Letter

Access to Optically Enriched α-Aryloxycarboxylic Esters via Carbene-Catalyzed Dynamic Kinetic Resolution and Transesterification

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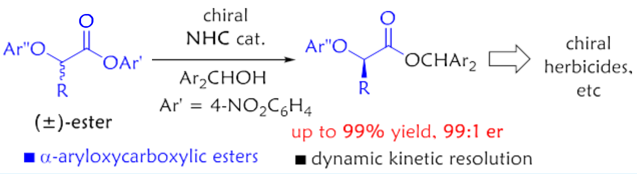
ABSTRACT: Optically active α-aryloxycarboxylic acids and their derivatives are important functional molecules. Disclosed here is a carbene-catalyzed dynamic kinetic resolution and transesterification reaction for access to this class of molecules with up to 99% yields and 99:1 er values. Addition of a chiral carbene catalyst to the ester substrate leads to two diastereomeric azolium ester intermediates that can quickly epimerize to each other and thus allows for effective dynamic kinetic resolution to be realized. The optically enriched ester products from our reaction can be quickly transformed to chiral herbicides and other bioactive molecules.



Carboxylic acids and their derivatives bearing two substituents at the α-carbon, with one of the substituents as an aryloxyl unit, have found proven applications especially as bioactive reagents.[1] For example, the α-aryloxycarboxylic acid containing fenoxaprop-p[1a,b] and dichlorprop[1c] are herbicides for the protection of dicotyledon crops such as potatoes and nanohanas. Derivatives of α-aryloxycarboxylic acid such as amides and esters have also been used for the development of new medicines[2] or catalysts.[3] Therefore, the development of efficient methods for access to enantiomerically enriched α-aryloxycarboxylic acids and their derivatives has received considerable attention. One approach is based on asymmetric transition-metal catalysis for the formation of new chiral bonds. Examples of elegant studies in this direction include metal-catalyzed asymmetric hydrogenations of unsaturated bonds or insertion of carbenoids into phenol O−H bonds, as reported by Zhou, Humphrey, and others.[4] Another approach is based on resolution of racemic α-aryloxycarboxylic acids and their derivatives, mostly by using enzymes.[5] In 2011, Birman reported amidine-based organic catalyst mediated kinetic resolution of racemic α-aryloxycarboxylic acids to separate the two enantiomers (Figure 1b).[6] We have previously reported a dynamic kinetic resolution of α-aryl-α-alkylcarboxylic esters via an N-heterocyclic carbene (NHC) catalyzed enantioselective transesterification reactions (Figure 1c).[7]

Here, we disclose an NHC-catalyzed dynamic kinetic resolution of α-aryloxycarboxylic esters via a transesterification reaction to afford enantiomerically pure products (Figure 1d). Mild conditions are involved, and the desired enantiomer can be obtained with over 90% yields (for most substrates) and up to 99:1 er values. Key mechanistic steps of our reaction include addition of a chiral NHC catalyst[8] to the racemic ester substrate (1) to form two azolium ester intermediates [(*S*)-I and (*R*)-I] that can readily isomerize to each other. Selective reaction of the azolium ester intermediates with the alcohol substrate (2) constitutes a dynamic kinetic resolution process[9] that leads to a stable ester product (3) with an excellent yield and optical purity. A broad range of α-aryloxycarboxylic esters work effectively with our approach. We have also demonstrated that straightforward transformations of our products can afford bioactive molecules with potential pharmaceutical applications.[2,10]

Key results of the condition optimization by using racemic ester 1a[11] and diarylmethanols (2a−2e) as the model substrates are summarized in Table 1. The reactions were first carried out using diphenylmethanol (2a) as the alcohol substrate, THF as the solvent, and Cs_2CO_3 as the base in the presence of 4 Å molecular sieves. The use of amino indanol-derived triazolium NHC precatalyst A[12a] led to very encouraging results, with the transesterification ester product 3a formed in 89% yield and 83:17 er (entry 1). Switching the NHC precatalyst to B[12b] with an *N*-mesityl substituent led to significant improvements on both yield and er value (94% yield, 94:6 er; entry 2). Precatalyst C (with a N-2,6-diethylphenyl substituent)[12c] also worked well to give 3a with 96% yield and 90:10 er (entry 3). Further screening of the alcohol substrates (2b−2e) showed that many diarylmethyl alcohols worked effectively (entries 4−7). The use of K_2CO_3 and Et_3N as bases could give satisfactory results as well (entries 8 and 9). The use of $CHCl_3$ and dichloroethane as solvents led to drops in product er values (entries 10 and 11).

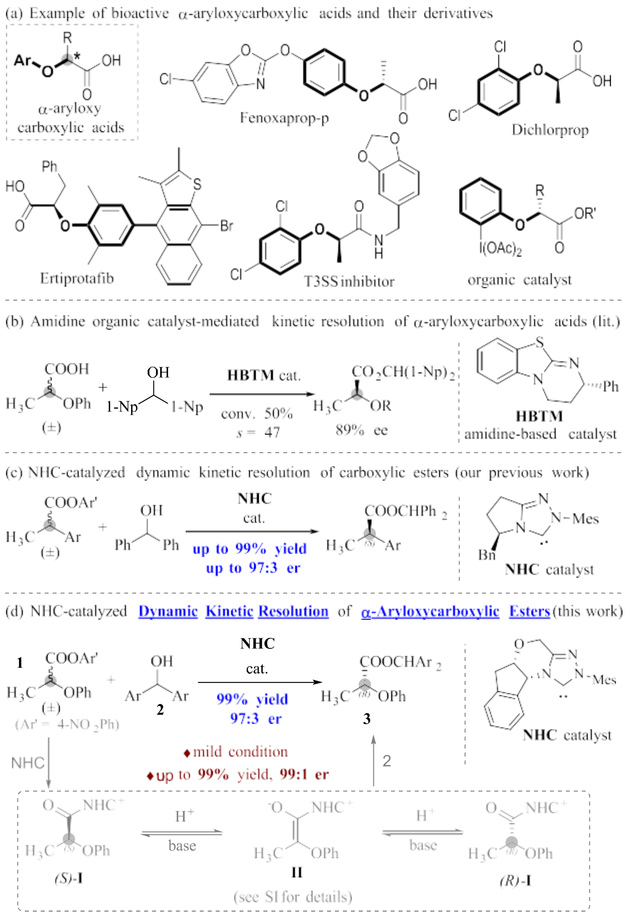
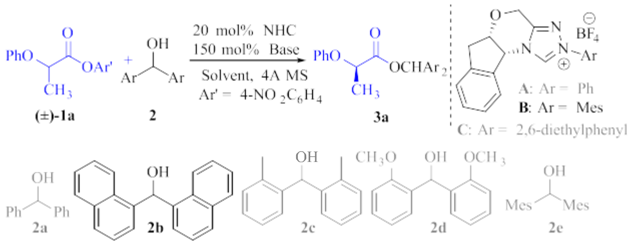


Figure 1. Enantiomerically enriched α-aryloxycarboxylic acids and their synthetic strategy/our method.

The NHC catalyst loadings could be decreased to 10 or 5 mol % with slight drops in the product yields and optical purities (entries 12 and 13).

We then chose the condition as illustrated in Table 1, entry 4, to explore the scope of our reaction (Table 2). Installation of various electron-donating or electron-withdrawing groups at the *para*-carbon of benzene ring of the ester 1 was tolerated. Most of the products could be isolated in quantitative yields and excellent er values (3b−3i). Placing the substituents at different positions of the benzene ring of the α-aryloxycarboxylic ester substrates has little effect on the reaction outcomes (3j−3s). The phenyl substituent on the ester substrate could be changed to naphthyl units, giving the corresponding products with quantitative yields and excellent er values (3t, 3u). When the α-methyl substituent of ester 1a was replaced with an ethyl group (3t), a longer reaction time (48 h) was necessary to achieve an optimal yield (94% yield, 94:6 er). When the methyl unit of 1a was replaced with an *n*-propyl or isopropyl substituent (3w, 3x), changing the NHC precatalyst from B to D[12d] was necessary to achieve effective reaction with high er values. The methyl group in 1a could also be replaced by a phenyl substituent (3y). Our approach also worked considerably well under the current conditions (without further optimization) when the α-aryloxy unit of the ester substrate was replaced with an alkoxy substituent (3z). It is worth noting that the α-aryloxy group on the substrate 1a could be switched to an α-ArS group, but the corresponding product (3aa) could only be afforded in racemic form in a poor yield. Replacing the α-aryloxy group with an α-imido group resulted in only trace formation of the desired product (3ab).

Table 1. Optimization of Reaction Conditions[a]



entry	NHC	base, solvent	2	yield[b] (%)	er[c]
1	A	Cs$_2$CO$_3$, THF	2a	89	83:17
2	B	Cs$_2$CO$_3$, THF	2a	94	94:6
3	C	Cs$_2$CO$_3$, THF	2a	96	90:10
4	B	Cs$_2$CO$_3$, THF	2b	99	97:3
5	B	Cs$_2$CO$_3$, THF	2c	98	97:3
6	B	Cs$_2$CO$_3$, THF	2d	97	94:6
7	B	Cs$_2$CO$_3$, THF	2e	trace	
8	B	K$_2$CO$_3$, THF	2b	91	97:3
9	B	Et$_3$N, THF	2b	76	97:3
10	B	Cs$_2$CO$_3$, CHCl$_3$	2b	92	86:14
11	B	Cs$_2$CO$_3$, DCE	2b	96	83:17
12[d]	B	Cs$_2$CO$_3$, THF	2b	93	95:5
13[e]	B	Cs$_2$CO$_3$, THF	2b	91	93:7

[a] General conditions (unless otherwise specified): 1a (0.10 mmol), 2 (0.20 mmol), NHC (0.02 mmol), base (0.15 mmol), solvent (1.0 mL), 4 Å MS (100 mg), rt, 24 h. [b] Isolated yield. [c] Er values were determined via HPLC on chiral stationary phase. [d] 10 mol % NHC-B. [e] 5 mol % NHC-B.

The chiral α-aryloxycarboxylic esters from our catalytic reactions could be readily transformed to other building blocks or bioactive molecules (Scheme 1). For example, reduction of 3a gave chiral primary alcohol 4 that is a key building block to prepare a mGlu$_3$ inhibitor[10] and activator for MT$_1$ and MT$_2$ melatonin receptors.[2a] The alcohol moiety of ester 3s could be removed under Pd/H$_2$ to give the chiral dichlorprop 5, a herbicide with broad use in crop protection. An amide derivative (6) of compound 5 can modulate the type III secretion system (T3SS) in Gram-negative bacteria.[2b] Preparation of 6 from 3s

Scheme 1. Synthetic Transformation of Chiral Products

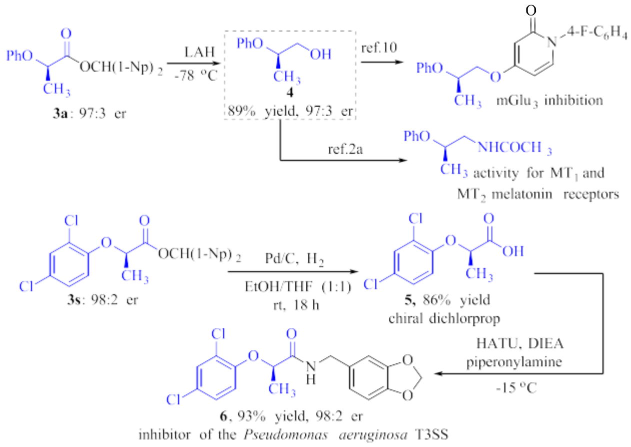
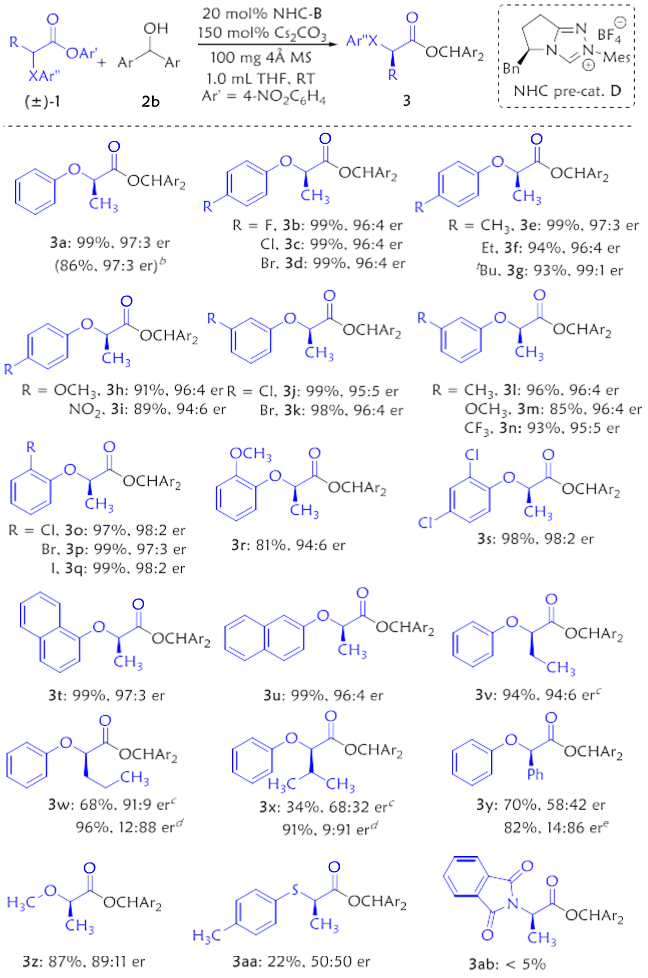


Table 2. Scope of Reactions[a]



[a] General conditions (unless otherwise specified): 1a (0.10 mmol), 2b (0.20 mmol), NHC-B (0.02 mmol), Cs_2CO_3 (0.15 mmol), THF (1.0 mL), 4 Å MS (100 mg), rt, 24 h. [b] The reaction was carried out on a 1.0 mmol scale based on 1a. [c] 48 h. [d] NHC-D (0.02 mmol), 48 h (see the Supporting Information). [e] NHC-D (0.02 mmol), K_2CO_3 (0.15 mmol), 24 h (see the Supporting Information).

took two steps that were both efficient with no erosions on enantiomeric purities.

In summary, we have developed a carbene-catalyzed transesterification approach for access to enantiomerically enriched α-aryloxycarboxylic esters via a dynamic kinetic resolution process. The reaction conditions are mild, and many functional groups can be tolerated. Both α-aryloxy- and alkyloxycarboxylic esters are effective substrates to give the corresponding products with nearly quantitative yields and high optical purifies. The α-aryloxycarboxylic ester products from our reactions are versatile building blocks for the preparation of chiral bioactive molecules such as herbicides. Further studies, including scale-up development and evaluation of functional chiral carboxylic acid derivatives for agricultural and medicinal use, are in progress in our laboratories.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at

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

Accession Codes

CCDC 1973614 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, or 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.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank Dr. Yongxin Li (NTU) and Dr. Rakesh Ganguly for assistance with X-ray structure analysis. We acknowledge financial support from the National Natural Science Foundation of China (21772029, 21801051 and 21961006); National Key Technologies R&D Program (2014BAD23B01); 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) Guizhou University; the Guizhou Province First-Class Disciplines Project [(Yiliu Xueke Jianshe Xiangmu)-GNYL(2017)008], 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, RG5/19, RG1/18, MOE2018-T3-1-003); A*STAR Individual Research Grant (A1783c0008); and Nanyang Research Award Grant, and Nanyang Technological University.

REFERENCES

(1) (a) Tal, A.; Zarka, S.; Rubin, B. *Pestic. Biochem. Physiol.* 1996, *56*, 134. (b) Friesen, L. F.; Jones, T. L.; Van Acker, R. C.; Morrison, I. N. *Weed Sci.* 2000, *48*, 532. (c) Kolmodin-Hedman, B.; Höglund, S.; Åkerblom, M. *Arch. Toxicol.* 1983, *54*, 257. (d) Shrestha, S.; Bhattarai, B. R.; Cho, H.; Choi, J.-K.; Cho, H. *Bioorg. Med. Chem. Lett.* 2007, *17*, 2728. (e) Feller, D. R.; Kamanna, V. S.; Newman, H. A. I.; Romstedt, K. J.; Witiak, D. T.; Bettoni, G.; Bryant, S. H.; Camerino, D. C.; Loiodice, F.; Tortorella, V. *J. Med. Chem.* 1987, *30* (8), 1265. (f) Zhang, Z.-Y.; Lee, S.-Y. *Expert Opin. Invest. Drugs* 2003, *12*, 223.

(2) (a) Carocci, A.; Catalano, A.; Lovece, A.; Lentini, G.; Duranti, A.; Lucini, V.; Pannacci, M.; Scaglione, F.; Franchini, C. *Bioorg. Med. Chem.* 2010, *18*, 6496. (b) Williams, J. D.; Torhan, M. C.; Neelagiri, V. R.; Brown, C.; Bowlin, N. O.; Di, M.; McCarthy, C. T.; Aiello, D.; Peet, N. P.; Bowlin, T. L.; Moir, D. T. *Bioorg. Med. Chem.* 2015, *23*, 1027.

(3) (a) Uyanik, M.; Yasui, T.; Ishihara, K. *Angew. Chem., Int. Ed.* 2010, *49*, 2175. (b) Fujita, M.; Yoshida, Y.; Miyata, K.; Wakisaka, A.; Sugimura, T. *Angew. Chem., Int. Ed.* 2010, *49*, 7068. (c) Fujita, M.; Wakita, M.; Sugimura, T. *Chem. Commun.* 2011, *47*, 3983.

(4) (a) Maligres, P. E.; Krska, S. W.; Humphrey, G. R. *Org. Lett.* 2004, *6*, 3147. (b) Chen, C.; Zhu, S.-F.; Liu, B.; Wang, L.-X.; Zhou, Q.-L. *J. Am. Chem. Soc.* 2007, *129*, 12616. (c) Li, S.; Zhu, S.-F.; Xie, J.-H.; Song, S.; Zhang, C.-M.; Zhou, Q.-L. *J. Am. Chem. Soc.* 2010, *132*, 1172. (d) Song, S.; Zhu, S.-F.; Li, Y.; Zhou, Q.-L. *Org. Lett.* 2013, *15*, 3722. (e) Xie, X.-L.; Zhu, S.-F.; Guo, J.-X.; Cai, Y.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* 2014, *53*, 2978. (f) Yao, L.; Wen, J.; Liu, S.; Tan, R.; Wood, N. M.; Chen, W.; Zhang, S.; Zhang, X. *Chem. Commun.* 2016, *52*, 2273.

(5) (a) Um, P.-J.; Drueckhammer, D. G. *J. Am. Chem. Soc.* 1998, *120*, 5605. (b) Kato, D.; Mitsuda, S.; Ohta, H. *Org. Lett.* 2002, *4*, 371. (c) Kato, D.; Mitsuda, S.; Ohta, H. *J. Org. Chem.* 2003, *68*, 7234.

(6) Yang, X.; Birman, V. B. *Chem. - Eur. J.* 2011, *17*, 11296.

(7) Chen, X.; Fong, J. Z. M.; Xu, J.; Mou, C.; Lu, Y.; Yang, S.; Song, B.-A.; Chi, Y. R. *J. Am. Chem. Soc.* 2016, *138*, 7212.

(8) For selected reviews on NHC catalysis, see: (a) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* 2007, *107*, 5606. (b) Marion, N.; Díez-Gonzalez, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* 2007, *46*, 2988. (c) Biju, A. T.; Kuhl, N.; Glorius, F. *Acc. Chem. Res.* 2011, *44*, 1182. (d) Douglas, J.; Churchill, G.; Smith, A. D. *Synthesis* 2012, *44*, 2295. (e) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* 2012, *41*, 3511. (f) Vora, H. U.; Wheeler, P.; Rovis, T. *Adv. Synth. Catal.* 2012, *354*, 1617. (g) Izquierdo, J.; Hutson, G. E.; Cohen, D. T.; Scheidt, K. A. *Angew. Chem., Int. Ed.* 2012, *51*, 11686. (h) Cohen, D. T.; Scheidt, K. A. *Chem. Sci.* 2012, *3*, 53. (i) Ryan, S. J.; Candish, L.; Lupton, D. W. *Chem. Soc. Rev.* 2013, *42*, 4906. (j) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. *Nature* 2014, *510*, 485. (k) Menon, R. S.; Biju, A. T.; Nair, V. *Chem. Soc. Rev.* 2015, *44*, 5040. (l) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. *Chem. Rev.* 2015, *115*, 9307. (m) Wang, M. H.; Scheidt, K. A. *Angew. Chem., Int. Ed.* 2016, *55*, 14912. (n) Wang, Z.; Pan, D.; Li, T.; Jin, Z. *Chem. - Asian J.* 2018, *13*, 2149. (o) Mondal, S.; Yetra, S. R.; Mukherjee, S.; Biju, A. T. *Acc. Chem. Res.* 2019, *52*, 425. (p) De Risi, C.; Bortolini, O.; Di Carmine, G.; Ragno, D.; Massi, A. *Synthesis* 2019, *51*, 1871.

(9) For selected examples on kinetic resolution via NHC catalyzed reaction, see: (a) Suzuki, Y.; Yamauchi, K.; Muramatsu, K.; Sato, M. *Chem. Commun.* 2004, 2770. (b) Kano, T.; Sasaki, K.; Maruoka, K. *Org. Lett.* 2005, *7*, 1347. (c) Li, G.-Q.; Li, Y.; Dai, L.-X.; You, S.-L. *Adv. Synth. Catal.* 2008, *350*, 1258. (d) De Sarkar, S.; Biswas, A.; Song, C.; Studer, A. *Synthesis* 2011, *2011*, 1974. (e) Binanzer, M.; Hsieh, S.-Y.; Bode, J. W. *J. Am. Chem. Soc.* 2011, *133*, 19698. (f) Kuwano, S.; Harada, S.; Kang, B.; Oriez, R.; Yamaoka, Y.; Takasu, K.; Yamada, K. *J. Am. Chem. Soc.* 2013, *135*, 11485. (g) Lu, S.; Poh, S. B.; Siau, W.-Y.; Zhao, Y. *Angew. Chem., Int. Ed.* 2013, *52*, 1731. (h) Lu, S.; Poh, S. B.; Zhao, Y. *Angew. Chem., Int. Ed.* 2014, *53*, 11041. (i) Wang, M.; Huang, Z.; Xu, J.; Chi, Y. R. *J. Am. Chem. Soc.* 2014, *136*, 1214. (j) Allen, S. E.; Hsieh, S.-Y.; Gutierrez, O.; Bode, J. W.; Kozlowski, M. C. *J. Am. Chem. Soc.* 2014, *136*, 11783. (k) Dong, S.; Frings, M.; Cheng, H.; Wen, J.; Zhang, D.; Raabe, G.; Bolm, C. *J. Am. Chem. Soc.* 2016, *138*, 2166. (l) Liu, B.; Yan, J.; Huang, R.; Wang, W.; Jin, Z.; Zanoni, G.; Zheng, P.; Yang, S.; Chi, Y. R. *Org. Lett.* 2018, *20*, 3447. (m) Bie, J.; Lang, M.; Wang, J. *Org. Lett.* 2018, *20*, 5866. (n) Chen, X.-Y.; Li, S.; Liu, Q.; Kumar, M.; Peuronen, A.; Rissanen, K.; Enders, D. *Chem. - Eur. J.* 2018, *24*, 9735. (o) Bhattacharya, A.; Shukla, P.; Kaushik, L. K.; Maji, B. *Org. Chem. Front.* 2019, *6*, 3523. For selected examples on dynamic kinetic resolution via NHC-catalyzed reaction, see: (p) Cohen, D. T.; Eichman, C. C.; Phillips, E. M.; Zarefsky, E. R.; Scheidt, K. A. *Angew. Chem., Int. Ed.* 2012, *51*, 7309. (q) Johnston, R. C.; Cohen, D. T.; Eichman, C. C.; Scheidt, K. A.; Cheong, P. H.-Y. *Chem. Sci.* 2014, *5*, 1974. (r) Goodman, C. G.; Johnson, J. S. *J. Am. Chem. Soc.* 2014, *136*, 14698. (s) Goodman, C. G.; Walker, M. M.; Johnson, J. S. *J. Am. Chem. Soc.* 2015, *137*, 122. (t) Wu, Z.; Li, F.; Wang, J. *Angew. Chem., Int. Ed.* 2015, *54*, 1629. (u) Zhao, C.; Li, F.; Wang, J. *Angew. Chem., Int. Ed.* 2016, *55*, 1820. (v) Zhang, G.; Yang, S.; Zhang, X.; Lin, Q.; Das, D. K.; Liu, J.; Fang, X. *J. Am. Chem. Soc.* 2016, *138*, 7932. (w) Mondal, S.; Mukherjee, S.; Das, T. K.; Gonnade, R.; Biju, A. T. *ACS Catal.* 2017, *7*, 3995. (x) Chen, K.-Q.; Gao, Z.-H.; Ye, S. *Angew. Chem., Int. Ed.* 2019, *58*, 1183.

(10) Engers, J. L.; Bollinger, K. A.; Weiner, R. L.; Rodriguez, A. L.; Long, M. F.; Breiner, M. M.; Chang, S.; Bollinger, S. R.; Bubser, M.; Jones, C. K.; Morrison, R. D.; Bridges, T. M.; Blobaum, A. L.; Niswender, C. M.; Conn, P. J.; Emmitte, K. A.; Lindsley, C. W. *ACS Med. Chem. Lett.* 2017, *8*, 925.

(11) (a) Hao, L.; Du, Y.; Lv, H.; Chen, X.; Jiang, H.; Shao, Y.; Chi, Y. R. *Org. Lett.* 2012, *14*, 2154. (b) Hao, L.; Chen, S.; Xu, J.; Tiwari, B.; Fu, Z.; Li, T.; Lim, J.; Chi, Y. R. *Org. Lett.* 2013, *15*, 4956.

(12) (a) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* 2002, *124*, 10298. (b) He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* 2006, *128*, 8418. (c) Raup, D. E. A.; Cardinal-David, B.; Holte, D.; Scheidt, K. A. *Nat. Chem.* 2010, *2*, 766. (d) Chiang, P.-C.; Rommel, M.; Bode, J. W. *J. Am. Chem. Soc.* 2009, *131*, 8714.