

Direct α -Functionalization of Simple Aldehydes via Oxidative N-Heterocyclic Carbene Catalysis

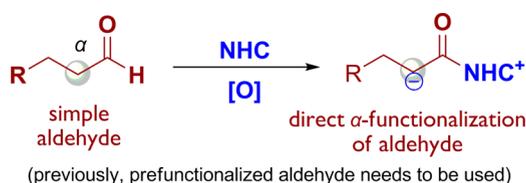
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ABSTRACT



A direct α -functionalization of simple aldehydes under N-Heterocyclic Carbene (NHC) catalysis and direct generation of ester enolate equivalents from nonfunctionalized aldehydes are disclosed. The catalysis involves selective enolate generation from an oxidatively generated NHC-bounded ester intermediate as a key step. The ester enolate intermediates undergo stereoselective reactions with enones and trifluoromethyl ketones.

Aldehydes are unambiguously an important class of basic building blocks in organic synthesis. In recent years, the enantioselective direct α -functionalization of simple aldehydes could be realized using amines as organocatalysts via

(1) For selected recent reviews on enamine catalytic α -functionalization of simple aldehydes: (a) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580. (b) List, B. *Acc. Chem. Res.* **2004**, *37*, 548. (c) Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102. (d) Marigo, M.; Jørgensen, K. A. *Chem. Commun.* **2006**, 2001. (e) Paloma, C.; Mielgo, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7876. (f) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (g) Moyano, A.; Rios, R. *Chem. Rev.* **2011**, *111*, 4703.

(2) For selected examples and recent reviews on SOMO activation catalysis: (a) Beeson, T. D.; Mastracchio, A.; Hong, J.; Ashton, K.; Macmillan, D. W. C. *Science* **2007**, *316*, 582. (b) Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 1360 and ref 1g.

(3) For selected recent reviews on NHC catalysis: (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. *TCI MAIL* **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) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 3512. (r) Grossmann, A.; Enders, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 314.

enamine catalytic pathways¹ or SOMO activation catalysis.² In another arena of organocatalysis, the development in N-heterocyclic carbene (NHC) catalysis³ has offered important strategies for a set of impressive asymmetric transformations. However, in the activation of simple aldehydes for new carbon–carbon bond formations, only the aldehyde carbonyl carbon could be used (via Breslow intermediates) as a reactive nucleophilic carbon under NHC catalysis. To functionalize the aldehyde α -carbon (via enolate intermediates), only indirect methods could be used. These indirect methods were primarily based on prefunctionalized aldehyde derivatives such as α -chloro aldehydes, as reported by Bode;⁴ α -aryloxy acetaldehydes, reported by Scheidt;⁵ α -aryloxy aldehydes, reported by Smith;⁶ and α,β -unsaturated aldehydes, as disclosed by Glorius, Bode, Scheidt, Nair, and our group.⁷ Alternatively, by using ketene (especially α,α' -disubstituted ketene) substrates, access to similar enolate

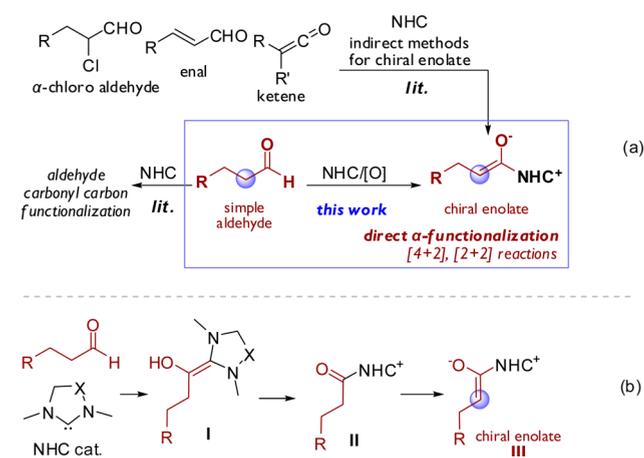
(4) For a selected example of NHC-catalyzed α -functionalization of α -chloro aldehydes, see: He, M.; Uc, G. J.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 15088.

(5) For selected examples of NHC-catalyzed α -functionalization of α -aryloxyacetaldehydes, see: (a) Maki, B. E.; Scheidt, K. A. *Org. Lett.* **2009**, *11*, 1651. (b) Kawanaka, Y.; Phillips, E. M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2009**, *131*, 13028.

(6) For a selected example of NHC-catalyzed α -functionalization of α -aryloxy aldehydes, see: Ling, K. B.; Smith, A. D. *Chem. Commun.* **2011**, *47*, 373.

intermediates via NHC catalysis was explored by the groups of Smith and Ye.⁸ Despite the impressive progress, the drawbacks of these otherwise very successful approaches include the relative instabilities of the substrates and/or somewhat undesired synthetic efforts in preparing these substrates. It has become clear that the employment of simpler and more readily available substrates (e.g., simple alcohols, aldehydes, carboxylic acids, and esters) will constitute a significant advancement in asymmetric catalytic enolate chemistry. Here we report a direct α -functionalization of simple aldehydes under oxidative NHC catalysis and the direct generation of ester enolates by using simple nonfunctionalized aldehydes as substrates. Our work provides solutions that are complementary to the direct enamine catalysis approach and indirect NHC catalysis methods for α -functionalization of simple aldehydes. It is of special note that Rovis and co-workers's independent research on similar chemistry just appeared online on the day of submission of our manuscript.⁹

Scheme 1. Direct α -Functionalization of Simple Aldehydes



Our working hypothesis is illustrated in Scheme 1b. One important step is the oxidation of Breslow intermediate I to form NHC-bounded ester intermediate II. This process in the oxidation of aldehydes to acids, esters, and amides as the final products has been pioneered by several groups.¹⁰ The related NHC-catalyzed oxidation of α,β -unsaturated

(7) For selected examples of NHC-catalyzed α -functionalization of 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.

(8) For selected examples of NHC-catalyzed α -functionalization of ketenes, see: (a) Zhang, Y. R.; He, L.; Wu, X.; Shao, P. L.; Ye, S. *Org. Lett.* **2008**, *10*, 277. (b) Duguet, N.; Campbell, C. D.; Slavin, A. M. Z.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1108. (c) Huang, X.-L.; He, L.; Shao, P.-L.; Ye, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 192.

(9) Zhao, X.; Ruhl, K. E.; Rovis, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 12330.

Table 1. Condition Optimization^a

entry	base	solvent	yield (%) ^b	dr ^c	ee ^d
1	DBU	THF	54	7:1	99
2	DIEA	THF	—	—	—
3	TEA	THF	—	—	—
4	DMAP	THF	<5	—	—
5	pyridine	THF	—	—	—
6	K ₂ CO ₃	THF	41	20:1	99
7	Cs ₂ CO ₃	THF	50	20:1	99
8 ^e	Cs ₂ CO ₃	THF	83	20:1	99
9 ^e	Cs ₂ CO ₃	MeCN	66	20:1	99
10 ^e	Cs ₂ CO ₃	CH ₂ Cl ₂	73	20:1	99
11 ^e	Cs ₂ CO ₃	DMF	19	4:1	n.d.
12 ^e	Cs ₂ CO ₃	toluene	62	20:1	99

^a Reaction conditions: 0.1 mmol of **1a**, 0.1 mmol of **2a**, 0.1 mmol of **B**. ^b Isolated yield based on **2a**. ^c Diastereomeric ratio of **3a**, determined via ¹H NMR analysis of crude reaction mixture. ^d Enantiomeric excess of **3a**, determined via chiral phase HPLC analysis; the absolute configuration of the major diastereomer was assigned based on the X-ray structure of **3i** (see Supporting Information). ^e 0.25 mmol of **1a**, 0.25 mmol of **B**.

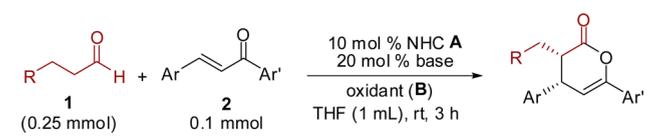
aldehydes has also been studied by the groups of Scheidt and others.^{10j-s} The other key step is a selective deprotonation of **II** to form chiral enolate intermediate **III**. This deprotonation step (**II** to **III**) should be feasible based on our recent work on NHC-catalyzed activation of esters for enolate formation.¹¹ In contrast, the high reactivity of the NHC-bounded ester intermediate (e.g., toward hydrolysis, etc.)¹² and potential competing reactions of the acyl anion intermediate **I** (e.g., Stetter reactions)¹³ with electrophiles have made the achievement of effective enolate chemistry difficult.

We started by using aldehyde **1a** and chalcone **2a** as model substrates and triazolium **A**⁴ as an NHC precatalyst

(10) For examples of (self- or external) oxidation of nonenals under NHC catalysis, see: (a) Chow, K. Y.-K.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 8126. (b) Reynolds, N. T.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 9518. (c) Zeitler, K. *Org. Lett.* **2006**, *8*, 637. (d) Maki, B. E.; Scheidt, K. A. *Org. Lett.* **2008**, *10*, 4331. (e) Noonan, C.; Baragwanath, L.; Connon, S. J. *Tetrahedron Lett.* **2008**, *49*, 4003. (f) Wang, L.; Thai, K.; Gravel, M. *Org. Lett.* **2009**, *11*, 891. (g) Yoshida, M.; Katagiri, Y.; Zhu, W.-B.; Shishido, K. *Org. Biomol. Chem.* **2009**, *7*, 4062. (h) Kawanaka, Y.; Phillips, E. M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2009**, *131*, 18028. (i) Xin, Y.-C.; Shi, S.-H.; Xie, D.-D.; Hui, X.-P.; Xu, P.-F. *Eur. J. Org. Chem.* **2011**, 6527. For examples of oxidation of enals under NHC catalysis, see: (j) Maki, B. E.; Chan, A.; Phillips, E. M.; Scheidt, K. A. *Org. Lett.* **2007**, *9*, 371. (k) De Sarkar, S.; Grimme, S.; Studer, A. *J. Am. Chem. Soc.* **2010**, *132*, 1190. (l) De Sarkar, S.; Studer, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 9266. (m) Reddy, R. S.; Rosa, J. N.; Veiros, L. F.; Caddick, S.; Gois, P. M. P. *Org. Biomol. Chem.* **2011**, *9*, 3126. (n) Rong, Z.-Q.; Jia, M.-Q.; You, S.-L. *Org. Lett.* **2011**, *13*, 4080. (o) Biswas, A.; De Sarkar, S.; Fröhlich, R.; Studer, A. *Org. Lett.* **2011**, *13*, 4966. (p) Maji, B.; Vedachalan, S.; Ge, X.; Cai, S.; Liu, X.-W. *J. Org. Chem.* **2011**, *75*, 3016. (q) Mo, J.; Chen, X.; Chi, Y. R. *J. Am. Chem. Soc.* **2012**, *134*, 8810. (r) Biswas, A.; De Sarkar, S.; Tebben, L.; Studer, A. *Chem. Commun.* **2012**, *48*, 5190. (s) Kravina, A. G.; Mahatthananchai, J.; Bode, J. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 9443.

(Table 1). With DBU as the base, among the oxidants examined,¹⁴ quinone **B** was found to be effective in giving the enol lactone product **3a** in an encouraging yield, dr, and ee (Table 1, entry 1). Weaker organic bases, such as DIEA, TEA, DMAP, and pyridine, were not effective in promoting this reaction (entries 2–5). In these cases, most aldehyde substrates remained unconsumed, as revealed by TLC and NMR analysis. When inorganic base Cs₂CO₃ was used with THF as the solvent, a higher dr (20:1 dr, entry 7) was obtained, compared to the reaction using DBU as the base (entry 1). The low 50% yield (entry 7) was mainly caused by the competing hydrolysis of intermediate **II** (Scheme 1b). By increasing the amount of aldehyde substrate to 2.5 equiv, an acceptable yield (83% isolated yield) along with an excellent dr and ee was obtained (entry 8). A brief evaluation of solvents showed that other common solvents (e.g., CH₃CN, CH₂Cl₂, toluene, DMF; entries 9–12) were also suitable for this oxidative enolate generation, suggesting that this chemistry might be further developed for a large set of reactions.

Table 2. Examples of Aldehydes and Chalcones^a



3	R	Ar, Ar'	yield (%) ^b	dr ^c	ee ^d
3a	Ph	Ph, Ph	83	20:1	99
3b	H	Ph, Ph	78	20:1	99
3c	Me	Ph, Ph	81	20:1	99
3d	<i>n</i> -C ₃ H ₇	Ph, Ph	88	20:1	99
3e	<i>n</i> -C ₇ H ₁₅	Ph, Ph	84	20:1	99
3f	4-MeOC ₆ H ₄	Ph, Ph	84	20:1	99
3g	4-BrC ₆ H ₄	Ph, Ph	80	20:1	99
3h	Ph	4-ClC ₆ H ₄ , Ph	91	20:1	99
3i	Ph	4-ClC ₆ H ₄ , 4-ClC ₆ H ₄	95	10:1	99
3j	Ph	3-Py, Ph	84	20:1	99
3k	Ph	Ph, 2-furyl	79	20:1	99
3l	4-MeOC ₆ H ₄	Ph, 4-ClC ₆ H ₄	94	20:1	99
3m	4-MeOC ₆ H ₄	4-MeC ₆ H ₄ , Ph	71	20:1	99
3n	4-MeOC ₆ H ₄	4-MeOC ₆ H ₄ , Ph	73	20:1	99
3o	4-MeOC ₆ H ₄	Ph, 4-MeOC ₆ H ₄	70	20:1	99

^a Reaction conditions same as those in Table 1, entry 8. ^b Isolated yield based on **2**. ^c Diastereomeric ratio of **3**, determined via ¹H NMR analysis of crude reaction mixture. ^d Enantiomeric excess of **3**, determined via chiral phase HPLC analysis.

With the optimized conditions in hand, the scope of the aldehydes and enones were examined (Table 2). Several representative aldehyde substrates were examined (Table 2, **3a–g**). Aldehydes with aryl (**3a**, **3f**, and **3g**) or alkyl substituents (**3b–e**) at the aldehyde β -carbon all

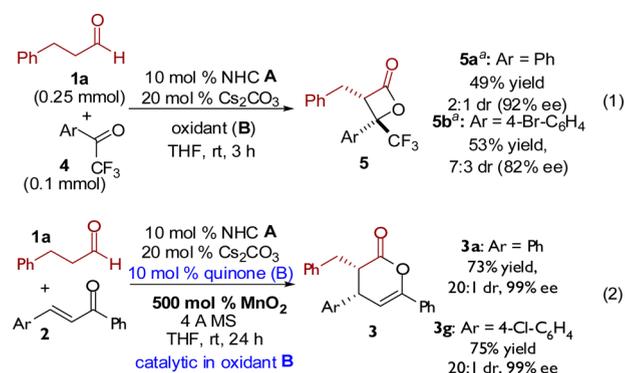
(11) Hao, L.; Du, Y.; Lv, H.; Chen, X.; Jiang, H.; Shao, Y.; Chi, Y. R. *Org. Lett.* **2012**, *14*, 2154.

(12) Vora, H. U.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 2860.

reacted well, giving products in good yields, with an excellent dr and ee. Aldehydes with α -aryl substituents, or with α,α' -disubstituents, led to no formation of the δ -lactone products; most of the aldehyde substrate and the oxidant (**B**) remained unreacted using anhydrous THF as the solvent.¹⁵ Chalcone substrates with different types of (hetero)aryl substituents all reacted well (**3a** and **3h–o**). Enones with alkyl substituents led to no observable conversions. As a special note, the δ -lactone products obtained in our studies could not be easily accessed using other reported approaches. For example, the related asymmetric enamine catalysis approach using aldehyde pre-nucleophiles worked well only with more reactive modified enones as the electrophiles.¹⁶

Given the relatively broad conditions (e.g., solvents, bases, etc.) available for this oxidative enolate generation chemistry, it is possible to develop reactions using other electrophiles. For example, trifluoromethyl aryl ketones (eq 1, Scheme 2) could react with simple aldehydes (e.g., **1a**) to form the corresponding β -lactones (**5a** and **5b**), albeit in moderate yields and dr's, under the conditions employed in Table 2.^{7a}

Scheme 2. Reactions Using Trifluoromethyl Aryl Ketone as Electrophile and MnO₂ as Terminal Oxidant^a



^a The relative configurations of β -lactones were assigned following ref 7a.

We also tried to develop protocols that could use more readily available terminal oxidants that were cheaper than

(13) For selected examples of acyl anion equivalents from aldehydes, see: (a) Stetter, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 639. (b) Stetter, H.; Hilboll, G.; Kuhlmann, H. *Chem. Ber.* **1979**, *112*, 84. (c) Stetter, H.; Jonas, F. *Chem. Ber.* **1981**, *114*, 564. (d) Enders, D.; Breuer, K.; Runsink, J.; Teles, J. H. *Helv. Chim. Acta* **1996**, *79*, 1899. (e) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298. (f) Hachisu, Y.; Bode, J. W.; Suzuki, K. *J. Am. Chem. Soc.* **2003**, *125*, 8432. (g) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876. (h) Mattson, A. E.; Bharadwaj, A. R.; Scheidt, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 2314. (i) Mattson, A. E.; Zuhl, A. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 4932. (j) DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2011**, *133*, 10402. (k) Fang, X.-Q.; Chen, X.-K.; Lv, H.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 11782. (l) Liu, G.; Wilkerson, P. D.; Toth, C. A.; Xu, H. *Org. Lett.* **2012**, *14*, 858.

(14) Quinone, TEMPO, acridine, and MnO₂ are not effective oxidants in the reaction.

(15) When the solvent was not dry enough, aldehyde was consumed and acid was detected by TLC and crude ¹H NMR.

(16) Wang, J.; Yu, F.; Zhang, X.; Ma, D. *Org. Lett.* **2008**, *10*, 2561.

quinone **B** (Aldrich price: \$100 per 50 mg). We found that by using a catalytic amount of **B** (10 mol %) in the presence of MnO_2 (Aldrich price: \$160 per 1000 g) as an oxidant, the oxidative enolate reaction could be realized to obtain the δ -lactone products (in gram scale) with excellent yields and selectivities (eq 2, Scheme 2). In the presence of MnO_2 alone, nearly no detectable formation of the δ -lactone product was observed (most of the aldehyde substrate could be recovered). This result suggests that the role of MnO_2 is to oxidize the reduced form of **B** back to quinone and thus a catalytic amount of **B** can be used. It is important to note that the groups of Scheidt,^{10d,j} Hui,¹⁰ⁱ and Liu^{10p} have used MnO_2 as the oxidant under NHC catalysis for the conversion of alcohols, aryl aldehydes, and enals to esters.

In summary, we have developed the oxidative generation of enolates for α -functionalization of simple nonfunctionalized aldehydes under NHC catalysis. The organic quinone oxidants can be made catalytic by using inexpensive

terminal oxidants. Given the wide use of enolate and enolate equivalents in organic synthesis, we expect this new approach for catalytic generation of chiral enolate intermediates from simple substrates to be broadly useful. The versatile conditions for this chemistry will likely allow for a set of other reactions to be developed.

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Supporting Information Available. Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.