

Cite this: *Chem. Sci.*, 2021, 12, 5458

All publication charges for this article have been paid for by the Royal Society of Chemistry

Asymmetric synthesis of dihydro-1,3-dioxepines by Rh(II)/Sm(III) relay catalytic three-component tandem [4 + 3]-cycloaddition†

Chaoran Xu, Jianglin Qiao, Shunxi Dong, * Yuqiao Zhou, Xiaohua Liu and Xiaoming Feng *

Heterocycles have been widely used in organic synthesis, agrochemical, pharmaceutical and materials science industries. Catalytic three-component ylide formation/cycloaddition enables the assembly of complex heterocycles from simple starting materials in a highly efficient manner. However, asymmetric versions remain a yet-unsolved task. Here, we present a new bimetallic catalytic system for tackling this challenge. A combined system of Rh(II) salt and chiral *N,N'*-dioxide–Sm(III) complex was established for promoting the unprecedented tandem carbonyl ylide formation/asymmetric [4 + 3]-cycloaddition of aldehydes and α -diazoacetates with β,γ -unsaturated α -ketoesters smoothly, affording various chiral 4,5-dihydro-1,3-dioxepines in up to 97% yield, with 99% ee. The utility of the current method was demonstrated by conversion of products to optically active multi-substituted tetrahydrofuran derivatives. A possible reaction mechanism was provided to elucidate the origin of chiral induction based on experimental studies and X-ray structures of catalysts and products.

Received 21st February 2021

Accepted 7th March 2021

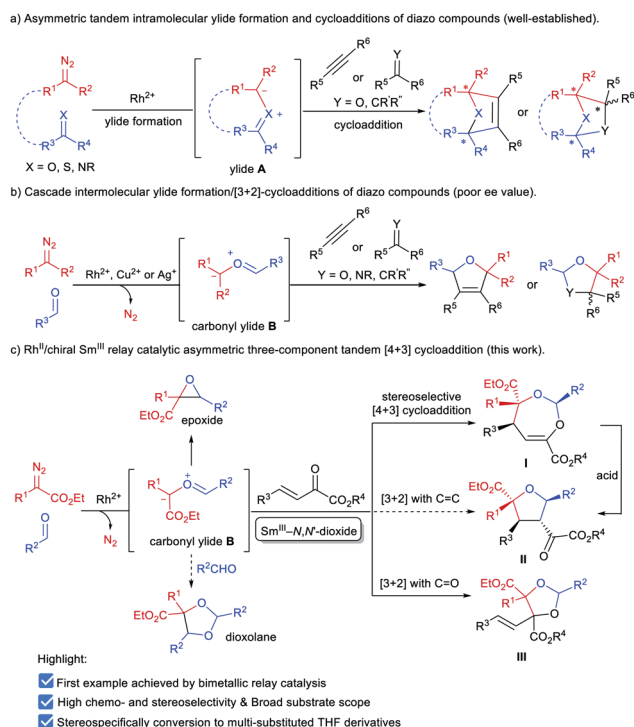
DOI: 10.1039/d1sc01019k

rsc.li/chemical-science

Introduction

α -Diazocarbonyl compounds are widely used in organic synthesis due to their diverse reactivity profiles.¹ In particular, formation of various ylides **A** between α -diazocarbonyl compounds and carbonyl,^{2*a-i*} imine^{2*j*} or thiocarbonyl^{2*k*} groups, followed by subsequent cycloaddition reactions provides a concise and efficient route to heterocyclic molecules with multiple stereocenters (Scheme 1a), and thus has attracted considerable attention in the past several decades. This strategy has been successfully applied to the total synthesis of complex natural products.³ Among them, catalytic asymmetric cycloadditions⁴ *via* intramolecular carbonyl ylide formation of functionalized diazo-compounds have been well-established using chiral dirhodium salts^{4*a-c*} or combined catalysts.^{4*d-f,2j*} On the other hand, the transformations of ylides initiated by an intermolecular reaction between an α -diazocarbonyl compound and aldehydes or imines⁵ have been extended to other reaction partners, including olefins,^{6*a-c*} alkynes,^{6*d-h*} aldehydes or ketones^{6*i-n*} and imines,^{6*o,p*} enabling rapid buildup of molecular complexity from simple starting materials (Scheme 1b).

However, to the best of our knowledge, the highly catalytic enantioselective versions have remained unknown to date.⁷ The difficulty stems mainly from the following: (1) the competing



Scheme 1 Ylide formation/cycloadditions of diazo compounds.

Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, China. E-mail: dongxs@scu.edu.cn; xmfeng@scu.edu.cn

† Electronic supplementary information (ESI) available: ¹H, ¹³C{¹H} and ¹⁹F{¹H} NMR, HPLC spectra, and CD spectra (PDF). CCDC 2015654, 2046337, 2053510, 2025197 and 2055726. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1sc01019k



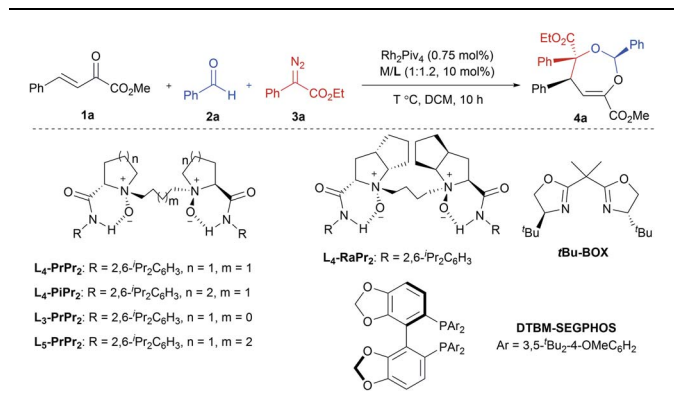
formation of epoxides^{6h,i,k,o} or dioxolanes^{6a,f,i,o} with additional aldehydes hampers the subsequent cycloaddition with dipolarophiles (Scheme 1c); (2) rhodium catalysts could induce a background reaction, and both a Rh-associated ylide^{7b} and a free ylide⁶ⁱ were proposed in the catalytic cycloaddition process, while chiral dirhodium catalysts only provided poor enantioselectivity.^{6i,7b}

Experiments in the literature reveal that in some cases Lewis acid catalysts are able to accelerate the cycloaddition of the *in situ* generated carbonyl ylide with several dipolarophiles.^{6a,o,p,7a} Intrigued by the high performance of chiral *N,N'*-dioxide metal complex catalysts⁸ in cycloaddition reactions⁹ and others, we speculated that a bimetallic relay catalysis¹⁰ could potentially realize this challenging three-component tandem reaction. First, in the presence of an achiral dirhodium complex, the reaction of an aldehyde and α -diazo compound leads to carbonyl ylide **B**.^{3a} Then a chiral Lewis acid catalyst preferably accelerates the subsequent stereoselective cycloaddition with a suitable dipolarophile, but not the side reactions. Herein, we wish to disclose our endeavor along this line. Rh₂Piv₄ and Sm(OTf)₃/L₄-PrPr₂ combined catalysts were identified to be efficient for triggering an unprecedented enantioselective tandem ylide formation/[4 + 3]-cycloaddition reaction among β,γ -unsaturated α -ketoesters, aldehydes and α -diazoacetates. A number of chiral and densely functionalized 4,5-dihydro-1,3-dioxepines **I** were obtained in high yield with excellent diastereo- and enantioselectivity (Scheme 1c). It is worth noting that 4,5-dihydro-1,3-dioxepines are important intermediates in the synthesis of γ -butyrolactone derivatives,¹¹ 2-arylpropionic acids,¹² and substituted tetrahydrofurans.¹³ Stereospecific conversion of the products to synthetically useful poly-substituted tetrahydrofuran derivatives **II**, the formal [3 + 2] adducts, was established as well.

Results and discussion

Our initial attempts involved using β,γ -unsaturated α -ketoester **1a**¹⁴ as the model dipolarophile together with benzaldehyde (**2a**) and ethyl 2-diazo-2-phenylacetate (**3a**) to optimize the reaction conditions. As depicted in Scheme 1c, several competition pathways were possible including [3 + 2] of either a C=C bond or C=O bond, or [4 + 3] of C=C-C=O bonds. The reaction took place smoothly under the influence of Rh₂Piv₄ and a chiral *N,N'*-dioxide L₄-PrPr₂/Yb(OTf)₃ complex at -20 °C in dichloromethane, affording 4,5-dihydro-1,3-dioxepine through a new paradigm of [4 + 3] route in 58% isolated yield with 67% ee for the major diastereomer (Table 1, entry 1). The ¹H NMR spectrum of the crude mixture indicated that the other diastereomer of 1,3-dioxepine (*ca.* 18% yield) and [3 + 2] adduct **III** with the C=O group of the α -ketoester (*ca.* 7% yield) were generated as well (for more details, see Table S6 in the ESI†). Subsequent investigation indicated that lowering the temperature from -20 °C to -78 °C resulted in a highly diastereoselective process, and the desired [4 + 3] product **4a** was yielded exclusively with maintaining the ee value (entry 2, 90% yield, 66% ee). Next, several rare-earth metal salts were tested with *N,N'*-dioxide L₄-PrPr₂ as the ligand (see the ESI for details†). It was found that

Table 1 Optimization of the reaction conditions



Entry ^a	Metal salt	Ligand	T (°C)	Yield ^b (%)	ee ^c (%)
1	Yb(OTf) ₃	L ₄ -PrPr ₂	-20	58	67
2	Yb(OTf) ₃	L ₄ -PrPr ₂	-78	90	66
3	Sm(OTf) ₃	L ₄ -PrPr ₂	-78	90	84
4	Sm(OTf) ₃	L ₄ -PiPr ₂	-78	68	32
5	Sm(OTf) ₃	L ₄ -RaPr ₂	-78	50	26
6	Sm(OTf) ₃	L ₃ -PrPr ₂	-78	38	26
7	Sm(OTf) ₃	L ₅ -PrPr ₂	-78	85	54
8	Sm(OTf) ₃	<i>t</i> Bu-Box	-78	56	11
9	Sm(OTf) ₃	DTBM-SEGPHOS	-78	57	0
10	—	—	-78	Trace	—
11	Sm(OTf) ₃	—	-78	Trace	—
12 ^d	Sm(OTf) ₃	L ₄ -PrPr ₂	-78	92	99

^a Unless otherwise noted, the reaction was carried out with Rh₂Piv₄ (0.75 mol%), metal salt/ligand (1 : 1.2, 10 mol%), β,γ -unsaturated α -ketoester **1a** (0.10 mmol), aldehyde **2a** (3.0 equiv.) and α -diazo ester **3a** (3.0 equiv.) at T °C for 10 h under a N₂ atmosphere. ^b Isolated yield of the major diastereomer. ^c Determined by HPLC analysis on a chiral stationary phase. ^d **2a** (4.0 equiv.) and **3a** (4.0 equiv.).

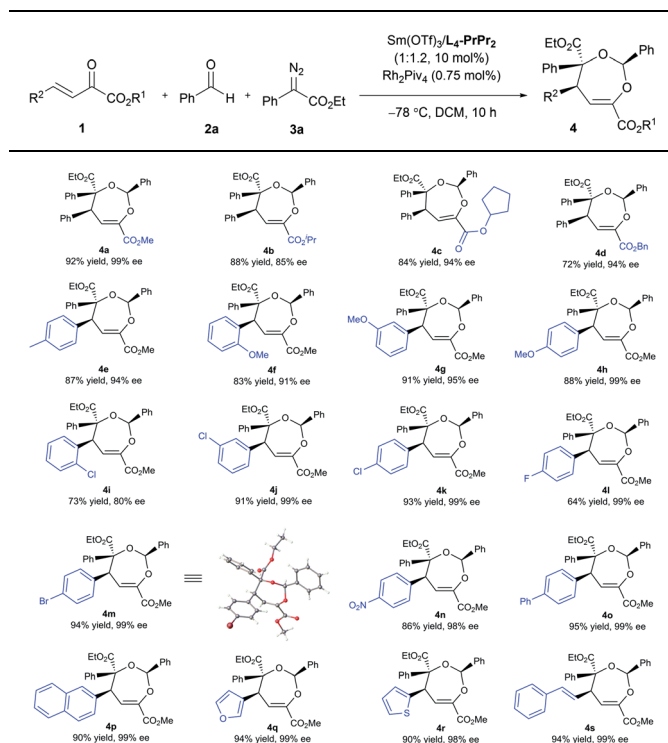
Sm(OTf)₃ gave a higher ee value (entry 3, 84% ee). Then, screening of the backbone of the ligands suggested that L-proline derived L₄-PrPr₂ afforded better results than (*S*)-piperidine-2-carboxylic acid or L-ramipril derived ones (entries 4 and 5). The length of the carbon tether of *N,N'*-dioxide ligands was found to have a significant influence on the outcomes, and a four-carbon linker was superior to three- or five-carbon ones in terms of yield and enantioselectivity (entry 3 vs. entries 6 and 7). Other chiral ligands, such as *t*Bu-Box and DTBM-SEGPHOS, gave poor results (entries 8 and 9). Without Rh₂Piv₄, the three-component reaction did not occur at all, even when camphor sulfonic acid¹⁵ was used as the alternative for carbene generation from diazo compounds (see Table S6 in the ESI for details†). When the reaction was carried out with only Rh(II), a mixture of at least four isomeric products (**I** and **III**) was obtained (entry 10, **4a**, trace yield). The use of chiral Rh₂(*S*-DOSP)₄ furnished a racemic product (see the ESI for more details†), implying that a free carbonyl ylide might be involved. Performing the reaction with Rh(II) and Sm(OTf)₃ led to the consumption of the aldehyde and diazoester and the recovery of the ketoester, but only a trace amount of the cycloaddition adduct (entry 11) was obtained. The aforementioned results clearly indicated that the chiral Lewis acid catalyst accelerated



the subsequent [4 + 3]-cycloaddition and controlled the chemo- and stereoselectivity of this process. To our delight, increasing the amounts of **2a** and **3a** can elevate the enantioselectivity obviously, affording **4a** in 92% yield and 99% ee (entry 12).

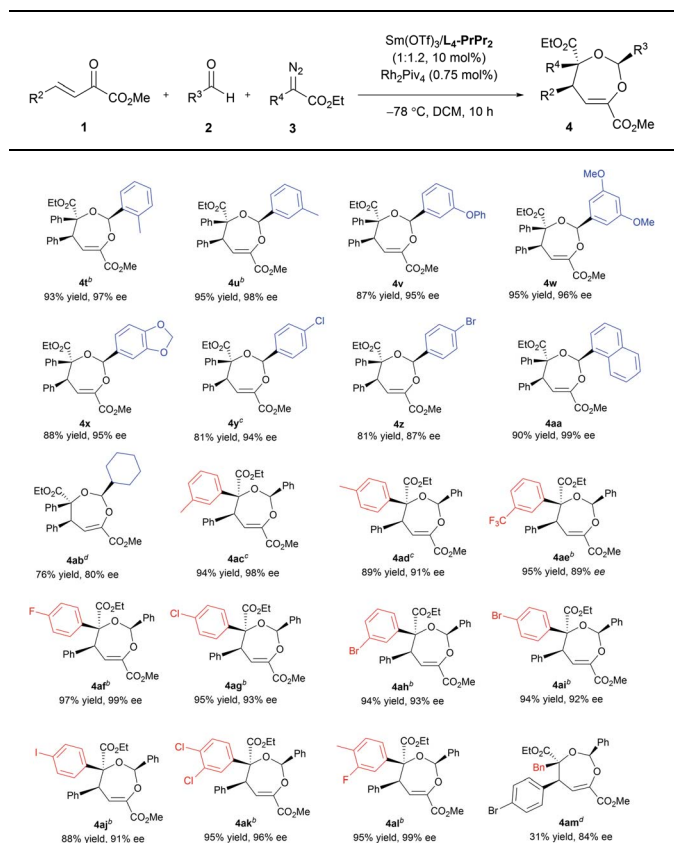
With the optimized conditions in hand, the substrate scope was next examined. As shown in Table 2, changing the ester group (R^1) of the β,γ -unsaturated α -ketoester from a methyl to an isopropyl, a cyclopentyl or a benzyl group led to slightly reduced yields and ee values (**4a–4d**, 72–92% yield, 85–99% ee). The γ -aryl substituted β,γ -unsaturated α -ketoesters with electron-withdrawing or electron-donating substituents at 2-, 3-, and 4-positions of the phenyl group can react with benzaldehyde **2a** and α -diazoester **3a** smoothly to furnish the corresponding products **4e–4o** in moderate to good yields (64–95% yield) and high ee values (80–99% ee). Generally, 2-substituted ones (**4f** and **4i**) provided diminished yield and enantiomeric excess. Additionally, 2-naphthyl and heteroaromatic substrates were tolerated in this cascade reaction as well (**4p–4r**). Notably, $\beta,\gamma,\delta,\varepsilon$ -unsaturated α -ketoester **1s** was a competent reaction partner, providing the desired [4 + 3] adduct **4s** in 94% yield and 99% ee. The absolute configuration of the major enantiomer of **4m** was determined to be (2*S*,4*S*,5*S*) by X-ray diffraction analysis, and the others were assigned by comparing their CD spectra with those of **4m**.¹⁶

Table 2 Substrate scope of β,γ -unsaturated α -ketoesters^a



^a The reaction was run with Rh_2Piv_4 (0.75 mol%), $\text{Sm}(\text{OTf})_3/\text{L}_4\text{-PrPr}_2$ (1:1.2, 10 mol%), β,γ -unsaturated α -ketoester **1** (0.10 mmol), aldehyde **2a** (4.0 equiv.) and α -diazo ester **3a** (4.0 equiv.) at -78°C for 10 h. Yield is the isolated yield of the *endo* diastereoisomer. ee value was determined by HPLC analysis on a chiral stationary phase.

Table 3 Substrate scope of aldehydes and α -diazoacetates^a

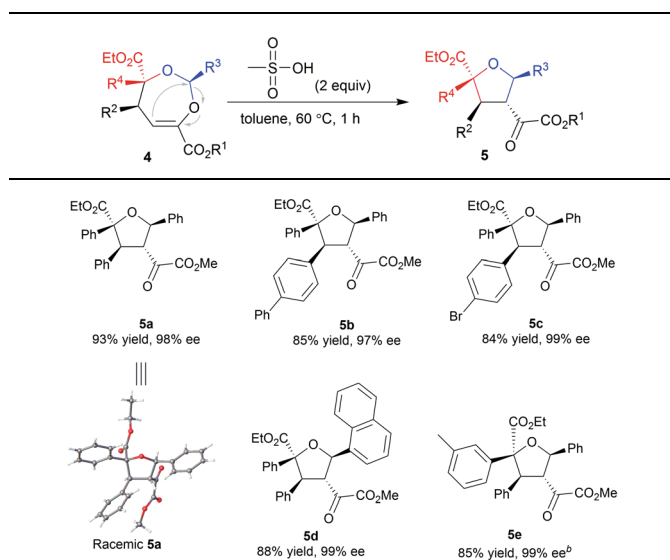


^a Unless otherwise noted, the reaction conditions were the same as those in Table 2. ^b α -Diazoester **3** (4.2 equiv.). ^c α -Diazoester **3** (3.7 equiv.). ^d Aldehyde **2** (4.2 equiv.) and Rh_2Piv_4 (1.5% mmol).

Next, various aldehydes **2** and α -diazoacetates **3** were tested (Table 3). According to the reactivity of the aldehydes, the amount of the α -diazoacetates was adjusted slightly in order to get high yield and ee. Satisfactorily, using β,γ -unsaturated α -ketoester **1a** and α -phenyl diazoacetate **3a** as the reaction partner, arylaldehydes **2b–2h** with different electron-withdrawing or electron-donating substituents were readily converted into the corresponding products **4t–4z** (81–95% yield and 87–98% ee). In this case, *para*-chloro- or bromo-substituted ones exhibited low reactivity and enantioselective control. 1-Naphthaldehyde **2i** and cyclohexyl formaldehyde **2j** were compatible in the current transformation, delivering the adducts **4aa** and **4ab** with good results. Furthermore, changing the phenyl group on the α -diazoacetates **3** had a limited influence on the reaction, regardless of the position and electronic effect of substituents on the phenyl group (**4ac–4al**, 88–97% yield, 89–99% ee). Benzyl substituted α -diazoacetate was suitable as well, affording the product **4am** with 84% ee. However, low yield (31% yield) was obtained due to the elimination reaction of the α -diazoacetate.^{6f}

To illustrate the utility of the current methodology, further conversion of the 4,5-dihydro-1,3-dioxepines **4** was carried out. As shown in Table 4, compound **4a** was stereospecifically

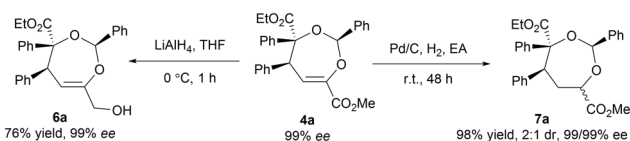
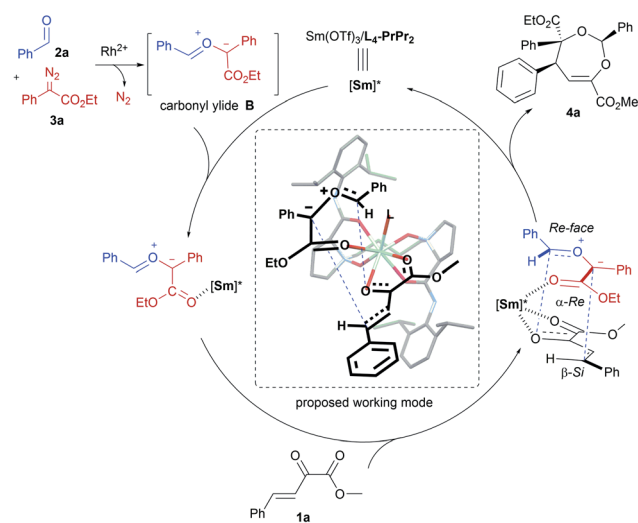


Table 4 Transformations to tetrahydrofuran^a

^a Compound **4** (99% ee) and methanesulfonic acid (2 equiv.) were stirred in toluene at 60 °C for 1 h under a N₂ atmosphere. Yield is the isolated yield. ee value was determined by HPLC analysis on a chiral stationary phase. ^b Substrate **4ac** with 98% ee was used.

transformed into tetrahydrofuran (THF) derivative **5a** with four continuous stereogenic centers in the presence of methanesulfonic acid at 60 °C. Under such conditions, representative products **4** with different substituents rearranged to THF-derivatives **5** in high yield (84–93% yield) without loss of enantioselectivity (97–99% ee). Interestingly, compounds **5** were the formal [3 + 2]-adducts of carbonyl ylide **B** with the C=C double bond of the β,γ-unsaturated α-ketoester (Scheme 1c, **II**), which could make up for the lack of the catalytic asymmetric version of the related [3 + 2] cascade reaction.¹⁷ The absolute configuration of **5a** was assigned as (2*S*,3*S*,4*R*,5*R*) on the basis of the absolute configuration of **4a** and the relative configuration of racemic **5a**.¹⁶ The others were assigned by comparing their CD spectra with those of **5a**. In addition, the alkenyl ester group in compound **4a** was reduced by LiAlH₄ (2.2 equiv.) to give the alcohol **6a** in 76% yield with 99% ee (Scheme 2, left). Hydrogenation of **4a** with Pd/C and H₂ yielded the saturated 1,3-dioxepane **7a** in 98% yield, 2 : 1 dr and 99/99% ee value (Scheme 2, right).

In order to understand the chiral induction of the *N,N'*-dioxide–Sm(III) Lewis acid catalyst, we got the crystals of the Sm(III) complexes of chiral *N,N'*-dioxides *L_n*-PrPr₂ with different lengths of the carbon tether (*n* = 3, 4, or 5).^{16,18} The X-ray crystal structures show that each *N,N'*-dioxide coordinates as

Scheme 2 Further transformations of **4a**.

Scheme 3 Possible reaction mechanism and working model.

a tetradentate ligand to Sm(III) with two amine oxide oxygen atoms and two amide oxygen atoms, forming a square antiprismatic geometry version through the coordination with four additional species. It is interesting that *L₄*-PrPr₂ is noteworthy in view of the angles between O^C–Sm–O^C (narrowest, 138.5°) and O^N–Sm–O^N (widest, 94.4°), and the shortest bond distance of O^C–Sm (2.393 and 2.423 Å) and O^N–Sm (2.266 and 2.286 Å) in comparison with *L₃*-PrPr₂ and *L₅*-PrPr₂ (see the ESI for more details[†]). It implies that the alkyl linker between the two aminoxides affects both the geography and the electronic nature of the catalyst, delivering distinct activity and stereoselectivity.

Based on the absolute configuration of the products and control experiments, a possible reaction pathway was proposed (Scheme 3). Initially, free carbonyl ylide **B** is generated *in situ* from α-diazoacetate **3a** and aldehyde **2a** with the assistance of achiral Rh(II). Considering the fact that excess amounts of aldehyde and α-diazoacetate are advantageous to improve the enantioselectivity, we speculated that interaction between carbonyl ylide intermediate **B** and chiral Sm^{III}-*N,N'*-dioxide exists, which is also supported by the operando IR experiment (see the ESI for details[†]). The high-coordination number of the rare-earth metal complex catalyst enabled the activation of the β,γ-unsaturated α-ketoester with Sm(III)/*L₄*-PrPr₂ in a bidentate-bonding manner at the same time. Therefore, a possible working mode was set forth to explain the stereoselectivity of the cycloaddition step. Due to the steric hindrance of the 2,6-*i*-Pr₂C₆H₃ moiety in the chiral *N,N'*-dioxide ligand, the β-*Re* face of the unsaturated ketoester was blocked, leaving the less-hindered β-*Si* face available for attack by ylide **B** with its *Re*–*Re* face in an *endo* fashion.¹⁹ As a result, (2*S*,4*S*,5*S*)-**4a** was formed as the major enantiomer.

Conclusions

In summary, a highly efficient asymmetric cascade carbonyl ylide formation/[4 + 3]-cycloaddition reaction of β,γ-unsaturated α-ketoesters, aldehydes, and α-diazoacetates was realized



by using a rhodium(II)/chiral *N,N'*-dioxide-Sm(III) complex bimetallic catalyst. Various chiral 4,5-dihydro-1,3-dioxepines were readily obtained in high yield with excellent ee values. Moreover, the 1,3-dioxepines can stereospecifically transform into multi-substituted tetrahydrofuran derivatives efficiently. A plausible catalytic cycle along with a working mode was proposed to explain the formation of enantioenriched products according to the experimental evidence and single crystal data. Further uses of the bimetallic relay catalysis strategy in other reactions are under investigation.

Author contributions

C. R. X. performed the experiments. J. L. Q. repeated data. S. X. D. participated in structure characterization and discussion. Y. Q. Z. analyzed the X-ray diffraction crystal data. X. M. F. and X. H. L. supervised the project. X. M. F., X. H. L., S. X. D. and C. R. X. co-wrote the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

We appreciate the financial support from the National Natural Science Foundation of China (21890723 and 21772127).

Notes and references

- For selected reviews on α -diazocarbonyl compounds: (a) N. R. Candeias, R. Paterna and P. M. P. Gois, *Chem. Rev.*, 2016, **116**, 2937; (b) A. Ford, H. Miel, A. Ring, C. N. Slattery, A. R. Maguire and M. A. McKerverey, *Chem. Rev.*, 2015, **115**, 9981; (c) S. F. Zhu and Q. L. Zhou, *Acc. Chem. Res.*, 2012, **45**, 1365; (d) Y. Zhang and J. B. Wang, *Chem. Commun.*, 2009, 5350; (e) H. M. L. Davies and J. R. Manning, *Nature*, 2008, **451**, 417; (f) G. Maas, *Chem. Soc. Rev.*, 2004, **33**, 183; for selected recent examples involving α -diazoesters: (g) J. Yang, P. R. Ruan, W. Yang, X. M. Feng and X. H. Liu, *Chem. Sci.*, 2019, **10**, 10305; (h) Z. K. Xue, Y. Li and S. Z. Luo, *ACS Catal.*, 2020, **10**, 10989; (i) R. D. C. Gallo, P. B. Momo, D. P. Day and A. C. B. Burtoloso, *Org. Lett.*, 2020, **22**, 2339; (j) Y. Li, Y. T. Zhao, T. Zhou, M. Q. Chen, Y. P. Li, M. Y. Huang, Z. C. Xu, S. F. Zhu and Q. L. Zhou, *J. Am. Chem. Soc.*, 2020, **142**, 10557.
- For selected examples: (a) M. E. Maier and K. Evertz, *Tetrahedron Lett.*, 1988, **29**, 1677; (b) R. Angell, M. Fengler-Veith, H. Finch, L. M. Harwood and T. T. Tucker, *Tetrahedron Lett.*, 1997, **38**, 4517; (c) H. Mizoguchi, H. Oguri, K. Tsuge and H. Oikawa, *Org. Lett.*, 2009, **11**, 3016; (d) S. N. Savinov and D. J. Austin, *Org. Lett.*, 2002, **4**, 1415; (e) S. A. Bonderoff and A. Padwa, *J. Org. Chem.*, 2017, **82**, 642; (f) K. Inoue, H. Suga, S. Inoue, H. Sato and A. Kakehi, *Synthesis*, 2003, **9**, 1413; (g) Q. Q. Cheng, J. Yedoyan, H. Arman and M. P. Doyle, *Angew. Chem., Int. Ed.*, 2016, **55**, 5573; (h) F. Rodier, M. Rajzmann, J. L. Parrain, G. Chouraqui and L. Commeiras, *Chem.-Eur. J.*, 2013, **19**, 2467; (i) T. Ibata and J. Toyoda, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 2489; (j) Z. J. Jia, G. Shan, C. G. Daniliuc, A. P. Antonchick and H. Waldmann, *Angew. Chem., Int. Ed.*, 2018, **57**, 14493; (k) A. Padwa, F. R. Kinder, W. R. Nadler and L. Zhi, *Heterocycles*, 1993, **35**, 367.
- For selected reviews involving cycloaddition of carbonyl ylides: (a) A. Padwa and S. F. Hornbuckle, *Chem. Rev.*, 1991, **91**, 263; (b) A. Padwa and M. D. Weingarten, *Chem. Rev.*, 1996, **96**, 223; (c) A. Padwa, *Chem. Soc. Rev.*, 2009, **38**, 3072; (d) J. J. Medvedev and V. A. Nikolaev, *Russ. Chem. Rev.*, 2015, **84**, 737.
- For selected examples: (a) D. M. Hodgson, P. A. Stupple, F. Y. T. M. Pierard, A. H. Labande and C. Johnstone, *Chem.-Eur. J.*, 2001, **7**, 4465; (b) S. Murarka, Z. J. Jia, C. Merten, C. G. Daniliuc, A. P. Antonchick and H. Waldmann, *Angew. Chem., Int. Ed.*, 2015, **54**, 7653; (c) S. Kitagaki, M. Anada, O. Kataoka, K. Matsuno, C. Umeda, N. Watanabe and S. Hashimoto, *J. Am. Chem. Soc.*, 1999, **121**, 1417; (d) C. R. Xu, K. X. Wang, D. W. Li, L. L. Lin and X. M. Feng, *Angew. Chem., Int. Ed.*, 2019, **58**, 18438; (e) H. Suga, Y. Hashimoto, S. Yasumura, R. Takezawa, K. Itoh and A. Kakehi, *J. Org. Chem.*, 2013, **78**, 10840; (f) H. Suga, K. Inoue, S. Inoue and A. Kakehi, *J. Am. Chem. Soc.*, 2002, **124**, 14836.
- Selected reviews on azomethine ylide obtained from other methods involving cycloadditions: (a) L. Wei, X. Chang and C. J. Wang, *Acc. Chem. Res.*, 2020, **53**, 1084; (b) G. Pandey, P. Banerjee and S. R. Gadre, *Chem. Rev.*, 2006, **106**, 4484; (c) R. Narayan, M. Potowski, Z. J. Jia, A. P. Antonchick and H. Waldmann, *Acc. Chem. Res.*, 2014, **47**, 1296.
- For selected examples: (a) Y. Hashimoto, K. Itoh, A. Kakehi, M. Shiro and H. Suga, *J. Org. Chem.*, 2013, **78**, 6182; (b) M. Alt and G. Maas, *Tetrahedron*, 1994, **50**, 7435; (c) A. J. Skaggs, E. Y. Lin and T. F. Jamison, *Org. Lett.*, 2002, **4**, 2277; (d) S. Muthusamy, C. Gunanathan and M. Nethaji, *J. Org. Chem.*, 2004, **69**, 5631; (e) M. P. Doyle, D. C. Forbes, M. N. Protopopova, S. A. Stanley, M. M. Vasbinder and K. R. Xavier, *J. Org. Chem.*, 1997, **62**, 7210; (f) T. Rajasekaran, G. Karthik, B. Sridhar and B. V. S. Reddy, *Org. Lett.*, 2013, **15**, 1512; (g) A. DeAngelis, M. T. Taylor and J. M. Fox, *J. Am. Chem. Soc.*, 2009, **131**, 1101; (h) Y. F. Liu, Z. Wang, J. W. Shi, B. L. Chen, Z. G. Zhao and Z. L. Chen, *J. Org. Chem.*, 2015, **80**, 12733; (i) A. DeAngelis, P. Panne, G. P. A. Yap and J. M. Fox, *J. Org. Chem.*, 2008, **73**, 1435; (j) P. D. March and R. Huisgen, *J. Am. Chem. Soc.*, 1982, **104**, 4952; (k) C. D. Lu, Z. Y. Chen, H. Liu, W. H. Hu and A. Q. Mi, *Org. Lett.*, 2004, **6**, 3071; (l) B. Jiang, X. B. Zhang and Z. H. Luo, *Org. Lett.*, 2002, **4**, 2453; (m) V. Nair, S. Mathai, S. C. Mathew and N. P. Rath, *Tetrahedron*, 2005, **61**, 2849; (n) A. E. Russell, J. Brekan, L. Gronenberg and M. P. Doyle, *J. Org. Chem.*, 2004, **69**, 5269; (o) Y. Toda, W. Kaku, M. Tsuruoka, S. Shinogaki, T. Abe, H. Kamiya, A. Kikuchi, K. Itoh and H. Suga, *Org. Lett.*, 2018, **20**, 2659; (p) J. J. Sheng, H. Chang, Y. Qian, M. L. Ma and W. H. Hu, *Tetrahedron Lett.*, 2018, **59**, 2141.



- 7 For selected enantioselective examples using chiral auxiliaries: (a) X. F. Xu, X. Guo, X. C. Han, L. P. Yang and W. H. Hu, *Org. Chem. Front.*, 2014, **1**, 181; (b) S. Torssell and P. Somfai, *Adv. Synth. Catal.*, 2006, **348**, 2421; (c) S. Torssell, M. Kienle and P. Somfai, *Angew. Chem., Int. Ed.*, 2005, **44**, 3096.
- 8 For selected reviews, see: (a) Z. Wang, X. H. Liu and X. M. Feng, *Aldrichimica Acta*, 2020, **53**, 3; (b) X. H. Liu, S. X. Dong, L. L. Lin and X. M. Feng, *Chin. J. Chem.*, 2018, **36**, 791; (c) X. H. Liu, H. F. Zheng, Y. Xia, L. L. Lin and X. M. Feng, *Acc. Chem. Res.*, 2017, **50**, 2621; (d) X. H. Liu, L. L. Lin and X. M. Feng, *Org. Chem. Front.*, 2014, **1**, 298; (e) M. Y. Wang and W. Li, *Chin. J. Chem.*, 2021, DOI: 10.1002/cjoc.202000508; for selected examples: (f) H. F. Zheng, Y. Wan, C. R. Xu, Q. Xiong, L. L. Lin and X. M. Feng, *Angew. Chem., Int. Ed.*, 2019, **58**, 5327; (g) Y. S. Chen, S. X. Dong, X. Xu, X. H. Liu and X. M. Feng, *Angew. Chem., Int. Ed.*, 2018, **57**, 16554.
- 9 For selected reviews of dipolar cycloadditions, see: (a) K. V. Gothelf and K. A. Jørgensen, *Chem. Rev.*, 1998, **98**, 863; (b) T. Hashimoto and K. Maruoka, *Chem. Rev.*, 2015, **115**, 5366; (c) M. Kissane and A. R. Maguire, *Chem. Soc. Rev.*, 2010, **39**, 845; (d) K. E. O. Ylijoki and J. M. Stryker, *Chem. Rev.*, 2013, **113**, 2244; (e) H. Pellissier, *Adv. Synth. Catal.*, 2018, **360**, 1551; (f) M. Harmata, *Chem. Commun.*, 2010, **46**, 8886; (g) A. G. Lohse and R. P. Hsung, *Chem.-Eur. J.*, 2011, **17**, 3812; (h) H. Lam and M. Lautens, *Synthesis*, 2020, **52**, 2427; for recent examples of [4 + 3]-cycloaddition: (i) F. Jiang, F. R. Yuan, L. W. Jin, G. J. Mei and F. Shi, *ACS Catal.*, 2018, **8**, 10234; (j) M. Sun, C. Ma, S. J. Zhou, S. F. Lou, J. Xiao, Y. C. Jiao and F. Shi, *Angew. Chem., Int. Ed.*, 2019, **58**, 8703; (k) P. Kumari, W. W. Liu, C. J. Wang, J. Dai, M. X. Wang, Q. Q. Yang, Y. H. Deng and Z. H. Shao, *Chin. J. Chem.*, 2020, **38**, 151; (l) C. S. Wang, T. Z. Li, S. J. Liu, Y. C. Zhang, S. Deng, Y. C. Jiao and F. Shi, *Chin. J. Chem.*, 2020, **38**, 543; (m) W. L. Yang, Z. S. Huang, Y. Z. Liu, X. X. Yu and W. P. Deng, *Chin. J. Chem.*, 2020, **38**, 1571.
- 10 For selected reviews involving relay catalysis, see: (a) Y. Wang, H. Lu and P. F. Xu, *Acc. Chem. Res.*, 2015, **48**, 1832; (b) N. T. Patil, V. S. Shinde and B. Gajula, *Org. Biomol. Chem.*, 2012, **10**, 211; (c) D. F. Chen, Z. Y. Han, X. L. Zhou and L. Z. Gong, *Acc. Chem. Res.*, 2014, **47**, 2365; (d) X. Guo and W. H. Hu, *Acc. Chem. Res.*, 2013, **46**, 2427; (e) Z. T. Du and Z. H. Shao, *Chem. Soc. Rev.*, 2013, **42**, 1337.
- 11 H. Frauenrath, D. Brethauer, S. Reim, M. Maurer and G. Raabe, *Angew. Chem., Int. Ed.*, 2001, **40**, 177.
- 12 T. Bando, Y. Namba and K. Shishido, *Tetrahedron: Asymmetry*, 1997, **8**, 2159.
- 13 A. K. Ghosh and M. R. Belcher, *J. Org. Chem.*, 2020, **85**, 10399.
- 14 For selected reviews on β,γ -unsaturated α -ketoesters: (a) G. Desimoni, G. Faita and P. Quadrelli, *Chem. Rev.*, 2013, **113**, 5924; (b) B. Eftekhari-Sis and M. Zirak, *Chem. Rev.*, 2015, **115**, 151.
- 15 H. Lam, Z. Qureshi, M. Wegmann and M. Lautens, *Angew. Chem., Int. Ed.*, 2018, **57**, 16185.
- 16 CCDC 2015654 [4m], 2046337 [5a], 2053510 [Sm(OTf)₃/L₃-PrPr₂], 2025197 [Sm(OTf)₃/L₄-PrPr₂], 2055726 [Sm(OTf)₃/L₅-PrPr₂][†]
- 17 For selected reviews on construction of tetrahydrofurans: (a) J. P. Wolfe and M. B. Hay, *Tetrahedron*, 2007, **63**, 261; (b) A. D. L. Torre, C. Cuyamendous, V. Bultel-Poncé, T. Durand, J. M. Galano and C. Oger, *Tetrahedron*, 2016, **72**, 5003; (c) G. Jalce, X. Franck and B. Figadère, *Tetrahedron: Asymmetry*, 2009, **20**, 2537; for selected recent examples: (d) S. Lee, H. Y. Bae and B. List, *Angew. Chem., Int. Ed.*, 2018, **57**, 12162; (e) P. D. Pohlhaus, S. D. Sanders, A. T. Parsons, W. Li and J. S. Johnson, *J. Am. Chem. Soc.*, 2008, **130**, 8642; (f) S. R. Angle, G. P. Wei, Y. K. Ko and K. Kubo, *J. Am. Chem. Soc.*, 1995, **117**, 8041.
- 18 X-ray crystal structures indicated that the chiral pocket changed with the catalysts bearing different carbon tethers of chiral ligands (see the ESI, page S15[†]). Further studies are needed to illustrate the effect of the catalyst structure on diastereo- and enantioselectivity.
- 19 Both *endo* and *exo*-selectivity were observed in previous studies (*endo*, **6a**, **f-i**; *exo*, **6c**).

