Organic LETTERS

Letter

pubs.acs.org/OrgLett

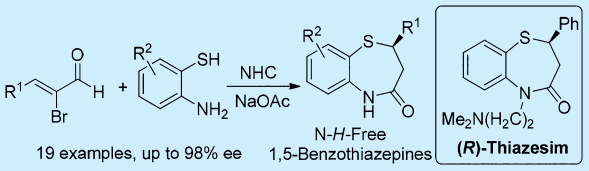
Formal [3 + 4] Annulation of α,β-Unsaturated Acyl Azoliums: Access to Enantioenriched N–*H*-Free 1,5-Benzothiazepines

Chao Fang, Tao Lu,* Jindong Zhu, Kewen Sun, and Ding Du*

State Key Laboratory of Natural Medicines, Department of Organic Chemistry, China Pharmaceutical University, Nanjing, 210009, P. R. China

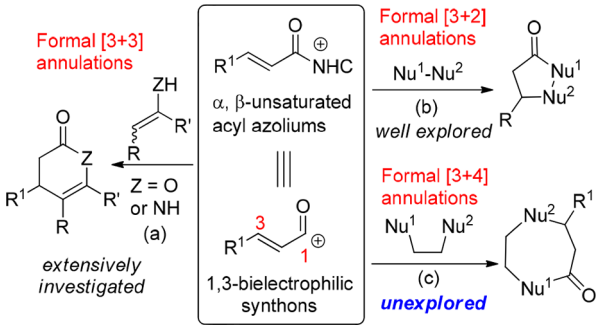
Supporting Information

ABSTRACT: An unprecedented formal [3 + 4] annulation of α,β-unsaturated acyl azoliums with 2-aminobenzenethiols has been utilized to synthesize enantioenriched N–*H*-free 1,5-benzothiazepines, which are recognized as privileged structures in numerous biologically active scaffolds. This protocol offers a rapid and direct pathway to access the target compounds with high enantioselectivities and has been applied in the concise synthesis of chiral drug (*R*)-thiazesim.



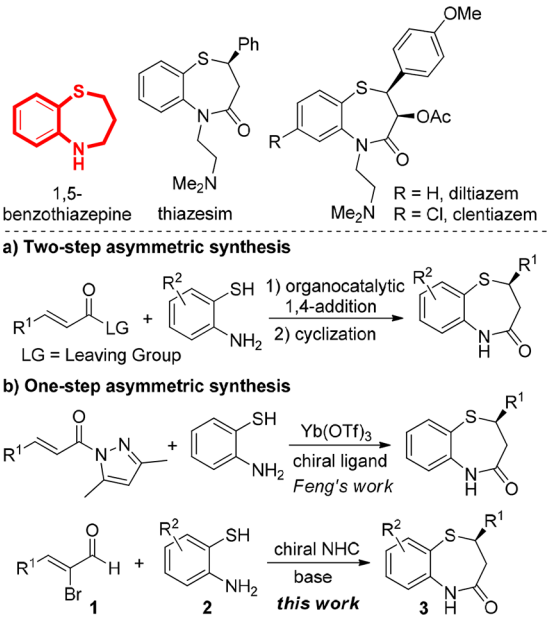
Over the past decade, N-heterocyclic carbenes (NHCs) have emerged as powerful organocatalysts for a large number of chemical transformations that cannot be achieved by traditional strategies.[1] Particularly, the application of α,β-unsaturated acyl azoliums as versatile 1,3-bielectrophilic synthons in annulation reactions has attracted much attention from organic chemists. The formal [3 + 3][2] and [3 + 2][3] annulations of α,β-unsaturated acyl azoliums have been intensively investigated respectively for the synthesis of diverse six-member or five-member heterocyclic compounds (Scheme 1a and 1b). However, the formal [3 + 4] annulations of α,β-unsaturated acyl azoliums for the synthesis of seven-member ring systems are challenging and have not yet been explored (Scheme 1c).

Scheme 1. Formal [3+m] annulations of α,β-unsaturated acyl azoliums



The 1,5-benzothiazepine heterocyclic motif is a fascinating versatile pharmacophore frequently found in numerous biologically active scaffolds such as thiazesim, diltiazem, and clentiazem, which have been widely investigated in the area of pharmaceutical drugs (Scheme 2).[4] Thus, the development of efficient and enantioselective synthetic approaches to diverse 1,5-benzothiazepine derivatives is of great importance for drug discovery. Although a number of synthetic methods to construct this framework have been documented,[4b,5] catalytic asymmetric synthesis is still challenging. Recently, Matsubara[6] and Glorius[7] developed two different efficient approaches to enantioenriched *N*-substituted 1,5-benzothiazepines via an organocatalytic [4 + 3] cycloaddition and transition-metal-catalytic hydrogenation, respectively. These two elegant methods afforded the target molecules which inevitably underwent *N*-deprotection processes for further *N*-function-

Scheme 2. Asymmetric synthesis of *N*-H-free 1,5-benzothiazepines



Received: May 13, 2017

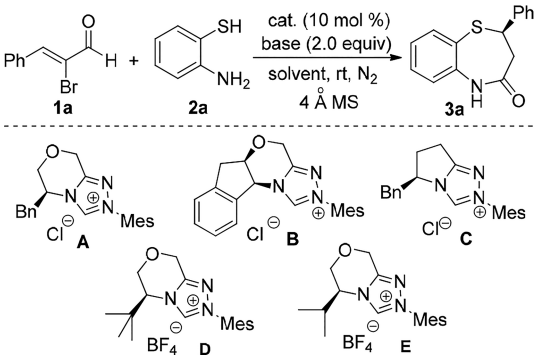
DOI: 10.1021/acs.orglett.7b01457
Org. Lett. XXXX, XXX, XXX–XXX

ality. Therefore, it is worthwhile to explore simple and efficient methods to access optically active N−H-free 1,5-benzothiazepines to circumvent the additional deprotection step for the purposes of atom-economy and sustainability. To date, a few asymmetric syntheses of N−H-free 1,5-benzothiazepines have been achieved typically through two steps involving sequential organocatalytic 1,4-addition of 2-aminobenzenethiols to diverse Michael acceptors and cyclization (Scheme 2a).[8] However, the direct one-step asymmetric synthesis of N−H-free 1,5-benzothiazepines remains very limited. There is only one type of reaction very recently reported by Feng[9] who applied a chiral *N,N′*-dioxide-Yb^{III} complex in the direct synthesis of the optically active N−H-free 1,5-benzothiazepine derivatives starting from *α,β*-unsaturated pyrazoleamides and 2-aminobenzenethiols (Scheme 2b). In continuation of our studies on the exploration of NHC-catalyzed formal [3 + *m*] annulations,[2k−m,3c,10] we envisioned a direct pathway to access optically active N−H-free 1,5-benzothiazepines **3** via the formal [3 + 4] annulation of *α,β*-unsaturated acyl azoliums with 2-aminobenzenethiols **2** (Scheme 2b). It is noteworthy that formal [3 + 4] annulations of homoenolates[11] and dienolates[12] with NHC catalysis have been successfully applied for the synthesis of seven-membered cyclic compounds. Herein, we report the first application of *α,β*-unsaturated acyl azoliums derived from 2-bromoenals **1** in the formal [3 + 4] annulations.

Since *α*-bromoenals[13] were frequently used as *α,β*-unsaturated acyl azolium precursors, we commenced our study with the reaction of *α*-bromoenal **1a** with 2-aminobenzenethiol **2a** in the presence of 10 mol % of a carbene precursor and 2.0 equiv of a base (Table 1). Initially, the efficiency of several commonly used chiral NHC precursors **A**−**E** was evaluated in PhMe employing NaOAc as the base (entries 1−5). To our delight, these catalysts except **D** proved to be effective for this transformation, while catalyst **E** was established as the optimal one which afforded the desired product **3a** with a moderate yield and high enantioselectivity (entry 5). Unfortunately, we did not obtain positive results when we tried to improve the reaction yield by using different solvents and bases (entries 6−12). However, increasing the catalyst loading to 20 mol % could enhance the yield to 63% with a maintained enantioselectivity (entry 13), which was finally established as the optimal condition for the scope exploration. The absolute configuration of **3a** was assigned as (*R*) by comparing the optical rotation with the literature value.[8c,9]

With the optimized conditions in hand, we focused our attention to exploring the reaction scope (Table 2). Initially, a series of *α*-bromoenals **1b**−**k** with diverse substituents on the phenyl ring were examined (entries 2−11). It seems that the electronic nature and steric hindrance of the substituents had little influence on the reaction yields and enantioselectivity since the desired products **3b**−**k** were all obtained in moderate yields and high enantioselectivities. Additionally, 1-naphthyl- and 2-heteroaromatic-substituted *α*-bromoenals **1l**−**n** were also suitable for this protocol, affording the desired products **3l**−**n** in 64−73% yields with 84−97% ee (entries 12−14). Gratifyingly, this protocol was also applicable for the synthesis of styryl- and alkyl-substituted benzothiazepines **3o** and **3p** although with somewhat decreased yields and enantioselectivities (entries 15 and 16). Then, the generality of this protocol was further evaluated by using several substituted 2-aminobenzenethiols **2b**−**d** as the 1,4-bisnucleophiles (entries 17−19). As expected, the reactions of these substrates worked equally

Table 1. Optimization of the Reaction Conditions[a]



entry	cat.	solvent	base	yield (%)[b]	ee (%)[c]
1	**A**	PhMe	NaOAc	40	78
2	**B**	PhMe	NaOAc	22	90
3	**C**	PhMe	NaOAc	18	79
4	**D**	PhMe	NaOAc	trace	–
5	**E**	PhMe	NaOAc	43	94
6	**E**	mesitylene	NaOAc	30	92
7	**E**	DCM	NaOAc	trace	–
8	**E**	THF	NaOAc	trace	–
9	**E**	PhMe	DIPEA	trace	–
10	**E**	PhMe	tBuOK	trace	–
11	**E**	PhMe	CsOAc	37	93
12	**E**	PhMe	LiOAc	31	93
13[d]	**E**	PhMe	NaOAc	63	94

[a]Unless otherwise noted, all reactions were performed on a 0.1 mmol scale with 1.0 equiv of **1a**, 1.5 equiv of **2a**, 10 mol % of a carbene precursor, 2.0 equiv of a base, and 100 mg of 4 Å MS in an anhydrous solvent (2 mL) at rt for 36 h under N_2. [b]Isolated yields based on **1a**. [c]Ee values were determined by HPLC analysis. [d]20 mol % **E** was used. Mes = 2,4,6-$(CH_3)_3C_6H_2$; DIPEA = *N,N*-diisopropylethylamine.

smoothly to give the desired products **3q**−**s** in moderate yields and high enantioselectivities.

We also tested the reactivity of (*E*)-**1a** that was found to be inferior to (*Z*)-**1a** in terms of both reaction yield and enantioselectivity (Scheme 3a). Therefore, it may be concluded that the stereochemistry of 2-bromoenals **1** has great impact on the reaction. As *α,β*-unsaturated acyl azoliums can be generated from other precursors other than *α*-bromoenals, we applied three activated esters **4a**−**c** and ynal **5** as the precursors to test their reactivity and feasibility for this formal [3 + 4] annulations. It was disappointing that activated esters **4a**−**c** afforded the desired product **3a** in 32−41% yields with poor enantioselectivities (Scheme 3b).[14] Ynal **5** was also unsuitable for this transformation due to the formation of an imine byproduct via the condensation of aldehyde **5** with **2a** (Scheme 3c).

In order to further explore the synthetic utility of this methodology, a scale-up synthesis of product **3a** and a concise one-step synthesis of the antidepressant drug (*R*)-thiazesim from **3a** were carried out as shown in Scheme 4. On one hand, the reaction yield and enantioselectivity of the scale-up synthesis were slightly decreased (Scheme 4a). It is noteworthy that the scale-up reaction should be carried out under a lower temperature to decrease the amount of imine byproduct formed between aldehyde **1a** and amine **2a**. On the other hand, natural product (*R*)-thiazesim was successfully synthesized from **3a** in 91% yield with 93% ee (Scheme 4b).

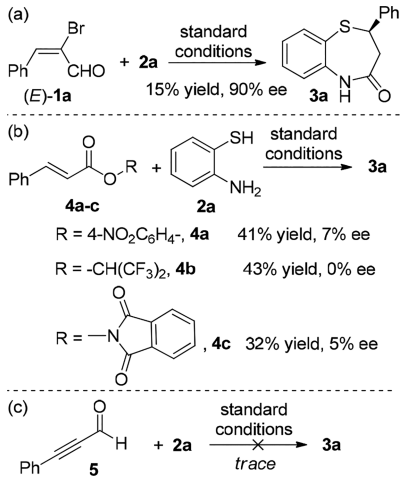
DOI: 10.1021/acs.orglett.7b01457
Org. Lett. XXXX, XXX, XXX−XXX

Table 2. Reaction Scope[a]

entry	R^1, 1	R^2, 2	3	yield (%)[b]	ee (%)[c]
1	C_6H_5, **1a**	H, **2a**	**3a**	63	94
2	2-FC_6H_4, **1b**	H, **2a**	**3b**	63	91
3	2-$OMeC_6H_4$, **1c**	H, **2a**	**3c**	66	91
4	3-FC_6H_4, **1d**	H, **2a**	**3d**	52	94
5	3-MeC_6H_4, **1e**	H, **2a**	**3e**	62	93
6	3-$OMeC_6H_4$, **1f**	H, **2a**	**3f**	50	90
7	4-ClC_6H_4, **1g**	H, **2a**	**3g**	65	98
8	4-BrC_6H_4, **1h**	H, **2a**	**3h**	54	97
9	4-$CF_3C_6H_4$, **1i**	H, **2a**	**3i**	50	94
10	4-MeC_6H_4, **1j**	H, **2a**	**3j**	52	92
11	4-$OMeC_6H_4$, **1k**	H, **2a**	**3k**	53	93
12	1-naphthyl, **1l**	H, **2a**	**3l**	65	94
13	2-thienyl, **1m**	H, **2a**	**3m**	64	97
14	2-furyl, **1n**	H, **2a**	**3n**	73	84
15	styryl, **1o**	H, **2a**	**3o**	61	86
16	*n*-propyl, **1p**	H, **2a**	**3p**	46	80
17	C_6H_5, **1a**	4-Cl, **2b**	**3q**	59	88
18	C_6H_5, **1a**	5-Cl, **2c**	**3r**	59	93
19	C_6H_5, **1a**	5-Me, **2d**	**3s**	70	91

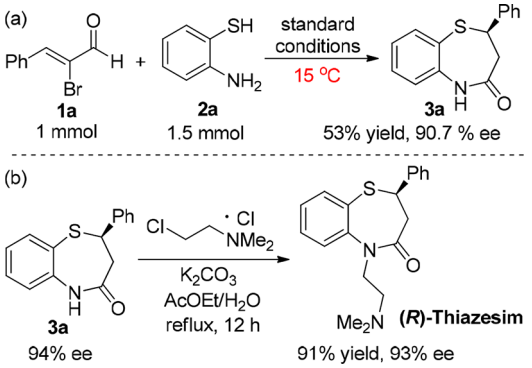
[a]Unless otherwise noted, all reactions were performed on a 0.1 mmol scale with 1.0 equiv of **1**, 1.5 equiv of **2**, 20 mol % of **E**, 2.0 equiv of NaOAc, and 100 mg of 4 Å MS in anhydrous PhMe (2 mL) at rt for 36 h under N_2. [b]Isolated yields based on **1**. [c]Ee values were determined by HPLC analysis.

Scheme 3. Application of Other α,β-Unsaturated Acyl Azolium Precursors for the Synthesis of 3a



In summary, we have demonstrated a direct and enantioselective synthesis of N−H-free 1,5-benzothiazepine derivatives via an NHC-mediated unprecedented formal [3 + 4] annulation of α,β-unsaturated acyl azoliums with substituted 2-aminobenzenethiols. This protocol offers an alternative and rapid access to a broad range of N−H-free 1,5-benzothiazepines with high enantioselectivities. Moreover, this protocol was successfully applied in the concise synthesis of chiral drug (*R*)-thiazesim. Further research and application of α,β-unsaturated acyl azoliums in the construction of diverse seven-membered heterocyclic systems are currently underway.

Scheme 4. A Scale-up Synthesis of 3a and a Concise Synthesis of (*R*)-Thiazesim from 3a



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01457.

Experimental procedures and spectral data for all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: lut163@163.com.
*E-mail: ddmn9999@cpu.edu.cn.

ORCID

Ding Du: 0000-0002-4615-5433

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work is funded by the National Natural Science Foundation of China (No. 21572270), the Qing Lan Project of Jiangsu Province, and the Priority Academic Program Development of Jiangsu Higher Education Institutions.

■ REFERENCES

(1) For selected reviews, see: (a) Zhang, C.-H.; Hooper, J. F.; Lupton, D. W. *ACS Catal.* **2017**, *7*, 2583. (b) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. *Chem. Rev.* **2015**, *115*, 9307. (c) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 3511. (d) Tang, W.; Du, D. *Chem. Rec.* **2016**, *16*, 1489. (e) Nair, V.; Vellalath, S.; Babu, B. P. *Chem. Soc. Rev.* **2008**, *37*, 2691. (f) Biju, A. T.; Kuhl, N.; Glorius, F. *Acc. Chem. Res.* **2011**, *44*, 1182. (g) Dominguez de Maria, P.; Shanmuganathan, S. *Curr. Org. Chem.* **2011**, *15*, 2083. (h) Albanese, D. C. M.; Gaggero, N. *Eur. J. Org. Chem.* **2014**, *2014*, 5631. (i) Ryan, S. J.; Candish, L.; Lupton, D. W. *Chem. Soc. Rev.* **2013**, *42*, 4906. (j) De Sarkar, S.; Biswas, A.; Samanta, R. C.; Studer, A. *Chem. - Eur. J.* **2013**, *19*, 4664. (k) Chen, X.-Y.; Ye, S. *Org. Biomol. Chem.* **2013**, *11*, 7991. (l) Grossmann, A.; Enders, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 314.

(2) For selected example, see: (a) Xia, W.; Yao, H.; Liu, D.; Zhao, L.; Zhou, Y.; Liu, H. *Adv. Synth. Catal.* **2016**, *358*, 1864. (b) Que, Y.; Lu, Y.; Wang, W.; Wang, Y.; Wang, H.; Yu, C.; Li, T.; Wang, X.-S.; Shen, S.; Yao, C. *Chem. - Asian J.* **2016**, *11*, 678. (c) Zhang, C.-L.; Wang, D.-L.; Chen, K.-Q.; Ye, S. *Org. Biomol. Chem.* **2015**, *13*, 11255. (d) Xie, D.; Yang, L.; Lin, Y.; Zhang, Z.; Chen, D.; Zeng, X.; Zhong, G. *Org. Lett.* **2015**, *17*, 2318. (e) Mao, J.-H.; Wang, Z.-T.; Wang, Z.-Y.; Cheng, Y. *J. Org. Chem.* **2015**, *80*, 6350. (f) Kaeobamrung, J.;

DOI: 10.1021/acs.orglett.7b01457
Org. Lett. XXXX, XXX, XXX−XXX

Mahatthananchai, J.; Zheng, P.; Bode, J. W. *J. Am. Chem. Soc.* **2010**, *132*, 8810. (g) De Sarkar, S. D.; Studer, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 9266. (h) Zhu, Z. Q.; Xiao, J. C. *Adv. Synth. Catal.* **2010**, *352*, 2455. (i) Kravina, A. G.; Mahatthananchai, J.; Bode, J. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 9433. (j) Mahatthananchai, J.; Kaeobamrung, J.; Bode, J. W. *ACS Catal.* **2012**, *2*, 494. (k) Lu, Y.; Tang, W.; Zhang, Y.; Du, D.; Lu, T. *Adv. Synth. Catal.* **2013**, *355*, 321. (l) Hu, S.; Wang, B.; Zhang, Y.; Tang, W.; Fang, M.; Lu, T.; Du, D. *Org. Biomol. Chem.* **2015**, *13*, 4661. (m) Xu, J.; Zhang, W.; Liu, Y.; Zhu, S.; Liu, M.; Hua, X.; Chen, S.; Lu, T.; Du, D. *RSC Adv.* **2016**, *6*, 18601.

(3) (a) Chen, K.-Q.; Li, Y.; Zhang, C.-L.; Sun, D.-Q.; Ye, S. *Org. Biomol. Chem.* **2016**, *14*, 2007. (b) Huang, W.; Zhao, Q.; Han, B.; Wang, B.; Leng, H.-J.; Peng, C. *RSC Adv.* **2015**, *5*, 26972. (c) Jiang, D.; Dong, S.; Tang, W.; Lu, T.; Du, D. *J. Org. Chem.* **2015**, *80*, 11593. (d) Wu, X.; Liu, B.; Zhang, Y.; Jeret, M.; Wang, H.; Zheng, P.; Yang, S.; Song, B.-A.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2016**, *55*, 12280.

(4) For selected examples, see: (a) Bariwal, J. B.; Upadhyay, K. D.; Manvar, A. T.; Trivedi, J. C.; Singh, J. S.; Jain, K. S.; Shah, A. K. *Eur. J. Med. Chem.* **2008**, *43*, 2279. (b) Lévai, A. *J. Heterocycl. Chem.* **2000**, *37*, 199. (c) Zhang, P.; Hu, H.-R.; Huang, Z.-H.; Lei, J.-Y.; Chu, Y.; Ye, D.-Y. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 7232. (d) Zhang, P.; Hu, H.-R.; Bian, S.-H.; Huang, Z.-H.; Chu, Y.; Ye, D.-Y. *Eur. J. Med. Chem.* **2013**, *61*, 95.

(5) For selected examples, see: (a) Phippen, C. B. W.; McErlean, C. S. P. *Tetrahedron Lett.* **2011**, *52*, 1490. (b) Dike, S. Y.; Ner, D. H.; Kumar, A. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 383. (c) Lévai, A.; Kiss-Szikszai, A. *ARKIVOC* **2008**, *i*, 65. (d) Wang, X.; Li, Z.; Zhu, X.; Mao, H.; Zou, X.; Kong, L.; Li, X. *Tetrahedron* **2008**, *64*, 6510. (e) Zhang, P.; Ye, D.; Chu, Y. *Tetrahedron Lett.* **2016**, *57*, 3743. (f) Corti, V.; Camarero Gonzalez, P.; Febvay, J.; Caruana, L.; Mazzanti, A.; Fochi, M.; Bernardi, L. *Eur. J. Org. Chem.* **2017**, *2017*, 49.

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

(7) Li, W.; Schlepphorst, C.; Daniliuc, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2016**, *55*, 3300.

(8) (a) Ogawa, T.; Kumagai, N.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 8551. (b) Fang, X.; Li, J.; Wang, C.-J. *Org. Lett.* **2013**, *15*, 3448. (c) Meninno, S.; Volpe, C.; Lattanzi, A. *Chem. - Eur. J.* **2017**, *23*, 4547.

(9) Wang, G.; Tang, Y.; Zhang, Y.; Liu, X.; Lin, L.; Feng, X. *Chem. - Eur. J.* **2017**, *23*, 554.

(10) (a) Du, D.; Hu, Z.; Jin, J.; Lu, Y.; Tang, W.; Wang, B.; Lu, T. *Org. Lett.* **2012**, *14*, 1274. (b) Xu, J.; Hu, S.; Lu, Y.; Dong, Y.; Tang, W.; Lu, T.; Du, D. *Adv. Synth. Catal.* **2015**, *357*, 923. (c) Zhang, Y.; Lu, Y.; Tang, W.; Lu, T.; Du, D. *Org. Biomol. Chem.* **2014**, *12*, 3009.

(11) (a) Lv, H.; Jia, W.-Q.; Sun, L.-H.; Ye, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 8607. (b) Guo, C.; Sahoo, B.; Daniliuc, C. G.; Glorius, F. *J. Am. Chem. Soc.* **2014**, *136*, 17402. (c) Siddiqui, I. R.; Srivastava, A.; Shamim, S.; Srivastava, A.; Shireen; Waseem, M. A.; Singh, R. K. P. *Synlett* **2013**, *24*, 2586. (d) Liang, Z.-Q.; Gao, Z.-H.; Jia, W.-Q.; Ye, S. *Chem. - Eur. J.* **2015**, *21*, 1868. (e) Wang, L.; Li, S.; Blümel, M.; Philipps, A. R.; Wang, A.; Puttreddy, R.; Rissanen, K.; Enders, D. *Angew. Chem., Int. Ed.* **2016**, *55*, 11110.

(12) Wang, M.; Huang, Z.; Xu, J.; Chi, Y. R. *J. Am. Chem. Soc.* **2014**, *136*, 1214.

(13) (a) Sun, F.-G.; Sun, L.-H.; Ye, S. *Adv. Synth. Catal.* **2011**, *353*, 3134. (b) Ni, Q.; Song, X.; Raabe, G.; Enders, D. *Chem. - Asian J.* **2014**, *9*, 1535. (c) Zhang, H.-M.; Jia, W.-Q.; Liang, Z.-Q.; Ye, S. *Asian J. Org. Chem.* **2014**, *3*, 462. (d) Gao, Z.-H.; Chen, X.-Y.; Zhang, H.-M.; Ye, S. *Chem. Commun.* **2015**, *51*, 12040. (e) Yao, C.; Wang, D.; Lu, J.; Li, T.; Jiao, W.; Yu, C. *Chem. - Eur. J.* **2012**, *18*, 1914.

(14) On one hand, it was found that the reactions of **4a−c** in the absence of catayst **E** did not work. On the other hand, we assumed that HOAc generated in the reaction of 2-bromoenals might play a significant role in the enantiocontrol. However, the reaction yields and enantioselectivity were not enhanced even if HOAc was used as an additive in the reactions of **4**.

DOI: 10.1021/acs.orglett.7b01457
Org. Lett. XXXX, XXX, XXX−XXX