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Asymmetric ring-opening reactions of donor–acceptor cyclopropanes with 1,3-cyclodiones†

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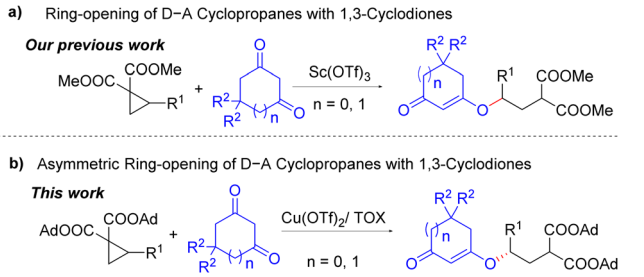
Asymmetric ring-opening reactions of donor–acceptor cyclopropanes with 1,3-cyclodiones have been established for the synthesis of enantioenriched γ-hydroxybutyric acid derivatives in the presence of Cu(II)/trisoxazoline catalyst. These reactions offered the desired products in 70% to 93% yields with 79% to 99% enantiomeric excesses.

Donor–acceptor (D–A) cyclopropanes are one of the most powerful 1,3-dipolar synthons for the construction of natural products and biologically active compounds.[1] The nucleophilic ring-opening reactions of D–A cyclopropanes have been recognized as useful strategies to access 1,3-bifunctionalized scaffolds.[1–3] Asymmetric ring-opening reactions of D–A cyclopropanes[3] with heteroatom containing nucleophiles have been well established.[3a–g] For example, Tang and co-workers reported chiral Ni/bisoxazoline (BOX)-catalyzed asymmetric ring-opening reactions of D–A cyclopropanes with secondary aliphatic amines for the synthesis of γ-aminobutyric acid derivatives.[3a,b] In addition, related asymmetric ring-opening processes using aromatic amines as nucleophiles were also reported by Feng, Wang and Cai.[3c–e] Using thiols as the nucleophiles, Feng and co-workers disclosed highly enantioselective ring-opening of D–A cyclopropanes in the presence of the chiral Sc/*N*,*N*′-dioxide catalyst to afford γ-thiobutyric acid derivatives.[3f] Furthermore, Tang's group developed a method to access enantioenriched γ-hydroxybutyric acid derivatives by Cu/trisoxazoline (TOX)-catalyzed ring-opening of D–A cyclopropanes with water and alcohols.[3g]

1,3-Cyclodiones can be used as both O- and C-nucleophiles due to easy formation of enol forms and have been applied in many domino and multi-component reactions.[4] Recently, we developed scandium triflate catalyzed O-selective nucleophilic ring-opening of D–A cyclopropanes with 1,3-cyclodiones,[5b] where the ring-opening products 1,3-cyclodione enol ether derivatives were obtained in good to excellent yields (Scheme 1a). In continuation of our research interests in the reactions between 1,3-dicarbonyl compounds and D–A cyclopropanes,[5] herein, we disclose the asymmetric version of the ring opening reactions of D–A cyclopropanes with 1,3-cyclodiones (Scheme 1b).

According to our previous initial attempts,[5b] reaction of **1a** and **2a** in the presence of $Sc(OTf)_3$ and ligand **L1** (Fig. 1) afforded desired product **3a** with 62% ee (Table 1, entry 1).



Scheme 1 Our previous work and present work.

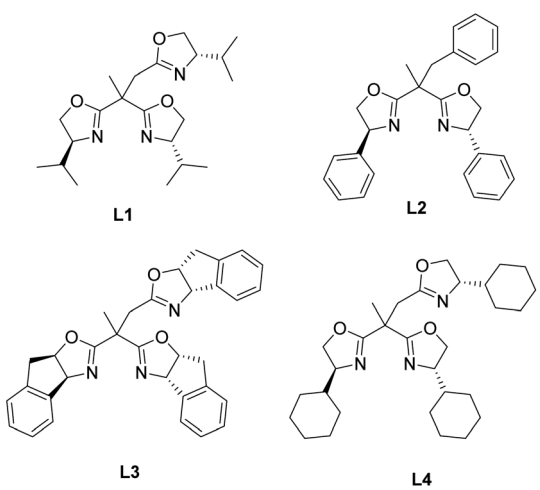


Fig. 1 Ligands used for the asymmetric ring-opening reactions of D–A cyclopropanes with 1,3-cyclodiones.

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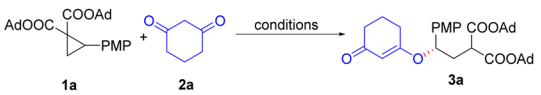
Table 1 Optimization of the reaction conditions[a]

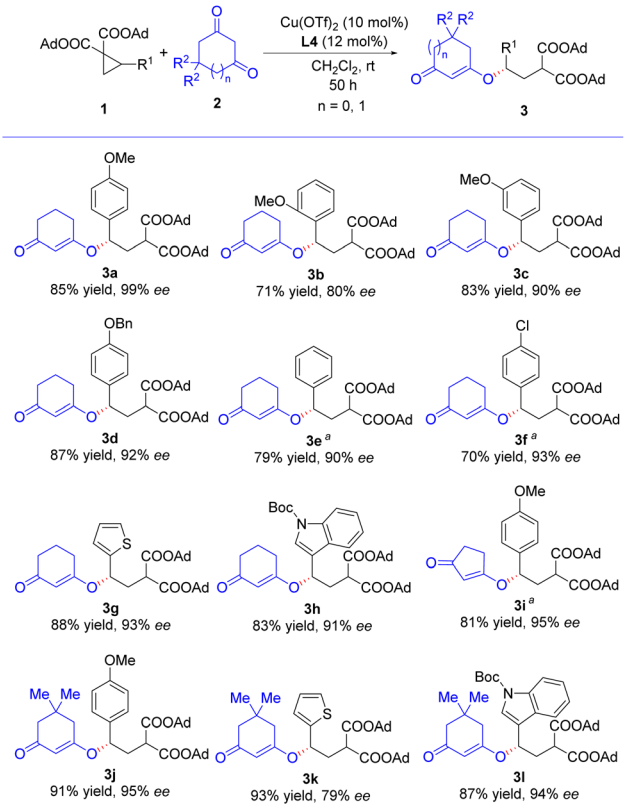


Entry	L*n*	Solvent	Yield[b] (%)	ee[c] (%)
1	L1	CH_2Cl_2	66	62
2[d]	L1	CH_2Cl_2	80	13
3	L2	CH_2Cl_2	58	60
4	L3	CH_2Cl_2	46	69
5	L4	CH_2Cl_2	70	99
6	L4	$PhCH_3$	65	89
7	L4	THF	49	71
8[e]	L4	CH_2Cl_2	83	97
9[f]	L4	CH_2Cl_2	85	99

[a] Unless otherwise noted, reactions were carried out using **1a** (0.20 mmol), **2a** (0.40 mmol), $Cu(OTf)_2$ (0.04 mmol) with ligand (0.048 mmol) in solvent (1.0 mL) at room temperature (25 °C) for 24 h. [b] Isolated yields. [c] Determined by chiral HPLC. [d] $Sc(OTf)_3$ was used as catalyst. [e] The reaction was carried out at 35 °C. [f] $Cu(OTf)_2$ (0.02 mmol) with ligand (0.024 mmol) was used and the reaction time was 50 h.

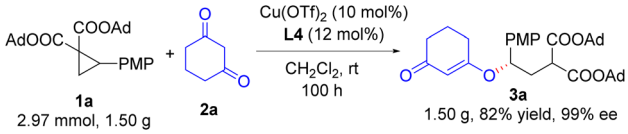
Thus, we started screening the reaction conditions using adamantlyl ester substituted D–A cyclopropane **1a** and 1,3-cyclohexanone **2a** as the model substrates (Table 1). When chiral ligand **L1** was used, $Cu(OTf)_2$ performed much better than $Sc(OTf)_3$ in terms of product enantioselectivity (Table 1, entry 1 *vs.* entry 2). After screening various bis-/trisoxazoline ligands, cyclohexyl-trisoxazoline (Cy-TOX) **L4** was found to give the best results with excellent enantioselectivity (Table 1, entries 3–5). When other solvent, such as toluene and THF, was used, the reaction results became poorer in terms of both yield and enantioselectivity (Table 1, entries 6 and 7). The enantiomeric excess of **3a** slightly decreased when the reaction temperature increased to 35 °C (Table 1, entry 8). Reducing the catalyst loading to 10 mol% did not affect the enantioselectivity of **3a**, and the yield of **3a** was able to be improved to 85% by prolonging the reaction time to 50 h (Table 1, entry 9).

Next, the substrate scope of the asymmetric ring-opening reactions was investigated under the optimized conditions (Table 1, entry 9). As shown in Scheme 2, the reactions of various D–A cyclopropanes **1** with different 1,3-cyclodiones **2** proceeded smoothly to furnish enantioenriched 1,3-cyclodione enol ether derivatives **3** in good yields and high enantioselectivities (70–93% yield, 79–99% ee). For the reactions of D–A cyclopropanes **1** with methoxyl group substituted on the phenyl ring, the position of the methoxyl group influenced the enantioselectivity of the corresponding products significantly (**3a–3c**). Reaction of *para*-methoxyl phenyl substituted D–A cyclopropane afforded product with highest enantioselectivity (**3a**, 99% ee). When *meta*- or *ortho*-methoxyl phenyl substituted D–A cyclopropane was used, the corresponding product enantioselectivity dropped to 90% and 80%, respectively. Similar to our previous studies, reactions of electron-rich D–A cyclopropanes with 1,3-cyclohexanone were faster than electron-deficient ones (**3a**, **3d** *vs.* **3e**, **3f**), whereas the electronic nature had no



Scheme 2 Reactions of various D–A cyclopropanes **1** with different 1,3-cyclodiones **2**. Unless otherwise noted, reactions were carried out using **1** (0.20 mmol), 1,3-cyclodiones **2** (0.40 mmol), $Cu(OTf)_2$ (0.02 mmol) with **L4** (0.024 mmol) in 1.0 mL CH_2Cl_2 at room temperature (25 °C) for 50 h. [a]The reaction time was 100 h.

significant effects on enantioselectivities (**3d–3f**). Heterocyclic substrates, such as 2-thienyl and 3-indolyl substituted D–A cyclopropanes, tolerated well in this asymmetric reaction, and the corresponding products **3g** and **3h** were accomplished in good yields and high enantioselectivities. Reactions using 1,3-cyclopentanedione (**2b**) and 5,5-dimethyl-1,3-cyclohexanedione (**2c**) as nucleophiles in the asymmetric ring-opening reactions were also studied. Reaction of **1a** and **2b** proceeded well to afford **3i** in 81% yield with 95% ee, though longer reaction time was necessary. Reactions of **2c** with **1a** and 3-indolyl substituted D–A cyclopropane afforded corresponding products in excellent yields and enantioselectivities (**3j** and **3l**), whereas the reaction with 2-thienyl substituted D–A cyclopropane provided **3k** with much lower enantiomeric excess, 79%. The absolute configurations of **3a–3l** were inferred to be (*S*) according to Tang's work.[3g]



Scheme 3 Gram-scale synthesis of **3a**.

The asymmetric ring-opening reaction was demonstrated in a gram-scale reaction (Scheme 3). In this gram-scale reaction of **1a** and **2a**, the chiral 1,3-cyclodione enol ether **3a** was obtained in 82% yield with 99% ee.

Conclusions

We have established the asymmetric ring-opening reactions of D–A cyclopropanes with 1,3-cyclodiones for the synthesis of enantioenriched γ-hydroxybutyric acid derivatives in the presence of Cu(II)/TOX catalyst. A range of 1,3-cyclodione enol ether derivatives were obtained in good yields and with high enantioselectivities. This methodology reported here may be of benefit for pharmaceutical research.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 For selected reviews of donor–acceptor cyclopropanes:(*a*) H. U. Reissig and R. Zimmer, *Chem. Rev.*, 2003, **103**, 1151–1196; (*b*) D. Agrawal and V. K. Yadav, *Chem. Commun.*, 2008, 6471–6488; (*c*) C. A. Carson and M. A. Kerr, *Chem. Soc. Rev.*, 2009, **38**, 3051–3060; (*d*) M. A. Cavitt, L. H. Phun and S. France, *Chem. Soc. Rev.*, 2014, **43**, 804–818; (*e*) T. F. Schneider, J. Kaschel and D. B. Werz, *Angew. Chem., Int. Ed.*, 2014, **53**, 5504–5523; (*f*) H. K. Grover, M. R. Emmett and M. A. Kerr, *Org. Biomol. Chem.*, 2015, **13**, 655–671; (*g*) M. Meazza, H. Guo and R. Rios, *Org. Biomol. Chem.*, 2017, **15**, 2479–2490; (*h*) A. U. Augustin and D. B. Werz, *Acc. Chem. Res.*, 2021, **54**, 1528–1541; (*i*) K. Ghosh and S. Das, *Org. Biomol. Chem.*, 2021, **19**, 965–982; (*j*) V. Pirenne, B. Muriel and J. Waser, *Chem. Rev.*, 2021, **121**, 227–263; (*k*) Y. Xia, X. Liu and X.-M. Feng, *Angew. Chem., Int. Ed.*, 2021, **60**, 9192–9204; (*l*) H. Huo and Y. Gong, *Org. Biomol. Chem.*, 2022, **20**, 3847–3869.

2 (*a*) M. R. Emmett, H. K. Grover and M. A. Kerr, *J. Org. Chem.*, 2012, **77**, 6634–6637; (*b*) F. de Nanteuil, J. Loup and J. Waser, *Org. Lett.*, 2013, **15**, 3738–3741; (*c*) A. Lucht, L. J. Patalag, A. U. Augustin, P. G. Jones and D. B. Werz, *Angew. Chem., Int. Ed.*, 2017, **56**, 10587–10591; (*d*) J. Wallbaum, L. K. B. Garve, P. G. Jones and D. B. Werz, *Org. Lett.*, 2017, **19**, 98–101; (*e*) S. Das, C. G. Daniliuc and A. Studer, *Angew. Chem., Int. Ed.*, 2017, **56**, 11554–11558; (*f*) X.-M. Feng, P. Yang, G. Yang, W. Chen and Z. Chai, *J. Org. Chem.*, 2018, **83**, 174–184; (*g*) A. U. Augustin, P. G. Jones and D. B. Werz, *Chem.–Eur. J.*, 2019, **25**, 11620–11624; (*h*) A. Lücht, S. Sobottka, L. J. Patalag, P. G. Jones, H. U. Reissig, B. Sarkar and D. B. Werz, *Chem.–Eur. J.*, 2019, **25**, 10359–10365; (*i*) A. U. Augustin, J. L. Merz, P. G. Jones, G. Mlostoń and D. B. Werz, *Org. Lett.*, 2019, **21**, 9405–9409; (*j*) U. K. Mishra, K. Patel and S. S. V. Ramasastry, *Org. Lett.*, 2020, **22**, 3815–3819; (*k*) Z. Zuo and A. Studer, *Org. Lett.*, 2022, **24**, 949–954; (*l*) P. Su, H. Li, W. Chen, G. Luo, G. Yang and Z. Chai, *Eur. J. Org. Chem.*, 2020, **33**, 5380–5387; (*m*) V. Pirenne, E. G. L. Robert and J. Waser, *Chem. Sci.*, 2021, **12**, 8706–8712; (*n*) Z. Liu, Y. Wei and M. Shi, *Org. Chem. Front.*, 2022, **9**, 1960–1966.

3 (*a*) Y. Y. Zhou, L. J. Wang, X. L. Sun and Y. Tang, *J. Am. Chem. Soc.*, 2012, **134**, 9066–9069; (*b*) Q. K. Kang, L. J. Wang, Z. B. Zheng, J. F. Li and Y. Tang, *Chin. J. Chem.*, 2014, **32**, 669–672; (*c*) Y. Xia, L. Lin, F. Chang, Y. Liao, X. Liu and X.-M. Feng, *Angew. Chem., Int. Ed.*, 2016, **55**, 12228–12232; (*d*) W. W. Luo, Z.-C. Sun, E. H. N. Fernando, V. N. Nesterov, T. R. Cundari and H. Wang, *ACS Catal.*, 2019, **9**, 8285–8293; (*e*) L. Xu, Q. Yang, S.-S. Zhong, H.-H. Li, Y.-R. Tang and Y.-F. Cai, *Org. Lett.*, 2020, **22**, 9016–9021; (*f*) Y. Xia, L. Lin, F. Chang, X. Fu, X. Liu and X.-M. Feng, *Angew. Chem., Int. Ed.*, 2015, **54**, 13748–13752; (*g*) Q.-K. Kang, L.-J. Wang, Q.-J. Liu, J.-F. Li and Y. Tang, *J. Am. Chem. Soc.*, 2015, **137**, 14594–14597; (*h*) O. Lifchits, D. Alberico, I. Zakharian and A. B. Charette, *J. Org. Chem.*, 2008, **73**, 6838–6840; (*i*) O. Lifchits and A. B. Charette, *Org. Lett.*, 2008, **10**, 2809–2812; (*j*) J. P. Qu, Y. Liang, H. Xu, X. L. Sun, Z. X. Yu and Y. Tang, *Chem.–Eur. J.*, 2012, **18**, 2196–2201; (*k*) S. M. Wales, M. M. Walker and J. S. Johnson, *Org. Lett.*, 2013, **15**, 2558–2561; (*l*) H. Xiong, H. Xu, S. Liao, Z. Xie and Y. Tang, *J. Am. Chem. Soc.*, 2013, **135**, 7851–7854; (*m*) H. Xu, J. P. Qu, S. Liao, H. Xiong and Y. Tang, *Angew. Chem., Int. Ed.*, 2013, **52**, 4004–4007; (*n*) J. Zhu, Y. Liang, L. Wang, Z. B. Zheng, K. N. Houk and Y. Tang, *J. Am. Chem. Soc.*, 2014, **136**, 6900–6903; (*o*) Q. J. Liu, W. G. Yan, L. Wang, X. P. Zhang and Y. Tang, *Org. Lett.*, 2015, **17**, 4014–4017; (*p*) H. P. Wang, H. H. Zhang, X. Q. Hu, P. F. Xu and Y. C. Luo, *Eur. J. Org. Chem.*, 2015, 3486–3494; (*q*) Y. Xia, F. Z. Chang, L. L. Lin, Y. L. Xu, X. H. Liu and X.-M. Feng, *Org. Chem. Front.*, 2018, **5**, 1293–1296; (*r*) S. Nicolai and J. Waser, *Angew. Chem., Int. Ed.*, 2022, **61**, e202209006.

4 (*a*) Z. B. Zhu, L. P. Liu, L. X. Shao and M. Shi, *Synlett.*, 2007, **1**, 115–118; (*b*) S. Liao, X. L. Sun and Y. Tang, *Acc. Chem. Res.*, 2014, **47**, 2260–2272; (*c*) X. Bugaut, T. Constantieux, Y. Coquerel, J. Rpdriguez, J. Zhu, Q. Wang and M. X. Wang, *Multicomponent Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, Germany, 2015, vol. 5, pp. 109–159; (*d*) H. Qian, D. Huang, G. Yan and L. Lu, *Curr. Org. Chem.*, 2018, **22**, 2055–2084; (*e*) Z. Liu, P. Sivaguru, G. Zanoni, E. A. Anderson and X. Bi, *Angew. Chem., Int. Ed.*, 2018, **57**, 1–6; (*f*) M. K. Foumani, J. Conrad, W. Frey and U. Beifuss, *J. Org. Chem.*, 2022, **87**, 8316–8341; (*g*) Y. Murakami, K. Hisano and H. Nishino, *J. Org. Chem.*, 2022, **87**, 8782–8787; (*h*) S. S. Sun, Z. Y. Mo, Y. Y. Chen and Y. L. Xu, *J. Org. Chem.*, 2022, **87**, 12447–12454; (*i*) H. Li, H. Gu, Y. Lu, N. Xu, N. Han, J. Li and J. Liu, *J. Org. Chem.*, 2022, **87**, 8142–8150; (*j*) Z. Zhong, M. Liang, Z. Zhang, H. Cui, N. Wang, S. Mai and H. Tao, *Org. Lett.*, 2022, **24**, 4850–4854.

5 (*a*) D. Zhang, L. Yin, J. Zhong, Q. Cheng, H. Cai, Y. Chen and Q.-F. Zhang, *Org. Biomol. Chem.*, 2020, **18**, 6492–6496; (*b*) D. Zhang, J. Zhong, L. Yin, Y. Chen, J. Man and Q.-F. Zhang, *J. Org. Chem.*, 2020, **85**, 5778–5786; (*c*) D. Zhang, H. Cai, Y. Chen, L. Yin, J. Zhong, Y. Zhang and Q.-F. Zhang, *J. Org. Chem.*, 2020, **85**, 14262–14270; (*d*) D. Zhang, Q. Cheng, L. Chen, H. Deng, H. Cai and Q.-F. Zhang, *Org. Biomol. Chem.*, 2021, **19**, 9645–9648; (*e*) H. Deng, Q. Cheng, H. Cai, D. Zhang and Q.-F. Zhang, *Tetrahedron Lett.*, 2023, **114**, 154257.