One-Pot Curtius Rearrangement Processes from Carboxylic Acids

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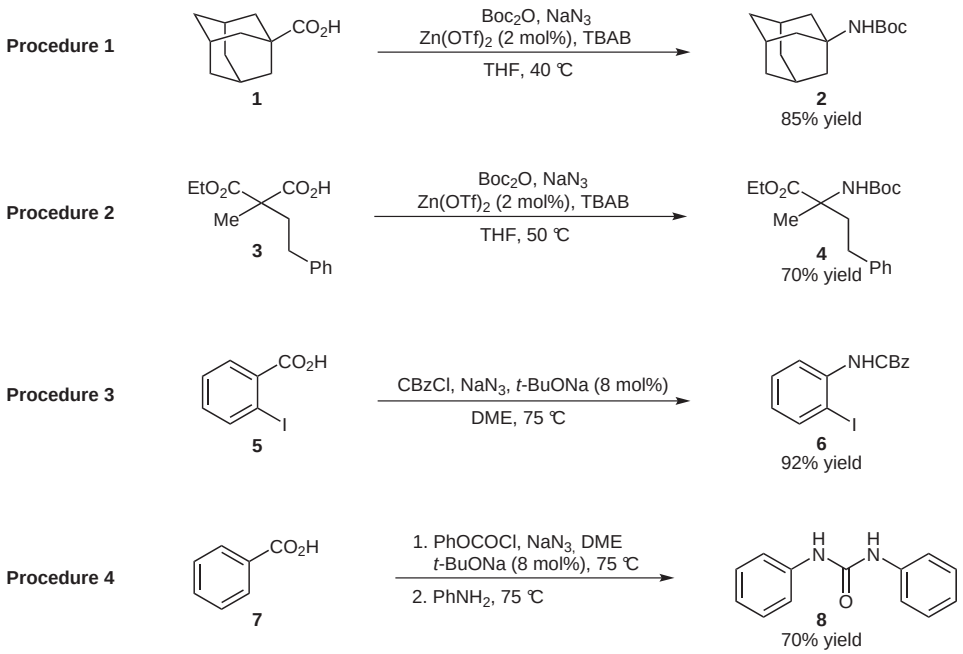
Abstract: An efficient and practical synthesis of amine derivatives from carboxylic acids is described using new one-pot Curtius rearrangement processes. The preparation of carbamate-protected amines and anilines, as well as ureas was achieved in good to excellent yields on a multigram scale.

Key words: Curtius rearrangement, acyl azides, carbamates, protected amino acids, anilines, ureas



Scheme 1

Introduction

Carbon–nitrogen bond formation is of high interest in organic chemistry as numerous nitrogen-containing molecules are found in natural and/or biologically active products. As a result, a variety of synthetic strategies have been developed to address the preparation of such molecules. Among them, the Curtius rearrangement,[1] which involves the concerted degradation of an acyl azide into an isocyanate (Scheme 2), has been used quite extensively.[2] The synthesis of a variety of carbamates and ureas using such a strategy is possible by trapping the isocyanate intermediate with an alcohol or an amine. The one-pot transformation of carboxylic acids into carbamates is most commonly achieved using diphenylphosphorazidate (DPPA), which not only provides a soluble source of azide, but also activates the carboxylic acid to form the corresponding acyl azide in situ.[3] This reagent has been widely used for the preparation of pharmacologically active compounds.[4] However, the requirement of high temperatures and the potential difficulties associated with the isolation of the desired product from the phosphorus residues remain as serious drawbacks. We have recently reported a mild and efficient one-pot Curtius rearrangement to convert aliphatic carboxylic acid into Boc-protected amines and amino acids (Scheme 1, Procedures 1 and 2).[5] The process is based on the in situ formation of acyl azides from carboxylic acids by treating with di-*tert*-butyl dicarbonate and sodium azide. These aliphatic acyl azides spontaneously rearrange at 40 °C to produce the corresponding isocyanates. No additional alcohol reagent is required to form the carbamate as the degradation of Boc

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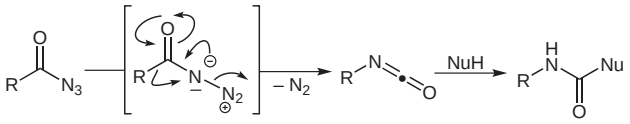
anhydride results in the formation of sodium *tert*-butoxide as a by-product. The latter alkoxide then reacts with the isocyanate, albeit slowly at 40 °C. Conversely, the use of a catalytic amount of tetrabutylammonium bromide and zinc triflate promoted the formation of the desired Boc-protected amine (presumably through the formation of a zinc carbamoyl bromide species).[6] α,α-Disubstituted protected amino acids are also available using such a procedure. Despite the lack of reactivity of aromatic carboxylic acids under these conditions (as a result of the inherent stability of aromatic acyl azides at 40 °C) the desired rearrangement occurred at 75 °C. Therefore, a variety of Alloc, CBz, and Troc-protected anilines were produced from aromatic carboxylic acids using the corresponding chloroformate reagent in the presence of sodium azide and a catalytic amount of sodium *tert*-butoxide (Scheme 1, Procedure 3).[7] Moreover, when phenyl chloroformate is used, the addition of an external nucleophile, such as an amine, to the isocyanate intermediate led to the corresponding aromatic urea (Scheme 1, Procedure 4), as the phenoxide by-product resulting from the degradation of the chloroformate is not nucleophilic enough. In this report, we wish to disclose convenient procedures (30 mmol scale) for one-pot Curtius rearrangement processes with aliphatic and aromatic carboxylic acids.



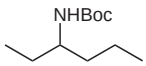
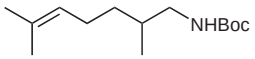
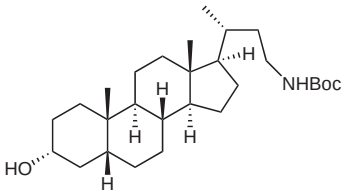
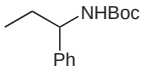
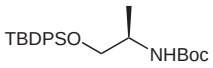
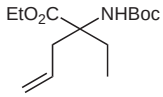
Scheme 2

Scope and Limitations

The catalytic Curtius rearrangement provided a variety of Boc-protected aliphatic amines from carboxylic acids in good to excellent yields. A large variety of substrates were tested under the optimal reaction conditions using 1.1 equivalents of di-*tert*-butyl dicarbonate, 3.5 equivalents of sodium azide, 15 mol% of tetrabutylammonium bromide, and 3.3 mol% of zinc triflate in THF at 40 °C.[8,9] The reaction proceeds easily with tertiary, secondary, and primary carboxylic acids to give access to protected amines in good yields (Table 1).

Unprotected ketones, alcohols, or silyl ether groups are compatible with the reaction conditions. The scope was extended to the synthesis of racemic α,α-disubstituted protected amino acids by increasing the temperature to 50 °C. All reagents are commercially available, easy to handle and are introduced simultaneously. The desired pure products are typically obtained after a simple flash chromatography. The only by-product observed is the corresponding *tert*-butyl ester, which affects the yield of some substrates (entries 5 and 6). The formation of this by-product might result from the addition of the *tert*-butoxy moiety onto the corresponding ketene, generated from the acyl azide by formal elimination of hydrazoic acid. Although the Curtius rearrangement is known to proceed with retention of configuration, carbamate **14** was recovered with a slight erosion of the enantiomeric excess (91% ee) under standard reaction conditions. To decrease the basicity of the reaction mixture, 0.5 equivalent of *tert*-butyl alcohol was added. Under these new reaction conditions, the Curtius rearrangement of enantioenriched α-chiral carboxylic acids led to the isolation of the carbamate with complete stereospecificity. The versatility of this procedure was further evaluated on a multigram scale. The one-pot procedure was scaled up to 30 mmol and the Boc-carbamate **2** was obtained in 87% yield under standard reaction conditions (Table 2, entry 1). Similar conversion was observed by decreasing the loading of zinc triflate and tetrabutylammonium bromide to 2 and 9 mol%, respectively (entry 2). In addition, the stoichiometry of sodium azide could be decreased to 2 equivalents and carbamate **2** could be consistently isolated in 85% yield (entry 3). To ensure the safety of the protocol, the reaction was quenched with a 10% aqueous solution of sodium nitrite to eliminate the azide residues.[10] This new set of reaction conditions provides a safe and efficient multigram scale procedure for the Curtius rearrangement. Furthermore, this protocol can also be used for the synthesis of protected unnatural amino acids (Procedure 2).

Table 1 Zinc-Catalyzed Curtius Rearrangement Using Procedures 1 and 2

Entry	Product		Yield (%)
1	**9**		94
2	**10**		80
3	**11**		68
4	**12**		72
5	**13**		58
6	**14**		49[a] (98% ee)
7	**15**		65[b]

[a] Starting material was 99% ee; 0.5 equiv of *t*-BuOH was added.
[b] Temp: 50 °C.

Table 2 Optimization of the Reaction Conditions for the Synthesis of Carbamate **2**[a]

Entry	NaN_3 (equiv)	$Zn(OTf)_2$ (mol%)	Bu_4NBr (mol%)	Conversion (%)[a]
1	3.5	3.3	15	87[b]
2	3.5	2	9	90
3	2	2	9	85[b]

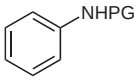
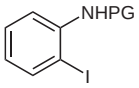
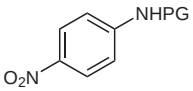
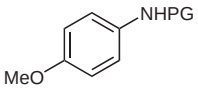
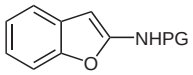
[a] Procedure 1 (30 mmol scale).
[a] Conversion measured by GC-MS.
[b] Isolated yield.

Aromatic carboxylic acids did not undergo rearrangement under the previously developed catalytic Curtius procedure, as higher temperatures are required to promote the rearrangement of the corresponding acyl azide intermediate. The synthesis of Boc-aniline derivatives was shown to occur in DME at 75 °C (with 1.1 equiv of Boc_2O and 1.5 equiv of NaN_3), but with a poor functional group tolerance possibly due to the generation of a stoichiometric amount of sodium *tert*-butoxide as a by-product.[11] Conversely, the use of chloroformates as acid activating agents (generating sodium chloride as a by-product) in the presence of 1.7 equivalents of sodium azide and 15 mol% of sodium *tert*-butoxide in DME at 75 °C produced a wide range of carbamates in high yields.[12] Allyl, benzyl and trichloroethyl chloroformate were successfully used to generate Alloc-, CBz-, and Troc-protected anilines. Such protecting groups can be selectively removed under mild reaction conditions. Both electron-rich and electron-withdrawing substituted aromatic carboxylic acids are compatible with the reaction conditions (Table 3, entries 2–4). The use of other sp^2-substituted carboxylic acids such as cinnamic acid or benzofuran carboxylic acid is also possible (entry 5). In contrast, pyridine carboxylic acid derivatives are not reactive under these conditions as the acyl azide intermediate appears not to be formed.

2-Iodobenzoic acid was the chosen substrate to scale up the procedure (30 mmol scale), because of the high synthetic value of the corresponding 2-iodoaniline, which is an important intermediate for indole derivatives synthesis through palladium-catalyzed heteroannulation.[13,14] The reaction was run at 0.3 M and the catalyst loading of sodium *tert*-butoxide was decreased to 8 mol% to produce the desired protected aniline in 92% yield (Table 4). Unfortunately, it was not possible to decrease the amount of sodium azide, as lower yield was observed with 1.2 equivalents instead of 1.5.

So far, the final product resulted from the addition of a nucleophilic alkoxide (arising from the degradation of the corresponding chloroformate) to the isocyanate. Addition of an external nucleophile would further expand the scope of such a procedure. For instance, the synthesis of ureas should be possible by trapping the isocyanate with a nucleophilic amine. To achieve this task, the carboxylic acid was treated with sodium azide and phenyl chloroformate

Table 3 Curtius Rearrangement with Benzoic Acid Derivatives Using Procedure 3

Entry	Carbamate	PG	Yield (%)
1		Alloc (**16**) CBz (**17**)	57 64
2		Alloc (**18**) CBz (**6**) Troc (**19**)	72 93 71[a]
3		Alloc (**20**) CBz (**21**)	78 84
4		Alloc (**22**) CBz (**23**)	45 62
5		Alloc (**24**) CBz (**25**)	69 80

[a] Temp: 85 °C.

Table 4 Optimization of the Reaction Conditions for the Synthesis of Carbamate **6**[a]

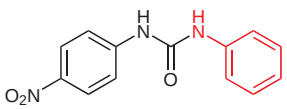
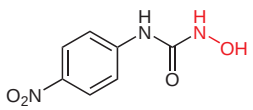
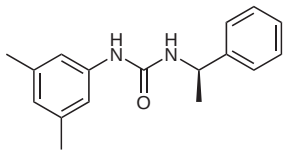
Entry	*t*-BuONa (mol%)	NaN_3 (equiv)	Yield (%)
1	15	1.5	88
2	8	1.5	92
3	8	1.2	82

[a] Procedure 3 (30 mmol scale).

to form the corresponding acyl azide. The reaction was then heated at 75 °C to promote the rearrangement, followed by the addition of an amine derivative to produce the desired urea (Table 5).

According to this protocol a variety of aromatic ureas were efficiently prepared via addition of substituted anilines, aliphatic amines and *N*-hydroxylamine. A gram scale procedure was developed for the synthesis of diphenylurea **8**. A mixture of benzoic acid, sodium azide, phe-

Table 5 Synthesis of Aromatic Ureas using Procedure 4

Entry	Carbamate		Yield (%)
1	**26**		74
2	**27**		54
3	**28**		63

nyl chloroformate, and sodium *tert*-butoxide was heated at 75 °C, then the aniline was added and stirred at 75 °C for 12 hours (Procedure 4). After precipitation in hexanes and trituration with diethyl ether, the desired urea **8** was isolated in 70% yield (Scheme 1).

In conclusion, we have developed very efficient one-pot processes for the Curtius rearrangement, which allows the direct conversion of carboxylic acids into amine derivatives. The new zinc-catalyzed Curtius rearrangement gives access to aliphatic Boc-protected amines at low temperature. An extension of the methodology using chloroformate reagent and a catalytic amount of sodium *tert*-butoxide leads to the formation of a wide range of protected anilines. Interestingly, these new conditions were also compatible with the synthesis of urea derivatives.

Procedures

Herein, we describe four typical synthetic procedures for the direct conversion of carboxylic acids into various amine derivatives through one-pot Curtius reaction. First, the zinc-catalyzed Curtius rearrangement can be performed on aliphatic carboxylic acids using THF as a solvent at 40 °C. This procedure was run on a 30 mmol scale using only 2 mol% of zinc triflate and 2 equiv of NaN_3 (**Procedure 1**). Carbamate **2** was isolated in 85% yield after recrystallization. Monoester of malonic acid was also compatible with this protocol at 50 °C. We also report the synthesis of carboxylic acid **3** from diethyl methylmalonate. The commercially available diethyl methylmalonate was alkylated with phenethyl bromide in quantitative yield in the presence of NaH in DMF at 25 °C. The monosaponification of the resulting disubstituted malonate with KOH in a H_2O–EtOH mixture at 50 °C affords the acid **3** in 62% yield. The racemic disubstituted protected amino acid **4** was isolated in 74% yield (**Procedure 2**). The large scale optimization was extended to aromatic carboxylic acids. The reaction was achieved on a 30 mmol scale and the best conditions required DME as solvent at 75 °C with 8 mol% of *t*-BuONa. This procedure enabled us to isolate the CBz-protected aniline **6** in 96% yield (**Procedure 3**). The same conditions have been used for the synthesis of aromatic urea **8** (**Procedure 4**). The poor solubility of the benzoate anion prompted us to modify the standard procedure reported for the urea synthesis. Indeed, the mixture was heated prior to the addition of aniline, and the diphenyl urea **8** was obtained in 70% yield.

Unless otherwise noted, all non-aqueous reactions were performed under an oxygen-free atmosphere of argon with rigid exclusion of moisture from reagents and glassware. The solvents were dried using standard methods prior to use. NaN_3 and sodium *tert*-butoxide are commercially available and were purchased from Aldrich. Sodium *tert*-butoxide was handled under inert atmosphere. Carboxylic acids are commercially available and were purified using standard methods prior to use. Analytical thin layer chromatography (TLC) was performed using EM Reagent 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by UV absorbance, aqueous cerium molybdate, ethanolic phosphomolybdic acid, or aqueous potassium permanganate. Flash chromatography was performed using EM Silica Gel 60 (230–400 mesh) with the indicated solvent system. Optical rotations were measured on a Perkin-Elmer 341 digital polarimeter at 589 nm. Data are reported as follows: $[\alpha]_D^{temp.}$, concentration (*c* g/100 mL), and solvent. ^{1}H NMR spectra were recorded in $CDCl_3$, unless otherwise noted, on Bruker AV-400, Bruker ARX-400, Bruker AMX-300 or Bruker AV-300 spectrometers (400, 400, 300 and 300 MHz, respectively), respectively. Chemical shifts are reported in ppm on the δ scale from an internal standard of residual chloroform (7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet and br = broad), coupling constant in Hz, integration. ^{13}C NMR spectra were recorded in $CDCl_3$, unless otherwise noted, on Bruker AV-400, Bruker ARX-400, Bruker AMX-300 or Bruker AV-300 spectrometers (100, 100, 75 and 75 MHz, respectively), respectively, with complete proton decoupling. Chemical shifts are reported in ppm from the central peak of $CDCl_3$ (77.0 ppm) on the δ scale. Mass spectra were obtained on a LC-MSD TOF (ESI) Agilent Technologies high resolution from the Centre régional de spectrométrie de masse de l'Université de Montréal. Analytical gas chromatography with a mass spectroscopy (GC-MS) was carried out on a Hewlett Packard 6890 series gas chromatograph equipped with a split mode capillary in*J*ector and electron impact mass detector. Unless otherwise noted, in*J*ector and detector temperatures were 250 °C and the carrier gas was hydrogen (2 mL/min) with a HP-5MS column. Data are reported as follows: column type, oven temperature, and retention time (t_R).

***N*-*tert*-Butyl Adamantan-1-yl-carbamate (2); Procedure 1**

To a solution of 1-adamantanecarboxylic acid (**1**; 5.40 g, 30.0 mmol), NaN_3 (3.90 g, 60.0 mmol), TBAB (870 mg, 2.70 mmol), and zinc triflate (220 mg, 0.600 mmol) in THF (150 mL) was added warm di-*tert*-butyl dicarbonate (7.60 mL, 33.0 mmol) via a syringe over 10 sec. The resulting reaction mixture was then stirred with a mechanical stirrer under argon at 40 °C for 64 h. The mixture was cooled to r.t. and quenched with aq 10% $NaNO_2$ (50 mL). The biphasic mixture was stirred for 30 min at r.t. The two layers were separated, and the organic layer was washed successively with sat. aq NH_4Cl (75 mL), brine (75 mL), and then dried (Na_2SO_4). The organic solution was filtered and concentrated at 40 °C by rotary evaporation to afford a white solid. The solid residue was dissolved in a boiling mixture of hexanes (90 mL) and EtOAc (2 mL). The complete dissolution of the solid led to the formation of a viscous orange oil. The clear solution was separated from this residue and then concentrated at 40 °C by rotary evaporation to afford a white solid, which was recrystallized from a mixture of hexanes (70 mL) and $CHCl_3$ (2 mL). The resulting crystalline product was filtered through a fritted funnel and dried under vacuum to yield 5.5 g of the product. The mother liquor was concentrated at 40 °C by rotary evaporation, and the resulting white solid recrystallized from hexanes (30 mL) to yield 0.85 g of additional product after filtration through a fritted funnel and drying as mentioned above. The solids were combined to provide 6.41 g (85%) of the desired carbamate **2** as a crystalline white solid; mp 101 °C; R_f = 0.46 (10% EtOAc–hexanes).

IR (neat): 3266, 3130, 2907, 2851, 1685, 1359, 1164, 1151, 1026, 778, 628 cm^{-1}.

^{1}H NMR (400 MHz, C_6D_6, 70 °C): δ = 4.37 (br s, 1 H), 2.05 (br s, 3 H), 1.91 (s, 6 H), 1.64 (m, 6 H), 1.42 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.0 (br), 78.4 (br), 50.3, 41.8, 36.3, 29.3, 28.4.

HMRS (ESI): *m*/*z* calcd for $C_{15}H_{25}NO_2$ + Na $[M + Na]^+$: 274.1777; found: 274.1778.

Anal. Calcd for $C_{15}H_{25}NO_2$: C, 71.67; H, 10.02; N, 5.57; O, 12.73. Found: C, 71.41; H, 9.81; N, 5.66.

Diethyl 2-Methyl-2-phenethylmalonate

To a solution of NaH (60% dispersion in mineral oil, 4.00 g, 100 mmol) in DMF (140 mL) at 0 °C was added dropwise a solution of diethyl methylmalonate (17.2 mL, 100 mmol) in DMF (30 mL). The colorless mixture was stirred for 45 min under argon at 0 °C. A solution of 2-bromoethylbenzene (13.7 mL, 100 mmol) in DMF (30 mL) was then added dropwise over 20 min. The resulting mixture was stirred under argon at r.t. for 4.5 h. The mixture was then

poured into cold H_2O (400 mL) and stirred for 15 min. The two layers were separated and the aqueous layer was extracted with EtOAc (2 × 350 mL). The combined organic layers were washed with brine (350 mL), dried (Na_2SO_4), filtered, and concentrated at 40 °C by rotary evaporation. The resulting oil was placed on a high vacuum pump for 24 h to remove the residual solvent traces affording the crude title product as a clear pale yellow oil, which was used in the next step without further purification; R_f = 0.38 (10% EtOAc–hexanes).

IR (neat): 2981, 1729, 1455, 1258, 1182, 1105, 1027, 700 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.27 (m, 2 H), 7.20–7.18 (m, 3 H), 4.19 (q, *J* = 7 Hz, 4 H), 2.60–2.56 (m, 2 H), 2.19–2.15 (m, 2 H), 1.50 (s, 3 H), 1.26 (t, *J* = 7 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2, 141.5, 128.37, 128.34, 125.9, 61.2, 53.6, 37.5, 30.8, 20.0, 14.1.

HMRS (ESI): *m*/*z* calcd for $C_{16}H_{23}NO_4$ $[M + H]^+$: 279.1591; found: 279.1588.

Anal. Calcd for $C_{16}H_{22}NO_4$: C, 69.04; H, 7.97; O, 22.99. Found: C, 69.03; H, 8.26; O, 22.48.

2-(Ethoxycarbonyl)-2-methyl-4-phenylbutanoic Acid (3)

To a solution of diethyl 2-methyl-2-phenethylmalonate (16.7 g, 60.0 mmol) in EtOH (150 mL) at 50 °C was added dropwise over 15 min a solution of KOH (3.40 g, 60.6 mmol) in a H_2O (15 mL)–EtOH (25 mL) mixture. The colorless homogeneous solution was then allowed to stir under argon at 50 °C for 64 h. The reaction mixture was then cooled to r.t., and concentrated at 50 °C by rotary evaporation. The resulting white solid was dissolved in H_2O (250 mL), and the resulting aqueous layer was washed with EtOAc (350 mL). The aqueous solution was then acidified with concd HCl (8 mL), and extracted with EtOAc (2 × 350 mL). The combined organic layers were washed with brine (250 mL), dried (Na_2SO_4), and concentrated at 40 °C by rotary evaporation. The resulting colorless oil was dried under vacuum, which smoothly crystallized at r.t. to afford 9.3 g (62%) of the monoester of malonic acid **3** as a white crystalline solid; mp 80 °C; R_f = 0.49 (10% MeOH–CH_2Cl_2).

IR (neat): 2966, 2941, 1744, 1701, 1453, 1280, 1179, 1066, 933, 751, 696 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.27 (m, 2 H), 7.21–7.18 (m, 3 H), 4.23 (q, *J* = 7 Hz, 2 H), 2.63–2.59 (m, 2 H), 2.27–2.14 (m, 2 H), 1.55 (s, 3 H), 1.29 (t, *J* = 7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.9, 172.2, 141.1, 128.4, 128.3, 126.1, 61.8, 53.6, 37.7, 30.9, 20.3, 14.6.

HMRS (ESI): *m*/*z* calcd for $C_{14}H_{18}O_4$ + Na $[M + Na]^+$: 273.1097; found: 273.1094.

Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.18; H, 7.25.

***N*-*tert*-Butyl 2-(Ethoxycarbonyl)-4-phenylbutan-2-ylcarbamate (4); Procedure 2**

To a solution of 2-(ethoxycarbonyl)-2-methyl-4-phenylbutanoic acid (**3**; 7.51 g, 30.0 mmol), NaN_3 (3.90 g, 60.0 mmol), TBAB (0.870 g, 2.70 mmol), and zinc triflate (220 mg, 0.600 mmol) in THF (150 mL) was added warm di-*tert*-butyl dicarbonate (7.60 mL, 33.0 mmol) via a syringe over 10 sec. The reaction mixture was stirred with a mechanical stirrer under argon at 50 °C for 50 h. The mixture was cooled to r.t. and quenched with aq 10% $NaNO_2$ (50 mL). The biphasic mixture was stirred for 30 min at r.t. and the two layers were separated, and the organic layer was washed successively with sat. aq NH_4Cl (75 mL), brine (75 mL), and dried (Na_2SO_4, 50 g). The organic layer was filtered and concentrated at 40 °C by rotary evaporation to afford an orange oil. Purification by column chromatography (2% EtOAc–hexanes, then 5% EtOAc–hexanes) afforded 6.75 g (70%) of the pure protected amino acid **4** as a colorless oil; R_f = 0.28 (10% EtOAc–hexanes).

IR (neat): 3425, 3265, 2978, 2932, 1704, 1495, 1365, 1252, 1163, 1055, 1028, 698 cm^{-1}.

^1H NMR (400 MHz, C_6D_6, 70 °C): δ = 7.11–6.99 (m, 11 H), 5.32 (br s, 1 H), 3.86 (q, *J* = 7 Hz, 2 H), 2.63–2.47 (m, 2 H), 2.44–2.37 (m, 1 H), 2.10–2.03 (m, 1 H), 1.52 (s, 3 H), 1.40 (s, 9 H), 0.89 (t, *J* = 7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.3, 154.1, 141.3, 128.3, 128.2, 125.9, 79.3, 61.5, 59.4, 38.4, 30.6, 28.3, 23.6, 14.1.

HMRS (ESI): *m*/*z* calcd for $C_{18}H_{27}NO_4$ + Na $[M + Na]^+$: 344.1832; found: 344.1817.

Anal. Calcd for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36; O, 19.91. Found: C, 67.24; H, 8.44; N, 4.46; O, 19.88.

Benzyl 2-Iodophenylcarbamate (6); Procedure 3

To a solution of 2-iodobenzoic acid (**5**; 7.44 g, 30.0 mmol), NaN_3 (2.92 g, 45.0 mmol), *t*-BuONa (231 mg, 2.40 mmol) in DME (100 mL) was added dropwise benzyl chloroformate[12] (4.71 mL, 33.0 mmol) over 15 min at 25 °C. The resulting reaction mixture was then stirred at 75 °C for 16 h. The mixture was cooled to r.t. and quenched with aq 10% $NaNO_2$ (50 mL). The biphasic mixture was stirred 30 min at r.t.. The two layers were separated, and the organic layer was washed successively with sat. aq NH_4Cl (75 mL), brine (75 mL), and dried (Na_2SO_4). The organic solution was filtered and concentrated at 40 °C by rotary evaporation to afford an orange oil. The solvent was removed under reduced pressure. The desired anilide **6** (9.74 g, 92%) was obtained as a white solid after flash chromatography (3% EtOAc–hexanes); mp 49 °C; R_f = 0.57 (20% EtOAc–hexanes).

IR (neat): 3383, 3031, 2953, 1732, 1586, 1514, 1432, 1201, 1036, 741 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 8 Hz, 1 H), 7.77 (d, *J* = 8 Hz, 1 H), 7.46–7.33 (m, 6 H), 7.05 (br s, 1 H), 6.81 (t, *J* = 8 Hz, 1 H), 5.24 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.2, 151.4, 138.8, 138.2, 135.7, 129.2, 128.6, 128.3, 125.1, 120.3, 88.8, 67.2.

HMRS (ESI): *m*/*z* calcd for $C_{14}H_{12}INO_2$ $[M + H]^+$: 353.9985; found: 353.9982.

1,3-Diphenylurea (8); Procedure 4

To a solution of benzoic acid (**7**, 3.66 g, 30.0 mmol), NaN_3 (2.92 g, 45.0 mmol), *t*-BuONa (231 mg, 2.40 mmol) in DME (100 mL) was added phenyl chloroformate[15] (4.14 mL, 33.0 mmol) over 15 min at 25 °C. The resulting reaction mixture was then stirred at 75 °C during 8 h, then aniline (4.10 mL, 45.0 mmol) was added and the mixture was stirred at 75 °C for 16 h. The mixture was cooled to r.t. and diluted with hexanes (70 mL). The solution was then cooled to 0 °C (ice bath) with continuous stirring; H_2O (10 mL) was added and the stirring maintained for 25 min at 0 °C. The solid was filtered and triturated with Et_2O (40 mL). The desired urea **8** (4.45 g, 70%) was obtained as a white solid; R_f = 0.51 (40% EtOAc–hexanes); mp 219 °C.

IR (neat): 3281, 3036, 1646, 1592, 1538, 1496, 1439, 1230, 893, 751 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.24 (br s, 2 H), 7.45 (d, *J* = 8 Hz, 4 H), 7.27 (t, *J* = 8 Hz, 4 H), 6.96 (t, *J* = 7 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.4, 139.6, 128.7, 121.7, 118.1.

HMRS (ESI): *m*/*z* calcd for $C_{13}H_{12}N_2O$ + Na $[M + Na]^+$: 235.0842; found: 235.0843.

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