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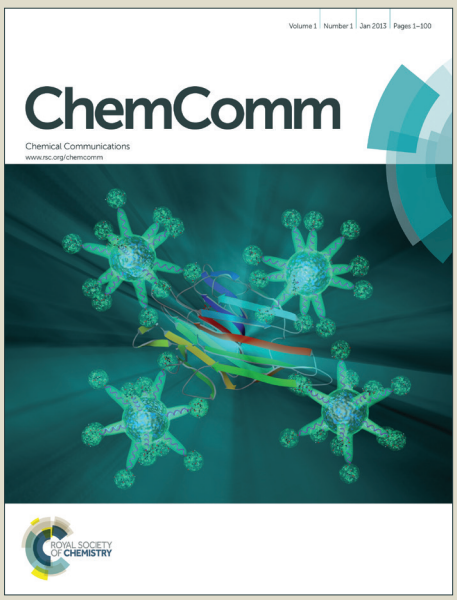

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Selective α-Amination and α-Acylation of Esters and Amides via Dual Reactivity of *O*-Acylhydroxylamines toward Zinc Enolates

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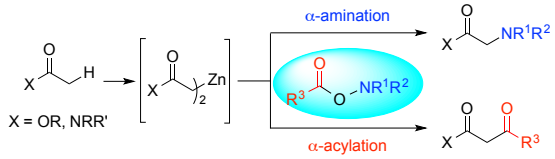
Selective α-amination and α-acylation of esters and amides have been developed; employing *O*-acylhydroxylamines as a dually reactive aminating and acylating reagent. Treatment of zinc enolates with *O*-acylhydroxylamines provides solely 1,3-dicarbonyl compounds under mild conditions. Introduction of a copper catalyst to the system shifts the reactivity entirely, yielding α-amination products exclusively.

Functionalization of carbonyl enolates represents one of the most general and efficient approaches to access biologically important α-functionalized carbonyl compounds. Toward this end, zinc enolates have received growing interests as valuable intermediates for carbonyl α-functionalization.[1] In comparison to commonly used carbonyl α-alkali and alkaline-earth enolates, they offer an ideal combination of good reactivity and tolerance toward many functional groups.[1] So far, zinc enolates have been successfully applied toward carbon-carbon bond formation with aldol additions to carbonyls,[2] nucelophilic additions to alkenes,[3] as well as a variety of transmetalation reactions such as α-arylations[1d, 4] and α-allylation.[5] However, the potential of zinc enolates remains underexplored for the synthesis of α-heteroatom substituted carbonyl molecules, such as α-amino carboxyl derivatives, one of the most biologically important carbonyl compounds.[6]

The direct installation of diverse amines at the carbonyl α-position has been a long-standing challenge in organic synthesis. The developed α-amination methods[7,8] often rely on the formation of α-hydrazinyl or α-oxy-amino products using highly reactive electrophilic aminating reagents[8] followed by reductive cleavage, and are therefore restricted to a narrow scope of substrates that must be compatible with the postreaction modifications and the installation of primary or secondary amines. To develop a more direct and general α-amination strategy,[9] we explored zinc enolates for the first time as a reactive intermediate toward electrophilic α-amination. We were interested in *O*-acylhydroxylamines as an electrophilic nitrogen source, inspired by the pioneering work on electrophilic aminations between organometallic reagents and *O*-acylhydroxylamines.[10,11] Simultaneously, we envisioned that *O*-acylhydroxylamines could also act as an electrophilic acylating agent[12] toward zinc enolates and lead to the alternative formation of 1,3-dicarbonyl compounds. Such dual reactivity of *O*-acylhydroxylamines is valuble and useful, providing a powerful and divergent strategy for direct and selective access to α-amino carbonyl and 1,3-dicarbonyl compounds, highly desirable motifs in organic synthesis and pharmaceuticals.[6, 13]



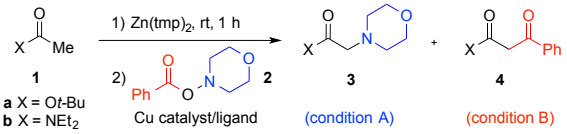
Scheme 1. Selective α-Amination and α-Acylation via the Dual Reactivity of *O*-Acylhydroxylamines

This paper reports our studies on zinc enolates of esters and amides for the development of selective α-amination and α-acylation reactions using *O*-acylhydroxylamines as either an aminating or acylating agent (Scheme 1). The developed amination conditions bypass the requirement for postreaction amine modification and overcome the limitation of a narrow amine scope in previous α-amination conditions. It provided the first example of electrophilic amination of zinc enolates for the direct installation of different amines at the carbonyl α-position in a one-step reaction. Such a direct and operationally convenient amination procedure represents a valued advance for the synthesis of α-amino carbonyl compounds. We also identified that acylation effectively occurred upon the treatment of these zinc enolates with *O*-acylhydroxylamines alone at elevated temperatures where *O*-acylhydroxylamines act as an acylating agent exclusively. Such an alternative α-acylation reaction provides an exceptionally simple entry to important 1,3-dicarbonyl compounds.[13] Collectively, these studies on the dual electrophilic reactivity of *O*-acylhydroxylamines provide further insight on their potential to develop selective and complementary amination and acylation reactions on a broader range of C–H bonds.

Our study started from the reaction of ester **1a** and *O*-acylhydroxylamine **2** as model substrates (Table 1). The generation of the nucleophilic zinc enolate was achieved by the treatment of ester **1a** with $Zn(tmp)_2$ solution.[14] Excitingly, we found that acylated product **4a** was formed in 58% yield when **2** was directly treated

with the zinc enolate of ester **1a** at room temperature for an extended period of time (24 h). At 60 °C, this α-acylation reaction proceeded more rapidly, providing **4a** in 82% yield within 3 h. On the other hand, when CuCl was applied as catalyst, the amination reaction occurred smoothly at room temperature and provided the aminated product **3a** in 81% yield in 1.5 h (entry 3). As a ligand, 1,10-phenanthroline resulted in the lower yield of **3a** in the amination reaction while 2,2'-bipyridine provided a quantitative formation of **3a** (entries 3 and 4). Thus, we subsequently looked into different copper sources in the amination reaction of ester **1a** with 2,2'-bipyridine as the ligand (entries 5–9). In comparison to CuCl, CuCN, CuOTf•tol and $Cu(OAc)_2$ were inferior while $Cu(acac)_2$ and $CuCl_2$ provided comparable efficacy. However, we immediately found that CuCl and $Cu(acac)_2$ were not applicable to the amination of amide substrates such as **1b** (entries 10 and 11). Encouragingly, the system of $CuCl_2$/bipyr was effective and afforded the desired **3b** in 53% yield (entry 12).

Table 1. Condition Optimization for Electrophilic Amination of Ester **1a** and Amide **1b** with *N*-(Benzoyloxy)morpholine **2**[a]

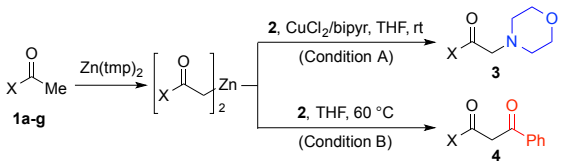


entry	1	catalyst	ligand	time (h)[b]	3 (yield)[c]	4 (yield)[c]
1	**1a**	-	-	24	-	**4a** (58%)
2[d]	**1a**	-	-	3	-	**4a** (82%)
3	**1a**	CuCl	-	1.5	**3a** (81%)	-
4	**1a**	CuCl	phen	24	**3a** (36%)	-
5	**1a**	CuCl	bipyr	1	**3a** (99%)	-
6	**1a**	CuCN	bipyr	24	**3a** (53%)	-
7	**1a**	CuOTf•tol	bipyr	1	**3a** (35%)	-
8	**1a**	$Cu(OAc)_2$	bipyr	24	**3a** (55%)	-
9	**1a**	$Cu(acac)_2$	bipyr	24	**3a** (85%)	-
10	**1a**	$CuCl_2$	bipyr	1	**3a** (99%)	-
11	**1b**	CuCl	bipyr	1	**3b** (6%)	-
12	**1b**	$CuCl_2$	bipyr	1	**3b** (53%)	-

[a]Reactions conducted in a 0.2–0.3 mmol scale: **1** (2.1 equiv), $Zn(tmp)_2$ (1.0 equiv); **2** (1.0 equiv); Cu catalyst (5 mol%), ligand (10 mol%), THF. [b]Time required for the complete consumption of **2**. [c]Determined by ^1H NMR spectroscopy with CH_2Br_2 as a quantitative internal standard. [d]Step 2 run at 60 °C. Phen = 1,10-phenanthroline. Bipyr = 2,2'-bipyridine.

With conditions identified for α-amination (condition A) and acylation (condition B), we next examined the generality of these two transformations on a variety of zinc enolate derivatives using hydroxylamine **2** (Table 2). For the amination reactions of different ester derivatives, *iso*-propyl acetate **1c** and ethyl acetate **1d**, both provided the desired α-amino esters **3c–d** in excellent yields (entries 3 and 4). Likewise, the amination of different cyclic and acyclic amides all effectively formed the aminated products **3e–g** (entries 5–7).[8a,15] However, the current conditions were ineffective for α-substituted esters and amides, (e.g. methyl phenylacetate and *N,N*-diethylpropionamide) presumably due to their preferential formation of *O*-zinc enolates rather than the desired *C*-zincates,[2b, 13b] which impedes an effective transmetalation with the copper catalyst. Meanwhile, we investigated the α-acylation reaction of these carbonyl substrates **1a–g** using hydroxylamine **2** in the absence of a copper catalyst. In all cases, the exclusive formation of 1,3-dicarbonyl products was observed. Once again, zinc enolates derived from α-substituted esters and amides were found unreactive toward acylation, suggesting the steric hindrance significantly reduces their nucleophilicity. Despite current limitations, the α-amination and α-acylation transformations nevertheless offer a rapid, efficient and complementary approach to prepare simple α-functionalized esters and amides, especially compared to the traditional α-halogenation/nucleophilic amination approach.

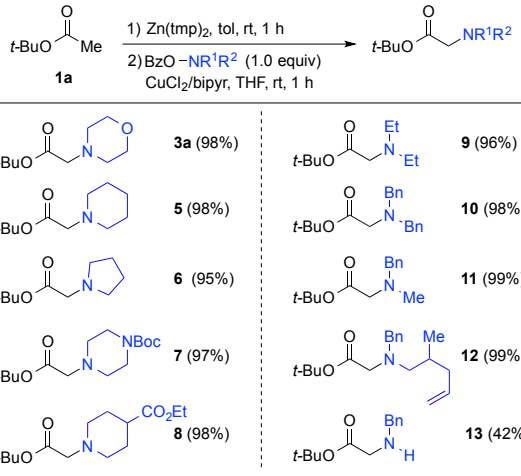
Table 2. Selective α-Amination and α-Acylation of Carbonyl Compound **1** Using *O*-Acylhydroxylamine **2**[a]



entry	carbonyl substrate **1**		3 (yield)[b]	4 (yield)[b]
1	*t*-BuO, Me	**1a**	**3a** (98%)	**4a** (82%)
2	Et_2N, Me	**1b**	**3b** (53%)	**4b** (61%)
3	*i*-PrO, Me	**1c**	**3c** (94%)	**4c** (90%)
4	EtO, Me	**1d**	**3d** (90%)	**4d** (87%)
5	Me, N, Me	**1e**	**3e** (95%)	**4e** (71%)
6	BocN, Me	**1f**	**3f** (70%)	**4f** (75%)
7	Ph, N, Me, Me	**1g**	**3g** (51%)	**4g** (68%)

[a]Reactions conducted on a 0.2 mmol scale: **1** (2.1 equiv), $Zn(tmp)_2$ (1.0 equiv); Condition A: **2** (1.0 equiv), $CuCl_2$ (5 mol%), bipyr (10 mol%), THF, rt. Condition B: **2** (1.0 equiv), THF, 60 °C. [b]Isolated yields.

Table 3. Copper-Catalyzed Electrophilic α-Amination of **1a** with Various *O*-Acylhydroxylamines[a]

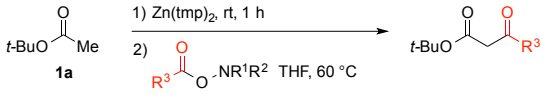


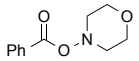
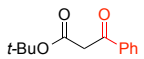
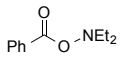
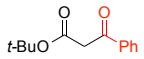
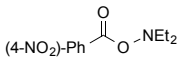
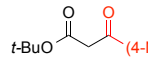
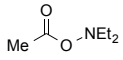
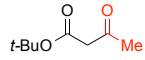
[a]Results as aminated products in isolated yield. Reactions conducted on a 0.2 mmol scale: **1a** (2.1 equiv), $Zn(tmp)_2$ (1.0 equiv), *O*-acylhydroxylamine (1.0 equiv), $CuCl_2$ (5 mol%), bipyr (10 mol%).

Next we surveyed the amine scope of the α-amination transformation using model substrate ester **1a** with a variety of hydroxylamines derived from simple amines (Table 3). The catalytic system of $CuCl_2$/bipyr was applicable for introducing different cyclic amines, such as piperidines, pyrolidine, and piperazine (**5–8**). The amination of acyclic hydroxylamines also proceeded efficiently with derivatives containing *N*,*N*-diethyl, *N*,*N*-dibenzyl, and *N*-benzyl-*N*-methyl groups (**9–12**). Note that the benzyl moiety can be a useful synthetic handle for further manipulations after the selective deprotection. Indeed, the secondary amine product **13** was also able to form directly from the amination reaction. The results with these hydroxylamines also demonstrate that the amination conditions are compatiblility with diverse functionalities including carbamate, ester, and olefin. On the mechanistic side, the formation of the aminated product **12** in a quantative yield suggested that no aminyl radical intermediates were involved in the amination pathway.[16]

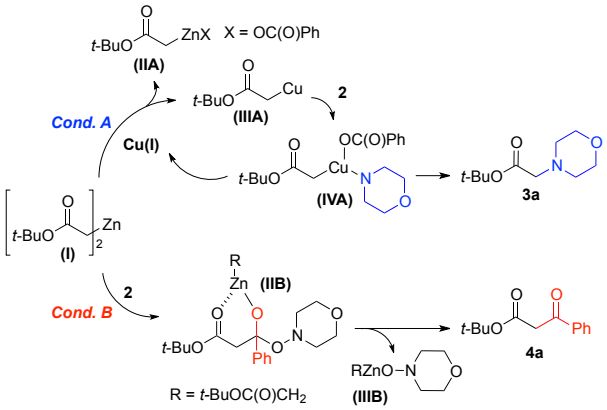
Concurrently, we briefly examined the utility of the acylation using different *O*-acylated hydroxylamines for the synthesis of 1, 3-dicarbonyl compounds (Table 4). With model substrate ester **1a**, all reactions provided the desired 1,3-dicarbonyl products in good yields (61–92%, entries 1–4). These results also suggest that the efficiency of the acylation reaction is independent of the amine moiety (entries 1–2).

Table 4. α-Acylation of **1** with *O*-Acylhydroxylamines **2**[a]



entry	*O*-acylated hydroxylamine	acylated product (yield)[b]
1		 **4a** (82%)
2		 **4a** (81%)
3		 **14** (92%)
4		 **15** (61%)

[a]Reactions conducted on a 0.2 mmol scale: **1a** (2.1 equiv), $Zn(tmp)_2$ (1.0 equiv), rt, 1 h; *O*-acylhydroxylamine (1.0 equiv), THF, 60 °C. [b]Isolated yields.



Scheme 2. Reaction Pathways for Amination and Acylation of Zinc Enolate with *O*-Acylhydroxylamine **2**

Based on our results, a plausible reaction mechanism is proposed in Scheme 2 for the observed dual reactivity of *O*-acylhydroxylamines (e.g. **2**) toward zinc enolate **(I)** in the amination and acylation of ester **1a**. When a copper catalyst is present (condition A), the transmetalation between the copper and zinc enolate **(I)** occurs and the resulting intermediate (**IIIA**) subsequently undergoes oxidative addition of hydroxylamine **2**. Finally, the reactive copper complex (**IVA**) would readily undergo reductive elimination to afford the aminated product **3a** and regenerate the copper catalyst.[17] On the other hand, in the absence of a copper catalyst (condition B), the nucleophilic zinc enolate (**I**) would preferably attack the electrophilic carbonyl group of **2**, possibly via an intermediate (**IIB**), and selectively afford the acylated product **4**.

Conclusions

In summary, this paper describes the development of selective α-amination and α-acylation of simple carbonyl compounds on the basis of the dual reactivity of *O*-acylhydroxylamines. α-Amination of esters and amides has been achieved by a copper-catalyzed eletrophilic amination of their zinc enolates using *O*-acylhydroxylamines. In the absence of a copper catalyst, the direct treatment of zinc enolates with *O*-acylhydroxylamines exclusively formed α-acylated 1,3-dicarbonyl products. These interesting results also provide insight into exploring the dual electrophilic reactivity of *O*-acylhydroxylamines for selective amination and acylation reactions of other C–H bonds. Currently, studies toward α-amination of substituted carbonyl compounds are underway.

Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details and characterization data for new compounds. See DOI: 10.1039/c000000x/

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