Carbene-Catalyzed Enantioselective Addition of Thioamides to Bromoenals for Access to Thiazinone Heterocycles

Changyi Liu,[†,⊥] Shuquan Wu,[†,⊥] Jun Xu,[‡,§,⊥] Lingzhu Chen,[†] Pengcheng Zheng,[*,†] and Yonggui Robin Chi[*,†,§]

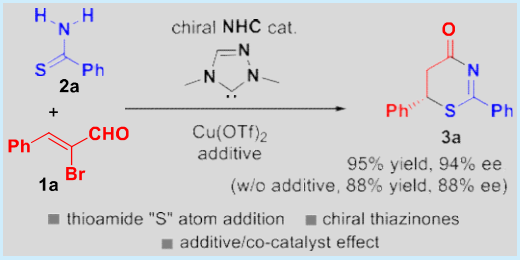
[†]Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Huaxi District, Guiyang 550025, China

[‡]Guizhou University of Traditional Chinese Medicine, Guiyang 550025, China

[§]Division of Chemistry & Biological Chemistry, School of Physical & Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore

Supporting Information

ABSTRACT: A carbene-catalyzed reaction between α-bromoenals and thioamides was developed. Key steps include enantioselective 1,4-addition of thioamide sulfur atoms to α,β-unsaturated acyl azolium intermediate. Subsequent intramolecular annulation eventually affords thiazinone heterocycles with high optical purities. The introduction of Lewis acid additives such as $Cu(OTf)_2$ to this NHC catalytic reaction could provide small but consistent improvements to reaction enantioselectivities.



Sulfur is a ubiquitous element for life with wide presence in natural products and medicines.[1] One class of such sulfur-containing molecules contains 1,3-thiazines and the related thiazinones, heterocycles containing four carbons, one nitrogen, and one sulfur atom (Figure 1a). For example, the thiazine-fused β-lactam Cefaclor belongs to the class of β-lactam antibiotics used for the treatment of bacterial infections.[2] The thiazinone-containing chlormezanone is a commercial drug used as an anxiolytic and a muscle relaxant.[3] The BTZ043 is used to kill *Mycobacterium tuberculosis*.[4] Many methods have been developed to prepare these thiazines and their derivatives, mostly as achiral molecules or in racemic forms.[5]

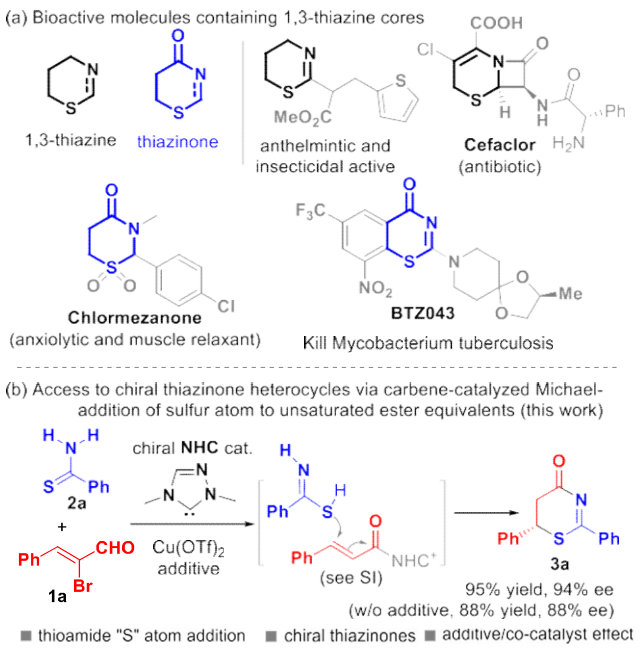


Figure 1. Thiazinones and our NHC-catalyzed synthetic method.

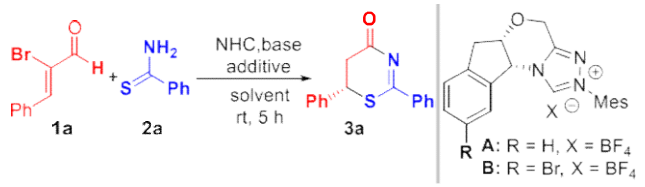
N-Heterocyclic carbenes (NHC) as organic catalysts have found impressive success in enantioselective reactions that turn readily available starting materials to optically enriched products.[6] For example, research from Ye,[7] Xu,[8] and Du[9] showed that the sulfur atom from thiophenol could undergo enantioselective addition to catalytically generated α,β-unsaturated acylazolium intermediate via NHC catalysis to prepare sulfur-containing heterocycles. Similar addition reaction of thiophenol could also be mediated by chiral isothiourea catalyst, as disclosed by Asano and Matsubara.[10] In the area of chiral amine iminium catalysis, enantioselective Michael addition of thiols to enals was reported by Jørgensen,[11a] Wang,[11b,c] He,[11e] and Melchiorre.[11d]

Here, we disclose a carbene-catalyzed enantioselective 1,4-addition of thioamide sulfur atoms to α,β-unsaturated acylazolium intermediates generated from α-bromoenals (Figure 1b). The thioamide can behave as dinucleophiles with the nitrogen atom as another nucleophile to react with the acylazolium moiety of the enal-derived intermediate and form an amide bond. The overall catalytic process converts thioamides and bromoenals to thiazinone derivatives with

high optical purities. The introduction of Lewis acid additives[12] such as $Cu(OTf)_2$ to this NHC catalytic reaction could provide small while consistent improvements to reaction enantioselectivities. Both thioamides and bromoenals are readily available and easy to handle starting materials, and our method provides efficient and enantioselective access to thiazinones. It is important to note that near the completion of our study, Biju et al. reported the carbene-catalyzed annulation of thioamides and α-bromoenals for the synthesis of chiral thiazinones.[13] In Biju's reaction products were obtained in good yields (up to 90%) and enantioselectivity (ee up to 88%). In our system, with Lewis acid used as an additive, our reactions afford the products with excellent yields (up to 96%) and enantioselectivities (ee up to 96%).

We started by using α-bromocinnamaldehyde 1a and thiobenzamide 2a as the model substrates with azolium salt A[14] as a NHC precatalyst and Cs_2CO_3 as a base (Table 1,

Table 1. Initial Studies and Condition Optimization



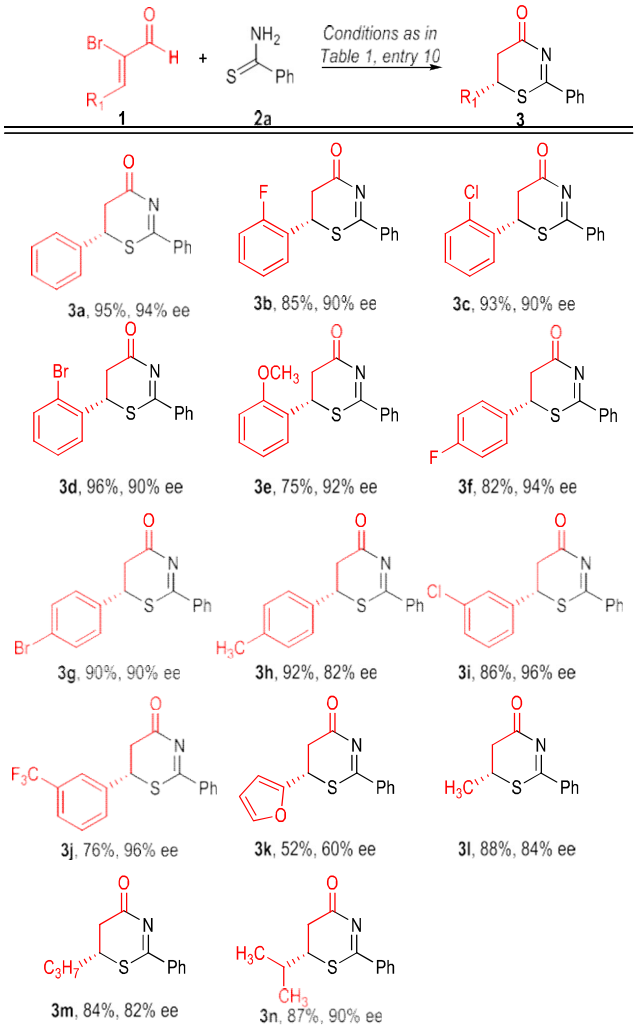
entry	NHC	base	additive	solvent	yield (%)[b]	ee (%)[c]
1	A	Cs_2CO_3		THF	37	0
2	A	Cs_2CO_3		DCM	12	14
3	A	Cs_2CO_3		toluene	56	64
4	A	DIPEA		toluene	35	64
5	A	NaOAc		toluene	12	84
6	B	NaOAc		toluene	11	88
7[d]	B	NaOAc		toluene	15	88
8[d]	B	NaOAc	$Cu(OTf)_2$	toluene	20	94
9[d,e]	B	NaOAc	$Cu(OTf)_2$	toluene	65	94
10[d,e,f]	B	NaOAc	$Cu(OTf)_2$	toluene	95	94
11[d,e,f]	B	NaOAc		toluene	88	88

[a]General conditions (unless otherwise specified): 1a (0.12 mmol), 2a (0.1 mmol), NHC (0.005 mmol), base (0.05 mmol), additive (0.005 mmol), and solvent (2.0 mL) at 25 °C for 5 h. [b]Isolated yield of 3a. [c]The ee values were determined via HPLC on chiral stationary phase. [d]Used 50 mg 4 Å MS. [e]NHC (0.02 mmol), base (0.12 mmol). [f]Temperature at 40 °C for 5 h.

entries 1−3). Toluene was found as the best solvent and gave the desired product in moderate yield and enantioselectivity (entry 3). Different organic and inorganic bases could work for this catalytic process (e.g., entries 4 and 5). The reaction enantioselectivity could be dramatically improved by switching Cs_2CO_3 to NaOAc, although with a drop on the product yield (entry 5). The enantioselectivity of the product 3a could be increased to 88% when using NHC B[15] as the reaction catalyst (entry 6). The product yield could be slightly increased with the addition of 4 Å molecular sieves (MS) to the catalytic system (entry 7). Lewis acids have been frequently used as effective additives for enhancing the product enantioselectivities in NHC organocatalytic reactions.[12] We therefore examined the effects of different Lewis acids on our reaction and found that $Cu(OTf)_2$ could provide the product 3a with a 94% ee (entry 8). Finally, our desired product 3a could be afforded in 95% yield with 94% ee value with increased amounts of NHC B and NaOAc used as the reaction catalyst and base, $Cu(OTf)_2$ as the additive in toluene at 40 °C (entry 10). It is worth noting that both the product yield and ee value dropped without addition of $Cu(OTf)_2$ under otherwise identical reaction conditions (entry 11).

With the optimized conditions in hand, the scope of α-bromo enals 2 was then examined (Scheme 1). The efficiencies

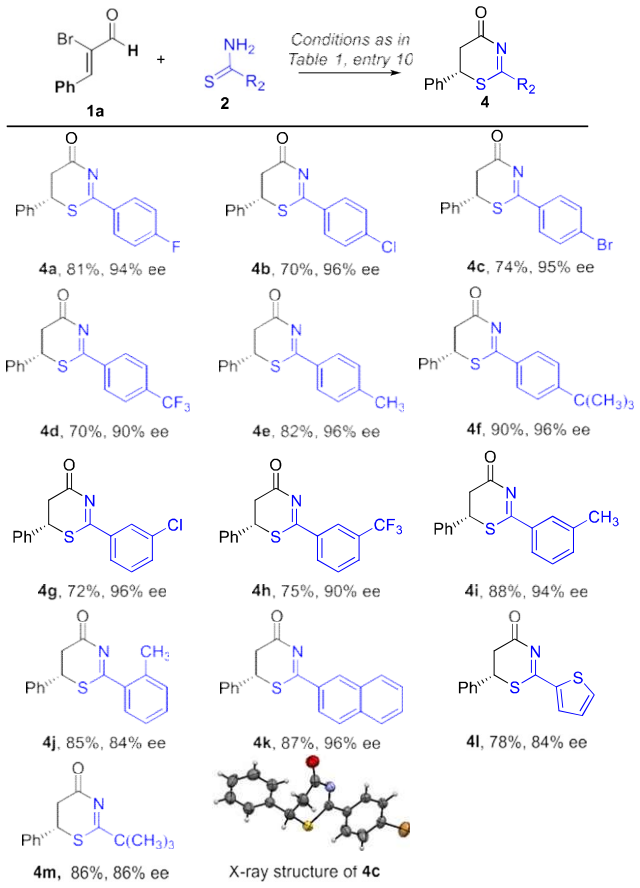
Scheme 1. Variation of α-Bromoenals



and enantioselectivities of this reaction were relatively insensitive when α-bromo enals 2 bearing different substituents or substitution patterns were used (3a−j). All of the corresponding products were afforded in good to excellent yields and enantioselectivities. The β-phenyl group of substrate 1a could also be replaced with a 2-furan group, although the product 3k could only be afforded in moderate yield and ee value under the current reaction conditions. To our delight, aliphatic α-bromoenals could also be used in this transformation with the target products afforded in good yields with good to excellent optical purities (3l−3n).

The scope of the thioamide substrates (2) was also examined to react with α-bromocinnamaldehyde 1a (Scheme 2). Both electron-withdrawing (4a−d) and electron-donating substituents (4e−f) were well tolerated on the *p*-position of the phenyl group, with the desired products afforded in good to excellent yields with excellent enantioselectivities. Sub-

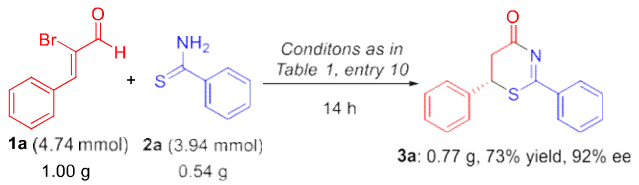
Scheme 2. Variation of Thiobenzamide



stituents on the *m*- or *o*-positions of the phenyl rings gave the desired products in good yields with good to excellent ee values (4g−j). Replacement of the phenyl group with a 2-naphthyl (4k) group had little effect on the reaction outcome. The use of hetero thioamide could give corresponding product 4l with moderate yield and ee value. Replacing the phenyl group of the thiobenzamide with alkyl group resulted in slight drops on the product yield and optical purity (4m).

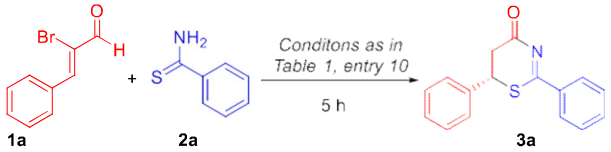
Our catalytic reaction could also be carried out at gram scale with the desired product 3a afforded in good yield and excellent enantioselectivity (Scheme 3).

Scheme 3. Gram Scale Synthesis of 3a



To further understand the role of the additives, we performed several additional control experiments (Table 2). Our optimal conditions used 20 mol % NHC catalyst and 5 mol % $Cu(OTf)_2$ additive (Table 2, entry 2, same as Table 1, entry 10). The loading of the Cu salt additive (e.g., the ratio between NHC and Cu salt) had clear influence on the reaction yields without affecting enantioselectivities (Table 2, entry 3). The drop on reaction yield with high loading of $Cu(OTf)_2$ is most likely attributed to the formation of Cu−NHC complex

Table 2. Control Experiments to Understand the Role of Additives[a]



entry	additive	equiv (mol %)	yield (%)	ee
1	no additive		88	88
2	$Cu(OTf)_2$	5	95	94
3	$Cu(OTf)_2$	20	66	94
4	$Cu(CF_3COO)_2$	5	80	89
5	$Cu(OAc)_2$	5	81	80
6	NaOTf	10	83	93
7	CH_3SO_3Na	10	92	86

[a]Unless otherwise specified, condition as in Table 1, entry 10.

that consumes part of the active NHC organic catalyst, as indicated via high resolution mass spectrometry anlysis of the reaction mixture (see Figure S1). Similar Cu−NHC complex formation has been observed in our earlier report on cooperative NHC and Cu relay catalysis.[12d,16] It appeared the triflate anion of the Cu(II) salt played important roles for the improvements of reaction yields and ee values, as the use of $Cu(CF_3CO_2)_2$ or $Cu(OAc)_2$ as the additive did not lead to enhanced results (entries 4 and 5). Interestingly, the use of NaOTf additive could also improve the reaction ee value from 88 to 93% without affecting the reaction yield (entry 5). Analysis of the reaction mixture via ^1H NMR suggested hydrogen-bonding interactions between the triflate anion and thioamide (see Figure S2), although it remains unclear how such interactions could affect the reaction outcomes. Our current experiments (Tables 1, 2) indicated that both the Cu(II) cation and triflate anion affected the reaction outcomes. Their exact interactions with the NHC catalyst, substrates, and intermediates during the rather complex catalytic reaction will require substantial additional studies.

In summary, we developed an enantioselective organic catalytic method for the synthesis of thiazinone heterocycles. Both thioamides and α-bromoenals are readily available and easy to handle starting materials. A broad scope of functional groups are well tolerated on both of the α-bromoenal and thioamide substrates with all the corresponding products afforded in good to excellent yields and enantioselectivities. The introduction of Lewis acids (such as $Cu(OTf)_2$) as additives provided small but consistent improvements to reaction enantioselectivities. Detailed mechanistic studies and further investigations of cooperative catalysis for asymmetric synthesis are in progress in our laboratories.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03685.

Experimental procedures and spectral data for all new compounds (PDF)

Accession Codes

CCDC 1954765 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge

via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Authors

*E-mail: zhengpc1986@163.com.

*E-mail: robinchi@ntu.edu.sg.

ORCID

Lingzhu Chen: 0000-0003-0453-1637

Pengcheng Zheng: 0000-0002-3575-4502

Yonggui Robin Chi: 0000-0003-0573-257X

Author Contributions

⊥C.L., S.W., and J.X. contributed equally to this work.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We acknowledge financial support from the National Natural Science Foundation of China (Grants 21772029 and 21807019), National Key Technologies R&D Program (Grant 2014BAD23B01), The 10 Talent Plan (Shicengci) of Guizhou Province ([2016]5649), the Natural Science Foundation of Guizhou Province ([2018]2802), Guizhou University, the Guizhou Province First-Class Disciplines Project (Yiliu Xueke Jianshe Xiangmu)-GNYL(2017)008, Natural Science Foundation of Guizhou University (No. GZU[2017]35), the Opening Foundation of the Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University (No. 2018GDGP0101), Guizhou University of Traditional Chinese Medicine, China, 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.

REFERENCES

(1) (a) Bentley, R. *Chem. Soc. Rev.* 2005, *34*, 609−624. (b) Jalilehvand, F. *Chem. Soc. Rev.* 2006, *35*, 1256−1268. (c) Ramachary, D. B.; Kishor, M.; Reddy, V. Y. *Eur. J. Org. Chem.* 2008, *2008*, 975−993. (d) Cloonan, S. M.; Keating, J. J.; Butler, S. G.; Knox, A. J. S.; Jørgensen, A. M.; Peters, G. H.; Meegan, M. *J. Eur. J. Med. Chem.* 2009, *44*, 4862−4888. (e) Hughes, C. C.; MacMillan, J. B.; Gaudêncio, S. P.; Jensen, P. R.; Fenical, W. *Angew. Chem., Int. Ed.* 2009, *48*, 725−727; *Angew. Chem.* 2009, *121*, 739−741. (f) Liu, C. M.; Li, B.; Shen, Y.-H.; Zhang, W.-D. *J. Nat. Prod.* 2010, *73*, 1582−1585. (g) Chauhan, P.; Mahajan, S.; Enders, D. *Chem. Rev.* 2014, *114*, 8807−8864. (h) Dunbar, K. L.; Scharf, D. H.; Litomska, A.; Hertweck, C. *Chem. Rev.* 2017, *117*, 5521−5577. (i) Wang, W.; Zeng, F.; Bie, Q.; Dai, C.; Chen, C.; Tong, Q.; Liu, J.; Wang, J.; Zhou, Y.; Zhu, H.; Zhang, Y. *Org. Lett.* 2018, *20*, 6817−6821.

(2) Ball, A. P.; Brookes, G. R.; Farrell, I. D.; Geddes, A. M.; Gould, I. *Chemotherapy* 1979, *25*, 214−221.

(3) Wollina, U.; Hipler, U.-C.; Seeling, A.; Oelschlager, H. *Skin Pharmacol Physiol* 2005, *18*, 132−138.

(4) Makarov, V.; Manina, G.; Mikusova, K.; Mollmann, U.; Ryabova, O.; Saint-Joanis, B.; Cole, S. T. *Science* 2009, *324*, 801−804.

(5) (a) Jagodzinski, T. S. *Chem. Rev.* 2003, *103*, 197−227. (b) Ma, D.; Xie, S.; Xue, P.; Zhang, X.; Dong, J.; Jiang, Y. *Angew. Chem., Int. Ed.* 2009, *48*, 4222−4225; *Angew. Chem.* 2009, *121*, 4286−42. (c) Liu, J.; Xue, Z.; Zeng, Z.; Chen, Y.; Chen, G. *Adv. Synth. Catal.* 2016, *358*, 3694−3699. (d) Dang, P.; Zheng, Z.; Liang, Y. *J. Org. Chem.* 2017, *82*, 2263−2268. (e) Wu, S.; Lei, X.; Fan, E.; Sun, Z. *Org. Lett.* 2018, *20*, 522−525. (f) Xiong, J.; Zhong, G.; Liu, Y. *Adv. Synth. Catal.* 2019, *361*, 550−555.

(6) For selected recent reviews on NHC catalysis: (a) Biju, A. T.; Kuhl, N.; Glorius, F. *Acc. Chem. Res.* 2011, *44*, 1182−1195. (b) Cohen, D. T.; Scheidt, K. A. *Chem. Sci.* 2012, *3*, 53−57. (c) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* 2012, *41*, 3511−3522. (d) Grossmann, A.; Enders, D. *Angew. Chem., Int. Ed.* 2012, *51*, 314−325; *Angew. Chem.* 2012, *124*, 320−332. (e) Ryan, S. J.; Candish, L.; Lupton, D. W. *Chem. Soc. Rev.* 2013, *42*, 4906−4917. (f) Connon, S. J. *Angew. Chem., Int. Ed.* 2014, *53*, 1203−1205; *Angew. Chem.* 2014, *126*, 1225−1227. (g) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. *Nature* 2014, *510*, 485−496. (h) Mahatthananchai, J.; Bode, J. W. *Acc. Chem. Res.* 2014, *47*, 696−707. (i) Menon, R. S.; Biju, A. T.; Nair, V. *Chem. Soc. Rev.* 2015, *44*, 5040−5052. (j) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. *Chem. Rev.* 2015, *115*, 9307−9387. (k) Wang, M. H.; Scheidt, K. A. *Angew. Chem., Int. Ed.* 2016, *55*, 14912−14922; *Angew. Chem.* 2016, *128*, 15134−15145. (l) Zhang, C. J.; Hooper, F.; Lupton, D. W. *ACS Catal.* 2017, *7*, 2583−2596. (m) Chen, X.-Y.; Li, S.; Vetica, F.; Kumar, M.; Enders, D. *iScience* 2018, *2*, 1−26. (n) Chen, X.-Y.; Liu, Q.; Chauhan, P.; Enders, D. *Angew. Chem., Int. Ed.* 2018, *57*, 3862−3873; *Angew. Chem.* 2018, *130*, 3924−3935. (o) Murauski, K. J. R.; Jaworski, A. A.; Scheidt, K. A. *Chem. Soc. Rev.* 2018, *47*, 1773−1782. (p) Mondal, S.; Yetra, S. R.; Mukherjee, S.; Biju, A. T. *Acc. Chem. Res.* 2019, *52*, 425−436.

(7) Xia, F.; Chen, X. Y.; Ye, S. *J. Org. Chem.* 2018, *83*, 15178−15185.

(8) Lu, H.; Zhang, J.-L.; Liu, J.-Y.; Li, H.-Y.; Xu, P.-F. *ACS Catal.* 2017, *7*, 7797−7802.

(9) Fang, C.; Lu, T.; Zhu, J.; Sun, K.; Du, D. *Org. Lett.* 2017, *19*, 3470−3473.

(10) Fukata, Y.; Asano, K.; Matsubara, S. *J. Am. Chem. Soc.* 2015, *137*, 5320−5323.

(11) (a) Marigo, M.; Schulte, T.; Franzen, J.; Jøergensen, K. A. *J. Am. Chem. Soc.* 2005, *127*, 15710−15711. (b) Wang, W.; Li, H.; Wang, J.; Zu, L. *J. Am. Chem. Soc.* 2006, *128*, 10354−10355. (c) Li, H.; Zu, L.; Xie, H.; Wang, J.; Jiang, W.; Wang, W. *Org. Lett.* 2007, *9*, 1833−1835. (d) Melchiorre, P. *Angew. Chem., Int. Ed.* 2012, *51*, 9748−9770; *Angew. Chem.* 2012, *124*, 9886−9909. (e) Cong, Z.-S.; Li, Y.-G.; Du, G.-F.; Gu, C.-Z.; Dai, B.; He, L. *Chem. Commun.* 2017, *53*, 13129−13132.

(12) (a) Raup, D. E. A.; Cardinal-David, B.; Holte, D.; Scheidt, K. A. *Nat. Chem.* 2010, *2*, 766−771. (b) Wang, M. H.; Scheidt, K. A. *Angew. Chem., Int. Ed.* 2016, *55*, 14912−14922; *Angew. Chem.* 2016, *128*, 15134−15145. (c) Chen, J.; Yuan, P.; Wang, L.; Huang, Y. *J. Am. Chem. Soc.* 2017, *139*, 7045−7051. (d) Zhang, Z.-J.; Zhang, L.; Geng, R.-L.; Song, J.; Chen, X.-H.; Gong, L. *Angew. Chem., Int. Ed.* 2019, *58*, 12190−12194; *Angew. Chem.* 2019, *131*, 12318−12322.

(13) Ghosh, A.; Barik, S.; Biju, A. T. *Org. Lett.* 2019, *21*, 8598−8602.

(14) Maki, B. E.; Chan, A.; Phillips, E. M.; Scheidt, K. A. *Org. Lett.* 2007, *9*, 371−374.

(15) Zhao, C.; Li, F.; Wang, J. *Angew. Chem., Int. Ed.* 2016, *55*, 1820−824; *Angew. Chem.* 2016, *55*, 1820−1824.

(16) Namitharan, K.; Zhu, T.; Cheng, J.; Zheng, P.; Li, X.; Yang, S.; Song, B.-A.; Chi, Y. R. *Nat. Commun.* 2014, *5*, 3982.