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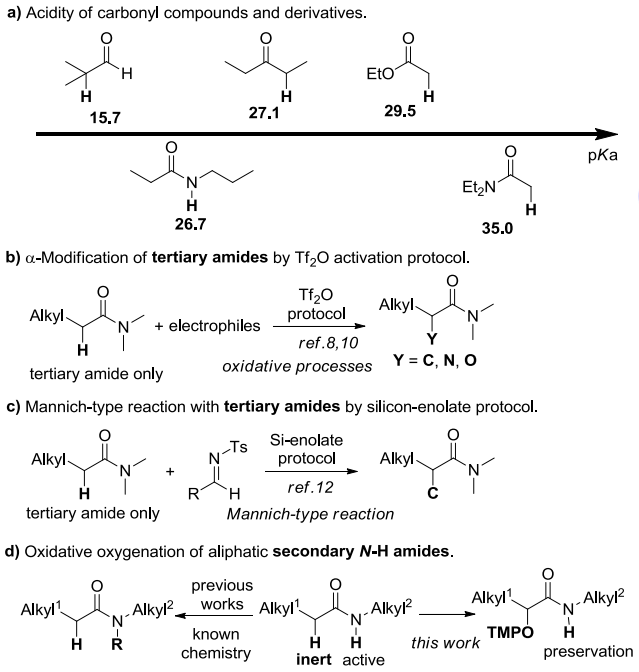
Selective α-Oxyamination and Hydroxylation of Aliphatic Amides

*Xinwei Li, Fengguirong Lin, Kaimeng Huang, Jialiang Wei, Xinyao Li, Xiaoyang Wang, Xiaoyu Geng and Ning Jiao**

Dedicated to Professor Chen-Ho Tung on the occasion of his 80th birthday

Abstract: *Compared to the α-functionalization of aldehydes, ketones, even esters, the direct α-modification of amides is still a big challenge because of the lowest α-CH acidity among all carbonyl chemicals. Most challengingly, α-functionalization of N-H (primary and secondary) amides simultaneous containing the unactived α-C-H bond and a competitively active N-H bond, remains elusive. Herein, we demonstrate a general and efficient oxidative α-oxyamination and hydroxylation of aliphatic amides including secondary N-H amides. This transition-metal-free chemistry with high chemoselectivity provides an efficient approach to α-hydroxyl amides. This oxidative protocol significantly enables the selective functionalization of inert α-C-H bond with the complete preservation of active N-H bond.*

Aldehydes, ketones, esters, acids, and amides are very common and readily available bulk chemicals as well as fundamental synthetic blocks. Among them, aliphatic amide skeletons are key building blocks in widespread natural compounds, peptides, fine chemicals, pharmaceuticals, and polymers.[1] The α-functionalization of carbonyl chemicals via enol or enolate strategy is one of the most important approaches to access C-C and C-heteroatom bond formation in synthetic chemistry.[2] Among the carbonyl compounds, α-functionalization of aldehydes and ketones to access C-C and C-heteroatom bond formation is relatively easier owing to the high α-CH acidity[3] (pK_a = 15.7, 27.1, Scheme 1a), and therefore have been widely applied in synthesis.[4] However, the α-CH pK_a of esters and amides increase to 29.5 and 35.0 respectively[5], which theoretically illustrates the difficulty of enolate formation and demonstrates that the α-functionalization of amides is big challenging issue. Most challengingly, α-functionalization of *N*-H (primary and secondary) amides simultaneous containing the unactived α-C-H bond and competitively active N-H bond, remains elusive.



Scheme 1. The significance and challenges for the α-modification o aliphatic amides.

Traditionally, the intermolecular α-modification of simpl amides relies on the strong halogenation reagents or strong base promoted processes with limited substrate scopes.[6] In past decades triflic anhydride (Tf_2O) was usually used as a powerful amid activation reagent to enhance the intrinsic electrophilicity o amides.[7] By using this strategy, milestones of α-arylation and o amination of tertiary amides have been achieved by Maulide' group through oxidative C-C or C-N bond formation.[8] α-Hydroxy amide derivatives have been proved important bioactive scaffolds i the marketed pharmaceuticals with various bioactivities an pharmacological activities.[9] Recently, Maulide and coworker significantly achieved the chemoselective oxidation of tertiar amides with C-O bond formation (Scheme 1b).[10] Alternatively silicon enolates have been widely used as convenient carbon equivalent donors.[11] By using this protocol, Kobayashi and co-workers disclosed a remarkable Mannich-type reaction with tertiary amides (Scheme 1c).[12] To the best of our knowledge, these fantastic oxygenation and nitrogenation of amides are limited to protected tertiary amides. The simple secondary amides containing N-H bond are not tolerated in these methods, because the electrophilically activated secondary amides preferred the formation of the corresponding nitrilium ions as previous work reported,[7b,13] which therefore inhibits the α-functionalization of N-H amides (Scheme 1c). Herein, we report an oxidative chemoselective α-oxyamination of aliphatic secondary *N*-H amides with TEMPO

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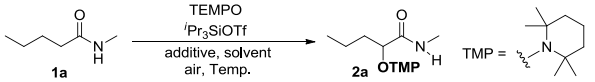
(Scheme 1d), which provides an efficient approach to α-hydroxy amides. This oxidative protocol with high selectivity enables the functionalization of inert α-C-H bond with the complete preservation of active N-H bond.

Recently, with the continuous efforts on the α-C-H oxygenation of aldehydes, ketones, and esters, we achieved the α-keto- amides and esters synthesis with O_2.[14] Considering the inertness of amides, we tried to use TEMPO[15] to complete the oxygenation of amides. The secondary *N*-methylpentanamide **1a** was initially selected as a challenging model substrate to explore this transformation (Table 1). At the outset of our study, the reaction was conducted in the presence of TEMPO (1.5 equiv) and $^{i}Pr_3SiOTf$ (1.1 equiv) at 100 °C under air atmosphere. Unfortunately, the desired product **2a** was not detected (Table 1, entry 1). To our delight, when 1.5 equiv of pyridine was added to the reaction, **2a** was obtained in 14% yield (entry 2). The results with different bases showed that the pyridine was special and critical to this reaction (entries 3-4 and see SI). The non-polar solvent such as hexane had a beneficial effect on the reaction compared to other solvents (entries 5-7). With the hypothesis that the $^{i}Pr_3SiOTf$ could be consumed by both amide substrate and TEMPO, we then increased the loading of $^{i}Pr_3SiOTf$. It is noteworthy that **2a** was obtained in 90% isolated yield in the presence of 3.3 equiv of $^{i}Pr_3SiOTf$ (entry 8). The highest efficiency was obtained by increasing the amount of TEMPO to 3.0 equiv, affording the target product **2a** in 94% isolated yield (entry 9).

Table 1. Screening of reaction conditions. [a]

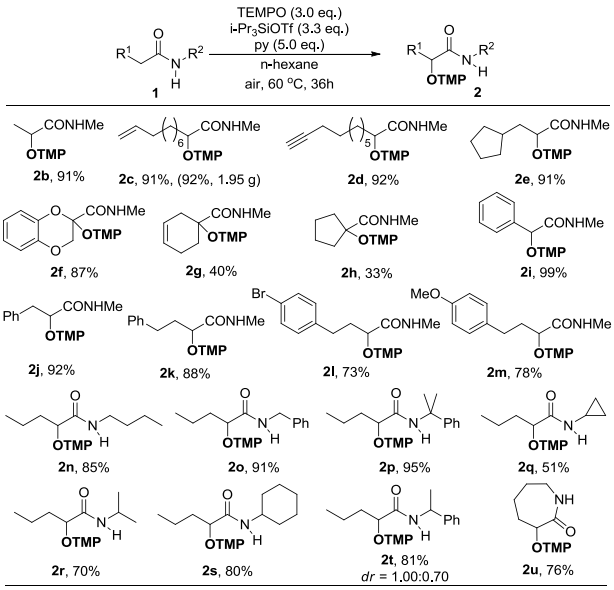


Entry	TEMPO/equiv	$^{i}Pr_3SiOTf$/equiv	additive(equiv)	solvent	T/℃	time/h	yield[b]/%
1	1.5	1.1	--	Toluene	100	11	0
2	1.5	1.1	py (1.5)	Toluene	100	11	14
3	1.5	1.1	K_2CO_3 (1.5)	Toluene	100	11	0
4	1.5	1.1	DBU (1.5)	Toluene	100	11	0
5	1.5	1.1	py (1.5)	Toluene	60	11	5
6	1.5	1.1	py (1.5)	DCE	60	11	6
7	1.5	1.1	py (1.5)	n-Hexane	60	11	26
8	2.0	3.3	Py (5.0)	n-Hexane	60	33	83 (90)
9	3.0	3.3	py (5.0)	n-Hexane	60	24	89 (94)

[a] Reaction conditions: **1a** (0.3 mmol), TEMPO, $^{i}Pr_3SiOTf$ and additives in solvent (1.0 mL) under air. [b] Determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as internal standard. The numbers in parentheses are the isolated yields.

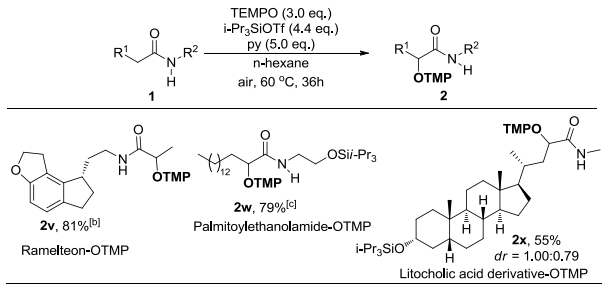
With the optimal conditions in hand (Table 1, entry 9), we set out to investigate the scope of this reaction (Scheme 2). As shown, it is found that this metal-free method can be applied to α-oxyamination of a series of aliphatic secondary *N*-H amides, furnishing the desired α-OTMP Amide in generally good to excellent yields (Scheme 2). Amides with alkene and alkyne groups both underwent selective α-C-H functionalizations to furnish α-OTMP amides in excellent yields (**2c** and **2d**, 91% and 92% yields, respectively). When heteroatom was linked to amide, the desired product could also be obtained in excellent yield (**2f**, 87%). Furthermore, amides bearing cycloalkyl moiety were also tolerated to give the desired product in acceptable yields (**2g** and **2h**, 40% and 44% yields, respectively). Benzyl amide **1i** almost quantitively afforded the desired product **2i** (99% yield). Phenyl ring bearing halide and methoxy groups worked well and gave products in good yields (**2l** and **2m**).

The effect of the *N*-substituted chain alkyl group was also examined. Compared to amide **1a** with a methyl group, comparable yield was isolated with the amide bearing linear butyl group (**2n**, 85% yield). Meanwhile the *N*-substituted substrates with benzyl groups afforded desired products in excellent yields (**2o**, **2p** and **2t**). The substrates with various alkyl group at *N*-position were further studied. The results showed that the efficiency was not affected by the *N*-substituent of the secondary amide substrates. Among them, the amide substrate with quaternary substituted carbon on nitrogen of *N*-H amide exhibited very good reactivity producing the expected product in quantitive yield (**2p**). It is noteworthy that even for the high strained *N*-cyclopropyl substituted amide **1q**, the corresponding α-oxyamination product **2q** was obtained in moderate yield. More interestingly, the lactam **1u** performed well affording the desired α-oxyamination lactam **2u** in 76% yield (Scheme 2). In addition, a gram-scale reaction (**2c**, 92% yield) indicates the potential application of the present chemistry in preparative-scale chemical synthesis.



Scheme 2. Scope of secondary amides. [a] Reactions were conducted on 0. mmol scale using 3.0 equiv of TEMPO, 3.3 equiv of $^{i}Pr_3SiOTf$ and 5.0 equi of pyridine at 0.3 M. Isolated yields.

Furthermore, this reaction was applied to the late-stag modification of several complex bioactive molecules containin secondary *N*-H amide (Scheme 3). To be specific, Ramelteor approved by the USA Food and Drug Administration (FDA) fc treatment of insomnia, furnished the transformation giving **2v** i 81% yield. Additionally, palmitoylethanolamide, featured wit regulating feeding and lipid metabolism and antiinflammator properties as endogenous amide, afforded the desired product **2w** i 79% yield. Moreover, **2x** bearing a steroid scaffold was prepared b this method in moderate yield with the hydroxyl group protected *i situ*. These results demonstrated that this protocol has potentia utilities in the late-stage modification of natural compounds an pharmaceuticals.



Scheme 3. Scope of complex secondary amides. [a] Reactions were conducted on 0.1 mmol scale using 3.0 equiv TEMPO, 4.4 equiv $^{i}Pr_3SiOTf$ and 5.0 equiv pyridine at 0.3 M. Isolated yields after chromatographic purification. [b]$^{i}Pr_3SiOTf$ (3.3 equiv). [c]TEMPO (4.0 equiv).

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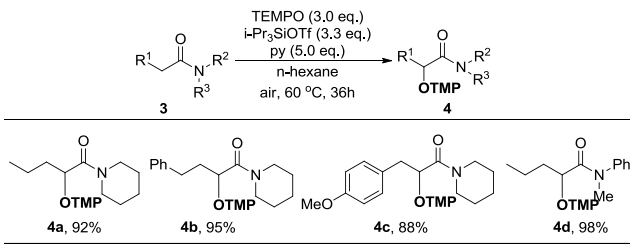
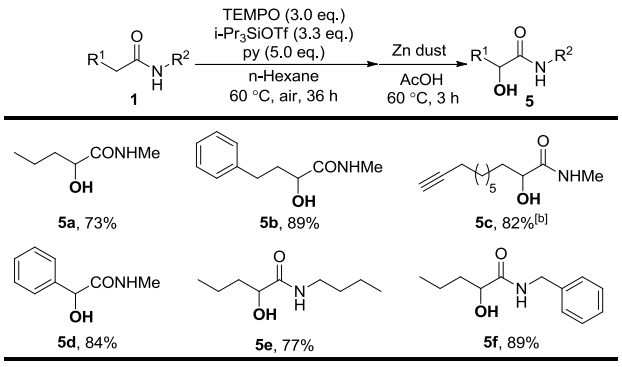
Encouraged by these results, we further investigated the reactivity of tertiary amides under these conditions (Scheme 4). Interestingly, *N*,*N*-disubstituted tertiary amides were significantly compatible in this protocol. Both alkyl (**3a**-**3c**) and aryl group (**3d**) substituted tertiary amides produced the desired α-oxyamination products **4** in excellent yields (88-98%). This protocol with different activation strategy would be a valuable complement to Maulide's Tf_2O-activation process.[10] Unfortunately, primary amides are not compatible in this reaction.



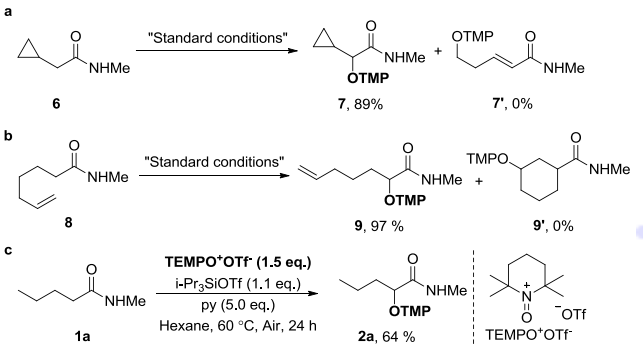
Scheme 4. Scope of tertiary amides. [a] Reactions were conducted on 0.3 mmol scale using 3.0 equiv of TEMPO, 3.3 equiv of $^{i}Pr_3SiOTf$ and 5.0 equiv of pyridine at 0.3 M. Isolated yields.

The α-hydroxy amide is an important skeleton in pharmaceuticals.[9] There is a great demand for synthesis of α-hydroxy *N*-H amides in an efficient and straightforward way. We therefore tried to prepare the α-hydroxy *N*-H amides from reduction of the α-OTMP amides. The α-hydroxy amides were produced in one-pot process from the corresponding simple secondary amides **1** (Scheme 5). α-Hydroxy amides **5** were easily prepared in good efficiencies by this one-pot reaction with the relay of α-oxyamination and the followed reductive workup using zinc dust, which provides a practical and general approach to α-hydroxy *N*-H amides. Alkyne substituent was tolerated in this simple reduction (**5c**, Scheme 5).



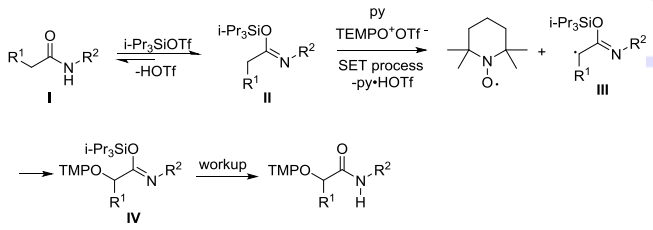
Scheme 5. One-pot synthesis of α-hydroxy amides from simple amides. [a] Reactions were conducted on 0.3 mmol scale using 3.0 equiv of TEMPO, 3.3 equiv of $^{i}Pr_3SiOTf$ and 5.0 equiv of pyridine at 0.3 M. Then add Zn (40 equiv), AcOH (2.0 mL), 60 °C, 3h. Determined by ^1H NMR analysis. [b]Zn (20 equiv), HCl in MeOH (1.5 M, 8.0 mL), 25 °C, 3h.

In order to probe the mechanism, some control experiments were designed and investigated (Scheme 6). In our previous studies, radical process was involved in TEMPO-mediated oxidation reactions.[16] As shown in Scheme **2a**, the reaction of **6** with TEMPO generated the cyclopropyl substituted α-oxyamination product **7** as the sole product in 89% yield under the standard conditions without detection of any ring-open product **7'**. Furthermore, compound **8** could not generate the ring-closed product **9'** (Scheme 6b). For these two cases, we believe that the generated carbon radical intermediates are very active and quickly couple with the excess amount of persisitant TEMPO radical. In addition, we assumed that the $TEMPO^+$ salt[17] generated *in situ* through the disproportionation reaction with $^{i}Pr_3SiOTf$, is more reactive and might be the key intermediate in this transformation. This hypothesis also reasonably explains the requirement of more than 2.0 equiv of TEMPO and $^{i}Pr_3SiOTf$ in this oxidative C-H bond oxyamination of the amides. Therefore, the $TEMPO^+$ OTf^- salt[18] **10** was prepared and used it in the control experiment with amide **1a** (Scheme 2c). To our delight, the target product **2a** could be obtained in 64% yield (Scheme 6c). Furthermore, after adding 1.1 equiv of $^{i}Pr_3SiOTf$ to a $CDCl_3$ solution of amide **1a**, the silicon enolate intermediate **Int-1a** was clearly detected by ^1H NMR analysis (Fig. S2, SI).



Scheme 6. Radical clock experiments and NMR study.

On the basis of the above experiments, a plausible mechanism was proposed (Scheme 7). The amide **I** is activated in the presence of $^{i}Pr_3SiOTf$, forming the imidate **II**. The imidate **II** is then oxidized immediately to radical **III** through single electron oxidation process by $TEMPO^+OTf^-$,[19] which is generated by disproportionation of TEMPO in the presence of $^{i}Pr_3SiOTf$. The process is so fast that radical clock reation can not caputure the radical intermediate. Then the radical coupling between the excess amount of persisitant TEMPO radical and carbon radical **III** affords intermediate **IV**. After workup, the desired product is generated.



Scheme 7. Proposed mechanism.

In summary, we described a novel flexible and chemoselective oxyamination of aliphatic amides. This oxidative approach significantly executes the selective functionalization of inert α-C-H bond with the complete survival of active N-H bond. The $^{i}Pr_3SiOTf$ is demonstrated an efficient activation reagent in the oxidative modification of simple amides. This transition-metal-free chemistry also provides an efficient approach to α-hydroxyl amides, which are significant scaffolds in pharmaceuticals and materials. The excellent scalability and good functional-group compatibility enable the further application of this protocol in chemical synthesis. We anticipate that these results could inspire the development of direct transformation of amides and acids.

Keywords: oxidations • synthetic methods •C-H functionalization • amides • • radical reactions

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Entry for the Table of Contents

Oxidation of Amides

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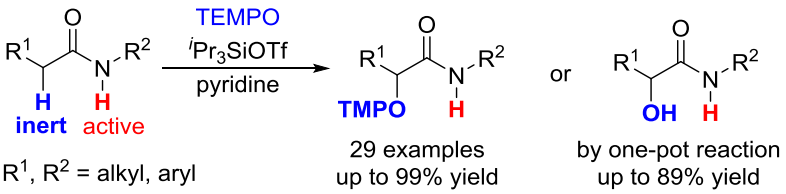
Selective α-Oxyamination and Hydroxylation of Aliphatic Amides



A general and efficient oxidative α-oxyamination of aliphatic amides including secondary N-H amides was developed. This transition-metal-free chemistry with high chemoselectivity provides an efficient approach to α-hydroxyl amides. This oxidative protocol significantly enables the selective functionalization of inert α-C-H bond with the complete preservation of active N-H bond.