

Direct Activation of β -sp³-Carbons of Saturated Carboxylic Esters as Electrophilic Carbons via Oxidative Carbene Catalysis

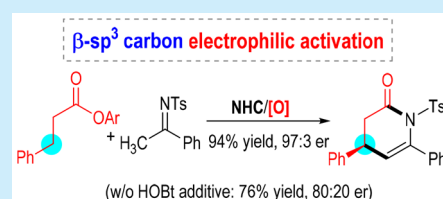
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S Supporting Information

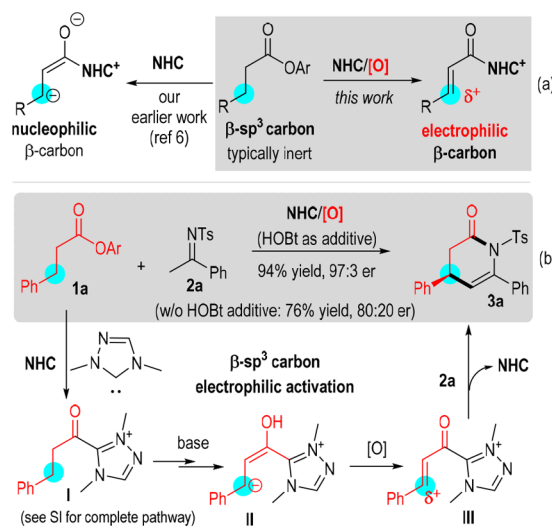
ABSTRACT: An N-heterocyclic carbene-catalyzed oxidative LUMO activation of the β -carbons of saturated carboxylic esters is disclosed. This approach allows for efficient asymmetric access to lactams and lactones by directly installing functional groups to the typically inert β -sp³ carbons of saturated esters. The use of HOBT as an additive was found to significantly improve both yields and enantioselectivities of the reactions.



Carbonyl compounds are among the most widely used starting materials in organic synthesis. Numerous approaches have been developed for the functionalization of the α -carbons of saturated carbonyl compounds and the β -sp² carbons of α,β -unsaturated carbonyl molecules.¹ However, when saturated carbonyl compounds such as carboxylic esters are used, direct functionalizations of the β -sp³ carbons are difficult. Progress in catalytic functionalization of these otherwise inert β -sp³ carbons mainly comes from transition-metal-catalyzed C–H activations.² The combined use of amine organic catalyst and transition metal photocatalyst has been developed for the β -activation of saturated ketones and aldehydes through a radical pathway.³ Recently, organocatalytic oxidative approaches have also been developed for the direct β -carbon functionalization of saturated aldehydes.⁴

Our laboratory is interested in new activation and reaction modes of simple organic molecules by using N-heterocyclic carbene (abbreviated as NHC or carbene) as a key organic catalyst.⁵ In particular, we have previously shown that the β -sp³ carbon of saturated carboxylic ester can be activated as a reactive nucleophilic carbon via an overall redox-neutral process by using NHC as the catalyst under metal-free conditions (Scheme 1a, left part).⁶ Here we report that the β -sp³ carbon of saturated ester can be activated as a reactive electrophilic carbon in the presence of an NHC catalyst under oxidative conditions (Scheme 1a, right part). This approach allows for a direct reaction of the otherwise inert β -sp³ carbon of a saturated ester (e.g., 1a) with a nucleophilic substrate (e.g., 2a) (Scheme 1b). Briefly, the addition of an NHC catalyst to the saturated ester gives acylazolium intermediate I that is then converted to II bearing a nucleophilic β -carbon under basic conditions, as disclosed in our previous studies.⁶ In the presence of an oxidant, intermediate II undergoes an oxidation process to generate α,β -unsaturated acylazolium intermediate III. The

Scheme 1. NHC-Catalyzed β -sp³ Carbon Functionalization of Saturated Esters



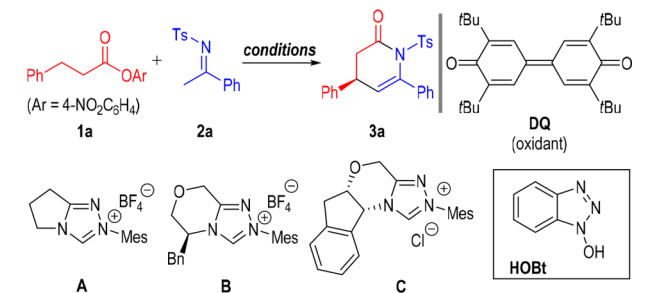
overall process converts the inert β -sp³ carbon of the saturated ester (1a) to a reactive electrophilic β -sp² carbon (III). With imine 2a (precursor of enamine) as the nucleophilic substrate, the lactam product 3a could be obtained in 94% yield and 97:3 er. We noticed that the use of HOBT as an additive is beneficial to significantly improve both the reaction yield and er value.⁷ Notably, HOBT as an additive was mainly found to enhance the yields in our earlier NHC-mediated reactions.^{7c}

Results of our initial studies and condition optimizations with ester 1a and enamine precursor 2a as the model substrates are

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summarized in Table 1. Triazolium NHC precatalyst **A** was found to mediate the formation of **3a** in 53% yield with the

Table 1. Optimization of Reaction Conditions^a



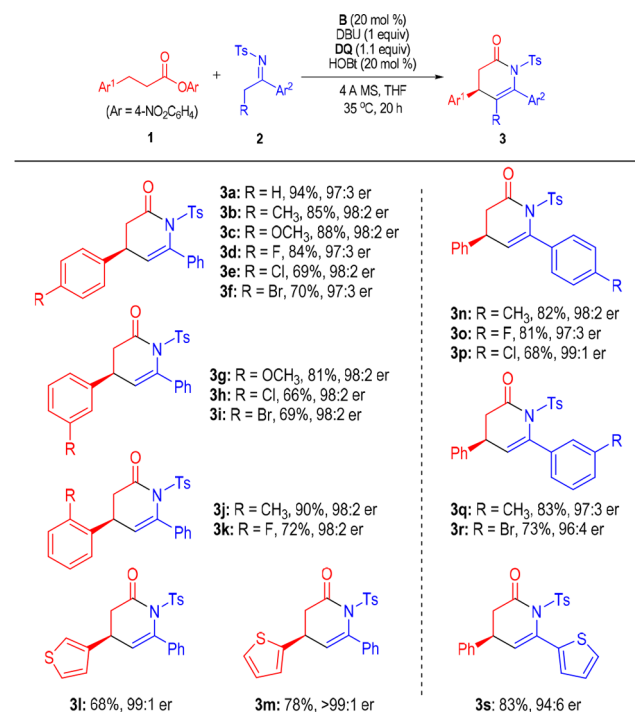
entry	conditions	yield ^b	er ^c
1	A	53	—
2	B	76	80:20
3	C	41	23:77
4	B , Cs ₂ CO ₃ instead of DBU	84	76:24
5	B , DMAP instead of DBU	27	74:26
6	B , tBuOK instead of DBU	34	54:46
7	B , K ₂ CO ₃ instead of DBU	30	56:44
8	B , 100 mol % LiCl	86	71:29
9	B , 5 mol % HOBt	78	95:5
10	B , 10 mol % HOBt	88	96:4
11	B , 20 mol % HOBt	94	97:3

^aGeneral conditions (unless otherwise specified): **1a** (0.10 mmol), **2a** (0.15 mmol), NHC (0.02 mmol), DBU (0.10 mmol), DQ (0.11 mmol), 4 Å MS (50 mg), THF (2.0 mL), 35 °C, 20 h. ^bIsolated yield of **3a**. ^cEr was determined via HPLC on chiral stationary phase.

presence of DQ⁸ as the oxidant (entry 1). As a technical note, only trace product could be obtained (<5% yield) when the reaction was carried out at room temperature (around 25 °C). L-Phenylalanine-derived NHC precatalyst **B**⁹ performed better than **A** and **C**,¹⁰ giving **3a** with a 76% yield and 80:20 er (entry 2). Switching the base from DBU to Cs₂CO₃ led to a better yield (84%) but with a slight loss of er (entry 4 vs 2). Several other bases (e.g., DMAP, tBuOK, K₂CO₃) examined here led to drops on both yields and er values (entries 5 to 7). We then decided to use **B** as the NHC precatalyst and DBU as the base for further optimizations. The use of LiCl as an additive^{4d,11} led to a drop in er value (entry 8). We later found that the use of 5 mol % HOBt⁷ as an additive improved the product er from 80:20 to 95:5 (entry 9 vs 2). Additional studies found that with the use of 20 mol % HOBt as the additive, lactam **3a** could be formed in 94% yield and 97:3 er (entry 11). In two previous studies on NHC-catalyzed reactions of esters, HOBt as an additive was found to improve the reaction yields.^{7b,c} In the present reaction, HOBt significantly enhances the reaction er values. HOBt may facilitate the final amide formation/cyclization step and, thus, minimize the retro-Michael reaction step that cause racemization of the final product.¹² Additionally, noncovalent interactions involving HOBt may also play important roles for enantioselectivity controls in this reaction.¹³ Experimental investigations at this point toward the origins on the roles of HOBt did not come to concrete conclusions. Further studies with both experimental and computational approaches are in progress.

With optimized reaction conditions in hand, we then examined the substrate scope using saturated esters **1** and imines **2** with different substitution patterns (Scheme 2).

Scheme 2. Scope of Esters **1** and Imines **2**^a

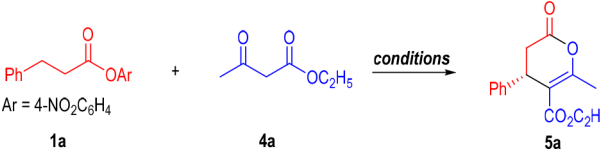


^aReaction conditions as stated in Table 1, entry 11. Yields are isolated yields after purification via SiO₂ column chromatography. Er values were determined via HPLC on chiral stationary phase.

Substituents on the β -benzene rings of the saturated ester **1** could be both electron-donating and -withdrawing groups with all the products afforded in good to excellent yields and er values (**3a** to **3k**). The substituted β -benzene rings of the ester **1** could also be replaced with heteroaromatic rings without deteriorating the product yields and enantioselectivities (**3l** to **3m**). The aromatic groups on imines **3** could be either benzene rings with various substitution patterns (**3n** to **3r**) or heteroaromatic groups (**3s**). The corresponding lactam products were generally afforded in good yields with excellent er values (**3n** to **3s**).

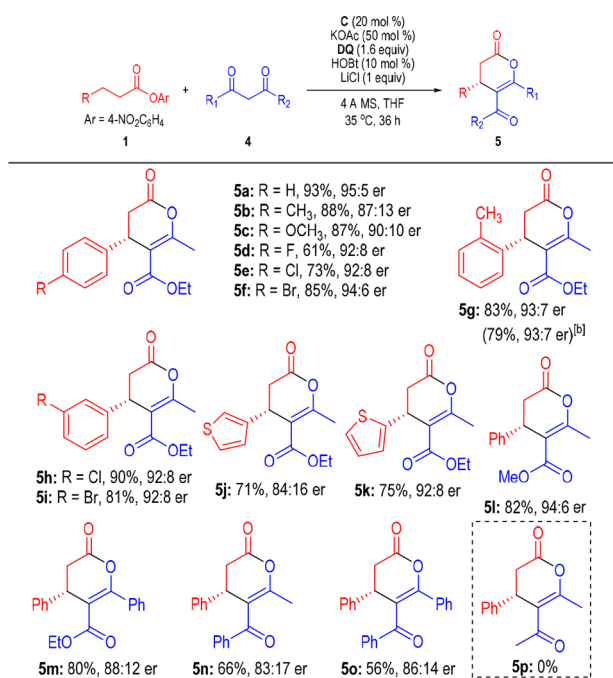
Our saturated ester β -carbon oxidative functionalization can be developed as a general approach (Table 2). For example, β -ketoester **4a** could react with saturated ester **1a** effectively to form lactone product **5a**. Initially, the enantioselectivity is very poor (54:46 er) when using the above conditions optimized for the lactam forming reactions (Table 2, entry 1). After switching the NHC catalyst from **B** to **C**, the er value of **5a** could be dramatically increased from 54:46 to 74:26 (entry 2). The use of 1 equiv of LiCl in this process could further improve the enantioselectivity (91:9 er, entry 3). Finally, product **5a** could be obtained in excellent yields and er values when using KOAc as the base instead of DBU (entry 4, 5). It is worth noting that the use of HOBt in this process is crucial to the yield of the final product. Reaction without using HOBt as the additive would afford the product with a moderate yield (entry 6).

We also examined the scope of various substituted β -ketoesters and 1,3-diketones (**4**) to react with saturated esters **1** in order to demonstrate the generality of our oxidative ester β -C(sp³)-H activation approach (Scheme 3). Different substitution patterns on the benzene rings on the β -carbon of the saturated esters **1** were well tolerated. The corresponding lactone products **5** could be afforded in moderate to good

Table 2. Optimization of Reaction Conditions^a


entry	conditions	yield ^b	er ^c
1	B, DBU, 20 mol % HOBt	93	54:46
2	C, DBU, 20 mol % HOBt	42	74:26
3 ^d	C, DBU, 20 mol % HOBt	70	91:9
4 ^d	C, KOAc, 20 mol % HOBt	78	93:7
5 ^d	C, KOAc, 10 mol % HOBt	93	95:5
6 ^d	C, KOAc	53	94:6

^aGeneral conditions (unless otherwise specified): **1a** (0.15 mmol), **4a** (0.10 mmol), NHC (0.02 mmol), base (0.05 mmol), DQ (0.16 mmol), 4 A MS (50 mg), THF (2.0 mL), 35 °C, 36 h. ^bIsolated yield of **5a**. ^cEr was determined via HPLC on chiral stationary phase. ^d1 equiv of LiCl was added.

Scheme 3. Examples of Substituted Ketones^a

^aReaction conditions as stated in Table 2, entry 5. Yields are isolated yields after purification by column chromatography. Er was determined via HPLC on chiral stationary phase. ^bThe reaction was carried out at 1.0 mmol scale.

yields and enantioselectivities (**5a** to **5i**). β -Thienyl substituted propionic esters also worked well in this process (**5j**, **5k**). The ester moiety of substrate **4** could be a methyl (**5a**) or ethyl alcohol (**5l**) ester. The α -methyl (CH₃) unit next to the ketone moiety of the 1,3-dicarbonyl substrate can be replaced with a phenyl unit as well (**5m–o**). But no product could be observed when using pentane-2,4-dione as the nucleophile in the lactone-forming reaction (**5p**). The chiral products obtained through our approach (Scheme 2 and Scheme 3) are versatile building blocks for quick access to amino alcohols, substituted piperidines, and related functional molecules.^{5c,14}

In summary, we have developed a carbene-catalyzed oxidative β -C(sp³)-H functionalization of saturated carboxylic

esters. The β -carbons of saturated esters were activated as electrophilic species to react with nucleophilic substrates. HOBt was found as a crucial additive in this process to significantly enhance both of the reaction yields and enantioselectivities. Our approach of direct saturated ester β -sp³ carbon functionalization allows quick access to lactams and lactones with good to excellent yields and enantioselectivities. Mechanistic studies, and other activation modes of the inert carbons of saturated ester, are currently underway in our laboratories.

■ ASSOCIATED CONTENT

§ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03650.

Experimental procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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