Access to all-carbon spirocycles through a carbene and thiourea cocatalytic desymmetrization cascade reaction

Zhuo, Shitian; Zhu, Tingshun; Zhou, Liejin; Mou, Chengli; Chai, Huifang; Lu, Yunpeng; Pan, Lutai; Jin, Zhichao; Chi, Robin Yonggui

2018

Zhuo, S., Zhu, T., Zhou, L., Mou, C., Chai, H., Lu, Y., ... Chi, R. Y. (2019). Access to all-carbon spirocycles through a carbene and thiourea cocatalytic desymmetrization cascade reaction. *Angewandte Chemie International Edition*, 58(6), 1784-1788.
doi:10.1002/ange.201810638

<https://hdl.handle.net/10356/137748>

<https://doi.org/10.1002/anie.201810638>

This is the peer reviewed version of the following article: Zhuo, S., Zhu, T., Zhou, L., Mou, C., Chai, H., Lu, Y., ... Chi, R. Y. (2019). Access to all-carbon spirocycles through a carbene and thiourea cocatalytic desymmetrization cascade reaction. *Angewandte Chemie International Edition*, 58(6), 1784-1788. which has been published in final form at <https://doi.org/10.1002/anie.201810638>. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Use of Self-Archived Versions.

Access to All-Carbon Spirocycles via Carbene and Thiourea Co-Catalytic Desymmetrization and Cascade Reaction

Shitian Zhuo, Tingshun Zhu, Leijin Zhou, Chengli Mou, Huifang Chai, Lutai Pan,* Zhichao Jin, Yunpeng Lu, and Yonggui Robin Chi*

Abstract: A new catalytic approach for asymmetric quick access to spirocycles is disclosed. The reaction involves a carbene and thiourea co-catalyzed desymmetrization process with simultaneous installation of a spirocyclic core. The use of a thiourea co-catalyst is critical to turn on this reaction, as no product was formed without the presence of the thioureas. Our study constitutes the first success in carbene-catalyzed enantioselective synthesis of all-carbon spirocycles. Products from our reactions can be readily transformed to sophisticated multi-cyclic molecules and chiral ligands.

Spirocyclic skeletons enable special spatial arrangements of functional groups that pose specific properties for organic molecules.^[1] For example, spiro[4.4]nonane constitutes a privileged scaffold in chiral ligands for highly efficient and stereoselective metal catalysis (Figure 1a).^[2] This scaffold is also found as a core component in complex natural products^[3] such as Vannusals A and B,^[4] secondary metabolites isolated from the marine ciliate *Euplotes Vannus*. To date, it remains challenging to prepare such all-carbon spirocyclic structures, especially in enantiomerically enriched forms.^[5] Most of the available methods require multiple steps to first prepare the molecules in racemic forms, followed by the use of chiral resolution techniques to obtain the desired products in optically pure forms.^[6]

Here we disclose a single-step asymmetric catalytic method for quick access to such all-carbon spirocycles bearing up to two spirocyclic centers (Figure 1b). The reaction cascade involves an intermolecular Stetter reaction^[7] catalyzed by NHC catalysts,^[8] followed by an intramolecular aldol reaction. The Stetter reaction is also a desymmetrization process,^[9] with which a remote chiral carbon center is controlled by the chiral catalyst. The subsequent aldol reaction step sets up a newly formed spirocyclic carbon center with high enantioselectivity. It is worth to note that both an *N*-heterocyclic carbene (abbreviated as NHC or carbene) catalyst and a thiourea co-catalyst are

essential in this catalytic reaction: no product is formed without the presence of the thiourea co-catalyst. The spirocycles prepared through this approach bear multiple functional groups that are amenable for further transformations. We expect our method to provide shortcut routes to sophisticated chiral functional molecules with spirocyclic structures.

Figure 1. Chiral Spiro[4.4]nonanes and Our Synthetic Design.

Key results of the condition optimization are summarized in Table 1. Substrate **1a** was slowly added to the reaction mixture to react with cyclic enone **2a** at room temperature with spiro bicyclic **3a** afforded as the final product (Table 1). After extensive optimizations, an acceptable result could be obtained by using triazolium salt **A**^[10a] as the NHC precatalyst, thiourea **E** as the co-catalyst, DIPEA as the base, and a mixture of CHCl₃/BuOH (2:1, v/v) as the solvent (entry 1). The product **3a** could not be afforded without either the NHC catalyst (entry 2) or the thiourea co-catalyst (entry 3). Replacement of the *N*-mesityl substituent on the NHC pre-catalyst **A** with an *N*-pentafluorophenyl (**B**)^[7d] or *N*-phenyl (**C**)^[10b] substituent led to no formation of the desired product (entry 4). Switching the NHC pre-catalyst **A** to **D** with a NO₂ group installed on the benzene ring of the indane motif^[10c-d] led to drops on both the enantio- and diastereoselectivities in this transformation (entry 5). The thiourea co-catalyst likely activates the 1,3-cyclopentenedione substrate (**2a**) via hydrogen bonding.^[11] Additional screening of

[*] S. Zhuo, T. Zhu, L. Zhou, Y. Lu, Prof. Dr. Y. R. Chi
Division of Chemistry & Biological Chemistry, School of Physical & Mathematical Sciences, Nanyang Technological University, Singapore 637371 (Singapore)
E-mail: robinchi@ntu.edu.sg
Z. Jin, Prof. Dr. Y. R. Chi
Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Huaxi District, Guiyang 550025 (China)
C. Mou, H. Chai, L. Pan
E-mail: ltpan@sina.cn
School of Pharmacy, Guiyang College of Traditional Chinese Medicine, Guiyang 550025 (China)

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under:
<https://doi.org/10.1002/anie.xxxxxxxx>

chiral thiourea co-catalysts (**F-H**, entries 6-8) did not lead to obvious improvements on the reaction outcomes (see Supporting Information for more details). The screening of either the bases or the solvents used in this catalytic system resulted in no improvements of the product yields, although the stereoselectivities were not affected (entries 9-12; see Supporting Information for details). The significant distinctions between the reaction yields with various solvents indicated that hydrogen bonding had played important roles in this transformation.^[11d] As a technical note, slow addition of the dialdehyde substrate **1a** can attenuate the side reaction of the homocoupling of the aldehydes^[12] and favor the formation of the desired product. In contrast, lower yield was observed with **1a** added in one-portion (29%, entry 13).

Table 1. Condition Optimization^[a]

entry	variation from standard condition	yield [%]	d.r.	e.r.
1	standard condition ^[a]	63	9:1	96:4
2	no NHC	0	-	-
3	no thiourea	0	-	-
4	NHC: B or C	<5	-	-
5	NHC: D	60	3:1	94:6
6	thiourea: F	44	10:1	96:4
7	thiourea: G	53	9:1	96:4
8	thiourea: H	50	9:1	96:4
9	other bases (Cs ₂ CO ₃ , K ₃ PO ₄ , tBuOK, DBU)	0–20	9:1	95:5–96:4
10	other solvents (THF, acetone, Et ₂ O, DMF)	0–9	9:1	96:4
11	tBuOH as solvent	32	9:1	96:4
12	CHCl ₃ as solvent	45	9:1	96:4
13	without slow addition of 1a	29	9:1	96:4

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.1 mmol), NHC (0.02 mmol), base (0.02 mmol), thiourea (0.02 mmol), solvent (1 mL), rt, 12 h. Yields are isolated yields based on **2a**; d.r. was determined by ¹H NMR; e.r. was determined via chiral phase HPLC analysis.

With an acceptable reaction condition in hand, the generality of the reaction was then evaluated (Scheme 1). Phthalaldehyde **1a** was selected as a model substrate to study the scope of the 1,3-cyclopentenedione substrates **2**. When R¹ was fixed with a methyl group, R² could be benzyl groups with various substitution patterns (**3a-j**). The benzene rings of the benzyl group could also be replaced with either a naphthene or a thiophene group, with little erosion of the product diastereoselectivities (**3k-l**). Increasing the steric hindrance of the benzyl group with a benzhydryl group resulted in a slight enhancement of the product enantioselectivity (**3m**). Switching the benzyl group on substrate **2a** to either a phenyl or a

Scheme 1. Substrate Scope^[a]

[a] Reaction conditions as in Table 1, entry 1, unless otherwise noted. The absolute configuration of the major enantiomer was assigned based on the X-ray structure of **3c**. [b] Used **D** instead of **A**.

naphthene group led to drops on both the enantio- and diastereoselectivities of the final products (**3n-o**). Spirocyclic 1,3-cyclopentenedione substrates could also give the desired products bearing two all-carbon spirocycles in moderate yields and enantioselectivities (**3p-q**). The benzene ring on substrate **2a** could also be replaced with a benzaceto group or an alkyne group, with corresponding products afforded in moderate yields and stereoselectivities (**3s-t**). The R¹ group could also be switched to an ethyl group (**3r**), although both of the dr and er values of the product were decreased. It is worth noting that 2,5-pyrroledione bearing a prochiral axial could also be used in this transformation, with the axial chiral product afforded in excellent diastereo- and enantioselectivities (**3u**). Replacing the methyl group on the dione substrate **2** with either a F or Cl group led to no product formation, since these substrates decomposed under the current catalytic reaction condition (see Supporting Information for details). The aromatic 1,2-dialdehydes **1** bearing

various substitution patterns also worked well in this desymmetrization process, with the spirocyclic products afforded in moderate yields with good to excellent stereoselectivities (**3v-x**).

The postulated reaction pathway is illustrated in Scheme 2. The reaction starts with an NHC-catalyzed Stetter reaction of one aldehyde moiety with the electron-deficient alkene. A related mechanistic study from Glorius' group^[文獻] on the Stetter reaction between aldehydes and alkenes suggested that this Stetter-typed process might be a concerted process and the intermediate **II** could be formed directly or through a fast protonation step from intermediate **I**. This suggests that the 5-membered ring product observed in our reaction shall be favored. This observation is consistent with our experimental results that the possible 6-membered ring adduct is not observed. DFT calculation (see Supporting Information for details) also suggests that intermediate **I**, the key precursor of the 6-membered ring adduct, is much less stable than intermediate **II** that leads to the 5-membered ring product.

Scheme 2. Postulated Pathway for the Selective 5 Membered Ring Formation

Scheme 3. Mechanistic Studies

a. quenching test with competitive hydrogen-bonding acceptors

b. ¹HNMR shift test for H-bonding

To better understand the hydrogen-bonding activation effect, several control tests were carried out. As shown in Scheme 3a, the reactions could be terminated on the addition of several competitive hydrogen-bonding acceptors such as DMSO or HMPA. A mixture of thiourea/diketone showed obvious changes in chemical shifts (Scheme 3b). These results indicate that the thiourea co-catalysts have activated the diketone substrates via hydrogen-bonding interactions in our cascade transformation.

Scheme 4. Synthetic Transformations

The reaction products were amenable for further transformations through simple protocols (Scheme 4). For example, the hydroxyl group of **3a** could be transformed to azido compound **5** through an S_N2 substitution with $TMSN_3$ in 62% yield and 96:4 *e.r.* value. Product **3a** could also be stereoselectively reduced by DIBAL-H / $t-BuLi$ to afford **6** in moderate yield without erosion of the optical purity. Product **3j** could be stereoselectively reduced to give tetrahydrospiro cyclopenta[b]quinoline **7** in good yield with little erosion of the optical purity. The spiro cyclopenta[b]pyrrole **8** could be efficiently afforded from chiral product **3s** through simple protocols with retention of the *er* value. Notably, the chiral spiro

heterocyclic molecules afforded here (**5-8**) have great values in various biological and pharmaceutical investigations^[3] and had been difficult to be synthesized through traditional methods. Moreover, the product **3** could also transform to chiral ligands with interesting applications in transition metal catalysis. For example, phosphite ligand **9** derived from **3a** and BINOL showed good activity and moderate enantioselectivity in rhodium catalyzed 1,2-addition of arylboronic acid to aldehyde. It is worth to note that the configuration of the product was dominated by the chiral **3a** moiety of the BINOL-**3a** derived phosphite ligand (Scheme 4b)

In summary, we have developed a new approach for direct asymmetric access to spirocycles bearing multiple chiral centers. Our method involves a desymmetrization process with reaction stereo-selectivity controlled by a chiral NHC catalyst. Thiourea co-catalyst was essential in this reaction. Our study represents the first success in carbene-catalyzed formation of all-carbon spirocyclic skeletons. Products afforded in this transformation are rich in functionalities and are amenable for further transformations. Sophisticated multi-cyclic molecules and chiral phosphite ligands could be prepared from our products. We expect our cooperative catalytic process to encourage re-evaluations of many possible reactions that do not occur with only carbene catalysts used. Our study shall also provide useful tools in building complex functional molecules bearing spirocyclic cores.

Acknowledgements

We acknowledge financial support by the Singapore National Research Foundation (NRF-NRFI2016-06), the Ministry of Education of Singapore (MOE2013-T2-2-003; MOE2016-T2-1-032; RG108/16), A*STAR Individual Research Grant (A1783c0008), Nanyang Research Award Grant, and Nanyang Technological University; Guizhou Province First-Class Disciplines Project (Yiliu Xueke Jianshe Xiangmu)-GNYL(2017)008, Guiyang College of Traditional Chinese Medicine, China; National Natural Science Foundation of China (No. 21772029, 21472028), National Key Technologies R&D Program (No. 2014BAD23B01), "Thousand Talent Plan", The 10 Talent Plan (Shicengci) of Guizhou Province, and Guizhou University.

Keywords: all-carbon quaternary chiral center • remote chirality control • metal-free dual catalysis • desymmetrization • spirocyclic • *N*-heterocyclic carbene

- [1] A. Baeyer, *Ber. Dtsch. Chem. Ges.* **1900**, 33, 3771.
- [2] For selected examples, see: a) X. M. Wang, Z. B. Han, Z. Wang, K. L. Ding, *Angew. Chem.* **2012**, 124, 960; *Angew. Chem., Int. Ed.* **2012**, 51, 936; b) Z. Freixa, M. S. Beentjes, G. D. Batema, C. B. Dieleman, G. P. F. van Strijdonck, J. N. H. Reek, P. C. J. Kamer, J. Fraanje, K. Goubitz, P. W. N. M. van Leeuwen, *Angew. Chem.* **2003**, 115, 1322; *Angew. Chem., Int. Ed.* **2003**, 42, 1284; c) K. Ding, Z. Han, Z. Wang, *Chem.-Asian J.* **2009**, 4, 32; d) Q. L. Zhou, J. H. Xie, *Top. Organomet. Chem.* **2011**, 36, 1; e) Z. Zheng, Y. Cao, Q. Chong, Z. Han, J. Ding, C. Luo, Z.

- Wang, D. Zhu, Q. L. Zhou, K. Ding, *J. Am. Chem. Soc.* **2018**, 140, 10374; f) V. B. Birman, A. L. Rheingold, K. C. Lam, *Tetrahedron: Asymmetry* **1999**, 10, 125; g) A. K. Franz, N. V. Hanhan, N. R. Ball-Jones, *ACS Catal.* **2013**, 3, 540; h) R. Rios, *Chem. Soc. Rev.* **2012**, 41, 1060; i) J. H. Xie, Q. L. Zhou, *Acc. Chem. Res.* **2008**, 41, 581; j) K. Ding, Z. Han, Z. Wang, *Chem. Asian J.* **2009**, 4, 32; k) G. B. Bajracharya, M. A. Arai, P. S. Koranne, T. Suzuki, S. Takizawa, H. Sasai, *Bull. Chem. Soc. Jpn.* **2009**, 82, 285; l) S. F. Zhu, Q. L. Zhou, *Acc. Chem. Res.* **2012**, 45, 1365; m) A. S. C. Chan, W. Hu, C. C. Pai, C. P. Lau, Y. Jiang, A. Mi, M. Yan, J. Sun, R. Lou, J. Deng, *J. Am. Chem. Soc.* **1997**, 119, 9570; n) M. A. Arai, T. Arai, H. Sasai, *Org. Lett.* **1999**, 1, 1795; o) Y. Fu, J. H. Xie, A. G. Hu, H. Zhou, L. X. Wang, Q. L. Zhou, *Chem. Commun.* **2002**, 480; p) S. L. Wu, W. C. Zhang, Z. G. Zhang, X. M. Zhang, *Org. Lett.* **2004**, 6, 3565; q) K. Shibatomi, T. Muto, Y. Sumikawa, A. Narayama, S. Iwasa, *Synlett* **2009**, 2009, 241; r) Z. Han, Z. Wang, X. Zhang, K. Ding, *Angew. Chem.* **2009**, 121, 5449; *Angew. Chem., Int. Ed.* **2009**, 48, 5345; s) J. Li, G. Chen, Z. Wang, R. Zhang, X. M. Zhang, K. Ding, *Chem. Sci.* **2011**, 2, 1141. 时间顺序从早到晚
- [3] a) R. F. Keeler, *Phytochemistry* **1969**, 8, 223; b) M. Yamazaki, E. Okuyama, M. Kobayashi, H. Inoue, *Tetrahedron Lett.* **1981**, 22, 135; c) E. A. Jares-Erijman, A. L. Ingram, J. R. Carney, K. L. Rinehart, R. Sakai, *J. Org. Chem.* **1993**, 58, 4805; d) J. Kennedy, I. A. Selby, R. H. Thomson, *Phytochemistry* **1988**, 27, 1761.
- [4] a) K. C. Nicolaou, H. Zhang, A. Ortiz, *Angew. Chem.* **2009**, 121, 5752; *Angew. Chem., Int. Ed.* **2009**, 48, 5642; b) K. C. Nicolaou, A. Ortiz, H. Zhang, *Angew. Chem.* **2009**, 121, 5758; *Angew. Chem., Int. Ed.* **2009**, 48, 5648; c) K. C. Nicolaou, A. Ortiz, H. Zhang, P. Dagneau, A. Lanver, M. P. Jennings, S. Arseniyadis, R. Faraoni, D. E. Lizos, *J. Am. Chem. Soc.* **2010**, 132, 7138; d) K. C. Nicolaou, A. Ortiz, H. Zhang, G. Guella, *J. Am. Chem. Soc.* **2010**, 132, 7153; e) G. Guella, F. Dini, F. Pietra, *Angew. Chem.* **1999**, 111, 1217; *Angew. Chem., Int. Ed.* **1999**, 38, 1134.
- [5] R. Rios, *Chem. Soc. Rev.* **2012**, 41, 1060.
- [6] a) V. B. Birman, A. L. Rheingold, K.-C. Lam, *Tetrahedron: Asymmetry* **1999**, 10, 125; b) K. Ding, Y. Wang, H. Yun, J. Liu, Y. Wu, M. Terada, Y. Okubo, K. Mikami, *Chem. Eur. J.* **1999**, 5, 1734; c) K. Tanaka, T. Okada, F. Toda, *Angew. Chem.* **1993**, 105, 1266; *Angew. Chem. Int. Ed.* **1993**, 32, 1147; d) J.-H. Zhang, J. Liao, X. Cui, K.-B. Yu, J. Zhu, J.-G. Deng, S.-F. Zhu, L.-X. Wang, Q.-L. Zhou, L. W. Chung, T. Ye, *Tetrahedron: Asymmetry* **2002**, 13, 1363; e) Z. Li, X. Liang, F. Wu, B. Wan, *Tetrahedron: Asymmetry* **2004**, 15, 665; f) Z. Li, X. Liang, B. Wan, F. Wu, *Synthesis* **2004**, 2805.
- [7] For reviews and selected examples of Stetter reactions, see: a) H. Stetter, H. Kuhlmann, *Org. React.* **1991**, 40, 407; b) E. Ottow, K. Schollkopf, B.-G. Schulz, Eds, D. Enders, *In Stereoselective Synthesis; Springer: Heidelberg*, **1993**, p 63; c) J. R. de Alaniz, T. Rovis, *Synlett* **2009**, 1189; d) M. S. Kerr, T. Rovis, *J. Am. Chem. Soc.* **2004**, 126, 8876; e) A. E. Mattson, A. R. Bharadwaj, K. A. Scheidt, *J. Am. Chem. Soc.* **2004**, 126, 2314; f) J. Read de Alaniz, T. Rovis, *J. Am. Chem. Soc.* **2005**, 127, 6284; g) M. C. Myers, A. R. Bharadwaj, B. C. Milgram, K. A. Scheidt, *J. Am. Chem. Soc.* **2005**, 127, 14675; h) S. M. Mennen, J. T. Blank, M. B. Tran-Dube, J. E. Imbriglio, S. Miller, *J. Chem. Commun.* **2005**, 195; i) Q. Liu, T. Rovis, *J. Am. Chem. Soc.* **2006**, 128, 2552; j) Q. Liu, S. P. Perreault, T. Rovis, *J. Am. Chem. Soc.* **2008**, 130, 14066; k) K. Hirano, A. T. Biju, I. Piel, F. Glorius, *J. Am. Chem. Soc.* **2009**, 131, 14190; l) D. A. DiRocco, K. M. Oberg, D. M. Dalton, T. Rovis, *J. Am. Chem. Soc.* **2009**, 131, 10872; m) A. T. Biju, N. E. Wurz, F. Glorius, *J. Am. Chem. Soc.* **2010**, 132, 5970; n) A. T. Biju, F. Glorius, *Angew. Chem.* **2010**, 122, 9955; *Angew. Chem., Int. Ed.* **2010**, 49, 9761; o) C. M. Filloux, S. P. Lathrop, T. Rovis, *Proc. Natl. Acad. Sci. U.S.A.* **2010**, 107, 20666; p) DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2011**, 133, 10402; q) X. Fang, X. Chen, H. Lv, Y. R. Chi, *Angew. Chem.* **2011**, 123, 11986; *Angew. Chem., Int. Ed.* **2011**, 50, 11782; r) D. A. DiRocco, E. L. Noey, K. N. Houk, T. Rovis, *Angew. Chem.* **2012**, 124, 2441; *Angew. Chem., Int. Ed.* **2012**, 51, 2391; s) M.-Q. Jia, S.-L. You, *Chem. Commun.* **2012**, 48, 6363; t) A. Bhunia, S. R. Yetra, S. S. Bhojgude, A.

- T. Biju, *Org. Lett.* **2012**, *14*, 2830; u) M. Schedler, D.-S. Wang, F. Glorius, *Angew. Chem.* **2013**, *125*, 2645; *Angew. Chem., Int. Ed.* **2013**, *52*, 2585; v) J. Zhang, C. Xing, B. Tiwari, Y. R. Chi, *J. Am. Chem. Soc.* **2013**, *135*, 8113.
- [8] Selected reviews on NHC catalysis: a) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606; b) N. Marion, S. Díez-González, S. P. Nolan, *Angew. Chem.* **2007**, *119*, 3046; *Angew. Chem. Int. Ed.* **2007**, *46*, 2988; c) V. Nair, S. Vellalath, B. P. Babu, *Chem. Soc. Rev.* **2008**, *37*, 2691; d) A. T. Biju, N. Kuhl, F. Glorius, *Acc. Chem. Res.* **2011**, *44*, 1182; e) J. Douglas, G. Churchill, A. D. Smith, *Synthesis* **2012**, *44*, 2295; f) J. Izquierdo, G. E. Hutson, D. T. Cohen, K. A. Scheidt, *Angew. Chem.* **2012**, *124*, 11854; *Angew. Chem. Int. Ed.* **2012**, *51*, 11686; g) S. J. Ryan, L. Candish, D. W. Lupton, *Chem. Soc. Rev.* **2013**, *42*, 4906; h) M. N. Hopkinson, C. Richter, M. Schedler, F. Glorius, *Nature* **2014**, *510*, 485; i) D. M. Flanagan, F. Romanov-Michailidis, N. A. White, T. Rovis, *Chem. Rev.* **2015**, *115*, 9307; j) M. H. Wang, K. A. Scheidt, *Angew. Chem.* **2016**, *128*, 15134; *Angew. Chem. Int. Ed.* **2016**, *5*, 14912.
- [9] Selected examples of NHC-catalyzed desymmetrization reactions: a) N. T. Reynolds, J. Read de Alaniz, T. Rovis, *J. Am. Chem. Soc.* **2004**, *126*, 9518; b) Q. Liu, T. Rovis, *J. Am. Chem. Soc.* **2006**, *128*, 2552; c) M. Wadamoto, E. M. Phillips, T. E. Reynolds, K. A. Scheidt, *J. Am. Chem. Soc.* **2007**, *129*, 10098; d) B. E. Maki, A. Chan, E. M. Phillips, K. A. Scheidt, *Org. Lett.* **2007**, *9*, 371; e) M.-Q. Jia, S.-L. You, *Chem. Commun.* **2012**, *48*, 6363; f) M.-Q. Jia, C. Liu, S.-L. You, *J. Org. Chem.* **2012**, *77*, 10996; g) T. Ema, K. Akihara, R. Obayashi, T. Sakai, *Adv. Synth. Catal.* **2012**, *354*, 3283; h) M.-Q. Jia, S.-L. You, *Synlett* **2013**, *24*, 1201; i) Q. Lin, Y. Li, D. K. Das, G. Zhang, Z. Zhao, S. Yang, X. Fang, *Chem. Commun.* **2016**, *52*, 6459; j) Y. Li, S. Yang, G. Wen, Q. Lin, G. Zhang, L. Qiu, X. Zhang, G. Du, X. Fang, *J. Org. Chem.* **2016**, *81*, 2763; k) Z. Huang, X. Huang, B. Li, C. Mou, S. Yang, B.-A. Song, Y. R. Chi, *J. Am. Chem. Soc.* **2016**, *138*, 24, 7524.
- [10] a) M. He, J. R. Struble, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 8418; b) M. S. Kerr, J. Read de Alaniz, T. Rovis, *J. Am. Chem. Soc.* **2002**, *124*, 10298; c) S. Kuwano, S. Harada, B. Kang, R. Oriez, Y. Yamaoka, K. Takasu, K. Yamada, *J. Am. Chem. Soc.* **2013**, *145*, 11485; d) C. Zhao, F. Li, J. Wang, *Angew. Chem.* **2016**, *128*, 1852; *Angew. Chem. Int. Ed.* **2016**, *55*, 1820.
- [11] a) M. S. Taylor, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 1550; *Angew. Chem. Int. Ed.* **2006**, *45*, 1520; b) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999; c) K. M. Lippert, K. Hof, D. Gerbig, D. Ley, H. Hausmann, S. Guenther, P. R. Schreiner, *Eur. J. Org. Chem.* **2012**, 5919; d) A. Wittkopp, P. R. Schreiner, *Chem. Eur. J.* **2003**, *9*, 407.
- [12] Y. Cheng, J.-H. Peng, Y.-J. Li, X.-Y. Shi, M.-S. Tang, T.-Y. Tan, *J. Org. Chem.* **2011**, *76*, 1844.

All-carbon spirocycles: A new catalytic approach for asymmetric quick access to spirocycles is disclosed. The reaction involves a carbene and thiourea co-catalyzed desymmetrization process with simultaneous installation of a spirocyclic core. Our study constitutes the first success in carbene-catalyzed enantioselective synthesis of all-carbon spirocycles. Products from our reactions can be readily transformed to sophisticated multi-cyclic molecules and chiral ligands.

Shitian Zhuo, Tingshun Zhu, Leijin Zhou, Chengli Mou, Huifang Chai, Lutai Pan, Zhichao Jin, Yunpeng Lu, and Yonggui Robin Chi

Page No. – Page No.

Access to All-Carbon Spirocycles via Carbene and Thiourea Co-Catalytic Desymmetrization and Cascade Reaction