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Introduction

The Hauser–Kraus annulation is arguably one of the most effective strategies for synthesizing oxygenated polycyclic aromatic compounds (**1**, Scheme 1),^{1,2} which are ubiquitous in pharmaceutical agents and biologically active natural products.³ The power of this reaction manifold is the ability to generate a broad range of polycyclic products in a convergent manner, which is best depicted by the union of synthons **4** and **5**. Despite the widespread utility of Hauser–Kraus annulations, some drawbacks persist. First, the reaction requires stoichiometric strong bases such as LDA, LTB, or LHMDS ($pK_{aH} > 30$ in DMSO),⁴ which limits the functional group tolerance of the reaction. Secondly, the substituted phthalide substrates **2** are accessed from simple precursors such as lactol **6** through multi-step syntheses, which often require toxic chemicals such as potassium and sodium cyanide.⁵

We were interested in developing a catalytic platform for the synthesis of oxygenated polycyclic aromatic compounds that would maintain all of the advantages of traditional Hauser–Kraus annulations while also addressing the major drawbacks. Although this classical reaction has been known for more than 40 years, no catalytic versions have been reported in the literature. We envisioned that synthon **4** could be accessed catalytically by treating phthalaldehydes such as **7**, which can be synthesized from lactols **6** in one step, with N-heterocyclic carbene (NHC) catalyst **8**.⁶ A cascade of reactions would then furnish the desired polycyclic product without the use of stoichiometric strong bases. In this Communication, we describe the development of the first catalytic Hauser–Kraus

N-Heterocyclic carbene based catalytic platform for Hauser–Kraus annulations†

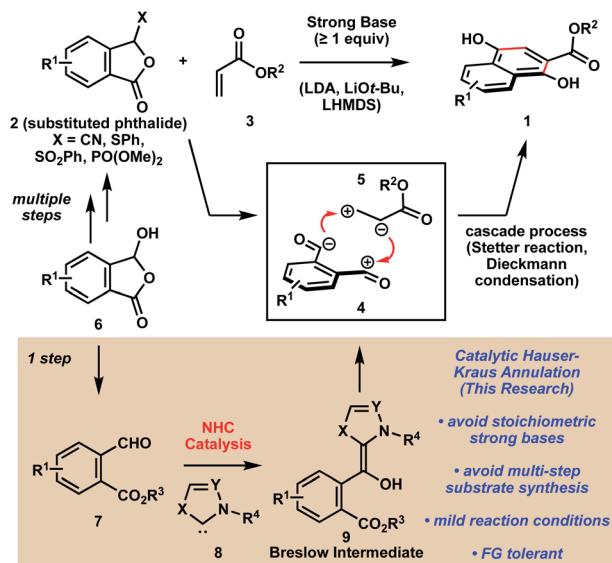
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The venerable Hauser–Kraus annulation is an effective and convergent method for generating oxygenated polycyclic aromatic compounds. Despite its application in complex molecule synthesis, the harsh and strongly basic conditions can limit its utility in more functionalized molecular settings. We have developed the first catalytic Hauser–Kraus annulation based on N-heterocyclic carbene catalysis that proceeds under milder conditions. We demonstrate the scope of the transformation in the presence of several functional groups. We also propose a concerted mechanism for the annulation that proceeds through a non-canonical Breslow intermediate.

annulation system and we explore the generality of this method. We also provide mechanistic data to support a concerted mechanism for the transformation that proceeds through a non-canonical Breslow intermediate that is unprecedented for NHC-catalyzed annulations.

Results and discussion

Initial attempts to realize our proposal for a catalytic Hauser–Kraus annulation commenced with the examination of ethyl phthalaldehydate **10a** and ethyl acrylate **11** (Table 1). In the presence of NHC precursors **A** or **B** and DBU as base ($pK_{aH} = 12$ in DMSO),⁴ we did not observe any annulation product **12** (Table



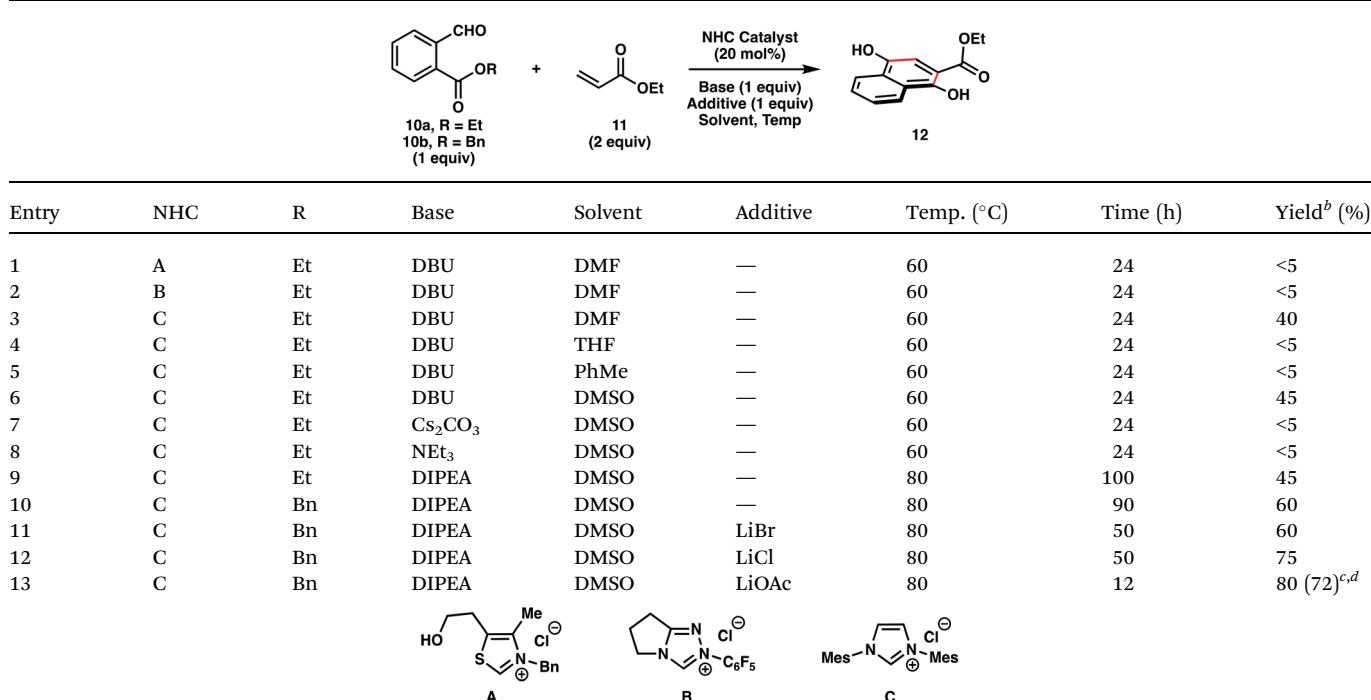
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Scheme 1 Design of a catalytic platform for Hauser–Kraus annulations.



Table 1 Development of catalytic Hauser–Kraus annulation^a



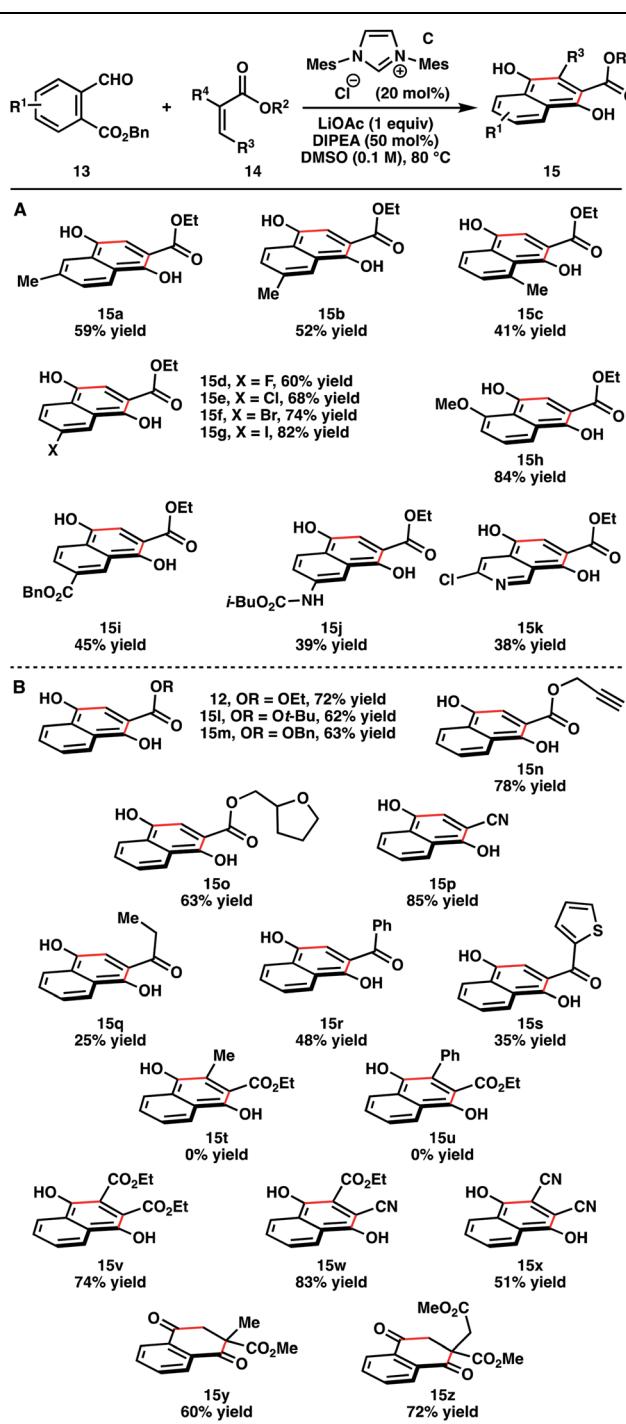
^a Reaction conditions: **10** (0.25 mmol, 1 equiv.), **11** (0.5 mmol, 2 equiv.), NHC catalyst (0.05 mmol, 20 mol%), base (0.25 mmol, 1 equiv.), additive (0.25 mmol, 1 equiv.), solvent (2.5 ml, 0.1 M). ^b NMR yield (trimethoxybenzene as internal standard). ^c 0.5 equiv. DIPEA. ^d Isolated yield in parentheses.

1, entries 1–2). Gratifyingly, the NHC catalyst derived from imidazolium salt **C**, which is at least 10^3 times more nucleophilic than the carbene derived from thiazolium salt **B**,⁷ afforded the desired product in 40% yield (entry 3). An examination of other reaction solvents revealed that polar aprotic solvents such as DMF and DMSO were the best media for the reaction, with DMSO proving to be a slightly better solvent (entries 3–6). We measured the conversion of the reaction in the presence of DBU to be 95% (entry 6), suggesting that an alternate choice of base may lead to less decomposition and more product formation. Cs_2CO_3 ($\text{p}K_{\text{aH}} = 10$ in DMSO)⁴ did not yield the desired product because of its diminished basicity (entry 7). In addition, product was not observed in the presence of the more basic NEt_3 ($\text{p}K_{\text{aH}} = 9$ in DMSO),⁴ presumably because of the nucleophilicity of the amine (entry 8). Ultimately, sterically hindered DIPEA ($\text{p}K_{\text{aH}} = 8.5$ in DMSO)⁴ facilitated the formation of Hauser–Kraus annulation product **12** in 45% yield and only 60% conversion, suggesting considerably less decomposition (entry 9). The use of benzyl phthalaldehydate **10b** increased the yield of product formation to 60% (entry 10). Finally, the addition of lithium salts improved the efficiency of the reaction (entries 11–13), with LiOAc proving to be the most effective additive.⁸ Under the optimal reaction conditions, including only 0.5 equivalents of DIPEA, the desired Hauser–Kraus annulation product **12** was obtained in 72% isolated yield (entry 13).

With optimal conditions in hand, we explored the generality of the catalytic Hauser-Kraus annulation towards different

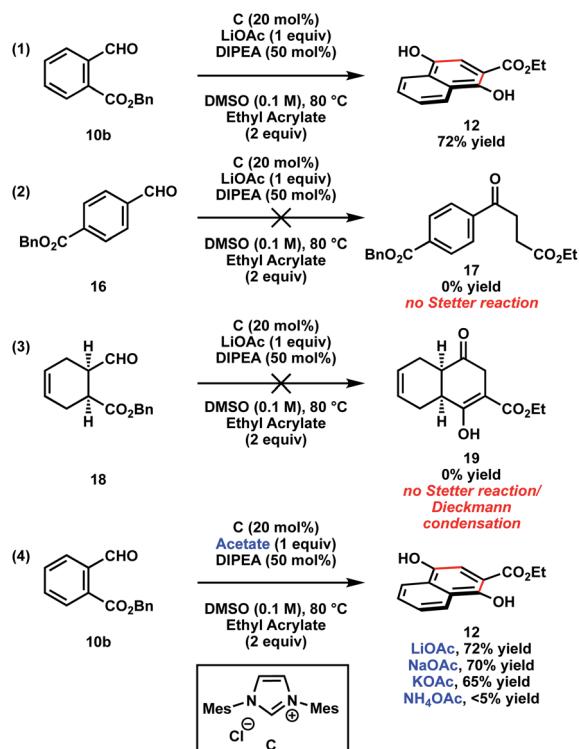
benzyl phthalaldehyde substrates (Table 2A). Methyl substitution at various positions in the backbone of the phthalaldehyde were tolerated (**15a–15c**). Various halogens were also compatible with the reaction, including fluorine, chlorine, bromine, and iodine (**15d–15g**). The presence of halogens may be problematic with traditional Hauser–Kraus annulation protocols with strong lithium amides that could undergo lithium–halogen exchange. Products with an electron-donating methoxy substituent (**15h**) and electron-withdrawing benzyloxy substituent (**15i**) were also generated. Because of the mildness of the catalytic reaction conditions, the presence of an acidic proton of an aniline-based carbamate did not prevent the formation of the desired product **15j**. Finally, we extended the catalytic chemistry to the synthesis of polycyclic heteroaromatic systems, such as isoquinoline **15k**.

Next, we examined the scope of electrophilic coupling partners (Table 2B). Several acrylates were employed in the reaction without affecting product yield (**12**, **15l–15o**). Acrylonitrile was also a competent substrate for the reaction (**15p**). α,β -Unsaturated ketones furnished Hauser–Kraus annulation products (**15q–15s**) in slightly diminished yields. Although crotyl and cinnamyl esters did not yield the desired products (**15t**, **15u**), internal alkenes activated by two electron-withdrawing groups proved to be effective substrates for the reaction (**15v–15x**). We were also pleased to observe the formation of benzoquinone products **15y** and **15z** with quaternary carbons when 1,1-disubstituted electron-deficient alkenes were used as substrates.

Table 2 Generality of catalytic Hauser–Kraus annulation^a

^a Reaction conditions: **13** (0.25 mmol, 1 equiv.), **14** (0.5 mmol, 2 equiv.), NHC catalyst (0.05 mmol, 20 mol%), DIPEA (0.125 mmol, 0.5 equiv.), LiOAc (0.25 mmol, 1 equiv.), solvent (2.5 ml, 0.1 M).

We performed a series of experiments to distinguish between a stepwise or concerted mechanism for the catalytic Hauser–Kraus annulation (Scheme 2). As discussed previously (Table 1, entry 13), *ortho*-aldehyde ester **10b** yielded annulation product **12**

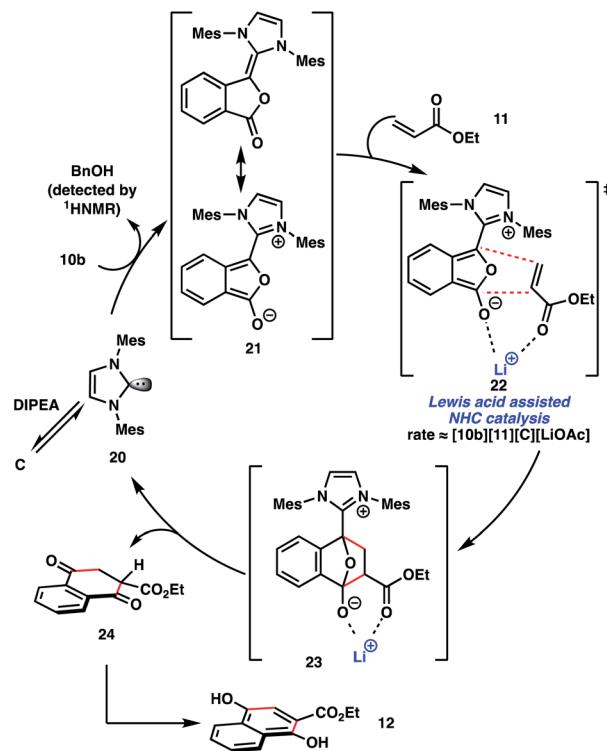


Scheme 2 Mechanistic studies.

(eqn (1)). Surprisingly, electronically similar *para*-aldehyde ester **16** did not yield Stetter reaction product **17** (eqn (2)), which was expected to form if these reaction conditions facilitated the formation of a traditional Breslow intermediate (**9**, Scheme 1). In addition, non-aromatic aldehyde ester **18** did not form the product that would have resulted from a Stetter reaction/ Dieckmann condensation sequence (eqn (3)). These observations suggest that the traditional Breslow intermediate may not be operative under the catalytic Hauser–Kraus reaction conditions. Moreover, the results are more consistent with a concerted [4 + 2] cycloaddition mechanism than a stepwise Stetter reaction/ Dieckmann condensation mechanism (*vide infra*).

Although multiple lithium salts with different counter anions improved the efficiency of the reaction, LiOAc proved to be the optimal additive (Table 1, entry 13). We were therefore interested in probing the role of various counter cations of acetate salts (eqn (4)). Whereas lithium, sodium, and potassium acetate salts yielded the desired product **12**, non-Lewis acidic ammonium acetate did not furnish the product, suggesting the importance of a Lewis acidic counter cation in activating the substrates (*vide infra*).

Based on these observations, we propose the mechanism depicted in Scheme 3. Deprotonation of imidazolium salt **C** with DIPEA results in the formation of the catalytically active NHC **20**. Coupling of the catalyst with benzyl phthalaldehyde **10b** and concomitant liberation of benzyl alcohol, which can be detected by ¹H NMR,⁹ results in the formation of non-canonical Breslow intermediate **21**. To the best of our knowledge, the formation of this type of O-acylated intermediate from the



Scheme 3 Proposed mechanism with non-canonical Breslow intermediate.

coupling of an aldehyde and an NHC catalyst is unprecedented,^{10,11} and its reactivity may be distinct from that of a traditional Breslow intermediate. Catalytically generated dienes such as **21** are not accessible from aldehyde esters **16** and **18**, which accounts for the lack of product formation with these substrates (eqn (2) and (3), Scheme 2). Subsequent concerted [4 + 2] cycloaddition of intermediate **21** with acrylate **11** results in the formation of cycloadduct **23**. The quaternary complex depicted in transition structure **22** is consistent with the experimentally determined rate orders,⁹ and it suggests the cooperative roles of the NHC catalyst **20** and Lewis acidic LiOAc.^{8,12} Decomposition of cycloadduct **23** reforms the active catalytic NHC **20** and unveils coupled product **24**, which spontaneously tautomerizes to the observed Hauser-Kraus annulation product **12**. Interestingly, when non-aromatic aldehyde ester **18** was subjected to the optimized reaction conditions in the absence of ethyl acrylate, liberation of benzyl alcohol was detected by ¹H NMR, suggesting the formation of an *O*-acylated Breslow intermediate. The lack of Hauser-Kraus product formation with substrate **18** under optimized conditions (Scheme 2, eqn (3)) and the inability of this substrate to form a diene analogous to non-canonical Breslow intermediate **21** are consistent with a concerted [4 + 2] cycloaddition mechanism in the catalytic Hauser-Kraus annulation.

Conclusions

We have developed the first catalytic platform for Hauser-Kraus annulations. Given the mildness of the reaction conditions, we

are able to generate a broad range of functionalized products in synthetically useful yields. Mechanistic studies are consistent with a concerted [4 + 2] cycloaddition that proceeds *via* Lewis acid assisted NHC catalysis. The application of this catalytic platform for the synthesis of complex functionalized molecules and the development of an enantioselective reaction are areas of ongoing interest in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

- (a) F. M. Hauser and R. P. Rhee, *J. Org. Chem.*, 1978, **43**, 178–180; (b) G. A. Kraus and H. Sugimoto, *Tetrahedron Lett.*, 1978, **19**, 2263–2266.
- (a) A. S. Mitchell and R. A. Russell, *Tetrahedron*, 1995, **51**, 5207–5236; (b) D. Mal and P. Pahari, *Chem. Rev.*, 2007, **107**, 1892–1918; (c) K. Rathwell and M. A. Brimble, *Synthesis*, 2007, 643–662.
- For recent examples of Hauser–Kraus annulations in complex molecule synthesis, see: (a) K. C. Nicolaou, H. Zhang, J. S. Chen, J. J. Crawford and L. Pasunoori, *Angew. Chem., Int. Ed.*, 2007, **46**, 4704–4707; (b) D. Mal and S. R. De, *Org. Lett.*, 2009, **11**, 4398–4401; (c) J. Li and D. R. Mootoo, *Synthesis*, 2013, **45**, 2287–2293; (d) M. A. Brimble, N. P. S. Hassan, B. J. Naysmith and J. Sperry, *J. Org. Chem.*, 2014, **79**, 7169–7178; (e) M. Dischmann, T. Frassetto, M. A. Breuning and U. Koert, *Chem.-Eur. J.*, 2014, **20**, 11300–11302; (f) C. L. Hugelshofer and T. Magauer, *Angew. Chem., Int. Ed.*, 2014, **53**, 11351–11355; (g) K. Tatsuta and S. Hosokawa, *Chem. Rec.*, 2014, **14**, 28–40; (h) N. P. S. Hassan, B. J. Naysmith, J. Sperry and M. A. Brimble, *Tetrahedron*, 2015, **71**, 7137–7143; (i) T. Kim, K. H. Jeong, K. S. Kang, M. Nakata and J. Ham, *Eur. J. Org. Chem.*, 2017, 1704–1712; (j) R. Peng and M. S. VanNieuwenhze, *J. Org. Chem.*, 2019, **84**, 760–768.
- F. G. Bordwell, *Acc. Chem. Res.*, 1988, **21**, 456–463.
- Hydrogen cyanide, potassium cyanide and sodium cyanide, *The MAK-Collection for Occupational Health and Safety: Occupational Toxicants*, 2003, vol. 19, pp. 190–210.
- For seminal reviews of N-heterocyclic carbene catalysis, see: (a) A. T. Biju, N. Kuhl and F. Glorius, *Acc. Chem. Res.*, 2011, **44**, 1182–1195; (b) A. Grossmann and D. Enders, *Angew. Chem., Int. Ed.*, 2012, **51**, 314–325; (c) S. J. Ryan, L. Candish



and D. W. Lupton, *Chem. Soc. Rev.*, 2013, **42**, 4906–4917; (d) J. Mahatthananchai and J. W. Bode, *Acc. Chem. Res.*, 2014, **47**, 696–707; (e) D. M. Flanigan, F. Romanov-Michailidis, N. A. White and T. Rovis, *Chem. Rev.*, 2015, **115**, 9307–9387; (f) S. R. Yetra, A. Patra and A. T. Biju, *Synthesis*, 2015, **47**, 1357–1378; (g) A. T. Davies and A. D. Smith, *In Recent advances in N-heterocyclic carbene organocatalysis*, Georg Thieme Verlag, 2017, pp. 395–442.

7 B. Maji, M. Breugst and H. Mayr, *Angew. Chem., Int. Ed.*, 2011, **50**, 6915–6919.

8 For early discussions of dual activation with N-heterocyclic carbenes and Lewis acids, see: (a) D. T. Cohen and K. A. Scheidt, *Chem. Sci.*, 2012, **3**, 53–57; (b) M. H. Wang and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2016, **55**, 14912–14922.

9 See ESI† for details.

10 For examples of *O*-acylated Breslow intermediates derived from 1,2-diketones, see: (a) C. R. Sinu, E. Suresh and V. Nair, *Org. Lett.*, 2013, **15**, 6230–6233; (b) K. Takaki, A. Ohno, M. Hino, T. Shitaoka, K. Komeyama and H. Yoshida, *Chem. Commun.*, 2014, **50**, 12285–12288; (c) X. W. Kong, G. X. Zhang, S. Yang, X. Z. Liu and X. Q. Fang, *Adv. Synth. Catal.*, 2017, **359**, 2729–2734; (d) K. Takaki, M. Hino, A. Ohno, K. Komeyama, H. Yoshida and H. Fukuoka, *Beilstein J. Org. Chem.*, 2017, **13**, 1816–1822; (e) J. Liu, D. K. Das, G. Zhang, S. Yang, H. Zhang and X. Fang, *Org. Lett.*, 2018, **20**, 64–67; (f) L. Ping, J. Bak, Y. Kim and J. Bouffard, *J. Org. Chem.*, 2018, **83**, 9240–9249.

11 For other examples of dearomatized Breslow intermediates, see: (a) X. Chen, S. Yang, B.-A. Song and Y. R. Chi, *Angew. Chem., Int. Ed.*, 2013, **52**, 11134–11137; (b) D. Janssen-Müller, S. Singha, T. Olyschläger, C. G. Daniliuc and F. Glorius, *Org. Lett.*, 2016, **18**, 4444–4447; (c) J. Xu, S. Yuan and M. Miao, *Org. Lett.*, 2016, **18**, 3822–3825; (d) D.-F. Chen and T. Rovis, *Synthesis*, 2017, **49**, 293–298; (e) X. Chen, H. Wang, K. Doitomi, C. Y. Ooi, P. Zheng, W. Liu, H. Guo, S. Yang, B.-A. Song, H. Hirao and Y. R. Chi, *Nat. Commun.*, 2017, **8**, 15598; (f) H. Wang, X. Chen, Y. Li, J. Wang, S. Wu, W. Xue, S. Yang and Y. R. Chi, *Org. Lett.*, 2018, **20**, 333–336; (g) X. Yang, G. Luo, L. Zhou, B. Liu, X. Zhang, H. Gao, Z. Jin and Y. R. Chi, *ACS Catal.*, 2019, **9**, 10971–10976; (h) K. Balanna, K. Madica, S. Mukherjee, A. Ghosh, T. Poisson, T. Basset, G. Jindal and A. T. Biju, *Chem.-Eur. J.*, 2020, **26**, 818–822; (i) Y. Liu, G. Luo, X. Yang, S. Jiang, W. Xue, Y. R. Chi and Z. Jin, *Angew. Chem., Int. Ed.*, 2020, **59**, 442–448.

12 The dual activation of annulations with NHC catalysts and Lewis acids is an established mode of reactivity: (a) B. Cardinal-David, D. E. A. Raup and K. A. Scheidt, *J. Am. Chem. Soc.*, 2010, **132**, 5345–5347; (b) D. E. A. Raup, B. Cardinal-David, D. Holte and K. A. Scheidt, *Nat. Chem.*, 2010, **2**, 766–771; (c) J. Dugal-Tessier, E. A. O'Bryan, T. B. H. Schroeder, D. T. Cohen and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2012, **51**, 4963–4967; (d) J. Mo, X. Chen and Y. R. Chi, *J. Am. Chem. Soc.*, 2012, **134**, 8810–8813; (e) A. M. ElSohly, D. A. Wespe, T. J. Poore and S. A. Snyder, *Angew. Chem., Int. Ed.*, 2013, **52**, 5789–5794; (f) J. Qi, X. Xie, R. Han, D. Ma, J. Yang and X. She, *Chem.-Eur. J.*, 2013, **19**, 4146–4150; (g) S. R. Yetra, A. Bhunia, A. Patra, M. V. Mane, K. Vanka and A. T. Biju, *Adv. Synth. Catal.*, 2013, **355**, 1089–1097; (h) S. Bera, R. C. Samanta, C. G. Daniliuc and A. Studer, *Adv. Synth. Catal.*, 2014, **53**, 9622–9626; (i) S. Mukherjee, S. Joseph, A. Bhunia, R. G. Gonnade, S. R. Yetra and A. T. Biju, *Org. Biomol. Chem.*, 2017, **15**, 2013–2019; (j) K. J. R. Murauski, D. M. Walden, P. H.-Y. Cheong and K. A. Scheidt, *Adv. Synth. Catal.*, 2017, **359**, 3713–3719.

