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Chemoselective Umpolung of Enals for Asymmetric Homoenolate Cross-Annulation of Enals and Aldehydes Catalyzed by N-Heterocyclic Carbene

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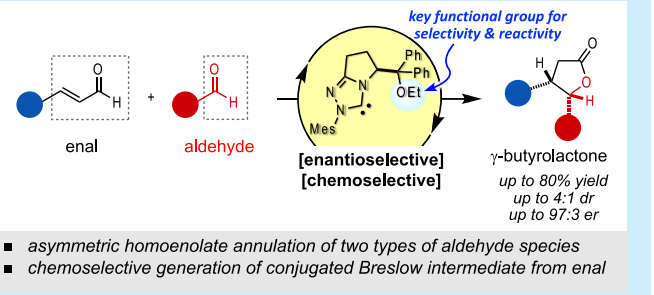
Supporting Information

ABSTRACT: An asymmetric homoenolate cross-annulation of enals and aldehydes with high enantioselectivity is realized by NHC-catalyzed chemoselective umpolung of enals. The reaction proceeds in a highly chemoselective manner, selectively generating the conjugated Breslow intermediates from enals rather than aldehydes, enabling the homoenolate addition of enals to aldehydes in preference to competing acyl anion-mediated reactions. Enantioenriched substituted γ-butyrolactones are formed in good yields with high enantioselectivities.



Catalytic generation of homoenolate equivalents from α,β-unsaturated aldehydes (enal) by N-heterocyclic carbenes (NHCs) enables the formation of unique bonds at the β-carbonyl carbon, producing a variety of carbocycles and heterocycles in a single step from easily available starting materials.[1] Although significant progress has been made since two seminal reports on the diastereoselective additions of homoenolates to aldehydes,[2] enantioselective cross-annulations with carbonyl electrophiles affording enantioenriched γ-butyrolactones remain a significant challenge.[3] Current methods include cooperative catalysis with a Lewis acid, Brønsted acid, or hydrogen bond donor for activating carbonyl electrophiles[4] and promoting the enantioselective annulations with highly activated ketones such as isatins,[5] trifluoromethyl ketones,[2a,6] acyl phosphonates,[7] or α-ketoesters[8] to give the functionalized γ-butyrolactones with high enantioselectivity (Figure 1a). Because the addition of NHC to these ketones is reversible, these homoenolate systems can suppress the competing reactions derived from ketones. Thus, NHC essentially reacts only with the enal to generate a conjugated Breslow intermediate, which can be trapped stereoselectively with reactive ketone electrophiles to provide the corresponding γ-butyrolactones.

A long-standing goal in this area is the highly enantioselective annulation with reactive aldehyde electrophiles, including aryl aldehydes that were used in the initial reports[2] (Figure 1b). The aldehydes that show sufficient reactivity toward conjugated Breslow intermediates also react with NHC to generate undesired Breslow intermediates that would undergo competing acyl anion-mediated reactions such as benzoin[9] and Stetter[10] reactions. In addition, circumstances in which the use of aldehydes with reactivity lower than that of enals is undesirable have often been found, because of either a decreased overall efficiency or homodimerization of the enals.[2b,11] For these reasons, enantioselective homoenolate cross-annulation with aldehydes requires not only the control of stereoselective homoenolate addition to aldehydes but also the chemoselective generation of conjugated Breslow intermediates from enals. To date, a few reports on the NHC-catalyzed enantioselective homoenolate annulation employing aldehydes have been published,[11,12] but only low to modest yields and enantioselectivities have been observed.

In this report, we describe an NHC-catalyzed enantioselective γ-butyrolactone formation, directly from enals and aryl aldehydes, through the chemoselective generation of conjugated Breslow intermediates. A newly designed NHC catalyst with an (ethoxydiphenyl)methyl group that shows unique reactivity toward enals allows the chemoselective generation of conjugated Breslow intermediates, facilitating a stereoselective homoenolate addition. Importantly, this catalysis avoids the

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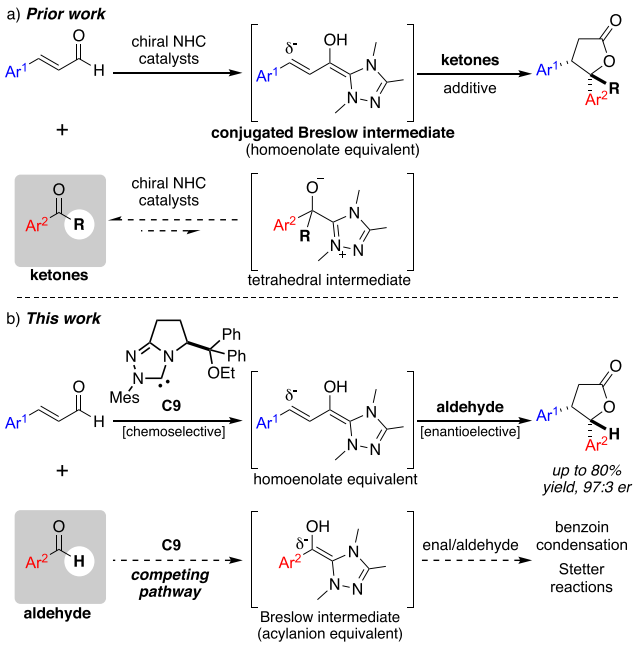
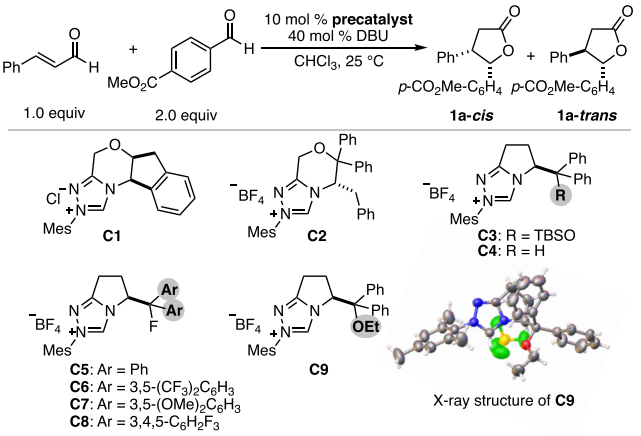


Figure 1. Enantioselective homoenolate annulation (a) employing ketone electrophiles and (b) employing aldehyde electrophiles (this work).

need for an additive or co-catalyst to increase the yield and selectivity, providing direct access from enals and aldehydes to chiral substituted γ-butyrolactones in good yields and high to excellent enantioselectivities.

Our study began with the identification of a potential catalyst structure for the asymmetric homoenolate cross-annulation of cinnamaldehyde and methyl terephthalaldehydate. Several NHC catalysts (10 mol %) in the presence of DBU (40 mol %) in $CHCl_3$ were screened (Table 1 and the Supporting Information). The aminoindane-based precatalyst (**C1**)[13] showed sluggish reactivity, affording many products, including the desired annulation product (**1a**) in a 1.9:1 diastereomeric ratio (dr) with preferable formation of the *cis* isomer, and with a 62:38 enantiomeric ratio (er) (Table 1, entry 1). Using a morpholine-based precatalyst (**C2**),[5b,8c,14] a slightly increased yield was obtained without any increase in stereoselectivity (entry 2). The pyrrolidine-based precatalyst (**C3**)[8c] was found to improve the enantioselectivity, delivering the product in a 91:9 er, albeit with a low diastereoselectivity (entry 3). On the basis of the encouraging results of pyrrolidine-based scaffolds, we began to optimize the structure of **C3**. First, we speculated that the large steric bulk of the TBS ether group of **C3** could underlie the low reactivity. As expected, using **C4**,[15] which lacks the TBS ether group, increased the chemical yield and diastereoselectivity but decreased the enantioselectivity (entry 4). The introduction of a fluorine group to subject the phenyl group(s) positioned close to the reaction site to the fluorine gauche effect[16] led to the recovery of the enantioselectivity (85:15 er) for the *cis* isomer with the *trans* isomer in a 77:23 er (entry 5). Modification of the aryl groups of **C5** was effective for the enantioselectivity, and catalyst **C6** with 3,5-bis-(trifluoromethyl)phenyl groups furnished **1a**-*cis* in a 98:2 er and **1a**-*trans* in a 96:4 er (entry 6). Though several of the fluorine-type catalysts provide high enantioselectivity, the reactivity decreased with the aryl groups, giving the product in lower yields (entries 7 and 8). High levels of reactivity and

Table 1. Catalyst Optimization[a]



entry	precatalyst	conversion (%)[b]	yield (%)[c]	dr[b]	er[d] (*cis*)	er[d] (*trans*)
1	**C1**	90	12	1.9:1	62:38	–
2	**C2**	>95	38	2.2:1	51:49	–
3	**C3**	14	10	1.1:1	91:9	–
4	**C4**	>95	44	3.8:1	62:38	–
5	**C5**	>95	62	2.7:1	85:15	77:23
6	**C6**	>95	51	1.2:1	98:2	96:4
7	**C7**	94	43	2.2:1	88:12	–
8	**C8**	>95	45	1.8:1	93:7	–
9	**C9**	>95	80	1.7:1	93:7	90:10
10[e]	**C9**	>95	45	2.0:1	92:8	89:11
11[f]	**C9**	>95	76	1.7:1	93:7	88:12

[a]Reaction conditions: cinnamaldehyde (0.30 mmol, 1.0 equiv), methyl terephthalaldehydate (0.60 mmol, 2.0 equiv), 40 mol % DBU, and 0.2 M $CHCl_3$ at 25 °C for 24 h. [b]Conversion and dr were determined by ^{1}H NMR analysis of the crude mixture. [c]The yield is a combined yield of both diastereomers and determined by ^{1}H NMR analysis of the crude mixture utilizing *tert*-butylanisole as an internal standard. [d]er was determined by chiral HPLC analysis. [e]With 1.0 equiv of methyl terephthalaldehydate. [f]With 5 mol % precatalyst.

enantioselectivity were achieved with catalyst **C9** with an EtO group in place of the fluorine, affording the product in 80% yield with a 93:7 er for **1a**-*cis* and a 90:10 er for **1a**-*trans* (entry 9). NMR analysis of the reaction with **C9** revealed that acyl anion-derived products such as benzoin and Stetter products could not be observed until the cinnamaldehyde had been consumed, indicating that the conjugated Breslow intermediates were generated chemoselectively. The reaction with an equimolar amount of methyl terephthalaldehydate furnished **1a** in 45% yield and similar selectivity with a trace amount of cinnamaldehyde-derived butyrolactone via homodimerization after 24 h (entry 10). Decreasing the catalyst loading to 1 mol % proved to be unreactive, but the reaction with the 5 mol % catalyst loading gave the products in 76% yield with comparable selectivities (entry 11). After screening the bases, Lewis acids,[17] and solvents (see the Supporting Information), we have found lactone formation in high yield and with high enantioselectivity is facilitated by a combination of catalyst **C9** and DBU in $CHCl_3$ at 25 °C.

With the optimal conditions in hand, we investigated the substrate scope of the substituted enals, employing methyl terephthalaldehydate as the electrophile (Scheme 1). The reaction is tolerant of various functionalities, including bromide, chloride, ether, and esters. A single *ortho* substitution

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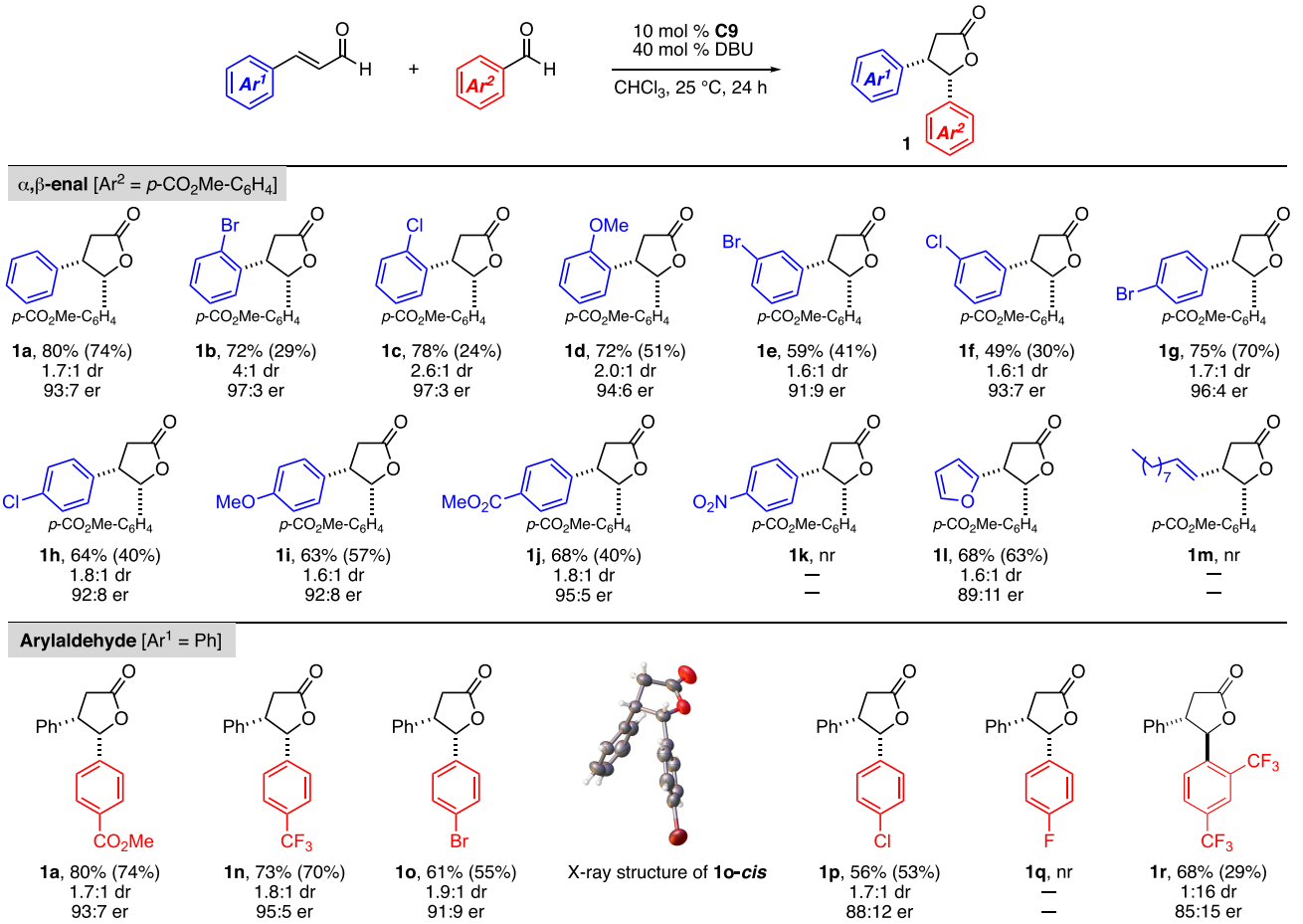
Scheme 1. Scope of Asymmetric Homoenolate Cross-Annulation[a]



[a]Reaction conditions: enal (0.30 mmol), arylaldehyde (0.60 mmol), 40 mol % DBU, and 0.2 M $CHCl_3$ at 25 °C for 24 h. The yield is a combined yield of both diastereomers and determined by ^{1}H NMR analysis of the crude mixture utilizing *tert*-butylanisole as an internal standard. In parentheses, the isolated yield is shown after preparative HPLC for the analytical sample. dr was determined by ^{1}H NMR analysis of the crude mixture. er was determined by chiral HPLC analysis.

led to the diastereoselectivity and enantioselectivities that were higher than those of cinnamaldehyde, as *o*-bromo-substituted γ-butyrolactone (**1b**) is formed in 72% yield with a 4:1 dr and a 97:3 er. On the other hand, a *meta* substitution resulted in lower yields with comparable selectivities (**1e** and **1f**), probably due to the reactivity of *meta* substitution being lower than those of other substitutions. The enals with a *para* substituent were also eligible to stereoselectively provide the corresponding γ-butyrolactones (**1g**−**1j**), except the nitro substitution. Additionally, γ-butyrolactones with a heteroaromatic ring were obtained in good yields and high enantioselectivities (**1l**). Unfortunately, using an enal with an alkyl group instead of an aromatic ring failed to provide the desired products (**1m**).

Next, we examined the substrate scope of the aryl aldehydes. Replacement of the ester with a trifluoromethyl group gave **1n** in 73% yield with a 1.8:1 dr and a 95:5 er. Similarly, 4-bromo and 4-chloro substitutions afforded the corresponding γ-butyrolactones (**1o** and **1p**, respectively) in moderate yields with high enantioselectivity, but 4-fluoro substitution resulted in no reaction (**1q**). The absolute stereochemistry at the stereogenic centers of **1o** was determined by X-ray crystallography. It is noteworthy that the diastereoselectivity of the reaction with 2,4-bis(trifluoromethyl)benzaldehyde was completely reversed, affording the corresponding γ-butyrolactones (**1r**) in 68% yield with a 1:16 dr and a 85:15 er. Under these conditions, heteroaromatic aldehyde and aliphatic aldehydes were not productive (see the Supporting Information). These results suggested the reaction is highly sensitive to the reactivity of aryl aldehydes, which is consistent with the previous reports.[2]

To gain some insight into the observed chemoselectivity in the annulation reaction with catalyst **C9**, several mechanistic studies were conducted. The fact that the reactivity observed in these annulations is highly dependent on the substituents of the diphenylmethyl group on the catalyst raises the possibility that those substituents may play a key role in the chemoselective induction. To evaluate this, the rates of the consumption of each aldehyde in the presence of 5 mol % catalyst **C4** or **C9** were evaluated by NMR spectroscopy. Figure 2 shows the time course of each reaction of cinnamaldehyde and methyl terephthalaldehydate in terms of the consumption of the starting materials. In the presence of catalyst **C4** with a diphenylmethyl group that shows low levels of reactivity and enantioselectivity, reaction of cinnamaldehyde with **C4** follows an exponential decay, in which the time to reach 10% consumption is ∼60 min (Figure 2a). In contrast, a different reactivity against cinnamaldehyde can be observed for

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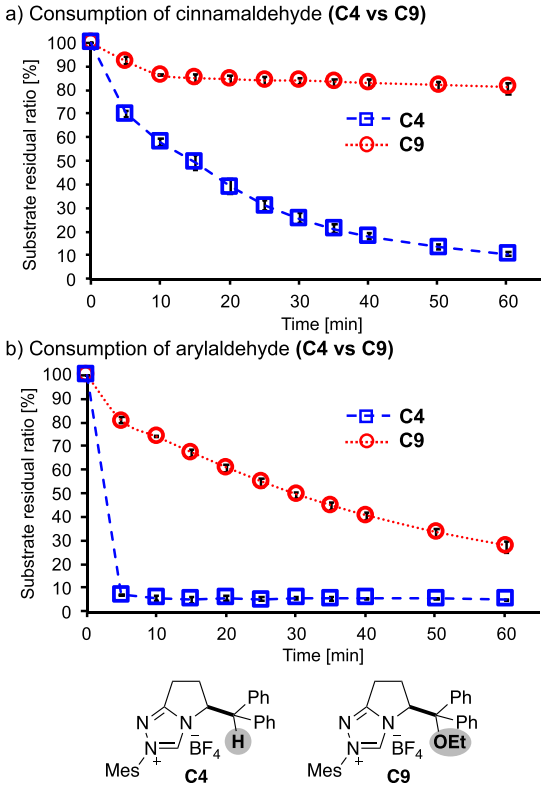

Figure 2. Kinetic profiles of substrate consumption with **C4** or **C9**. (a) Consumption of cinnamaldehyde and (b) consumption of alaldehyde. Standard conditions: precatalyst (0.0175 mmol), cinnamaldehyde or methyl terephthalaldehydate (0.350 mmol), and DBU (0.070 mmol) in $CDCl_3$ (0.5 M) at 25 °C.

catalyst **C9** with an (ethoxydiphenyl)methyl group that shows high levels of reactivity and enantioselectivity. The consumption of cinnamaldehyde was slower than that for **C4**, and the rate of decrease becomes much slower after 10 min. To our surprise, ~80% of cinnamaldehyde remained even after 60 min, but only a trace amount of the lactone products can be detected. For the methyl terephthalaldehydate (Figure 2b), while the reaction with catalyst **C4** was too fast to be measured by NMR, the reaction with **C9** resulted in consumption of methyl terephthalaldehydate that was slower than that for **C4**. A comparison of the time courses of the reactions with **C4** and **C9** revealed that the catalyst reactivity against two types of aldehydes is significantly affected by the substituents of the diphenylmethyl group and that introduction of an EtO group decreases the reactivity against both aldehydes. In particular, the unique reactivity of **C9** against cinnamaldehyde demonstrates that the reaction with enals of conjugated Breslow intermediates derived from **C9** does not occur easily, resulting in the suppression of the undesired reactions, including enal dimerizations. Efforts to elucidate the effects of the EtO group on chemoseletivity are currently under investigation.[18]

In summary, we have developed an NHC-catalyzed asymmetric homoenolate annulation of two types of aldehyde species. Although the diastereoselectivity is modest, the reaction proceeds with readily available enals and aldehydes under mild conditions and allows for a direct and efficient access to enantiomerically enriched substituted γ-butyrolactones. The NHC-catalyzed asymmetric process presented here highlights the chemoselective generation of the conjugated Breslow intermediates, controlling the difference in reactivity between enals and aldehydes. The result is the formation of the cross-annulation products with high enantioselectivity over the dimerization products. Our laboratory is currently studying the mechanism of this transformation for the observed stereoselectivity and chemoselectivity and is also expanding the utility of the identified catalyst with a pendant alkoxy group to additional asymmetric NHC catalysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03509.

Experimental details and characterization data for all new compounds as well as crystal data and data collection parameters (PDF)

Accession Codes

CCDC 1903388−1903389 contain 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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#R.I. and R.K. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected recent reviews of NHC catalysis, see: (a) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606. (b) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. *Nature* **2014**, *510*, 485. (c) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. *Chem. Rev.* **2015**, *115*, 9307. (d) Wang, M. H.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2016**, *55*, 14912. (e) Zhao, M.; Zhang, Y.-T.; Chen, J.; Zhou, L. *Asian J. Org. Chem.* **2018**, *7*, 54.

(2) (a) Burstein, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 6205. (b) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370.

(3) Murauski, K. J. R.; Jaworski, A. A.; Scheidt, K. A. *Chem. Soc. Rev.* **2018**, *47*, 1773.

(4) Selected examples: (a) Raup, D. E. A.; Cardinal-David, B.; Holte, D.; Scheidt, K. A. *Nat. Chem.* **2010**, *2*, 766. (b) Zhao, X.; DiRocco, D.

DOI: 10.1021/acs.orglett.9b03509
Org. Lett. XXXX, XXX, XXX−XXX

A.; Rovis, T. *J. Am. Chem. Soc.* **2011**, *133*, 12466. (c) Wang, M. H.; Cohen, D. T.; Schwamb, C. B.; Mishra, R. K.; Scheidt, K. A. *J. Am. Chem. Soc.* **2015**, *137*, 5891. (d) Guo, C.; Fleige, M.; Janssen-Müller, D.; Daniliuc, C. G.; Glorius, F. *J. Am. Chem. Soc.* **2016**, *138*, 7840. (e) Guo, C.; Janssen-Müller, D.; Fleige, M.; Lerchen, A.; Daniliuc, C. G.; Glorius, F. *J. Am. Chem. Soc.* **2017**, *139*, 4443.

(5) Selected examples: (a) Sun, L.-H.; Shen, L.-T.; Ye, S. *Chem. Commun.* **2011**, *47*, 10136. (b) Dugal-Tessier, J.; O'Bryan, E. A.; Schroeder, T. B. H.; Cohen, D. T.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 4963. (c) Li, J.-L.; Sahoo, B.; Daniliuc, C.-G.; Glorius, F. *Angew. Chem., Int. Ed.* **2014**, *53*, 10515. (d) Xu, J.; Yuan, S.; Miao, M.; Chen, Z. *J. Org. Chem.* **2016**, *81*, 11454.

(6) Matsuoka, Y.; Ishida, Y.; Sasaki, D.; Saigo, K. *Chem. - Eur. J.* **2008**, *14*, 9215.

(7) Jang, K. P.; Hutson, G. E.; Johnston, R. C.; McCusker, E. O.; Cheong, P. H.-Y.; Scheidt, K. A. *J. Am. Chem. Soc.* **2014**, *136*, 76.

(8) Selected examples: (a) Li, Y.; Zhao, Z.-A.; He, H.; You, S.-L. *Adv. Synth. Catal.* **2008**, *350*, 1885. (b) Check, C. T.; Jang, K. P.; Schwamb, C. B.; Wong, A. S.; Wang, M. H.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2015**, *54*, 4264. (c) Goodman, C. G.; Walker, M. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2015**, *137*, 122.

(9) Selected examples: (a) Enders, D.; Han, J. *Tetrahedron: Asymmetry* **2008**, *19*, 1367. (b) Baragwanath, L.; Rose, C. A.; Zeitler, K.; Connon, S. J. *J. Org. Chem.* **2009**, *74*, 9214. (c) Jia, M.-Q.; You, S.-L. *ACS Catal.* **2013**, *3*, 622. (d) Langdon, S. M.; Wilde, M. M. D.; Thai, K.; Gravel, M. *J. Am. Chem. Soc.* **2014**, *136*, 7539.

(10) Selected examples: (a) Liu, Q.; Rovis, T. *Org. Lett.* **2009**, *11*, 2856. (b) Sánchez-Larios, E.; Thai, K.; Bilodeau, F.; Gravel, M. *Org. Lett.* **2011**, *13*, 4942. (c) DiRocco, D. A.; Noey, E. L.; Houk, K. N.; Rovis, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 2391.

(11) Cardinal-David, B.; Raup, D. E. A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 5345.

(12) Struble, J. R.; Kaeobamrung, J.; Bode, J. W. *Org. Lett.* **2008**, *10*, 957.

(13) He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418.

(14) Wadamoto, M.; Phillips, E. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 10098.

(15) Wurz, N. E.; Daniliuc, C. G.; Glorius, F. *Chem. - Eur. J.* **2012**, *18*, 16297.

(16) Paul, S.; Schweizer, B.; Ebert, M.-O.; Gilmour, R. *Organometallics* **2010**, *29*, 4424.

(17) The combination use of Lewis acids, $Ti(O^iPr)_4$, LiCl, $Mg(OTf)_2$, and Et_2Zn as an additive or co-catalyst resulted in a significant decrease in reaction efficiency and selectivity (see the Supporting Information). For selected examples of NHC/Lewis acid cooperative catalysis, see refs 1d, 4a, 5b, and 11. Also see: Cohen, D. T.; Scheidt, K. A. *Chem. Sci.* **2012**, *3*, 53.

(18) With our current understanding of this reaction, the difference in observed reactivity with respect to the aldehydes between **C4** (H-cat.) and **C9** (OEt-cat.) is difficult to rationalize. Related studies to elucidate the role of the OEt substituent in the NHC catalyst compared with other substituents are currently in progress and will be reported in due course.

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