Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: K. Wang, Y. Xiang, Z. Shi, H. Wang, N. Li and B. Tang, *Org. Biomol. Chem.*, 2019, DOI: 10.1039/C9OB01065C.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

View Article Online
DOI: 10.1039/C9OB01065C

COMMUNICATION

Asymmetric Kinetic Resolution of Sulfides for the Construction of Unsymmetric Sulfides and Chiral 3,3-Disubstituted Oxindoles

Kaiye Wang, Yanan Xiang, Zhujun Shi, Hongyu Wang,* Na Li * and Bo Tang *

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

A range of 3,3-disubstituted oxindoles accessed by *para*-quinone methides derived from isatins with thiols was used for the formation of unsymmetrical disulfides, and 3,3-disubstituted oxindoles with chiral quaternary carbon center and unsymmetric disulfides could also be directly obtained with high selectivities catalyzed by chiral phosphines in one step.

Disulfide bonds, as important structural motifs, are present in numerous natural products and bioactive molecules, which also play a significant role in controlling the three-dimensional structure of protein in biological systems.[1] Because disulfide bonds can be reduced by glutathione and cysteine in cancer cells, unsymmetrical disulfides have been widely applied in controlled drug release and targeted drug delivery (Figure 1).[2]

Up to now, great efforts have been focused on the development of efficient synthetic methods to prepare unsymmetrical and symmetrical disulfides.[3] In particular, nucleophile substitution reactions present an simple and convenient approach for constructing disulfides, and many sulfonation reagents, such as 1-chlorobenzotriazole, *N*-trifuoroacetyl arenesulfenamides and R-S-S-OMe, have since been developed over the past decades.[4] Although great advances have been made over the past decades, little attention was paid to the construction of disulfide bonds in the discovery of new reactions for simultaneously obtaining other useful compounds. In 1988, Yoneda and co-workers found that 5-arylidene-1,3-dimethylbarbituric acid derivative **I** could be efficiently reduced by thiols to generate 1,3-dicarbonyl compound **II** at high temperature, which can further react with R-S-Cl and thiols to prepare unsymmetrical disulfides (Scheme 1a).[5] Recently, our group found that *para*-quinone methides derived from isatins possess excellent properties to prepare 3,3-disubstituted oxindoles,[6] which represent important structural motifs widely existing in natural products.[7] In view of the similar structures between **I** and **IV** (Scheme 1), we anticipated that it will be an ideal method to construct unsymmetrical sulfides using **IV** and simultaneously generate 3,3-disubstituted oxindoles (Scheme 1b). Furthermore, chiral 3,3-disubstituted oxindoles would be synthesized via asymmetric kinetic resolution in one step, which would expand the applications of

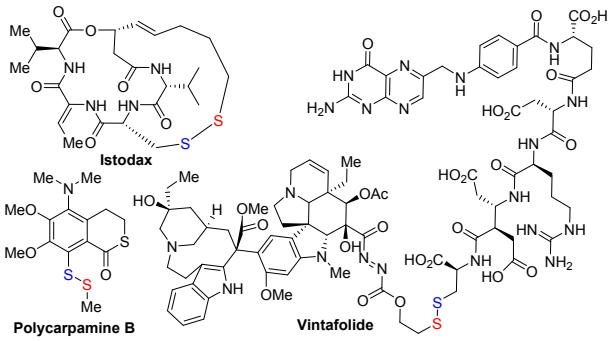
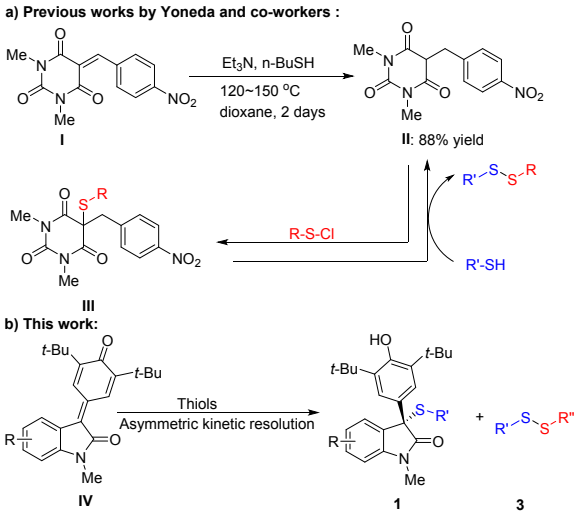


Fig. 1 Representative natural products and drugs containing unsymmetrical disulfide bonds.

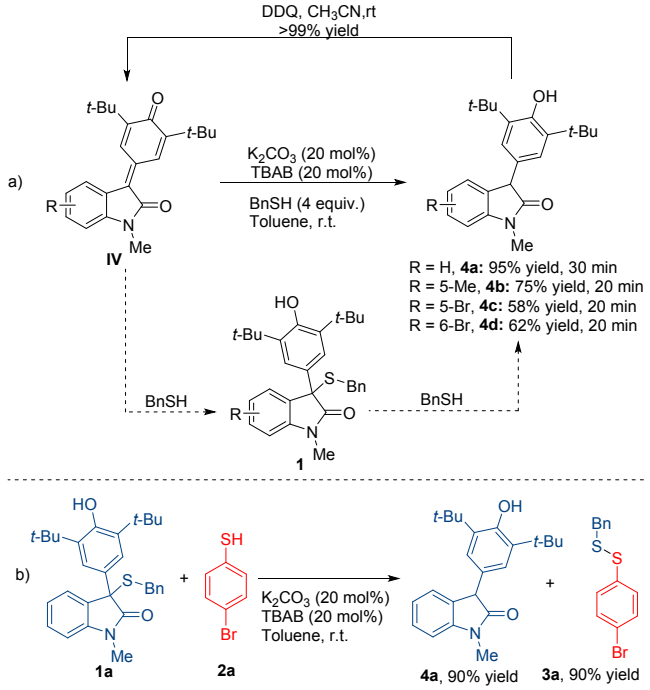


Scheme 1. Synthesis of disulfides and chiral 3,3-disubstituted oxindoles.

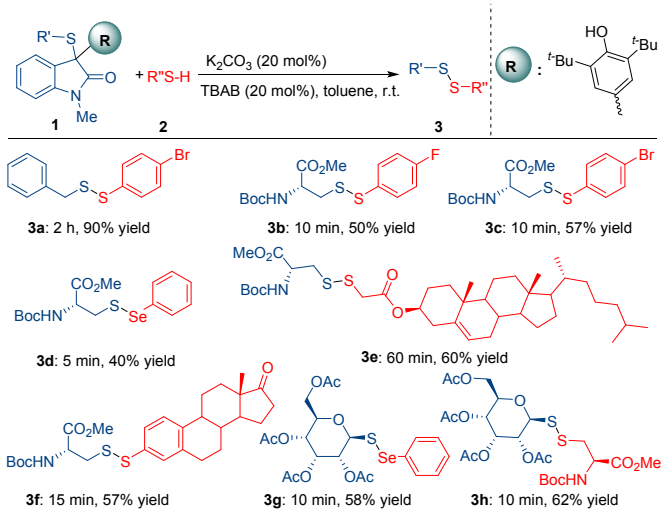
[a] *College of Chemistry, Chemical Engineering and Materials Science, Key Laboratory of Molecular and Nano Probes, Ministry of Education Collaborative Innovation Center of Functionalized Probes for Chemical Imaging in Universities of Shandong, Institute of Molecular and Nano Science, Shandong Normal University Jinan, 250014 (P.R. China). E-mail: wanghongyu@sdnu.edu.cn, lina@sdnu.edu.cn, tangb@sdnu.edu.cn.*

Electronic Supplementary Information (ESI) available: [Experimental details and supplementary figures. CCDC 1906989. For ESI and crystallographic data in CIF or other electronic format. See DOI: 10.1039/x0xx00000x

DOI: 10.1039/C9OB01065C



Scheme 2. Synthesis of disulfide bonds via the reduction of *para*-quinone methides using thiols. The yields of the isolated products are given.

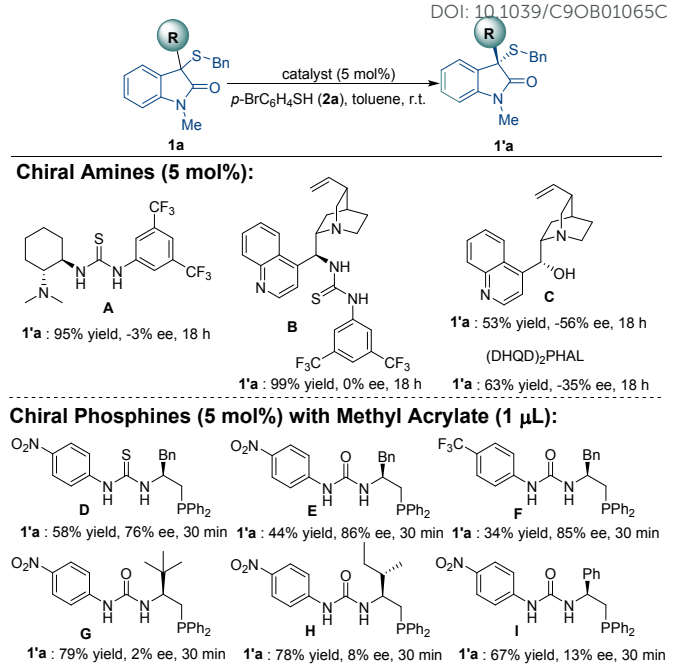


Scheme 3. Substrate scope for the synthesis of unsymmetrical disulfides. All the reactions were carried out with **1** (0.1 mmol) and **2** (0.2 mmol) in the presence of K_2CO_3 (20 mol%) and TBAB (20 mol%) in toluene (2 mL) at r.t.. The yields of the isolated products are given. TBAB: tetrabutylammonium bromide.

para-quinone methides derived from isatins in organic synthesis.[8]

Initially, 1,6-conjugate addition reactions between **IV** and BnSH were investigated under basic conditions, and the reduced product **4** and 1,2-dibenzyldisulfane were detected in high yield (Scheme 2a). While *para*-quinone methides derived from aryl aldehydes were also examined, but no reduzates and disulfides were observed, and only the addition product 4-((benzylthio)(4-fluorophenyl)methyl)-2,6-di-tert-butylphenol was obtained (see *Supporting Information*, Figure S1). Based on

Table 1. Screening the chiral catalysts.[a]



[a]Unless otherwise noted, all the reactions were carried out with **1a** (0.1 mmol) in the presence of chiral catalyst (5 mol%) in toluene (2.0 mL) at r.t.. The yields of the isolated products are given, and the ee value was determined by HPLC analysis

these results and those of previous works,[9] we hypothesized that 1,6-conjugate adduct **1** may be first generated, and then another BnSH would react with **1** via the S_N2 reaction to furnish the reduced product **4** under basic conditions. Subsequently, a control experiment was performed using **1a** and *p*-BrC_6H_4SH, whereby **4a** was successfully synthesized with 90% yield, and the unsymmetrical disulfide **3a** was also obtained with 90% yield (Scheme 2b). Notably, **4** could easily be oxidized by DDQ to regenerate the *para*-quinone methides **IV**.

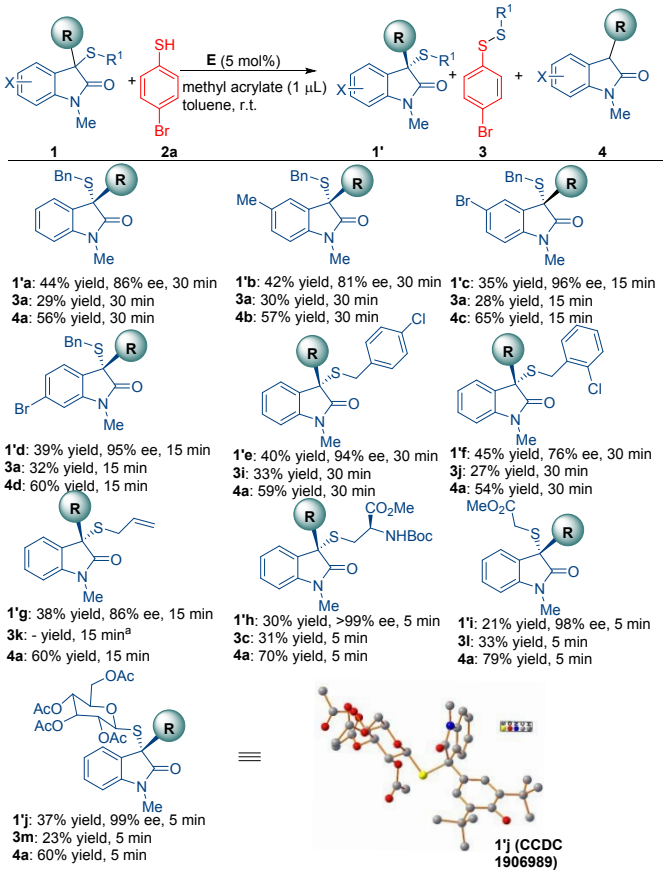
To explore the generality of the method for the construction of unsymmetrical disulfides, a series of substituted oxindoles and thiols were examined under mild conditions, aryl-thiols (or selenol) and alkyl-thiols were all suitable for the catalytic system to obtain various unsymmetrical disulfides. In addition, cysteine and sugar derivatives could be easily functionalized via this method (Scheme 3). Owing to the importance of chiral 3,3-disubstituted oxindoles in natural products, we decided to explore an enantioselective process for the above reaction via asymmetric kinetic resolution. In this way, not only could chiral 3,3-disubstituted oxindoles be furnished, but unsymmetrical disulfides could also be obtained in one step. First, many chiral Brønsted bases were carefully investigated,[10] however, no high ee values were obtained (Table 1). Recently, Zhao and coworkers found that the cooperation of chiral phosphines and methyl acrylate provided an excellent method for asymmetric Mannich-type reactions.[11] Inspired by this, the dual-reagent catalytic system was then tested for the reaction. The urea moiety of these catalysts seemed better than thiourea, and the urea catalyst **E** bearing a 4-nitrophenyl group turned out to be the optimum one for the reaction. Notably, the chiral skeleton

Journal Name COMMUNICATION

derived from L-phenyl-alanine was found to be crucial for improving the enantioselectivity of this reaction after several catalysts were screened. Via the optimization of these catalysts, chiral phosphine **E** showed to be the best choice with 86% ee and 44% yield.

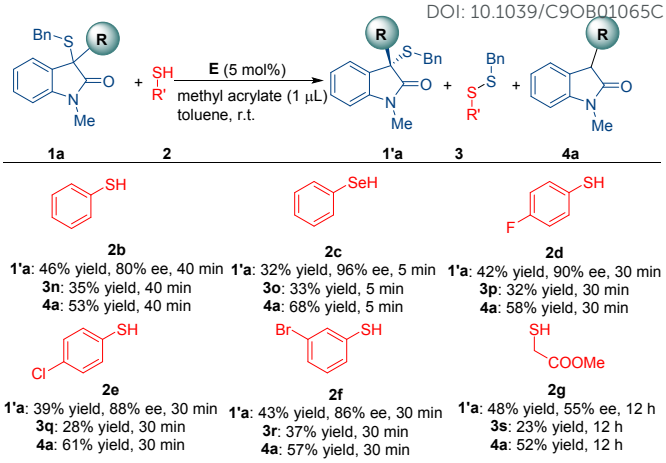
With the optimized conditions in hand, the scope of the enantioselective method for the generation of chiral 3,3-disubstituted oxindoles and disulfides was then carefully explored (Table 2). The substituents (5-Me, 5-Br, 6-Br) on the benzene ring of the isatin skeleton were first examined, and all gave excellent results with excellent enantioselectives in a short time. In addition, the absolute configuration of **1'j** was determined by X-ray crystallographic analysis (CCDC 1906989).[12] Moreover, different substituents on the "S" atom, including benzyl thiols, allyl thiol, cysteine, glucoside thiol, were all well tolerated in the reactions (up to >99% ee) (Table 3). Afterwards, many substituted nucleophiles (aryl-thiols) were then investigated, and were also found to be well tolerated with high ee values. Notably, benzeneselenol was also examined in this system, which gave the product **1'a** with 96% ee. Meanwhile, the alkyl-thiol **2g** could also react with **1a** furnishing the product **1'a** with moderate enantioselectivity.

Table 2. Scope of the 3-alkylthio-3-aryl-oxindoles **1**.[a]



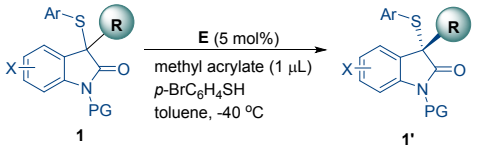
[a]All the reactions were carried out with **1** (0.1 mmol) with **2a** (0.2 mmol) in the presence of **E** (5 mol%) and methyl acrylate (1 μL) at r.t.; Yields of isolated products are given, and the ee value was determined by HPLC analysis; Supplementary crystallographic data for **1j** can be found in CCDC 1906989.

Table 3. Scope of thiols **2** in the asymmetric kinetic resolution.[a]



[a]All the reactions were carried out with **1a** (0.1 mmol) with **2** (0.2 mmol) in the presence of **E** (5 mol%) and methyl acrylate (1 μL) at r.t.; Yields of isolated products are given, and the ee value was determined by HPLC analysis.

Table 4. Scope of the 3-arylthio-3-aryl-oxindoles **1**.[a]



Entry	Ar	X	PG	Time	1'	(yield, ee)[b]
1	4-BrC_6H_4	5-Br	Me	1.3 h	**1'k**	34%, 94%
2	4-BrC_6H_4	5-I	Me	1.3 h	**1'l**	38%, 94%
3	4-BrC_6H_4	H	PMB	12 h	**1'm**	39%, 94%
4	4-FC_6H_4	H	Me	11.5 h	**1'n**	42%, 90%
5	4-BrC_6H_4	H	Me	12 h	**1'o**	40%, 92%
6	4-MeC_6H_4	H	Me	12 h	**1'p**	34%, 95%
7	4-EtC_6H_4	H	Me	18 h	**1'q**	42%, 86%
8	3-BrC_6H_4	H	Me	12 h	**1'r**	30%, 92%
9	2-MeC_6H_4	H	Me	12 h	**1's**	30%, 90%

[a]All the reactions were carried out with **1** (0.1 mmol) with **2a** (0.2 mmol) in the presence of **E** (5 mol%) and methyl acrylate (1 μL) at –40 °C. [b]Yields of isolated products are given, and the ee value was determined by HPLC analysis.

To further expand the generality of this reaction, 3-arylthio-3-aryl-oxindoles were then investigated under the dual-reagent catalytic system (Table 4). In virtue of their instability under basic conditions, the reactions were carried out at -40 °C. Then, a range of substituted 3-arylthio-3-aryl-oxindoles **1** was screened, and all the reactions performed well and gave the desired products with excellent enantioselectivities.

In summary, we developed an enantioselective method for preparing unsymmetrical disulfides and chiral 3,3-disubstituted oxindoles in one step. Many substituted thiols and 3,3-disubstituted oxindoles were well tolerated, and produced high yields and enantioselectivities under mild conditions, which enriched the disulfide bond chemistry and open new avenues

to the synthesis of unsymmetrical disulfides and chiral 3,3-disubstituted oxindoles.

Financial support from the National Natural Science Foundation of China (21535004, 91753111, 21874086, 21602125, and 21390411), the Key Research and Development Program of Shandong Province (2018YFJH0502), the Natural Science Foundation of Shandong Province (ZR2016BQ38), and the China Postdoctoral Science Foundation (40411585) is gratefully acknowledged.

Conflicts of interest

The authors declare no competing financial conflicts.

Notes and references

1 For selected reviews, see: (a) J. M. Chalker, G. J. L. Bernardes and B. G. Davis, *Acc. Chem. Res.*, 2011, **44**, 730; (b) C.-S. Jiang, W. E. G. Müller, H. C. Schröder and Y.-W. Guo, *Chem. Rev.*, 2012, **112**, 2179; (c) M. S. T. Amatov and U. Jahn, *Angew. Chem. Int. Ed.*, 2014, **53**, 3312; (d) O. Boutureira and G. J. L. Bernardes, *Chem. Rev.*, 2015, **115**, 2174; (e) M. Feng, B. Tang, S. Liang and X. Jiang, *Curr. Top. Med. Chem.*, 2016, **16**, 1200; (f) D. Fass and C. Thorpe, *Chem. Rev.*, 2018, **118**, 1160.

2 (a) M. H. Lee, Z. Yang, C. W. Lim, Y. H. Lee, S. Dongbang, C. Kang and J. S. Kim, *Chem. Rev.*, 2013, **113**, 5071; (b) M. H. Lee, J. L. Sessler and J. S. Kim, *Acc. Chem. Res.*, 2015, **48**, 2935; (c) X. Du, F. Kleitz, X. Li, H. Huang, X. Zhang and S.-Z. Qiao, *Adv. Funct. Mater.*, 2018, **28**, 1707325; (d) P. Zhang, J. Wu, F. Xiao, D. Zhao and Y. Luan, *Med. Res. Rev.*, 2018, **38**, 1485.

3 For selected reviews, see: (a) M. Musiejuka and D. Witt, *Org. Prep. Proced. Int.*, 2015, **47**, 95; (b) M. Wang and X. Jiang, *Top Curr. Chem.*, 2018, **376**, 14.

4 (a) M. Arisawa and M. Yamaguchi, *J. Am. Chem. Soc.*, 2003, **125**, 6624; (b) M. Bao and M. Shimizu, *Tetrahedron*, 2003, **59**, 9655; (c) R. Hunter, M. Caira and N. Stellenboom, *J. Org. Chem.*, 2006, **71**, 8268; (d) S. Antoniow and D. Witt, *Synthesis*, 2007, **22**, 363; (e) K. J. Vandavasi, W. P. Hu, C. Y. Chen and J. J. Wang, *Tetrahedron*, 2011, **67**, 8895; (f) M. Oba, K. Tanaka, K. Nishiyama, W. Ando, *J. Org.* Chem. 2011, **76**, 4173; (g) A. Corna, T. Rodenas, M. J. Sabater, *Chem. Sci.* 2012, **3**, 398; (h) N. Taniguchi, *Tetrahedron*, 2017, **73**, 2030; (i) X. Xiao, J. Xue and X. Jiang, *Nat. Commun.*, 2018, **9**, 2191; (j) D. H. Dethe, A. Srivastava, B. D. Dherange, B. V. Kumar, *Adv. Synth. Catal.*, 2018, **360**, 3020.

5 K. Tanaka, X. Chen and F. Yoneda, *Tetrahedron*, 1988, **44**, 3241.

6 (a) H. Wang, K. Wang, Y. Man, X. Gao, L. Yang, Y. Ren, N. Li, B. Tang, G. Zhao, *Adv. Synth. Catal.* 2017, **359**, 3934; (b) H. Wang, K. Wang, Y. Xiang, H. Jiang, X. Wan, N. Li, B. Tang, *Adv. Synth. Catal.* 2018, **360**, 2352.

7 (a) L. A. McAllister, R. A. McCormick, S. Brand and D. J. Procter, *Angew. Chem. Int. Ed.*, 2005, **44**, 452; (b) H. Chen and D. Shi, *Tetrahedron*, 2011, **67**, 5686; (c) Y. Cai, J. Li, W. Chen, M. Xie, X. Liu, L. Lin and X. Feng, *Org. Lett.*, 2012, **14**, 2726; (d) Z. Han, W. Chen, S. Dong, C. Yang, H. Liu, Y. Pan, L. Yan and Z. Jiang, *Org. Lett.*, 2012, **14**, 4670; (e) X. Li, C. Liu, X.-S. Xue and J.-P. Cheng, *Org. Lett.*, 2012, **14**, 4374; (f) J. Zuo, Z.-J. Wu, J.-Q. Zhao, M.-Q. Zhou, X.-Y. Xu, X.-M. Zhang and W.-C. Yuan, *J. Org. Chem.*, 2015, **80**, 634.

8 (a) A. Parra and M. Tortosa, *ChemCatChem*, 2015, **7**, 1524; (b) P. Chauhan, U. Kaya and D. Enders, *Adv. Synth. Catal.*, 2017, **359**, 888; (c) W. Li, X. Xu, P. Zhang and P. Li, *Chem. Asian J.*, 2018, **13**, 2350.

9 (a) W.-D. Chu, L.-F. Zhang, X. Bao, X.-H. Zhao, C. Zeng, J.-Y. Du, G.-B. Zhang, F.-X. Wang, X.-Y. Ma and C.-A. Fan, *Angew. Chem. Int. Ed.*, 2013, **52**, 9229; (b) Z. Wang, Y. F. Wong and J. Sun, Angew. *Chem. Int. Ed.*, 2015, **54**, 13711; (c) K. Zhao, Y. Zhi, T. Shu, A. Valkonen, K. Rissanen and D. Enders, *Angew. Chem. Int. Ed.*, 2016, **55**, 12104; (d) M. Chen and J. Sun, *Angew. Chem. Int. Ed.*, 2017, **56**, 4583.

10 (a) C. Palomo, M. Oiarbide, R. López, *Chem. Soc. Rev.* 2009, **38**, 632; (b) X. Fang, C.-J. Wang, *Chem. Commun.* 2015, **51**, 1185; (c) F. Giacalone, M. Gruttadauria, P. Agrigento, R. Noto, *Chem. Soc. Rev.* 2012, **41**, 2406.

11 (a) H.-Y. Wang, K. Zhang, C.-W. Zheng, Z. Chai, D.-D. Cao, J.-X. Zhang and G. Zhao, *Angew. Chem. Int. Ed.*, 2015, **54**, 1775; (b) Y.-P. Lou, C.-W. Zheng, R.-M. Pan, Q.-W. Jin and G. Zhao, *Org. Lett.*, 2015, **17**, 688; (c) H.-Y. Wang, C.-W. Zheng, Z. Chai, J.-X. Zhang and G. Zhao, *Nat. Commun.*, 2016, **7**, 12720.

12 CCDC 1906989 (**1'j**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.