Organocatalysis

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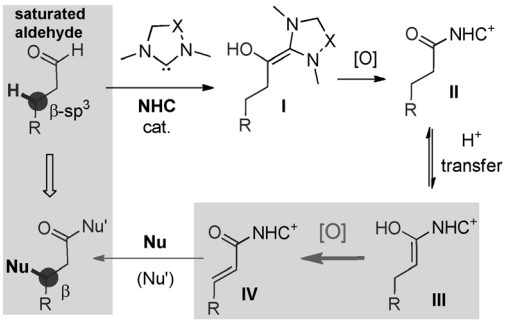
Direct β-Activation of Saturated Aldehydes to Formal Michael Acceptors through Oxidative NHC Catalysis**

*Junming Mo, Liang Shen, and Yonggui Robin Chi**

Saturated carbonyl compounds, such as aldehydes and esters, are basic building blocks for the synthesis of organic molecules and materials. Reactions with carbonyl compounds as substrates primarily occur at the carbonyl carbon atom (as an electrophilic center) or the α-carbon atom (as a prenucleophile). In organocatalysis, several powerful approaches have been developed for the asymmetric functionalization of α-CH of aldehydes and esters. For example, many elegant transformations at the α-carbon atom of aldehydes have been realized by employing enamine[1] or SOMO[2] catalysis. Very recently, Rovis and co-workers[3] and our laboratory[4] independently reported α-carbon functionalization of saturated aldehydes through oxidative catalysis mediated by N-heterocyclic carbenes (NHCs).[5] We have also realized NHC-mediated α-functionalization of saturated esters.[6] To functionalize the β-carbon atoms of carbonyl compounds, the corresponding α,β-unsaturated compounds are typically used. For example, several groups have developed NHC catalysis[7–9] for the activation of α,β-unsaturated aldehydes (enals and α-bromoenals)[7,8] and ynals,[9] to form unsaturated esters[7,9a] or formal Michael acceptors.[8,9b–e,20] In particular, Studer pioneered the addition of 1,3-dicarbonyl compounds to α,β-unsaturated acyl triazoliums generated from α,β-unsaturated aldehydes.[8a] Lupton and co-workers have recently pioneered the NHC-mediated activation of α,β-unsaturated enol ester and acyl fluorides for eventual functionalizations of the β-sp^2 carbon atoms.[10] The enal β-sp^2 carbon atom can also be activated through iminium organocatalysis, as pioneered by MacMillan and co-workers.[11]

Several catalytic approaches are available for the direct activation of α-carbon atoms of carbonyl compounds (and β-sp^2 carbon atoms of unsaturated carbonyl compounds), but the direct activation of the typically inert β-C(sp^3) of saturated carbonyl compounds is challenging. Notably, C–H activation involving the β-carbon atom of saturated esters and amides is pursued by several groups employing transition-metal catalysis.[12] In organocatalysis, the groups of Wang, Hayashi, and Enders have successfully oxidized the catalytically generated enamine intermediates to the corresponding α,β-unsaturated iminium species as Michael acceptors.[13] Despite the impressive progress, catalytic direct β-activation of saturated carbonyl compounds has largely remained underdeveloped, and new strategies that contribute to this subject should be of broad interests.[14]

Here, we disclose the first direct activation of the β-C(sp^3) of saturated aldehydes through oxidative NHC catalysis (Scheme 1). The oxidation of Breslow intermediates to



Scheme 1. Direct β-functionalization of saturated aldehydes: a working hypothesis.

NHC-bound ester intermediates (**I**→**II**, Scheme 1) had been studied in early 1980s and was recently further advanced by several groups.[15] The deprotonation of α-CH of the NHC-bound ester intermediate can form an enolate equivalent (**II**→**III**). This transformation (**II**→**III**) was reported in our earlier work on ester activation[6] and in the recent studies by Rovis and co-workers[3] and our group[4] on oxidative NHC-catalyzed α-functionalization of aldehydes. In the present study, we realized one additional oxidative process, which transformed the ester enolate intermediate (**III**) to an NHC-bound α,β-unsaturated ester intermediate (**IV**). This intermediate (**IV**) can effectively react with 1,3-dicarbonyl compounds.[7g,8a,b,d] The overall reaction involves two oxidative processes and constitutes a direct functionalization of the β-C(sp^3) of saturated aldehydes.

Experimentally, we treated 3-phenylpropionaldehyde (**1a**, 1.0 equiv) with acetyl acetone (**2a**, 1.0 equiv) in the presence of 10 mol% triazolium NHC **A** as precatalyst, and 50 mol% Cs_2CO_3 as base (Table 1, entry 1). When we used quinone **B** (an oxidant pioneered by Studer[7d] for NHC catalysis), we observed the formation of product **3a**, resulting from the activation of β-CH of the aldehyde functionality,

[*] J. Mo, L. Shen, Prof. Dr. Y. R. Chi
Division of Chemistry & Biological Chemistry
School of Physical & Mathematical Sciences
Nanyang Technological University
Singapore 637371 (Singapore)
E-mail: robinchi@ntu.edu.sg
Homepage: http://www.ntu.edu.sg/home/robinchi

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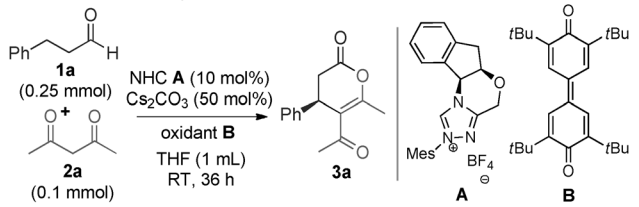
Table 1: Condition optimization.[a]

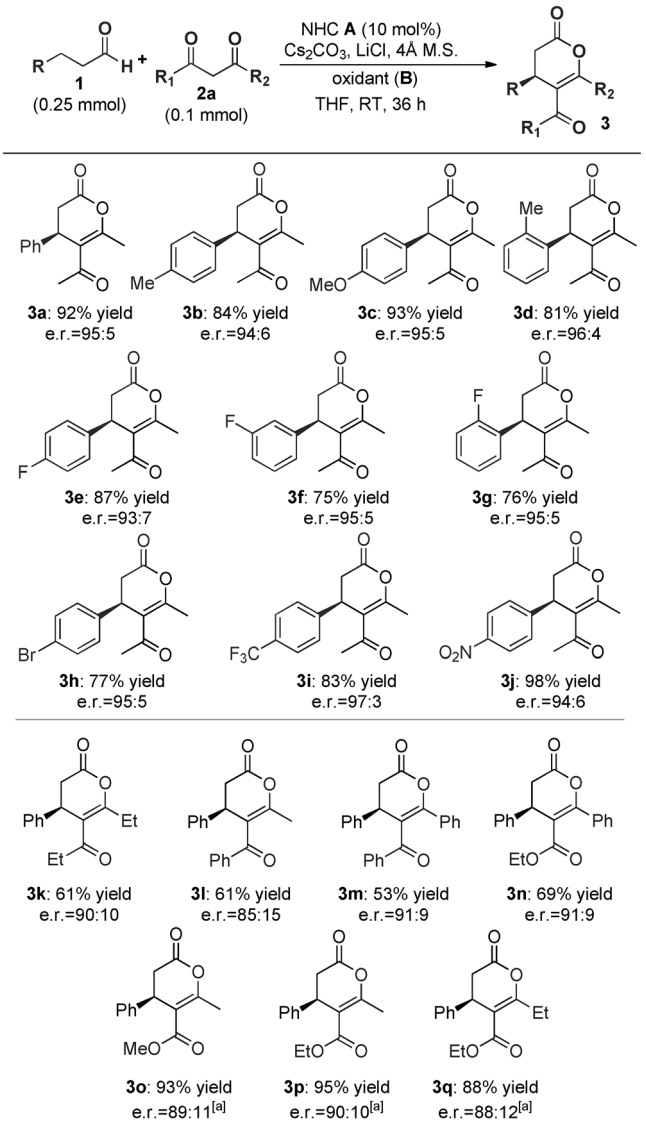


Entry	Solvent	Lewis acid	Yield [%][c]	e.r.[d]
1 (1.0 equiv **1a**)[b]	THF	–	33	76:24
2	THF	–	88	76:24
3	toluene	-	54	91:9
4	THF	LiCl[e]	92	89:11
5	toluene	LiCl[e]	41	94:6
6	THF	4 Å M.S.[f]	81	85:15
7	toluene	4 Å M.S.[f]	51	80:20
8	THF	LiCl[e] + 4 Å M.S.[f]	92	95:5

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.1 mmol), **A** (0.01 mmol), **B** (0.4 mmol), solvent (1 mL), 36 h. [b] **1a** (0.1 mmol), **2a** (0.1 mmol), **A** (0.01 mmol), **B** (0.2 mmol), solvent (1 mL), 36 h. [c] Yields of isolated products based on **2a**. [d] Enantiomeric ratio of **3a**, determined by HPLC on a chiral stationary phase; absolute configuration of the major enantiomer was assigned based on optical rotation of **3a** (see the Supporting Information). [e] 0.1 mmol LiCl. [f] 20 mg 4 Å M.S. powder.

with low but encouraging yield and e.r. (33 % yield, 76:24 e.r.; Table 1, entry 1). Once this proof-of-principle result was established, we started to optimize the reaction conditions. ^{1}H NMR and TLC analysis of the crude reaction mixture showed the formation of the corresponding saturated and unsaturated acids as by-products, resulting in a relatively low yield of **3a**. Therefore, by using 2.5 equivalents of the aldehyde substrate, the yield could be improved to 88 %. Cs_2CO_3 remained the best base among several bases that were studied (DBU, DIEA, KOAc, K_2CO_3, see the Supporting Information). The use of toluene as a solvent resulted in a lower yield (54 %), but a higher e.r. (91:9; entry 3), compared to the reaction in THF (entry 2). We next focused on the improvement of the enantioselectivity by using THF and toluene as solvents (entries 4–8). The groups of Scheidt, You, and Zhao, and our own group observed that Lewis acids can enhance the enantioselectivity of NHC-catalyzed reactions.[16] In the present reaction, we eventually found that LiCl can improve the e.r. for reactions in both THF and toluene (entries 4 and 5). It is worth noting that Scheidt and co-workers reported the improvement of *ee* values when LiCl was used as a mild Lewis acid additive in NHC-catalyzed additions of enal homoenolates to isatines,[16c] and You and co-workers found improved enantioselectivities when $NaBF_4$ was used as promoter for reactions between enals and 1,3-dicarbonyl compounds.[8b] The use of molecular sieves (M.S.) could lead to a slight increase of the e.r. in THF, but a drop of the e.r. in toluene (entries 6 and 7). At last, we found that a combined use of LiCl and 4 Å molecular sieves as additives in THF could consistently give the reaction product with e.r. = 95:5 and excellent yield (entry 8).

With the optimized reaction conditions in hand, the scope of the reaction was examined with regard to the aldehyde substrate. All β-aryl-substituted propionaldehydes that were

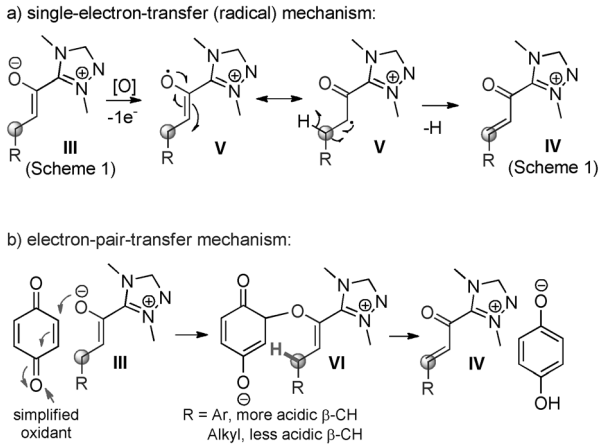


Scheme 2. Scope of the reaction. Reaction conditions: **1** (0.25 mmol), **2** (0.1 mmol), **A** (0.01 mmol), **B** (0.4 mmol), 4 Å M.S. powder, THF (1 mL), 36 h. Yields of isolated products based on **2a**. Enantiomeric ratio of **3a**, determined by HPLC on a chiral stationary phase. [a] Reactions performed without LiCl. When LiCl was used as an additive, the desired product was not obtained.

evaluated in this study reacted well with 1,3-diketone **2a** (Scheme 2, products **3a**–**j**). The β-aryl groups of aldehydes with electron-withdrawing or electron-donating groups were tolerated, and the products were afforded with good yields and enantiomeric ratios. However, aldehydes with β-alkyl substituents or two substituents at the β-position did not react under these conditions, and only the corresponding acids could be observed as products of the reaction of the acyl azolium intermediate (**II**) with the residual water over a longer reaction time. These types of aldehydes were also challenging substrates in the related oxidative enamine catalysis reported by the groups of Wang, Hayashi, and Enders.[13] Possible origins for the failure of β-alkyl-substituted aldehydes will be discussed in the later part of this manuscript.

The scope of the reaction was also studied with regard to 1,3-dicarbonyl compounds (Scheme 2, products **3k–q**). Dicarbonyl compounds with both aryl and alkyl substituents (**3a**, **3k–m**) were tolerated. β-Keto esters could be used as well (**3n–q**). Interestingly, in the case of **3o–q**, the use of the standard reaction conditions (Table 1, entry 8; with LiCl as an additive), did not lead to any Michael addition product. Most of the aldehyde substrate remained unreacted under the reaction condition over 36 h. When the reaction mixture was exposed to moisture, the corresponding saturated carboxylic acid was formed. We later found that in the absence of LiCl additive, the desired product (**3o–p**) could be obtained in good yields and enantiomeric ratios. It is unclear why LiCl inhibited the desired reactions in the cases of **3o** and **3p**.

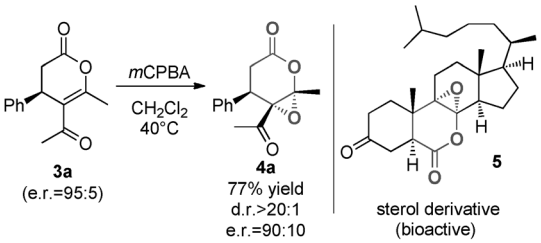
Two distinct pathways are possible for the oxidation of the NHC-bound enolate intermediate to the α,β-unsaturated ester equivalent (**III**→**IV**, Scheme 1). The first postulated pathway involves single-electron transfer[17] (Scheme 3a), and



Scheme 3. Proposed pathways for key oxidation steps.

the second postulated pathway involves electron-pair transfer[18] for the oxidation (Scheme 3b). The first pathway (Scheme 3a) would generate a radical intermediate. To shed some light on the actual mechanism, we added TEMPO (a common scavenger) to our reaction. When one equivalent (relative to **2a**) of TEMPO was added, δ-lactone **3a** was still obtained in an acceptable yield (68%; compared to 88% yield without TEMPO, Table 1, entry 2; the enantioselectivity was not affected). No adduct between TEMPO and aldehyde was detected. This result suggested that the radical pathway was unlikely the dominating one. Additionally, the proposed radical intermediate **V** (a positively charged triazolium ester radical) is electron-deficient. Removal of one hydrogen atom from **V** to initiate the formation of **IV** is likely unfavorable. The electron-pair-transfer pathway (Scheme 3b) seems to be possible. In our reaction, β-alkyl-substituted aldehydes failed to undergo the sequential oxidation (Scheme 2). This result may be explained by the different acidity of β-CH of intermediate **VI**: an aryl substituent in β-position (**VI**, R = Ar) led to a more acidic β-CH, compared to the corresponding β-alkyl-substituted aldehyde.

The enol δ-lactone product (e.g., **3a**) could undergo further transformations by adopting established chemistry. For example, **3a** could be converted to optically enriched δ-lactone epoxide **4a** as essentially a single diastereomer with good yield [Eq. (1); *m*CPBA = *meta*-chloroperoxybenzoic



(1)

acid]. The epoxide moiety is widely known to be critical for compounds in order to display useful biological activities. For example, a sterol derivative [compound **5**, Eq. (1)] that contains this type of δ-lactone epoxide skeleton is effective in promoting proliferation of nerve stem cells.[19]

In summary, we have developed a direct functionalization of the β-carbon atom of saturated aldehydes through oxidative NHC catalysis. We realized the first oxidation of NHC-bound enolate intermediates to α,β-unsaturated ester intermediates, which can react as formal Michael acceptors. We expect this direct β-C(sp^3) functionalization to offer alternative, concise, and/or better strategies for the development of new reactions and useful transformations.

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