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An N-Heterocyclic Carbene-Catalyzed Oxidative γ-Aminoalkylation of Saturated Carboxylic Acids through in Situ Activation Strategy: Access to δ-Lactam

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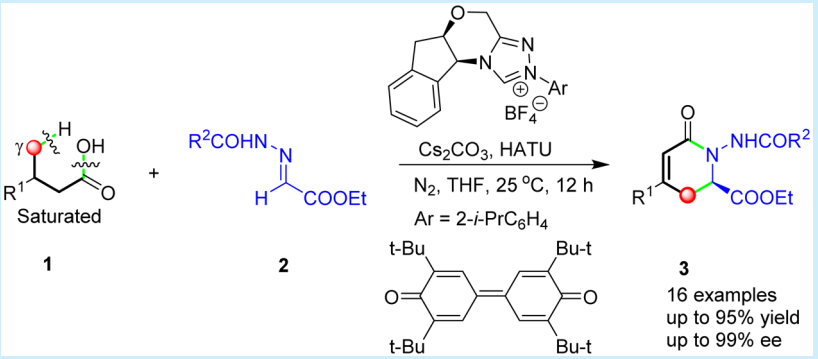
Supporting Information



ABSTRACT: An N-Heterocyclic Carbene (NHC)-catalyzed oxidative formal [4 + 2] annulation of acylhydrazones with saturated carboxylic acids bearing γ-H to assemble δ-lactams featuring a chiral carbon stereogenic center was developed through an in situ activation strategy. The ready availability of the starting materials, excellent enantioselectivity, facile assembly, high yields, and potential biological significance of the final products make this protocol an attractive alternative for the construction of the pyridinone scaffold.

Carbonyl compounds, such as esters, ketones, and aldehydes, are versatile building blocks that have been employed widely for the production of pharmaceuticals and materials. Thus, plenty of effort has been devoted to the efficient transformations of these kinds of compounds. The introduction of a functional unit at the α-position of carbonyl compounds could be achieved easily using enolates as key intermediates.[1] However, the direct installation of a functional group at nonreactive sp^3 hybridized carbon atoms remote from the carbonyl group is a long-term challenge for organic chemists. Recent reports disclosed the transition-metal-catalyzed direct remote C−H functionalization with the assistance of auxiliary groups or directing groups.[2] In addition, organocatalytic remote activation of $C(sp^3)$−H has also progressed.[3] Even so, the convenient and straightforward introduction of a functional group at the remote nonreactive site, e.g. the γ-position of readily available saturated carboxylic acids are still worthy of further research.

N-heterocyclic carbenes (NHCs) have shown excellent catalytic activity for several "umpolung" reactions,[4] such as a^1−d^1 polarity inversion of the aldehyde to involve benzoin condensation and Stetter reaction[5] and a^3−d^3 umpolung of enal (homoenolate).[6] Thus, much exertion has been directed toward the formation and reactivity of NHC-bounded intermediates, e.g., an NHC-bounded vinyl enolate (**I**). Ye et al. proposed an exquisite conversion of α,β-unsaturated acyl chlorides into **I**.[7] Later, the Chi group reported efficient oxidative generation of **I** from enal.[8] Our prior study demonstrated that the debromination and deprotonation of the Breslow intermediate derived from NHC and 2-bromo-2-enal bearing γ-H could deliver **I** readily.[9] More recently, Chi et al. and our group disclosed the successful formation of **I** via the reaction of NHC and the α,β-unsaturated carboxylic esters under basic conditions (Scheme 1).[10] The reaction of these NHC-bounded vinyl enolates as novel synthones with activated double bonds could provide new access to highly functionalized molecular scaffolds.

Carboxylic acids are not only readily available but also more stable compared with the α-functionalized aldehydes and enals used previously in NHC-catalyzed reactions. Besides, they are less liable to enolize than ketone and activated esters, which may avoid the occurrence of the side reaction including aldol condensation, Michael addition, and Claisen condensation. These noticeable advantages make the carboxylic acids ideal starting materials for organic synthesis, and considerable attention has been focused on their organocatalytic transformations.[11] In 2014, Scheidt and co-workers devised an NHC-catalyzed shortcut to enolates from the acyl imidazoles

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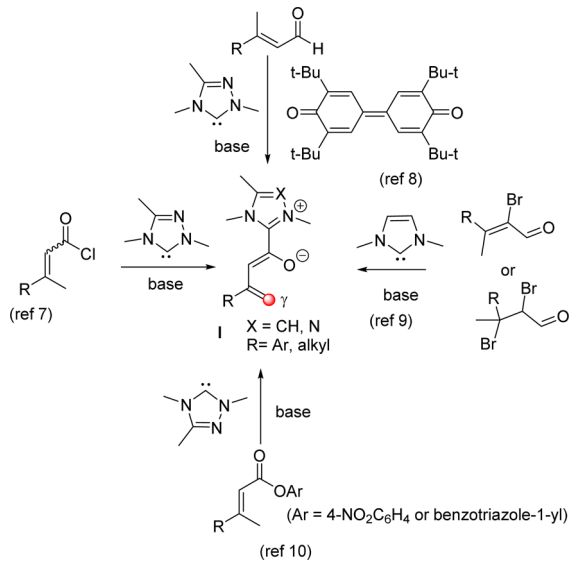
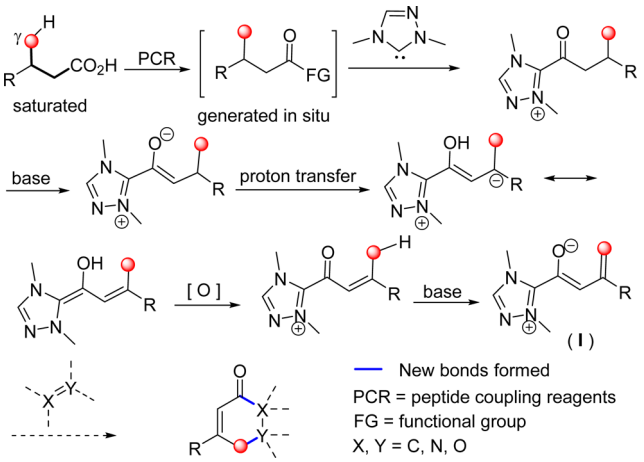
Scheme 1. Generation of NHC-Bounded Vinyl Enolate (I)



generated in situ from the carboxylic acid and carbonyldiimidazole (CDI), which provided an easy means for the direct functionalization of the α-carbon of carboxylic acids.[12] Later, Ye et al. presented the mild conversion of mixed anhydrides of α,β-unsaturated carboxylic acids into α,β-unsaturated acyl azoliums.[13] More recently, our group proposed the direct formation of homoenolates from carboxylic acids via the in situ activation strategy presented by peptide coupling reagents.[14] We envisaged that the above-mentioned homoenolates could be transformed into vinyl enolate **I** via oxidation and deprotonation if they possessed γ-H. The subsequent reaction of these key intermediates with polar double bond could pave a new avenue to a six-membered ring from readily available carboxylic acids (Scheme 2).

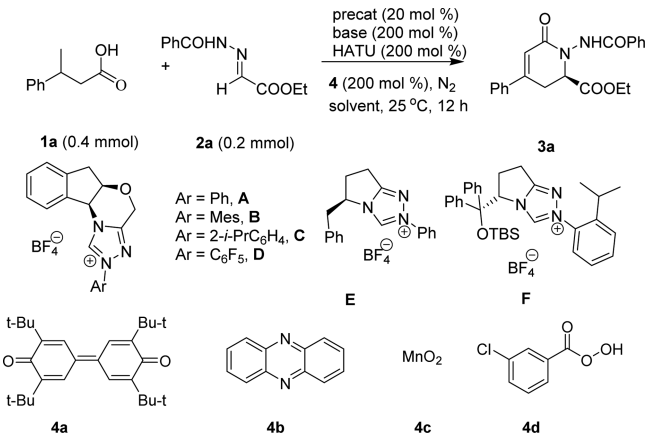
To continue our work on NHC-catalyzed cascade synthesis of heterocycles,[8b,9,10b,14,15] herein we shall report our preliminary study of the NHC-promoted oxidative asymmetric formal [4 + 2] synthesis of δ-lactams with biological interest and great synthetic potential in the presence of peptide coupling reagents through an in situ activation strategy.[16]

Scheme 2. Our Proposal for the Oxidative Generation of Vinyl Enolate from Saturated Carboxylic Acids through the in Situ Activation Strategy



We started by using saturated acid **1a** and hydrazone **2a** as model substrates to optimize the reaction conditions, and the results are reported in Table 1. Under the basic reaction conditions, no formation of the desired product **3a** was observed in the absence of the NHC catalyst (Table 1, entry 1). Several acid activating reagents such as 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), carbonyldiimidazole (CDI), and dicyclohexylcarbodiimide (DCC) were screened. We were pleased to find that the desired product **3a** was obtained in good yield with 98% ee during the preliminary screening when HATU was employed as an activator (Table 1, entry 2). CDI was not effective for the annulation, and DCC/HOBt could give a 21% yield with 98% ee. Then we explored the influence of oxidants (Table 1, entries 2–5). The oxidant **4a** could deliver better results compared with other ones. Subsequently, the effect of chiral catalysts was studied (Table 1, entries 6–10). The chiral catalyst **C** indicated good catalytic ability in 82% yield with 99% ee (Table 1, entry 7). The catalyst **E** could also catalyze the reaction to give **3a** with similar ee but a lower yield (Table 1, entry 9). The solvent optimization revealed that THF was superior to others (Table 1, entries 11–13). Besides, other organic and inorganic bases were examined and the product **3a** was not observed (Table 1,

Table 1. Optimization of the Reaction Conditions



entry	4	precat.	solvent	base	yield (%)[a]	ee (%)[b]
1	4a		THF	Cs_2CO_3	–	–
2	4a	B	THF	Cs_2CO_3	70	98
3	4b	B	THF	Cs_2CO_3	–	–
4	4c	B	THF	Cs_2CO_3	34	99
5	4d	B	THF	Cs_2CO_3	trace	–
6	4a	A	THF	Cs_2CO_3	trace	–
7	4a	C	THF	Cs_2CO_3	82	99
8	4a	D	THF	Cs_2CO_3	–	–
9	4a	E	THF	Cs_2CO_3	44	99
10	4a	F	THF	Cs_2CO_3	–	–
11	4a	C	toluene	Cs_2CO_3	16	99
12	4a	C	DME	Cs_2CO_3	63	99
13	4a	C	DCM	Cs_2CO_3	trace	–
14	4a	C	THF	K_2CO_3	–	–
15	4a	C	THF	DABCO	–	–
16	4a	C	THF	Et_3N	–	–
17[c]	4a	C	THF	Cs_2CO_3	80	99
18[d]	4a	C	THF	Cs_2CO_3	73	98

[a]Yield of the isolated product. [b]Determined by HPLC. [c]Reactions were run at 15 °C. [d]Reactions were run at 35 °C.

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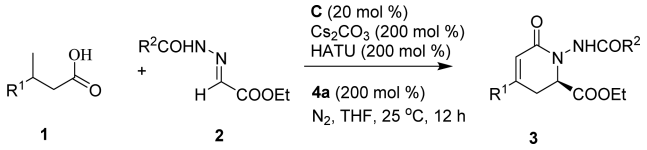
entries 14−16). After temperature screening, 25 °C was optimal in view of yields and enantioselectivity (Table 1, entries 17−18).

With the optimized reaction conditions in hand, the scope of saturated acids and hydrazones was examined (Table 2). It was

Table 2. Scope of Substrates



1 2 3

entry	R^1	R^2	3	yield (%)[a]	ee (%)[b]
1	Ph	Ph	**3a**	82	99
2	Ph	4-BrC_6H_4	**3b**	83	99
3	Ph	4-ClC_6H_4	**3c**	90	99
4	Ph	4-FC_6H_4	**3d**	93	99
5	Ph	4-$MeOC_6H_4$	**3e**	86	99
6	Ph	4-*t*-BuC_6H_4	**3f**	95	99
7	Ph	4-$NO_2C_6H_4$	**3g**	77	98
8	Ph	3-BrC_6H_4	**3h**	81	99
9	Ph	3-MeC_6H_4	**3i**	90	99
10	Ph	2-MeC_6H_4	**3j**	85	99
11	Ph	Thien-2-yl	**3k**	62	99
12	4-BrC_6H_4	Ph	**3l**	84	99
13	2-Naphthyl	Ph	**3m**	94	99
14	2-Naphthyl	3-MeC_6H_4	**3n**	88	98
15	4-MeC_6H_4	Ph	**3o**	86	99
16	Thien-2-yl	Ph	**3p**	72	99

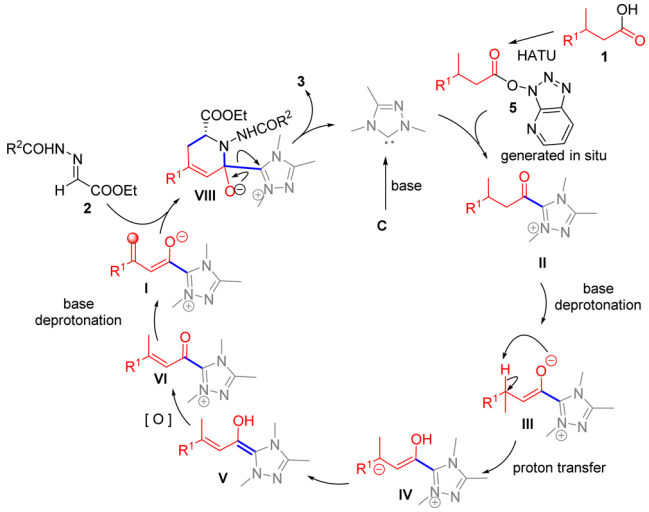
[a]Yield of the isolated product. [b]Determined by HPLC.

found that both electron-withdrawing groups (4-Br, 4-Cl, 4-F) and electron-donating groups (4-MeO, 4-*t*-Bu) on the aromatic ring of hydrazones were well tolerated and gave the desired products (**3b**−**3f**). To our delight, the hydrazones with an aromatic ring having a strong electron-withdrawing group (4-NO_2) could also give a good yield with 98% ee (**3g**). The hydrazones bearing a *meta*-substituted phenyl ring (3-BrC_6H_4 and 3-MeC_6H_4) also worked well (**3h**−**3i**). Notably, the challenging *ortho*-substituted substrate (2-MeC_6H_4) was compatible successfully (**3j**). Interestingly, the oxidative annulation through in situ activation of saturated carboxylic acids could also be applied to heterocyclic hydrazone (**3k**). These results highlighted the broad application scope of hydrazones for the assembly of the scaffolds of *δ*-lactam through an in situ activation strategy. The scope of saturated acids also was tested for the reaction, and the results showed that the reactions turned out to be tolerant of various *β*-arylated saturated acids (**3l**−**3p**). Unfortunately, the *β*-dialkylated saturated aliphatic acids were not suitable for the reaction conditions, which may be attributed to the lack of conjugate effect of the alkyl group.

The HPLC analysis data and optical rotation of *δ*-lactam product **3b** were consistent with those reported in the literature;[10a] thus, the absolute configuration of the final products can be determined by comparison.

A plausible reaction pathway for this NHC-catalyzed oxidative annulation through in situ activation is illustrated in Scheme 3. The reaction of NHC with esters **5** generated in situ from saturated carboxylic acids and HATU gave the acyl azolium **II**, which was transformed into enolate **III** upon deprotonation. Its following *β*-sp^3-H shift gave homoenolate **IV**,

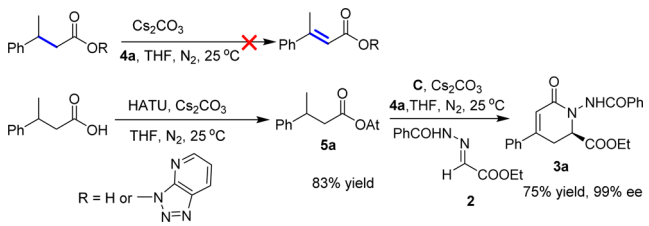
Scheme 3. A Putative Reaction Mechanism for the Oxidative Formal [4 + 2] Synthesis of *δ*-Lactams



i.e., Breslow intermediate **V**, which was similar to the reported NHC-catalyzed reactions of esters of carboxylic acids.[17] The subsequent oxidation of **V** delivered *α*,*β*-unsaturated acyl azolium **VI**, which was converted into NHC-bounded vinyl enolate **I** via deprotonation. The successive formal [4 + 2] reaction of **I** with acylhydrazones yielded the *δ*-lactams finally, which was akin to the known results.[10a]

To shed some light on the reaction mechanism, a few control experiments were carried out, which gave experimental evidence for our proposed reaction mechanism (Scheme 4;

Scheme 4. Some Control Experiments for Validating the Reaction Mechanism



for details, please see the Supporting Information, SI). The oxidation of saturated carboxylic acids (or their esters) into their *α*,*β*-unsaturated counterparts was not achieved, and the key intermediate, 3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl 3-phenylbutanoate (**5**), could be isolated successfully via stepwise reaction. Besides, intermediate **5** could react with **2** to give the desired cycloadduct catalyzed by NHC presented by oxidants. These results demonstrated that **5** should be a crucial intermediate for this oxidative formal [4 + 2] annulation, and the oxidation of Breslow intermediate **V** was decisive.[10a]

To explore the generality of this approach, isatin and 2,2,2-trifluoro-1-phenylethanone containing an activated carbonyl group were subjected to this protocol, and the expected *δ*-lactones were obtained in good yields with moderate enantioselectivity (Scheme 5), which highlighted the wide substrate scope of our strategy.

In conclusion, an NHC-catalyzed oxidative *γ*-aminoalkylation of saturated carboxylic acids possessing *γ*-H was realized through an in situ activation strategy. This organocatalytic cascade process afforded a new approach to *δ*-lactams (or *δ*-

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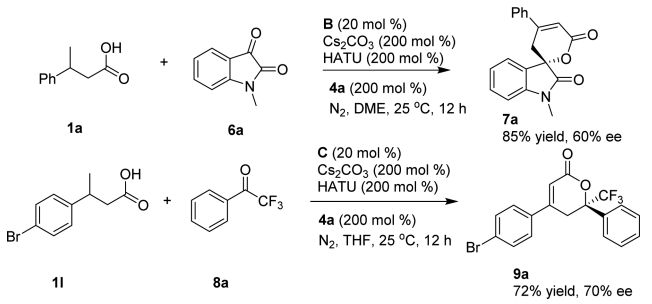
Scheme 5. Oxidative Formal [4 + 2] Synthesis of δ-Lactones



lactones) with ready availability of the starting materials, excellent enantioselectivity, high yields, convergent assembly, and mild reaction conditions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03223.

Experimental details, copies of ^{1}H and ^{13}C NMR spectra for all products (PDF)

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Notes

The authors declare no competing financial interest.

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