



Cite this: *RSC Adv.*, 2019, 9, 15466

Received 10th April 2019

Accepted 3rd May 2019

DOI: 10.1039/c9ra02694k

rsc.li/rsc-advances

Efficient access to chiral dihydrobenzoxazinones via Rh-catalyzed hydrogenation†

Ziyi Chen,^a Xuguang Yin,^a Xiu-Qin Dong[✉]^a and Xumu Zhang^{id}^{ab}

Rh/(S)-DTBM-SegPhos-catalyzed asymmetric hydrogenation of prochiral (Z)-2-(2-oxo-2H-benzo[b][1,4]oxazin-3(4H)-ylidene)acetate esters was successfully developed. A series of chiral dihydrobenzoxazinones were prepared through this efficient methodology with good to excellent results (up to >99% conversion, 93% yield and >99% ee), which are important motifs in the biologically active molecules.

Introduction

Chiral dihydrobenzoxazinones and derivatives are an important class of heterocycles, and are frequently found in biologically active molecules.^{1–4} For example, compound **A** is a potent anti-cholesteremic agent (Fig. 1).² Compound **B** (Kinin B1) is used for the treatment of inflammation and pain in septicemia.³ Compound **C** is a pyruvate kinase activator, which can increase the lifetime of red blood cells.⁴

Due to the great importance of chiral dihydrobenzoxazinones and derivatives, the investigation on the construction of these intriguing motifs has been an important research topic in organic synthesis. Therefore, enormous efforts were made to the development of efficient enantioselective methods, and some asymmetric synthetic methodologies have been established to access chiral

dihydrobenzoxazinones and derivatives over the past decades.^{5–11} The asymmetric catalytic reduction of prochiral benzoxazinones and derivatives is one of the most important methods,^{5–7} including asymmetric hydrosilylation,⁵ asymmetric transfer hydrogenation,⁶ and asymmetric hydrogenation.^{3b,7} In addition, other efficient enantioselective methods were involved to prepare chiral dihydrobenzoxazinones and derivatives,^{4b,8–11} such as addition reaction of indoles or pyrroles with benzoxazinones,⁸ Rh-catalyzed asymmetric arylation of benzoxazinones and quinoxalinones with arylboroxines,^{4b} dynamic kinetic resolution of α -bromo arylacetates in nucleophilic substitution with N-alkylated 2-aminophenols,⁹ asymmetric Mannich reaction of ketones with benzoxazinones,¹⁰ and organo-catalytic reductive amination.¹¹ Transition-metal-catalyzed asymmetric hydrogenation has been regarded as a straightforward and efficient method for the synthesis of chiral compounds with high atom-economic advantage.¹² Based on our continuing research in the field of asymmetric hydrogenation, much attention were paid to the synthesis of chiral dihydrobenzoxazinones and derivatives through asymmetric hydrogenation. We herein successfully developed Rh-catalyzed asymmetric hydrogenation of (Z)-2-(2-oxo-2H-benzo[b][1,4]oxazin-3(4H)-ylidene)acetate esters using commercial (S)-DTBM-SegPhos ligand, affording a series of chiral dihydrobenzoxazinones with good to excellent results (Scheme 1, >99% conversion, 93% yield, >99% ee).

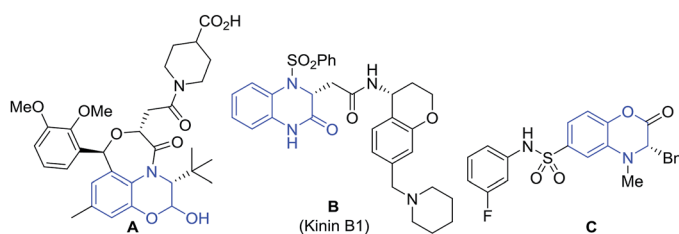
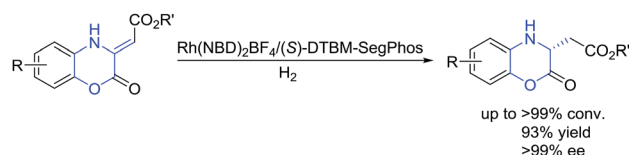


Fig. 1 Examples of biologically active molecules containing chiral dihydrobenzoxazinone or related framework.

^aKey Laboratory of Biomedical Polymers, Engineering Research Centre of Organosilicon Compounds & Materials, Ministry of Education, College of Chemistry and Molecular Sciences, Wuhan University, Wuhan, Hubei, 430072, P. R. China. E-mail: xiuqindong@whu.edu.cn

^bDepartment of Chemistry and Shenzhen Grubbs Institute, Southern University of Science and Technology, Shenzhen, Guangdong, 518055, P. R. China

† Electronic supplementary information (ESI) available: Experimental procedures, NMR spectra of compounds. CCDC 1905706. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9ra02694k



Scheme 1 Preparation of chiral dihydrobenzoxazinones through Rh-catalyzed asymmetric hydrogenation.

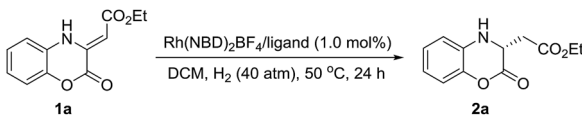


Results and discussion

The initial investigation of $\text{Rh}(\text{NBD})_2\text{BF}_4$ -catalyzed asymmetric hydrogenation of model substrate ethyl (*Z*)-2-(2-oxo-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate **1a**¹³ was started to evaluate a series of chiral diphosphine ligands (Fig. 2) under 40 atm H_2 at 50 °C in CH_2Cl_2 for 24 h. As shown in Table 1, poor conversion and good enantioselectivity was obtained in the presence of easily available (*R*)-Binap (22% conversion, 87% ee, Table 1, entry 1). In addition, poor to moderate results were obtained with (*R*_C, *S*_P)-DuanPhos, (*S*, *S*)-f-Binaphane, (*R*, *S*)-JosiPhos, (*S*)-Binapine, ZhaoPhos, (*S*, *S*)-Ph-BPE and (*S*)-SegPhos as the ligand (3–62% conversions, 20–72% ee, Table 1, entries 2, 4–9). No reaction was observed using the (*S*, *S*)-Me-DuPhos as the ligand (Table 1, entry 3). To our delight, the ligand (*S*)-DTBM-SegPhos provided the promising reaction result with 73% conversion and 94% ee (Table 1, entry 10).

The solvent played an important role in asymmetric catalytic reaction, and the $\text{Rh}(\text{NBD})_2\text{BF}_4$ /(*S*)-DTBM-SegPhos-catalyzed asymmetric hydrogenation of model substrate ethyl (*Z*)-2-(2-oxo-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate **1a** was then carried out in different solvents. We found that moderate conversions and enantioselectivities were obtained in ethyl acetate, CHCl_3 and i -PrOH (40–66% conversions, 42–70% ee, Table 2, entries 1, 5, 9). Toluene, THF, 1,4-dioxane and DCE gave very poor enantioselectivities (Table 2, entries 2–4, 11). Although full conversion was achieved in TFE, moderate enantioselectivity was provided (>99% conversion, 56% ee,

Table 1 Screening ligands for the asymmetric hydrogenation of ethyl (*Z*)-2-(2-oxo-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate **1a**^a



Entry	Ligand	Conv. ^b (%)	ee ^c (%)
1	(<i>R</i>)-Binap	22	87
2	(<i>R</i> _C , <i>S</i> _P)-DuanPhos	4	28
3	(<i>S</i> , <i>S</i>)-Me-DuPhos	NR	NA
4	(<i>S</i> , <i>S</i>)-f-Binaphane	5	49
5	(<i>R</i> , <i>S</i>)-JosiPhos	62	41
6	(<i>S</i>)-Binapine	22	20
7	ZhaoPhos	3	67
8	(<i>S</i> , <i>S</i>)-Ph-BPE	29	65
9	(<i>S</i>)-SegPhos	62	72
10	(<i>S</i>)-DTBM-SegPhos	73	94

^a Reaction condition: substrate **1a** (0.10 mmol), $\text{Rh}(\text{NBD})_2\text{BF}_4$ (1.0 mol%), ligand (1.1 mol%), 1 mL DCM, H_2 (40 atm), 50 °C, 24 h.

^b Determined by ^1H NMR analysis. ^c Determined by HPLC analysis using a chiral stationary phase. DCM is CH_2Cl_2 . NR = no reaction. NA = no available.

Table 2, entry 6). Trace conversions were observed in MeOH and EtOH (Table 2, entries 7–8). Among these solvents, DCM was still provided the highest enantioselectivity (94% ee, Table 2, entry 10).

In order to obtain high conversion and excellent enantioselectivity, the ratio of mixture of CH_2Cl_2 and TFE was inspected (Table 3). When the volumetric ratio of TFE and

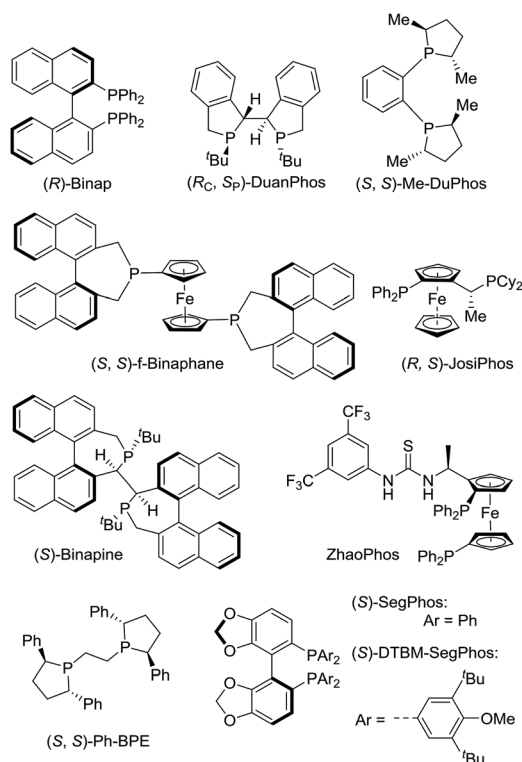
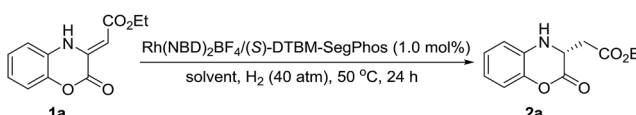


Fig. 2 The structure of chiral diphosphine ligands.

Table 2 Screening of solvents for the asymmetric hydrogenation of ethyl (*Z*)-2-(2-oxo-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate **1a**^a



Entry	Solvent	Conv. ^b (%)	ee ^c (%)
1	EtOAc	64	66
2	Toluene	32	27
3	THF	75	16
4	1,4-Dioxane	50	6
5	CHCl_3	40	70
6	TFE	>99	56
7	MeOH	Trace	NA
8	EtOH	Trace	NA
9	i -PrOH	66	42
10	DCM	73	94
11	DCE	64	22

^a Reaction condition: substrate **1a** (0.10 mmol), $\text{Rh}(\text{NBD})_2\text{BF}_4$ (1.0 mol%), (*S*)-DTBM-SegPhos (1.1 mol%), 1 mL solvent, H_2 (40 atm), 50 °C, 24 h. ^b Determined by ^1H NMR analysis. ^c Determined by HPLC analysis using a chiral stationary phase. THF is tetrahydrofuran. TFE is trifluoroethanol. DCE is dichloroethane.



Table 3 Optimization of reaction conditions for the asymmetric hydrogenation of ethyl (*Z*)-2-(2-oxo-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate **1a**^a

Entry	Metal precursor	Solvent	H ₂ (atm)	Conv. ^b (%)	ee ^c (%)
1	Rh(NBD) ₂ BF ₄	TFE/DCM = 1 : 2	40	61	94
2	Rh(NBD) ₂ BF ₄	TFE/DCM = 1 : 4	40	59	93
3	Rh(NBD) ₂ BF ₄	TFE/DCM = 1 : 8	40	66	96
4	Rh(NBD) ₂ BF ₄	TFE/DCM = 2 : 1	40	56	91
5	Rh(NBD) ₂ BF ₄	TFE/DCM = 4 : 1	40	96	95
6	Rh(NBD) ₂ BF ₄	TFE/DCM = 8 : 1	40	90	95
7	[Rh(COD)Cl] ₂	TFE/DCM = 4 : 1	40	72	90
8	[Ir(COD)Cl] ₂	TFE/DCM = 4 : 1	40	37	73
9	Ni(OAc) ₂	TFE/DCM = 4 : 1	40	NR	NA
10	Rh(NBD) ₂ BF ₄	TFE/DCM = 4 : 1	20	96	97

^a Reaction condition: substrate **1a** (0.10 mmol), metal precursor (1.0 mol%), (*S*)-DTBM-SegPhos (1.1 mol%), 1 mL solvent, H₂, 50 °C, 24 h.^b Determined by ¹H NMR analysis. ^c Determined by HPLC analysis using a chiral stationary phase.

DCM is 4 : 1, the best results can be afforded with 96% conversion and 95% ee (Table 3, entry 5). In addition, several metal precursors were investigated in this asymmetric hydrogenation. Moderate conversion and excellent enantioselectivity was achieved with [Rh(COD)Cl]₂ as metal precursor (72% conversion, 90% ee, Table 3, entry 7). [Ir(COD)Cl]₂ gave poor reactivity and moderate enantioselectivity (37% conversion, 73% ee, Table 3, entry 8). There was no reaction in the presence of Ni(OAc)₂ (Table 3, entry 9). To our delight, nearly the same reaction result can be achieved when the pressure of H₂ was decreased from 40 atm to 20 atm (96% conversion, 97% ee, Table 3, entry 10).

After establishing the optimized reaction conditions, we focused our attention on the exploration of the substrate scope generality of this Rh-catalyzed asymmetric hydrogenation of various prochiral (*Z*)-2-(2-oxo-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate esters. As listed in Table 4, the Rh-catalyzed asymmetric hydrogenation of a series of (*Z*)-2-(2-oxo-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate esters could proceed smoothly, affording the desired hydrogenation products chiral dihydrobenzoxazinones (**2a–2k**) with good to excellent results (81% to >99% conversions, 80–93% yields, 88% to >99% ee). The substrates (*Z*)-2-(2-oxo-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate esters bearing electron-withdrawing (**1b–1d**, **1j**) or electron-donating (**1e–1i**) substituted groups on the benzo ring worked well in this asymmetric hydrogenation. In addition, we found that the position of substituted group on the benzo ring had little effect on the reactivity and enantioselectivity. Moreover, the ester group was well tolerated in this catalytic system. When the ethyl ester group was changed to methyl ester group, the substrate methyl (*Z*)-2-(2-oxo-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate (**1k**) was hydrogenated with high conversion and excellent enantioselectivity (92% conversion, 87% yield and 99% ee).

Table 4 Substrate scope study for the Rh-catalyzed asymmetric hydrogenation of (*Z*)-2-(2-oxo-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate esters^a

2a	2b	2c	2d	2e	
96% conv. 93% yield 97% ee	92% conv. 92% yield 97% ee	>99% conv. 85% yield >99% ee	>99% conv. 89% yield >99% ee	>99% conv. 92% yield 97% ee	
2f	2g	2h	2i	2j	2k
>99% conv. 89% yield 99% ee	>99% conv. 85% yield 98% ee	>99% conv. 86% yield 92% ee	92% conv. 88% yield 97% ee	81% conv. 80% yield 88% ee	92% conv. 87% yield 99% ee

^a Reaction condition: substrate **1** (0.10 mmol), Rh(NBD)₂BF₄ (1.0 mol%), (*S*)-DTBM-SegPhos (1.1 mol%), 1 mL solvent, H₂ (20 atm), 50 °C, 24 h. Conversion was determined by ¹H NMR analysis. Yield is isolated yield. ee was determined by HPLC analysis using a chiral stationary phase. The configuration of **2d** was determined by X-ray analysis.¹⁴

Conclusions

In conclusion, the Rh/(S)-DTBM-SegPhos-catalyzed asymmetric hydrogenation of a variety of prochiral (Z)-2-(2-oxo-2H-benzo[b][1,4]oxazin-3(4H)-ylidene)acetate esters was successfully realized. This efficient methodology afforded chiral dihydrobenzoxazinones with good to excellent results (81% to >99% conversions, 80–93% yields, 88% to >99% ee), which are important and unique building blocks in the biologically active molecules.

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgements

We are grateful for financial support from the National Natural Science Foundation of China (Grant No. 21432007, 21502145), Wuhan Morning Light Plan of Youth Science and Technology (Grant No. 2017050304010307), Shenzhen Nobel Prize Scientists Laboratory Project (Grant No. C17783101) and the Fundamental Research Funds for Central Universities (Grant No. 2042018kf0202). The Program of Introducing Talents of Discipline to Universities of China (111 Project) is also appreciated.

Notes and references

- (a) D. V. Smil, S. Manku, Y. A. Chantigny, S. Leit, A. Wahhab, R. Deziel, T. P. Yan, M. Fournel, C. Maroun, Z. Li, A.-M. Lemieux, A. Nicolescu, J. Rahil, S. Lefebvre, A. Panetta, J. M. Besterman, S. Lefebvre, A. Panetta, J. M. Besterman and R. Déziel, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 688–692; (b) P. E. Mahaney, M. B. Webb, F. Ye, J. P. Sabatucci, R. J. Steffan, C. C. Chadwick, D. C. Harnish and E. J. Trybulski, *Bioorg. Med. Chem.*, 2006, **14**, 3455–3466; (c) D.-S. Su, M. K. Markowitz, R. M. DiPardo, K. L. Murphy, C. M. Harrell, S. S. O'Malley, R. W. Ransom, R. S. L. Chang, S. Ha, F. J. Hess, D. J. Pettibone, G. S. Mason, S. Boyce, R. M. Freidinger and M. G. Bock, *J. Am. Chem. Soc.*, 2003, **125**, 7516–7517; (d) F. Grant, S. Bartulis, L. Brogley, M. S. Dappan, R. Kasar, A. Khan, M. Neitzel, M. A. Pleiss, E. D. Thorsett, J. Tucker, M. Ye and J. Hawkinson, PCT Int. Appl., WO 2003093245 A1, 2003; (e) Z. Jones, R. Groneberg, M. Drew and C. T. Eary, *US Pat.*, 20050282812 A1, 2005; (f) D.-S. Su and M. G. Bock, *U.S. Pat. Appl. Publ.* US 20050020591 A1, 2005; (g) J. Ilaš, P. Š. Anderluh, M. S. Dolenc and D. Kikelj, *Tetrahedron*, 2005, **61**, 7325–7348; (h) C. J. Abraham, D. H. Paull, M. T. Scerba, J. W. Grebinski and T. Lectka, *J. Am. Chem. Soc.*, 2006, **128**, 13370–13371; (i) M. Rueping, M. Stoeckel, E. Sugiono and T. Theissmann, *Tetrahedron*, 2010, **66**, 6565–6568.
- (a) C. M. Hayward and D. A. Scully, *US Pat.*, US 6207664 B1, 2001; (b) T. Tanaka, I. Mizota, K. Umezū, A. Ito and M. Shimizu, *Heterocycles*, 2017, **95**, 830–843.
- (a) J. J. Chen, W. Qian, K. Biswas, V. N. Viswanadhan, B. C. Askew, S. Hitchcock, R. W. Hungate, L. Arik and E. Johnson, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 4477–4481; (b) M.-W. Chen, Z. Deng, Q. Yang, J. Huang and Y. Peng, *Org. Chem. Front.*, 2019, **6**, 746–750.
- (a) S. S.-S. Michael, WO2012151440, 2012; (b) X. Zhang, B. Xu and M.-H. Xu, *Org. Chem. Front.*, 2016, **3**, 944–948.
- (a) A. V. Maikov, K. Vranková, S. Stončius and P. Kočovský, *J. Org. Chem.*, 2009, **74**, 5839–5849; (b) Z.-Y. Xue, Y. Jiang, X.-Z. Peng, W.-C. Yuan and X.-M. Zhang, *Adv. Synth. Catal.*, 2010, **352**, 2132–2136.
- (a) M. Rueping, A. P. Antonchick and T. Theissmann, *Angew. Chem., Int. Ed.*, 2006, **45**, 6751–6755; (b) F. Shi, W. Tan, H.-H. Zhang, M. Li, Q. Ye, G.-H. Ma, S.-J. Tu and G. Li, *Adv. Synth. Catal.*, 2013, **355**, 3715–3726; (c) Y. Zhang, R. Zhao, R. L.-Y. Bao and L. Shi, *Eur. J. Org. Chem.*, 2015, 3344–3351; (d) X. Zhang, A. Kormos and J. Zhang, *Org. Lett.*, 2017, **19**, 6072–6075.
- (a) Q.-A. Chen, M.-W. Chen, C.-B. Yu, L. Shi, D.-S. Wang, Y. Yang and Y.-G. Zhou, *J. Am. Chem. Soc.*, 2011, **133**, 16432–16435; (b) Q.-A. Chen, K. Gao, Y. Duan, Z.-S. Ye, L. Shi, Y. Yang and Y.-G. Zhou, *J. Am. Chem. Soc.*, 2012, **134**, 2442–2448; (c) L.-Q. Lu, Y. Li, K. Junge and M. Beller, *J. Am. Chem. Soc.*, 2015, **137**, 2763–2768; (d) J. Wang, Z.-H. Zhu, M.-W. Chen, Q.-A. Chen and Y.-G. Zhou, *Angew. Chem., Int. Ed.*, 2019, **58**, 1813–1817.
- (a) T. Kano, R. Takechi, R. Kobayashi and K. Maruoka, *Org. Biomol. Chem.*, 2014, **12**, 724–727; (b) H. Lou, Y. Wang, E. Jin and X. Lin, *J. Org. Chem.*, 2016, **81**, 2019–2026.
- E. Youk, W. Park and Y. S. Park, *Synth. Commun.*, 2018, **48**, 1331–1337.
- M. Viji, J. Sim, S. Li, H. Lee, K. Oh and J.-K. Jung, *Adv. Synth. Catal.*, 2018, **360**, 4464–4469.
- R. I. Storer, D. E. Carrera, Y. Ni and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2006, **128**, 84–86.
- Selected examples: (a) W. Tang and X. Zhang, *Chem. Rev.*, 2003, **103**, 3029–3070; (b) S. J. Roseblade and A. Pfaltz, *Acc. Chem. Res.*, 2007, **40**, 1402–1411; (c) G. Erre, S. Enthaler, K. Junge, S. Gladiali and M. Beller, *Coord. Chem. Rev.*, 2008, **252**, 471–491; (d) T. L. Church and P. G. Andersson, *Coord. Chem. Rev.*, 2008, **252**, 513–531; (e) J.-H. Xie, S.-F. Zhu and Q.-L. Zhou, *Chem. Rev.*, 2011, **111**, 1713–1760; (f) D.-S. Wang, Q.-A. Chen, S.-M. Lu and Y.-G. Zhou, *Chem. Rev.*, 2012, **112**, 2557–2590; (g) J.-H. Xie and Q.-L. Zhou, *Acta Chim. Sin.*, 2012, **70**, 1427–1438; (h) J. J. Verendel, O. Pàmies, M. Diéguez and P. G. Andersson, *Chem. Rev.*, 2014, **114**, 2130–2169; (i) Z. Zhang, N. A. Butt and W. Zhang, *Chem. Rev.*, 2016, **116**, 14769–14827; (j) S.-F. Zhu and Q.-L. Zhou, *Acc. Chem. Res.*, 2017, **50**, 988–1001.
- G. Choudhary and R. K. Peddinti, *Green Chem.*, 2011, **13**, 3290–3299.
- The X-ray crystal data of compound **2d** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1905706.†

