho*- and *meta*-methyl substituuents of the diaziridine influence reaction stereoselectivities (*meta*-**3u** was obtained in 89% yield, 7:1 dr, and 89% ee, but *ortho*-**3v** was obtained in 87% yield, >20:1 dr, and 55% ee). 1-Naphthyl- and 2-thienyl-substituted diaziridines (**2g**) gave the corresponding bridged nitrogen heterocyclic derivatives **3w** and **3x** with lower diastereocontrol. The [6,3]-bicyclic diaziridine substrate (**2h**) also underwent cycloaddition to the corresponding chiral 1,5-diazabicyclo[4.3.1]non-2-ene product **3y** in 59% yield with 12:1 dr and 95% ee. In addition, the chiral product **3f** was further transformed to products **5f** and **6f** in good yields without loss of stereoselectivities (Scheme 6b). The absolute configuration of **3t** was determined to be (1*R*,4*S*,5*S*,9*R*) by X-ray diffraction of the related derivative **5t** (Scheme 6c).[15]



Scheme 6. Scope, transformation and single crystal structure

Based on the absolute configuration of **3t** and previous reports,[14] we propose in Figure 1 the probable mechanism and stereocontrol model for the catalytic asymmetric formal [3+3] cycloaddition. The chiral Cu(I)/**L10** complex catalyzed dinitrogen (N_2) extrusion of enoldiazo compound (*Z*-**1**) forms the *Z*-metalloenolcarbene intermediate; and, alternatively, the chiral Cu(I)/**L10** catalyst reacts with the cyclopropene to also afford only

10.1002/anie.201906754

the *Z*-metalloenolcarbene intermediate. Subsequently, the diaziridine attacks the *Z*-metallo-enolcarbene from the β-*Si* face to form intermediate **8** (Figure 1b, **TS-I**). Then, the silyl enol ether induced nucleophilic substitution onto the second nitrogen occurs with cleavage of the N-N bond to produce the corresponding product **3t** with the (1*R,*4*S*,5*S*,9*R*,)-configuration. However, for the *E*-enoldiazo compound, steric hindrance between R group and the Cu(I) complex weakens the metal carbene bond, resulting lower reactivity and enantioselectivity (Figure 1b, **TS-II)**.

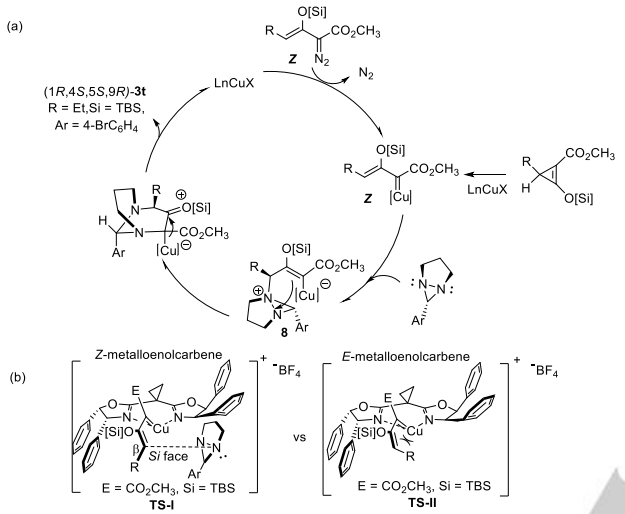


Figure 1. Proposed mechanism and stereocontrol model.

In summary, we have realized the catalytic [3+3] cycloaddition of achiral diaziridines with diazo compounds via metal carbene transfer to form four chiral centers with high stereocontrol. The novel N-N bond cleavage occurs because of nucleophilic displacement on nitrogen (intermediate **8**) that releases a tertiary amine leaving group.[16] By using the $Cu(CH_3CN)_4BF_4$/**L10** catalyst, diaziridines react with enoldiazo compounds to afford a variety of 1,5-diazabicyclo[*n*.3.1]non-2-ene products in good to high yields and stereoselectivities. In addition, the asymmetric [3+3] version was accomplished by using donor–acceptor-substituted cyclopropenes as the metalloenolcarbene precursors in the presence of the same Cu(I)/bisoxazoline complex catalyst with higher enantioselectivities. These results demonstrated the intriguing reactivity of saturated nitrogen heterocyclic derivatives in metal-carbene transfer chemistry, and also provided a fascinating methodology for the synthesis of nitrogenous heterocycles.

Acknowledgements

We acknowledge the U.S. National Science Foundation (CHE−1763168) for funding this research. The NMR spectrometer used in this research was supported by a grant from the U.S. National Science Foundation (CHE−1625963).

Keywords: enoldiazo compounds• diaziridines• metal carbene • cyclopropenes • asymmetric [3+3] cycloadditions

[1] a) M. P. Doyle, M. A. McKervey, T. Ye, Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides, Wiley, New York, **1998**; b) A. Ford, H. Miel, A. Ring, C. N. Slattery, A. R. Maguire, M. A. McKervey, *Chem. Rev.* **2015**, *115*, 9981; c) N. R. Candeias, R. Paterna, P. M. P. Gois, *Chem. Rev.* **2016**, *116*, 2937; d) M. Marinozzi, F. Pertusati, M. Serpi, *Chem. Rev.* **2016**, *116*, 13991; e) L. Liu, J. Zhang, *Chem. Soc. Rev.* **2016**, *45*, 506.

[2] a) R. A. Moss, M. P. Doyle, Contemporary Carbene Chemistry, Wiley, New York, **2013**, pp 404-451; b) Q. Q. Chen, Y. M. Deng, M. Lankelma, M. P. Doyle, *Chem. Soc. Rev.* **2017**, *46*, 5425.

[3] Selected recent references: a) Z. J. Li, V. Boyarskikh, J. H. Hansen, J. Autschbach, D. G. Musaev, H. M. Davis, *J. Am. Chem. Soc.* **2012**, *134*, 15497; b) B. Xu, U. K. Tambar, *J. Am. Chem. Soc.* **2016**, *138*, 12073; c) .Z. K. Zhang, Z. Sheng, W. Z. Yu, G. J. Wu, R. Zhang, W. D. Chu, Y. Zhang, J. B. Wang, *Nat. Chem.* **2017**, 9, 970; d) D. J. Tindall, C. Werlé, R. Goddard, P. Philipps, C. Farès, A. Fürstner, *J. Am. Chem. Soc.* **2018**, *140*, 1884; e) X. B. Lin, Y. Tang, W. Yang, F. Tan, L. L. Lin, X. H. Liu, X. M. Feng, *J. Am. Chem. Soc.* **2018**, *140*, 3299.

[4] a) H. M. L. Davies, J. R. Manning, *Nature* **2008**, *451*, 417; b) M. P. Doyle, R. Duffy, M. Ratnikov, Z. Zhou, *Chem. Rev.* **2010**, *110*, 704; c) S.-F. Zhu, Q.-L. Zhou, *Natl. Sci. Rev.* **2014**, *1*, 580; d) Y. Xia, J. B. Wang, *Chem. Rev.* **2017**, *117*, 13810.

[5] a) A. Padwa, M. D. Weingarten, *Chem. Rev.* **1996**, *96*, 223; b) X. Guo, W. H. Hu, *Acc. Chem. Res.* **2013**, *46* , 2427.

[6] a) S. Edmondson, S. J. Danishefsky, L. S. Lorenzino, N. Rosen, *J. Am. Chem. Soc.* **1999**, *121*, 2147; b) J. C. Barrow, C. Forray, et al., *J. Med. Chem.* **2000**, *43*, 2703; c) H. Lin, S. J. Danishefsky, *Angew. Chem. Int. Ed.* **2003**, *42*, 36; *Angew. Chem.* **2003**, *115*, 38; d) M. Rottmann, T. T. Diagana, et al., *Science* **2010**, *329*, 1175; e) J. J. Liu, M. Y. Zhao, X. Zhang, X. Zhao, H. L. Zhu, *Mini-Rev. Med. Chem.* **2013**, *13*, 1957; f) N. Kato, S. L. Schreiber, et al., *Nature* **2016**, *538*, 344.

[7] a) A. Sharma, L. Guénée, J. –V. Naubron, J. Lacour, *Angew. Chem. Int. Ed.* **2011**, *50*, 3677; *Angew. Chem.* **2011**, *123*, 3761.

[8] S. C. Schmid, I. A. Guzei, J. M. Schomaker, *Angew. Chem. Int. Ed.* **2017**, *56*, 12229, *Angew. Chem.* **2017**, *129*, 12397.

[9] a) N. N. Makhova, A. V. Shevtsov, V. Y. Petukhova, *Russ. Chem. Rev.* **2011**, *80*, 1035; b) M. I. Pleshchev, V. V. Kachala, A. S. Goloveshkin, I. S. Bushmarinov, V. V. Kuznetsov, D. V. Khakimov and N. N. Makhova, *Mendeleev Commun.* **2013**, *23*, 271.

[10] A. O. Chagarovskiy, V. S. Vasin, V. V. Kuznetsov, O. A. Ivanova, V. B. Rybakov, A. N. Shumsky, N. N. Makhova, I. V. Trushkov, *Angew. Chem. Int. Ed.* **2018**, *57*, 10338; *Angew. Chem.* **2018**, *130*, 10495.

[11] X. C. Xu, P. Y. Zavalij, M. P. Doyle, *J. Am. Chem. Soc.* **2013**, *135*, 12439.

[12] a) A. M. Jadhav, V. V. Pagar, R.-S. Liu, *Angew. Chem. Int. Ed.* **2012**, *51*, 11809; *Angew. Chem.* **2012**, *124*, 11979; b) J. F. Briones, H. M. L. Davies, *J. Am. Chem. Soc.* **2013**, *135*, 13314; c) E. López, G. Lonzi, J. Gonzälez, L. A. López, *Chem. Commun.* **2016**, *52*, 9398; d) C. H. Zhu, G. Y. Xu, J. T. Sun, *Angew. Chem. Int. Ed.* **2016**, *55*, 11867; *Angew. Chem.* **2016**, *128*, 12046.

[13] a) Q. Q. Cheng, J. Yedoyan, H. Arman, M. P. Doyle, *J. Am. Chem. Soc.* **2016**, *138*, 44; b) K. O. Marichev, F. G. Adly, A. M. Carranco, E. C. Garcia, H. Arman, M. P. Doyle, *ACS Catal.* **2018**, *8*, 10392; c) F. G. Adly, K. O. Marichev, J. A. Jensen, H. Arman, M. P. Doyle, *Org. Lett.* **2019**, *21*, 40.

[14] a) H. M. L. Davies, B. H. Hu, E. Saikali, P. R. Bruzinski, *J. Org. Chem.***1994**, *59*, 4535; b) H. M. L. Davies, J. H. Houser, C. Thornley, *J. Org. Chem.* **1995**, *60*, 7529; c) Y. M. Deng, C. C. Jing, M. P. Doyle, *Chem. Commun.* **2015**, *51*, 12924.

[15] CCDC 1910545 (**5t**)..

[16] Displacement of bialkylsulfide in a [3+1]-cycloaddition reaction has been reported:Y.-M. Deng, L .A. Massey, P. Y. Zavalij, M. P. Doyle, *Angew. Chem. Int. Ed.* **2017**, *56*, 7479; *Angew. Chem.* **2017**, *129*, 7587..

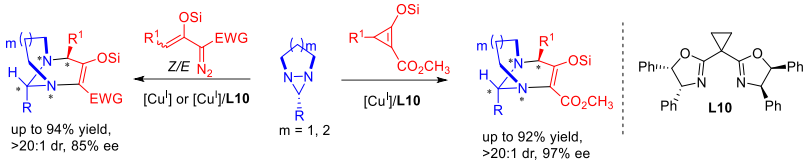
10.1002/anie.201906754

WILEY-VCH

COMMUNICATION

Entry for the Table of Contents

COMMUNICATION



H. F. Zheng, M. P. Doyle

Page No. – Page No.
Catalytic Desymmetric Cycloaddition of Diaziridines with Metalloenolcarbenes. The Special Role of Donor-Acceptor Cyclopropenes

Herein, we introduced symmetrical diaziridines in metalloenolcarbenes chemistry, and found novel N-N bond ring opening with formal [3+3] desymmetrization cycloaddition. In addition, chiral copper(I) catalyst could realize the high stereoselective formal [3+3] cycloaddition of enoldiazo compounds. Futhermore, the excellent asymmetric version was achieved by using donor–acceptor-substituted cyclopropenes as the metalloenolcarbene precursors in the presence of same chiral Cu(I)/bisoxazoline complex catalyst, delivering a various of chiral 1,5-diazabicyclo[*n*.3.1]non-2-ene derivatives.