JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Oxidative γ-Addition of Enals to Trifluoromethyl Ketones: Enantioselectivity Control via Lewis Acid/N-Heterocyclic Carbene Cooperative Catalysis

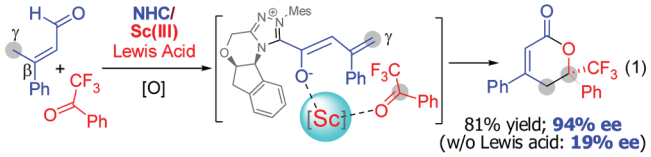
Junming Mo,[†] Xingkuan Chen,[†] and Yonggui Robin Chi*

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore

Supporting Information

ABSTRACT: An oxidative γ-functionalization of enals under N-heterocyclic carbene (NHC) catalysis to give unsaturated δ-lactones is disclosed. Enantioselectivity control involving the relatively remote enal γ-carbon was achieved via Lewis acid [$Sc(OTf)_3$ or combined $Sc(OTf)_3/Mg(OTf)_2$] and NHC cooperative catalysis.

Enantioselective activation of nonreactive C−H units that are remote to activating groups is of fundamental and practical significance but often challenging. Under N-heterocyclic carbene (NHC) catalysis,[1] for example, the activation of enals offers homoenolate,[2] enolate,[3] and acyl anion equivalents[4] for enantioselective reactions.[5] These reactions primarily involve β, α, and carbonyl carbons, respectively, as the prenucleophiles.[2−5] The activation of enal γ-carbons via NHC catalysis, on the other hand, poses significant challenges and remains underdeveloped. Examples of the apparent difficulties in NHC-mediated γ-functionalization of enals include (a) difficulties in activating the enal γ-carbons as nucleophiles; (b) competing reactions of the homoenolate, enolate, and acyl anion intermediates; and (c) the fact that chiral information from the NHC catalyst may be relatively remote from the enal γ-carbon, making stereocontrol difficult. Here we report the first enantioselective γ-addition of enals to activated ketones via oxidatively generated NHC-bounded vinyl enolate intermediates (eq 1). The typical NHC-mediated enal reactions,[2−4,6]



oxidatively generated vinyl enolate; Lewis acid-assisted chiral control

such as those involving homoenolate intermediates as the nucleophiles, were suppressed by introducing one substituent at the enal β-carbon. The high enantioselectivity (~90% ee) was achieved via NHC and Sc- or Sc/Mg-based Lewis acid cooperative catalysis. In the absence of the Lewis acid cocatalyst, only 5−23% ee was observed in all cases. The Lewis acid cocatalyst assists the stereocontrol at the enal γ-carbon presumably by coordinating with the reaction partners (eq 1). As an important note, relevant γ-functionalization of some enals was previously realized via dienamine catalysis,[7] and γ-activation of α,β-unsaturated ketenes mediated by cinchona alkaloid and NHC-based nucleophilic catalysts was reported by the groups of Peters and Ye.[8] Our present work constitutes the first study of NHC-catalyzed oxidative γ-functionalization of enals.

The oxidation of enals to the corresponding α,β-unsaturated esters as Michael acceptors under NHC catalysis has been pioneered by the groups of Scheidt, Studer, You, and Gois.[9] In our reactions, the substituent at the enal β-carbon, introduced to suppress typical NHC-catalyzed enal reactions,[2−4,6] also prevented the oxidatively generated unsaturated ester intermediates from behaving as Michael acceptors. The seminal work on NHC/Lewis acid co-operative catalysis is from Scheidt and co-workers.[10] In 2010, they found that $Ti(O^iPr)_4$ as a Lewis acid could induce diastereoselectivity switching in NHC-mediated reactions of enal homoenolates with chalcones.[10a] They also reported that the Lewis acid $[Mg(O^tBu)_2]$ could induce relatively small (e.g., from 72 to 86%) but consistent enantioselectivity improvements in NHC-catalyzed additions of enal homoenolates to hydrazones.[10b] In 2011, the You group found that the use of a sodium salt ($NaBF_4$) could significantly improve the ee of an NHC-catalyzed redox Michael reaction.[7e] Very recently, during the preparation of our manuscript, Scheidt and co-workers reported a large ee enhancement when LiCl was used as a mild Lewis acid additive in NHC-catalyzed additions of enal homoenolates to isatines.[10c] Our work demonstrates that enantioselective control involving the relatively remote enal γ-carbon can be nicely achieved through the introduction of $Sc(OTf)_3$ or $Sc(OTf)_3/Mg(OTf)_2$ as a relatively strong Lewis acid cocatalyst. Sc-based Lewis acids have been found to be effective in cooperative NHC catalysis for the first time.

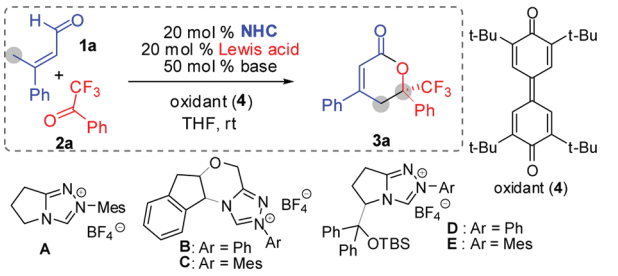
We first set out to develop an oxidative γ-addition of enals **1** to trifluoroacetophenone (**2a**) for the synthesis of unsaturated δ-lactones **3**. Quinone **4**, previously explored in NHC-catalyzed oxidations,[9] was found to be a good oxidant in our studies. Not surprisingly, β-monosubstituted enals (such as crotonaldehyde) were not effective because of competing typical NHC-mediated enal reactions[2−4,6] such as those involving the homoenolate[4] nucleophiles. Fortunately, the use of enal **1a**, obtained by installing a phenyl group at the β-position of butenal, afforded the desired γ-addition and cyclization product **3a** in 70%

Received: April 16, 2012
Published: May 9, 2012

dx.doi.org/10.1021/ja303618z | J. Am. Chem. Soc. 2012, 134, 8810−8813

isolated yield using NHC precatalyst **A** (Table 1, entry 1). We next attempted to develop enantioselective catalysis by using

Table 1. Development of the Oxidative Cooperative Catalytic γ-Functionalization of Enals[a]



entry	NHC	Lewis acid	base	yield (%)[b]	ee (%)[c]
1	**A**	–	Cs_2CO_3	70	–
2	**B**	–	Cs_2CO_3	50	21
3	**C**	–	Cs_2CO_3	63	29
4	**D**	–	Cs_2CO_3	–	–
5	**E**	–	Cs_2CO_3	<5	–
6	**C**	–	K_2CO_3	67	16
7	**B**	$Sc(OTf)_3$	Cs_2CO_3	52	64
8	**C**	$Sc(OTf)_3$	Cs_2CO_3	64	73
9	**E**	$Sc(OTf)_3$	Cs_2CO_3	–	–
10	**C**	$Mg(OTf)_2$	Cs_2CO_3	59	60
11	**C**	$Mg(OTf)_2$	K_2CO_3	55	55
12	**C**	**$Sc(OTf)_3$**	**K_2CO_3**	**72**	**88**
13[d]	**C**	$Sc(OTf)_3/Mg(OTf)_2$	K_2CO_3	69	91
14[e]	**C**	$Sc(OTf)_3$	K_2CO_3	84	91
15[d,e]	**C**	**$Sc(OTf)_3/Mg(OTf)_2$**	**K_2CO_3**	**81**	**94**

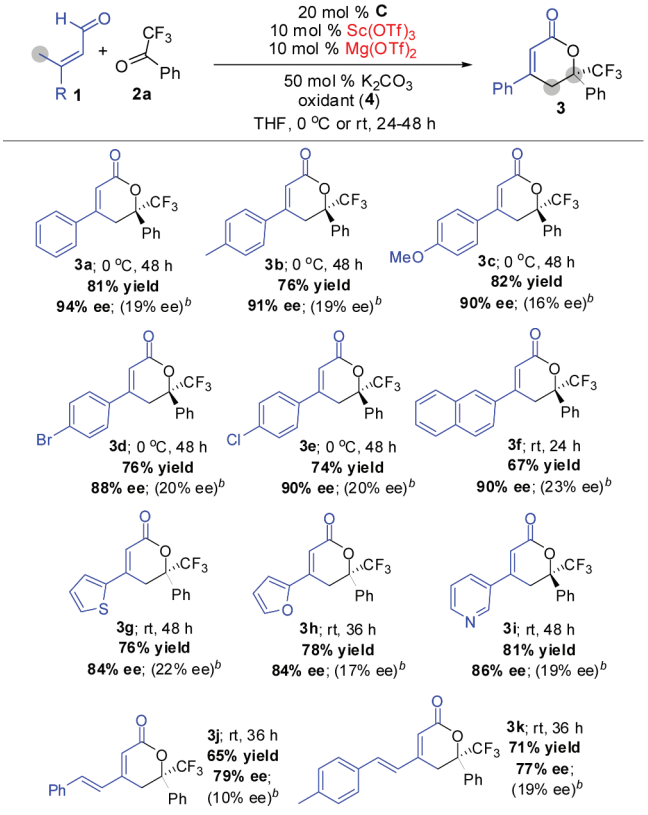
[a]Reaction conditions: **1a** (0.15 mmol), **2a** (0.15 mmol), **4** (0.15 mmol), solvent (1.5 mL). Reaction times: entries 1–6, 12 h; entries 7–13, 24 h; entries 14 and 15, 48 h. [b]Isolated yields based on **2a**. [c]Enantiomeric excess of **3a**, determined via chiral-phase HPLC analysis. The absolute configuration was assigned on the basis of a comparison of the optical rotation of **3a** with the literature value: observed, $[\alpha]_D^{20} = -80.3°$ (10 mg/mL, $CHCl_3$); literature value, $[\alpha]_D^{25} = -73.2°$ (10 mg/mL, $CHCl_3$).[8d] [d]$Sc(OTf)_3$ (10 mol %), $Mg(OTf)_2$ (10 mol %). [e]0.18 mmol of **1a** at 0 °C; under these conditions without Lewis acid, the product was obtained in 19% ee.

chiral NHCs that were previously found to be successful in the related homoenolate, enolate, and acyl anion reactions. The aminoindanol-based catalysts **B** and **C** could catalyze the reactions in only 16–29% ee after extensive optimization with respect to typical parameters such as base, solvent, and temperature (entries 2, 3, and 6). Relatively bulky triazolium compounds **D** and **E** led to little or no formation of **3a** under oxidative NHC catalysis (entries 4 and 5).

Instead of modifying the NHC catalysts, we decided to introduce a second catalyst to interact with either or both of the reaction partners (the ketone and the vinyl enolate intermediate; see eq 1 or Scheme 1). Our efforts with chiral hydrogen-bond-donating catalysts (e.g, thioureas, tartaric acids, and BINOL derivatives) were unsuccessful. Encouraging results emerged when $Sc(OTf)_3$ was used as a Lewis acid cocatalyst. The product ee jumped from 29 to 73% in the presence of $Sc(OTf)_3$ with **C** as the NHC precatalyst and Cs_2CO_3 as the base (Table 1, entry 8 vs 3). The reaction with NHC precatalyst **B** showed a similar ee enhancement (entry 7). In general, the addition of the Lewis acid cocatalyst led to slower reactions, and a longer reaction time (24 h) was necessary (entries 7–13). The use of the NHC and Lewis acid in 1:1 molar ratio gave optimal results in terms of both reaction yield and enantioselectivity. Ethers were good solvents, and tetrahydrofuran (THF) was the best among the solvents screened in this study.[11] It is worth noting that in the presence of $Sc(OTf)_3$, catalysts **B** (*N*-Ph) and **C** (*N*-Mes) showed similar enantioselectivities (entries 7 and 8). Among the other Lewis acids screened [$Mg(OTf)_2$, $Ti(OMe)_4$, $ScCl_3$, $Mg(O^tBu)_2$, $MgSO_4$] that afforded good conversions, $Mg(OTf)_2$ was the only other one that offered similar benefits in remote enantioselective control (entry 10). We next found that K_2CO_3 was superior to Cs_2CO_3[12] and that catalyst **C** was slightly better than **B** with K_2CO_3, affording **3a** with 88% ee in 72% yield (entry 12). The combined use of the two effective Lewis acids [$Mg(OTf)_2$ and $Sc(OTf)_3$, 10 mol % each] offered a small (~3%) but consistent additional ee enhancement (entry 13), for reasons that are unclear at this point. When the reaction was carried out at 0 °C over a longer reaction time (48 h) in the presence of **C** and the two Lewis acid cocatalysts, product **3a** was obtained in 81% isolated yield and 94% ee (entry 15). The exact mode of cooperative catalytic activation remains unknown (also see Scheme 1).

Having established an optimal protocol for the reaction, the scope of the enal substrate reacting with ketone **2a** was examined (Chart 1). To demonstrate the generality of the Lewis acid effects, the ee's of the products formed in the presence and absence of the Lewis acid cocatalysts are included for all of the reactions. Both electron-donating (**3b** and **3c**) and -withdrawing (**3d** and **3e**) substituents on the β-phenyl unit

Chart 1. Variation of the Enal 1[a]



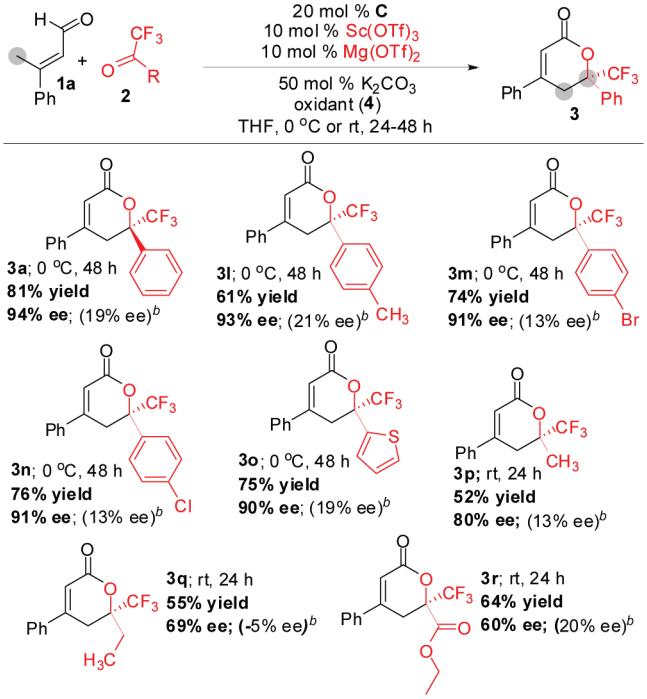
[a]Similar conditions as in Table 1, entry 15. [b]The ee for the reaction without the presence of the Lewis acid under otherwise identical conditions is given in parentheses.

dx.doi.org/10.1021/ja303618z | J. Am. Chem. Soc. 2012, 134, 8810–8813

were tolerated. Replacing the β-phenyl substituent with a naphthyl (**3f**) or heteroaryl (**3g–i**) unit did not significantly change the reaction yield or ee. When the β-aryl group of the enal was changed to a vinyl substituent (**3j** and **3k**), a slight decrease in enantioselectivity to 77–79% ee was observed. Replacing the β-phenyl group in enal **1a** with an alkyl substituent or the β-methyl unit of **1a** with a longer carbon unit (e.g., an ethyl group) led to little conversion to the δ-lactone product. Instead, self-redox of the enal leading to the corresponding carboxylic acid was observed as the major reaction pathway.

The scope of the activated ketone substrate was also examined (Chart 2). All of the (hetero)aryltrifluoroacetones

Chart 2. Variation of the Ketone 2[a]

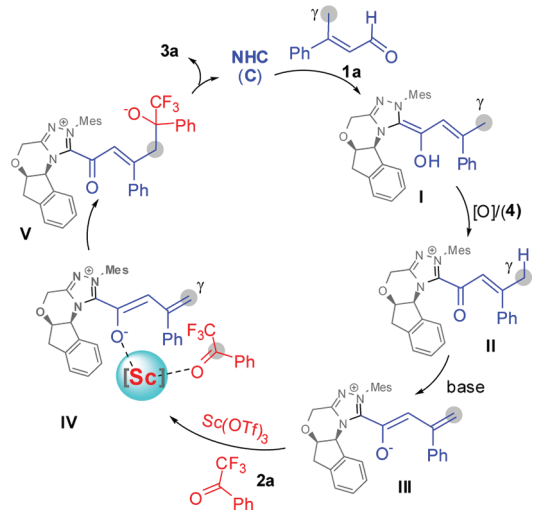


[a]Similar conditions as in Table 1, entry 15. [b]The ee for the reaction without the presence of the Lewis acid under otherwise identical conditions is given in parentheses.

examined in this work reacted well with good enantioselectivities. For example, installing a methyl (**3l**), bromo (**3m**), or chloro (**3n**) on the phenyl unit of ketone **2a** did not affect the reaction outcome. Switching the phenyl group of **2a** to a heteroaryl substituent (**3o**) led to excellent results as well (75% yield, 90% ee). Very encouragingly, replacing the aryl group of ketone **2a** with an alkyl substituent [methyl (**3p**), ethyl (**3q**)] also led to effective reactions, albeit with decreased yields and ee's. Switching the phenyl group in **2a** to an electron-withdrawing ester unit (**3r**) afforded a good yield (65%) but decreased enantioselectivity (60% ee) without further optimization of this particular substrate.

A postulated reaction pathway is illustrated in Scheme 1. The vinyl enolate intermediate (**III**) likely comes from γ-deprotonation of the oxidatively generated unsaturated ester intermediate (**II**), although direct oxidation of the enal γ-carbon of the homoenolate intermediate **I** leading to **III** cannot be completely ruled out. Vinyl enolate **III** then undergoes nucleophilic addition to ketone **2a**, eventually affording product

Scheme 1. Postulated Reaction Pathway



3a.[13] The Sc(III) Lewis acid, which is known to have good affinities for carbonyl oxygens and carboxylates,[14] likely is involved in multisite coordination to bring the ketone electrophile into close proximity with intermediate **III** and the chiral NHC catalyst, as illustrated by **IV**.[15] This coordination amplifies the otherwise weak chiral induction by the chiral NHC catalyst.

In summary, we have disclosed the first oxidative generation of vinyl enolates for γ-functionalization of enals under NHC catalysis. The challenging remote chiral control was realized through the introduction of a Lewis acid cocatalyst. Mechanistic details, functionalization of less reactive sites of common substrates such as enals and simple aldehydes, and further exploration of the use of cooperative catalysis for remote asymmetric control are under study in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

robinchi@ntu.edu.sg

Author Contributions

†J.M. and X.C. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Generous financial support for this work was provided by Singapore National Research Foundation, Singapore Economic Development Board (EDB), GlaxoSmithKline (GSK), and Nanyang Technological University. We also appreciate the thoughtful comments from the referees.

■ REFERENCES

(1) For selected recent reviews of NHC catalysis, see: (a) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534. (b) Zeitler, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 7506. (c) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606. (d) Marion, N.; Diez-Gonzalez, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988. (e) Nair, V.;

Vellalath, S.; Babu, B. P. *Chem. Soc. Rev.* **2008**, *37*, 2691. (f) Rovis, T. *Chem. Lett.* **2008**, *37*, 2. (g) Arduengo, A. J., III; Iconaru, L. I. *Dalton Trans.* **2009**, 6903. (h) Phillips, E. M.; Chan, A.; Scheidt, K. A. *Aldrichimica Acta* **2009**, *42*, 55. (i) Moore, J. L.; Rovis, T. *Top. Curr. Chem.* **2010**, *291*, 77. (j) Biju, A. T.; Kuhl, N.; Glorius, F. *Acc. Chem. Res.* **2011**, *44*, 1182. (k) Hirano, K.; Piel, I.; Glorius, F. *Chem. Lett.* **2011**, *40*, 786. (l) Chiang, P.-C.; Bode, J. W. *TCIMeru* **2011**, *149*, 2. (m) Nair, V.; Menon, R. S.; Biju, A. T.; Sinu, C. R.; Paul, R. R.; Jose, A.; Sreekumar, V. *Chem. Soc. Rev.* **2011**, *40*, 5336. (n) Rong, Z. Q.; Zhang, W.; Yang, G. Q.; You, S.-L. *Curr. Org. Chem.* **2011**, *15*, 3077. (o) Vora, H. U.; Rovis, T. *Aldrichimica Acta* **2011**, *44*, 3. (p) Cohen, D. T.; Scheidt, K. A. *Chem. Sci* **2012**, *3*, 53. (q) Grossmann, A.; Enders, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 314.

(2) For selected examples of homoenolates from enals, see: (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. (c) Chan, A.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 905. (d) Nair, V.; Vellalath, S.; Poonoth, M.; Suresh, E. *J. Am. Chem. Soc.* **2006**, *128*, 8736. (e) Bode, J. W.; Kaeobamrung, J.; Kozlowski, M. C. *Proc. Nat'l. Acad. Sci., USA* **2010**, *107*, 20661. (f) Zhao, X.-D.; DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2011**, *133*, 12466. (g) Fang, X.; Jiang, K.; Xing, C.; Hao, L.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 1910.

(3) For selected examples of enolate generation from enals, see: (a) Glorius, F.; Burstein, C.; Tschan, S.; Xie, X. *Synthesis* **2006**, 2418. (b) Bode, J. W.; He, M.; Struble, J. R. *J. Am. Chem. Soc.* **2006**, *128*, 8418. (c) Scheidt, K. A.; Phillips, E. M.; Wadamoto, M.; Chan, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3107. (d) Fang, X.; Chen, X.; Chi, Y. R. *Org. Lett.* **2011**, *13*, 4708. (e) Nair, V.; Paul, R. R.; Lakshmi, K. C. S.; Menon, R. S.; Jose, A.; Sinu, C. R. *Tetrahedron Lett.* **2011**, *52*, 5992.

(4) For selected examples of acyl anion equivalents from enals, see: (a) Stetter, H.; Hilboll, G.; Kuhlmann, H. *Chem. Ber.* **1979**, *112*, 84. (b) Stetter, H.; Jonas, F. *Chem. Ber.* **1981**, *114*, 564. (c) DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2011**, *133*, 10402. (d) Fang, X.-Q.; Chen, X.-K.; Lv, H.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 11782. (e) Liu, G.; Wilkerson, P. D.; Toth, C. A.; Xu, H. *Org. Lett.* **2012**, *14*, 858.

(5) For selected examples of NHC-catalyzed enolate generation from α-functionalized aldehydes, ketenes, and other substrates, see: (a) He, M.; Uc, G. J.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *128*, 15088. (b) Zhang, Y. R.; He, L.; Wu, X.; Shao, P. L.; Ye, S. *Org. Lett.* **2008**, *10*, 277. (c) Duguet, N.; Campbell, C. D.; Slavin, A. M. Z.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1108. (d) He, M.; Beahm, B. J.; Bode, J. W. *Org. Lett.* **2008**, *10*, 3817. (e) Huang, X.-L.; He, L.; Shao, P.-L.; Ye, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 192. (f) Kobayashi, S.; Kinoshita, T.; Uehara, H.; Sudo, T; Ryu, I. *Org. Lett.* **2009**, *11*, 3934. (g) Scheidt, K. A.; Kawanaka, Y.; Phillips, E. M. *J. Am. Chem. Soc.* **2009**, *131*, 18028. (h) Vora, H. U.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 2860. (i) Ling, K. B.; Smith, A. D. *Chem. Commun.* **2011**, *47*, 373. (j) Lv, H.; Mo, J.-M.; Fang, X.; Chi, Y. R. *Org. Lett.* **2011**, *13*, 5366. For selected examples of (non-enal) acyl anion chemistry, see: (k) Enders, D.; Kallfass, U. *Angew. Chem., Int. Ed.* **2002**, *41*, 1743. (l) Takikawa, H.; Hachisu, Y.; Bode, J. W.; Suzuki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 3492. (m) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 4558. (n) Li, G.-Q.; Dai, L.-X.; You, S.-L. *Chem. Commun.* **2007**, 852. (o) Bode, J. W.; Sohn, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 13798. (p) Vora, H. U.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 13796. (q) Enders, D.; Grossmann, A.; Fronert, J.; Raabe, G. *Chem. Commun.* **2010**, *46*, 6282.

(6) For additional examples of NHC-mediated enal reactions, see: (a) Nair, V.; Vellalath, S.; Poonoth, M.; Mohan, R.; Suresh, E. *Org. Lett.* **2006**, *8*, 507. (b) Chiang, P.-C.; Kaeobamrung, J.; Bode, J. W. *J. Am. Chem. Soc.* **2007**, *129*, 3520. (c) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 5334. (d) Seayad, J.; Patra, P. K.; Zhang, Y.; Ying, J. Y. *Org. Lett.* **2008**, *10*, 953. (e) Yang, L.; Tan, B.; Wang, F.; Zhong, G. *J. Org. Chem.* **2009**, *74*, 1744.

(7) For selected examples of dienamine catalysis, see: (a) Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, P.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 12973. (b) Hong, B.-C.; Wu, M.-F.; Tseng, H.-C.; Huang, G.-F.; Su, C.-F.; Liao, J.-J. *J. Org. Chem.* **2007**, *72*, 8459. (c) Utsumi, N.; Zhang, H.; Tanaka, F.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2007**, *46*, 1878. (d) de Figueiredo, R. M.; Fröhlich, R.; Christmann, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 1450. (e) Liu, K.; Chougnet, A.; Woggon, W.-D. *Angew. Chem., Int. Ed.* **2008**, *47*, 5827. (f) Han, B.; Xiao, Y.-C.; He, Z.-Q.; Chen, Y.-C. *Org. Lett.* **2009**, *11*, 4660. (g) Li, J.-L.; Kang, T.-R.; Zhou, S.-L.; Li, R.; Wu, L.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2010**, *49*, 5418. (h) Bencivenni, G.; Galzerano, P.; Mazzanti, P.; Bartoli, G.; Melchiorre, P. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20642. (i) Bergonzini, G.; Vera, S.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 9685. (j) Stiller, J.; Marqués-López, E.; Herrera, R. P.; Fröhlich, R.; Strohmann, C.; Christmann, M. *Org. Lett.* **2011**, *13*, 70. Also see cited references therein.

(8) (a) Tiseni, P. S.; Peters, R. *Angew. Chem., Int. Ed.* **2007**, *46*, 5325. (b) Tiseni, P. S.; Peters, R. *Org. Lett.* **2008**, *10*, 2019. (c) Tiseni, P. S.; Peters, R. *Chem.—Eur. J* **2010**, *16*, 2503. (d) Shen, L.-T.; Shao, P.-L.; Ye, S. *Adv. Synth. Catal.* **2011**, *353*, 1943. (e) Shen, L.-T.; Sun, L.-H.; Ye, S. *J. Am. Chem. Soc.* **2011**, *133*, 15894. It should be noted that NHCs generally showed poor enantioselectivity control in such remote activations (e.g., ref 8e), and thus, functionalized cinchona alkaloid catalysts were often used (refs 8a–c,e).

(9) (a) Maki, B. E.; Chan, A.; Phillips, E. M.; Scheidt, K. A. *Org. Lett.* **2007**, *9*, 371. (b) De Sarkar, S.; Grimme, S.; Studer, A. *J. Am. Chem. Soc.* **2010**, *132*, 1190. (c) De Sarkar, S.; Studer, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 9266. (d) Reddy, R. S.; Rosa, J. N.; Veiros, L. F.; Caddick, S.; Gois, P. M. P. *Org. Biomol. Chem.* **2011**, *9*, 3126. (e) Rong, Z.-Q.; Jia, M.-Q.; You, S.-L. *Org. Lett.* **2011**, *13*, 4080. (f) Biswas, A.; De Sarkar, S.; Fröhlich, R.; Studer, A. *Org. Lett.* **2011**, *13*, 4966. For examples of (self- or external) oxidation of non-enals under NHC catalysis, see: (g) Chow, K. Y.-K.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 8126. (h) Reynolds, N. T.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 9518. (i) Zeitler, K. *Org. Lett.* **2006**, *8*, 637. (j) Noonan, C.; Baragwanath, L.; Connon, S. J. *Tetrahedron Lett.* **2008**, *49*, 4003. (k) Wang, L.; Thai, K.; Gravel, M. *Org. Lett.* **2009**, *11*, 891. (l) Yoshida, M.; Katagiri, Y.; Zhu, W.-B.; Shishido, K. *Org. Biomol. Chem.* **2009**, *7*, 4062. (m) Kawanaka, Y.; Phillips, E. M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2009**, *131*, 18028.

(10) (a) Cardinal-David, B.; Raup, D. E. A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 5345. (b) Raup, D. E. A.; Cardinal-David, B.; Holte, D.; Scheidt, K. A. *Nat. Chem.* **2010**, *2*, 766. (c) Dugal-Tessier, J.; O'Bryan, E. A.; Schroeder, T. B. H.; Cohen, D. T.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 4963. Also see: (d) Phillips, E. M.; Riedrich, M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 13179. (e) Cohen, D. T.; Cardinal-David, B.; Roberts, J. M.; Sarjeant, A. A.; Scheidt, K. A. *Org. Lett.* **2011**, *13*, 1068. (f) Cohen, D. T.; Cardinal-David, B.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 1678.

(11) The ee values for reactions carried out in several ethers: $(Et)_2O$, 78%; *t*-BuOMe, 83%; $(n\text{-Bu})_2O$, 54%; DME, 56%; 2,2,5,5-tetramethyl-THF, 70%.

(12) The ee values for reactions using different bases: LiOH, 55%; Na_2CO_3, 81%; $NaHCO_3$, 84%; K_2CO_3, 88%; KOAc, 85%; K_2HPO_4, 85%; Et_3N, low conversion, 14% ee. Organic bases (DBU, DMAP, DABCO) gave little formation of **3a**.

(13) A concerted pathway for this transformation (from **IV** to **3a**) cannot be ruled out.

(14) (a) For a review, see: Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W.-L. *Chem. Rev.* **2002**, *102*, 2227. (b) Other potential roles of the Lewis acid may include coordination with the acylazolium intermediate **II** to facilitate deprotonation to generate vinyl enolate **III**.

(15) For instance, the addition of acetate anions (1.0 equiv of $Bu_4N^+Ac^-$) to the reaction mixture (identical to that for Table 1, entry 13) led to a decreased ee of 79%, presumably due to competing binding of the Lewis acid with Ac^- vs the reaction partners (**2a** or **III**, Scheme 1).