

Organocatalysis

N-Heterocyclic Carbene-Catalyzed Atroposelective Annulation for Access to Thiazine Derivatives with C–N Axial Chirality

Tingting Li[†], Chengli Mou[†], Puying Qi, Xiaolin Peng, Shichun Jiang, Gefei Hao, Wei Xue, Song Yang, Lin Hao, Yonggui Robin Chi, and Zhichao Jin*

Abstract: A catalytic atroposelective cycloaddition reaction between thioureas and ynals is developed. This reaction features the first NHC-catalyzed addition of thioureas to acetylenic acylazolium intermediates to eventually set up C–N axial chirality with excellent optical purities. The obtained axially chiral thiazine derivative products bear multiple functional groups and are feasible for further transformations.

Thiazine is an important heterocyclic structural motif that accounts for bioactivities with significant applications in medicines^[1] and agricultural chemicals^[2] (Figure 1a). For example, cephalosporins such as Cefradine contain thiazine fragments and have found wide uses as human drugs to cure and / or prevent bacterial infections.^[1a,b] Omonasteine is a simple carboxylic acid bearing a hydrothiazine moiety and can be used in the treatment of respiratory diseases. Buprofezin^[2a] is a commercially available and extensively used pesticide for the protection of crops from various insects. Therefore, many thiazine derivatives, either in achiral or enantiomerically enriched forms, have received considerable attentions in synthetic chemistry and relevant fields.^[3] To date, most of the chiral thiazine derivatives are obtained through the introduction of central chirality.^[3d–f,h] On the other hand, it has been well established that molecules with axial chirality show exceptional performance in a broad range of areas such as catalysis^[4] and medicines.^[5]

Here we report an N-heterocyclic carbene (NHC) catalytic approach for atroposelective access to axially chiral thiazine derivatives (Figure 1b). The nitrogen atom of the thiazine moiety is directly installed as part of chiral C–N axis

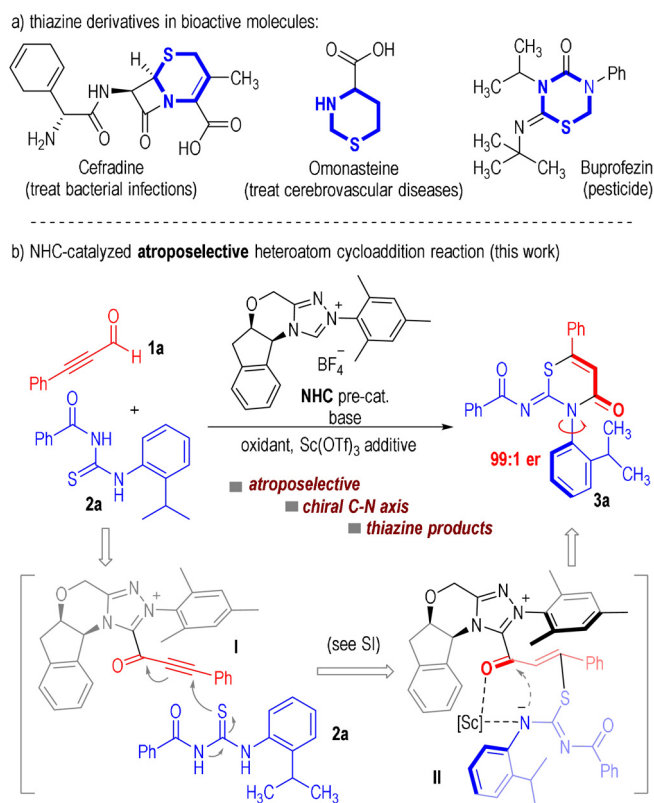


Figure 1. Bioactive thiazine derivatives and NHC-catalyzed atroposelective heteroatom cycloaddition reaction.

via a face-selective process. It is worth noting that the atroposelective synthesis with C–N chiral axes is an important topic in synthetic chemistry.^[6] For instance, Miller,^[6e–g] Gustafson^[6k] and co-workers developed organocatalytic atroposelective bromination reactions for the formation of chiral C–N axes. Jørgensen,^[6a,b] Tan,^[6h] Zhang,^[6j] and Yang^[6l] reported the syntheses of axially chiral N-aryl compounds through organocatalytic atroposelective Friedel–Crafts amination reactions. The N-nucleophilic reactions promoted by chiral Lewis acids or bases have also been used in the preparations of axially chiral compounds containing C–N chiral axes.^[6c,d,i] In the field of NHC catalysis, to the best of our knowledge, reported reactions are mainly used to prepare central chiral molecules.^[7] The rather limited examples of axially chiral products via NHC catalysis are based on forming C–C chiral axes, as disclosed by Zhao, Wang, Zhu and others.^[8] In a larger content, NHC-catalyzed atroposelective annulation reactions involving heteroatom-centered nucleophiles remain undeveloped.

[*] T. Li,^[†] P. Qi, X. Peng, S. Jiang, Prof. Dr. G. Hao, Prof. Dr. W. Xue, Prof. Dr. S. Yang, Prof. Dr. Y. R. Chi, Prof. Dr. Z. Jin
Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University
Guiyang 550025 (China)
E-mail: zcjin@gzu.edu.cn

Dr. C. Mou^[†]
School of Pharmacy, Guizhou University of Traditional Chinese Medicine
Guiyang 550025 (China)

Dr. L. Hao, Prof. Dr. Y. R. Chi
Division of Chemistry & Biological Chemistry, School of Physical & Mathematical Sciences, Nanyang Technological University
Singapore 637371 (Singapore)

[†] These authors contributed equally to this work.

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.202010606>.

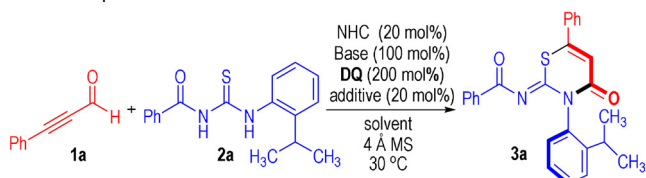
Key steps of our reaction involve NHC-catalyzed addition of a thiourea (**2a**)^[9] to ynal (**1a**)-derived acetylenic acylazolum intermediate (**I**)^[8c,10] to form a new C(sp²)-S bond (intermediate **II**). Subsequent catalyst-controlled face-selective intramolecular lactam formation of **II** gives atropisomeric thiazine derivative **3a** with a 99:1 enantiomeric ratio. Lewis acid (Sc(OTf)₃) additive^[7d,11] was found to facilitate the reaction with an appreciable improvement on the product yield with retention of the optical purity. The axially chiral thiazine derivative products from our reactions are rich in functionalities and are feasible for further transformations.

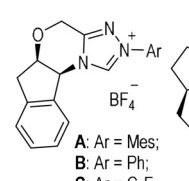
We initially tested the atroposelective annulation reaction between alkynyl aldehyde **1a** and benzoylthiourea **2a** using various NHC catalysts in the presence of the **DQ**^[12] as an oxidant at 30 °C (Table 1, entries 1 to 5). NHC catalysts bearing N-mesityl groups could give the desired products (**3a**) in promising yields with good to excellent enantioselectivities (entries 1, 4, 5).^[13] No target products could be observed when using the NHC catalysts with N-Ph or N-C₆F₅ substituents (entries 2 & 3).^[14] We then used the aminoindanol-derived NHC pre-catalyst **A**^[13a] for additional condition optimizations. Organic or inorganic bases other than DMAP examined

here were not effective for this atroposelective annulation reaction (entry 6). Solvent also had significant impact on the reaction yields (entries 7 to 9). To our delight, the yield of the product **3a** could be dramatically increased when using furan as the solvent (entry 9). Lewis acids have proven to be effective additives for improving the chemo- and stereoselectivities in NHC organocatalytic reactions.^[15] In this scenario, Sc(OTf)₃ could serve as an efficient additive to improve the reaction yield of **3a** without diminishing the product *er* value (entry 10 vs. entry 9). Finally, the product (**3a**) could be obtained in 63% isolated yield and 99:1 *er* when using an excess amount of ynal **1a** in the presence of 5 Å MS and Sc(OTf)₃ as the additives (entry 11).

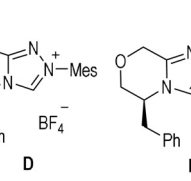
Having established an optimal reaction condition for the atroposelective annulation reaction (Table 1, entry 11), we then examined the substrate scope using various substituted ynals (Scheme 1). Both electron-donating and electron-withdrawing substituents could be installed on each position of the β-benzene rings of the ynal **1**, with the atropisomeric thiazine products afforded in moderate to good yields with excellent optical purities (**3b** to **3i**). The β-benzene ring of the ynal **1a** could be switched to a 1-naphthyl group, with the product **3j**

Table 1: Optimization of reaction conditions.^[a]

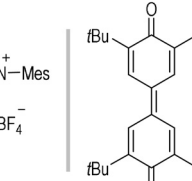




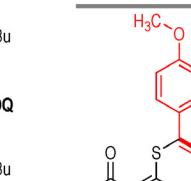
A: Ar = Mes;
B: Ar = Ph;
C: Ar = C₆F₅



D



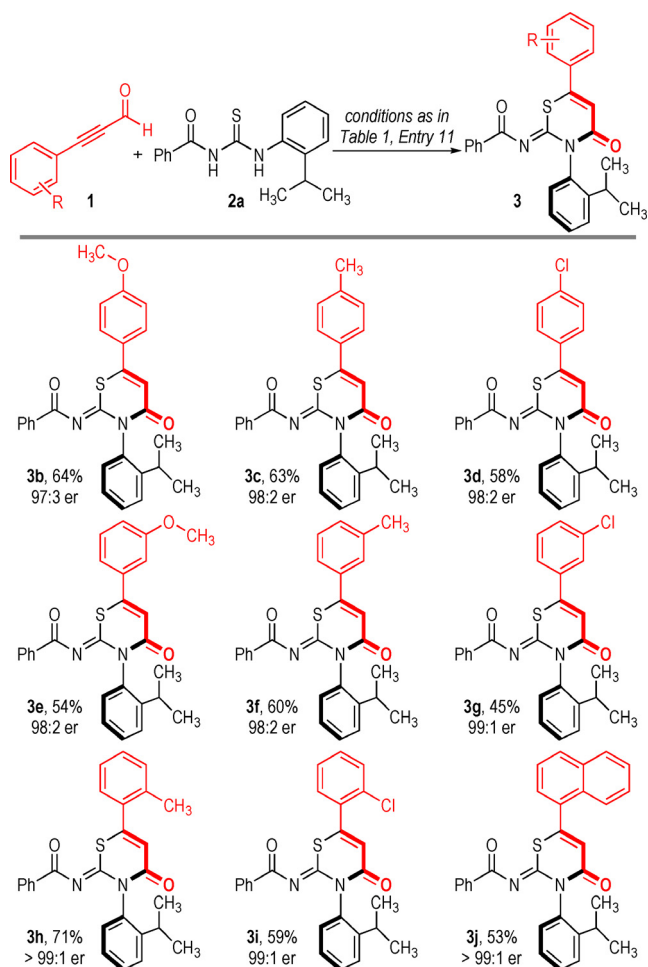
E



DQ

Entry	NHC	Base	Solvent	Additive	Yield [%] ^[b]	Er ^[c]
1	A	DMAP	THF		31	97:3
2	B	DMAP	THF		< 5	
3	C	DMAP	THF		< 5	
4	D	DMAP	THF		26	91:9
5	E	DMAP	THF		20	91:9
6	A	Et ₃ N/ Cs ₂ CO ₃ / DABCO etc.	THF		< 5	
7	A	DMAP	EtOAc		31	96:4
8	A	DMAP	CHCl ₃		< 5	
9	A	DMAP	furan		43	97:3
10	A	DMAP	furan	Sc(OTf) ₃	55	97:3
11 ^[d]	A	DMAP	furan	Sc(OTf) ₃	63	99:1

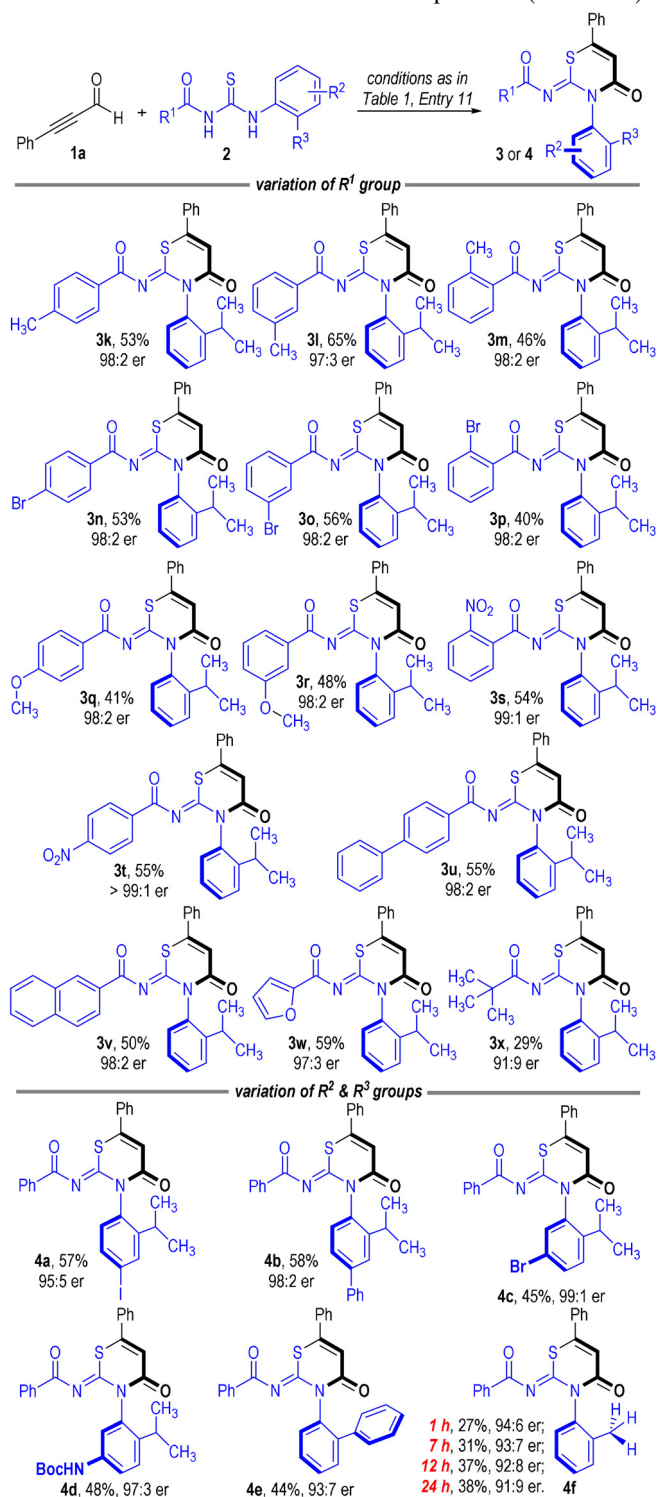
[a] Unless otherwise specified, the reactions were carried using **1a** (0.20 mmol), **2a** (0.10 mmol), **DQ** (0.20 mmol), NHC (0.02 mmol), base (0.10 mmol), 4 Å MS (150 mg), solvent (2.0 mL) at 30 °C for 12 h. The absolute configurations of the products were estimated based on the X-ray analysis on the single crystals of **3a** (CCDC 2009386). [b] Isolated yield of **3a**. [c] The *er* values were determined via UPLC on chiral stationary phase. [d] **1a** (0.30 mmol), **2a** (0.10 mmol), **DQ** (0.30 mmol), **A** (0.02 mmol), DMAP (0.10 mmol), 5 Å MS (150 mg), Sc(OTf)₃ (0.02 mmol), furan (2.0 mL), 30 °C, 12 h.



Scheme 1. Scope of ynals **1**.^[a] [a] Reaction conditions as stated in Table 1, entry 11. Yields are isolated yields after purification by column chromatography. *Er* values were determined by HPLC or UPLC on chiral stationary phase.

afforded in 53 % yield as a single atropisomer. Aliphatic ynal substrates led to complex reaction mixtures in this NHC organocatalytic process without any identifiable products formed.

The acylthiourea substrate **2** also showed good tolerance to various substituents and substitution patterns (Scheme 2).



Scheme 2. Scope of acylthioureas **2**.^[a] [a] Reaction conditions as stated in Table 1, entry 11. Yields are isolated yields after purification by column chromatography. Er values were determined by HPLC or UPLC on chiral stationary phase.

Substituents could be installed on each position of the benzene ring of the benzoyl group regardless of their electronic properties, with the corresponding products afforded in moderate yields and excellent enantioselectivities (**3k** to **3v**). The R^1 group of the acyl unit could be switched to a heteroaromatic furanyl group without erosion on the product yield and er value (**3w**). The R^1 group could also be replaced with an alkyl group, although the product yield and er value dropped under the current catalytic conditions (**3x**).

The 2-isopropyl group on the N-benzene rings of the NHC-catalyzed annulation reaction, since it blocks the rotation of the N-phenyl groups around the C–N axis of the thiazine products. Substituents were well tolerated on the 4- and 5-positions of the N-phenyl group of the substrate **2**, with the target products afforded in excellent optical purities (**4a** to **4d**). Replacing the 2-isopropyl group on the N-benzene ring of the substrate **2a** with a less bulky 2-phenyl or 2-methyl group led to slight drops in the product er values (e.g., **4e**, **4f**). It is worth noting that the er value of the product **4f** can be gradually decreased under our current catalytic conditions.

The stereochemical stabilities of the atroposelective thiazine products were evaluated through both experimental and computational methods.^[16] The er value of **3a** was stable at 50 °C, but severely dropped to 55:45 after stirring at 100 °C in mesitylene for 24 h (Table 2, entry 1). The chiral product **4e** was less stable than **3a** at 50 °C, and the er value of **4e** dropped a lot after stirring for 12 h at 75 °C in mesitylene (entry 2). As a sharp contrast, the er value of **4f** deteriorated significantly even at 50 °C and became racemic after stirring for 12 h at 75 °C (entry 3).

The barrier to rotation for **3a** was measured at 100 °C in mesitylene (Table 2, **3a**, $\Delta G^\ddagger = 29.5$ kcal mol^{−1}), and the result is in accordance with the value ($\Delta G^\ddagger = 30.4$ kcal mol^{−1}) calculated through density functional theory (DFT). Similarly, the barriers to rotations for **4e** and **4f** were measured experimentally at 75 °C in mesitylene (**4e**, $\Delta G^\ddagger = 28.4$ kcal mol^{−1}; **4f**, $\Delta G^\ddagger = 26.9$ kcal mol^{−1}). The results clearly show that the size of the 2-substituents on the N-phenyl moieties of the thiazine products play significant roles in both chirality inductions and stereochemical stabilities of the axially chiral thiazine molecules. Thiazines bearing the 2-isopropyl groups on the N-phenyl moieties (e.g., **3a**) can generally be formed in excellent enantioselectivities and the products are stable at our reaction conditions. In contrast, the lower er value obtained with the product **4f** bearing a N-(2-methyl)phenyl group was believed to be resulted from both weaker steric controls during the atroposelective reaction and the less stability of the afforded chiral thiazine product.

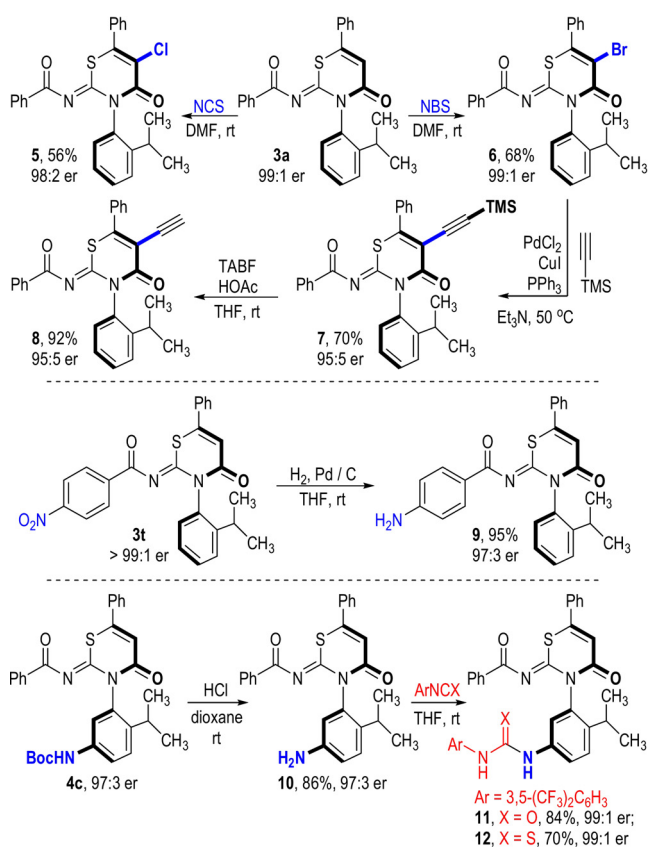
The thiazine molecules bearing axial chirality can be further functionalized through simple protocols (Scheme 3). The α -sp² carbon of the lactam moiety of **3a** can be halogenated under mild conditions to give the products (e.g., **5** and **6**) in moderate yields without obvious erosions on the optical purities. The α -brominated product **6** can be coupled with alkynes and give the atroposelective cross-coupling alkyne product **7** in a good yield with an excellent enantioselectivity. The TMS group of **7** can be efficiently removed to give the chiral terminal alkyne **8** in an excellent

Table 2: Stereochemical stabilities of the thiazine products **3a**, **4e** and **4f**^[a] and their rotation barriers.

Entry	Thiazine	er ₀ ^[b]	er (50 °C)	er (75 °C)	er (100 °C)
1 ^[c]	3a	99:1	98:2	92:8	55:45
2	4e	93:7	88:12	55:45	51:49
3	4f	91:9	76:24	50:50	50:50

3a 99:1 er $\Delta G^\ddagger = 29.5$ kcal/mol (100 °C in mesitylene) $\Delta G^\ddagger_{\text{cal}} = 30.4$ kcal/mol	4e 93:7 er $\Delta G^\ddagger = 28.4$ kcal/mol (75 °C in mesitylene)	4f 91:9 er $\Delta G^\ddagger = 26.9$ kcal/mol (75 °C in mesitylene)
---	--	--

[a] Unless otherwise specified, the chiral thiazine product (0.05 mmol) was dissolved in mesitylene (1 mL) and stirred at the corresponding temperature for 12 h. [b] Er₀ indicates the initial er values of the thiazine products. [c] Thiazine **3a** was stirred at the corresponding temperatures for 24 h.

**Scheme 3.** Synthetic transformations of the Axially Chiral Thiazine Products.

yield. Note that, the terminal alkynyl group in **8** is a versatile functional group that can be used as linkers for macro-molecule modification^[17] and in various small molecular synthetic transformations.^[18] The nitro group existed in the axially chiral product **3t** can be efficiently reduced to a free amino group (**9**), although a slight drop in the er value was

observed. The Boc protecting group on the product **4d** can be removed under acidic conditions and the afforded atroposelective aniline product **10** can be further transformed to a urea **11** or a thiourea **12** with retention of the optical purities. It is worth noting that ureas and thioureas are rich in functionalities and have been widely used in both catalytic and biological research.^[19]

In summary, we have developed an NHC-catalyzed atroposelective cycloaddition reaction for the synthesis of enantiomerically enriched thiazine derivatives. Chiral C–N axis is readily constructed for the first time through NHC organic catalysis. Our reaction tolerates various functionalities, with the axially chiral products generated in excellent optical purities. The thiazine derivatives obtained from our method are rich in functionalities and can be transformed to various functional molecules containing chiral C–N axes with retention of the optical purities. Further studies on atroposelective synthesis with applications in agricultural chemicals are being pursued in our laboratories.

Acknowledgements

We acknowledge financial support from the National Natural Science Foundation of China (21772029, 21801051, 21961006, 22071036), The 10 Talent Plan (Shicengci) of Guizhou Province ([2016]5649), the Guizhou Province Returned Oversea Student Science and Technology Activity Program [(2014)-2], the Science and Technology Department of Guizhou Province ([2018]2802, [2019]1020), the Program of Introducing Talents of Discipline to Universities of China (111 Program, D20023) at Guizhou University, Frontiers Science Center for Asymmetric Synthesis and Medicinal Molecules, Department of Education, Guizhou Province [Qianjiaohe KY (2020)004], the Guizhou Province First-Class Disciplines Project [(Yiliu Xueke Jianshe Xiangmu)-GNYL(2017)008], Guizhou University of Traditional Chinese Medicine, and Guizhou University (China). Singapore National Research Foundation under its NRF Investigatorship (NRF-NRFI2016-06), the Ministry of Education, Singapore, under its MOE AcRF Tier 1 Award (RG108/16, RG5/19, RG1/18), MOE AcRF Tier 3 Award (MOE2018-T3-1-003), the Agency for Science, Technology and Research (A*STAR) under its A*STAR AME IRG Award (A1783c0008, A1783c0010), GSK-EDB Trust Fund, Nanyang Research Award Grant, Nanyang Technological University.

Conflict of interest

The authors declare no conflict of interest.

Keywords: atroposelective reaction · chiral C–N axis · N-heterocyclic carbenes · organocatalysis

[1] For selected reviews, see: a) D. D. DePestel, M. S. Benninger, L. Danziger, K. L. LaPlante, C. May, A. Luskin, M. Pichichero, J. A. Hadley, *J. Am. Pharm. Assoc.* **2008**, *48*, 530; b) G. G.

- Zhanel, A. Lam, F. Schweizer, K. Thomson, A. Walkty, E. Rubinstein, A. S. Gin, D. J. Hoban, A. M. Noreddin, J. A. Karlovsky, *Am. J. Clin. Dermatol.* **2008**, *9*, 245; c) S. L. Badshah, A. Naeem, *Molecules* **2016**, *21*, 20; d) A. Rai, A. K. Singh, V. Raj, S. Saha, *Mini-Rev. Med. Chem.* **2018**, *18*, 42.
- [2] a) R. Mansour, L. P. Belzunces, P. Suma, L. Zappalà, G. Mazzeo, K. Grissa-Lebdi, A. Russo, A. Biondi, *Agron. Sustainable Dev.* **2018**, *38*, 37; b) M. I. A. Shah, R. Khan, M. Arfan, A. Wadood, M. Ghufuran, *J. Heterocycl. Chem.* **2019**, *56*, 3073.
- [3] For selected reviews, see: a) S. Choudhary, O. Silakari, P. K. Singh, *Mini-Rev. Med. Chem.* **2018**, *18*, 1452; b) E. V. Nosova, G. N. Lipunova, V. N. Charushin, O. N. Chupakhin, *Mini-Rev. Med. Chem.* **2019**, *19*, 999; c) S. Mir, A. M. Dar, B. A. Dar, *Mini-Rev. Org. Chem.* **2020**, *17*, 148; for selected examples, see: d) N. Mizutani, W. H. Chiou, I. Ojima, *Org. Lett.* **2002**, *4*, 4575; e) D. A. Evans, K. R. Fandrick, H.-J. Song, K. A. Scheidt, R. Xu, *J. Am. Chem. Soc.* **2007**, *129*, 10029; f) A. La-Venia, P. Ventosa-Andres, L. Hradilova, V. Krchnak, *J. Org. Chem.* **2014**, *79*, 10378; g) W. P. Unsworth, G. Coulthard, C. Kitsiou, R. J. K. Taylor, *J. Org. Chem.* **2014**, *79*, 1368; h) W. Liu, H. J. Li, M. Y. Xu, Y. C. Ju, L. Y. Wang, J. Xu, D. P. Yang, W. J. Lan, *Org. Lett.* **2015**, *17*, 5156.
- [4] a) Y. Chen, S. Yekta, A. K. Yudin, *Chem. Rev.* **2003**, *103*, 3155; b) J. M. Brunel, *Chem. Rev.* **2005**, *105*, 857; c) H. Shimizu, I. Nagasaki, T. Saito, *Tetrahedron* **2005**, *61*, 5405; d) S. Schenker, A. Zamfir, M. Freund, S. B. Tsogoeva, *Eur. J. Org. Chem.* **2011**, 2209.
- [5] a) J. Clayden, W. J. Moran, P. J. Edwards, S. R. LaPlante, *Angew. Chem. Int. Ed.* **2009**, *48*, 6398; *Angew. Chem.* **2009**, *121*, 6516; b) S. R. LaPlante, P. J. Edwards, L. D. Fader, A. Jakalian, O. Hucke, *ChemMedChem* **2011**, *6*, 505; c) S. R. Laplante, L. D. Fader, K. R. Fandrick, D. R. Fandrick, O. Hucke, R. Kemper, S. P. Miller, P. J. Edwards, *J. Med. Chem.* **2011**, *54*, 7005.
- [6] a) S. Brandes, M. Bella, A. Kjærsgaard, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2006**, *45*, 1147; *Angew. Chem.* **2006**, *118*, 1165; b) S. Brandes, B. Niess, M. Bella, A. Prieto, J. Overgaard, K. A. Jørgensen, *Chem. Eur. J.* **2006**, *12*, 6039; c) H. Liu, W. Feng, C. W. Kee, D. Leow, W.-T. Loh, C.-H. Tan, *Adv. Synth. Catal.* **2010**, *352*, 3373; d) N. Suzumura, M. Kageyama, D. Kamimura, T. Inagaki, Y. Dobashi, H. Hasegawa, H. Fukaya, O. Kitagawa, *Tetrahedron Lett.* **2012**, *53*, 4332; e) K. T. Barrett, S. J. Miller, *J. Am. Chem. Soc.* **2013**, *135*, 2963; f) K. T. Barrett, A. J. Metrano, P. R. Rablen, S. J. Miller, *Nature* **2014**, *509*, 71; g) M. E. Diener, A. J. Metrano, S. Kusano, S. J. Miller, *J. Am. Chem. Soc.* **2015**, *137*, 12369; h) J. W. Zhang, J. H. Xu, D. J. Cheng, C. Shi, X. Y. Liu, B. Tan, *Nat. Commun.* **2016**, *7*, 10677; i) L. Zhang, J. Zhang, J. Ma, D. J. Cheng, B. Tan, *J. Am. Chem. Soc.* **2017**, *139*, 1714; j) H.-Y. Bai, F.-X. Tan, T.-Q. Liu, G.-D. Zhu, J.-M. Tian, T.-M. Ding, Z.-M. Chen, S.-Y. Zhang, *Nat. Commun.* **2019**, *10*, 3063; k) S. D. Vaidya, S. T. Toenjes, N. Yamamoto, S. M. Maddox, J. L. Gustafson, *J. Am. Chem. Soc.* **2020**, *142*, 2198; l) D. Wang, Q. Jiang, X. Yang, *Chem. Commun.* **2020**, *56*, 6201.
- [7] For selected reviews on NHC organocatalysis, see: a) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606; b) A. T. Biju, N. Kuhl, F. Glorius, *Acc. Chem. Res.* **2011**, *44*, 1182; c) X. Bugaut, F. Glorius, *Chem. Soc. Rev.* **2012**, *41*, 3511; d) D. T. Cohen, K. A. Scheidt, *Chem. Sci.* **2012**, *3*, 53; e) A. Grossmann, D. Enders, *Angew. Chem. Int. Ed.* **2012**, *51*, 314; *Angew. Chem.* **2012**, *124*, 320; f) S. J. Ryan, L. Candish, D. W. Lupton, *Chem. Soc. Rev.* **2013**, *42*, 4906; g) S. J. Connon, *Angew. Chem. Int. Ed.* **2014**, *53*, 1203; *Angew. Chem.* **2014**, *126*, 1225; h) M. N. Hopkinson, C. Richter, M. Schedler, F. Glorius, *Nature* **2014**, *510*, 485; i) J. Mahatthananchai, J. W. Bode, *Acc. Chem. Res.* **2014**, *47*, 696; j) D. M. Flanagan, F. Romanov-Michailidis, N. A. White, T. Rovis, *Chem. Rev.* **2015**, *115*, 9307; k) R. S. Menon, A. T. Biju, V. Nair, *Chem. Soc. Rev.* **2015**, *44*, 5040; l) M. H. Wang, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2016**, *55*, 14912; *Angew. Chem.* **2016**, *128*, 15134; m) C. Zhang, J. F. Hooper, D. W. Lupton, *ACS Catal.* **2017**, *7*, 2583; n) K. J. R. Murauski, A. A. Jaworski, K. A. Scheidt, *Chem. Soc. Rev.* **2018**, *47*, 1773; o) A. T. Biju, *N-Heterocyclic Carbenes in Organocatalysis*, Wiley-VCH, Weinheim, **2019**; p) X. Chen, H. Wang, Z. Jin, Y. R. Chi, *Chin. J. Chem.* **2020**, *38*, 1167.
- [8] a) S. Lu, S. B. Poh, Y. Zhao, *Angew. Chem. Int. Ed.* **2014**, *53*, 11041; *Angew. Chem.* **2014**, *126*, 11221; b) C. Zhao, D. Guo, K. Munkerup, K. W. Huang, F. Li, J. Wang, *Nat. Commun.* **2018**, *9*, 611; c) J. Bie, M. Lang, J. Wang, *Org. Lett.* **2018**, *20*, 5866; d) S. Lu, S. B. Poh, Z. Q. Rong, Y. Zhao, *Org. Lett.* **2019**, *21*, 6169; e) K. Xu, W. Li, S. Zhu, T. Zhu, *Angew. Chem. Int. Ed.* **2019**, *58*, 17625; *Angew. Chem.* **2019**, *131*, 17789; f) G. Yang, D. Guo, D. Meng, J. Wang, *Nat. Commun.* **2019**, *10*, 3062.
- [9] For reactions of acylthioureas in NHC organocatalysis, see: a) A. Ghosh, S. Barik, A. T. Biju, *Org. Lett.* **2019**, *21*, 8598; b) C. Liu, S. Wu, J. Xu, L. Chen, P. Zheng, Y. R. Chi, *Org. Lett.* **2019**, *21*, 9493; for thio-addition reactions in NHC organocatalysis, see: c) Z. S. Cong, Y. G. Li, G. F. Du, C. Z. Gu, B. Dai, L. He, *Chem. Commun.* **2017**, *53*, 13129; d) H. Lu, J.-L. Zhang, J.-Y. Liu, H.-Y. Li, P.-F. Xu, *ACS Catal.* **2017**, *7*, 7797; e) L. Yi, K.-Q. Chen, Z.-Q. Liang, D.-Q. Sun, S. Ye, *Adv. Synth. Catal.* **2017**, *359*, 44.
- [10] a) C. Mou, J. Wu, Z. Huang, J. Sun, Z. Jin, Y. R. Chi, *Chem. Commun.* **2017**, *53*, 13359; b) J. Cao, K. Sun, S. Dong, T. Lu, Y. Dong, D. Du, *Org. Lett.* **2017**, *19*, 6724; c) Y. Xie, J. Wang, *Chem. Commun.* **2018**, *54*, 4597.
- [11] For pioneering studies, see: D. E. A. Raup, C. B. David, D. Holte, K. A. Scheidt, *Nat. Chem.* **2010**, *2*, 766.
- [12] a) S. De Sarkar, S. Grimme, A. Studer, *J. Am. Chem. Soc.* **2010**, *132*, 1190; b) S. De Sarkar, A. Studer, *Angew. Chem. Int. Ed.* **2010**, *49*, 9266; *Angew. Chem.* **2010**, *122*, 9452.
- [13] a) M. He, J. R. Struble, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 8418; b) M. Wadamoto, E. M. Phillips, T. E. Reynolds, K. A. Scheidt, *J. Am. Chem. Soc.* **2007**, *129*, 10098; c) P.-C. Chiang, M. Rommel, J. W. Bode, *J. Am. Chem. Soc.* **2009**, *131*, 8714.
- [14] a) M. S. Kerr, J. Read de Alaniz, T. Rovis, *J. Am. Chem. Soc.* **2002**, *124*, 10298; b) M. S. Kerr, T. Rovis, *J. Am. Chem. Soc.* **2004**, *126*, 8876.
- [15] For selected examples, see: a) B. Cardinal-David, D. E. Raup, K. A. Scheidt, *J. Am. Chem. Soc.* **2010**, *132*, 5345; b) D. E. Raup, B. Cardinal-David, D. Holte, K. A. Scheidt, *Nat. Chem.* **2010**, *2*, 766; c) D. T. Cohen, B. Cardinal-David, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2011**, *50*, 1678; *Angew. Chem.* **2011**, *123*, 1716; d) J. Dugal-Tessier, E. A. O'Bryan, T. B. H. Schroeder, D. T. Cohen, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2012**, *51*, 4963; *Angew. Chem.* **2012**, *124*, 5047; e) J. Mo, X. Chen, Y. R. Chi, *J. Am. Chem. Soc.* **2012**, *134*, 8810.
- [16] a) M. Reist, B. Testa, P.-A. Carrupt, M. Jung, V. Schurig, *Chirality* **1995**, *7*, 396; b) D. P. Curran, W. Liu, C. H.-T. Chen, *J. Am. Chem. Soc.* **1999**, *121*, 11012; c) S. Shirakawa, K. Liu, K. Maruoka, *J. Am. Chem. Soc.* **2012**, *134*, 916; d) C. Ma, F. T. Sheng, H. Q. Wang, S. Deng, Y. C. Zhang, Y. Jiao, W. Tan, F. Shi, *J. Am. Chem. Soc.* **2020**, *142*, 15686; e) Q. Wang, W. W. Zhang, H. Song, J. Wang, C. Zheng, Q. Gu, S. L. You, *J. Am. Chem. Soc.* **2020**, *142*, 15678.
- [17] a) J. S. Moore, *Acc. Chem. Res.* **1997**, *30*, 402; b) S. Klyatskaya, N. Dingenouts, C. Rosenauer, B. Muller, S. Hoyer, *J. Am. Chem. Soc.* **2006**, *128*, 3150; c) A. D. Finke, D. E. Gross, A. Han, J. S. Moore, *J. Am. Chem. Soc.* **2011**, *133*, 14063; d) Y. Zhong, Y. Yang, Y. Shen, W. Xu, Q. Wang, A. L. Connor, X. Zhou, L. He, X. C. Zeng, Z. Shao, Z. L. Lu, B. Gong, *J. Am. Chem. Soc.* **2017**, *139*, 15950.
- [18] a) L. L. Cheung, A. K. Yudin, *Org. Lett.* **2009**, *11*, 1281; b) X. Li, X. Shi, M. Fang, X. Xu, *J. Org. Chem.* **2013**, *78*, 9499; c) Q. Gu, H. H. Al Mamari, K. Graczyk, E. Diers, L. Ackermann, *Angew. Chem. Int. Ed.* **2014**, *53*, 3868; *Angew. Chem.* **2014**, *126*, 3949; d) J. Xiang, R. Yuan, R. Wang, N. Yi, L. Lu, H. Zou, W. He, J. Org. Chem. **2014**, *79*, 11378; e) Y.-T. He, Q. Wang, J. Zhao, X.-Y.

- Liu, P.-F. Xu, Y.-M. Liang, *Chem. Commun.* **2015**, *51*, 13209; f) Y. Kim, C.-J. Li, *Green Synth. Catal.* **2020**, *1*, 1.
- [19] a) M. Koketsu, H. Ishihara, *Curr. Org. Synth.* **2006**, *3*, 439; b) Z. Zhang, P. R. Schreiner, *Chem. Soc. Rev.* **2009**, *38*, 1187; c) X. Fang, C. J. Wang, *Chem. Commun.* **2015**, *51*, 1185; d) A. Jagtap, N. Kondekar, A. Sadani, J.-W. Chern, *Curr. Med. Chem.* **2017**, *24*, 622; e) C. Brullo, F. Rapetti, O. Bruno, *Molecules* **2020**, *25*, 3457.
- Manuscript received: August 4, 2020
Accepted manuscript online: February 2, 2021
Version of record online: March 17, 2021
-