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Amide Bond Formation through Iron-Catalyzed Oxidative Amidation of Tertiary Amines with Anhydrides

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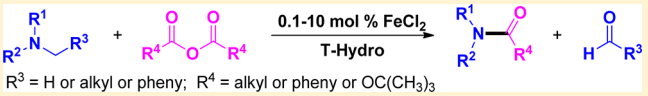
Supporting Information

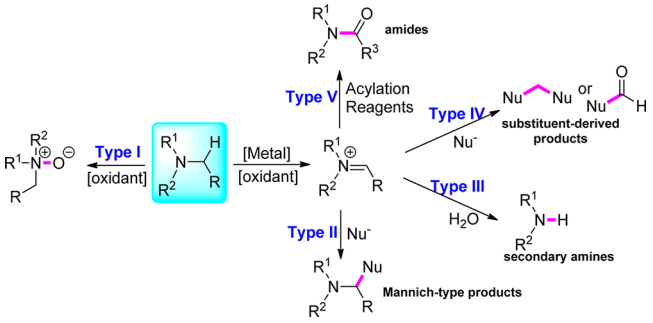
ABSTRACT: A general and efficient method for amide bond synthesis has been developed. The method allows for synthesis of tertiary amides from readily available tertiary amines and anhydrides in the presence of $FeCl_2$ as catalyst and *tert*-butyl hydroperoxide in water (T-Hydro) as oxidant. Mechanistic studies indicated that the in situ-generated α-amino peroxide of tertiary amine and iminium ion act as key intermediates in this oxidative transformation.



INTRODUCTION

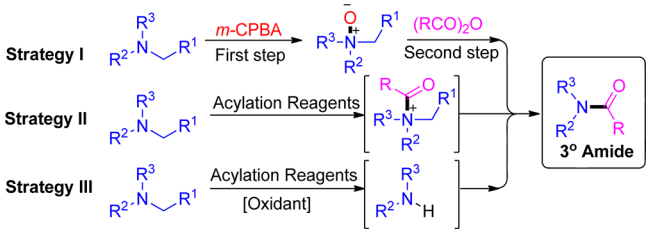
The oxidation of tertiary amines plays a vital role in biochemistry[1] and chemistry[2] from both transformative and mechanistic aspects. Inspired by nature, significant progress has been made in the transition metal-catalyzed oxidation of tertiary amines. The oxidative transformation of tertiary amines is summarized in Scheme 1. N-Oxidation of tertiary amines by a variety of oxidants presents an efficient method for the preparation of amine oxides (type I).[3] By taking an advantage of oxidation of C−H bond adjacent to the N atom, iminium ion, a useful synthetic intermediate, is generated toward various types of transformation (types II−V). α-Functionalized tertiary amines, the Mannich-type products, are formed in the presence of nucleophiles (type II),[4] and secondary amines are obtained by the use of H_2O (type III).[5] The alkyl substituent of tertiary amines can be transformed into the methylene-bridged or formyl compounds (type IV).[6] In addition, we recently disclosed an oxidative amidation of tertiary amines with aldehydes (type V).[7]

Scheme 1. Oxidative Transformation of Tertiary Amines



Amide bond formation is one of the often used reactions in the synthesis of natural products, pharmaceuticals, and fine chemicals.[8] Generally, primary and secondary amines are used as nitrogen sourses in the synthesis of amides.[9] Because tertiary amines are widely found in natural products and easily available, the development of amide formation from tertiary amines provides an attractive alternative to amide bond formation from a synthetic point of view (Scheme 2). The Polonovski reaction is a classic reaction for the preparation of amide in two steps from a tertiary amine, in which a nitrogen oxide is required to be synthesized and isolated (strategy I).[10] To realize the transformation of tertiary amines into amides by one-pot synthesis, two strategies have been developed: (1) quaternization of amines with active carbonyls, such as chloroformates[11] and anhydrides,[12] followed by dealkylation of the generated quaternary ammonium salts to give the amides (strategy II); and (2) oxidative dealkylation of tertiary amines in the presence of acylation reagents, such as aldehydes[7] and anhydrides,[13] in which secondary amines are generated in situ by oxidation of tertiary amines (strategy III). Both developed strategies present excellent methods for amide bond formation from tertiary amines; however, the methods have limited substrate scopes and also suffer poor selectivity. A general and efficient method for amide bond synthesis from tertiary amines is still valuable from a synthetic point of view.

Scheme 2. Strategies for the Amidation of Tertiary Amines



In our previous works of the oxidative amidation using aldehydes as acylation reagents, aromatic aldehydes efficiently reacted with tertiary amines to afford the amides;[7a] however,

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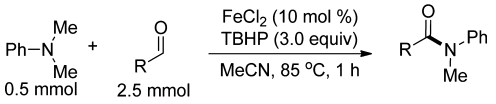
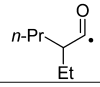
Table 1. Reactions of Tertiary Amine with Aliphatic Aldehydes



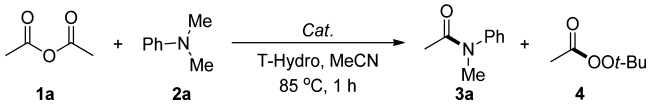
Entry	1	2	3	4	5	6	7
Aldehyde							
NMR Yield	trace	58%	90%	30%	0%	0%	0%
Kinetic data for decarbonylation of acyl radicals: (k_d at 296K, s^{-1})							
Acyl Radical							
Kinetic Data	4.0	2×10^2	1.4×10^4	8.1×10^6	4.2×10^7	8.3×10^5	

aliphatic aldehydes are not suitable carbonyl sources in this method (Table 1). One of the major reasons derives from the side reactions of aliphatic aldehydes, such as self-condensation (entries 1 and 2). The other reason is attributed to the decarbonylation of the branched acyl radicals (entries 4–7),[14] which are generated in situ through hydrogen abstraction by the *tert*-butoxyl radical in the oxidative system.[15] To overcome these shortcomings, we herein wish to disclose a general, efficient, and selective iron-catalyzed oxidative amidation of tertiary amines by the use of anhydrides as acylation reagents.

RESULTS AND DISCUSSION

The oxidative amidation of **1a** with **2a** was chosen as a model to establish the reaction conditions (Table 2). Various transition metals were screened by the use of 70 wt % *tert*-butyl hydroperoxide in water, abbreviated as T-Hydro (entries 1–7). $FeCl_2$ was found to be one of the best catalysts for the oxidative amidation (entries 1). The increasing amount of **1a** and T-Hydro further improved the efficiency of the desired transformation (entries 8). To our satisfaction, an excellent yield of **3a** was obtained when pyridine was added as an additive (entry 9);[16] however, an inorganic base, such as Cs_2CO_3, led to peroxyester **4** as the major product (entry 10). It is worth noting that a 77% yield of **3a** was still achieved in the presence of 0.1 mol % of $FeCl_2$ (entry 11). The efficiency and selectivity of the reaction dramatically decreased in the absence of an iron catalyst (entry 12).

Table 2. Optimization Studies for Oxidative Amidation of Acetic Anhydride with 2a[a]



1a **2a** **3a** **4**

entry	1a (equiv)	T-Hydro (equiv)	cat.	additive (1 equiv)	NMR yield (%)[b] 3a	4
1	1	1	$FeCl_2$		47	
2	1	1	$Fe_2(CO)_9$		45	
3	1	1	$FeCl_3$		36	
4	1	1	$K_3Fe(CN)_6$		10	
5	1	1	$FeBr_3$		28	
6	1	1	$CoCl_2$		30	
7	1	1	CuCl		43	
8	2	2	$FeCl_2$		68	
9[c]	2	2	$FeCl_2$	pyridine	91 (85)	38
10	2	2	$FeCl_2$	Cs_2CO_3	17	144
11[d]	2	2	$FeCl_2$	pyridine	77 (70)	62
12[e]	2	2		pyridine	32	98

[a]Conditions: **2a** (0.5 mmol), catalyst (2.5 mol %), MeCN (3.0 mL), 85 °C, 1 h, under N_2. [b]Reported yields were based on **2a** and determined by ^1H NMR using an internal standard; the yields are given in parentheses. [c]2 h. [d]$FeCl_2$ (0.1 mol %), 6 h. [e]6 h.

Subsequently, various *N*,*N*-dimethylaniline derivatives were investigated under the optimized conditions (Table 3). Aniline with an electron-donating group, such as **2b**, reacted efficiently with **1a** (entry 1), whereas electron-withdrawing groups on the benzene ring reduced the efficiency of the oxidative amidation (entries 2–5). Notably, the yield of **3e** was up to 89% from 23% when the reaction temperature was increased to 115 °C from 85 °C (entry 4). These results were consistent with the oxidative activities of 4-substituted -*N*,*N*-dimethylanilines.[17] Moreover, the hindered[18] and bis-acylated amides were also obtained smoothly (entries 6–8).

The scope and generality of this transformation with other amines were also investigated (Table 4). Not only the methyl group but also other alkyl groups reacted with acetic anhydride smoothly to give the corresponding tertiary amides in good yields (entries 1 and 2). The reaction of tributylamine **2l** with **1a** gave **3l** in 70% yield (entry 3), but 4-methylmorpholine **2m** could not give the desired amide (entry 4). For unsymmetrical anilines **2n** and **2o**, removing the methyl group is the priority over the removal of the ethyl substituent (entry 5), whereas the benzyl group was slightly faster than methyl (entry 6). The chemoselectivity of the present transformation is the same as the results of oxidation of tertiary amines.[17a,19]

Next, the scope of the anhydrides was investigated under the standard reaction conditions (Table 5). Propionic anhydride **1b** reacted efficiently with **2a** (entry 1). To our delight, the reaction of isobutyl anhydride **1c** with **2a** also gave the desired amide **3q** in a good yield (entry 2), which is difficult to synthesize by the use of aldehyde because of the decarbonylation of the aldehyde (as shown in Scheme 3). Importantly, α,β-unsaturated amides **3r** and **3s** were obtained smoothly (entries 3 and 4). Both benzyl and phenyl acetic anhydrides **1f** and **1g** led to the corresponding amides with good to excellent yields (entries 5 and 6).

Direct transformation of an *N*-methyl to an *N*-acyl group provides efficient access to a variety of intermediates that are useful in pharmacological developments.[20] To demonstrate the generality and the practicality of this methodology, we extended

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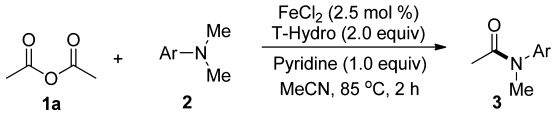
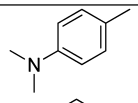
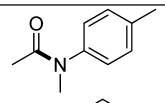
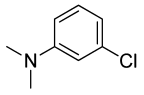
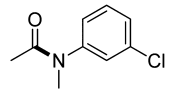
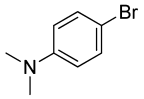
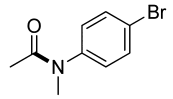
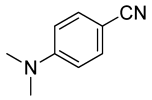
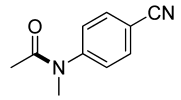
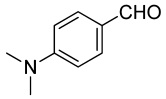
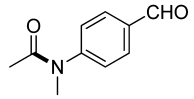
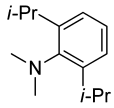
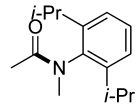
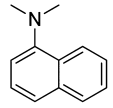
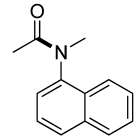
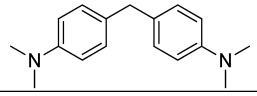
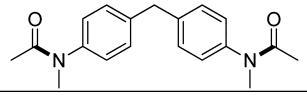
Table 3. Reactions of *N*,*N*-Dimethylanilines with Acetic Anhydride[a]

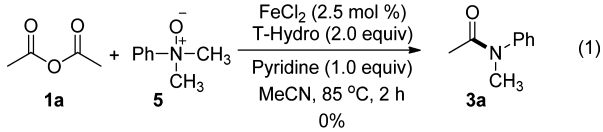


Entry	Amine		Product		Yield (%)[b]
1		**2b**		**3b**	92(90)
2		**2c**		**3c**	75(73)
3		**2d**		**3d**	74(74)
4		**2e**		**3e**	23(18) 89(85)[c]
5		**2f**		**3f**	38(31)
6		**2g**		**3g**	85(71)
7		**2h**		**3h**	62(60)[d]
8		**2i**		**3i**	95(90)[e]

[a]Reaction conditions: **1a** (1.0 mmol), **2** (0.5 mmol), T-Hydro (1.0 mmol), pyridine (0.5 mmol), $FeCl_2$ (2.5 mol %), MeCN (3 mL), 85 °C, 2 h. [b]Reported yields were based on **2** and determined by ^{1}H NMR using an internal standard; the yields are given in parentheses. [c]**1a** (5.0 mmol), 115 °C, in the absence of MeCN. [d]**1a** (2.5 mmol). [e]**1a** (2.0 mmol), T-Hydro (2.0 mmol), pyridine (1.0 mmol), $FeCl_2$ (5 mol %), MeCN (6 mL).

the study to tropinone and its derivatives (Table 6). The efficiency of the reactions of tropinone **2h** with anhydrides depended on the steric effect caused by anhydrides, in which the reaction of acetic anhydride **1a** with **2h** gave a good yield of the desired acyl product **3v** (entry 1), whereas benzoic anhydride **1g** and isobutyl anhydride **1c** led to only moderate yields of the expected products (entries 2 and 3). Boc anhydride (Boc_2O) reacted with tropinone **2h** and acyl tropine **2i** efficiently (entries 4 and 5); however, tropine **2j** gave the oxidized product **3y** as the major product together with the desired product **3y′** (entry 6). It is worth mentioning that the efficiency of the oxidative amidation of tropinone **2h** was diminished by the use of pyridine as an additive. Only 40% yield of **3v** was obtained when pyridine was added. In this case, the peroxyester **4** was formed as the major product. We hypothesized that the stronger basicity of aliphatic tertiary amines than aromatic tertiary amines is beneficial in formation of the peroxyester **4** by the reaction of anhydride (or the acylpyridium salt, $AcPy^+AcO^-$) with T-Hydro.

To clarify the possible reaction pathways, we carried out mechanistic studies on the present oxidative amidation of tertiary amines with anhydrides. First, *N*-oxide **5** was synthesized and submitted into the reaction (eq 1). Compound **3a** was not detected by ^{1}H NMR under our standard reaction conditions, which indicated that the sequence of the oxidation of tertiary amine to *N*-oxide, followed by the Polonovski



(1)

reaction to give the desired amide, could be excluded in the present transformation.

It is well-known that an α-amino radical is generated and acts as one of the key intermediates in tertiary amine oxidation by the use of peroxides or O_2 as oxidant. Two possible routes are commonly accepted for the generation of α-amino radical **A** (Scheme 3): direct hydrogen atom transfer (HAT) (path a) or a sequence of single electron transfer (SET) followed by proton transfer (PT) (paths b and c). According to the literature studies,[13,21] a HAT mechanism (path a) will be suppressed by the addition of a radical inhibitor. However, if the efficiency of the oxidation of amine is not affected by a radical inhibitor, an α-amino radical is most likely generated through SET (path b), followed by PT (path c). Accordingly, the addition of 2,6-di-*tert*-butyl-4-methylphenol (BHT) and 2,2,6,6-tetramethylpiperidinooxy (TEMPO) into the standard reactions were investigated (eqs 2 and 3). The results supported that the oxidation of amine **2a** is initiated by SET (path b) followed by PT (path c) to form an α-radical amine species.

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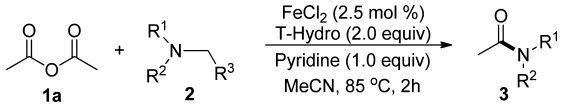
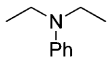
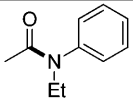
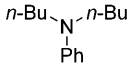
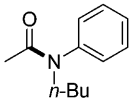
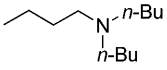
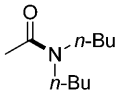
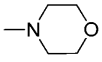
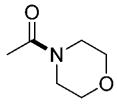
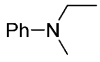
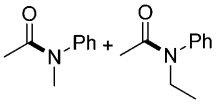
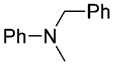
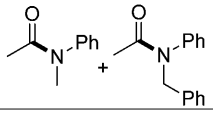
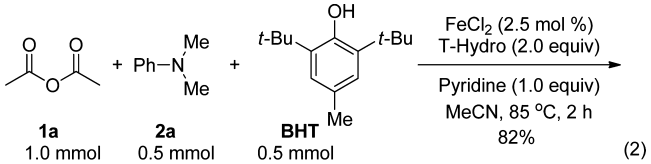
Table 4. Reactions of Tertiary Amines with Acetic Anhydride[a]

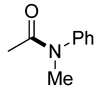


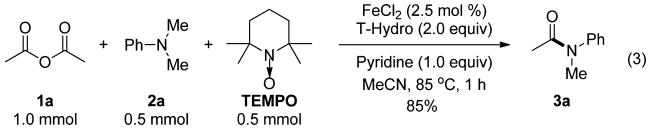
Entry	Amine		Products		Yield(%)[b]
1		**2j**		**3j**	81(75)
2		**2k**		**3k**	82(81)
3		**2l**		**3l**	70(65)
4		**2m**		**3m**	0
5		**2n**		**3a+3j**	18 + 76
6		**2o**		**3a+3o**	47 + 38

[a]Reaction conditions: **1a** (1.0 mmol), **2** (0.5 mmol), T-Hydro (1.0 mmol), pyridine (0.5 mmol), $FeCl_2$ (2.5 mol %), MeCN (3 mL), 85 °C, 2 h. [b]Reported yields were based on **2** and determined by ^1H NMR using an internal standard; the yields are given in parentheses.



(2)

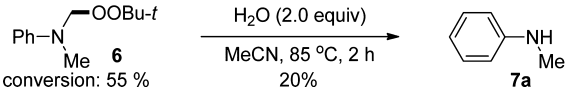




(3)

As a matter of fact, α-amino peroxide **6** was observed in the formation of **3a** by the reaction of **1a** with **2a**. Subsequently, the transformation of **6** to **3a** was investigated (Table 7). Compound **6** was smoothly transformed into **3a** in the presence and absence of pyridine (entries 1 and 2). The efficiencies of the reactions of **1a** with **6** are in line with the reactions of **1a** with **2a** (Table 1, entry 8), which indicated that **6** most likely acts as a possible intermediate in the present oxidative amidation. Meanwhile, the results are also consistent with the mechanistic studies by Klussmann[22] that the peroxide **6** acts as the reactive intermediates in the catalytic cycle. Moreover, **3a** was indeed formed in excellent yield without a catalyst (entry 3). This result agrees with the studies of Doyle's group, in which a Lewis acid catalyst is not necessary for the formation of an iminium intermediate from an α-substituted intermediate.[17a] Compound **3a** was obtained in only 27% yield in the absence of T-Hydro (entry 4), but the yield of **3a** was increased to 82% by the use of 2.0 equiv of water instead of T-Hydro (entry 5). These results indicated that water acts as a promoter in the transformation of **6** to **3a**.

Importantly, the possible peroxide intermediate, such as **6**, could be transformed into the corresponding secondary amine **7a** in the absence of anhydride (eq 4). Moreover, the generation



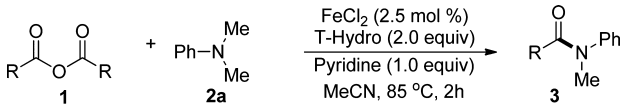
(4)

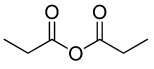
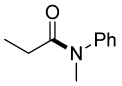
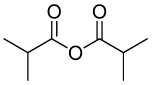
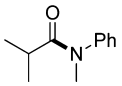
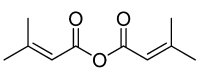
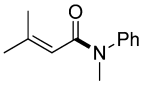
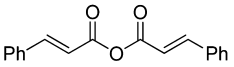
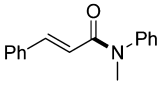
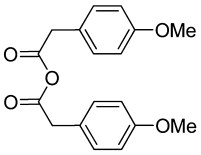
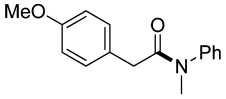
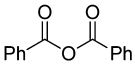
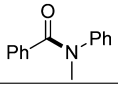
of secondary amines **7** was also confirmed by demethylation of tertiary amines **2** under the standard reaction conditions in the absence of anhydride (Table 8). The results indicated that the α-amino peroxides of tertiary amine and secondary amine most likely act as key intermediates in the present transformation.

On the basis of the above results and discussions, a tentative mechanism for this oxidative amide bond formation is proposed (Scheme 4). The decomposition of *t*-BuOOH assisted by an iron catalyst leads to *tert*-butoxyl and *tert*-butylperoxy radicals.[15] The α-amino radical **A** is generated by SET, followed by irreversible PT. The selective termination of kinetically stable *tert*-butylperoxy radical and unstable **A** furnishes a peroxide intermediate **C**,[22−25] followed by the elimination of **C** to give an iminium intermediate **D**. However, the possibility of the formation of **D** from **A** by a second SET could not be ruled out at this stage.[17a] The secondary amine **7** is formed by hydrolysis of **D** via **E**. Finally, **7** reacts with acetylpyridinium ion, generated by the reaction of anhydride and pyridine, to give the desired amide **3**. It is worth noting that the rapid reaction of **7** with acetylpyridinium ion plays a driving force for the oxidation of tertiary amine **2** to secondary amine **7** in the present transformation.

dx.doi.org/10.1021/jo400804p | J. Org. Chem. 2013, 78, 5638−5646

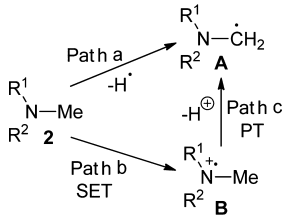
Table 5. Reactions of 2a with Anhydrides[a]



Entry	Anhydride		Product		Yield (%)[b]
1		**1b**		**3p**	88(81)
2		**1c**		**3q**	73(72)[c]
3		**1d**		**3r**	60(56)
4		**1e**		**3s**	83(82)
5		**1f**		**3t**	92(87)
6		**1g**		**3u**	82(80)

[a]Reaction conditions: **1** (1.0 mmol), **2a** (0.5 mmol), T-Hydro (1.0 mmol), pyridine (0.5 mmol), $FeCl_2$ (2.5 mol %), MeCN (3 mL), 85 °C, 2 h. [b]Reported yields were based on **2a** and determined by ^1H NMR using an internal standard; the yields are given in parentheses. [c]**1c** (2.5 mmol).

Scheme 3. Possible Paths for the Generation of a α-Amino Radical



CONCLUSION

In summary, a general and efficient method for the transformation of tertiary amine into tertiary amide had been developed. A variety of anhydrides were smoothly used as acylation reagents, which presents an excellent complement to our previous method of the oxidative amidation of tertiary amines with aldehydes. The method is also highlighted by the use of $FeCl_2$ as catalyst and T-Hydro as oxidant. The possible reaction pathways were investigated. The results indicated that the in situ-generated α-amino peroxide of tertiary amine and iminium ion play the role of key intermediates in the present oxidative transformation of tertiary amines. Further studies on the scope, mechanism, and synthetic applications of this reaction are in progress.

EXPERIMENTAL SECTION

General Information. All reagents were weighed and handled in air at room temperature. Unless otherwise noted, all reactions were performed under a nitrogen atmosphere. All reagents were purchased from a commercial source and were used without further purification. Compounds **2k**,[26] **1d**,[27] **1e**,[27] **1f**,[27] **2i**,[28] **5**,[29] and **6**[7a] were synthesized by the reported methods. The HRMS measurements were recorded on a FTMS analyzer using an ESI source in the positive mode.

General Procedure for Products 3. To a mixture of anhydride **1** (1.0 mmol), tertiary amine **2** (0.5 mmol), and $FeCl_2$ (1.6 mg, 0.0125 mmol), pyridine (40 μL, 0.5 mmol) and acetonitrile (3.0 mL) were added under nitrogen at room temperature. *tert*-Butyl hydroperoxide (70% aqueous solution, 136 μL, 1.0 mmol) was dropped into the mixture under nitrogen at room temperature. The resulting mixture was stirred at 85 °C for 2 h. The temperature of the reaction was cooled to room temperature. The reaction mixture was diluted with ethyl acetate (40 mL), washed with 1 M HCl (5 mL) two times, and a saturated solution of NaCl (5 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel with ethyl acetate/petroleum ether (1:5) as an eluent to afford the pure product **3**.

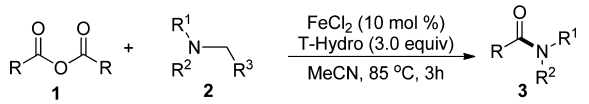
***N*-Methyl-*N*-phenylacetamide (3a).**[30] 126.8 mg, 85% yield. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:5, R_f = 0.3). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.39 (t, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.16 (d, *J* = 7.4 Hz, 2H), 3.24 (s, 3H), 1.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.4, 144.5, 129.6, 127.3, 127.0, 37.0, 22.3.

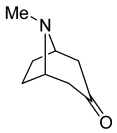
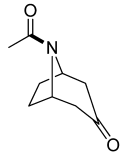
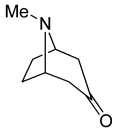
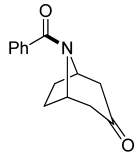
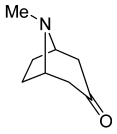
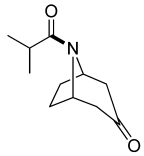
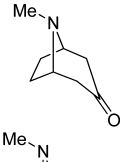
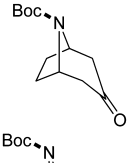
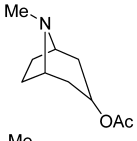
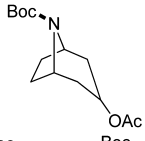
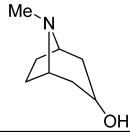
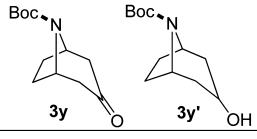
***N*-Methyl-*N*-(*p*-tolyl)acetamide (3b).**[31] 146.9 mg, 90% yield. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:2, R_f = 0.3). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.18 (d, *J* = 7.8 Hz, 2H), 7.04 (d, *J* = 7.6 Hz, 2H), 3.21 (s, 3H), 2.35 (s, 3H), 1.83 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.7, 142.0, 137.5, 130.2, 126.7, 37.1, 22.2, 20.9.

***N*-(3-Chlorophenyl)-*N*-methylacetamide (3c).**[32] 134.0 mg, 73% yield. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:1, R_f = 0.4). IR (neat): ν_{max} 3051, 2930, 2359,

dx.doi.org/10.1021/jo400804p | J. Org. Chem. 2013, 78, 5638−5646

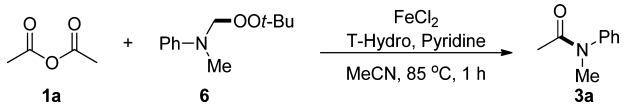
Table 6. Reactions of Tropinones with Anhydrides[a]



Entry	Amine		Products		Yield (%)[b]
1		**2h**		**3v**	72
2		**2h**		**3w**	50
3		**2h**		**3x**	52
4		**2h**		**3y**	68
5[c]		**2i**		**3z**	90
6[c]		**2j**			45 + 22

[a]Reaction conditions: **1** (1.0 mmol), **2** (0.5 mmol), T-Hydro (1.5 mmol), $FeCl_2$ (10 mol %), MeCN (3 mL), 85 °C, 3 h. [b]The yields were based on **2**. [c]*tert*-Butyl hydroperoxide (TBHP, 5.0−6.0 M in decane, 1.5 mmol).

Table 7. Transformation of 6 under Different Conditions[a]



entry	pyridine, equiv	$FeCl_2$, mol %	T-Hydro[c], equiv	additive	yield (%)[b]
1	1.0	2.5	2.0		73
2		2.5	2.0		66
3	1.0		2.0		91
4	1.0	2.5			27
5	1.0	2.5		2.0 equiv H_2O	82

[a]Reaction conditions: **1a** (1.0 mmol), **6** (0.5 mmol), MeCN (3 mL), 85 °C, 1 h. [b]Reported yields were based on **6** and determined by ^1H NMR using an internal standard. [c]2.0 equiv of T-Hydro (70% aq. soln) contains 2.1 equiv of H_2O.

1667, 1593, 1572, 1477, 1418, 1383, 1294, 1144, 1105, 1087, 974, 910, 797, 773, 707, 675, 411 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.37−7.27 (m, 2H), 7.19 (s, 1H), 7.08 (d, J = 7.4 Hz, 1H), 3.20 (s, 3H), 1.87 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.1, 145.6, 135.0, 130.6, 127.9, 127.4, 125.3, 77.3, 77.0, 76.7, 37.0, 22.4.

***N*-(4-Bromophenyl)-*N*-methylacetamide (3d).**[32] 168.0 mg, 74% yield. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:5, R_f = 0.1). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.51 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.4 Hz, 2H), 3.20 (s, 3H), 1.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.1, 143.4, 132.8, 128.7, 121.2, 37.0, 22.3.

***N*-(4-Cyanophenyl)-*N*-methylacetamide (3e).**[32] 148.0 mg, 85% yield. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:1, R_f = 0.3). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.68 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 3.26 (s, 3H), 2.05−1.81 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.8, 148.1, 133.4, 127.4, 119.2, 117.9, 37.1, 22.4.

***N*-(4-Formylphenyl)-*N*-methylacetamide (3f).** 54.9 mg, 31% yield. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:1, R_f = 0.4). Yellow oil. IR (neat): ν_{max} 3285, 2953, 2922, 2851, 1697, 1634, 1599, 1375, 1206, 1136, 1082, 974, 826, 702, 534, 419 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 10.02 (s, 1H), 7.94 (d, J = 8.3 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 3.32 (s, 3H), 1.97 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 190.9, 170.0, 149.7, 135.0, 131.0, 127.4, 37.2, 22.6. HRMS calcd for $C_{10}H_{12}NO_2$ (M^+ + H), 178,0863; found, 178.0858.

***N*-(2,6-Diisopropylphenyl)-*N*-methylacetamide (3g).** 165.6 mg, 71% yield. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:5, R_f = 0.1). Yellow solid, mp 56−57 °C. IR (neat): ν_{max} 3064, 3018, 2962, 1660, 1587, 1527, 1460, 1373, 1284, 1138, 1055, 812, 769, 734, 605, 570, 472 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.35−7.30 (t, J = 7.7 Hz 1H), 7.18 (d, J = 7.7 Hz, 2H), 3.13 (s, 3H), 2.99−2.90 (m, 2H), 1.72 (s, 3H), 1.20 (d, J = 2.8 Hz, 6H), 1.18 (d, J = 2.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$)

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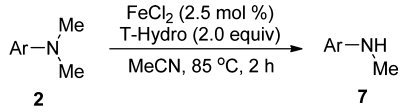
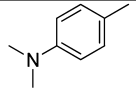
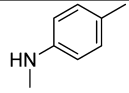
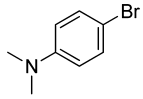
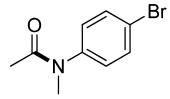
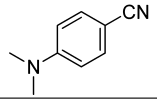
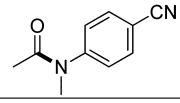
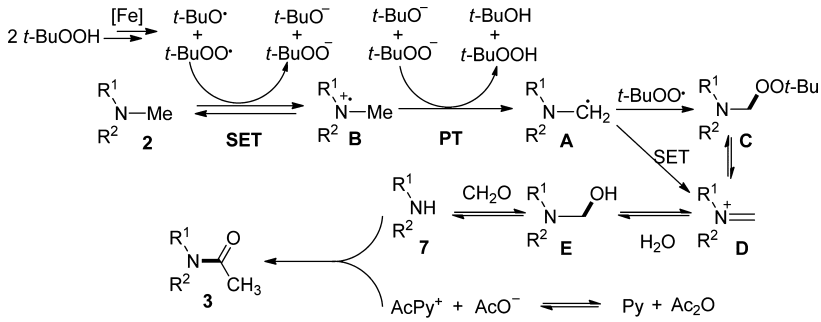
Table 8. Demethylation of Tertiary Amines[a]



Entry	Amine		Product		Yield (%)[b]
1		**2b**		**7b**	15(10)
2		**2d**		**7c**	33(33)
3		**2e**		**7d**	25(24)

[a]Reaction conditions: **2** (0.5 mmol), T-Hydro (1.0 mmol), $FeCl_2$ (2.5 mol %), MeCN (3 mL), 85 °C, 2 h. [b]Reported yields were based on **2** and determined by ^1H NMR using an internal standard; the isolated yields are given in parentheses.

Scheme 4. A Tentative Mechanism for Oxidative Amidation with Tertiary Amines



δ = 171.3, 145.9, 138.8, 128.8, 124.5, 36.8, 28.0, 25.0, 23.6, 21.7. HRMS calcd for $C_{15}H_{24}NO$ (M^+ + H), 234.1852; found, 234.1854.

***N*-Methyl-*N*-(naphthalen-1-yl)acetamide (3h).**[33] 119.5 mg, 60% yield. Isolated by flash column chromatography (dichloromethane/methanol = 10:1, R_f = 0.5). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.91 (dd, J = 6.9, 2.2 Hz, 1H), 7.86 (d, J = 8.3 Hz, 1H), 7.81−7.78 (m, 1H), 7.59−7.52 (m, 2H), 7.51−7.43 (m, 1H), 7.35 (d, J = 7.2 Hz, 1H), 3.35 (s, 3H), 1.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.5, 140.6, 134.6, 130.0, 128.6, 127.4, 126.7, 125.8, 125.2, 122.2, 36.9, 21.9.

***N*,*N*′-(Methylenebis(4,1-phenylene))bis(*N*-methylacetamide) (3i).**[34] 279.2 mg, 90% yield. Isolated by flash column chromatography (dichloromethane/methanol = 10:1, R_f = 0.4). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.23 (d, J = 8.2 Hz, 4H), 7.12 (d, J = 8.2 Hz, 4H), 4.0 (s, 2H), 3.25 (s, 6H), 1.87 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.2, 142.5, 139.8, 129.8, 126.8, 40.5, 36.8, 22.1.

***N*-Ethyl-*N*-phenylacetamide (3j).**[35] 122.3 mg, 75% yield. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:1, R_f = 0.5). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.40 (t, J = 7.5 Hz, 2H), 7.32 (t, J = 7.3 Hz, 1H), 7.13 (d, J = 7.3 Hz, 2H), 3.72 (t, J = 7.2 Hz, 2H), 1.79 (s, 3H), 1.08 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.9, 142.8, 129.6, 128.1, 127.8, 43.7, 22.8, 13.0.

***N*-Butyl-*N*-phenylacetamide (3k).**[36a] 154.8 mg, 81% yield. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:1, R_f = 0.4). IR (neat): ν_{max} 3061, 3038, 2959, 2932, 2872, 1728, 1651, 1595, 1495, 1396, 1300, 1217, 1092, 1074, 775, 702, 596 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.39 (t, J = 7.5 Hz, 2H), 7.32 (t, J = 7.3 Hz, 1H), 7.13 (d, J = 7.5 Hz, 2H), 3.66 (t, J = 7.6 Hz, 2H), 1.79 (s, 3H), 1.51−1.39 (m, 2H), 1.31−1.22 (m, 2H), 0.85 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.2, 143.0, 129.5, 128.0, 127.7, 48.7, 29.7, 22.7, 19.9, 13.7. HRMS calcd for $C_{12}H_{18}NO$ (M^+ + H), 192.1383; found, 192.1381.

***N*,*N*-Dibutylacetamide (3l).**[36b] 111.3 mg. 65% yield. Isolated by flash column chromatography (dichloromethane/methanol = 10:1, R_f = 0.7). ^1H NMR (400 MHz, $CDCl_3$) δ = 3.27 (t, J = 7.7 Hz, 2H), 3.18 (t, J = 7.7 Hz, 2H), 2.05 (s, 3H), 1.58−1.41 (m, 4H), 1.37−1.21 (m, 4H), 0.92 (t, J = 7.3 Hz, 3H), 0.89 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.0, 48.5, 45.4, 31.0, 29.8, 21.5, 20.2, 20.0, 13.8, 13.8.

***N*-Benzyl-*N*-phenylacetamide (3o).**[37] 85.5 mg, 38% yield. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:2, R_f = 0.4). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.35−7.27 (m, 3H), 7.27−7.21 (m, 3H), 7.21−7.16 (m, 2H), 6.98 (dd, J = 7.8, 1.5 Hz, 2H), 4.89 (s, 2H), 1.88 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.3, 142.8, 137.4, 129.4, 128.7, 128.3, 128.1, 127.8, 127.2, 52.7, 22.7.

***N*-Methyl-*N*-phenylpropionamide (3p).**[38] 132.1 mg, 81% yield. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:5, R_f = 0.2). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.40 (t, J = 7.5 Hz, 2H), 7.32 (t, J = 7.3 Hz, 1H), 7.16 (d, J = 7.4 Hz, 2H), 3.25 (s, 3H), 2.06 (q, J = 7.3 Hz, 2H), 1.03 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.0, 144.1, 129.7, 127.6, 127.2, 37.2, 27.4, 9.7.

***N*-Methyl-*N*-phenylisobutyramide (3q).**[39] 127.5 mg, 72% yield. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:5, R_f = 0.2). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.44−7.38 (m, 2H), 7.33 (t, J = 7.3 Hz, 1H), 7.20−7.16 (m, 2H), 3.24 (s, 3H), 2.52−2.46 (m, 1H), 1.01 (d, J = 6.7 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.30, 144.25, 129.69, 127.65, 127.24, 37.43, 30.95, 19.62.

***N*,3-Dimethyl-*N*-phenylbut-2-enamide (3r).**[40] 105.9 mg, 56% yield. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:1, R_f = 0.4). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.35 (t, J = 7.6 Hz, 2H), 7.26 (t, J = 7.4 Hz, 1H), 7.13 (d, J = 7.5 Hz, 2H), 5.45 (s, 1H), 3.28 (s, 3H), 2.10 (s, 3H), 1.65 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.18, 150.17, 144.18, 129.23, 126.96, 117.53, 36.85, 27.03, 26.33, 20.02.

***N*-Methyl-*N*-phenylcinnamamide (3s).**[41] 194.4 mg, 82% yield. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:5, R_f = 0.4). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.68 (d, J = 15.5 Hz, 1H), 7.47 −7.40 (m, 2H), 7.39−7.33 (m, 1H), 7.33−7.21

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(m, 7H), 6.37 (d, J = 15.5 Hz, 1H), 3.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.1, 143.5, 141.6, 135.1, 129.5, 129.4, 128.6, 127.7, 127.5, 127.2, 118.7, 77.3, 76.7, 37.5.

2-(4-Methoxyphenyl)-*N*-methyl-*N*-phenylacetamide (3t). 222.0 mg, 87% yield. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:5, R_f = 0.5). Oil. IR (neat): ν_{max} 3061, 3036, 2999, 2953, 2934, 2910, 2835, 1728, 1645, 1635, 1614, 1595, 1514, 1495, 1454, 1373, 1300, 1248, 1179, 1121, 1034, 916, 855, 822, 789, 773, 700, 557, 409 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.43−7.32 (m, 3H), 7.12 (d, J = 7.2 Hz, 2H), 6.96 (d, J = 8.4 Hz, 2H), 6.77 (d, J = 8.5 Hz, 2H), 3.77 (s, 3H), 3.39 (s, 2H), 3.27 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.3, 158.2, 144.0, 130.0, 129.6, 127.8, 127.6, 127.4, 113.7, 55.2, 39.9, 37.5. HRMS calcd for $C_{16}H_{18}NO_2$ (M^+ + H), 256.1332; found, 256.1332.

***N*-Methyl-*N*-phenylbenzamide (3u).**[7a] 168.9 mg, 80% yield. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:5, R_f = 0.5). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.31−7.27 (m, 2H), 7.25−7.18 (m, 3H), 7.18−7.10 (m, 3H), 7.06−7.00 (m, 2H), 3.49 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.6, 144.8, 135.8, 129.5, 129.0, 128.6, 127.6, 126.8, 126.4, 38.3.

8-Acetyl-8-azabicyclo[3.2.1]octan-3-one (3v).[42] 120.3 mg, 72% yield. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:1, R_f = 0.3). IR (neat): ν_{max} 2959, 2928, 2887, 1715, 1645, 1634, 1418, 1344, 1236, 1202, 1155, 1036, 1005, 970, 947, 907, 741, 619, 594, 498, 436 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.96−4.80 (m,1H), 4.44−4.33 (m, 1H), 2.76−2.62 (m, 1H), 2.58−2.47 (m, 1H), 2.46−2.27 (m, 2H), 2.22−1.93 (m, 5H), 1.83−1.71 (m, 1H), 1.70−1.59 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 207.1, 167.0, 54.3, 50.7, 49.5, 48.7, 29.8, 27.9, 21.5. HRMS calcd for $C_9H_{14}NO_2$ (M^+ + H), 168.1019; found, 168.1016.

8-Benzoyl-8-azabicyclo[3.2.1]octan-3-one (3w).[20a] 114.6 mg, 50% yield. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:2, R_f = 0.4). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.53−7.48 (m, 2H), 7.48−7.38 (m, 3H), 5.03 (s, 1H), 4.37 (s, 1H), 2.99−2.83 (m, 1H), 2.60−2.23 (m,3H), 2.13 (s, 2H), 1.73 (d, J = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 207.4, 168.8, 135.8, 130.5, 128.5, 127.0, 55.8, 51.3, 49.5, 48.7, 29.5, 27.9.

8-Isobutyryl-8-azabicyclo[3.2.1]octan-3-one (3x). 101.5 mg, 52% yield. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:1, R_f = 0.5). Yellow oil. IR (neat): ν_{max} 2968, 2886, 1717, 1643, 1472, 1427, 1344, 1271, 1198, 1007, 984, 742 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.00−4.87 (m, 1H), 4.60−4.40 (m, 1H), 2.82−2.63 (m, 2H), 2.60−2.48 (m, 1H), 2.48−2.33 (m, 2H), 2.20−1.95 (m, 2H), 1.87−1.59 (m, 2H), 1.16 (d, J = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 207.5, 173.8, 53.4, 50.8, 50.0, 49.0, 31.7, 30.0, 27.8, 20.1, 19.1. HRMS calcd for $C_{11}H_{18}NO_2$ (M^+ + H), 196.1332; found, 196.1331.

***tert*-Butyl 3-Oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (3y).**[43] 153.1 mg, 68% yield. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:1, R_f = 0.7). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.46 (s, 2H), 2.90−2.46 (m, 2H), 2.41−2.25 (m, 2H), 2.07 (s, 2H), 1.64 (d, J = 7.6 Hz, 2H), 1.47 (s,9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 208.4, 153.3, 80.2, 53.1, 52.9, 48.8, 48.5, 29.2, 28.6, 28.4.

***tert*-Butyl 3-Acetoxy-8-azabicyclo[3.2.1]octane-8-carboxylate (3z).** 242.2 mg, 90% yield. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:1, R_f = 0.3). Colorless oil. IR (neat): ν_{max} 2974, 2882, 1738, 1694, 1394, 1366, 1238, 1165, 1101, 1078, 1034, 870, 777 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.05 (t, J = 5.0 Hz, 1H), 4.16 (d, J = 32.7 Hz, 2H), 2.25−1.64 (m, 11H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.2, 153.3, 79.3, 67.9, 52.6, 51.8, 35.7, 35.0, 28.4, 28.2, 27.6, 21.5. HRMS calcd for $C_{14}H_{23}NO_4$ (M^+ + Na), 292.1519; found, 292.1518.

***tert*-Butyl 3-Hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate (3y′).**[20b] 50.0 mg, 22% yield. Isolated by flash column chromatography (ethyl acetate/petroleum ether = 1:1, R_f = 0.4). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.28−4.16 (br, 1H), 4.16−4.03 (m, 2H), 2.22−1.85 (m, 6H), 1.78−1.57 (m, 3H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.4, 79.0, 65.3, 53.0, 52.2, 38.6, 38.1, 28.5, 27.8, 28.3.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H NMR and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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