Chapter 2
Selective α-Amination and α-Acylation of Esters and Amides via Dual Reactivity of O-Acylhydroxylamines Toward Zinc Enolates

2.1 α-Functionalization of Esters and Amides

α-Amino carbonyl and 1,3-dicarbonyl compounds are highly desirable motifs in organic synthesis and are present in many pharmaceutically and biologically relevant molecules [1–3]. α-Amino carbonyl compounds are of particular importance because of their presence in α-amino acids and derivatives, as well as α-amino aldehydes and α-amino alcohols. For example, Plavix is an antiplatelet drug used to inhibit blood clots and to prevent heart attack and stroke in people who are at high risk of these events (Fig. 2.1), and in 2010, it was the second-most prescribed drug in the world [4]. Valaciclovir, another example of an α-amino carbonyl, is an antiviral drug used in the management of herpes—shingles and cold sores [5]. Aspartame is used as an artificial sweetener in some food and beverages. As for 1,3-dicarbonyl compounds, they are often used as building blocks for the synthesis of drugs [6]. Therefore, it is important to be able to access these motifs. Functionalization of carbonyl enolates represents one of the most general and efficient approaches to access these biologically important α-functionalized carbonyl compounds.

2.1.1 α-Amination of Carbonyl Compounds

The ubiquity of nitrogen-containing compounds among functionally and biologically important molecules continues to drive the development of new C–N bond-forming transformations [7]. The formation of α-amino carbonyl compounds


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is of particular importance because of their presence in α-amino acids, α-amino aldehydes, and α-amino alcohols. However, the direct installation of diverse amines at the carbonyl α-position has been a long-standing challenge in organic synthesis [8–13]. Umpolung electrophilic aminations have received significant attention as an alternative and complementary strategy to traditional nucleophilic aminations for C–N bond formation [14–16]. Electrophilic amination of α-carbanions represents one of the most general and important methods for the synthesis of α-amino carbonyl compounds [10–12]. Towards this, a variety of electrophilic nitrogen-transfer reagents have been developed for the amination of enolates and enamines (Fig. 2.2). Electrophilic aminating reagents used for the preparation of α-aminocarbonyl compounds include diazene dicarboxylates [17–30], azides [31], nitroso compounds [32–38], oxaziridines [39], O-diarylphosphinyl hydroxylamine [40], N-halo amines [41, 42], and O-acylhydroxylamines [43].

Fig. 2.1 Selected examples of biologically important α-amino carbonyls

![Fig. 2.1 Selected examples of biologically important α-amino carbonyls](image)

Fig. 2.2 Electrophilic aminating reagents for amination of carbonyls compounds

![Fig. 2.2 Electrophilic aminating reagents for amination of carbonyls compounds](image)
2.1.1.1 Electrophilic α-Aminations of Carbonyl Compounds via Sp$^2$ N-Containing Reagents

Early electrophilic α-aminations of carbonyl compounds often utilized [NR$_2$]$^+$ synthons containing an sp$^2$ nitrogen. Many of these reactions exploited the use of diazene dicarboxylates for the amination of enolates because they are both stable and commercially available. The use of diazene dicarboxylates for electrophilic α-amination was first reported for achiral enolates of diethyl malonates [44], acetylacetone and ethyl acetoacetate [45], and cyclohexanone-derived enolates [46]. They have since been used in several asymmetric α-aminations (Scheme 2.1) [17–22]. Evans and co-workers used a chiral magnesium sulphonamide complex to generate chiral enolate derivatives of N-acyloxazolidinones (Scheme 2.1a) [22].

![Scheme 2.1](image)

Scheme 2.1 Direct asymmetric catalytic α-amination of carbonyl derivatives using diazene dicarboxylates
Their amination procedure is applicable to a variety of aryl-substituted imides, and the \( \alpha \)-amino compounds were obtained in good yield. Jørgensen and co-workers reported the catalytic asymmetric direct \( \alpha \)-amination of 2-keto esters with modest yields (Scheme 2.1b) \([17, 18]\). List \([19]\) and Jørgensen \([20, 21]\) independently reported asymmetric \( \alpha \)-aminations of carbonyl compounds via enamine derivatives prepared using \( L \)-proline (Schemes 2.1c, d). In their respective reactions, good to high yields were obtained. For all of these asymmetric \( \alpha \)-aminations, the chiral enolate or enamine derivatives were generated catalytically, and high enantioselectivities were observed in each transformation \([17–22]\).

Organic azides and nitroso compounds have also been used for the electrophilic \( \alpha \)-amination of carbonyls. Because azides can also function as diazo transfer agents \([47]\), their use for the amination of enolates has been limited \([31]\). Nitroso compounds, on the other hand, have been used for \( N \)-selective nitroso aldol reactions \([32–38]\). Read de Alaniz and co-workers recently reported the copper-catalyzed \( N \)-selective nitroso aldol reaction of nitrosoformates (Scheme 2.2) \([36]\). The nitrosoformates are produced by the in situ oxidation of \( N \)-hydroxycarbamate precursors. The reaction proceeded with good yield; however, it was limited to the construction of primary and secondary amines. Moreover, relatively harsh conditions are required for the cleavage of the resultant \( N \)–\( O \) bond of the aminated products.

### 2.1.1.2 Electrophilic \( \alpha \)-Aminations of Carbonyl Compounds via \( \text{sp}^3 \) \( N \)-Containing Reagents

In addition to \( \text{sp}^2 \) \( N \)-containing reagents, several \( \text{sp}^3 \) \( N \)-containing compounds have been developed for the electrophilic amination of \( \alpha \)-carbanions \([39–43]\). Collet and

![Scheme 2.2 Copper-catalyzed \( N \)-selective nitrosoformate aldol reaction](image-url)
Co-workers reported the synthesis of a series of N-protected oxaziridines and their use as electrophilic aminating reagents [39]. These oxaziridines reacted readily with a propiophenone lithium enolate to afford the racemic α-N-Boc amino compound in modest yield (Scheme 2.3). They also observed a parallel aldol condensation between the released aldehyde from the oxaziridine and enolate. Additionally, amide and ester enolates similarly afforded α-N-Boc amino compounds.

Direct amination of carbanions has also been reported using a variety of hydroxylamines as electrophilic [NH₂]+ equivalents [14], including O-diarylphosphinyl hydroxylamines [40]. With this in mind, Vedejs and co-workers reported enolate amination using O-diarylphosphinyl hydroxylamines as the nitrogen source (Scheme 2.4). Amination proceeded efficiently with stabilized sodium or potassium enolates derived from malonates, phenylacetates, and phenylacetonitriles. Amination yields varied from moderate to excellent depending on the enolate and O-diarylphosphinyl hydroxylamine used for the reaction. The highly stabilized sodium and potassium enolates gave the best results, while the more basic phenylacetate and phenylacetonitrile anions also gave good yields. However, like other methods using sp² N-containing reagents, the use of oxaziridines and O-diarylphosphinyl hydroxylamines is limited to the construction of primary and secondary amines.

Scheme 2.3 Electrophilic amination of lithium enolates via oxaziridines

Scheme 2.4 Electrophilic amination of stabilized carbanions using O-diarylphosphinyl hydroxylamines
Recently, introducing tertiary amines at the $\alpha$-position of esters has been successfully achieved by electrophilic amination of silyl ketene acetals using either $N$-chloramines or $O$-benzoylhydroxylamines \[41, 43\]. Previously, $N$-chloramines had been used to introduce an amino group at the $\alpha$-position of carbonyls via their corresponding lithium enolates \[42, 48, 49\]. However the substrate scope is limited due to the strongly basic reaction conditions as well as the competing chlorination reaction. To overcome this, the Murakami group developed a copper-catalyzed electrophilic amination of silyl ketene acetals using $N$-chloramines (Scheme 2.5) \[41\]. Their mild reaction conditions readily afforded the corresponding $\alpha$-amino esters in good to moderate yields. A variety of $N$-chloramines, cyclic and acyclic, worked well; however silyl ketene acetals were limited to benzyl methyl esters.

Simultaneously, Miura and co-workers developed a copper-catalyzed electrophilic amination of silyl ketene acetals using $O$-acylhydroxylamines as the electrophilic nitrogen source (Scheme 2.6) \[43\]. Various silyl ketene acetals underwent amination with $O$-benzoyl-$N,N$-dibenzylhydroxylamine to give the corresponding $\alpha$-amino esters. In addition to $O$-benzoyl-$N,N$-dibenzylhydroxylamine, other acyclic and cyclic $O$-benzoylhydroxylamines participated in the reaction. However, reaction conditions must be varied depending on the electronic and steric nature of different substrates, and in some cases only moderate yields were obtained. Additionally, both amination methods are efficient for ester precursors of silyl ketene acetals, but are not suitable for other carbonyl compounds (e.g., amides) \[50, 51\]. Therefore, a general and direct $\alpha$-amination method is highly desirable.

**Scheme 2.5** Copper-catalyzed electrophilic amination of silyl ketene acetals via $N$-chloramines
2.1.2 α-Acylation of Carbonyl Compounds

1,3-Dicarbonyl compounds constitute one of the most important classes of organic compounds as they are widely used as building blocks in organic synthesis and exhibit interesting biological properties [52]. They are traditionally synthesized by the Claisen condensation, either through a classic Claisen with two enolizable esters or crossed Claisen with an enolizable ester or ketone and nonenolizable ester (Scheme 2.7a) [53]. In addition to the Claisen condensation, the Blaise reaction also

Scheme 2.6 Copper-catalyzed electrophilic amination of silyl ketene acetals via O-benzoylhydroxylamines
allows for the synthesis of β-keto esters via the zinc-mediated reaction of nitriles with α-haloesters (Scheme 2.7b) [54].

### 2.1.3 Zinc Enolates for α-Functionalization of Carbonyl Compounds

Zinc enolates have received growing interest as valuable intermediates for carbonyl α-functionalization [55–73]. 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 [55–59]. So far, zinc enolates have been successfully applied toward carbon–carbon bond formation with aldol additions to carbonyls [68, 69], nucleophilic additions to alkenes [70, 71], as well as a variety of transmetallation reactions such as α-arylation [55, 56, 60–67] and α-allylation [72, 73]. 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 [1, 2].

### 2.2 Results and Discussion

To develop a more direct and general α-amination strategy [40, 41, 43], we explored zinc enolates for the first time as a reactive intermediate toward electrophilic α-amination because of their good reactivity and tolerance toward many functional groups. 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 [74–87]. Simultaneously, we envisioned that various O-acylhydroxylamines could also act as an electrophilic acylating agent [77, 78, 80] toward zinc enolates and lead to the alternative formation of 1,3-dicarbonyl compounds. Such dual reactivity of O-acylhydroxylamines is valuable 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 [1, 2].

#### 2.2.1 Electrophilic Amination and Acylation of Esters and Amides via Zinc Enolates

The initial goal of this project was to develop an electrophilic α-amination of zinc enolates of esters and amides using O-acylhydroxylamines as our electrophilic
nitrogen source. During our studies, we found that the $O$-acylhydroxylamines could be used as either an aminating or acylating agent for selective $\alpha$-amination and $\alpha$-acylation reactions (Scheme 2.8). The developed amination conditions bypass the requirement for postreaction amine modification, such as the reduction of nitrogen-heteroatom bonds for aminations using $sp^2$ electrophilic nitrogen sources. Additionally, they overcome the limitation of a narrow amine scope under previous $\alpha$-amination conditions. It provided the first example of electrophilic amination of zinc enolates for the direct installation of different amines at the carbonyl $\alpha$-position in a one-step reaction. Such a direct and operationally convenient amination procedure represents a valuable advance in the synthesis of $\alpha$-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 $\alpha$-acylation reaction provides an exceptionally simple entry to important 1,3-dicarbonyl compounds [3]. Collectively, these studies on the dual electrophilic reactivity of $O$-acylhydroxylamines provide further insight into their potential for developing selective and complementary amination and acylation reactions in a broader range of C–H bonds.

### 2.2.2 Initial Amination Studies Using the Reformatsky Reagent

The Reformatsky enolate was first reported by Sergey Reformatsky in the late 1800s for condensation with aldehydes and ketones to give $\beta$-hydroxy esters [88, 89]. The organozinc reagent is easily prepared by treating $\alpha$-halo esters with zinc (Scheme 2.9) and is less nucleophilic than lithium enolates or Grignard reagents.
With this we chose to start the development of our α-amination method using Reformatsky enolate 2.

Initial experiments screened Reformatsky enolate 2 and O-benzoylhydroxylamine 3 in the presence of CuCl and carbene ligands (Table 2.1). Using ICy-BF$_4$ as the ligand, α-amino ester 4 was observed in 13% (entry 1). Minor amination was observed using IMes-HCl and iPr (entries 3 and 4), while no amination was observed for SIMes-HBF$_4$ or iPr-HCl (entries 2 and 5). It should be noted that 13% amination was observed when pre-formed catalyst [(iPr)CuCl] was used for the reaction. With these exciting results, ICy-BF$_4$ was used as the ligand for further screening and reaction optimization.

After identifying ICy-BF$_4$ as our best ligand, we screened copper sources for the reaction (Table 2.2). In comparison to CuCl, CuCN and Cu(OTf)$_2$ were inferior (entries 2 and 3). On the other hand, CuBr, CuI, and Cu(acac)$_2$ gave increased amination yields with CuBr giving the best amination yields at 23% (entries 4–6). With this, CuBr was chosen as catalyst along with ICy-BF$_4$ as ligand for further reaction optimization.

Finally we finished reaction optimization by investigating the effect of the nucleophile, base, solvent, and reactant equivalence (Table 2.3). For the nucleophile effect we looked into two different ways of making the Reformatsky enolate. The Reformatsky enolate can either be prepared by treating the α-halo ester with zinc dust or by deprotonation of the ester with LDA followed by quenching with either ZnCl$_2$ or ZnBr$_2$. For the first method, amination was achieved in 23% (entry 1); however for the second method, β-keto ester 6 was the only product detected (entries 2 and 3). We believe this is due to the presence of excess lithium from n-BuLi, which can coordinate with the carbonyl of the O-acylhydroxylamine therefore increasing

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**Table 2.1 Carbene ligand screen for the amination of Reformatsky enolate $2^a$**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Time (h)$^b$</th>
<th>Yield (%)$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ICy-BF$_4$</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>SIMes-HBF$_4$</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>IMes-HCl</td>
<td>2</td>
<td>Trace</td>
</tr>
<tr>
<td>4</td>
<td>iPr</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5$^d$</td>
<td>iPr-HCl</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

$^a$Reactions conducted on a 0.2–0.3 mmol scale  
$^b$Time required for the complete consumption of 3  
$^c$Yields determined by $^1$H NMR spectroscopy with CH$_2$Br$_2$ as a quantitative internal standard  
$^d$Reaction with pre-formed catalyst [(iPr)CuCl] gave 13% amination
reactivity at the carbonyl carbon. We next looked at the cation effect for the different tert-butoxide bases. As the metal cation increased in size, the amination amount decreased (entries 4 and 5). As for solvents, MeCN gave comparable results to THF, while toluene gave a mixture of amination and β-keto ester 6 (entries 7 and 8). Amination increased slightly when DCM was used (entry 9). Finally, we looked into the effects of nucleophile and electrophile equivalence as well as catalyst and ligand loading. To this point, we had only been using a slight excess of 2. When the equivalence of 2 was increased to 2.0, the overall yield of the reaction doubled (entry 10). Conversely, when Reformatsky enolate 2 was used as the limiting reagent, the yield decreased slightly (entry 11). Lastly, we lowered the catalyst and ligand loading and observed comparable yields for the reaction (entry 12).

2.2.3 Amination Studies Using Zn(tmp)2 for Zinc Enolate Formation

With promising results using the Reformatsky enolate, we wanted to look into the analogous and more reactive bis zinc enolate. Our study started from the amination reaction of ester 7 and O-benzoylhydroxylamine 3 as model substrates (Table 2.4). The generation of the nucleophilic zinc enolate was achieved by the treatment of ester 7 with Zn(tmp)2 solution [55, 56]. In the initial examination of transition metal catalysts, CuCl was found effective to readily promote the desired amination reaction at room temperature, and the aminated product 4 was formed in 81% yield in 1.5 h (entry 1). Without a copper catalyst, no reaction occurred between zinc

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**Table 2.2 Copper catalyst screen for the amination of Reformatsky enolate 2a**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Time (h)b</th>
<th>4 (%)c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuCl</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>CuCN</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Cu(OTf)2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>CuBr</td>
<td>2</td>
<td>23</td>
</tr>
<tr>
<td>5</td>
<td>CuI</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>Cu(acac)2</td>
<td>2</td>
<td>17</td>
</tr>
</tbody>
</table>

aReactions conducted on a 0.2–0.3 mmol scale
bTime required for the complete consumption of 3
cYields determined by 1H NMR spectroscopy with CH2Br2 as a quantitative internal standard
enolate of 7 and O-benzoylhydroxylamine 3 (entry 2). Next we evaluated the effect of ligands. The addition of 1,10-phenanthroline resulted in decreased yield of 4 while 2,2'-bipyridine provided quantitative yield of 4 (entries 3 and 4). We then screened the equivalence of O-benzoylhydroxylamine 3. Comparable yields were

<table>
<thead>
<tr>
<th>Entry</th>
<th>Enolate (equiv)</th>
<th>Base (equiv)</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Temp (°C)</th>
<th>4 (%)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>6 (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 (1.1)</td>
<td>LiO&lt;sub&gt;t&lt;/sub&gt;-Bu (1.1)</td>
<td>THF</td>
<td>2</td>
<td>60</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>2&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2 (1.1)</td>
<td>LiO&lt;sub&gt;t&lt;/sub&gt;-Bu (1.1)</td>
<td>THF</td>
<td>2</td>
<td>60</td>
<td>0</td>
<td>28</td>
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<tr>
<td>3&lt;sup&gt;e&lt;/sup&gt;</td>
<td>5 (1.1)</td>
<td>LiO&lt;sub&gt;t&lt;/sub&gt;-Bu (1.1)</td>
<td>THF</td>
<td>2</td>
<td>60</td>
<td>0</td>
<td>38</td>
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<tr>
<td>4</td>
<td>2 (1.1)</td>
<td>NaO&lt;sub&gt;t&lt;/sub&gt;-Bu (1.1)</td>
<td>THF</td>
<td>2.5</td>
<td>60</td>
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<td>0</td>
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<td>60</td>
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<td>0</td>
</tr>
<tr>
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<td>THF</td>
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<td>rt</td>
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<td>0</td>
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<td>7</td>
<td>2 (1.1)</td>
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<td>MeCN</td>
<td>4</td>
<td>rt</td>
<td>11</td>
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<td>8</td>
<td>2 (1.1)</td>
<td>LiO&lt;sub&gt;t&lt;/sub&gt;-Bu (1.1)</td>
<td>tol</td>
<td>2</td>
<td>rt</td>
<td>8</td>
<td>13</td>
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<td>9</td>
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<td>10</td>
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<td>12&lt;sup&gt;f&lt;/sup&gt;</td>
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<td>DCM</td>
<td>2</td>
<td>rt</td>
<td>49</td>
<td>0</td>
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</tbody>
</table>

<sup>a</sup>Reactions conducted on a 0.2–0.3 mmol scale

<sup>b</sup>Time required for the complete consumption of 3

<sup>c</sup>Yields determined by <sup>1</sup>H NMR spectroscopy with CH<sub>2</sub>Br<sub>2</sub> as a quantitative internal standard

<sup>d</sup>2 was made by deprotonation of tert-butyl acetate with LDA then quenching the reaction with ZnBr<sub>2</sub>

<sup>e</sup>5 was made by deprotonation of tert-butyl acetate with LDA then quenching the reaction with ZnCl<sub>2</sub>

<sup>f</sup>Reaction run using 5 mol% of CuBr and 5 mol% of ICy·BF<sub>4</sub>
observed when either 1.0 or 1.5 equivalents of 3 were used in the reaction; however when the equivalents of 3 was increased to 2.0, the yield of 4 decreased (entries 5–7). While screening amination conditions for 7, we simultaneously screened amide 8. We immediately found that the above conditions were not applicable to the amination of amide 8 (entry 8). Thus, we then looked into different copper sources. CuCN, [CuOTf]2-tol and Cu(OAc)2 were inferior to CuCl in the reaction of ester 1 while Cu(acac)2 and CuCl2 provided comparable efficacy (entries 9–14). Most encouragingly, the system of CuCl2 and bipyr was also effective for the amide

![Diagram of amination reaction](image)

**Table 2.4** Condition optimization for electrophilic amination of ester 7a and amide 7b with O-benzyloxyhydroxylamine 3a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Carbonyl</th>
<th>3 (equiv)</th>
<th>Catalyst</th>
<th>Ligand</th>
<th>Time (h)b</th>
<th>Results%c</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>1.0</td>
<td>CuCl</td>
<td>–</td>
<td>1.5</td>
<td>4 (81 %)</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>1.0</td>
<td>–</td>
<td>–</td>
<td>1.5</td>
<td>4 (0 %)</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>1.0</td>
<td>CuCl</td>
<td>phen</td>
<td>24</td>
<td>4 (36 %)</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>1.0</td>
<td>CuCl</td>
<td>bipyr</td>
<td>1.0</td>
<td>4 (99 %)</td>
</tr>
<tr>
<td>5</td>
<td>7</td>
<td>0.5</td>
<td>CuCl</td>
<td>bipyr</td>
<td>1.0</td>
<td>4 (98 %)</td>
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<tr>
<td>6</td>
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<td>1.5</td>
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<td>bipyr</td>
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<td>9 (6 %)</td>
</tr>
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<td>7</td>
<td>1.0</td>
<td>Cu(OTf)2</td>
<td>bipyr</td>
<td>1.0</td>
<td>4 (36 %)</td>
</tr>
<tr>
<td>12</td>
<td>7</td>
<td>1.0</td>
<td>Cu(acac)2</td>
<td>bipyr</td>
<td>1.0</td>
<td>4 (85 %)</td>
</tr>
<tr>
<td>13</td>
<td>7</td>
<td>1.0</td>
<td>Cu(OAc)2</td>
<td>bipyr</td>
<td>1.0</td>
<td>4 (55 %)</td>
</tr>
<tr>
<td>14</td>
<td>7</td>
<td>1.0</td>
<td>CuCl2</td>
<td>bipyr</td>
<td>1.0</td>
<td>4 (99 %)</td>
</tr>
<tr>
<td>15d</td>
<td>7</td>
<td>1.0</td>
<td>CuCl2</td>
<td>bipyr</td>
<td>1.0</td>
<td>4 (99 %)</td>
</tr>
<tr>
<td>16</td>
<td>8</td>
<td>1.0</td>
<td>CuCl2</td>
<td>bipyr</td>
<td>1.0</td>
<td>9 (53 %)</td>
</tr>
<tr>
<td>17</td>
<td>8</td>
<td>1.0</td>
<td>Cu(OTf)2</td>
<td>bipyr</td>
<td>1.0</td>
<td>9 (0 %)</td>
</tr>
<tr>
<td>18</td>
<td>8</td>
<td>1.0</td>
<td>Cu(acac)2</td>
<td>bipyr</td>
<td>1.0</td>
<td>9 (15 %)</td>
</tr>
<tr>
<td>19</td>
<td>8</td>
<td>1.0</td>
<td>Cu(OAc)2</td>
<td>bipyr</td>
<td>1.0</td>
<td>9 (0 %)</td>
</tr>
</tbody>
</table>

aReactions conducted on a 0.2–0.3 mmol scale. 7 or 8 (2.1 equiv.), Zn(tmp)2 (1.0 equiv.); 3 (1.0 equiv.); Cu catalyst (5 mol%), ligand (10 mol%)

bTime required for the complete consumption of 3

cYields determined by 1H NMR spectroscopy with CH2Br2 as a quantitative internal standard
dReaction run in the dark
substrate 7, and afforded the desired product 9 in 53 % yield (entry 16). Therefore, the use of CuCl₂ and 2,2'-bipyridine were selected as the standard amination conditions for subsequent studies.

With conditions identified for α-amination, we surveyed the amine scope of the α-amination transformation using model substrate ester 7 with a variety of O-benzoylhydroxylamines derived from simple amines (Table 2.5). In addition to 3 (entry 1), functionalizing the α-position of 7 with different cyclic amines, such as 11 and 13, was also achieved in excellent yields (entries 2 and 3). The amination reactions of acyclic O-benzoylhydroxylamines also proceeded efficiently with derivatives containing N,N-diethyl, N,N-dibenzyl, and N-benzyl-N-methyl groups (entries 4–6). Note that the benzyl moiety can be a useful synthetic handle for further manipulations after selective deprotection. Excitingly, the secondary hydroxylamine was effective for the direct amination (entry 7). Additionally, O-benzoylhydroxylamines containing carbamate, ester, and olefin groups all participated in the amination smoothly (entries 8–10), demonstrating the great compatibility of this transformation with diverse functionality. Importantly, the amination reaction of 26 gave the aminated product 27 exclusively in quantitative yield, and no pyrrolidine-containing compound was detected for a conceivable copper-catalyzed radical cyclization [91].

We also examined the generality of α-amination using O-benzoylhydroxylamine 3 on a variety of zinc enolate derivatives (Table 2.6). Compared to the model substrate tert-butyl acetate 7, other acetate ester including iso-propyl acetate 28 and ethyl acetate 30 also provided the aminated products in excellent yields (entries 1, 3 and 4). Besides 8, other amides also effectively underwent electrophilic amination reactions (entries 5–7), while cyclic amides 32 and 34 proceeded more efficiently than acyclic amides 8 and 36. However, the current conditions were ineffective for esters and amides bearing a substitution at the α-position, suggesting steric may possibly influence the conformation of zinc enolates to impede an effective transmetallation reaction with the copper intermediate [55, 56, 68]. The demonstrated generality of this copper-catalyzed α-amination transformation on a variety of zinc carbanions suggest its potential in the synthesis of functionally important α-amino carbonyl compounds.

### 2.2.4 α-Acylation of Ester and Amide Zinc Enolates

During our studies, we found that acylated product 6 was formed in 58 % yield when 3 was treated with the zinc enolate of ester 7 in the absence of a copper catalyst at room temperature for an extended period of time (24 h). At 60 °C, this reaction proceeded more rapidly and provided β-keto ester 6 in 82 % yield within 3 h (Table 2.7). We were intrigued by such a highly selective acylation resulting from the dual reactivity of O-benzoylhydroxylamine 3 toward the zinc enolate of ester 7.
Table 2.5  Copper-catalyzed electrophilic \(\alpha\)-amination of ester 7 with various \(O\)-benzoylhydroxylamines\(^a\)

\[
\begin{align*}
\text{entry} & \quad \text{O-acylhydroxylamine} & \quad \text{product} & \quad \text{yield (%)} \\
1 & \begin{array}{c}
\text{BzO} - N \\
\text{Me}
\end{array} & 3 & 4 & 98 \\
2 & \begin{array}{c}
\text{BzO} - N \\
\text{Et}
\end{array} & 10 & 11 & 98 \\
3 & \begin{array}{c}
\text{BzO} - N \\
\text{Bn}
\end{array} & 12 & 13 & 95 \\
4 & \begin{array}{c}
\text{BzO} - N \\
\text{Bn}
\end{array} & 14 & 15 & 98 \\
5 & \begin{array}{c}
\text{BzO} - N \\
\text{Bn}
\end{array} & 16 & 17 & 99 \\
6 & \begin{array}{c}
\text{BzO} - N \\
\text{Et}
\end{array} & 18 & 19 & 96 \\
7 & \begin{array}{c}
\text{BzO} - N \\
\text{Bn}
\end{array} & 20 & 21 & 42 \\
8 & \begin{array}{c}
\text{BzO} - N \\
\text{NBOc}
\end{array} & 22 & 23 & 97 \\
9 & \begin{array}{c}
\text{BzO} - N \\
\text{CO}_2\text{Et}
\end{array} & 24 & 25 & 98 \\
10 & \begin{array}{c}
\text{BzO} - N \\
\text{Me}
\end{array} & 26 & 27 & 99
\end{align*}
\]

\(^a\)Isolated yields. Reactions conducted in a 0.2–0.3 mmol scale: 7 (2.1 equiv), Zn(tmp)\(_2\) (1.0 equiv), O-acylhydroxylamine (1.0 equiv), CuCl\(_2\) (5 mol%), bipy (10 mol%)
We then examined the generality of this acylation transformation for the preparation of 1,3-dicarbonyl compounds (Table 2.8). With model substrate ester 7, 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 and 2). Similarly, acylation reactions of hydroxylamine 3 with different ester and amide substrates also proceeded efficiently (entries 5–10). Once again, zinc enolates derived from α-substituted esters

Table 2.6 Copper-catalyzed electrophilic α-amination of esters and amides with O-acylhydroxylamine 3

<table>
<thead>
<tr>
<th>entry</th>
<th>ester or amide</th>
<th>time (h)b</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>t-BuO Me</td>
<td>1; 1</td>
<td>4</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>Et₂N Me</td>
<td>1; 1.5</td>
<td>9</td>
<td>53</td>
</tr>
<tr>
<td>3</td>
<td>i-PrO Me</td>
<td>1; 1.5</td>
<td>29</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>EtO Me</td>
<td>1; 3</td>
<td>31</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>BocN Me</td>
<td>1; 1.5</td>
<td>33</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>PhN Me</td>
<td>2; 3</td>
<td>35</td>
<td>70</td>
</tr>
<tr>
<td>7</td>
<td>PhN Me</td>
<td>0.5; 3</td>
<td>37</td>
<td>51</td>
</tr>
</tbody>
</table>

aIsolated yields. Reactions conducted in a 0.2–0.3 mmol scale: ester or amide (2.1 equiv), Zn(tmp)₂ (1.0 equiv), 3 (1.0 equiv), CuCl₂ (5 mol%), bipy (10 mol%) bReaction time for step 1 and 2, respectively
and amides were found unreactive toward acylation, suggesting that the steric hindrance significantly reduces their nucleophilicity. Despite current limitations, the \( \alpha \)-acylation transformation nevertheless offers a rapid and efficient approach to prepare simple 1,3-dicarbonyl compounds.

### 2.2.5 Proposed Mechanism for the \( \alpha \)-Amination and \( \alpha \)-Acylation Reactions

Based on our results, a plausible reaction mechanism is proposed in Scheme 2.10 for the observed dual reactivity of \( O \)-acylhydroxylamines (e.g. 3) toward zinc enolate (I) in the amination and acylation of ester 7. When a copper catalyst is present (condition A), the transmetallation between copper and zinc enolate (I) occurs and the resulting intermediate (IIIA) subsequently undergoes oxidative addition of \( O \)-acylhydroxylamine 3. Finally, the reactive copper complex (IVA) would readily undergo reductive elimination to afford the aminated product 4 and regenerate the copper catalyst. A radical pathway cannot be excluded despite lacking indication of any radical intermediates involved in the amination reactions. Additionally, we cannot exclude an alternative that includes (1) oxidative addition of the hydroxylamine to a low-valent copper species, (2) transmetallation with a zinc enolate, and (3) reductive elimination to form desired C–N bond. 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 3, possibly via an intermediate (IIB), and selectively afford the acylated product 6.

### Table 2.7 \( \alpha \)-Acylation of ester 7 using \( O \)-benzoylhydroxylamine 3

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>6 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>rt</td>
<td>1.5</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>rt</td>
<td>24</td>
<td>58</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>3</td>
<td>82</td>
</tr>
</tbody>
</table>

\(^a\)Reactions conducted on a 0.2–0.3 mmol scale  
\(^b\)Time required for the complete consumption of 3  
\(^c\)Yields determined by \(^1\)H NMR spectroscopy with \( \text{CH}_2\text{Br}_2 \) as a quantitative internal standard
Table 2.8 \(\alpha\)-Acylation of esters and amides via \(O\)-acylhydroxylamines\(^ a\)

![Chemical structure]

<table>
<thead>
<tr>
<th>entry</th>
<th>ester or amide</th>
<th>(O)-acylhydroxylamine</th>
<th>time (h)(^ b)</th>
<th>product yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(t)-BuO&lt;sub&gt;Me&lt;/sub&gt;</td>
<td>(\text{Ph}O)</td>
<td>1; 3</td>
<td>6; 82</td>
</tr>
<tr>
<td>2</td>
<td>(7)</td>
<td>(4\text{-NO}_2\text{-Ph}O)</td>
<td>1; 5</td>
<td>6; 81</td>
</tr>
<tr>
<td>3</td>
<td>(7)</td>
<td>(\text{Me}O)</td>
<td>1; 3</td>
<td>39; 92</td>
</tr>
<tr>
<td>4</td>
<td>(7)</td>
<td>(\text{Me}O)</td>
<td>1; 5</td>
<td>41; 61</td>
</tr>
<tr>
<td>5</td>
<td>(i\text{-PrO}Me)</td>
<td>(3)</td>
<td>1; 3</td>
<td>42; 90</td>
</tr>
<tr>
<td>6</td>
<td>(\text{EtO}Me)</td>
<td>(3)</td>
<td>1; 3</td>
<td>43; 87</td>
</tr>
<tr>
<td>7</td>
<td>(\text{Et}_2\text{N}Me)</td>
<td>(3)</td>
<td>1; 5</td>
<td>44; 61</td>
</tr>
<tr>
<td>8</td>
<td>(\text{Me})</td>
<td>(3)</td>
<td>1; 5</td>
<td>45; 71</td>
</tr>
<tr>
<td>9</td>
<td>(\text{Boc}N)</td>
<td>(3)</td>
<td>1; 5</td>
<td>46; 75</td>
</tr>
<tr>
<td>10</td>
<td>(\text{Ph}N)</td>
<td>(3)</td>
<td>1; 5</td>
<td>47; 68</td>
</tr>
</tbody>
</table>

\(^ a\)Isolated yields. Reactions conducted in a 0.2–0.3 mmol scale: ester or amide (2.1 equiv), Zn(tmp)<sub>2</sub> (1.0 equiv), \(O\)-acylhydroxylamine (1.0 equiv)

\(^ b\)Reaction time for step 1 and 2, respectively
2.3 Conclusion

In summary, we describe 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 electrophilic 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 the dual electrophilic reactivity of O-acylhydroxylamines for selective amination and acylation reactions of other C–H bonds. Currently, studies on α-amination of substituted carbonyl compounds are underway.

2.3.1 Supplemental Information

2.3.1.1 General Information

General Procedures. Glassware and stir bars were dried in an oven at 140 °C for at least 12 h and then cooled in a desiccator cabinet over Drierite prior to use. Optimization and substrate screens were performed in Biotage 8 mL microwave
vials. Vials were fitted with crimp top septa under a positive pressure of nitrogen that had been passed through a column (5 × 20 cm) of Drierite, unless otherwise noted. Reaction vials were sealed with Teflon tape. All other reactions were performed in round-bottom flasks sealed with rubber septa. Plastic syringes or glass pipets were used to transfer liquid reagents. Reactions were stirred magnetically using Teflon-coated, magnetic stir bars. Analytical thin-layer chromatography (TLC) was performed using aluminum plates pre-coated with 0.25 mm of 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light and/or exposure to KMnO₄ stain. Organic solutions were concentrated under reduced pressure using a Büchi rotary evaporator. Flash-column chromatography was performed on silica gel (60 Å, standard grade) or on a CombiFlash companion system with pre-packed FLASH silica gel columns (Teledyne ISCO, Inc.).

Materials. Commercial reagents and solvents were purchased from Sigma-Aldrich or Strem and used as received. Dry THF and toluene were obtained using an Innovative Technologies solvent purification system. O-acylhydroxylamine derivatives were prepared according to literature procedure [77].

Instrumentation. Proton and carbon nuclear magnetic resonance (¹H and ¹³CNMR) spectra were recorded on a Varian INOVA 400 (400 MHz and 100 or 125 MHz respectively) spectrometer at ambient temperature. Chemical shifts for ¹H NMR are reported in parts per million (ppm, δ) and referenced to residual protium in the NMR solvent (CHCl₃: δ 7.26). Chemical shifts for ¹³C NMR are reported in ppm and referenced to the carbon resonances of the solvent (CDCl₃: δ 77.0). NMR data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broad), coupling constant (Hz), integration. Infrared spectroscopic data was obtained using an Thermo Scientific Nicolet 380 FT-IR. IR data is reported in wavenumbers (cm⁻¹) with only select peaks shown. High-resolution mass spectra were obtained through the Duke University Mass Spectrometry Facility using an Agilent 1100 Series liquid chromatography-electrospray ionization mass spectrometer.

2.3.1.2 Experimental Procedures

Procedure for formation of Reformatsky enolate 2 [90]
To activated Zn powder (305 mg, 4.67 mmol, 1.15 equiv) in 2-neck RBF was added THF (10 mL) and TMSCl (0.06 mL, 0.41 mmol, 0.1 equiv). The reaction mixture was stirred at room temperature for 10 min then warmed to 40 °C for an additional 20 min. The reaction mixture was brought to reflux and 1 (0.6 mL, 4.06 mmol, 1.0 equiv) was added dropwise. After 2.5 h, the reaction was removed from heat. Reformatsky solution turned a pale green color.

**General experimental procedure for the amination of Reformatsky enolate 2**

\[
\begin{align*}
\text{ZnBr}_2 & \quad \text{CuBr (10 mol%), ICy-BF}_4 (10 \text{ mol%}) \\
& \quad \text{LiO-t-Bu, THF, rt}
\end{align*}
\]

\[O\text{-Acylhydroxylamine 3 (0.200 mmol, 1.0 equiv), CuBr (0.01 mmol, 0.05 equiv), ICy-BF}_4 (0.01 \text{ mmol, 0.05 equiv), and LiO-t-Bu (0.220 mmol, 1.1 equiv) added to microwave tube. Flask evacuated and refilled with N}_2 (3x). DCM (1 mL) added followed by Reformatsky enolate 2 (0.36 M, 0.400 mmol, 2.0 equiv). Reaction stirred at room temperature. Consumption of O-acylhydroxylamine 3 monitored by TLC (50:50 ethyl acetate–hexanes). Upon complete consumption of O-acylhydroxylamine 3, the reaction was quenched with NaHCO\textsubscript{3} (10 mL), extracted into Et\textsubscript{2}O (2 × 20 mL). Organic layers were combined and washed with brine (20 mL), and dried over Na\textsubscript{2}SO\textsubscript{4}. The mixture was filtered and evaporated under reduced pressure.

**Typical procedure 1 (TP1): General experimental procedure for the α-amination reaction using Zn(tmp)\textsubscript{2} as base**

\[
\begin{align*}
\text{Y} & \quad \text{Me} \\
& \quad 1) \text{Zn(tmp)}_2, \text{tol, rt} \\
& \quad 2) \text{BzO–NR}_1 \text{R}_2 \\
& \quad \text{Cu catalyst (5 mol%), ligand (10 mol%), THF, rt}
\end{align*}
\]

To an 8 mL microwave tube was added Zn(tmp)\textsubscript{2} (0.5 M solution in tol, 0.36 mL, 0.18 mmol, 1.0 equiv) followed by dropwise addition of the carbonyl compound (0.37 mmol, 2.1 equiv). The reaction was stirred at room temperature for 1 h and was added dropwise a mixture of O-acylhydroxylamine (0.18 mmol, 1.0 equiv), CuCl\textsubscript{2} (0.0089 mmol, 0.05 equiv), and 2,2′-bipyridyl (0.018 mmol, 0.1 equiv) in THF (2 mL). The reaction mixture was allowed to stir at room temperature. Upon complete consumption of O-acylhydroxylamine (monitored by TLC=50 % ethyl
acetate–hexanes), the reaction was diluted with a saturated aqueous solution of NaHCO₃ (10 mL) and extracted into Et₂O. The combined organic layers were washed with brine (10 mL) and dried over MgSO₄. The mixture was filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified by either column chromatography or acid-base extraction using 2 M HCl and 2 M NaOH.

**Typical procedure 2 (TP2):** General experimental procedure for the α-acylation reaction using Zn(tmp)₂ as base

\[
\begin{align*}
\text{Y} & \quad \text{Me} \\
\text{O} & \\
1) \quad \text{Zn(tmp)₂, tol, rt} \\
2) \quad \text{BzO – NR}^{1}R^{2} \\
& \quad \text{Cu catalyst (5 mol%), ligand (10 mol%), THF, rt}
\end{align*}
\]

To an 8 mL microwave tube was added Zn(tmp)₂ (0.5 M solution in tol, 0.36 mL, 0.18 mmol, 1.0 equiv) followed by dropwise addition of the carbonyl compound (0.37 mmol, 2.1 equiv). The reaction was stirred at room temperature for 1 h and was added dropwise a solution of O-acylhydroxylamine (0.20 mmol, 1.0 equiv) in THF (2 mL). The reaction mixture was heated to 60 °C. Upon complete consumption of O-acylhydroxylamine (monitored by TLC – 50 % ethyl acetate–hexanes), the reaction was diluted with a saturated aqueous solution of NaHCO₃ (10 mL) and extracted into Et₂O. The combined organic layers were washed with brine (10 mL) and dried over MgSO₄. The mixture was filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified by column chromatography.

### 2.3.2 Characterization of Compounds

**tert-Butyl-2-morpholinoacetate (4).** Compound prepared according to TP1. Purification by column chromatography (50 % ethyl acetate–hexanes) gave 4 as a pale yellow oil (35.1 mg, 98 %); Rf = 0.28 (50 % ethyl acetate–hexanes); ¹H NMR (CDCl₃, 400 MHz): δ 3.75 (t, J = 4.8 Hz, 4H), 3.10 (s, 2H), 2.57 (t, J = 4.8 Hz,
4H), 1.46 (s, 9H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 169.2, 81.1, 66.7, 60.2, 53.2, 28.0; FTIR (thin film): cm$^{-1}$ 2854, 1741, 1147, 1115; HRMS-ESI (m/z) Calcd for (C$_{10}$H$_{20}$NO$_3$) ([M + H]$^+$): 202.1438; found 202.1441.

$N,N$-Diethyl-2-morpholinoacetamide (9). Compound prepared according to TP1. Purification by acid-base extraction gave 9 as a pale yellow oil (18.9 mg, 53%); $R_f = 0.10$ (100 % ethyl acetate); $^1$H NMR (CDCl$_3$, 400 MHz): 3.72 (t, $J = 4.8$ Hz, 4H), 3.38 (q, $J = 7.2$ Hz, 2H), 3.35 (q, $J = 7.2$ Hz, 2H), 3.14 (s, 2H), 2.52 (t, $J = 4.8$ Hz, 4H), 1.18 (t, $J = 7.2$ Hz, 3H), 1.10 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz): 168.1, 66.8, 61.1, 53.7, 41.6, 40.0, 14.3, 12.9; FTIR (thin film): cm$^{-1}$ 2851, 1629, 1131, 1113, 1069; HRMS-ESI (m/z) Calcd for (C$_{10}$H$_{21}$N$_2$O$_2$) ([M + H]$^+$): 201.1598; found 201.1601.

$t$-Butyl-2-(piperidin-1-yl)acetate (11). Compound prepared according to TP1. Purification by column chromatography (50 % ethyl acetate-hexanes) gave 11 as a pale yellow oil (34.8 mg, 98 %); $R_f = 0.38$ (50 % ethyl acetate-hexanes); $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 3.07 (s, 2H), 2.49 (t, $J = 5.4$ Hz, 4H), 1.60 (quin, $J = 5.4$ Hz, 4H), 1.45 (s, 9H), 1.42–1.40 (m, 2H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 169.9, 80.8, 60.8, 54.2, 28.1, 25.9, 24.0; FTIR (thin film): cm$^{-1}$ 2933, 2853, 1746, 1367, 1149; HRMS-ESI (m/z) Calcd for (C$_{11}$H$_{22}$NO$_2$) ([M + H]$^+$): 200.1645; found 200.1647.

$t$-Butyl-2-(pyrrolidin-1-yl)acetate (13). Compound prepared according to TP1. Purification by column chromatography (50 % ethyl acetate-hexanes) gave 13 as a pale yellow oil (31.3 mg, 95 %); $R_f = 0.37$ (50 % ethyl acetate-hexanes); $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 3.23 (s, 2H), 2.65–2.62 (m, 4H), 1.80 (t, $J = 3.6$ Hz, 2H), 1.78 (t, $J = 3.6$ Hz, 2H), 1.5 (s, 9H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 169.7, 81.0,
57.3, 53.7, 28.1, 23.5; FTIR (thin film): cm$^{-1}$ 2930, 1744, 1151; HRMS-ESI (m/z) Calcd for (C$_{10}$H$_{20}$NO$_2$) ([M + H]$^+$): 186.1489; found 186.1488.

**tert-Butyl-2-(dibenzylamino)acetate (15).** Compound prepared according to TP1. Purification by column chromatography (25 % ethyl acetate-hexanes) gave 15 as a white solid (54.3 mg, 98 %); R$_f$ = 0.80 (50 % ethyl acetate-hexanes); $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.40 (d, $J$ = 7.2, 4H), 7.32 (t, $J$ = 7.2 Hz, 4H), 7.26 (t, $J$ = 7.2 Hz, 2H), 3.80 (s, 4H), 3.18 (s, 2H), 1.47 (s, 9H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 170.8, 139.2, 128.9, 128.2, 127.0, 80.7, 57.6, 54.4, 28.2; FTIR (thin film): cm$^{-1}$ 3026, 2802, 1719, 1364, 1137; HRMS-ESI (m/z) Calcd for (C$_{20}$H$_{26}$NO$_2$) ([M + H]$^+$): 312.1958; found 312.1959.

**tert-Butyl-2-(benzyl(methyl)amino)acetate (17).** Compound prepared according to TP1. Purification by column chromatography (50 % ethyl acetate-hexanes) gave 17 as a pale yellow oil (41.7 mg, 99 %); R$_f$ = 0.66 (50 % ethyl acetate-hexanes); $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.36–7.25 (m, 5H), 3.68 (s, 2H), 3.17 (s, 2H), 2.37 (s, 3H), 1.48 (s, 9H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 170.3, 138.5, 129.1, 128.2, 127.1, 80.8, 60.9, 58.4, 42.0, 28.2; FTIR (thin film): cm$^{-1}$ 2976, 2930, 1730, 1366, 1149; HRMS-ESI (m/z) Calcd for (C$_{14}$H$_{22}$NO$_2$) ([M + H]$^+$): 236.1645; found 236.1649.

**tert-Butyl-2-(diethylamino)acetate (19).** Compound prepared according to TP1. Purification by column chromatography (50 % ethyl acetate-hexanes) gave 19 as a pale yellow oil (32.0 mg, 96 %); R$_f$ = 0.21 (50 % ethyl acetate-hexanes); $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 3.23 (s, 2H), 2.61 (q, $J$ = 7.2 Hz, 4H), 1.46 (s, 9H), 1.07 (t, $J$ = 7.2 Hz, 6H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 170.6, 80.7, 54.7, 47.6, 28.2, 12.3; FTIR (thin film): cm$^{-1}$ 2970, 2931, 1733, 1367, 1151; HRMS-ESI (m/z) Calcd for (C$_{10}$H$_{22}$NO$_2$) ([M + H]$^+$): 188.1645; found 188.1646.
**tert-Butyl-2-(benzylamino)acetate (21).** Compound prepared according to TP1. Purification by column chromatography (20 % ethyl acetate-hexanes) gave 21 as a white solid (16.5 mg, 42 %); $R_f = 0.58$ (50 % ethyl acetate-hexanes); $^1$H NMR (CDCl$_3$, 400 MHz): 7.34–7.24 (m, 5H), 3.79 (s, 2H), 3.31 (s, 2H), 1.93 (s, 1H), 1.47 (s, 9H); $^{13}$C NMR (CDCl$_3$, 100 MHz): 171.6, 139.6, 128.3, 128.2, 127.0, 81.0, 53.2, 50.9, 28.0; FTIR (thin film): cm$^{-1}$ 3370, 2977, 1728, 1453, 1226, 1150; HRMS-ESI (m/z) Calcd for (C$_{13}$H$_{20}$NO$_2$) ([M + H]$^+$): 222.1489; found 222.1492.

**tert-Butyl-4-(2-(tert-butoxy)-2-oxoethyl)piperazine-1-carboxylate (23).** Compound prepared according to TP1. Purification by column chromatography (50 % ethyl acetate-hexanes) gave 23 as a pale yellow solid (51.8 mg, 97 %); $R_f = 0.52$ (50 % ethyl acetate-hexanes); $^1$H NMR (CDCl$_3$, 400 MHz): 3.46 (t, $J = 5.0$ Hz, 4H), 3.12 (s, 2H), 2.51 (t, $J = 5.0$ Hz, 4H), 1.45 (s, 9H), 1.44 (s, 9H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 169.4, 154.7, 81.2, 79.6, 60.0, 52.6 (2C), 28.4, 28.1; FTIR (thin film): cm$^{-1}$ 2975, 2861, 1741, 1688, 1365, 1147, 1124; HRMS-ESI (m/z) Calcd for (C$_{15}$H$_{29}$N$_2$O$_4$) ([M + H]$^+$): 301.2122; found 301.2126.

**Ethyl-1-(2-(tert-butoxy)-2-oxoethyl)piperidine-4-carboxylate (25).** Compound prepared according to TP1. Purification by column chromatography (50 % ethyl acetate-hexanes) gave 25 as a pale yellow oil (47.3 mg, 98 %); $R_f = 0.56$ (50 % ethyl acetate-hexanes); $^1$H NMR (CDCl$_3$, 400 MHz): 4.11 (q, $J = 7.2$ Hz, 2H), 3.09 (s, 2H), 2.89 (dt, $J = 11.6$, 3.6 Hz, 2H), 2.29–2.20 (m, 3H), 1.90–1.76 (m, 4H), 1.44 (s, 9H), 1.22 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 174.9, 169.7, 81.0, 60.2, 52.5 (2C), 40.7, 28.1 (2C), 14.2; FTIR (thin film): cm$^{-1}$ 2977, 2932, 2812, 1726, 1366, 1141; HRMS-ESI (m/z) Calcd for (C$_{14}$H$_{26}$NO$_4$) ([M + H]$^+$): 272.1856; found 272.1860.
tert-Butyl-2-(butyl(2-methylpent-4-en-1-yl)amino)acetate (27). Compound prepared according to TP1. Purification by column chromatography (20 % ethyl acetate-hexanes) gave 27 as a pale yellow oil (47.8 mg, 99 %); \( R_f = 0.83 \) (50 % ethyl acetate-hexanes); \(^1\)H NMR (CDCl\(_3\), 400 MHz): 5.84–5.74 (m, 1H), 5.01–4.96 (m, 2H), 3.19 (s, 2H), 2.56 (t, \( J = 7.2 \) Hz, 2H), 2.42 (dd, \( J = 12.8, 7.2 \) Hz, 1H), 2.32 (dd, \( J = 12.8, 7.2 \) Hz, 1H), 2.22 (dt, \( J = 13.8, 4.8 \) Hz, 1H), 1.81 (dt, \( J = 13.8, 4.8 \) Hz, 1H), 1.69–1.61 (m, 1H), 1.50–1.45 (m, 2H), 1.45 (s, 9H), 1.32 (q, \( J = 7.2 \) Hz, 2H), 0.89 (t, \( J = 7.2 \) Hz, 3H), 0.88 (t, \( J = 7.2 \) Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \( \delta \) 171.3, 137.5, 115.5, 80.5, 61.0, 56.5, 54.4, 39.7, 39.2, 28.2, 20.4, 17.8, 14.0; FTIR (thin film): cm\(^{-1}\) 2956, 2929, 1733, 1457, 1367, 1148, 910; HRMS-ESI (m/z) Calcd for (C\(_{16}\)H\(_{32}\)NO\(_2\)) ([M + H]\(^+\)): 270.2428; found 270.2431.

Isopropyl-2-morpholinoacetate (29). Compound prepared according to TP1. Purification by column chromatography (50 % ethyl acetate-hexanes) gave 29 as a pale yellow oil (31.3 mg, 94 %); \( R_f = 0.20 \) (50 % ethyl acetate-hexanes); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta \) 5.06 (tt, \( J = 6.4, 6.4 \) Hz, 1H), 3.75 (t, \( J = 4.6 \) Hz, 4H), 3.17 (s, 2H), 2.58 (t, \( J = 4.6 \) Hz, 4H), 1.25 (d, \( J = 6.4 \) Hz, 6H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \( \delta \) 169.6, 68.2, 66.8, 59.9, 53.3, 21.8; FTIR (thin film): cm\(^{-1}\) 2855, 1741, 1199, 1114; HRMS-ESI (m/z) Calcd for (C\(_{9}\)H\(_{19}\)NO\(_3\)) ([M + H]\(^+\)): 188.1281; found 188.128.

Ethyl-2-morpholinoacetate (31). Compound prepared according to TP1. Purification by column chromatography (60 % ethyl acetate-hexanes) gave 31 as a pale yellow oil (27.8 mg, 90 %); \( R_f = 0.16 \) (50 % ethyl acetate-hexanes); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta \) 4.18 (q, \( J = 7.2 \) Hz, 2H), 3.74 (t, \( J = 4.8 \) Hz, 4H), 3.19 (s, 2H), 2.57 (t, \( J = 4.8 \) Hz, 4H), 1.26 (t, \( J = 7.2 \) Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\),
100 MHz): δ 170.0, 66.8, 60.6, 59.7, 53.3, 14.2; FTIR (thin film): cm⁻¹ 2930, 2854, 1745, 1161, 1115; HRMS-ESI (m/z) Calcd for (C₈H₁₆NO₃) ([M + H]⁺): 174.1125; found 174.1128.

1-(3-Methylpiperidin-1-yl)-2-morpholinoethanone (33). Compound prepared according to TP1. Purification by acid-base extraction gave 33 (1:1 ratio of two conformers) as a white solid (38.3 mg, 95 %); ¹H NMR (CDCl₃, 400 MHz, 25 °C): δ 4.40 (d, J = 13.2 Hz, 1Hₐ), 4.37 (d, J = 13.2 Hz, 1Hₖ), 3.94 (d, J = 13.2 Hz, 1Hₐ), 3.86 (d, J = 13.2 Hz, 1Hₖ), 3.71 (t, J = 4.4 Hz, 8Hₕₐ), 3.22 (dd, J = 13.2, 7.2 Hz, 2Hₕₐ), 2.93 (td, J = 11.6, 3.2 Hz, 2Hₕₐ), 2.62 (dd, J = 12.8, 10.8 Hz, 2Hₕₐ), 2.54 (td, J = 11.6, 3.2 Hz, 2Hₕₐ), 2.50 (t, J = 4.4 Hz, 8Hₕₐ), 2.25 (dd, J = 12.8, 10.8 Hz, 2Hₕₐ), 1.81 (d, J = 12.8 Hz, 2Hₕₐ), 1.73–1.64 (m, 2Hₕₐ), 1.60–1.35 (m, 4Hₕₐ), 1.19–1.07 (m, 1Hₕₐ), 0.91 (d, J = 6.8 Hz, 3Hₕₐ), 0.89 (d, J = 6.8 Hz, 3Hₕₐ); ¹³C NMR (CDCl₃, 100 MHz): δ 167.3, 66.9, 61.6, 61.5, 53.5, 53.2, 49.2, 46.2, 42.4, 33.0, 33.0, 32.0, 31.2, 26.0, 25.0, 19.0, 18.9; FTIR (thin film): cm⁻¹ 2927, 2850, 1640, 1455, 1262, 1115; HRMS-ESI (m/z) Calcd for (C₁₂H₂₃N₂O₂) ([M + H]⁺): 227.1754; found 227.1755.

**tert-Butyl-4-(2-morpholinoacetyl)piperazine-1-carboxylate (35).** Compound prepared according to TP1. Purification by column chromatography (80 % ethyl acetate-hexanes) gave 35 as a white solid (39.1 mg, 70 %); Rₚ = 0.15 (90 % ethyl acetate-hexanes); ¹H NMR (CDCl₃, 400 MHz): δ 3.70 (t, J = 4.6 Hz, 4H), 3.57 (t, J = 5.2 Hz, 4H), 3.45 (t, J = 5.6 Hz, 2H), 3.39 (t, J = 5.6 Hz, 2H), 3.19 (s, 2H), 2.50 (t, J = 4.6 Hz, 4H), 1.47 (s, 9H); ¹³C NMR (CDCl₃, 100 MHz): δ 167.8, 154.5, 80.3, 66.8, 61.7, 53.5 (2C), 51.9, 45.5, 41.6, 28.3; FTIR (thin film): cm⁻¹ 2902, 1679, 1628, 1249, 1234, 1130, 1111; HRMS-ESI (m/z) Calcd for (C₁₅H₂₈N₃O₄) ([M + H]⁺): 314.2074; found 314.2077.
N-Methyl-2-morpholino-N-phenylacetamide (37). Compound prepared according to TP1. Purification by acid-base extraction gave 37 as a white solid (21.3 mg, 51 %); $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.41 (t, $J = 7.6$ Hz, 2H), 7.36–7.32 (m, 1H), 7.20 (d, $J = 7.6$ Hz, 2H), 3.66 (t, $J = 4.2$ Hz, 4H), 3.27 (s, 3H), 2.91 (s, 2H), 2.44 (s, 4H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 169.1, 143.4, 129.7, 127.9, 127.2, 66.8, 59.9, 53.6, 37.4; FTIR (thin film): cm$^{-1}$ 2954, 2852, 2801, 1656, 1594, 1262, 1112; HRMS-ESI (m/z) Calcd for (C$_{13}$H$_{19}$N$_2$O$_2$) ([M + H]$^+$): 235.1441; found 235.1447.

tert-Butyl-3-oxo-3-phenylpropanoate (6). Compound prepared according to TP2. Purification by column chromatography (20 % ethyl acetate-hexanes) gave 6 as a colorless oil (32.1 mg, 82 %); $R_f = 0.78$ (20 % ethyl acetate-hexanes); $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 12.72 (s, 1H enol tautomer), 7.94 (dt, $J = 6.4$, 1.6 Hz, 2H), 7.76 (dt, $J = 6.4$, 1.6 Hz, 2H enol tautomer), 7.58 (tt, $J = 6.4$, 1.6 Hz, 1H), 7.47 (t, $J = 7.6$ Hz, 2H), 7.44–7.38 (m, 3H enol tautomer), 5.58 (s, 1H enol tautomer), 3.89 (s, 2H), 1.54 (s, 9H enol tautomer), 1.43 (s, 9H); Spectroscopic data was identical to that reported previously [92].

tert-Butyl-3-(4-nitrophenyl)-3-oxopropanoate (39). Compound prepared according to TP2. Purification by column chromatography (20 % ethyl acetate-hexanes) gave 39 as a yellow oil (43.2 mg, 92 %); $R_f = 0.80$ (50 % ethyl acetate-hexanes); $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 12.70 (s, 1H enol tautomer), 8.33 (dt, $J = 9.2$, 2.0 Hz, 2H), 8.26 (dt, $J = 9.2$, 2.0 Hz, 2H enol tautomer), 8.10 (dt, $J = 9.2$, 2.0 Hz, 2H), 7.91 (dt, $J = 9.2$, 2.0 Hz, 2H enol tautomer), 5.68 (s, 1H enol tautomer), 3.94 (s, 2H), 1.55 (s, 9H enol tautomer), 1.43 (s, 9H). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 191.4, 172.4, 167.7, 165.8, 140.6, 139.7, 129.5, 126.8, 123.9, 123.7, 91.8, 82.8, 82.1, 47.6, 28.3, 27.9; FTIR (thin film): cm$^{-1}$ 2979, 2931, 1729, 1694, 1593, 1523,
1342, 1149; HRMS-ESI (m/z) Calcd for (C_{13}H_{14}NO_5) ([M – H]): 264.0877; found 264.0882.

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\begin{array}{c}
\text{Me} \\
\text{O} \\
\text{O} \\
\text{t-BuO} \\
\end{array}
\]

**tert-Butyl-3-oxobutanoate (41).** Compound prepared according to TP2. Purification by column chromatography (50 % ethyl acetate-hexanes) gave 41 as a colorless oil (17.1 mg, 61 %); R_f = 0.85 (50 % ethyl acetate-hexanes); ^1H NMR (CDCl_3, 400 MHz): δ 3.34 (s, 2H), 2.24 (s, 3H), 1.46 (s, 9H); Spectroscopic data was identical to that reported previously [93].

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\begin{array}{c}
\text{Ph} \\
\text{O} \\
\text{O} \\
i-\text{PrO} \\
\end{array}
\]

**Isopropyl-3-oxo-3-phenylpropanoate (42).** Compound prepared according to TP2 on 0.20 mmol scale. Purification by column chromatography (30 % ethyl acetate-hexanes) gave 42 as a pale yellow oil (37.0 mg, 90 %); R_f = 0.64 (50 % ethyl acetate-hexanes); ^1H NMR (CDCl_3, 400 MHz): δ 12.65 (s, 1H enol tautomer), 7.94 (d, J = 7.2 Hz, 2H), 7.78 (d, J = 7.2 Hz, 2H enol tautomer), 7.59 (t, J = 7.2 Hz, 1H), 7.47 (t, J = 7.2 Hz, 2H), 7.44–7.40 (m, 3H enol tautomer), 5.63 (s, 1H enol tautomer), 5.18–5.12 (m, 1H enol tautomer), 5.10–5.04 (m, 1H), 3.95 (s, 2H), 1.31 (d, J = 6.4 Hz, 6H enol tautomer), 1.22 (d, J = 6.4 Hz, 6H); ^13C NMR (CDCl_3, 125 MHz): δ 192.6, 167.0, 136.1, 133.6, 131.1, 128.7, 128.4, 126.0, 87.8, 69.0, 67.8, 46.3, 21.9, 21.6; FTIR (thin film): cm⁻¹ 2980, 1732, 1685, 1266, 1103; HRMS-ESI (m/z) Calcd for (C_{12}H_{15}O_3) ([M + Na]^+): 229.0835; found 229.0836.

\[
\begin{array}{c}
\text{Ph} \\
\text{O} \\
\text{O} \\
\text{EtO} \\
\end{array}
\]

**Ethyl-3-oxo-3-phenylpropanoate (43).** Compound prepared according to TP2 on 0.20 mmol scale. Purification by column chromatography (30 % ethyl acetate-hexanes) gave 43 as a pale yellow oil (33.3 mg, 87 %); R_f = 0.79 (50 % ethyl acetate-hexanes); ^1H NMR (CDCl_3, 400 MHz): δ 12.6 (s, 1H enol tautomer), 7.95 (dt, J = 6.4, 1.6 Hz, 2H), 7.78 (dt, J = 6.4, 1.6 Hz, 2H enol tautomer), 7.60 (tt, J = 6.4, 1.6 Hz, 1H), 7.48 (t, J = 7.6 Hz, 2H), 7.45–7.40 (m, 3H enol tautomer), 4.27 (q, J = 7.2 Hz, 2H enol tautomer), 4.22 (q, J = 7.2 Hz, 2H), 3.99
Spectroscopic data was identical to that reported previously [94].

**N,N-Diethyl-3-oxo-3-phenylpropanamide (44).** Compound prepared according to TP2. Purification by column chromatography (20 % ethyl acetate-hexanes) gave 44 as a colorless oil (23.8 mg, 61 %); R\(_f\) = 0.64 (50 % ethyl acetate-hexanes); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 8.02 (dt, \(J = 8.0, 2.0\) Hz, 2H), 7.77 (dd, \(J = 8.0, 1.6\) Hz, 2H \textit{enol tautomer}), 7.58 (tt, \(J = 7.2, 2.0\) Hz, 1H), 7.47 (t, \(J = 8.0\) Hz, 2H), 7.43–7.40 (m, 3H \textit{enol tautomer}), 5.73 (s, 1H \textit{enol tautomer}), 4.06 (s, 2H), 3.52–3.35 (m, 4H \textit{enol tautomer}), 3.39 (dq, \(J = 19.6, 7.2\) Hz, 4H), 1.66 (br s, 1H \textit{enol tautomer}), 1.28–1.16 (m, 6H \textit{enol tautomer}), 1.16 (dt, \(J = 20.4, 7.2\) Hz, 6H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 194.2, 171.4, 171.3, 166.0, 136.4, 135.3, 133.5, 130.5, 128.7, 128.4, 125.9, 110.0, 84.9, 45.8, 42.7, 40.2, 14.2, 12.9; FTIR (thin film): cm\(^{-1}\) 2974, 2933, 1690, 1627, 1281; HRMS-ESI (m/z) Calcd for (C\(_{13}\)H\(_{18}\)NO\(_2\)) (\([\text{M + H}]^+\)): 220.1332; found 220.1334.

**1-(3-Methylpiperidin-1-yl)-3-phenylpropane-1,3-dione (45).** Compound prepared according to TP2. Purification by column chromatography (20 % ethyl acetate-hexanes) gave 45 as a colorless oil (31.0 mg, 71 %); R\(_f\) = 0.58 (50 % ethyl acetate-hexanes); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 8.03 (d, \(J = 7.6\) Hz, 2H), 7.77 (dd, \(J = 8.0, 1.6\) Hz, 2H \textit{enol tautomer}), 7.58 (t, \(J = 7.6\) Hz, 1H), 7.47 (t, \(J = 7.6\) Hz, 2H), 7.43–7.37 (m, 3H \textit{enol tautomer}), 5.83 (s, 1H \textit{enol tautomer}), 4.49–4.38 (m, 1H), 4.10 (s, 1H) 3.76–3.65 (m, 1H \textit{enol tautomer}), 3.00 (tt, \(J = 11.2, 2.8\) Hz, 1H \textit{enol tautomer}), 2.70 (dd, \(J = 10.8, 2.4\) Hz, 1H), 2.63 (tt, \(J = 11.2, 2.8\) Hz, 1H \textit{enol tautomer}), 2.33 (dd, \(J = 10.8, 2.4\) Hz, 1H), 1.90–1.75 (m, 2H \textit{enol tautomer}), 1.75–1.40 (m, 5H \textit{enol tautomer}), 1.25–1.08 (m, 1H), 1.21 (s, 1H \textit{enol tautomer}), 0.95 (d, \(J = 6.8\) Hz, 2H), 0.86 (t, \(J = 6.0\) Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 193.9, 193.9, 171.4, 170.4, 164.8, 136.1, 136.1, 135.1, 133.4, 130.3, 128.6, 128.5, 128.2, 125.7, 84.2, 54.0, 45.9, 42.4, 32.7, 31.5, 30.7, 24.6, 18.8, 18.7, 18.7; FTIR (thin film): cm\(^{-1}\) 2926, 2850, 1686, 1628; HRMS-ESI (m/z) Calcd for (C\(_{15}\)H\(_{20}\)NO\(_2\)) (\([\text{M + H}]^+\)): 246.1489; found 246.1494.
**tert-Butyl-4-(3-oxo-3-phenylpropanoyl)piperazine-1-carboxylate (46).** Compound prepared according to TP2 on a 0.20 mmol scale. Purification by column chromatography (80 % ethyl acetate-hexanes) gave 46 as a pale yellow oil (49.7 mg, 75 %); \( R_f = 0.59 \) (50 % ethyl acetate-hexanes); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta \) 8.01 (d, \( J = 7.2 \) Hz, 2H), 7.77 (d, \( J = 7.2 \) Hz, 2H \textit{enol tautomer}), 7.60 (t, \( J = 7.2 \) Hz, 1H), 7.48 (t, \( J = 7.2 \) Hz, 2H), 7.44–7.39 (m, 3H \textit{enol tautomer}), 5.79 (s, 1H \textit{enol tautomer}), 4.13 (s, 2H), 3.63 (t, \( J = 4.8 \) Hz, 2H), 3.45 (br s, 2H), 3.42 (t, \( J = 4.8 \) Hz, 4H), 1.48 (s, 9H \textit{enol tautomer}), 1.45 (s, 9H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \( \delta \) 193.7, 154.5, 135.9, 133.8, 130.8, 128.8, 128.7, 128.4, 125.9, 80.3, 46.4, 45.8, 43.7, 42.9, 41.8, 28.3; FTIR (thin film): cm\(^{-1}\) 2974, 2926, 2860, 1686, 1637, 1412, 1160; HRMS-ESI (m/z) Calcd for (C\(_{18}\)H\(_{25}\)N\(_2\)O\(_4\)) ([M + H]\(^+\)): 333.1809; found 333.1809.

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\text{Ph} \quad \text{O} \quad \text{O} \\
\text{N} \quad \text{Boc} \quad \text{Ph}
\]

**N-Methyl-3-oxo-N,3-diphenylpropanamide (47).** Compound prepared according to TP2. Purification by column chromatography (20 % ethyl acetate-hexanes) gave 47 as a white solid (30.7 mg, 68 %); \( R_f = 0.61 \) (50 % ethyl acetate-hexanes); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta \) 7.77 (d, \( J = 8.4 \) Hz, 2H), 7.56–7.50 (m, 4H \textit{enol tautomer}), 7.46–7.44 (m, 4H \textit{enol tautomer}), 7.42–7.24 (m, 10H \textit{enol tautomer}), 5.39 (s, 1H \textit{enol tautomer}), 3.86 (s, 2H), 3.38 (s, 3H), 3.34 (s, 3H \textit{enol tautomer}), 1.66 (br s, 1H \textit{enol tautomer}); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \( \delta \); HRMS-ESI (m/z) Calcd for (C\(_{16}\)H\(_{15}\)NO\(_2\)) ([M + H]\(^+\)): 194.1, 180.2, 172.1, 167.0, 143.7, 143.4, 130.5, 129.9, 129.7, 128.5, 1128.3, 128.2, 128.2, 127.7, 127.3, 127.2, 125.8, 86.8, 45.5, 37.4; FTIR (thin film): cm\(^{-1}\) 3061, 2924, 1690, 1653, 1624, 1346, 1123; HRMS-ESI (m/z) Calcd for (C\(_{16}\)H\(_{16}\)NO\(_2\)) ([M + H]\(^+\)): 254.1176; found 254.1183.
References


References

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