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β-Carbon activation of saturated carboxylic esters through *N*-heterocyclic carbene organocatalysis

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The activation of the α-carbons of carboxylic esters and related carbonyl compounds to generate enolate equivalents as nucleophiles is one of the most powerful strategies in organic synthesis. We reasoned that the horizons of chemical synthesis could be greatly expanded if the typically inert β-carbons of saturated esters could be used as nucleophiles. However, despite the rather significant fundamental and practical values, direct use of the β-carbons of saturated carbonyl compounds as nucleophiles remains elusive. Here we report the catalytic activation of simple saturated ester β-carbons as nucleophiles (β-carbon activation) using *N*-heterocyclic carbene organocatalysts. The catalytically generated nucleophilic β-carbons undergo enantioselective reactions with electrophiles such as enones and imines. Given the proven rich chemistry of ester α-carbons, we expect this catalytic activation mode for saturated ester β-carbons to open a valuable new arena for new and useful reactions and synthetic strategies.

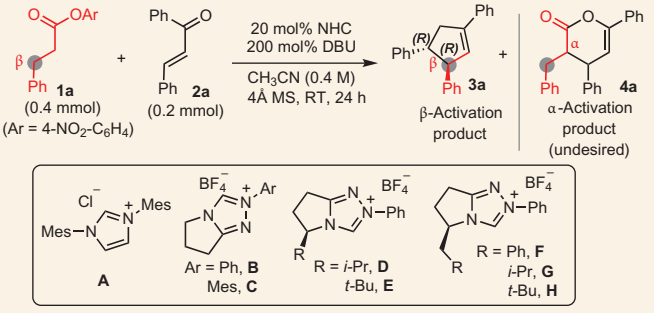
Carbonyl compounds such as esters, ketones and aldehydes are essential building blocks for the synthesis of fine chemicals, pharmaceuticals and materials, and, not surprisingly, manipulation of carbonyl groups is routinely involved in their preparation. Functionalization of the α-carbons of carbonyl compounds (Fig. 1a), such as esters, is a basic activation mode that prepares the α-carbons as nucleophiles for a wide range of applications. Among the many high-impact transformations based on α-carbons of carbonyl compounds are the aldol reactions[1–5] and Mannich reactions[6–8]. To obtain β-carbon functionalization of carbonyl compounds, the corresponding α,β-unsaturated substrates are typically used. In this case, the β-carbons in α,β-unsaturated compounds such as α,β-unsaturated aldehydes can behave as electrophiles via lowest unoccupied molecular orbital (LUMO) activation (for example, iminium organocatalysis)[9] or as nucleophiles via polarity inversion (for example, *N*-heterocyclic carbene (NHC) organocatalysis)[10–13]. Alternatively, oxidative approaches have also been developed to turn saturated carbonyl compounds (such as esters and aldehydes) into the corresponding α,β-unsaturated carbonyl derivatives as intermediates[14–16]. However, strategies for directly activating the β-carbons of simple saturated carbonyl compounds (such as esters) as nucleophiles remain elusive[17,18]. Perhaps the most relevant method is directing group-assisted metal insertion and C–H bond activation involving ester β-carbons, using palladium-based transition-metal catalysts[19–21]. Recently, during the resubmission of our manuscript, MacMillan and co-workers reported photoredox one-electron oxidation of enamine to the β-carbon radical for direct functionalization of saturated aldehydes and ketones (Fig. 1a)[22].

Here, we describe organocatalytic activation of saturated carboxylic esters for the direct generation of nucleophilic ester β-carbons (Fig. 1a). The reactivities of the ester β-carbon nucleophiles were demonstrated in enantioselective reactions with electrophiles such as enones, trifluoroketones and hydrazones to afford cyclopentenes, γ-lactones and γ-lactams, respectively.

Results and discussion

Our postulated catalytic cycle for the β-activation of an ester to react with enone as a model electrophile is illustrated in Fig. 1b. The addition of NHC catalyst to ester substrate **I** yields an NHC-bounded ester intermediate **II**. The reactive ester intermediate (**II**) bearing acidic α-CHs can undergo a deprotonation to form an enolate intermediate (**III**) containing a nucleophilic α-carbon. The feasibility of similar enolate chemistry (**I** to **III**) in relation to the reactivity of ester α-carbons has recently been demonstrated by our laboratory[23]. In the present study, we hypothesized that, because of the electron-withdrawing ability of the triazolium moiety and the conjugated nature of the triazolium-bounded

Table 1 | Reaction of ester (β-carbon) with enone.



Entry	NHC	3a:4a	3a Yield	3a d.r.	3a e.r.
1	**A**	n.d.	<5	n.d.	-
2	**B**	>20:1	80	14:1	-
3	**C**	5:1	75	7:1	-
4	**D**	>20:1	69	11:1	87:13
5	**E**	>20:1	27	8:1	95:5
6	**F**	8:1	54	16:1	87:13
7	**G**	>20:1	70	12:1	91:9
8*	**G**	>20:1	74	14:1	91:9
9*	**H**	**>20:1**	**66**	**7:1**	**96:4**

The ratio of **3a** to **4a**, and the d.r. of **3a**, were estimated by ^{1}H NMR analysis. The e.r. of **3a** (major diastereomer) was determined by chiral-phase high-performance liquid chromatography analysis, and the absolute configuration of **3a** was determined from the X-ray structure of **3y** (Table 2). The structure of α-activation product **4a** was confirmed by ^{1}H NMR analysis. Yields of **3a** were isolated yields after SiO_2 chromatography purification. *150 mol% DBU was used. MS, molecular sieve; Mes, 1,3,5-trimethylbenzene; *i*-Pr, isopropyl; *t*-Bu, *tert*-butyl; n.d., not determined.

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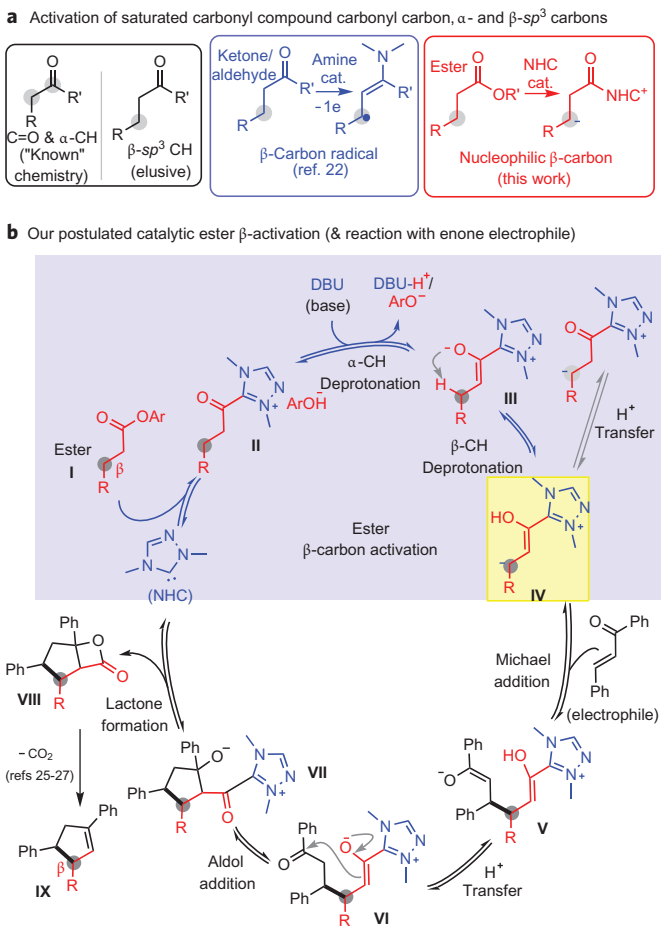
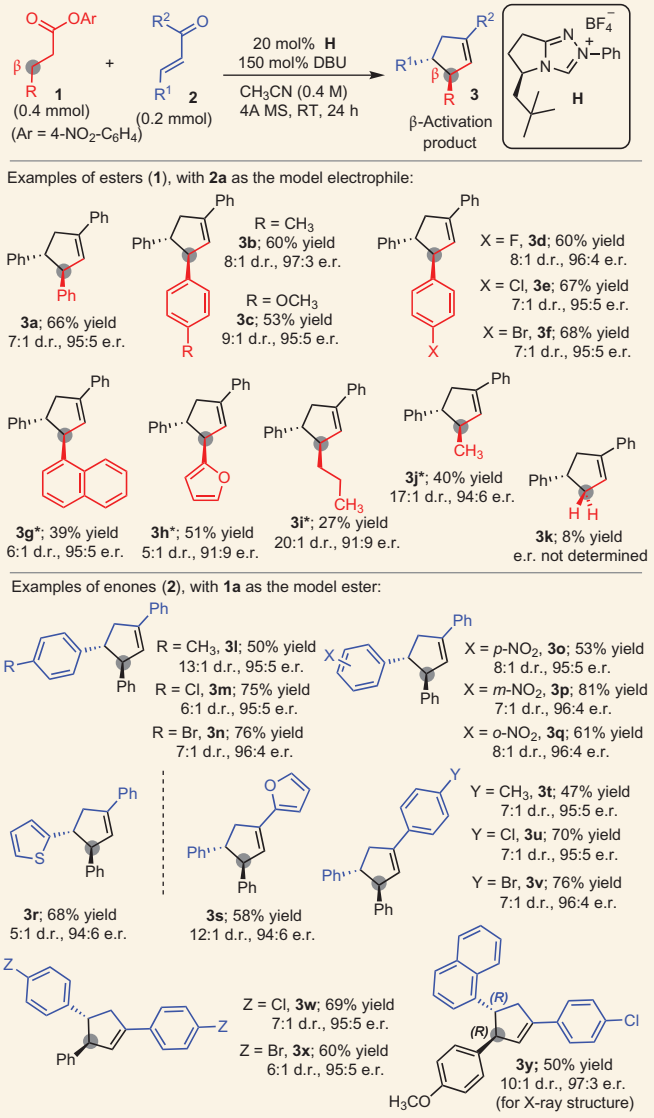


Figure 1 | Organocatalytic β-sp^3-CH activation of saturated ester. **a**, Carbonyl compounds can be selectively activated to react at the carbonyl carbon α- or β-positions. **b**, Addition of NHC to ester **I** gives NHC-bounded ester intermediate **II**, which undergoes successive deprotonations under basic conditions to generate intermediate **IV**. Intermediate **IV** reacts with enone to give cyclopentene **IX** via Michael addition, aldol addition, lactone formation and decarboxylation. NHC, *N*-heterocyclic carbene; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene.

enolate intermediate **III**, the formal ester β-CH protons (of **III**) could become acidic (Fig. 1b). Deprotonation of the β-CHs of enolate **III** could afford intermediate **IV** with β-carbon as a nucleophilic centre. The overall hypothesized pathway (from ester substrate **I** to intermediate **IV** with a nucleophilic β-carbon) may be considered as an analogous process, but inverse, to that found in the NHC-mediated activation of α,β-unsaturated aldehydes[12,13,24,25]. The β-carbon of intermediate **IV** might undergo nucleophilic additions to electrophiles. Shown in Fig. 1b is the addition of the ester β-carbon to chalcone to eventually form a cyclopentene product (**IV** to **VII**), via a cascade process similar to that in NHC-catalysed reactions of α,β-unsaturated aldehydes[26–28], involving a Michael reaction, an aldol reaction, lactonization and decarboxylation.

Experimentally, we set out to achieve a β-carbon activation (**I** to **IV**, Fig. 1b) using **1a** as a model ester substrate and enone **2a** as a model electrophile. The key results of extensive studies, with careful analysis of the reaction mixtures, are summarized in Table 1. With imidazolium **A** as the NHC pre-catalyst, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base and CH_3CN as the solvent, we observed a tiny amount of β-activation product **3a** following ^{1}H NMR spectroscopy and mass spectral analysis (Table 1, entry 1). Under this condition (entry 1), most of ester substrate

Table 2 | Examples of ester and enone substrates.

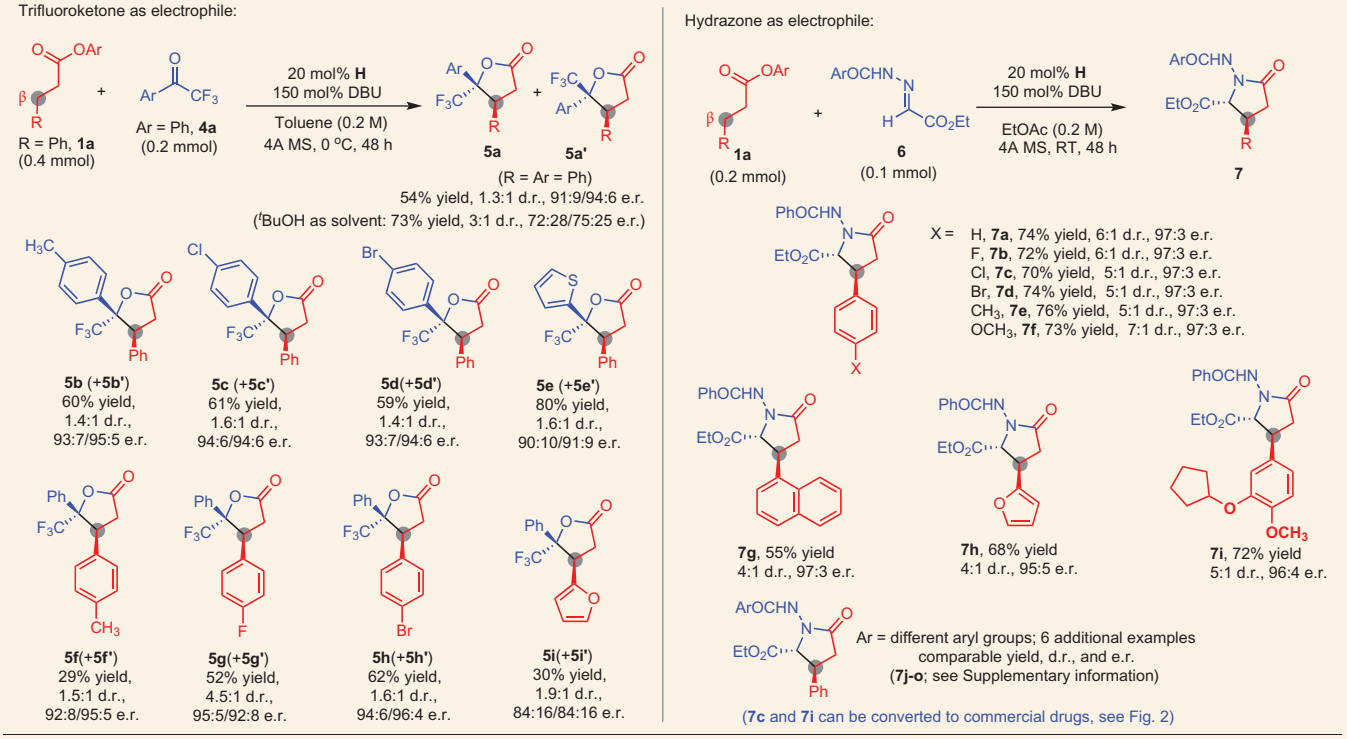


Conditions as in Table 1, entry 9. Yields (after SiO_2 chromatography purification) were based on enone **2**. *Reactions run with 3.0 equiv. ester and 200 mol% DBU for 48 h. The d.r. was estimated via ^{1}H NMR analysis and e.r. was determined via chiral-phase HPLC analysis (see Supplementary Information). Supplementary crystallographic data for **3y** can be found in CCDC 900975.

1a underwent hydrolysis with an elongated reaction time. The structure of **3a** was later confirmed after accumulating enough material from several batches of larger-scale reactions. This proof-of-principle result clearly suggests that activation of the β-carbon of a saturated ester as nucleophile using NHC organocatalysts is feasible. We then found that the use of achiral triazolium **B** as an NHC pre-catalyst could lead to desired product **3a** in good yield and diastereomeric ratio (d.r.), as well as the formation of trace α-activation adduct δ-lactone **4a** (entry 2). Switching to a sterically more bulky catalyst **C** (*N*-1,3,5-trimethylbenzene (*N*-Mes), instead of *N*-Ph in **B**) resulted in more side product **4a** (entry 3). Because the 4-nitrophenol released from the ester substrate in this reaction is weakly acidic, the use of a stoichiometric amount of base (for example, 200 mol% DBU) was necessary to achieve the two key deprotonation steps (Fig. 1b, **II** to **III** and **III** to **IV**).

We next examined chiral triazolium NHC catalysts with an *N*-Ph substituent (**D**–**H**) derived from α-amino acids for enantioselective reactions (entries 4–9). The use of L-valine-derived catalyst **D** led to

Table 3 | Reactions of ester β-carbon with trifluoroketone or hydrazone as electrophiles.



Yields (two diastereomers combined) are isolated yields after SiO_2 column chromatography. The d.r. was estimated via ^1H NMR analysis, and the e.r. was determined via chiral-phase HPLC analysis (see Supplementary Information). Supplementary crystallographic data for **7j** can be found in CCDC 910100. *t*-Bu, *tert*-butyl; EtOAc, ethyl acetate.

an effective reaction (69% yield) with encouraging d.r. (11:1) and enantiomeric ratio (e.r.) (87:13) (entry 4). Use of the more bulky catalyst **E** prepared from L-*tert*-leucine gave a better e.r. (95:5), but a significantly reduced yield (entry 5). Phenylalanine-derived triazolium **F** performed similarly to catalyst **D** (entries 6 and 4, respectively), affording **3a** with 54% yield, 16:1 d.r. and 87:13 e.r. Replacing the phenyl group from phenylalanine in **F** with an isopropyl substituent (that is, to obtain L-leucine-derived catalyst **G**) gave a better yield (70%) and e.r. (91:9) (entry 7). The use of 150 mol% DBU was then found to perform better, leading to a slightly higher yield of **3a** and a smaller amount of ester hydrolysis (compare entries 7 and 8). Finally, by using catalyst **H**, derived from L-neopentylglycine with a bulky *tert*-butyl substituent, the β-ester activation product **3a** could be obtained in good yield, acceptable d.r. and 96:4 e.r. (entry 9).

The generality of this ester β-activation strategy with respect to different ester substrates was then examined by using catalyst **H**. As outlined in Table 2, the efficiencies and selectivities of this reaction were relatively insensitive to changes to the (hetero)aryl substituents when various 3-(hetero)aryl-propanoic esters were used (**3a–h**). When the β-aryl unit in the propanoic esters was replaced by simple alkyl substituents, β-activation cyclopentene adducts (**3i**, **3j**) were obtained in lower yields (with good d.r. and e.r.). The relatively low yields for **3i** and **3j** were a result of competing ester hydrolysis and the formation of ester α-activation δ-lactone side products. Additional studies for β-alkyl ester substrates are in progress. The scope of the chalcone substrates was also investigated (Table 2). Variations of the (hetero)aryl substituents on either the carbonyl or alkene β-carbon side of the enones were all tolerated, giving the corresponding cyclopentene products in acceptable yields, good d.r. and excellent e.r. (**3l–3y**).

The applicability of the β-ester activation strategy was further demonstrated by using trifluoroketone (for example, **4a**)[13] or hydrazone (for example, **6a**)[29] as the electrophile (Table 3). With *tert*-butanol as the solvent, the corresponding γ-lactone product **5a** was obtained in 73% isolated yield with moderate d.r. (3:1) and e.r. Using toluene as the solvent led to better values of e.r. (91:9 and 94:6) for both diastereomers, albeit with a slight decrease in yield and d.r. Variations with both trifluoroketone and ester substrates were well tolerated, affording the β-activation products in moderate to good yields under current conditions (Table 3, left).

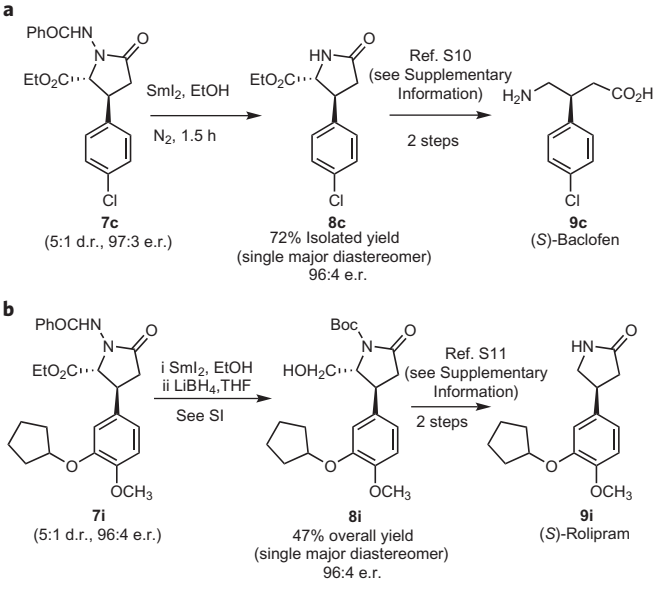
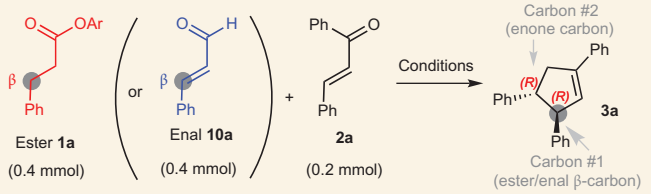


Figure 2 | Synthetic transformation to bioactive molecules. a, Preparation of drug (*S*)-Baclofen (**9c**) from lactam **7c**. **b**, Lactam **7i** could be converted to (*S*)-Rolipram (**9i**), which is a potent inhibitor for the treatment of central nervous disorders.

Table 4 | Comparison of enal and ester reactions.



Reaction	3a	Carbon #1	Carbon #2
Ester (1a)	66% yield, 7:1 d.r. 96:4 e.r. (*trans*-3a) 81:19 e.r. (*cis*-3a)	87:13 (*R*/*S*)	94:6 (*R*/*S*)
Enal (10a)	51% yield, 1.8:1 d.r. 57:43 e.r. (*trans*-3a) 88:12 e.r. (*cis*-3a)	44:56 (*R*/*S*)	66:34 (*R*/*S*)

Cyclopentane 3a is obtained by reaction of either ester 1a or enal 10a, but different (or even opposite) enantioselectivities are obtained. Similar trends hold for other NHC catalysts, substrates and conditions (see Supplementary Information).

Our examination also showed that hydrazone (for example, 6a) as the electrophile[29] could react with the β-carbons of esters, affording γ-lactams (for example, 7a) with good yield and e.r. (Table 3, right). For the two types of reactions illustrated in Table 3, formation of the corresponding ester α-activation product (β-lactone and β-lactam, respectively) was negligible. The major side reactions were ester substrate hydrolysis and NHC catalyst deactivation[23]. The success with trifluoroketone and hydrazone electrophiles provides strong evidence that, with further studies, the ester β-activation strategy can be made general for a diverse set of substrates.

The catalytic reaction products obtained here are bioactive molecules or important building blocks that can be readily converted into useful molecules such as pharmaceuticals. For example, the chiral cyclopentenes are precursors for optically enriched epoxides, 1,2-diols and amino alcohols[30–32]. γ-Butyrolactone is key unit in many natural products[33]. Here, we have demonstrated that the hydrozone reaction γ-lactam products could be effectively converted to pharmaceutical Baclofen (**9c**) (used to treat spasticity[34]) and potent phosphodiesterase inhibitor Rolipram (**9i**)[35] (Fig. 2).

Comparison between enal and ester reactions

Because α,β-unsaturated aldehydes (enals)[26–28] can be activated by NHC catalysts to also generate similar intermediates with nucleophilic β-carbons (**IV**, as shown in Fig. 1b), we compared the reaction outcomes from the enal approach and our ester activation strategy. It should be clarified that, for the three types of *trans*-selective products (for example, 3f and 7a) obtained here, our ester activation approach gave significantly better enantioselectivities than the reported approaches using enal substrates. For example, Bode's enal reactions[27] for the highly enantioselective formation of *cis*-cyclopentenes gave *trans*-3f with a moderate 77:23 e.r., whereas our ester approach gave *trans*-3f with an excellent 95:5 e.r. Another important point is that the ester and enal activations require different optimal NHC catalysts. For example, catalysts (for example, H) found effective in our ester reactions do not work well for the corresponding enal substrates. Remarkably, we found that with identical chiral NHC catalysts, the reactions with enals and esters as substrates gave very different and even opposite enantioselectivities (Table 4; Supplementary Tables S3–S5). For example, for carbon #1 of product 3a, the ester reaction favoured the *R*-configuration (87:13 *R*/*S*), whereas the enal reaction favoured the *S*-configuration (44:56 *R*/*S*). We have ruled out the effect of solvents or additives on the reaction enantioselectivities (see Supplementary Information). These results suggest that the 'similar' homoenolate intermediates obtained using the enal and our ester approaches showed different reactivities and selectivities. More specifically, the enal homoenolate intermediate comes from the addition of NHC to the aldehyde group of enal to form a Breslow intermediate. In contrast, our ester 'homoenolate' is obtained through β-carbon deprotonation of an 'enolate intermediate' (Fig. 1b). The ester 'homoenolate' intermediate with a formal nucleophilic β-carbon may be stabilized in a different form. Additional mechanistic studies are in progress. On the application side, our ester β-activation strategy can provide solutions (for example, the *trans*-selective formation of 3a or 7a with better e.r.) that are not readily available with enal reactions.

In short, we have undertaken the challenging task of developing an organocatalytic activation of the otherwise inert β-sp^3 carbon of saturated esters as nucleophiles. Given the broad utility of the ester α-carbons as nucleophiles, this long-awaited realization of nucleophilic β-carbons should significantly expand the use of esters for new reaction development. Furthermore, the direct use of ester β-carbons may offer previously unavailable insights into the design of concise synthetic strategies for complex molecules[36]. Further studies from both mechanistic and application perspectives are being pursued in our laboratory.

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Author contributions

Z.F. conducted most of the experiments. J.X. and W.W.Y.L. conducted some experiments on the hydrazone reactions. T.Z. contributed to the synthetic transformation of catalytic reaction products. Y.R.C. conceptualized and directed the project, and drafted the manuscript with assistance from all co-authors. All authors contributed to discussions.

Additional information

Supplementary information and chemical compounds are available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to Y.R.C.

Competing financial interests

The authors declare no competing financial interests.