



## **Accepted Article**

**Title:** Lewis Acid-Catalyzed Intramolecular [3+2] Cross-Cycloaddition of Donoracceptor Epoxides with Alkenes for Construction of Oxa-[n.2.1] Skeletons

Authors: Lu Chen, Jun Tian, Yizhou Zhan, Jun Ren, and Zhong-Wen Wang\*

This manuscript has been accepted and appears as an Accepted Article online.

This work may now be cited as: *Chin. J. Chem.* **2019**, *37*, 10.1002/cjoc.201900114.

The final Version of Record (VoR) of it with formal page numbers will soon be published online in Early View: http://dx.doi.org/10.1002/cjoc.201900114.

# WILEY-VCH SIOC CCS

ISSN 1001-604X • CN 31-1547/O6 mc.manuscriptcentral.com/cjoc www.cjc.wiley-vch.de

## Lewis Acid-Catalyzed Intramolecular [3+2] Cross-Cycloaddition of Donor-acceptor Epoxides with Alkenes for Construction of Oxa-[n.2.1] Skeletons<sup>†</sup>

Lu Chen,<sup>*a*†</sup> Jun Tian,<sup>*a*†</sup> Yizhou Zhan,<sup>*a*†</sup> Jun Ren,<sup>*a*</sup> and Zhong-Wen Wang\*,<sup>*a*,*b*</sup>

<sup>a</sup> State Key Laboratory and Institute of Elemento-Organic Chemistry, College of Chemistry, Nankai University, Tianjin 300071, China <sup>b</sup> Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Nankai University, Tianjin 300071, China

Cite this paper: Chin. J. Chem. 2019, 37, XXX-XXX. DOI: 10.1002/cjoc.201900XXX

Summary of main observation and conclusion The first LA-catalyzed [3+2]IMCC of GDA-epoxides with carbon-carbon double bonds has been developed. This provides an efficient and general strategy for construction of bridged oxa-[n.2.1] skeletons. A novel S<sub>N</sub>-like mechanism through a carbon-carbon bond cleavage of epoxide ring has been proposed.

#### **Background and Originality Content**

Development of highly efficient, general and novel strategies for construction of structurally complex and diverse polycyclic skeletons is one of the most important themes in organic synthesis. Intramolecular (formal) cycloaddition is proved to be one of the most appropriate options for achieving such tasks. One key issue in the intramolecular (formal) cycloadditions is the regioselectivity. From the perspective of organic synthesis, a switch of the regioselectivity will provide a strategy for construction of either fused or bridged bicyclic skeletons, which we named as "Intramolecular Cross-Cycloaddition (IMCC) and Parallel-Cycloaddition (IMPC)" strategy (Scheme 1).<sup>[1]</sup>





Tetrahydrofuran-based polycyclic skeletons exist in many biologically important natural products and synthetic molecules. Intramolecular 1,3-dipolar cycloadditions (1,3-DC) of carbonyl ylides with carbon-carbon double/triple bonds is one of the most efficient strategy for construction of the tetrahydrofuran-based polycyclic skeletons.<sup>[2]</sup> However, most of the reported examples afforded [3+2]IMPC products (Scheme 2, a). A strategy to switch the [3+2]IMPC to [3+2]IMCC (Scheme 2, b) is quite important both

\*E-mail: wzwrj@nankai.edu.cn

Homepage: http://wzw.nankai.edu.cn

Dedicated to the 100th Anniversary of Nankai University.

These authors contributed equally to this work.

For submission: https://mc.manuscriptcentral.com/cjoc For articles: https://onlinelibrary.wiley.com/journal/16147065

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/cjoc.201900114

theoretically and practically. While the [3+2]IMPC affords a fused oxa-[n.3.0] skeleton, the [3+2]IMCC of carbonyl ylides with carbon-carbon double bonds is expected to provide a novel strategy for construction of bridged oxa-[n.2.1] skeleton.

Scheme 2 [3+2]IMPC/[3+2]IMCC of carbonyl ylides with carbon-carbon double bonds.



Donor-acceptor epoxides can be used as precursors of polar carbonyl ylides via carbon-carbon bonds cleavage. Among such epoxides, those being activated by two geminal electron-withdrawing groups, can be named as GDA-epoxides (geminally double acceptors expoxides) and have received great attention recently. While thermal<sup>[3]</sup> or Lewis-acids (LAS)<sup>[4,5]</sup> intermolecular [3+2] cycloadditions of GDA-epoxides with various dipolarophiles have been widely studied, their intramolecular versions have seldom been investigated.<sup>[3d,3e,3h,3j,3k][6,7]</sup>

[3+2]IMCC of donor-acceptor epoxides with carbon-carbon double bonds was seldom investigated, <sup>[8]</sup> and to the best of our knowledge, there're no LA-catalyzed intramolecular [3+2] cycloadditions of GDA-epoxides with carbon-carbon double bonds reported yet. Inspired by our previously reported [3+2]IMCC of cyclopropanes and aziridines (Scheme 3, a/b),<sup>[9]</sup> we envisage to introduce a diene moiety to react with GDA-epoxides, by which the regioselectivity might be switched from the general [3+2]IMPC to [3+2]IMCC to construct the bridged oxa-[n.2.1] skeleton

This article is protected by copyright. All rights reserved.

#### Report

(Scheme 3, c).<sup>[10]</sup> Herein, we report the first LA-catalyzed [3+2]IMCC of GDA-epoxides with carbon-carbon double bonds.

**Scheme 3** [3+2]IMCC of cyclopropane 1,1-diesters, aziridine 2,2-diesters and GDA-epoxides with conjugated dienes.



#### **Results and Discussion**

0

00.14

We first prepared GDA-epoxide **1a** (2,2-diester-activated epoxide) to test our hypothesis. With DCE (1,2-dichloroethane) as a solvent, various LAs were screened (Table 1). To our delight, most of the LAs could promote the reaction and the [3+2]IMCC product **2a** was obtained successfully, among which Sc(OTf)<sub>3</sub> and Ni(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O gave satisfactory yields (entry 1 and entry 9). The structure of **2a** was unambiguously confirmed by X-ray crystal structure analysis.<sup>[12]</sup> When SnCl<sub>4</sub> was used, the reaction gave a rng-opening product (see supporting information).

We then prepared GDA-epoxide **3a** (2,2-diketone-activated epoxide) and screened the reaction conditions (Table 2). Under catalysis of LAs, the [3+2]IMCC product **4a** was also successfully obtained. We found that comparing with that of the diester-substrate **1a**, the reaction rate of **3a** was improved greatly. The yield of **3a** was also improved. Both Sc(OTf)<sub>3</sub> (0.1 equiv) and Ni(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O (0.2 equiv) gave excellent yields (entries 2 and 4).

Table 2 Optimization of reaction conditions of GDA-epoxide 3a<sup>a</sup>

COMe COMe 3a		Lewis acid Solvent		4a	
Entry	LAs	Solvent	Т	Time (h)	Yield (%) <sup>b</sup>
1	Sc(OTf)₃	DCE	r.t.	0.1	68
2	Sc(OTf)₃	DCE	r.t.	0.5	85 <sup>c</sup>
3	Yb(OTf)₃	DCE	r.t.	1.5	50
4	Ni(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	DCE	r.t.	2	83
5	Sc(OTf)₃	CH₃OH	r.t.	>48	NR
6	Sc(OTf)₃	Toluene	r.t.	6	75
7	Sc(OTf)₃	CH₃CN	r.t.	>48	NR
8	Sc(OTf)₃	DCM	r.t.	1.5	90

<sup>*a*</sup> Reaction conditions: **3a** (0.06 mmol), catalyst (0.2 equiv), activated 4Å MS (200 mg), solvent (2.0 mL), Ar. <sup>*b*</sup> Yield determined by <sup>1</sup>H NMR spectroscopy (internal standard: 1-chloro-2,4-dinitrobenzene). <sup>*c*</sup> 10 mol% of Sc(OTf)<sub>3</sub> was used. DCM = dichloromethane. NR = No Reaction.

The scope of substrates was investigated under the optimized conditions (Table 3). [3+2]IMCC of several substituted phenyl GDA-epoxides successfully afforded products (**2b**, **2c**, **4a-4h**) containing oxa-[2.2.1] skeletons. [3+2]IMCC of one indole substrate **1d** afforded product **2d** with a oxa-[3.2.1] skeleton. Unfortunately, [3+2]IMCC of GDA-epoxides with a linear alkyl linker failed, probably due to their flexibility comparing with the rigid benzene-substrates.

 Table 1
 Optimization of reaction conditions of GDA-epoxide 1a<sup>a</sup>

			Lewis acid		
			Solvent		CO <sub>2</sub> Me
C	 1a				2a
	Entry	LAs	T (°C)	Time (h)	Yield (%) <sup>b</sup>
	1	Sc(OTf)₃	r.t.	6	67
	2	Yb(OTf)₃	r.t60	20	57
	3	In(OTf)₃	r.t60	20	18
	4	Sn(OTf)₃	r.treflux	20	NR
	5	AI(OTf) <sub>3</sub>	r.t60	20	44
	6	TMSOTf	0-60	20	Decompose
	7	AICI <sub>3</sub>	0-40	20	Decompose
	8	TsOH	r.treflux	20	NR
	9	Ni(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	r.t.	3h	78

<sup>*a*</sup> Reaction conditions: **1a** (0.06 mmol), catalyst (0.2 equiv), activated 4Å MS (200 mg), solvent (2.0 mL), under argon. <sup>*b*</sup> Yield determined by <sup>1</sup>H NMR spectroscopy (internal standard: 1-chloro-2,4-dinitrobenzene).





Reaction conditions: Sc(OTf)<sub>3</sub> (0.1 equiv), 4 Å MS (0.1 g/mL), DCM (0.03 V), Ar, r.t.  $^{b}$  Isolated yield.

Several derivation reactions on [3+2]IMCC products were carried out (Scheme 4). Vinyl group of **4a** was oxidized to aldehyde **5**. Retro Claisen condensation of **4a** afforded **6** as a pair of epimers (d.r. = 13:1), and the major isomer **6a** undergo a Baeyer-Villiger oxidation to afford acetal **7** which was then converted to indane **8**.

Scheme 4 Derivations of [3+2]IMCC products. COMe .COMe OsO4, NalO4 COMe THF. H<sub>2</sub>O. 37% O<sup>2</sup> NaOMe -COMe (d.r. = 13:1) COMe COMe MeOH, 72% m-CPBA, NaHCO<sub>3</sub> Na<sub>2</sub>CO DCM, 18% MeOH. 95% 7 6a

In order to better understand the reaction mechanism, a chiral substrate **3a'** (46% e.e.) was prepared<sup>[11]</sup>. [3+2]IMCC of **3a'** afforded chiral products **4a'** (17% e.e.) (Scheme 5). This is quite different from that of the LA-catalyzed intermolecular versions reported by Zhang et al in which an intermolecular [3+2] cycloaddition of a chiral GDA-epoxide with alkyne afforded a completely racemic product.<sup>[4b]</sup> Theoretical investigations of the intermolecular reaction mechanism by Domingo/Mongin and Zhang/Ma et al also suggested a polar 1,3-DC of zwitterionic carbonyl ylide through the carbon-carbon bond cleavage of the GDA-epoxide.<sup>[3k,3q,4n]</sup> Although there was partial loss of *ee* value in

our experiment (from 46% to 17%), the mechanism of intramolecular cycloaddition is still different from that of the intermolecular one. We think that besides the generally accepted 1,3-DC of carbonyl ylide through the carbon-carbon bond cleavage of the epoxide ring, a stepwise  $S_N$ -like mechanism is also possible in which partial ee value was obtained (Scheme 6). To the best of our knowledge, this is probably the first [3+2] cycloaddition of GDA-epoxide through a carbon-carbon bond cleavage  $S_N$ -like mechanism. This result can make the chemistry of the donor-acceptor epoxides be better understood. Scheme 5 Asymmetric [3+2]IMCC.



 $\label{eq:scheme 6} \begin{array}{lll} \mbox{Proposed mechanism of } [3{+}2] \mbox{IMCC of GDA-epoxides with carbon-carbon double bonds.} \end{array}$ 



#### Conclusions

In conclusion, we have developed the first LA-catalyzed [3+2]IMCC of GDA-epoxides with carbon-carbon double bonds. This provides an efficient and general strategy for construction of bridged oxa-[n.2.1] skeletons. Additionally, a novel  $S_N$ -like mechanism through a carbon-carbon bond cleavage of epoxide ring is proposed.

#### Experimental

Substrate 1 (0.12 mmol, 1.0 equiv) and 4 Å MS (400 mg) in dry DCM (4 mL, 0.03 M) were degassed with argon atmosphere for 3 times.  $Sc(OTf)_3$  (5.9 mg, 0.012 mmol, 0.1 equiv) was then added to the mixture under argon atmosphere and the reaction mixture was stirred at room temperature until completion (determined by TLC). The mixture was passed through a short pad of silica gel and washed with Et<sub>2</sub>O (20 mL), the solvents were removed under reduced pressure and the residue was purified with flash column chromatography to afford the [3+2]IMCC product **2**.

### **Supporting Information**

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

#### Acknowledgement (optional)

We thank NSFC (Nos 21372126, 21572103 and 21421062) and MOST (2017YFD0200504) for financial support.

## References

and Microwave Irradiation. *Synth. Commun.* **2007**, *37*, 2935-2948; (p) Bentabed-Ababsa, G.; Derdour, A.; Roisnel, T.; Saez, J.; Domingo, L.; Mongin, F. Polar [3+2] cycloaddition of ketones with electrophilically activated carbonyl ylides. Synthesis of spirocyclic dioxolane indolinones. *Org. Biomol. Chem.* **2008**, *6*, 3144–3157; (q) Bentabed-Ababsa, G.; Derdour, A.; Roisnel, T.; Saez, J.; Perez, P.; Chamorro, E.; Domingo, L.; Mongin, F. A Combined Experimental and Theoretical Study of the Polar [3+2] Cycloaddition of Electrophilically Activated Carbonyl Ylides with Aldehydes and Imines. *J. Org. Chem.* **2009**, *74*, 2120-2133.

[4] LA-catalyzed [3+2] cycloadditions of GDA-epoxides. With carbon-carbon double/triple bonds: (a) Suga, H.; Higuchi, S.; Ohtsuka, M.; Ishimoto, D.; Arikawa, T.; Hashimoto, Y.; Misawa, S; Tsuchida, T.; Kakehi, A.; Baba, T. Inverse electron demand asymmetric cycloadditions of cyclic carbonyl ylides catalyzed by chiral Lewis acids-Scope and limitations of diazo and olefinic substrates. Tetrahedron 2010, 66, 3070-3089; (b) Liu, R.; Zhang, M.; Zhang, J. Highly regioselective Lewis acid-catalyzed [3+2] cycloaddition of alkynes with donor-acceptor oxiranes by selective carbon-carbon bond cleavage of epoxides. Chem. Commun. 2011, 47, 12870-12872; (c) Zhang, J.; Chen, Z.; Wu, H.; Zhang, J. Ni(ClO<sub>4</sub>)<sub>2</sub>-catalysed regio- and diastereoselective [3+2] cycloaddition of indoles and aryl oxiranyl-dicarboxylates/diketones: a facile access to furo[3,4-b]indoles. Chem. Commun. 2012, 48, 1817-1819; (d) Chen, W.; Fu, X.; Lin, L.; Yuan, X.; Luo, W.; Feng, J.; Liu, X.; Feng, X. An asymmetric [3+2] cycloaddition of alkynes with oxiranes by selective C-C bond cleavage of epoxides: highly efficient synthesis of chiral furan derivatives. Chem. Commun. 2014, 50, 11480-11483; (e) Chen, W.; Xia, Y.; Lin, L.; Yuan, X.; Guo, S.; Liu, X.; Feng, X. Asymmetric Synthesis of Furo[3,4-b]indoles by Catalytic [3+2] Cycloaddition of Indoles with Epoxides. Chem. Eur. J. 2015, 21, 15104-15107: (f) Yuan. X.: Lin. L.: Chen. W.: Wu. W.: Liu. X.: Feng. X. Synthesis of Chiral Tetrahydrofurans via Catalytic Asymmetric [3+2] Cycloaddition of Heterosubstituted Alkenes with Oxiranes. J. Org. Chem. 2016, 81, 1237-1243; (g) Wang, B.; Liang, M.; Tang, J.; Deng, Y.; Zhao, J.; Sun, H.; Tung, C.; Jia, J.; Xu, Z. Gold/Lewis Acid Catalyzed Cycloisomerization /Diastereoselective [3+2] Cycloaddition Cascade: Synthesis of Diverse Nitrogen-Containing Spiro Heterocycles. Org. Lett. 2016, 18, 4614-4617. With carbonyls/imines: (h) Chen, Z.; Wei, L.; Zhang, J. Lewis Acid Catalyzed Carbon-Carbon Bond Cleavage of Aryl Oxiranyl Diketones: Synthesis of cis-2,5-Disubstituted 1,3-Dioxolanes. Org. Lett. 2011, 13, 1170-1173; (i) Chen, Z.; Tian, Z.; Zhang, J.; Ma, J.; Zhang, J. C-O Versus C-C Bond Cleavage: Selectivity Control in Lewis Acid Catalyzed Chemodivergent Cycloadditions of Aryl Oxiranyldicarboxylates with Aldehydes, and Theoretical Rationalizations of Reaction Pathways. Chem. Eur. J. 2012, 18, 8591-8595; (j) Chen, Z.; Xiao, Y.; Zhang, J. Reaction of Two Differently Functionalized Oxiranes with Nickel Perchlorate: A Modular Entry to Highly Substituted 1.3-Dioxolanes, Eur. J. Org. Chem. 2013, 4748-4751; (k) Zhang, J.; Xiao, Y.; Zhang, J. Nickel-Catalyzed Annulation of Donor-Acceptor Oxiranes with Imines: Diastereoselective Access to Highly Substituted 2,4-trans-Oxazolidines. Adv. Synth. Catal. 2013, 355, 2793-2797; (I) Chen, W.; Lin, L.; Cai, Y.; Xia, Y.; Cao, W.; Liu, X.; Feng, X. Catalytic asymmetric [3+2] cycloaddition of aromatic aldehydes with oxiranes by C–C bond cleavage of epoxides: highly efficient synthesis of chiral 1,3-dioxolanes. Chem. Commun. 2014, 50, 2161-2163; (m) Tian, Z.; Xiao, Y.; Yuan, X.; Chen, Z.; Zhang, J.; Ma, J. Control of Chemoselectivity by Coordinated Water and Relative Size of Ligands to Metal Cations of Lewis Acid Catalysts for Cycloaddition of an Oxirane Derivative to an Aldehyde: Theoretical and Experimental Study. Organometallics 2014, 33, 1715-1725; (n) Alajarin, M.; Banon, D.; Egea, A.; Marin-Luna, M.; Orenes, R.; Vidal, A. Accessing polysubstituted oxazolidines, pyrrolidines and imidazolidines by regioselective [3 + 2] annulations of ketenimines with donor-acceptor oxiranes and aziridines. Org. Chem. Front. 2018, 5, 2020-2029; (o) Zhang, S.; Wang, D.; Xie, M.; Qu, G.; Guo, H. Highly Chemo- and Diastereoselective Dearomative [3+2] Cycloaddition Reactions of Benzazoles with Donor-Acceptor Oxiranes. Org. Lett. 2018, 20, 8026-8029. With nitriles: (p) Zhou, H.; Zeng, X.; Xie, Y.; Zhong, G. Synthesis of 3-Oxazolines via SnCl<sub>4</sub>-Promoted Formal [3+2]

 Wang, Z. Polar Intramolecular Cross-Cycloadditions of Cyclopropanes toward Natural Product Synthesis. Synlett 2012, 23, 2311-2327.

Reviews: (a) Nair, V.; Suja, T. Intramolecular 1, 3-dipolar cycloaddition reactions in targeted syntheses. *Tetrahedron* **2007**, *63*, 12247-12275; (b) Padwa, A. Intramolecular cycloaddition of carbonyl ylides as a strategy for natural product synthesis. *Tetrahedron* **2011**, *67*, 8057-8072.

[3+2] cycloadditions of GDA-epoxides. An earlier review: (a) Huisgen, R. Electrocyclic Ring Opening Reactions of Ethylene Oxides. Angew. Chem. 1977, 89, 589-602. Angew. Chem. Int. Ed. 1977, 16, 572-585. With carbon-carbon double/triple bonds: (b) Huisgen, R.; de March, P. Three-component reactions of diazomalonic ester, benzaldehyde, and electrophilic olefins. J. Am. Chem. Soc. 1982, 104, 4953-4954; (c) Clawson, P.; Lunn, P.; Whiting, D. Synthetic studies on O-heterocycles via cycloadditions. Part 2. Adducts from styrene oxides. J. Chem. Soc., Perkin Trans. 1, 1990, 159-162; (d) Bernaus, C.; Font, J.; de March, P. Synthesis of 2H, 4H, 9bH-furo[3,2-c][1]benzopyrans by a new intramolecular cycloaddition of a carbonyl ylide to an acetylene. Tetrahedron 1991, 47, 7713-7718; (e) Curtis, E.; Worsencroft, K.; Padwa, A. Cyclization of rhodium carbenoids using ester and amido carbonyl groups. Tetrahedron Lett. 1997, 38, 3319-3322; (f) Yoakim, C.; Ogilvie, W.; Goudreau, N.; Naud, J.: Hache, B.: O'Meara, J.: Cordinglev, M.: Archambault J.: White, P. Discovery of the first series of inhibitors of human papillomavirus type 11: inhibition of the assembly of the E1-E2-Origin DNA complex. Bioorg. Med. Chem. Lett. 2003, 13, 2539-2541; (g) Bentabed, G.; Derdour, A.; Benhaoua, H. Cycloaddition Reaction of Epoxides with Various Alkenes Under Microwave Irradiation. Synth. Commun. 2003, 33, 1861-1866; (h) Padwa, A.; Boonsombat, J.; Rashatasakhon, P.; Willis, J. Efficient Construction of the Oxatricyclo[6.3.1.0<sup>0,0</sup>]dodecane Core of Komaroviquinone Using a Cyclization/Cycloaddition Cascade of a Rhodium Carbenoid Intermediate. Org. Lett. 2005, 7, 3725-3727; (i) Goudreau, N.; Cameron, D.; Deziel, R.; Hache, B.; Jakalian, A.; Malenfant, E.; Naud, J.; Ogilvie, W.; O'Meara, J.; White, P.; Yoakim, C. Optimization and determination of the absolute configuration of a series of potent inhibitors of human papillomavirus type-11 E1-E2 protein-protein interaction: A combined medicinal chemistry, NMR and computational chemistry approach. Bioorg. Med. Chem. Lett. 2007, 15, 2690-2700; (j) Padwa, A.; Chughtai, M.; Boonsombat, J.; Rashatasakhon, P. A Rh(II)-catalyzed cycloaddition approach toward the synthesis of komaroviguinone. Tetrahedron 2008, 64. 4758-4767: (k) Bentabed-Ababsa, G.; Hamza-Reguig, S.; Derdour, A.; Domingo, L.; Saez, J.; Roisnel, T.; Dorcet, V.; Nassar, E.; Mongin, F. Experimental and theoretical study of the [3+2] cycloaddition of carbonyl ylides with alkynes. Org. Biomol. Chem. 2012, 10, 8434-8444. With carbonyls/imines: (I) Robert, A.; Pommeret, J.: Marchand, E.: Foucaud, A. Addition des vlures de carbonvle derives de gem-dicyanoepoxydes sur les benzylidene anilines substituees. Tetrahedron 1973, 29, 463-468; (m) de March, P.; Huisgen, R. Carbonyl vlides from aldehvdes and carbenes. J. Am. Chem. Soc. 1982. 104. 4952-4952; (n) Meier, K.; Lindena, A.; Mloston, G.; Heimgartner, H. 1,3-Dipolare Cycloadditionen eines Carbonyl-ylids mit 1,3-Thiazol-5(4H)-thionen und Thioketonen. Helv. Chim. Acta 1997, 80, 1190-1204; (o) Bentabed, G.; Rahmouni, M.; Mongin, F.; Derdour, A.; Hamelin, J.; Bazureau, J. 1,3-Dipolar Cycloadditions of Aldehydes or Imines with Carbonyl Ylides Generated from Epoxides: Classical Heating

- [5] [3+3] cycloadditions of GDA-epoxides: (a) Cheng, Q.; Qian, Y.; Zavalij, P.; Doyle, M. Lewis Acid/Rhodium-Catalyzed Formal [3+3]-Cycloaddition of Enoldiazoacetates with Donor-Acceptor Cyclopropanes. *Org. Lett.* 2015, 17, 3568-3571; (b) Varshnaya, R.; Banerjee, P. Construction of thiazines and oxathianes via [3+3] annulation of N-tosylaziridinedicarboxylates and oxiranes with 1,4-dithiane-2,5-diol: application towards the synthesis of bioactive molecules. *Org. Biomol. Chem.* 2017, *15*, 5182-5190.
- 6] Intramolecular [3+2] cycloadditions of epoxides being activated by one electron-withdrawing group: (a) Eberbach, W.; Brokatzky, J.; Fritz, H. Intramolecular Cycloadditions of Carbonyl Ylides. *Angew. Chem.* **1980**, *92*, 48-49. *Angew. Chem. Int. Ed.* **1980**, *19*, 47-48; (b) Brokatzky-Geiger, J.; Eberbach, W. Die stereoselektive Bildung von Polycyclen durch intramolekulare Cycloaddition von Carbonyl-Yliden an cyclische C=C-Bindungen Chem. Ber. **1983**, *116*, 2383-2389.
  - Intramolecular 1,3-DC of GDA-carbonyl ylides from diazo carbenes with carbon-carbon double bonds: (a) Maier, M.; Evertz, K.; Intramolecular [3+2] cycloadditions of mesoionic carbonyl ylides. Tetrahedron Lett. 1988, 29, 1677-1680; (b) Dauben, W.; Dinges, J.; Smith, T. A convergent approach toward the tigliane ring system. J. Org. Chem. 1993, 58, 7635-7637; (c) Padwa, A.; Hertzog, D.; Nadler, W.; Osterhout, M.; Price, A. Studies on the Intramolecular Cycloaddition Reaction of Mesoionics Derived from the Rhodium(II)-Catalyzed Cyclization of Diazoimides. J. Org. Chem. 1994, 59, 1418-1427; (d) Padwa, A.; Hertzog, D.; Nadler, W. Intramolecular Cycloaddition of Isomunchnone Dipoles to Heteroaromatic π-Systems J. Org. Chem. 1994, 59, 7072-7084; (e) Padwa, A.; Price, A. Tandem Cyclization-Cycloaddition Reaction of Rhodium Carbenoids as an Approach to the Aspidosperma Alkaloids. J. Org. Chem. 1995, 60, 6258-6259; (f) Padwa, A.; Brodney, M.; Marino, J.; Sheehan, S. Utilization of the Intramolecular Cycloaddition-Cationic  $\pi$ -Cyclization of an Isomünchnone Derivative for the Synthesis of (±)-Lycopodine. J. Org. Chem. 1997, 62, 78-87; (g) Hodgson, D.; Stupple, P.; Johnstone, C. Catalvtic Enantioselective Tandem Carbonvl Ylide Formation-Cycloaddition. Tetrahedron Lett. 1997, 38, 6471-6472; (h) Padwa, A.; Price, A. Synthesis of the Pentacyclic Skeleton of the Aspidosperma Alkaloids Using Rhodium Carbenoids as Reactive Intermediates. J. Org. Chem. 1998, 63, 556-565; (i) Hodgson, D.: Stupple. P.; Pierard, F.; Labande, A.; Johnstone, C. Development of Dirhodium(II)-Catalyzed Generation and Enantioselective 1,3-Dipolar Cycloaddition of Carbonyl Ylides. Chem. Eur. J. 2001, 7, 4465-4476; (j) Hodgson, D.; Glen, R.; Grant, G.; Redgrave, A. Catalytic Enantioselective [3+2]-Cycloadditions of Diazoketone-Derived Aryl-Substituted Carbonyl Ylides. J. Org. Chem. 2003, 68, 581-586; (k) Hodgson, D; Labande, A.; Pierard, F. Extended Scope of Dirhodium(II)-Catalysed Enantioselective Intramolecular 1,3-Dipolar Cycloadditions of Carbonyl Ylides with Alkene and Alkyne Dipolarophiles. Synlett 2003, 59-62; (I) Hodgson, D.; Labande, A.: Pierard, F.: Castro, M. The Scope of Catalytic Enantioselective Tandem Carbonyl Ylide Formation-Intramolecular [3+2] Cycloadditions. J. Org. Chem. 2003, 68, 6153-6159; (m) Mejia-Oneto, J.; Padwa, A. Intramolecular [3+2]-Cycloaddition Reaction of Push-Pull Dipoles Across Heteroaromatic  $\pi$ -Systems. Org. Lett. 2004, 6, 3241-3244; (n) Mejia-Oneto, J.; Padwa, A. Ligand effects in the Rh(II) catalyzed reaction of α-diazo ketoamides. *Tetrahedron Lett.* **2004**, *45*, 9115-9118; (o) Padwa, A.; Lynch, S.; Mejia-Oneto, J.; Zhang, H. Cycloaddition Chemistry of 2-Vinyl-Substituted Indoles and Related Heteroaromatic Systems. J. Org. Chem. 2005, 70, 2206-2218; (p) Hodgson, D.; Angrish, D.; Labande, A. One-pot cross-metathesis/tandem carbonyl ylide formationintramolecular cycloaddition of an unsaturated 2-diazo-3,6-diketoester. Chem. Commun. 2006, 627-628; (q) Hodgson, D.; Angrish, D. Oxapolycycles from One-Pot Cross-Metathesis/Carbonyl Ylide Formation-Intramolecular Cycloaddition of  $\alpha$ -Diazo- $\beta$ -keto Esters. Adv. Synth. Catal. 2006, 348, 2509-2514; (r) Hong, X.; France, S.; Mejia-Oneto,

J.; Padwa, A. Cycloaddition Protocol for the Assembly of the Hexacyclic Framework Associated with the Kopsifoline Alkaloids. Org. Lett. 2006. 8. 5141-5144; (s) Zhang, X.; Ko, R.; Li, S.; Miao, R.; Chiu, P. Allenes as Dipolarophiles in the Intramolecular Carbene Cyclization-Cycloaddition Cascade Reaction. Synlett 2006, 1197-1200; (t) Mejia-Oneto, J.; Padwa, A. Application of the Rh(II) Cyclization/Cycloaddition Cascade for the Total Synthesis of (±)-Aspidophytine. Org. Lett. 2006, 8, 3275-3278; (u) England, D.; Padwa, A. Synthesis of (±)-3H-Epivincamine via a Rh(II)-Triggered Cyclization /Cycloaddition Cascade. Org. Lett. 2007, 9, 3249-3252; (v) Hong, X.; France, S.; Padwa, A. A dipolar cycloaddition approach toward the kopsifoline alkaloid framework. Tetrahedron 2007, 63, 5962-5976; (w) Mejia-Oneto, J.; Padwa, A. Total Synthesis of the Alkaloid (±)-Aspidophytine Based on Carbonyl Ylide Cycloaddition Chemistry. Helv. Chim. Acta 2008, 91, 285-302; (x) Hodgson, D.; Glen, R.; Redgrave, A. Catalytic enantioselective tandem carbonyl ylide formation-intramolecular cycloaddition with unsaturated α-diazo-β,ε-diketo sulfones. Tetrahedron Asymm. 2009, 20, 754-757; (y) Nambu, H.; Hikime, M.; Krishnamurthi, J.; Kamiya, M.; Shimada, N.; Hashimoto, S. Asymmetric approach to the pentacyclic skeleton of Aspidosperma alkaloids via enantioselective intramolecular 1,3-dipolar cycloaddition of carbonyl ylides catalyzed by chiral dirhodium(II) carboxylates. Tetrahedron Lett. 2009, 50, 3675-3678; (z) Mizoguchi, H.; Oguri, H.; Tsuge, K.; Oikawa, H. Divergent and Expeditious Access to Fused Skeletons Inspired by Indole Alkaloids and Transtaganolides. Org. Lett. 2009, 11, 3016-3019; (aa) Grillet, F.; Sabot, C.; Anderson, R.; Babjak, M.; Greene, A.; Kanazawa, A. Intramolecular isomünchnone cycloaddition approach to the antitumor agent camptothecin. Tetrahedron 2011, 67, 2579-2584; (ab) Li, H.; Cheng, B.; Boonnak, N.; Padwa, A. An approach toward the alkaloid (±)-mersicarpine using a rhodium(II) carbenoid cyclization-cycloaddition cascade of an  $\alpha$ -diazo dihydroindolinone. Tetrahedron 2011, 67, 9829-9836; (ac) Rodier, F.; Rajzmann, M.; Parrain, J.; Chouraqui, G.; Commeiras, L. Diastereoselective Access to Polyoxygenated Polycyclic Spirolactones through a Rhodium-Catalyzed [3+2] Cycloaddition Reaction: Experimental and Theoretical Studies. Chem. Eur. J. 2013, 19, 2467-2477; (ad) Rodier, F.; Parrain, J.; Chouraqui, G.; Commeiras, L. First studies directed towards the diastereoselective synthesis of the BCD tricyclic core of brownin F. Org. Biomol. Chem. 2013, 11, 4178-4185; (ae) Bonderoff, S.; Padwa, A. Rh(II)-Catalyzed Reactions of Differentially Substituted Bis(diazo) Functionalities. Org. Lett. 2013, 15, 4114-4117: (af) Li. H.: Bonderoff, S.: Cheng, B.: Padwa, A. Model Studies Directed toward the Alkaloid Mersicarpine Utilizing a Rh(II)-Catalyzed Insertion/Cycloaddition Sequence. J. Org. Chem. 2014, 79, 392-400; (ag) Muthusamy, S.; Gangadurai, C. Domino Reactions of Bis-Diazo Compounds: Rhodium(II) Acetate Catalyzed Diastereoselective Synthesis of Epoxy- and Epithio-Bridged Heterocycle-Fused Quinolizinone Analogues. Synthesis 2016, 48, 2213-2225.

- [8] Only one intramolecular [3+2] cycloadditions of epoxides being activated by one electron-withdrawing group with carbon-carbon double bonds was reported to give a mixture of two regioisomers in which a longer linker was necessary and a macro ring was formed: Brokatzky-Geiger, J.; Eberbach, W. Intramolekulare Cycloadditionen mit Carbonyl-Yliden: Von Oxiranen zu großen Ringen. *Chem. Ber.* **1984**, *117*, 2157-2192.
- [9] (a) Zhu, W.; Fang, J.; Liu, Y.; Ren, J.; Wang, Z. Lewis Acid Catalyzed Formal Intramolecular [3+2] Cross-Cycloaddition of Cyclopropane 1,1-Diesters with Alkenes: General and Efficient Strategy for Construction of Bridged [n.2.1] Carbocyclic Skeletons. *Angew. Chem.* 2013, *125*, 2086 –2091. *Angew. Chem. Int. Ed.* 2013, *52*, 2032-2037; (b) Zhan, Y.; Liu, T.; Ren, J.; Wang, Z. Lewis Acid-Catalyzed Intramolecular [3+2] Cross-Cycloaddition of Aziridine 2,2-Diesters with Conjugated Dienes for Construction of Aza-[n.2.1] Skeletons. *Chem. Eur. J.* 2017, *23*, 17862-17866.
- [10] Comparing with the linear examples (dipolarophiles being directly linked to either of the two carbon atoms of the carbonyl ylides) in the context, branched examples (in the case of cyclic carbonyl ylides, dipolarophiles being linked to atoms other than the two carbon atoms of the carbonyl ylides) generally gave a mixture of two regioisomers. However, a more

5

#### Report

suitable model to exhibit the switch of regioselectivity between IMPC and IMCC is the linear examples (Scheme 2). For brached examples: (a) Gilton, A.; Ovadia, D.; Kapon, M.; Bien, S. Intramolecular cycloaddition of carbonyl ylides generated from  $\alpha$ -diazo ketones. *Tetrahedron* **1982**, *38*, 1477-1484; (b) Padwa, A.; Austin, D.; Hornbuckle, S.; Price, A. Rhodium (II) catalyzed intramolecular dipolar cycloaddition reactions of carbonyl ylides. Computational and empirical studies of the regio- and chemoselective effect of catalyst ligand. *Tetrahedron Lett.* **1992**, *33*, 6427-6430; (c) Padwa, A.; Austin, D.; Hornbuckle, S. Ligand-Induced Selectivity in the Rhodium(II)-Catalyzed Reactions of  $\alpha$ -Diazo Carbonyl Compounds. *J. Org. Chem.* **1996**, *61*, 63-72; (d) Kim, C.; Jang, K.; Choi, S.; Chung, Y.; Lee, E. A Carbonyl Ylide Cycloaddition Approach to Platensimycin. *Angew. Chem.* **2008**, *120*, 4073-4075. *Angew. Chem. Int. Ed.* **2008**, *47*, 4009-4011.

- [11] Russo, A.; Lattanzi, A. Asymmetric epoxidation of 2-arylidene-1,3-diketones: facile access to synthetically useful epoxides. Org. Biomol. Chem. 2010, 8, 2633-2638.
- [12] CCDC 1867903 (2a) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif.

(The following will be filled in by the editorial staff) Manuscript received: XXXX, 2019 Manuscript revised: XXXX, 2019 Manuscript accepted: XXXX, 2019 Accepted manuscript online: XXXX, 2019 Version of record online: XXXX, 2019

#### **Entry for the Table of Contents**

Page No. E O Lewis Acid-Catalyzed Intramolecular [3+2] Ο Donor-acceptor ,COR<sup>2</sup> of Cross-Cycloaddition COR<sup>2</sup> [3+2]IMCC  $R^1$ .COR<sup>2</sup> Epoxides with Alkenes for Construction of Table height R Oxa-[n.2.1] Skeletons COR<sup>2</sup> Lewis acids 1 12 examples up to 90% yield

Lu Chen, Jun Tian, Yizhou Zhan, Jun Ren, and Zhong-Wen Wang\*

The first LA-catalyzed [3+2]IMCC of GDA-epoxides with carbon-carbon double bonds has been developed. This provides an efficient and general strategy for construction of bridged oxa-[n.2.1] skeletons.