

# The effective use of substituted benzoic anhydrides for the synthesis of carboxamides

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**Abstract**—Various carboxamides are synthesized from the corresponding carboxylic acids and amines with high product-selectivities using 2-methyl-6-nitrobenzoic or 2,4,6-trichlorobenzoic anhydride in the presence of 4-(dimethylamino)pyridine.  
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## 1. Introduction

Recently, we reported several useful methods for the synthesis of carboxylic acid derivatives using substituted benzoic anhydrides under acidic or basic conditions.<sup>1,2</sup> For example, nearly equimolar amounts of carboxylic acids and alcohols or  $\omega$ -hydroxycarboxylic acids react in the presence of 2-methyl-6-nitrobenzoic anhydride (MNBA) with basic catalysts such as 4-(dimethylamino)pyridine (DMAP) to produce the corresponding carboxylic esters or lactones in high yields.<sup>2</sup> During the reaction process using MNBA, the intermediary mixed anhydride was initially formed and it functions as a reactive acylating reagent of alcohols to give the desired carboxylic esters in high yields with high product-selectivities. In this report, we would describe an effective method for the accelerated synthesis of carboxamides<sup>3,4</sup> including sterically-hindered compounds using substituted benzoic anhydrides by basic promoters.

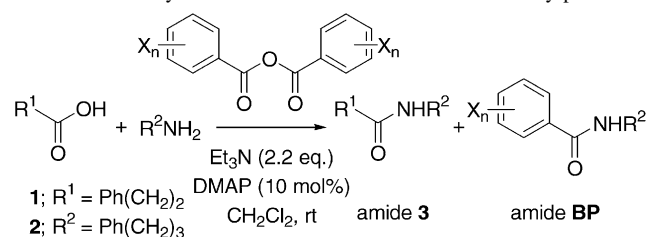
## 2. Results and discussion

### 2.1. Amidation reaction via mixed-anhydrides using benzoic anhydrides

First, benzoic or several substituted benzoic anhydrides were screened for the reaction of 3-phenylpropanoic acid (**1**) with 3-phenylpropylamine (**2**) as shown in Table 1. The desired carboxamide, 3-phenyl-*N*-(3-phenylpropyl)propanamide (**3**), was obtained in 55% yield along with the 10% formation of the undesired benzamide by the addition of **2** to the reaction mixture of **1** and benzoic anhydride

(entry 1). When 4-methoxybenzoic anhydride was employed for the model case, the amount of undesirable benzamide increased to 34% (entry 2). The addition of electron withdrawing substituents, such as the trifluoromethyl or cyano group, on the 4-position of the aromatic moiety increased the reactivity of the anhydride but the selectivity was not satisfactory (entries 3 and 4). Although the reaction using 2,6-dichlorobenzoic anhydride afforded **3** in medium yield as listed in entry 5, an excellent chemical yield of **3** and relatively good product-selectivity were obtained when using 2,4,6-trichlorobenzoic anhydride (TCBA, entry 6). As shown in entry 7, MNBA also

**Table 1.** Isolated yields of carboxamide **3** and ratios of **3** to by-products



| Entry          | X <sub>n</sub>         | Yield of <b>3</b> (%) | Yield of <b>BP</b> (%) | <b>3</b> / <b>BP</b> <sup>a</sup> |
|----------------|------------------------|-----------------------|------------------------|-----------------------------------|
| 1 <sup>b</sup> | H                      | 55                    | 10                     | 5.5/1                             |
| 2 <sup>b</sup> | 4-MeO                  | 48                    | 34                     | 1.4/1                             |
| 3 <sup>b</sup> | 4-CF <sub>3</sub>      | 52                    | 12                     | 4.3/1                             |
| 4 <sup>b</sup> | 4-CN                   | 77                    | 5                      | 15/1                              |
| 5 <sup>b</sup> | 2,6-Cl <sub>2</sub>    | 64                    | 8                      | 8.0/1                             |
| 6 <sup>b</sup> | 2,4,6-Cl <sub>3</sub>  | 97                    | 3                      | 32/1                              |
| 7 <sup>b</sup> | 2-Me-6-NO <sub>2</sub> | 83                    | 1                      | 83/1                              |
| 8 <sup>c</sup> | 2,4,6-Cl <sub>3</sub>  | 63                    | 25                     | 2.5/1                             |
| 9 <sup>c</sup> | 2-Me-6NO <sub>2</sub>  | 84                    | 14                     | 6.0/1                             |

<sup>a</sup> Determined by <sup>1</sup>H NMR using a crude mixture.

<sup>b</sup> **2** (1.0 equiv.) was added to the mixture of **1** (1.0 equiv.) and benzoic anhydride or substituted ones (1.2 equiv.).

<sup>c</sup> TCBA or MNBA (1.2 equiv.) was added to the mixture of **1** (1.0 equiv.) and **2** (1.0 equiv.).

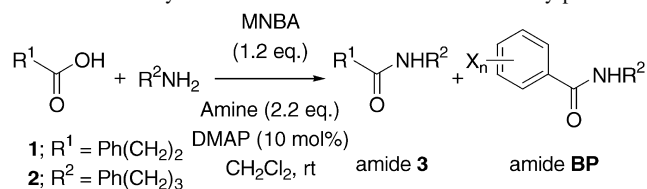
**Keywords:** Carboxamides; 2-Methyl-6-nitrobenzoic anhydride; 2,4,6-Trichlorobenzoic anhydride; Mixed-anhydrides; 4-(Dimethylamino)pyridine.

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functions as a suitable benzoic anhydride to produce the desired carboxamide although the yield was somewhat lower than that of entry 6. Furthermore, TCBA or MNBA was added to the reaction mixture of **1** and **2** in order to determine the best structure of the benzoic part of the anhydride for maintaining high product-selectivity. According to this procedure, it was revealed that the reaction using MNBA gave preferable product-selectivity compared to that obtained by the reaction using TCBA (entries 8 and 9).

Next, some bases were screened for the reaction of **1** with **2** by the promotion of MNBA as shown in Table 2. When the reaction was carried out using a 2.2 molar amount of triethylamine in the absence of DMAP, the product selectivity significantly decreased as compared to that of the DMAP catalyzed reaction (entries 1 and 2). Furthermore, by employing other typical bases, such as *N,N,N',N'*-tetramethylethylenediamine (TMEDA) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), poor product-selectivities and low yields of the desired amide **3** were obtained (entries 3 and 4). On the other hand, the yield of **3** increased to 92% without any loss of the high product-selectivity when the present reaction was performed in the presence of a 2.2 molar amount of DMAP as a stoichiometric base (entry 5). It was found that the use of a stoichiometric amount of 4-pyrrolidinopyridine (PPY) was also effective for this reaction and the desired amide **3** was obtained in excellent yield with high chemoselectivity (entry 6).

**Table 2.** Isolated yields of carboxamide **3** and ratios of **3** to by-products



| Entry          | Base              | Yield of <b>3</b> (%) | Yield of <b>BP</b> (%) | <b>3/BP</b> <sup>a</sup> |
|----------------|-------------------|-----------------------|------------------------|--------------------------|
| 1 <sup>b</sup> | Et <sub>3</sub> N | 20                    | 68                     | 0.29/1                   |
| 2              | Et <sub>3</sub> N | 84                    | 14                     | 6.0/1                    |
| 3              | TMEDA             | 47                    | 47                     | 1/1                      |
| 4              | DBU               | 16                    | 64                     | 0.25/1                   |
| 5 <sup>c</sup> | DMAP              | 92                    | trace                  | 141/1                    |
| 6 <sup>d</sup> | PPY               | 93                    | 1.0                    | 93/1                     |

<sup>a</sup> Determined by <sup>1</sup>H NMR using a crude mixture.

<sup>b</sup> The reaction was carried out in the absence of DMAP.

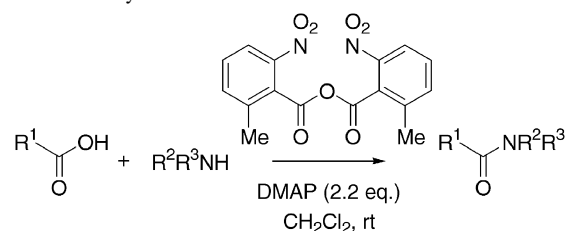
<sup>c</sup> The reaction was carried out in the presence of DMAP (2.2 equiv.) without any tertiary amine.

<sup>d</sup> The reaction was carried out in the presence of PPY (2.2 equiv.) without any tertiary amine.

The amidation proceeded at room temperature in several other polar solvents, such as DMI (95%, **3/BP**=32/1), DMF (92%, 50/1), MeCN (91%, 85/1), THF (83%, 7.7/1) and MeNO<sub>2</sub> (49%, 64/1) under the same reaction conditions as entry 5 in the Table 2.

Table 3 shows the yields for a variety of carboxamides including ones derived from bulky substrates. The reactions of **1** with benzylamine (**4**), diphenylmethanamine (**6**), 1-phenylethylamine (**8**), 1-adamantanamine (**10**), benzylmethylamine (**12**), piperidine (**14**) and aniline (**16**) proceeded to form the corresponding coupling products in high

**Table 3.** Isolated yields of various carboxamides



| Entry            | Carboxylic acid          | Amine  | Product   | Yield (%)       |
|------------------|--------------------------|--|-----------|-----------------|
| 1 <sup>a</sup>   | <b>1</b>                 | <b>2</b>                                       | <b>3</b>  | 92 <sup>b</sup> |
| 2 <sup>a,c</sup> | <b>1</b>                 | <b>2</b>                                       | <b>3</b>  | 84 <sup>d</sup> |
| 3 <sup>a,c</sup> | <b>1</b>                 | PhCH <sub>2</sub> NH <sub>2</sub> ( <b>4</b> ) | <b>5</b>  | 87 <sup>d</sup> |
| 4 <sup>a</sup>   | <b>1</b>                 | Ph <sub>2</sub> CHNH <sub>2</sub> ( <b>6</b> ) | <b>7</b>  | 91 <sup>d</sup> |
| 5 <sup>e</sup>   | <b>1</b>                 | PhCHMeNH <sub>2</sub> ( <b>8</b> )             | <b>9</b>  | 82 <sup>d</sup> |
| 6 <sup>f</sup>   | <b>1</b>                 | 1-Adamantyl-NH <sub>2</sub> ( <b>10</b> )      | <b>11</b> | 96 <sup>d</sup> |
| 7 <sup>e</sup>   | <b>1</b>                 | PhCH <sub>2</sub> NHMe ( <b>12</b> )           | <b>13</b> | 96 <sup>d</sup> |
| 8 <sup>e</sup>   | <b>1</b>                 | Piperidine ( <b>14</b> )                       | <b>15</b> | 81 <sup>d</sup> |
| 9 <sup>e</sup>   | <b>1</b>                 | PhNH <sub>2</sub> ( <b>16</b> )                | <b>17</b> | 78 <sup>d</sup> |
| 10 <sup>e</sup>  | PhCHMeCOOH ( <b>18</b> ) | <b>2</b>                                       | <b>19</b> | 94 <sup>d</sup> |
| 11 <sup>e</sup>  | <b>18</b>                | <b>4</b>                                       | <b>20</b> | 90 <sup>d</sup> |
| 12 <sup>a</sup>  | <b>18</b>                | <b>6</b>                                       | <b>21</b> | 90 <sup>d</sup> |
| 13 <sup>e</sup>  | <b>18</b>                | <b>8</b>                                       | <b>22</b> | 88 <sup>d</sup> |
| 14 <sup>f</sup>  | <b>18</b>                | <b>10</b>                                      | <b>23</b> | 92 <sup>d</sup> |
| 15 <sup>e</sup>  | <b>18</b>                | <b>12</b>                                      | <b>24</b> | 93 <sup>d</sup> |
| 16 <sup>e</sup>  | <b>18</b>                | <b>14</b>                                      | <b>25</b> | 82 <sup>d</sup> |
| 17 <sup>e</sup>  | <b>18</b>                | <b>16</b>                                      | <b>26</b> | 85 <sup>d</sup> |

<sup>a</sup> Amines (1.0 equiv.) were added to the mixture of carboxylic acids (1.2 equiv.) and MNBA (1.2 equiv.).

<sup>b</sup> **3/BP**=141/1.

<sup>c</sup> The reaction was carried out at -78 °C.

<sup>d</sup> Carboxamide/benzamide=>200/1.

<sup>e</sup> Amines (1.0 equiv.) were added to the mixture of carboxylic acids (1.1 equiv.) and MNBA (1.1 equiv.).

<sup>f</sup> Amines (1.0 equiv.) were added to the mixture of carboxylic acids (1.3 equiv.) and MNBA (1.3 equiv.).

yields (entries 3–9). It is noteworthy that the undesired benzamide was not produced at all except for entry 1. 2-Phenylpropanoic acid (**18**), a 2-branched carboxylic acid, also reacted with **2** to form the desired 2-phenyl-*N*-(3-phenylpropyl)propanamide (**19**) in high yield (entry 10). The amidation of **18** with other typical amines including bulky ones gave the corresponding carboxamides in good to excellent yields with perfect product-selectivities (entries 11–17).

### 3. Conclusion

It is noted that the present reaction provides a convenient and high-yielding method for the preparation of carboxamides from nearly equimolar amounts of free carboxylic acids and amines which involve bulky alkyl groups. The experimental procedure is quite simple and almost pure carboxamides are obtained just by mixing the substrates at room temperature.

## 4. Experimental

### 4.1. General methods

All reactions were carried out under argon atmosphere in dried glassware. Dichloromethane was distilled from

diphosphorus pentoxide, then calcium hydride, and dried over MS 4 Å. Thin layer chromatography was performed on Wakogel B5F. All melting points are uncorrected.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded with tetramethylsilane (TMS) or chloroform (in chloroform-*d*) as internal standard.

## 4.2. Starting materials

All reagents were purchased from Tokyo Kasei Kogyo Co., Ltd, Kanto Chemical Co., Inc. or Aldrich Chemical Co., Inc., and used without further purification unless otherwise noted. 2-Methyl-6-nitrobenzoic anhydride (MNBA) was purchased from Tokyo Kasei Kogyo Co., Ltd (TCI, M1439) or synthesized from 2-methyl-6-nitrobenzoic acid.<sup>2d</sup>

## 4.3. Typical experimental procedure for the amidation reaction

A typical experimental procedure is described for the reaction of 3-phenylpropanoic acid (**1**) with 3-phenylpropylamine (**2**); to a solution of DMAP (59.6 mg, 0.488 mmol) in dichloromethane (2.0 mL) were added MNBA (91.6 mg, 0.266 mmol) and **1** (40.0 mg, 0.266 mmol). After having been stirred for 5 min, a solution of **2** (30.0 mg, 0.222 mmol) in dichloromethane (1.0 mL) was added. The reaction mixture was stirred for 14 h at room temperature and then saturated aqueous sodium hydrogencarbonate was added. The mixture was extracted with dichloromethane, and the organic layer was washed with water and brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin layer chromatography to afford 54.6 mg (92%) of 3-phenyl-*N*-(3-phenylpropyl)propanamide (**3**).

**4.3.1. 3-Phenyl-*N*-(3-phenylpropyl)propanamide (3).** Mp 57 °C. IR (KBr) 3260, 1640, 1540  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ =7.35–7.10 (m, 10H), 5.46 (br s, 1H), 3.15 (dt,  $J$ =6.2, 7.0 Hz, 2H), 2.85 (t,  $J$ =7.7 Hz, 2H), 2.48 (t,  $J$ =7.7 Hz, 2H), 2.34 (t,  $J$ =7.7 Hz, 2H), 1.67 (tt,  $J$ =7.0, 7.7 Hz, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ =172.0, 141.3, 140.7, 128.4, 128.3, 128.2, 128.2, 126.1, 125.8, 39.0, 38.3, 33.1, 31.6, 30.9. HR MS: Calcd for  $\text{C}_{18}\text{H}_{22}\text{NO}$  ( $\text{M}+\text{H}^+$ ) 268.1701, found 268.1700.

**4.3.2. *N*-Benzyl-3-phenylpropanamide<sup>5</sup> (5).** Mp 80 °C. IR (KBr) 3290, 1650, 1540  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ =7.30–7.09 (m, 10H), 5.68 (br s, 1H), 4.36 (d,  $J$ =5.6 Hz, 2H), 2.96 (t,  $J$ =7.6 Hz, 2H), 2.48 (t,  $J$ =7.6 Hz, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ =171.8, 140.7, 138.1, 128.6, 128.5, 128.4, 127.7, 127.4, 126.2, 43.5, 38.4, 31.7.

**4.3.3. *N*-(Diphenylmethyl)-3-phenylpropanamide (7).** Mp 149 °C. IR (KBr) 3340, 1640, 1540  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ =7.33–7.06 (m, 15H), 6.28–6.18 (m, 1H), 6.01 (br s, 1H), 3.02 (t,  $J$ =7.5 Hz, 2H), 2.58 (t,  $J$ =7.5 Hz, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ =171.0, 141.3, 140.6, 140.6, 128.6, 128.6, 128.5, 128.4, 128.4, 128.3, 127.4, 127.4, 126.3, 56.8, 38.4, 31.6. HR MS: Calcd for  $\text{C}_{22}\text{H}_{22}\text{NO}$  ( $\text{M}+\text{H}^+$ ) 316.1701, found 316.1699.

**4.3.4. 3-Phenyl-*N*-[(1*S*)-1-phenylethyl]propanamide<sup>4a</sup> (9).** 98% ee. Mp 92 °C. IR (KBr): 3280, 1640, 1560  $\text{cm}^{-1}$ .  $[\alpha]_{\text{D}}^{25}$ =−63.6° (c 1.03, EtOH).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ =7.21–

7.00 (m, 10H), 5.90 (br s, 1H), 4.97 (quin,  $J$ =7.6 Hz, 1H), 2.83 (t,  $J$ =7.3 Hz, 2H), 2.35 (t,  $J$ =7.3 Hz, 2H), 1.28 (d,  $J$ =7.6 Hz, 3H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ =171.1, 143.1, 140.7, 128.4, 128.4, 128.3, 127.1, 126.1, 126.0, 48.4, 38.4, 31.7, 21.5. HR MS: Calcd for  $\text{C}_{17}\text{H}_{20}\text{NO}$  ( $\text{M}+\text{H}^+$ ) 254.1545, found 254.1542.

**4.3.5. *N*-1-Adamantyl-3-phenylpropanamide (11).** Mp 125 °C. IR (KBr) 3250, 1640, 1540  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ =7.31–7.19 (m, 5H), 5.00 (br s, 1H), 2.92 (t,  $J$ =7.6 Hz, 2H), 2.37 (t,  $J$ =7.6 Hz, 2H), 2.04 (br s, 3H), 1.92 (br d, 6H), 1.65 (br s, 6H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ =171.1, 141.1, 128.4, 127.1, 126.1, 51.8, 41.5, 39.5, 36.3, 31.8, 29.4. HR MS: Calcd for  $\text{C}_{19}\text{H}_{26}\text{NO}$  ( $\text{M}+\text{H}^+$ ) 284.2014, found 284.2015.

**4.3.6. *N*-Benzyl-*N*-methyl-3-phenylpropanamide (13).** A mixture of two stereoisomers A and B. IR (neat) 1640  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ =7.33–7.06 (m, 10H, A+B), 4.59 (s, 2aH, A), 4.45 (s, 2bH, B), 3.05–2.96 (m, 2H, A+B), 2.70–2.64 (m, 2H, A+B), 2.94 (s, 3bH, B), 2.84 (s, 3aH, A).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ =172.5 (B), 172.2 (A), 141.3, 141.2, 137.3, 136.4, 128.8, 128.8, 128.5, 128.4, 127.9, 127.9, 127.5, 127.5, 127.2, 127.2, 126.1, 126.0, 53.1 (B), 50.8 (A), 35.3 (A), 34.9 (B), 34.7 (A), 33.9 (B), 31.5 (B), 31.3 (A). HR MS: Calcd for  $\text{C}_{17}\text{H}_{20}\text{NO}$  ( $\text{M}+\text{H}^+$ ) 254.1545, found 254.1541.

**4.3.7. 3-Phenylpropanoylpiperidine<sup>6</sup> (15).** IR (neat) 1640  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ =7.24–7.11 (m, 5H), 3.55 (br t,  $J$ =5.3 Hz, 2H), 3.32 (br t,  $J$ =5.3 Hz, 2H), 2.96 (t,  $J$ =8.0 Hz, 2H), 2.61 (t,  $J$ =8.0 Hz, 2H), 1.65–1.45 (br m, 6H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ =170.2, 141.4, 128.3, 128.3, 125.9, 46.5, 42.6, 35.0, 31.5, 26.3, 25.4, 24.4.

**4.3.8. *N*-Phenyl-3-phenylpropanamide<sup>7</sup> (17).** Mp 98 °C. IR (neat) 3320, 1660, 1530  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ =7.73 (br s, 1H), 7.42 (d,  $J$ =7.8 Hz, 2H), 7.27–7.14 (m, 7H), 7.05 (t,  $J$ =7.4 Hz, 1H), 2.98 (t,  $J$ =7.8 Hz, 2H), 2.60 (t,  $J$ =7.8 Hz, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ =170.8, 140.5, 137.8, 128.8, 128.5, 128.2, 126.2, 124.2, 120.1, 39.1, 31.5.

**4.3.9. 2-Phenyl-*N*-(3-phenylpropyl)propanamide<sup>4a</sup> (19).** Mp 93 °C. IR (KBr): 3250, 1640, 1560  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ =7.34–7.05 (m, 10H), 5.44 (br s, 1H), 3.50 (q,  $J$ =7.3 Hz, 1H), 3.24–3.15 (m, 2H), 2.51 (br t, 2H), 1.76–1.69 (m, 2H), 1.50 (d,  $J$ =7.3 Hz, 3H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ =174.1, 141.4, 141.3, 128.8, 128.3, 128.2, 127.5, 127.2, 125.9, 47.0, 39.1, 33.0, 31.0, 18.4. HR MS: Calcd for  $\text{C}_{18}\text{H}_{21}\text{NONa}$  ( $\text{M}+\text{Na}^+$ ) 290.1521, found 290.1495.

**4.3.10. *N*-Benzyl-2-phenylpropanamide<sup>4a</sup> (20).** Mp 78 °C. IR (KBr): 3280, 1640, 1550  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ =7.32–7.09 (m, 10H), 6.02 (br s, 1H), 4.34 (dd,  $J$ =14.9, 5.9 Hz, 1H), 4.30 (dd,  $J$ =14.9, 5.9 Hz, 1H), 3.57 (q,  $J$ =7.1 Hz, 1H), 1.51 (d,  $J$ =7.1 Hz, 3H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$ =174.1, 141.3, 138.4, 128.8, 128.5, 127.6, 127.4, 127.2, 47.0, 43.4, 18.5. HR MS: Calcd for  $\text{C}_{16}\text{H}_{17}\text{NONa}$  ( $\text{M}+\text{Na}^+$ ) 262.1208, found 262.1210.

**4.3.11. *N*-(Diphenylmethyl)-2-phenylpropanamide<sup>4a</sup> (21).** Mp 134 °C. IR (KBr): 3280, 1640, 1540  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ =7.37–6.95 (m, 15H), 6.19–6.00 (m, 1H), 3.59 (q,  $J$ =7.1 Hz, 1H), 1.48 (d,  $J$ =7.1 Hz, 3H).  $^{13}\text{C}$  NMR

(CDCl<sub>3</sub>)  $\delta$ =173.1, 141.5, 141.3, 141.2, 128.8, 128.5, 128.3, 127.5, 127.4, 127.3, 127.2, 127.1, 127.0, 56.7, 46.8, 18.3. HR MS: Calcd for C<sub>22</sub>H<sub>21</sub>NONa (M+Na<sup>+</sup>) 338.1521, found 338.1528.

**4.3.12. (2RS)-2-Phenyl-N-[(1SR)-1-phenylethyl]propanamide<sup>4a</sup> (22a).** Mp 127 °C. IR (KBr): 3350, 1640, 1540 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ =7.37–7.19 (m, 10H), 5.56 (br d, 1H), 5.09 (quin,  $J$ =6.9 Hz, 1H), 3.53 (q,  $J$ =7.1 Hz, 1H), 1.51 (d,  $J$ =7.1 Hz, 3H), 1.34 (d,  $J$ =6.9 Hz, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$ =173.2, 143.2, 141.4, 128.9, 128.6, 127.6, 127.2, 126.0, 48.7, 47.1, 21.5, 18.6. HR MS: Calcd for C<sub>17</sub>H<sub>19</sub>NONa (M+Na<sup>+</sup>) 276.1365, found 276.1374.

**4.3.13. (2RS)-2-Phenyl-N-[(1RS)-1-phenylethyl]propanamide<sup>4a</sup> (22b).** Mp 127 °C. IR (KBr): 3240, 1640, 1540 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ =7.34–7.17 (m, 8H), 7.08 (dd,  $J$ =7.7, 1.2 Hz, 2H), 5.59 (d,  $J$ =7.1 Hz, 1H), 5.08 (quin,  $J$ =7.1 Hz, 1H), 3.57 (q,  $J$ =7.3 Hz, 1H), 1.51 (d,  $J$ =7.3 Hz, 3H), 1.39 (d,  $J$ =7.1 Hz, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$ =173.1, 143.2, 141.3, 128.8, 128.5, 127.6, 127.2, 127.1, 125.7, 48.6, 47.1, 21.9, 18.4. HR MS: Calcd for C<sub>17</sub>H<sub>19</sub>NONa (M+Na<sup>+</sup>) 276.1365, found 276.1320.

**4.3.14. N-1-Adamantyl-2-phenylpropanamide<sup>4a</sup> (23).** Mp 136 °C. IR (KBr): 3300, 1640, 1550 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ =7.34–7.22 (m, 5H), 5.11 (br s, 1H), 3.45 (q,  $J$ =7.1 Hz, 1H), 2.02 (br s, 3H), 1.90 (br d, 6H), 1.63 (br t, 6H), 1.46 (d,  $J$ =7.1 Hz, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$ =173.2, 142.1, 128.7, 127.5, 127.0, 51.7, 47.8, 41.4, 36.3, 29.4, 18.7. HR MS: Calcd for C<sub>19</sub>H<sub>25</sub>NONa (M+Na<sup>+</sup>) 306.1834, found 306.1841.

**4.3.15. N-Benzyl-N-methyl-2-phenylpropanamide<sup>4a</sup> (24).** A mixture of two stereoisomers A and B. IR (neat): 1640 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ =7.31–7.15 (m, 8H, A+B), 7.01 (d,  $J$ =7.3 Hz, 2H, A+B), 4.66 (d,  $J$ =14.6 Hz, 1aH, A), 4.65 (d,  $J$ =16.7 Hz, 1bH, B), 4.54 (d,  $J$ =14.6 Hz, 1aH, A), 4.24 (d,  $J$ =16.7 Hz, 1bH, B), 3.92 (q,  $J$ =6.8 Hz, 1aH, A), 3.87 (q,  $J$ =6.8 Hz, 1bH, B), 2.93 (s, 3bH, B), 2.79 (s, 3aH, A), 1.49 (d,  $J$ =6.8 Hz, 3aH, A), 1.46 (d,  $J$ =6.8 Hz, 3bH, B). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$ =174.1 (B), 173.7 (A), 141.9, 141.7, 137.4, 136.6, 128.8, 128.8, 128.8, 128.4, 127.8, 127.4, 127.3, 127.2, 127.1, 126.8, 126.7, 126.2, 52.9 (B), 51.1 (A), 43.4 (A), 43.1 (B), 34.7 (A), 34.2 (B), 20.9 (B), 20.8 (A). HR MS: Calcd for C<sub>17</sub>H<sub>19</sub>NONa (M+Na<sup>+</sup>) 276.1365, found 276.1349.

**4.3.16. 2-Phenylpropanoylpiperidine<sup>4a</sup> (25).** IR (neat): 1640 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ =7.33–7.19 (m, 5H), 3.88 (q,  $J$ =6.8 Hz, 1H), 3.70–3.35 (br m, 4H), 1.52–1.37 (m, 6H), 1.44 (d,  $J$ =6.8 Hz, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$ =171.7, 142.4, 128.8, 127.2, 126.6, 43.2, 43.2, 25.7, 24.5, 20.8. HR MS: Calcd for C<sub>14</sub>H<sub>19</sub>NONa (M+Na<sup>+</sup>) 240.1365, found 240.1377.

**4.3.17. N-Phenyl-2-phenylpropanamide<sup>8</sup> (26).** Mp 136 °C. IR (neat): 3360, 1660, 1540 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ =7.47 (br s, 1H), 7.42 (d,  $J$ =7.8 Hz, 2H), 7.34–7.20 (m, 7H), 7.04 (t,  $J$ =7.3 Hz, 1H), 3.70 (q,  $J$ =7.0 Hz, 1H), 1.56 (d,  $J$ =7.3 Hz, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$ =172.5, 140.9, 137.9, 129.0, 128.8, 127.6, 127.4, 124.2, 119.8, 47.9, 18.5.

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