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Enantioselective Activation of Stable Carboxylate Esters as Enolate Equivalents *via* N-Heterocyclic Carbene Catalysts

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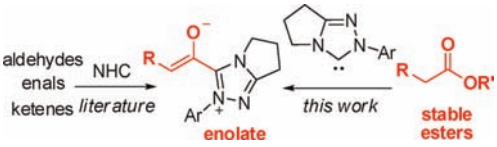
ABSTRACT



The first N-Heterocyclic Carbene (NHC) mediated activation of stable carboxylate esters to generate enolate intermediates is disclosed. The catalytically generated arylacetic ester enolates undergo enantioselective reactions with α,β-unsaturated imines.

Asymmetric organocatalytic generation of chiral enolate equivalents is a powerful approach in organic synthesis. Ketenes are one of the most studied classes of enolate precursors. The asymmetric activation of ketenes has been realized with nucleophilic catalysts, such as planar-chiral DMAP derivatives,[1] cinchona alkaloids,[2] and chiral N-heterocyclic carbenes (NHCs).[3−6] A drawback of this otherwise very successful approach lies in the relatively unstable nature of ketenes (and their carboxyl chloride precursors) that can pose operational challenges. With NHCs[7] as the catalysts, recently the chiral ester enolate equivalents have also been generated from functionalized aldehydes[8] and enals.[9] The overall process (the "forward" pathway) starts from enals (or functional aldehydes), goes

(1) Reviews: (a) Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412–420. (b) Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542–547. (c) Wurz, R. P. *Chem. Rev.* **2007**, *107*, 5570–5595.

(2) Reviews: (a) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985–3012. (b) France, S.; Weatherwax, A.; Taggi, A. E.; Lectka, T. *Acc. Chem. Res.* **2004**, *37*, 592–600. (c) Gaunt, M. J.; Johansson, C. C. C. *Chem. Rev.* **2007**, *107*, 5596–5605. (d) Paull, D. H.; Weatherwax, A.; Lectka, T. *Tetrahedron* **2009**, *65*, 6771–6803.

(3) For selected examples: (a) Duguet, N.; Campbell, C. D.; Slawin, A. M. Z.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1108–1113. (b) Concellon, C.; Duguet, N.; Smith, A. D. *Adv. Synth. Catal.* **2009**, *351*, 3001–3009. (c) Douglas, J.; Ling, K. B.; Concellon, C.; Churchill, G.; Slawin, A. M. Z.; Smith, A. D. *Eur. J. Org. Chem.* **2010**, 5863–5869. (d) He, L.; Lv, H.; Zhang, Y.; Ye, S. *J. Org. Chem.* **2008**, *73*, 8101–8103. (e) Zhang, Y. R.; He, L.; Wu, X.; Shao, P. L.; Ye, S. *Org. Lett.* **2008**, *10*, 277–280. (f) Huang, X. L.; He, L.; Shao, P. L.; Ye, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 192–195. (g) Jian, T. Y.; He, L.; Tang, C.; Ye, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 9104–9107. (h) Jian, T. Y.; Shao, P. L.; Ye, S. *Chem. Commun.* **2011**, *47*, 2381–2383.

(4) Smith reported an elegant activation of *in situ* formed anhydrides using chiral isothiourea catalysts to generate enolate intermediates; see: (a) Belmessieri, D.; Morrill, L. C.; Simal, C.; Slawin, A. M. Z.; Smith, A. D. *J. Am. Chem. Soc.* **2011**, *133*, 2714–2720. (b) Morrill, L. C.; Lebl, T.; Slawin, A. M. Z.; Smith, A. D. *Chem. Sci.* **2012**DOI: 10.1039/C2SC20171B.

(5) For a selected review of enolate generations using phase-transfer catalysts, see: Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013–3028.

(6) For a recent review on the related "chiral enol equivalents" (enamine catalysis), see: Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569.

(7) For reviews on NHC catalysis: (a) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534–541. (b) Zeitler, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 7506–7510. (c) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606–5655. (d) Marion, N.; Diez-Gonzalez, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988–3000. (e) Nair, V.; Vellalath, S.; Babu, B. P. *Chem. Soc. Rev.* **2008**, *37*, 2691–2698. (f) Rovis, T. *Chem. Lett.* **2008**, *37*, 2–7. (g) Arduengo, A. J., III; Iconaru, L. I. *Dalton Trans.* **2009**, 6903–6914. (h) Phillips, E. M.; Chan, A.; Scheidt, K. A. *Aldrichimica Acta* **2009**, *42*, 55–66. (i) Moore, J. L.; Rovis, T. *Top. Curr. Chem.* **2011**, *291*, 77–144. (j) Biju, A. T.; Kuhl, N.; Glorius, F. *Acc. Chem. Res.* **2011**, *44*, 1182–1195. (k) Hirano, K.; Piel, I.; Glorius, F. *Chem. Lett.* **2011**, *40*, 786–791. (l) Chiang, P.-C.; Bode, J. W. *TCI MAIL* **2011**, *149*, 2–17. (m) Nair, V.; Menon, R. S.; Biju, A. T.; Sinu, C. R.; Paul, R. R.; Jose, A.; Sreekumar, V. *Chem. Soc. Rev.* **2011**, *40*, 5336–5346. (n) Rong, Z. Q.; Zhang, W.; Yang, G. Q.; You, S. L. *Curr. Org. Chem.* **2011**, *15*, 3077–3090. (o) Vora, H. U.; Rovis, T. *Aldrichimica Acta* **2011**, *44*, 3–11. (p) Glorius, F.; Hirano, K. *Ernst Schering Foundation Symposium Proceedings* **2008**, *2*, 159–181. (q) Grossmann, A.; Enders, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 314–325. (r) Cohen, D. T.; Scheidt, K. A. *Chem. Sci.* **2012**, *3*, 53–57.

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through a few key intermediates such as enolates, and ends up as carboxylic acid derivatives (Scheme 1a).[9] As part of a larger program to explore and understand the rich chemistry enabled by NHC catalysis, we wondered whether the "backward" pathways starting from stable carboxylic ester substrates[10] could be realized (Scheme 1a). Our design is further illustrated in Scheme 1b. A stable ester (**I**) bearing a good leaving group (OR′) may react with an NHC to form a more reactive intermediate (**II**) with increased acidities of the α C-H's. The ester intermediate **II** subsequently undergoes a deprotonation to generate enolate **III** as a key intermediate that can react with electrophiles. In addition to intrinsic scientific values provided with asymmetric catalytic activation of esters, we expect that the use of stable carboxylic esters as substrates will offer synthetic advantages over the previously employed ketenes and aldehydes in certain cases.

We started by first identifying suitable phenylacetic esters (**1**) that could be activated by NHCs to react with α,β-unsaturated imine **2a** as a model substrate (Table 1). The results briefed in Table 1 showed that chromatographically stable esters with good leaving groups (electro-deficient phenols) could behave as effective substrates (Table 1, entries 5−6). The use of excess base (200 mol % DIEA) was necessary to neutralize the acidic phenols released during the ester activations. No DIEA-catalyzed background reaction in the absence of NHC was observed (entry 7).

Scheme 1. NHC-Mediated Activation of Stable Carboxylate Esters To Generate Enolate Intermediates: A Working Hypothesis

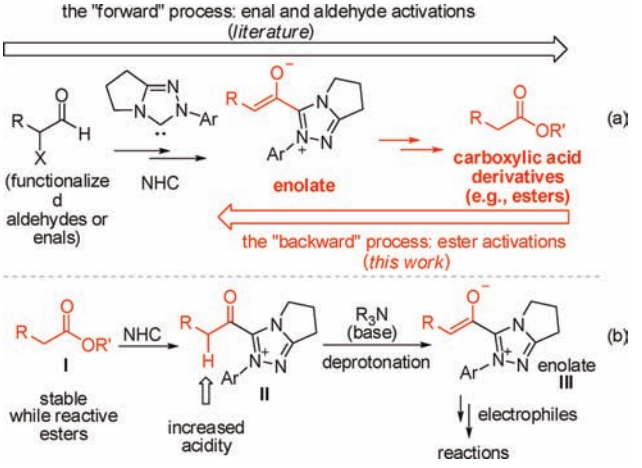
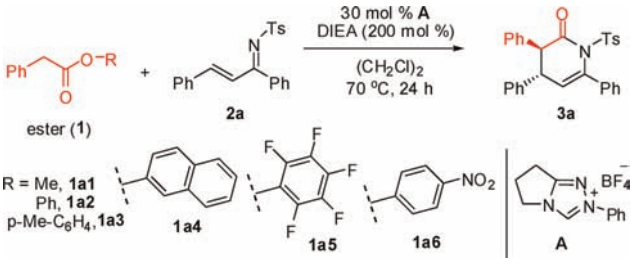
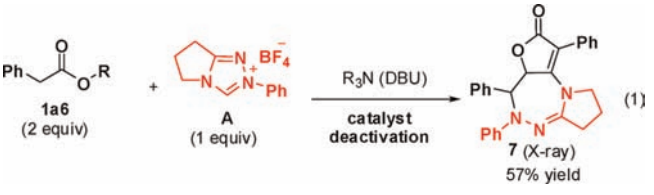


Table 1. Identification of Suitable Ester Substrates and Conditions



entry[a]	ester (**1**)	yield (%)[b]	dr[c]
1	**1a1**	<1[d]	N.D.
2	**1a2**	<1[d]	N.D.
3	**1a3**	<1[d]	N.D.
4	**1a4**	~10[e]	N.D.
5	**1a5**	81	10:1
6	**1a6**	83	11:1
7[f]	**1a6**	<1[d]	N.D.

[a] Reaction condition: **1** (0.15 mmol), **2a** (0.10 mmol), solvent (0.5 mL). [b] Isolated yield (major diastereomer) based on **2a**. [c] Diastereomeric ratio of **3a**, determined *via* ^{1}H NMR analysis of unpurified reaction mixtures. Relative configuration of the product was determined *via* X-ray of **3o** (Scheme 3, see Supporting Information). [d] No detectable formation of product as indicated *via* TLC and crude ^{1}H NMR analysis. [e] Estimated *via* crude ^{1}H NMR analysis. [f] In the absence of NHC **A**. N.D. = Not determined.



(8) For a review, see ref 7n; for selected examples, see: (a) Chow, K. Y. K.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 8126–8127. (b) Reynolds, N. T.; de Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 9518–9519. (c) Kawanaka, Y.; Phillips, E. M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2009**, *131*, 18028–18029. (d) Reynolds, N. T.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 16406–16407. (e) He, M.; Uc, G. J.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 15088–15089. (f) Alcaide, B.; Almendros, P.; Cabrero, G.; Ruiz, M. P. *Chem. Commun.* **2007**, 4788–4790. (g) Bode, J. W.; Sohn, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 13798–13799. (h) Li, G. Q.; Li, Y.; Dai, L. X.; You, S. L. *Org. Lett.* **2007**, *9*, 3519–3521. (i) Vora, H. U.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 13796–13797. (j) Du, D.; Li, L. X.; Wang, Z. W. *J. Org. Chem.* **2009**, *74*, 4379–4382. (k) Kobayashi, S.; Kinoshita, T.; Uehara, H.; Sudo, T.; Ryu, I. *Org. Lett.* **2009**, *11*, 3934–3937. (l) Li, G. Q.; Dai, L. X.; You, S. L. *Org. Lett.* **2009**, *11*, 1623–1625. (m) Phillips, E. M.; Wadamoto, M.; Roth, H. S.; Ott, A. W.; Scheidt, K. A. *Org. Lett.* **2009**, *11*, 105–108. (n) Wang, L.; Thai, K.; Gravel, M. *Org. Lett.* **2009**, *11*, 891–893. (o) Vora, H. U.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 2860–2861. (p) Ling, K. B.; Smith, A. D. *Chem. Commun.* **2011**, *47*, 373–375. Also see: (q) He, M.; Beahm, B. J.; Bode, J. W. *Org. Lett.* **2008**, *10*, 3817–3820 and ref 7.

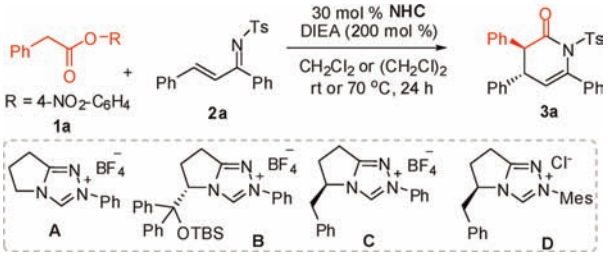
(9) For selective protonations of enal β-carbons leading to NHC-bounded ester enolates for new C−C and carbon−heteroatom bond formations, see: (a) He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418–8420. (b) Burstein, C.; Tschan, S.; Xie, X. L.; Glorius, F. *Synthesis* **2006**, 2418–2439. (c) Phillips, E. M.; Wadamoto, M.; Chan, A.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3107–3110. (d) Wadamoto, M.; Phillips, E. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 10098–10099. (e) Kaeobamrung, J.; Kozlowski, M. C.; Bode, J. W. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20661–20665. (f) Fang, X.; Chen, X.; Chi, Y. R. *Org. Lett.* **2011**, *13*, 4708–4711. For relevant mechanistic studies in enal activation, see: (g) Schrader, W. W.; Handayani, P. P.; Burstein, C.; Glorius, F. *Chem. Commun.* **2007**, 716–718. (h) Mahatthananchai, J.; Bode, J. W. *Chem. Sci.* **2012**, *3*, 192–197. Enolate intermediates are also involved in other NHC-mediated enal reactions, such as homoenolate-enolate cascades and self-redox processes; see ref 7. Also see: (i) Zhao, Y. M.; Tam, Y.; Wang, Y. J.; Li, Z.; Sun, J. *Org. Lett.* **2012**, *14*, 1398–1401. (j) Liu, G.; Wilkerson, P. D.; Toth, C. A.; Xu, H. *Org. Lett.* **2012**, *14*, 858–861.

(10) For NHC-catalyzed transesterifications, see: (a) Grasa, G. A.; Singh, R.; Nolan, S. P. *Synthesis* **2004**, 971–985. For NHC-catalyzed carboxyl transfer reactions involving carbonates activations, see: (b) Thomson, J. E.; Rix, K.; Smith, A. D. *Org. Lett.* **2006**, *8*, 3785–3788. (c) Ryan, S. J.; Candish, L.; Lupton, D. W. *J. Am. Chem. Soc.* **2009**, *131*, 14176–14177. (d) Candish, L.; Lupton, D. W. *Org. Lett.* **2010**, *12*, 4836–4839. (e) Grasa, G. A.; Kissling, R. M.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 3583–3586. (f) Nyce, G. W.; Lamboy, J. A.; Connor, E. F.; Waymouth, R. M.; Hedrick, J. L. *Org. Lett.* **2002**, *4*, 3587–3590. (g) Sarkar, S. D.; Grimme, S.; Studer, A. *J. Am. Chem. Soc.* **2010**, *132*, 1190–1191.

Mechanistically, the enolate key intermediate (**III**, Scheme 1b) was likely formed through deprotonation of the NHC-bounded activated ester intermediate (**II**, Scheme 1b). We postulated that intermediate **II** (Scheme 1b) was formed through a direct nucleophilic addition of NHC to ester substrate **I**. Our studies (see Supporting Information (SI)) suggested that a ketene intermediate was unlikely to be involved in the reactions.[11] One catalyst deactivation pathway was observed during the reaction optimizations (eq 1), which further confirmed the involvement of NHC in the catalytic activation of esters to generate enolate intermediates (see SI).[12]

We next chose the readily available and chromatographically stable 4-nitro-phenol esters (e.g., **1a6**) to develop enantioselective reactions. With achiral precatalyst **A**, increasing the reaction temperature led to a better yield with similar dr. Triazolium-based chiral catalyst **B** was not effective even at elevated temperatures. Fortunately, by using a less bulky catalyst **C**, the product could be obtained in 59% yield and 94:6 er at rt (Table 2, entry 5). Catalyst **D** was less enantioselective than **C** (Table 2, entry 6). We next sought to improve the reaction yield and found that the use of tetraalkylammonium halides was beneficial for unclear reasons (Table 2, entry 7). By using 1 equiv of Me_4NCl additive and an excess (5−10 equiv) of DIEA, the reaction could also be efficiently carried out at 0 °C to give the product with excellent yield, dr, and ee (Table 2, entry 8).

Table 2. Enantioselective Activation of Esters

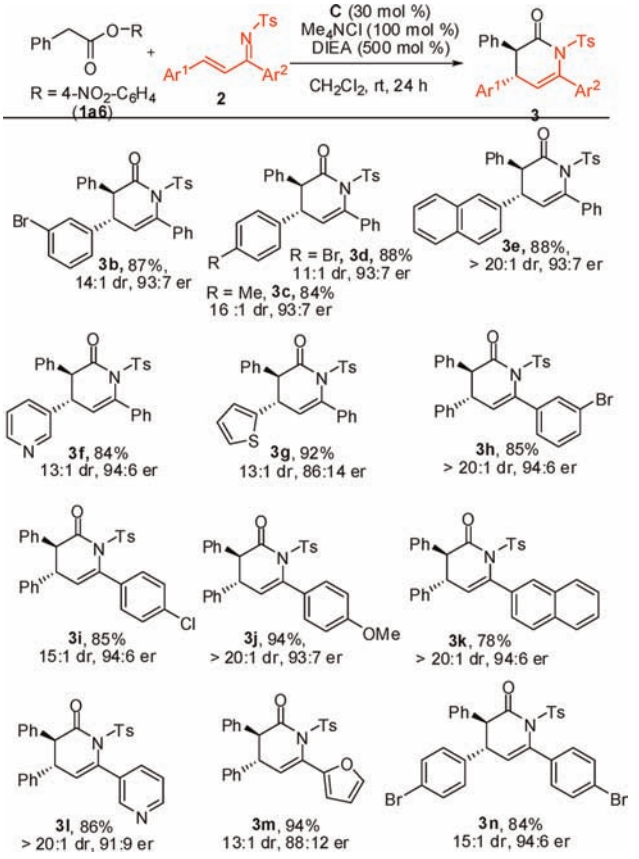


entry[a]	NHC	add.[b]	temp (°C)	yield (%)[c]	dr[d]	er[e]
1	**A**	–	rt	61	7:1	–
2	**A**	–	70	83	10:1	–
3	**B**	–	70	14	N.D.	N.D.
4	**C**	–	70	72	12:1	86:14
5	**C**	–	rt	59	12:1	94:6
6	**D**	–	rt	78	10:1	84:16
7	**C**	Me_4NCl	rt	87	20:1	94:6
8[f]	**C**	Me_4NCl	0	89	20:1	96:4

[a] Reaction condition: **1a6** (0.15 mmol), **2a** (0.10 mmol), solvent (0.5 mL). [b] Additive (100 mol %; see SI). [c] Isolated yield (major diastereomer) based on **2a**. [d] Diastereomeric ratio of **3a** determined *via* ^{1}H NMR analysis of unpurified reaction mixtures. [e] er of the major diastereomer (**3a**), determined *via* chiral phase HPLC analysis; absolute configuration of product was determined *via* X-ray of **3o** (Scheme 3; see SI). [f] 10 equiv of DIEA were used. N.D. = Not determined.

It is interesting to note that such formal [4 + 2] products (**3**) with a single aryl substituent at the lactam α-carbon could not be prepared using either NHC[7,13] or enamine[14] catalysis.[15] For example, ketenes from monoaryl acetyl chlorides were ineffective substrates under NHC catalysis; arylacetyl aldehydes in enamine catalysis pose special challenges due to competing (and even dominated) self-aldol reactions and easy α-carbon chiral center racemization of the resulting aldehyde products.

Scheme 2. Scope of the Unsaturated Imine Substrate **2**[a]



[a] Reaction conditions (Table 2, entry 7).

The scope of the reaction with respect to the α,β-unsaturated imine substrates (**2**) was then examined

(11) (a) Radt, C. W.; Ried, W. *Angew. Chem., Int. Ed.* **1963**, *2*, 397. (b) Bekele, T.; Shah, M. H.; Wolfer, J.; Abraham, C. J.; Weatherwax, A.; Lectka, T. *J. Am. Chem. Soc.* **2006**, *128*, 1810–1811. (c) Paull, D. H.; Wolfer, J.; Grebinski, J. W.; Weatherwax, A.; Lectka, T. *Chimia* **2007**, *61*, 240–246. (d) Abraham, C. J.; Paill, D. H.; Bekele, T.; Scerba, M. T.; Lectka, T.; Dudding, T. *J. Am. Chem. Soc.* **2008**, *130*, 17085–17094.

(12) A conclusive kinetic picture of the reaction (Table 1) is difficult to obtain due to catalyst deactivation and other unidentified side reactions. A preliminary single-point kinetic study suggested that only one ester molecule was involved in the rate-determine step for the formation of **3**.

(13) (a) Struble, J. R.; Kaeobamrung, J.; Bode, J. W. *Org. Lett.* **2008**, *10*, 957–960. (b) Fang, X. Q.; Chen, X. K.; Chi, Y. R. *Org. Lett.* **2011**, *13*, 4708–4711. (c) Lv, H.; Mo, J. M.; Fang, X. Q.; Chi, Y. R. *Org. Lett.* **2011**, *13*, 5366–5369. For α,α-disubstituted ketenes reacted with 1-azadienes, see: ref 3h.

(14) Enamine catalysis approach (with nonarylacetyl aldehyde substrates): (a) Han, B.; Li, J. L.; Ma, C.; Zhang, S. J.; Chen, Y. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 9971–9974. (b) Han, B.; He, Z. Q.; Li, J. L.; Li, R.; Jiang, K.; Liu, T. Y.; Chen, Y. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5474–5477.

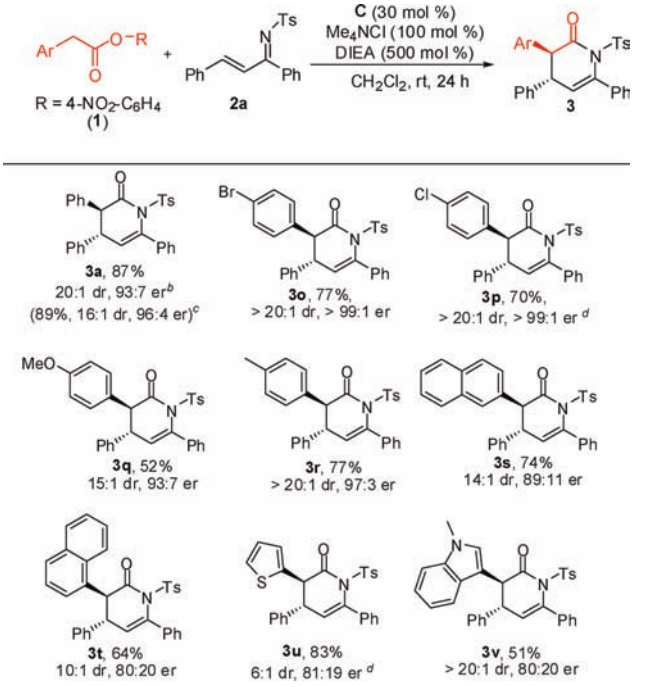
(Scheme 2). The rt condition in the presence of an ammonium halide additive and 5 equiv of DIEA (a slight modification of Table 2, entries 7–8) could generally give products with good yields and stereoselectivities for most substrates within 24 h. The imine substrates with electron-withdrawing or -donating or heteroaryl groups at Ar^1 substituents were all tolerated (Scheme 2, **3a**–**g**). Similarly, substitutions at Ar^2 did not lead to significant changes in reaction outcomes (Scheme 2, **3h**–**n**).

We next evaluated the effects of the arylacetic ester substrates (Scheme 3). The Ar group of esters (**1**) with electron-withdrawing bromo, chloro and electron-donating methoxyl or methyl substituents were all excellent substrates, giving products with good to excellent dr's and er's (Scheme 3, **3o**–**r**). Sterically bulkier esters with naphthyl substituents (**3s, t**) and heteroaryl substituted esters (**3u, v**) gave products with relatively low er's without further extensive condition optimizations. We also attempted to replace the Ar substituent of ester **1** with alkyl units (e.g., $PhCH_2$). Under conditions evaluated in this work, no product such as **3** was obtained. The esters underwent hydrolysis with the residual water present in the reaction mixture with a prolonged reaction time. It appears that a different set of conditions (base, NHC, etc.) must be developed for these esters with relatively low acidities of the α-CH's. α,α-Disubstituted esters and the related α,β-unsaturated ketones (such as chalcones) were also not effective substrates under current conditions.

In summary, we have developed the first NHC-catalyzed activation of stable carboxylate esters to form enolate intermediates. The catalytically generated NHC-bounded ester enolate intermediates undergo enantioselective reactions with α,β-unsaturated imines. The catalytic process likely proceeds through a direct addition of NHC to the ester substrate without involving a ketene intermediate. We expect our studies to shed insightful light on the fundamentally challenging process of catalytic activations of stable esters to generate chiral enolate equivalents and possibly other important intermediates (e.g., homoenolates). The use of esters will also offer operationally simpler synthetic methods. Further studies with respect to the activation of other esters and mechanistic evaluations are in progress in our laboratory.

(15) After submission of this manuscript, Smith's group reported a chiral isothiourea-catalyzed transformation of carboxylic acids to similar products. Simal, C.; Lebl, T.; Slawin, A. M. Z.; Smith, A. D. *Angew. Chem., Int. Ed.* **2012**, 10.1002/anie.201109061.

Scheme 3. Scope of the Ester Substrate **1**[a]



[a] Reaction conditions: same as those in Scheme 2. [b] 2.0 equiv of DIEA. [c] 10 equiv of DIEA, and reaction at 0 °C. [d] 2.0 equiv of DIEA without Me_4NCl, and reaction at 60 °C in 1,2-dichloroethane.

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

The authors declare no competing financial interest.