Asymmetric Catalysis

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A Cooperative N-Heterocyclic Carbene/Chiral Phosphate Catalysis System for Allenolate Annulations**

*Anna Lee and Karl A. Scheidt**

Dedicated to the memory of Jeremiah P. Freeman

Abstract: *The highly enantioselective NHC-catalyzed [3+2] annulation reaction with α,β-alkynals and α-ketoesters has been developed. A new mode of cooperative catalysis involving the combination of a chiral Brønsted acid and a C_1-symmetric biaryl saturated-imidazolium precatalyst was required to generate the desired γ-crotonolactones in high yields and levels of enantioselectivity.*

Homoenolate additions to various electrophiles catalyzed by N-heterocyclic carbenes (NHCs)[1] represent an enabling class of transformations that have been employed for the construction of complex hetero- and carbocyclic systems through unconventional reactivity achieved by Umpolung.[2] While significant advancements have been achieved through this approach, only a limited number of reports on NHC-catalyzed homoenolate additions involving alkynyl aldehydes have appeared. In 2006, Zeitler reported the NHC-catalyzed redox esterification of alkynal aldehydes[3] and subsequently Bode, Xiao, Du, and Alexakis independently reported NHC-catalyzed oxidative transformations of alkynals.[4] Common to these studies is the protonation of the allenolate intermediate to afford activated, electrophilic α,β-unsaturated carbonyl intermediates. To date, the complimentary reaction of nucleophilic NHC-bound allenolates and electrophiles to forge new C–C bonds at the β position of the alkynal has received significantly less attention.[5] There have been a few pioneering studies of this type of reaction, however, the development of efficient and highly enantioselective methods has remained elusive. For example, the She group recently extended the NHC/Lewis acid catalysis concept and reported an approach for the relatively unselective [3+2] annulation of alkynals and β,γ-unsaturated α-ketoesters to generate γ-crotonolactones with low stereoinduction.[6] Independently, the Snyder group has shown the potentially powerful application of the allenolate reactivity through NHC/Lewis acid catalysis for diastereoselective annulation reactions toward the securinega family of alkaloids.[5b]

Cooperative NHC catalysis has been employed as a strategy to expand the capabilities of NHC catalysis and has resulted in marked improvements in efficiency and selectivity in several cases. Notably, the use of NHC/Lewis acid or Brønsted acid cooperative catalysis for enhancing selectivity and incorporating previously inactive reaction partners has seen significant success.[7,8] Despite the demonstrated utility of chiral Brønsted acids (CBAs) for a variety of asymmetric transformations,[9–11] the combination of NHCs and chiral Brønsted acids represents new opportunity for small molecule activation. Herein we report a general cooperative NHC/chiral Brønsted acid strategy to achieve a highly enantioselective addition of alkynals to α-ketoesters (Figure 1).

We postulated that the lack of reports detailing NHC-catalyzed reactions with alkynals in new C–C bond-forming processes might be explained by the nature of the allenolate intermediate,[12] wherein this transient species is rapidly protonated rather than productively interacting with a more complex electrophile. We envisioned that under a more

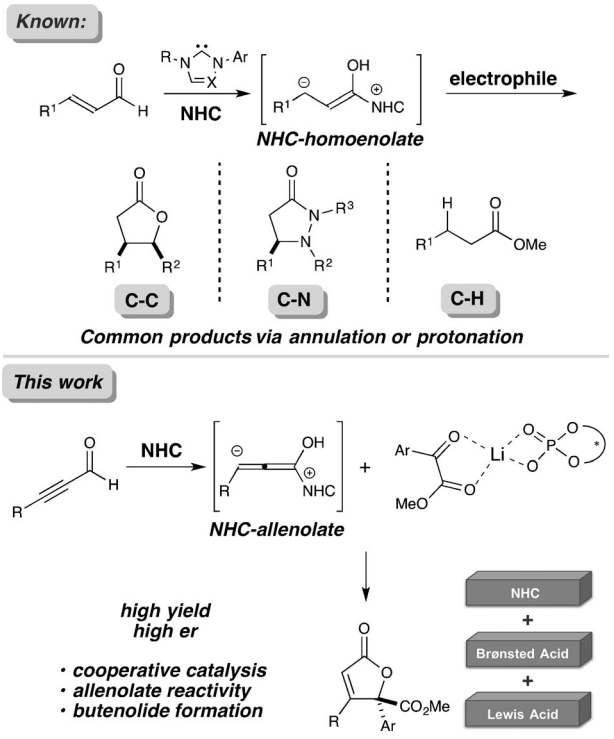

Figure 1. NHC-catalyzed annulation of alkynals.

[*] Dr. A. Lee, Prof. K. A. Scheidt
Department of Chemistry Center for Molecular Innovation and Drug Discovery, Northwestern University
2145 Sheridan Road, Evanston, IL 60208 (USA)
E-mail: scheidt@northwestern.edu

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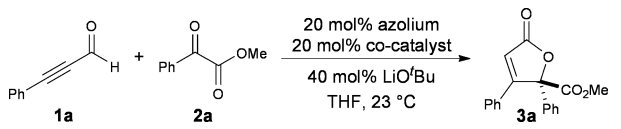
efficient mode of activation, α-ketoesters could be a suitable class of allenolate acceptors. Hence, the combination of alkynal **1a** with α-ketoester **2a** in the presence of lithium *tert*-butoxide and IMes·Cl as precatalyst was explored (**A**, Table 1,

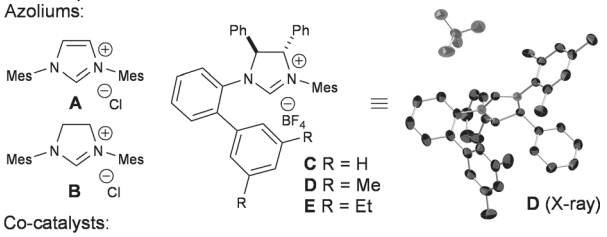
Table 1: Optimization of reaction conditions.[a]



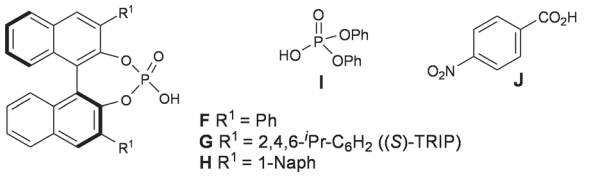
Entry	Azolium	Co-catalyst	Yield [%][b]	e.r.[c]
1	**A**	–	no reaction	–
2	**B**	–	trace	–
3	**B**	LiCl (1 equiv)	24	–
4	**B**	**F**	54	52:48
5	**C**	–	trace	n.d.
6	**C**	**F**	90	79:21
7[d]	**C**	**F**	85	90:10
8[d]	**D**	LiCl (1 equiv)	34	89:11
9[d]	**D**	**F**	**85**	**93:7**
10[d]	**D**	**G**	85	91:9
11[d]	**D**	**H**	trace	n.d.
12[d]	**E**	**F**	52	92:8
13[d]	**D**	*ent*-**F**	84	93:7
14[d]	**D**	*rac*-**F**	74	91:9
15[d]	**D**	**I**	77	89:11
16[d,e]	**C**	**F**	trace	n.d.
17[d,f]	**C**	**F**	no reaction	–
18[d,g]	**C**	**F**	no reaction	–
19[d]	**C**	**J**	no reaction	–

[a] Conditions: **1a** (0.05 mmol, 1 equiv), **2a** (1.5 equiv), azolium (0.2 equiv), phosphoric acid (0.2 equiv), LiO*t*Bu (0.4 equiv) in THF (0.15 M) at 23 °C for 48 h. [b] Determined by GC-MS with *n*-dodecane as internal standard. [c] Determined by HPLC analysis. [d] 4 Å molecular sieves (M.S.) were used at 0.014 M concentration in THF. [e] 20 mol% LiO*t*Bu was used. [f] NaO*t*Bu was used as the base instead of LiO*t*Bu. [g] $Mg(OtBu)_2$ was used as the base instead of LiO*t*Bu. Entry in bold marks optimized conditions.

Azoliums:



Co-catalysts:



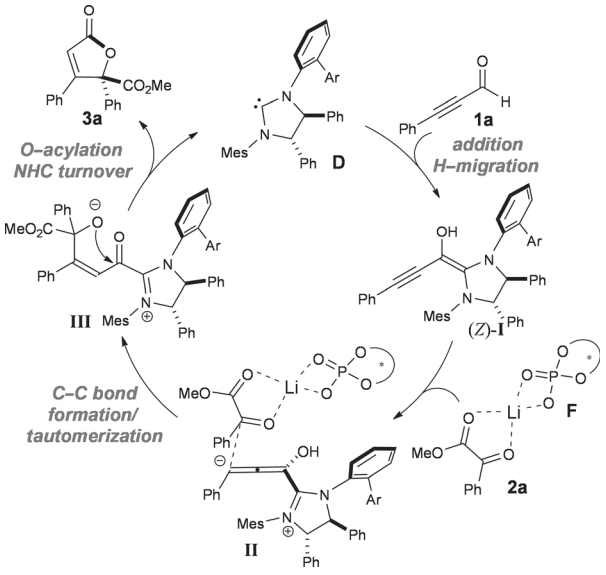
entry 1). These conditions did not produce any of the desired product. However, the use of saturated imidazolium (SIMes·Cl) **B** afforded trace amounts of butenolide **3a** (entry 2). Guided by our previous NHC/Lewis acid studies, a slightly improved yield was observed with one equivalent of lithium chloride (entry 3).[7f] Even though the reaction yield was poor, this result indicated that lithium cations may be activating methyl benzoylformate toward addition. The introduction of chiral Brønsted acid **F** (20 mol%) with achiral NHC from **B** produced a significant increase in yield (54%), but the annulation product was effectively racemic (entry 4). We then turned our attention toward exploring the use of a chiral NHC in combination with a chiral Brønsted acid (CBA). While established chiral triazolium-based NHC catalysts are ineffective for this transformation (see the Supporting Information), it became apparent that C_1-symmetric biaryl saturated-imidazolium-derived NHC catalyst **C**, originally developed by the Hoveyda group,[13,14] provided the desired product in excellent yield (entry 6). Indeed, the use of these 2,3-dihydroimidazole-2-ylinene structures in carbene catalysis is far less developed than their imidazolium- and triazolium- derived counterparts. Interestingly, conducting the reaction under more dilute conditions in the presence of molecular sieves resulted in a further enhancement in enantioselectivity (from 79:21 to 90:10 e.r., entry 7). With these intriguing results in hand, we investigated various C_1-symmetric biaryl saturated-imidazolium precatalysts, with the highest yield and enantioselectivity observed with catalyst **D** (entry 9). The introduction of more sterically demanding aryl or naphthyl groups on the chiral phosphoric acid, such as **G** (i.e., (*S*)-TRIP) and **H**, or on the imidazolium salt, such as **E**, resulted in decreased reactivity and enantioselectivity (entries 10–12). Therefore, precatalyst **D** and chiral phosphoric acid **F** were chosen as our optimized catalysts for further study (entry 9). The use of the (*R*)-phosphoric acid instead of its (*S*)-enantiomer did not diminish catalyst reactivity and enantiomeric ratio, thereby indicating a lack of an expected match/mismatch relationship between the phosphoric acid chirality and the NHC (entry 13). However, racemic phosphoric acid **F** provides the desired product with slightly decreased yield and enantioselectivity (entry 14). At our current level of understanding of this complex reaction, we assume that unexpected inactive species might be formed between the lithium ion and the (*R*)- and (*S*)-phosphate that generates the product in lower yield and a slightly decreased enantiomeric ratio. Clearly, this is a multivariable system and further investigations to delineate more fully the specific roles of the lithium cation, NHC, and Brønsted acid/chiral phosphate are ongoing. In addition, achiral phosphoric acid **I** can also serve as a co-catalyst, albeit with diminished yield and selectivity (entry 15). However, other Brønsted acids, such as 4-nitrobenzoic acid, did not provide any desired product (entry 19).

To gain further information about the role of the CBA, the reaction was performed using a decreased amount of base (20 mol%; Table 1, entry 16). This modification provided only trace amounts of the product. Considering the pK_a values of the azolium and Brønsted acids,[15,16] it is likely that under these conditions phosphoric acid **F** would be deprotonated initially, and the NHC might not be generated in high enough concentrations from the azolium salt precatalyst. A second aspect is whether the lithium cation is involved in organizing the transition state[7f,17] or if lithium *tert*-butoxide was simply acting as a base. To probe this possibility, sodium *tert*-butoxide or magnesium di-*tert*-butoxide were employed as the base, but no product was obtained, suggesting the involvement of the

lithium cation in the reaction mechanism (entries 17 and 18). Furthermore, ^{31}P NMR spectroscopy was employed to probe the state of the phosphoric acid/phosphate under the reaction conditions, and we observed a noticeable change in chemical shift of phosphoric acid **F** in the presence of LiO*t*Bu (see the Supporting Information for details). Notably, alkali or alkaline salts of BINOL-derived phosphates are known as efficient catalysts,[11a,18] and in some cases, the counterion plays a significant role.[18b,19] Based on this precedent, our working hypothesis is that the lithium ion coordinates the phosphate and α-ketoester, and could be part of an activation system under the reaction conditions (see Figure 1).

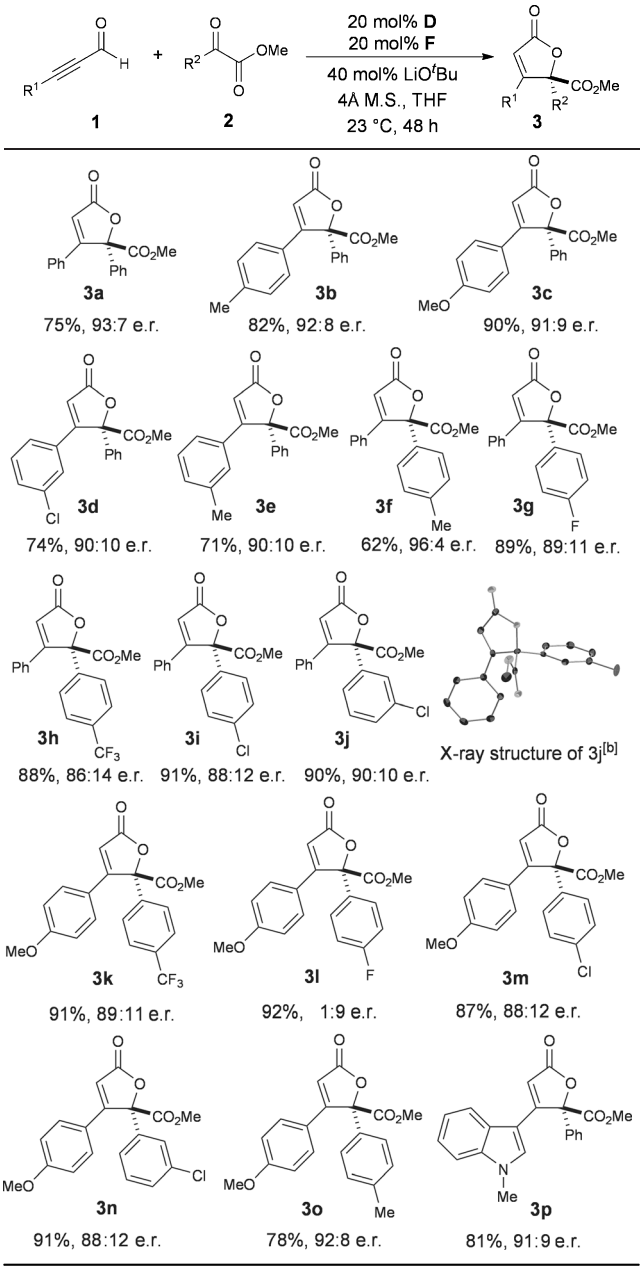
Subsequent to these initial mechanistic probe experiments, the scope of this formal [3+2] annulation was explored (Table 2). The reaction is tolerant of both electron-deficient and electron-rich aromatic alkynals and α-ketoesters. The desired products are obtained in good to excellent yield (62–92%) with high enantioselectivities (up to 96:4 e.r.). In particular, alkynals that possess *meta* or *para* substituents on the aromatic structure perform well (**3b**–**3e**), however, *ortho*-substituted aromatic alkynals are not suitable substrates under the current optimized conditions.[20] The variation of the α-ketoester was also explored. The α-ketoester that bears a *para*-methyl group provides the butenolide product (**3f**) with excellent enantioselectivity (96:4 e.r.). α-Ketoesters that possess an electron-withdrawing group afford the products in excellent yield (**3g**–**3j**), but with a slight decrease in enantioselectivity (up to 90:10 e.r.). The combination of substituted alkynals with α-ketoesters enabled the preparation of various highly functionalized butenolides (**3k**–**3o**). In addition, the indole-derived alkynal produces indole-substituted lactone **3p** in good yield and high enantioselectivity.

The proposed pathway for this annulation reaction is shown in Scheme 1. The initial addition of catalyst **D** to alkynyl aldehyde **1a** and subsequent formal 1,2-H migration generates Breslow intermediate (*Z*)-**I**.[21] The NHC-bound allenolate may undergo addition to the α-ketoester activated by the chiral Brønsted acid derived co-catalyst (**II**). Carbon–carbon bond formation and subsequent tautomerization gives acyl azolium intermediate **III**, which then undergoes O acylation to afford the lactone product (**3a**) and retrieve the NHC catalyst.



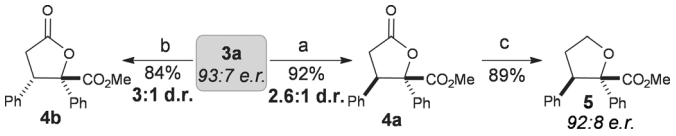
Scheme 1. Proposed reaction pathway.[6,14]

Table 2: Substrate scope.[a]



[a] See the Supporting Information for details. Yields are of isolated product after column chromatography. Enantiomeric ratio was determined by HPLC analysis using a chiral stationary phase. [b] Absolute configuration was determined by X-ray crystallography.

The butenolide products can be converted into enantioenriched γ-butyrolactones by selective hydrogenation reactions (Scheme 2). The use of Pearlman's catalyst furnished *cis*-γ-butyrolactone **4a** as the major product (2.6:1 d.r.) in 92% yield. An ester-directed homogeneous hydrogenation with Crabtree's catalyst afforded *trans*-γ-butyrolactone **4b** as



Scheme 2. Synthetic transformations. Conditions: a) $Pd(OH)_2/C$, H_2, EtOAc. b) Crabtree's catalyst, H_2, CH_2Cl_2. c) $InBr_3$ (10 mol%), Et_3SiH, $CHCl_3$.

the major product (3.1:1 d.r.).[22] In the presence of catalytic indium(III) bromide and triethylsilane, γ-butyrolactone **4a** can also be selectively reduced to provide the corresponding multisubstituted tetrahydrofuran (**5**),[23] a scaffold found in numerous biologically active compounds.[24]

In conclusion, a highly efficient asymmetric [3+2] annulation reaction of alkynyl aldehydes with α-ketoesters through NHC/chiral phosphate cooperative catalysis has been developed. Alkynyl aldehydes can be converted into the corresponding enantiomerically enriched substituted butenolides in good yield and enantioselectivity. This challenging transformation features a new mode of cooperative catalysis, utilizing the combination of an underexplored saturated-imidazolium catalyst and a chiral phosphoric acid, which was required to achieve the observed enhanced yields and enantioselectivities. Investigations involving the use of these C_1-symmetric catalysts and this new mode of cooperative catalysis are ongoing.

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[1] For a recent review on NHC-derived homoenolate additions, see: a) V. Nair, R. S. Menon, A. T. Biju, C. R. Sinu, R. R. Paul, A. Jose, V. Sreekumar, *Chem. Soc. Rev.* **2011**, *40*, 5336 – 5346. For the first reports on NHC-catalyzed homoenolate reactions, see: b) C. Burstein, F. Glorius, *Angew. Chem.* **2004**, *116*, 6331 – 6334; *Angew. Chem. Int. Ed.* **2004**, *43*, 6205 – 6208; c) S. S. Sohn, E. L. Rosen, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 14370 – 14371.

[2] For selected reviews on NHC organocatalysis, see: a) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606 – 5655; b) E. M. Phillips, A. Chan, K. A. Scheidt, *Aldrichimica Acta* **2009**, *42*, 55 – 66; c) X. Bugaut, F. Glorius, *Chem. Soc. Rev.* **2012**, *41*, 3511 – 3522; d) H. U. Vora, P. Sheeler, T. Rovis, *Adv. Synth. Catal.* **2012**, *354*, 1617 – 1639.

[3] K. Zeitler, *Org. Lett.* **2006**, *8*, 637 – 640.

[4] a) J. Kaeobamrung, J. Manattananchai, P. Zheng, J. W. Bode, *J. Am. Chem. Soc.* **2010**, *132*, 8810 – 8812; b) Z.-Q. Zhu, J.-C. Xiao, *Adv. Synth. Catal.* **2010**, *352*, 2455 – 2458; c) Z.-Q. Zhu, X.-L. Zheng, N.-F. Jiang, X. Wan, J.-C. Xiao, *Chem. Commun.* **2011**, *47*, 8670 – 8672; d) D. Du, Z. Hu, J. Jin, Y. Lu, W. Tang, B. Wang, T. Lu, *Org. Lett.* **2012**, *14*, 1274 – 1277; e) F. Romanov-Michailidis, C. Besnard, A. Alexakis, *Org. Lett.* **2012**, *14*, 4906 – 4909.

[5] a) Y.-M. Zhao, Y. Tam, Y.-J. Wang, Z. Li, J. Sun, *Org. Lett.* **2012**, *14*, 1398 – 1401; b) A. M. ElSohly, D. A. Wespe, T. J. Poore, S. A. Snyder, *Angew. Chem.* **2013**, *125*, 5901 – 5906; *Angew. Chem. Int. Ed.* **2013**, *52*, 5789 – 5794; c) R. Han, J. Qi, J. Gu, D. Ma, X. Xie, X. She, *ACS Catal.* **2013**, *3*, 2705 – 2709.

[6] J. Qi, X. Xie, R. Han, D. Ma, J. Yang, X. She, *Chem. Eur. J.* **2013**, *19*, 4146 – 4150. Only moderate enantioselectivities (up to 53% *ee*) were obtained for this reaction.

[7] a) B. Cardinal-David, D. E. A. Raup, K. A. Scheidt, *J. Am. Chem. Soc.* **2010**, *132*, 5345 – 5347; b) E. M. Phillips, M. Riedrich, K. A. Scheidt, *J. Am. Chem. Soc.* **2010**, *132*, 13179 – 13181; c) D. E. A. Raup, B. Cardinal-David, D. Holte, K. A. Scheidt, *Nat. Chem.* **2010**, *2*, 766 – 770; d) D. T. Cohen, B. Cardinal-David, J. M. Roberts, A. A. Sarjeant, K. A. Scheidt, *Org. Lett.* **2011**, *13*, 1068 – 1071; e) D. T. Cohen, B. Cardinal-David, K. A. Scheidt, *Angew. Chem.* **2011**, *123*, 1716 – 1720; *Angew. Chem. Int. Ed.* **2011**, *50*, 1678 – 1682; f) J. Dugal-Tessier, E. A. O'Bryan, T. B. H. Schroeder, D. T. Cohen, K. A. Scheidt, *Angew. Chem.* **2012**, *124*, 5047 – 5051; *Angew. Chem. Int. Ed.* **2012**, *51*, 4963 – 4967; g) J. Mo, X. Chen, Y. R. Chi, *J. Am. Chem. Soc.* **2012**, *134*, 8810 – 8813.

[8] a) X. Zhao, D. A. DiRocco, T. Rovis, *J. Am. Chem. Soc.* **2011**, *133*, 12466 – 12469; b) G. Liu, P. D. Wilkerson, C. A. Toth, H. Xu, *Org. Lett.* **2012**, *14*, 858 – 861; c) Z. Fu, H. Sun, S. Chen, B. Tiwari, G. Li, Y. R. Chi, *Chem. Commun.* **2013**, *49*, 261 – 263; d) E. O. McCusker, K. A. Scheidt, *Angew. Chem.* **2013**, *125*, 13861 – 13865; *Angew. Chem. Int. Ed.* **2013**, *52*, 13616 – 13620.

[9] a) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999 – 1010; b) S. J. Connon, *Angew. Chem.* **2006**, *118*, 4013 – 4016; *Angew. Chem. Int. Ed.* **2006**, *45*, 3909 – 3912; c) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744 – 5758; d) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713 – 5743; e) B. List, *Chem. Rev.* **2007**, *107*, 5413 – 5415; f) S. J. Connon, *Chem. Commun.* **2008**, 2499 – 2510; g) A. Dondoni, A. Massi, *Angew. Chem.* **2008**, *120*, 4716 – 4739; *Angew. Chem. Int. Ed.* **2008**, *47*, 4638 – 4660; h) D. W. C. MacMillan, *Nature* **2008**, *455*, 304 – 308; i) G. Bartoli, G. Bencivenni, R. Dalpozzo, *Chem. Soc. Rev.* **2010**, *39*, 4449 – 4465; j) D. Kampen, C. M. Reisinger, B. List, *Top. Curr. Chem.* **2010**, *291*, 395 – 456; k) M. Terada, *Synthesis* **2010**, 1929 – 1982; l) M. Rueping, A. Kuenkel, I. Atodiresei, *Chem. Soc. Rev.* **2011**, *40*, 4539 – 4549; m) K. Brak, E. N. Jacobsen, *Angew. Chem.* **2013**, *125*, 558 – 588; *Angew. Chem. Int. Ed.* **2013**, *52*, 534 – 561; n) J. Lv, S. Z. Luo, *Chem. Commun.* **2013**, *49*, 847 – 858; o) M. Mahlau, B. List, *Angew. Chem.* **2013**, *125*, 540 – 556; *Angew. Chem. Int. Ed.* **2013**, *52*, 518 – 533. For a review on super Brønsted acid catalysis, see: C. H. Cheon, H. Yamamoto, *Chem. Commun.* **2011**, *47*, 3043 – 3056. For selected examples of super Brønsted acid catalysis, see: D. Nakashima, H. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 9626 – 9627; C. H. Cheon, H. Yamamoto, *J. Am. Chem. Soc.* **2008**, *130*, 9246 – 9247.

[10] For selected reviews on metal/Brønsted acid combined catalysis, see: a) Z. Shao, H. Zhang, *Chem. Soc. Rev.* **2009**, *38*, 2745 – 2755; b) M. Rueping, R. M. Koenigs, I. Atodiresei, *Chem. Eur. J.* **2010**, *16*, 9350 – 9365; c) see Ref. [9n].

[11] For selected examples of metal/Brønsted acid combined catalysis, see: a) K. Shen, X. Liu, Y. Cai, L. Lin, X. Feng, *Chem. Eur. J.* **2009**, *15*, 6008 – 6014; b) T. Yue, M.-X. Wang, D.-X. Wang, G. Masson, J. Zhu, *J. Org. Chem.* **2009**, *74*, 8396 – 8399; c) Q.-W. Zhang, C.-A. Fan, H.-J. Zhang, Y.-Q. Tu, Y.-M. Zhao, P. Gu, Z.-M. Chen, *Angew. Chem.* **2009**, *121*, 8724 – 8726; *Angew. Chem. Int. Ed.* **2009**, *48*, 8572 – 8574; d) B. Zhao, H. Du, Y. Shi, *J. Org. Chem.* **2009**, *74*, 8392 – 8395; e) M. Hatano, K. Moriyama, T. Maki, K. Ishihara, *Angew. Chem.* **2010**, *122*, 3911 – 3914; *Angew. Chem. Int. Ed.* **2010**, *49*, 3823 – 3826; f) F. Drouet, C. Lalli, H. Liu, G. Masson, J. Zhu, *Org. Lett.* **2011**, *13*, 94 – 97; g) G. K. Ingle, Y. Liang, M. G. Mormino, G. Li, F. R. Frondzek, J. C. Antilla, *Org. Lett.* **2011**, *13*, 2054 – 2057; h) Z. Zhang, W. Zheng, J. C. Antilla, *Angew. Chem.* **2011**, *123*, 1167 – 1170; *Angew. Chem. Int. Ed.* **2011**, *50*, 1135 – 1138; i) W. Zheng, Z. Zhang, M. J. Kaplan, J. C. Antilla, *J. Am. Chem. Soc.* **2011**, *133*, 3339 – 3341.

[12] For a mechanistic investigation involving NHC catalysis with alkynals, see: J. Mahatthananchai, P. Zheng, J. W. Bode, *Angew. Chem.* **2011**, *123*, 1711 – 1715; *Angew. Chem. Int. Ed.* **2011**, *50*, 1673 – 1677.

[13] For selected examples, see: a) J. J. Van Veldhuizen, S. B. Garber, J. S. Kingsbury, A. H. Hoveyda, *J. Am. Chem. Soc.* **2002**, *124*, 4954 – 4955; b) J. J. Van Veldhuizen, D. G. Gillingham, S. B. Barber, O. Kataoka, A. H. Hoveyda, *J. Am. Chem. Soc.* **2003**, *125*, 12502 – 12508; c) A. H. Hoveyda, D. G. Gillingham, J. J. Van Veldhuizen, O. Kataoka, S. B. Garber, J. S. Kingsbury, J. P. A. Harrity, *Org. Biomol. Chem.* **2004**, *2*, 8 – 23; d) K.-s. Lee, M. K. Brown, A. W. Hird, A. H. Hoveyda, *J. Am. Chem. Soc.* **2006**, *128*, 7182 – 7184; e) M. K. Brown, T. L. May, C. A. Baxter, A. H. Hoveyda, *Angew. Chem.* **2007**, *119*, 1115 – 1118; *Angew. Chem. Int. Ed.* **2007**, *46*, 1097 – 1100; f) Y. Lee, K. Akiyama, D. G. Gillingham, M. K. Brown, A. H. Hoveyda, *J. Am. Chem. Soc.* **2008**, *130*, 446 – 447; g) H. Wu, S. Radomkit, J. M. O'Brien, A. H. Hoveyda, *J. Am. Chem. Soc.* **2012**, *134*, 8277 – 8285.

[14] K. P. Jang, G. E. Hutson, R. C. Johnston, E. O. McCusker, P. U.-Y. Cheong, K. A. Scheidt, *J. Am. Chem. Soc.* **2014**, *136*, 76 – 79.

[15] For examples of pK_a value determination of NHCs, see: a) R. W. Alder, P. R. Allen, S. J. Williams, *J. Chem. Soc. Chem. Commun.* **1995**, 1267 – 1268; b) Y. J. Kim, A. Streitweiser, *J. Am. Chem. Soc.* **2002**, *124*, 5757 – 5761; c) T. L. Amyes, S. T. Diver, J. P. Richard, F. M. Rivas, K. Toth, *J. Am. Chem. Soc.* **2004**, *126*, 4366 – 4374; d) A. M. Magill, K. J. Cavell, B. F. Yates, *J. Am. Chem. Soc.* **2004**, *126*, 8717 – 8724; e) Y. Chu, H. Deng, J. P. Cheng, *J. Org. Chem.* **2007**, *72*, 7790 – 7793; f) E. M. Higgins, J. A. Sherwood, A. G. Lindsay, J. Armstrong, R. S. Massey, R. W. Alder, A. C. O'Donoghue, *Chem. Commun.* **2011**, *47*, 1559 – 1561.

[16] For examples of pK_a value determination of Brønsted acids, see: a) P. Christ, A. G. Lindsay, S. S. Vormittag, J.-M. Nuudoerfl, A. Berkessel, A. C. O'Donoghue, *Chem. Eur. J.* **2011**, *17*, 8524 – 8528; b) D. Seebach, A. K. Beck, H. Bichsel, A. Pichota, C. Sparr, R. Wünsch, W. B. Schweizer, *Helv. Chim. Acta* **2012**, *95*, 1303 – 1324; c) C. Yang, X.-S. Xue, J.-L. Jin, X. Li, J.-P. Cheng, *J. Org. Chem.* **2013**, *78*, 7076 – 7085.

[17] a) Z.-Q. Rong, M.-Q. Jia, S.-L. You, *Org. Lett.* **2011**, *13*, 4080 – 4083; b) see Ref. [6].

[18] M. Hatano, T. Ikeno, T. Matsumura, S. Torii, K. Ishihara, *Adv. Synth. Catal.* **2008**, *350*, 1776 – 1780.

[19] a) S. Xu, Z. Wang, X. Zhang, X. Zhang, K. Ding, *Angew. Chem.* **2008**, *120*, 2882 – 2885; *Angew. Chem. Int. Ed.* **2008**, *47*, 2840 – 2843; b) M. Rueping, T. M. Theissmann, A. Kuenkel, R. M. Koenigs, *Angew. Chem.* **2008**, *120*, 6903 – 6906; *Angew. Chem. Int. Ed.* **2008**, *47*, 6798 – 6801.

[20] We also tested aliphatic alkynals, however, the reaction provided numerous peaks by UPLC and no desired product was observed. Current studies to engage this substrate class are ongoing.

[21] A computational study at the M06-2X/6-31 + G(2df,p)/PCM-(THF)//M06-2X/6-31G(d) level of theory indicates that the *Z*-alkene isomer is more stable by ≈ 0.6 kcal mol^{-1} compared to the *E*-alkene isomer because of the minimization of steric interactions.

[22] For a comprehensive review on substrate-directed reactions, see: A. H. Hoveyda, D. A. Evans, G. C. Fu, *Chem. Rev.* **1993**, *93*, 1307 – 1370.

[23] a) N. Sakai, T. Moriya, T. Konakahara, *J. Org. Chem.* **2007**, *72*, 5920 – 5922; b) N. Sakai, T. Moriya, K. Fujii, T. Konakahara, *Synthesis* **2008**, 3533 – 3536.

[24] a) F. M. Dean, *Adv. Heterocycl. Chem.* **1982**, *30*, 167 – 238; b) Y. Zhu, C. Zhai, L. Yang, W. Hu, *Chem. Commun.* **2010**, *46*, 2865 – 2867.

