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Ynoate-Initiated Selective C–N Esterification of Tertiary Amines under Transition-Metal and Oxidant-Free Conditions

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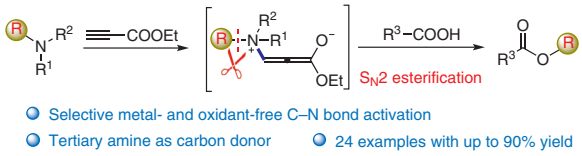

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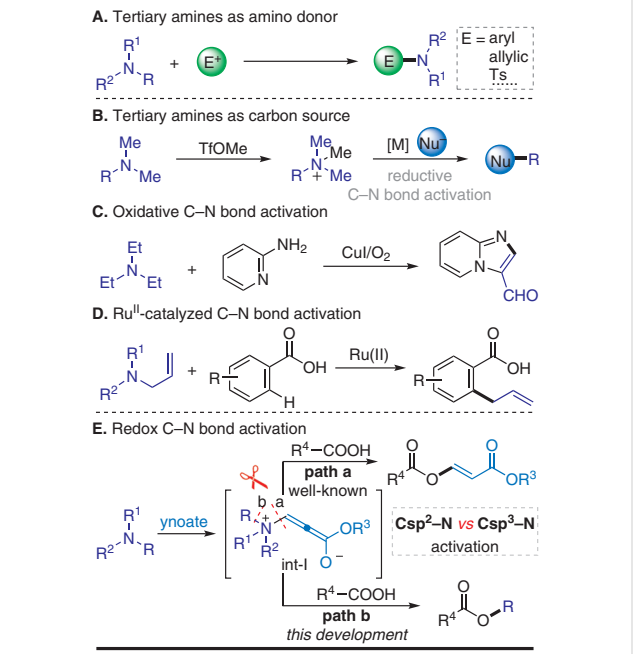
Abstract An efficient and selective method for metal- and oxidant-free deaminated esterification of tertiary amines is presented. In this protocol, ynoates play a key role to activate the Csp^3–N bond through a process of *in situ* generation of zwitterionic salts. The transformations show that Csp^3–N bond in the zwitterionic species has a lower dissociation energy than Csp^2–N bond, leading to break preferentially and be trapped by carboxylic acids to generate the corresponding products in moderate to good yield.

Key words C–N activation, esterification, chemoselectivity, ynoate, amines

Amines play an important role in diverse fields, ranging from biochemistry and medicinal chemistry to organic synthesis and material science.[1] In addition, they also widely exist in natural products and functional molecules.[2] Among the transformation of amines, C–N bond activations are ubiquitous processes in living organisms[3] and successfully applied in the modification of organic molecules.[4] For example, tertiary amines are usually introduced as the amino donors through a process of N-dealkylation or dealkylative nucleophilic substitution (Scheme 1A).[5] However, the use of tertiary amines as carbon sources has yet to be broadly recognized,[6] one traditional strategy involves the transition-metal-catalyzed aryl and benzyl C–N functionalization via a reductive coupling of produced ammonium salts (Scheme 1B).[7] Very recently, Song and co-workers reported the Cu-catalyzed cyclization of 2-aminopyridines with acrolein which was in situ formed by oxidative C–N bond activation employing ethyl-containing tertiary amines as carbon sources (Scheme 1C).[8] In 2018, Gooßen and co-workers described the [Ru(*p*-cymene)Cl_2]$_2$-catalyzed *ortho*-C–H allylation of benzoic acids using allyl amines as an allyl group (Scheme 1D).[9] Although some innovative methods have been exploited,[10] these synthetic approaches generally require transition metals or supplementary oxidants to facilitate the process of C–N bond cleavage.[11] Therefore, a potential general metal- and oxidant-free strategy for the C–N bond activation of tertiary amines is still highly desirable and needs to be formulated.



Scheme 1 C–N bond activations of tertiary amines

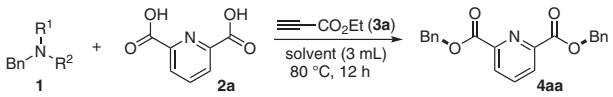
Notably, alkyne-induced C–N bond activation reactions of cyclic amines have emerged as powerful protocols for the rapid assembly of N-containing compounds.[12] For example, Oguri and co-workers reported a modular access to indole alkaloids by a ynoate-initiated Hofmann elimination.[13] In

recent years, this strategy has been extended to the C–O bond activation of carboxylic acids through enol ester species.[14] In this area, we found that the α-acyl enol esters could be produced effortlessly by a procedure of the Csp^2–N bond cleavage through *in situ* generated zwitterionic salts **int-I** (Scheme 1E, path a).[15] Inspired by these results, we herein hypothesize a novel redox-neutral Csp^3–N esterification instead of the Csp^2–N activation under metal- and oxidant-free conditions (Scheme 1E, path b). Undoubtedly, the most challenging of this protocol is the selective Csp^3–N and Csp^2–N cleavage as well as the site-selective activation of the N–R, N–R^1, and N–R^2 bond when the relatively complex tertiary amines are used. To our delight, the combined process of pathway a and pathway b was observed when dicarboxylic acids were used, leading to the unsymmetric dicarbonyl compounds.[16] In this work, we disclose an efficient and selective alkyne-induced Csp^3–N esterification in which amines proved to be critical to the reactivity.

In line with the difunctionalization of the dicarboxylic acid, we proposed that a suitable tertiary amine could enable this selective Csp^3–N esterification. Owing to the p–π conjugation, the benzyl cation seems to be more stable. Therefore, we initially investigated the reactions of different substituted benzylamines **1** with pyridine-2,6-dicarboxylic acid (**2a**) in the presence of ethyl propiolate (**3a**). As expected, *N*,*N*-dimethyl-1-phenylmethanamine (**1a**) afforded the desired diester product (**4aa**, 69% yield) in dioxane at 80 °C (Table 1, entry 1). Interestingly, the alkyl chains length and steric hindrance of the N-substituted group on the benzylamine are vitally important to the yield of the target product, revealing that either longer chain or bulkier amines led to a reduced yield (entries 2–6). It is to be noted that the highly sterically hindered *N*,*N*-dicyclohexylbenzylamine fails to afford the esterification product. The screening of solvents revealed that others were no better than dioxane, providing the desired products in 22–60% yield (entries 7–11). Furthermore, the amount evaluation of amine **1a** and ethyl propiolate (**3a**) was carried out (entries 12–16). Using 3 equivalents of **1a** could offer a satisfactory result, promoting the yield to 72% (entry 13). By contrast, the use of 2 equivalents or 4 equivalents of **1a** did not deliver better results (entries 12 and 14). By increasing the amounts of **3a** to 3.2 equivalents provided the target product in a good yield (81%, entry 16). In comparison with the metal-catalyzed and aerobic conditions, our results revealed the advance of a redox-neutral approach for the selective C–N bond cleavage.

With the optimized reaction conditions in hand, the substrate scope of carboxylic acids was studied using *N*,*N*-dimethylbenzylamine as the benzyl source (Scheme 2). A series of heterocyclic dicarboxylic acids were selected to capture the benzyl group by ethyl propiolate induced Csp^3–N activation, all of them proceed well and provided the target esters in 57–86% yield (**4aa**–**ac**). Subsequently, a diverse set of isophthalic acids and terephthalic acids bearing either electron-donating or electron-withdrawing groups such as methyl or nitro were well tolerated (**4ad**–**ai**). Whereas there was no target product isolated when using 5-aminoisophthalic acid (**4ae**). The transformation proceeded smoothly with naphthol carboxylic acids, not only dicarboxylic acids but also monocarboxylic acid, to afford the corresponding esterification products **4aj**–**al**) in 51–63% yield. Moreover, various monocarboxylic acids including 4-methoxylbenzoic acid, 2-iodobenzoic acid, benzoic acid, and lauric acid were tested (**4am**–**ap**), but unfortunately no target product was obtained when the substrate was switched to benzoic acid or lauric acid.

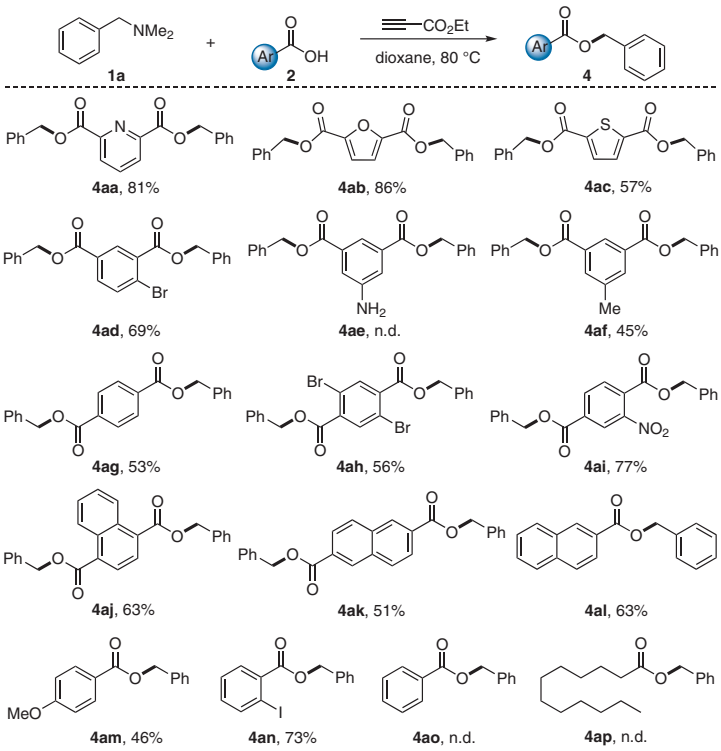
Table 1 Reaction Optimization[a]



Entry	Ratio of **1**/**2a**/**3a**	R^1	R^2	Solvent	Yield (%)[b]
1	0.8:0.5:1.1	Me	Me	dioxane	69
2	0.8:0.5:1.1	Me	*n*-Bu	dioxane	44
3	0.8:0.5:1.1	*n*-Bu	*n*-Bu	dioxane	32
4	0.8:0.5:1.1	*n*-Hex	*n*-Hex	dioxane	32
5	0.8:0.5:1.1	$-(CH_2)_4-$		dioxane	30
6	0.8:0.5:1.1	Cy	Cy	dioxane	0
7	0.8:0.5:1.1	Me	Me	MeCN	45
8	0.8:0.5:1.1	Me	Me	EtOH	34
9	0.8:0.5:1.1	Me	Me	THF	22
10	0.8:0.5:1.1	Me	Me	DCE	53
11	0.8:0.5:1.1	Me	Me	chloroform	60
12	1.0:0.5:1.1	Me	Me	dioxane	58
13	1.5:0.5:1.1	Me	Me	dioxane	72
14	2.0:0.5:1.1	Me	Me	dioxane	54
15	1.5:0.5:1.4	Me	Me	dioxane	63
16	1.5:0.5:1.6	Me	Me	dioxane	81

[a] Reaction conditions: to a stirred solution of **2a** (0.5 mmol), **3a** (1.6 mmol) in solvent (2 mL) was added **1**/solvent (1.5 mmol/1 mL) over 10 min, and the mixture was stirred for 12 h at 80 °C under atmosphere.
[b] Isolated yield.

In view of the organic halides are a versatile class of building blocks in coupling reactions,[15] 2-iodobenzoic acid was chosen as a nucleophile to evaluate the substrate scope of tertiary amines (Scheme 3). The application of methyl propiolate to active Csp^3–N bond of *N*,*N*-dimethylbenzyl amines was initially explored, giving the corresponding products (**4bn**–**fn**,**hn**,**in**) in good to excellent yield with a good functional-group tolerance. However, dichloro-substituted amine afforded the product only in 26% yield (**4gn**). Further investigations showed that dibenzyl amine was unable to produce the desired product. These results indicate a direct correlation between the reactivity and steric hin-



Scheme 2 Scope of carboxylic acids. *Reagents and conditions*: to a stirred solution of carboxylic acid (0.5 mmol) and ethyl propiolate (1.6 mmol) in dioxane (2 mL) was added *N*,*N*-dimethylbenzylamine/dioxane (1.5 mmol/1 mL) over 10 min, and the mixture was stirred for 12 h at 80 °C under atmosphere; isolated yields are given; n.d. = not determined.

drance in molecules. Furthermore, the trialkyl amines such as triethylamine and tripropylamine yielded the corresponding product **4jn** and **4kn** in 57% and 66% yield, respectively. No target product **4ln** was detected when *N*,*N*-dimethyl-2-phenylethanamine was submitted to the standard conditions. To our delight, a good result was also obtained using pyridine-2,6-dicarboxylic acid as a nucleophile, and the corresponding symmetric diester **4ca** was obtained in 81% yield.

In summary, we have developed a selective esterification of tertiary amines with aromatic acids that proceeds by ynoate-initiated metal- and oxidant-free Csp^3–N bond activation.[17] In this reaction, both electron-poor and electron-rich *N*,*N*-dimethylbenzyl amines except dichloro-substituted revealed good reactivity, as well as the trialkyl amines. Broad substrate scope of carboxylic acids makes this method much more attractive. Further studies of other capture reagents are currently ongoing in our laboratories.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1326-6973.

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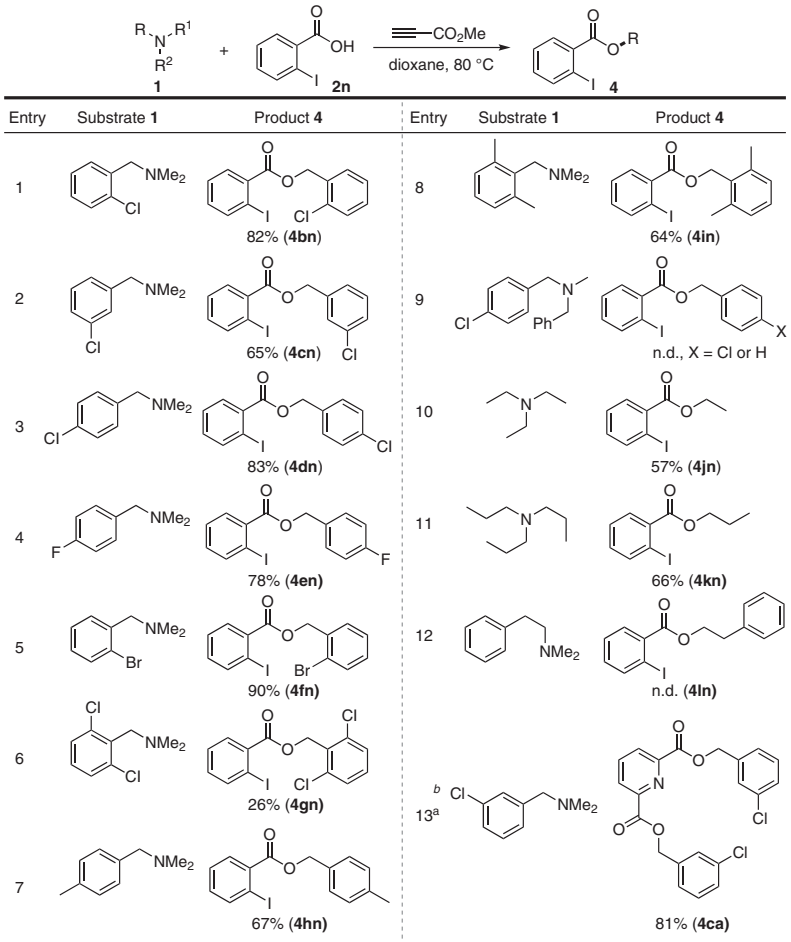

Scheme 3 Substrate scope of the tertiary amines as carbon donor. *Reagents and conditions*: to a solution of 2-iodobenzoic acid (0.5 mmol) and methyl propiolate (0.9 mmol) in dioxane (2 mL) was added a mixture of tertiary amines/dioxane (0.8 mmol/1 mL) over 10 min, and the reaction mixture was stirred for 12 h at 80 °C under the atmosphere; isolated yields are given; n.d. = not determined. [a] Pyridine-2,6-dicarboxylic acid (0.5 mmol), methyl propiolate (1.6 mmol), and tertiary amines (1.5 mmol) were used.

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(17) **General Procedure for the Synthesis of Dibenzyl 2,6-Pyridine-dicarboxylate (4aa)**

A mixture of pyridine-2,6-dicarboxylic acid (**2a**, 83.5 mg, 0.5 mmol, 1.0 equiv) and ethyl propiolate (**3a**, 157 mg, 1.6 mmol, 3.2 equiv) was added a 10 mL tube along with a magnetic stir bar, and then 2 mL 1,4-dioxane was added. The tube was stirred and refluxed in oil bath at 80 °C. Subsequently, *N*,*N*-dimethylbenzylamine (**1a**, 202 mg, 1.5 mmol, 3 equiv) solved in 1 mL 1,4-dioxane was added to the tube slowly for 10 min. And the tube was stirred again and refluxed at 80 °C for 12 h. After the removal of the volatiles in vacuo, the crude residue was loaded on a silica gel (100–200 mesh) column and flashed with 20% ethyl acetate in petroleum ether to afford the desired product **4aa** in 81% yield.

Dibenzyl 2,6-Pyridine-dicarboxylate (4aa)

White solid; 140 mg, 81% yield; mp 111–113 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27 (d, *J* = 7.8 Hz, 2 H), 7.97 (t, *J* = 7.8 Hz, 1 H), 7.48 (m, *J* = 7.7 Hz, 4 H), 7.42–7.31 (m, 6 H), 5.45 (s, 4 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.90, 148.01, 137.79, 134.97, 128.27, 127.88, 127.58, 67.26.

Dibenzyl 2,6-Furan-dicarboxylate (4ab)

White solid; 144 mg, 86% yield; mp 73–75 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.33 (m, 10 H), 7.20 (d, *J* = 4.1 Hz, 2 H), 5.36 (s, 4 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.39, 146.36, 134.75, 128.30, 127.97, 118.22, 66.66.

Dibenzyl 2,6-Thiophene-dicarboxylate (4ac)

White solid; 101 mg, 57% yield; mp 56–58 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (s, 2 H), 7.46–7.33 (m, 10 H), 5.35 (s, 4 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.38, 139.01, 135.35, 133.25, 128.60, 128.28, 67.30. HRMS (EI): *m*/*z* calcd for $C_{20}H_{16}O_4S$ [M]$^+$: 352.0764; found: 352.0765.