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NHC-Catalyzed Enantioselective [3 + 3] Annulation to Construct 5,6-Dihydropyrimidin-4-ones

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c02832 Read Online

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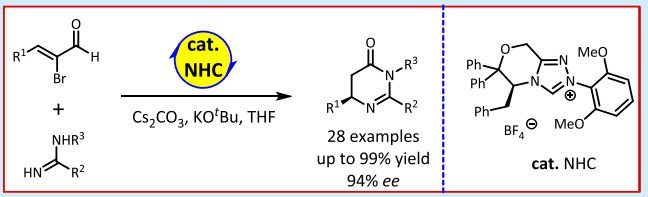
ABSTRACT: The unprecedented enantioselective NHC-catalyzed [3 + 3] annulation of α-bromoenals with amidines via a dual C−N bond formation is described. The protocol allows a rapid preparation of 5,6-dihydropyrimidinones in acceptable yields with good enantioselectivities.



Molecules possessing a pyrimidinones scaffold are of great interest in medicinal chemistry[1] and industry[2] for their biological activities, such as antiviral, antitumor, and antibacterial properties. For example, applycyanin **A**[3a] was proven to have antitumor and antiproliferative activity; BACE-1 inhibitors **B**[3b] and **C**[3c] exhibited potent inhibition of β-secretase in the treatment of Alzheimer's disease. For the construction of chiral pyrimidinone cores, the most common way to introduce chiral centers is through multicomponent condensation or multistep synthesis.[4] Therefore, seeking a new and efficient method to rapid construct chiral pyrimidinones is still in high demand.

In the past few decades, N-heterocyclic carbenes (NHCs) were developed prominently.[5] Especially, NHC organocatalysis has received great attention for its efficiency in the construction of six-membered heterocycles.[6] To our knowledge, catalytic [3 + 3] annulation was widely explored by utilizing NHC-bounded α,β-unsaturated acylazolium with several bisnucleophiles. In 2009, Lupton[7] reported the synthesis of dihydropyranones by the reaction of NHC-bounded α,β-unsaturated acylazoliums with enolates. Other elegant works for enantioselective construction of dihydropyranones via similar strategies were independently presented by the groups of Biju,[8] Bode,[9] Chi,[10] Ma,[11] Studer,[12] Ye,[13] You,[14] and others. Later on, Bode and co-workers reported the catalytic [3 + 3] annulation of stabilized enamines[15a] or *N*-sulfonylimines[15b] as bisnucleophiles to react with α,β-unsaturated acylazoliums. In 2013, the Chi group[16] uncovered a [3 + 3] annulation example of NHC-bounded α,β-unsaturated acylazoliums with enamides. Enders[17] utilized simliar strategy to fuse various tricyclic dihydropyridinones. More recently, Biju[18] and Chi[19] independently disclosed the example of thioamides as bisnucleophiles to construct thiazinones via [3 + 3] annulation. Despite these achievements, the trial of amidines as bisnucleophiles with α,β-unsaturated acylazoliums has not yet been reported in NHC organocatalysis. Herein, we report the unprecedented NHC-catalyzed [3 + 3] annulation of α-bromoenals with N-substituted amidines, affording a variety of functionalized chiral 5,6-dihydropyrimidinones. (See Scheme 1.) Note that this chemistry includes a significant dual C−N bond formation.[20]

Our study was started by examining the model reaction of α-bromoenals **1a** with protected amidines **2a** under the initial conditions of catalyst A, Na_2CO_3 as the base, and tetrahydrofuran (THF) as the solvent (see Table 1). First, unprotected amidine was tested and no desired product was formed. A few protected amidines then were examined. The benzyl protecting group gave better performance than Boc, tosyl, and phenyl groups, resulting in 45% yield and 36% enantiomeric excess (ee) (Table 1, entries 1−4). By switching from catalyst A to catalyst B, ee was decreased dramatically, which indicated the importance of the Mes substituent in the catalyst (Table 1, entry 5). Second, taking into account the fact that the amino-indane-based carbene catalyst C is a more rigid structure, it only achieves 15% ee and a slightly higher yield (49%) (Table 1, entry 6). To further understand the effect of catalyst, triazoline D and E,[21] which are based on a morpholine scaffold, were tested. Pleasingly, ee was increased to 65% (Table 1, entries 7 and 8). Subsequently, bases and solvents were screened. Cs_2CO_3 and THF led to a higher yield (85%) and ee (75%) than others (Table 1, entries 9−14). Meanwhile, by adding KO^{t}Bu and HO^{t}Bu, the reaction rate was improved, affording 91% yield and 77% ee (Table 1, entry 15). In the absence of KO^{t}Bu or HO^{t}Bu, lower yields and ee were identified (see the Supporting Information (SI)). An excellent yield (96%) and a high ee (85%) were achieved by further decreasing the reaction temperature to −20 °C (Table 1, entry

Received: August 24, 2020

https://dx.doi.org/10.1021/acs.orglett.0c02832
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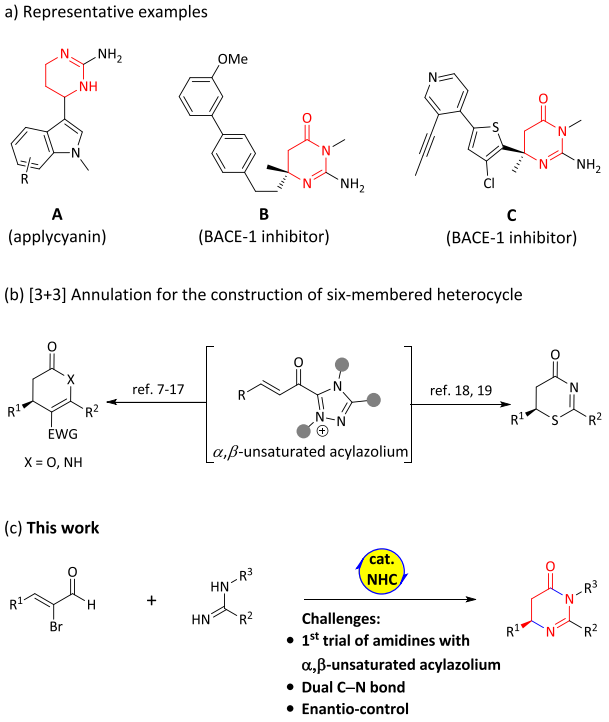
Scheme 1. NHC-Catalyzed [3 + 3] Annulation for the Construction of 5,6-Dihydropyrimidinones

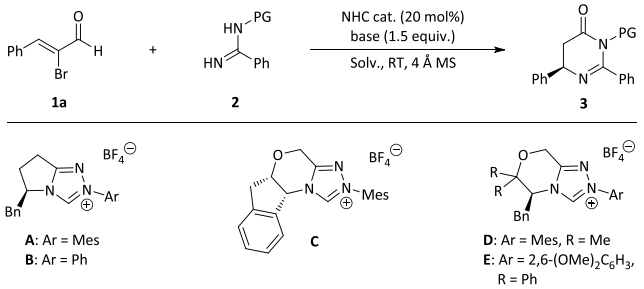


16). In the proton transfer phase, we postulated that the influence of KO^{t}Bu and HO^{t}Bu on the reaction rate is considered to be crucial. In fact, the role of KO^{t}Bu has been discussed by the group of Glorius in the report of an enantioseletive NHC-catalyzed Stetter reaction.[22] In this case, KO^{t}Bu is found to significantly reduce the transition states more than the pathways without it, and HO^{t}Bu is considered to have an impact in the proton transfer step. By further lowering the catalytic amount to 10 mol % or 5 mol %, the reaction can still afford high yield and maintain a good ee, although it takes a longer time (Table 1, entries 17 and 18).

With the optimal condition in hand (Table 1, entry 17), we turned our attention to expanding the substrate scope. A variety of α-bromoenals were tested first (see Scheme 2). Electron-rich or electron-withdrawing groups at the *para*-position of the β-phenyl group led to high yields and good ee (**3b**–**3e**). Substituents at the *meta*- or *ortho*-position were also tolerated and afforded good to high yields and good ee (**3f**–**3h**). Pleasingly, naphthyl- or benzodioxin-substituted α-bromoenals also afforded high yields and good ee (**3i**–**3k**). Substrates bearing heterocycle rings such as furan, benzofuran, or thiophene resulted in lower yields but maintained good ee (**3l**–**3n**). When the R substituent is an alkyl group, the reaction is still occurred, but the yield and enantioselectivity are only moderate (**3o**).

The scope of the amidines was investigated next (see Scheme 3). Either electron-donating or electron-withdrawing

Table 1. Optimization of the Reaction Conditions[a]



entry	PG	catalyst	base	solvent	yield[b] (%)	enantiomeric excess, ee[c] (%)
1	Boc	A	Na_2CO_3	THF	trace	–
2	Ts	A	Na_2CO_3	THF	trace	–
3	Ph	A	Na_2CO_3	THF	31	5
4	Bn	A	Na_2CO_3	THF	45	36
5	Bn	B	Na_2CO_3	THF	38	5
6	Bn	C	Na_2CO_3	THF	49	−15
7	Bn	D	Na_2CO_3	THF	47	47
8	Bn	E	Na_2CO_3	THF	54	65
9	Bn	E	K_2CO_3	THF	73	60
10	Bn	E	KO^{t}Bu	THF	53	71
11	Bn	E	Cs_2CO_3	THF	85	75
12	Bn	E	Cs_2CO_3	toluene	65	67
13	Bn	E	Cs_2CO_3	MeCN	47	55
14	Bn	E	Cs_2CO_3	CH_2Cl_2	61	33
15[d]	Bn	E	Cs_2CO_3/KO^{t}Bu	THF	91	77
16[d,e]	Bn	E	Cs_2CO_3/KO^{t}Bu	THF/HO^{t}Bu	96	85
17[d,e,f]	**Bn**	**E**	**Cs_2CO_3/KO^{t}Bu**	**THF/HO^{t}Bu**	**93**	**85**
18[d,e,g]	Bn	E	Cs_2CO_3/KO^{t}Bu	THF/HO^{t}Bu	78	84

[a]Reaction conditions: **1a** (0.15 mmol), **2a** (0.1 mmol), catalyst (20 mol %), base (0.15 mmol), solvent (1.0 mL), room temperature, 4 Å MS (100 mg), 12 h. [b]Isolated yield. [c]As determined by chiral HPLC. [d]With the addition of Cs_2CO_3 (1.0 equiv), KO^{t}Bu (0.3 equiv), HO^{t}Bu (0.1 mL), THF (0.9 mL), 2.5 h. [e]Conditions: −20 °C, 5 h. [f]Catalyst **E** (10 mol %), 15 h. [g]Catalyst **E** (5 mol %), 48 h.

https://dx.doi.org/10.1021/acs.orglett.0c02832
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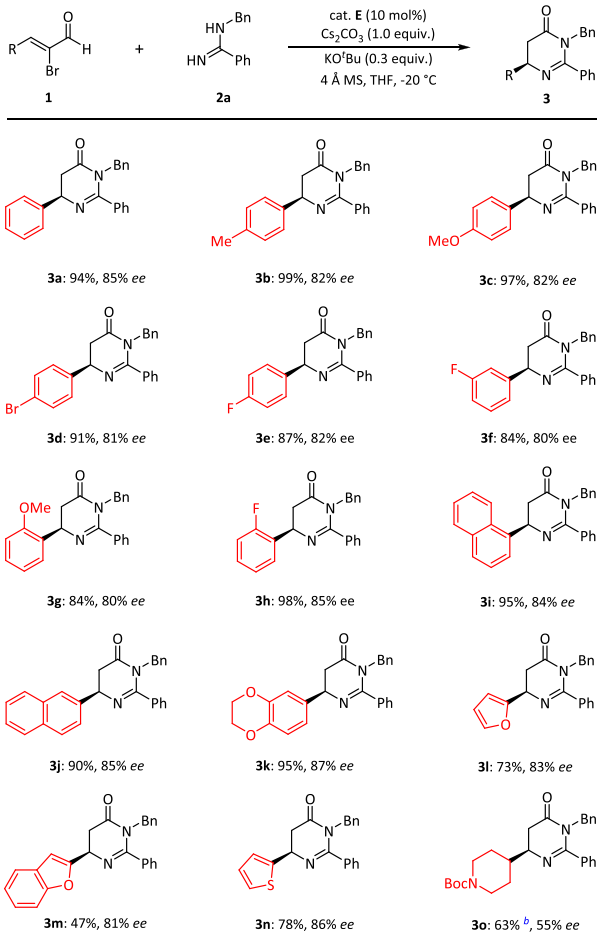
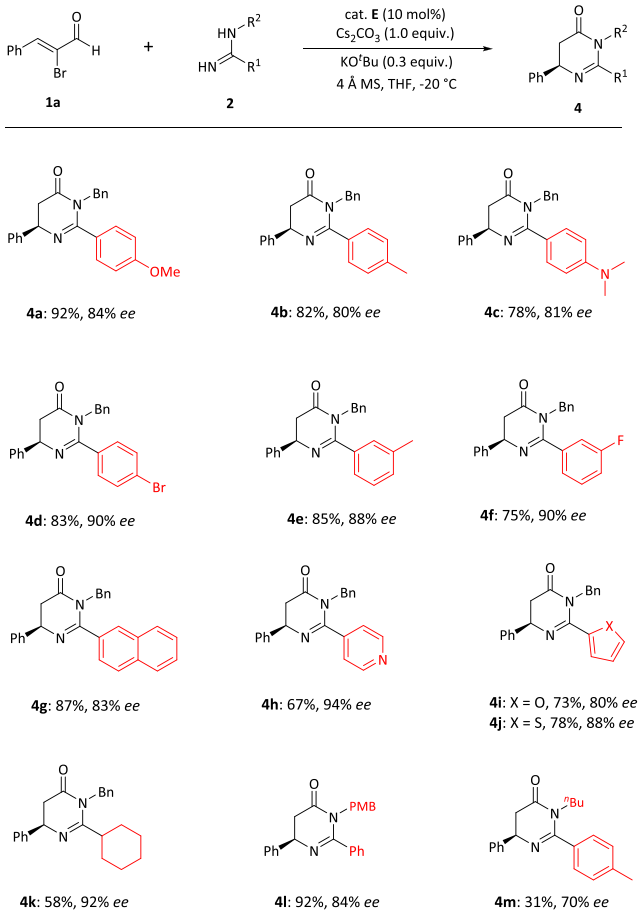
Scheme 2. Scope of α-Bromoenals[a]



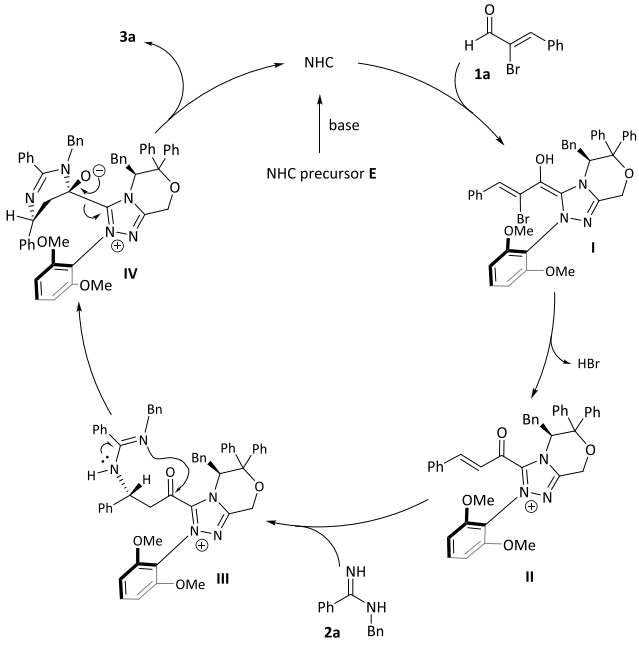
[a]Reaction conditions: **1a** (0.15 mmol), **2a** (0.1 mmol), catalyst E (10 mol %), Cs_2CO_3 (1.0 equiv), KO^{t}Bu (0.3 equiv), HO^{t}Bu (0.1 mL), and THF (0.9 mL), −20 °C, 4 Å MS (100 mg). [b]Catalyst E (20 mol %), 48 h.

Scheme 3. Substrate Scope of Amidines[a]



[a]Reaction conditions: 1a (0.15 mmol), **2a** (0.1 mmol), catalyst E (10 mol %), Cs_2CO_3 (1.0 equiv), KOtBu (0.3 equiv), HOtBu (0.1 mL), and THF (0.9 mL), −20 °C, 4 Å MS (100 mg).

Scheme 4. Postulated Mechanism



groups at the *para* position of phenyl ring were both tolerated (**4a**−**4d**). Bearing a methyl or fluorine at the *meta* position was also compatible with the optimal reaction conditions (**4e**, **4f**). The 2-naphthyl group or heterocycles (e.g., pyridine, furan, or thiophene) were compatible with the catalytic manner (**4g**−**4j**). When the aryl group was replaced by an alkyl substituent, 92% ee could still be obtained, but only 58% yield was achieved (**4k**). When the benzyl group was replaced by *p*-methoxybenzyl (**4l**) or *n*-butyl substituent (**4m**), acceptable yields and good enantioselectivities were still obtained. Unfortunately, no desired product was achieved when the *N*,*N*-diphenyl guanidine was employed as a substrate. The absolute configuration of the **4d** was determined by single-crystal X-ray crystallography, and other products were assigned by analogy (see the Supporting Information).

A postulated mechanism is illustrated in Scheme 4. The reaction starts from the release of NHC from its precursor in the presence of base. The addition of NHC to α-bromoenal **1a** forms homoenolate **I**, which then undergoes a tautomerization and debromination to afford α,β-unsaturated acyl azolium intermediate **II**. Intermediate **II** reacting with amidine **2a** can quickly convert to intermediate **III** after 1,4-addition. After the intramolecular cycloaddition of intermediate **III**, intermediate

https://dx.doi.org/10.1021/acs.orglett.0c02832
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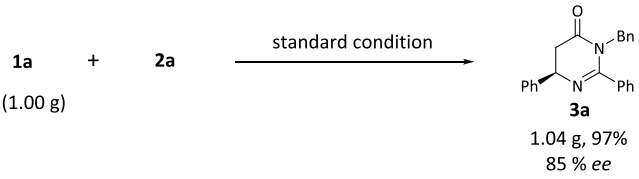
IV is formed. With the collapse of IV, product 3a is released and the active catalyst is regenerated.

To demonstrate the practical utility of this protocol, a gram-scale synthesis was conducted under the standard reaction conditions (Scheme 5), and 3a was obtained without any loss of yield and enantioselectivity (97%, 85% ee).

Scheme 5. Gram-Scale Synthesis



In summary, we have developed an unprecedented carbene-catalyzed [3 + 3] annulation of α-bromoenals with amidines to yield 5,6-dihydropyrimidin-4-ones with good enantiocontrol. This new protocol provides a rapid assembly of optically active 5,6-dihydropyrimidin-4-ones from simple and readily available starting materials under mild reaction conditions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02832.

Experimental procedures, product characterization, copies of NMR spectra, X-ray diffraction data, and HPLC spectra (PDF)

Accession Codes

CCDC 2024823 contains the supplementary crystallographic data for this paper. These data can be obtained free of chargeviawww.ccdc.cam.ac.uk/data_request/cif, or by emailingdata_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (Nos. 21871160, 21672121), the National "Thousand Plan" Youth Program of China, the National "Ten Thousand Plan (Leading Talents)" of China, the Innovation Promotion Program of Ministry of Science & Technology (China),Tsinghua University, the Bayer Investigator Fellow Award, and the Fellowship of Tsinghua-Peking Centre for Life Sciences (CLS) for their generous financial support.

■ REFERENCES

(1) (a) Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043−1052. (b) Kaur, R.; Chaudhary, S.; Kumar, K.; Gupta, M. K.; Rawal, R. K. *Eur. J. Med. Chem.* **2017**, *132*, 108−134. (c) Matos, L. H. S.; Masson, F. T.; Simeoni, L. A.; Homem-de-Mello, M. *Eur. J. Med. Chem.* **2018**, *143*, 1779−1789.

(2) (a) Atwal, K. S.; Swanson, B. N.; Unger, S. E.; Floyd, D. M.; Moreland, S.; Hedberg, A.; O'Reilly, B. C. *J. Med. Chem.* **1991**, *34*, 806−811. (b) Rovnyak, G. C.; Atwal, K. S.; Hedberg, A.; Kimball, S. D.; Moreland, S.; Gougoutas, J. Z.; O'Reilly, B. C.; Schwartz, J.; Malley, M. F. *J. Med. Chem.* **1992**, *35*, 3254−3263. (c) Crespo, A.; El Maatougui, A.; Biagini, P.; Azuaje, J.; Coelho, A.; Brea, J.; Loza, M. I.; Cadavid, M. I.; García-Mera, X.; Gutiérrez-de-Terán, H.; Sotelo, E. *ACS Med. Chem. Lett.* **2013**, *4*, 1031−1036.

(3) (a) Šíša, M.; Pla, D.; Altuna, M.; Francesch, A.; Cuevas, C.; Albericio, F.; Álvarez, M. *J. Med. Chem.* **2009**, *52*, 6217−6223. (b) Edwards, P. D.; Albert, J. S.; Sylvester, M.; Aharony, D.; Andisik, D.; Callaghan, O.; Campbell, J. B.; Carr, R. A.; Chessari, G.; Congreve, M.; Frederickson, M.; Folmer, R. H. A.; Geschwindner, S.; Koether, G.; Kolmodin, K.; Krumrine, J.; Mauger, R. C.; Murray, C. W.; Olsson, L.-L.; Patel, S.; Spear, N.; Tian, G. *J. Med. Chem.* **2007**, *50*, 5912−5925. (c) Stamford, A. W.; Scott, J. D.; Li, S. W.; Babu, S.; Tadesse, D.; Hunter, R.; Wu, Y.; Misiaszek, J.; Cumming, J. N.; Gilbert, E. J.; Huang, C.; McKittrick, B. A.; Hong, L.; Guo, T.; Zhu, Z.; Strickland, C.; Orth, P.; Voigt, J. H.; Kennedy, M. E.; Chen, X.; Kuvelkar, R.; Hodgson, R.; Hyde, L. A.; Cox, K.; Favreau, L.; Parker, E. M.; Greenlee, W. J. *ACS Med. Chem. Lett.* **2012**, *3*, 897−902.

(4) (a) Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360−416. (b) Kappe, C. O. The Biginelli Reaction. In *Multicomponent Reactions*; Zhu, J., Bienayme, H., Eds.; Wiley−VCH: Weinheim, Germany, 2005; pp 95−120. (c) Chen, X.-H.; Xu, X.-Y.; Liu, H.; Cun, L.-F.; Gong, L.-Z. *J. Am. Chem. Soc.* **2006**, *128*, 14802−14803. (d) Goss, J. M.; Schaus, S. E. *J. Org. Chem.* **2008**, *73*, 7651−7656. (e) Singh, O. M.; Devi, N. S. *J. Org. Chem.* **2009**, *74*, 3141−3144. (f) Mohammadnejad, M.; Hashtroudi, M. S.; Balalaie, S. *Heterocycl. Commun.* **2009**, *15*, 459−465. (g) Yu, J.; Shi, F.; Gong, L.-Z. *Acc. Chem. Res.* **2011**, *44* (11), 1156−1171. (h) Oberg, K. M.; Rovis, T. *J. Am. Chem. Soc.* **2011**, *133*, 4785−4787. (i) Wan, J.-P.; Lin, Y.; Hu, K.; Liu, Y. *Beilstein J. Org. Chem.* **2014**, *10*, 287−292. (j) Ghandi, M.; Vazifeh, M. J. *J. Iran. Chem. Soc.* **2015**, *12*, 1131−1137. (k) Lillo, V. J.; Mansilla, J.; Saá, J. M. *Angew. Chem., Int. Ed.* **2016**, *55*, 4312−4316. (l) Meng, F.-J.; Shi, L.; Feng, G.-S.; Sun, L.; Zhou, Y.-G. *J. Org. Chem.* **2019**, *84*, 4435−4442. (m) Hu, X.; Guo, J.; Wang, C.; Zhang, R.; Borovkov, V. *Beilstein J. Org. Chem.* **2020**, *16*, 1875−1880. (n) Pair, E.; Levacher, V.; Brière, J.-F. *RSC Adv.* **2015**, *5*, 46267−46271. (o) Ametovski, J.; Dutta, U.; Burchill, L.; Maiti, D.; Lupton, D. W.; Hooper, J. F. *Chem. Commun.* **2017**, *53*, 13071−13074.

(5) (a) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606−5655. (b) Nair, V.; Menon, R. S.; Biju, A. T.; Sinu, C. R.; Paul, R. R.; Jose, A.; Sreekumar, V. *Chem. Soc. Rev.* **2011**, *40*, 5336−5346. (c) Ryan, S. J.; Candish, L.; Lupton, D. W. *Chem. Soc. Rev.* **2013**, *42*,

4906−4917. (d) Mahatthananchai, J.; Bode, J. W. *Acc. Chem. Res.* **2014**, *47*, 696−707. (e) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. *Chem. Rev.* **2015**, *115*, 9307−9387. (f) Menon, R. S.; Biju, A. T.; Nair, V. *Chem. Soc. Rev.* **2015**, *44*, 5040−5052.
(6) (a) Zhang, C.; Hooper, J. F.; Lupton, D. W. *ACS Catal.* **2017**, *7*, 2583−2596. (b) Mondal, S.; Yetra, S. R.; Mukherjee, S.; Biju, A. T. *Acc. Chem. Res.* **2019**, *52*, 425−436.
(7) Ryan, S. J.; Candish, L.; Lupton, D. W. *J. Am. Chem. Soc.* **2009**, *131*, 14176−14177.
(8) Yetra, S. R.; Bhunia, A.; Patra, A.; Mane, M. V.; Vanka, K.; Biju, A. T. *Adv. Synth. Catal.* **2013**, *355*, 1089−1097.
(9) Kaeobamrung, J.; Mahatthananchai, J.; Zheng, P.; Bode, J. W. *J. Am. Chem. Soc.* **2010**, *132*, 8810−8812.
(10) Mo, J.; Shen, L.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2013**, *52*, 8588−8591.
(11) Wang, G.; Chen, X.; Miao, G.; Yao, W.; Ma, C. *J. Org. Chem.* **2013**, *78*, 6223−6232.
(12) De Sarkar, S.; Studer, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 9266−9269.
(13) Sun, F.-G.; Sun, L.-H.; Ye, S. *Adv. Synth. Catal.* **2011**, *353*, 3134−3138.
(14) Li, G.-T.; Gu, Q.; You, S.-L. *Chem. Sci.* **2015**, *6*, 4273−4278.
(15) (a) Wanner, B.; Mahatthananchai, J.; Bode, J. W. *Org. Lett.* **2011**, *13*, 5378−5381. (b) Kravina, A. G.; Mahatthananchai, J.; Bode, J. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 9433−9436.
(16) Cheng, J.; Huang, Z.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2013**, *52*, 8592−8596.
(17) Ni, Q.; Xiong, J.; Song, X.; Raabe, G.; Enders, D. *Synlett* **2015**, *26*, 1465−1469.
(18) Ghosh, A.; Barik, S.; Biju, A. T. *Org. Lett.* **2019**, *21*, 8598−8602.
(19) Liu, C.; Wu, S.; Xu, J.; Chen, L.; Zheng, P.; Chi, Y. R. *Org. Lett.* **2019**, *21*, 9493−9496.
(20) (a) Wu, X.-X.; Liu, B.; Zhang, Y.-Z.; Jeret, M.; Wang, H.-L.; Zheng, P.-C.; Yang, S.; Song, B.-A.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2016**, *55*, 12280−12284. (b) Zhang, H.-R.; Dong, Z.-W.; Yang, Y.-J.; Wang, P.-L.; Hui, X.-P. *Org. Lett.* **2013**, *15*, 4750−4753. (c) Fang, C.; Cao, J.; Sun, K.; Zhu, J.; Lu, T.; Du, D. *Chem. - Eur. J.* **2018**, *24*, 2103−2108. (d) Lang, M.; Wang, J. *Eur. J. Org. Chem.* **2018**, *2018*, 2958−2962.
(21) The electronic-rich NHC catalyst **E** bearing a 2,6-dimethoxyphenyl substituent at the $N-1$ position was first designed by the Glorius group (F. Liu et al. *Angew. Chem., Int. Ed.* **2011**, *50*, 12626−12630, DOI: 10.1002/anie.201106155) and is used for enhancing the E/Z ratio of the Breslow intermediate. We herein propose that it may have a similar function to tune the E/Z ratio of the α,β-unsaturated acyl azolium intermediate **I** and also further improve the enantiomeric excess (ee) of the product.
(22) (a) Kuniyil, R.; Sunoj, R. B. *Org. Lett.* **2013**, *15*, 5040−5043. (b) Jousseaume, T.; Wurz, N. E.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1410−1414.

https://dx.doi.org/10.1021/acs.orglett.0c02832
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