

# Synthesis and Explosion Hazards of 4-Azido-L-phenylalanine

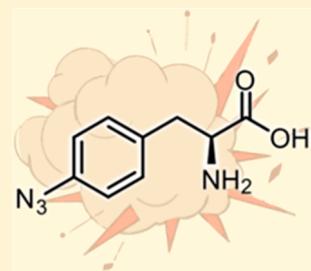
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## Supporting Information

**ABSTRACT:** A reliable, scalable, cost-effective, and chromatography-free synthesis of 4-azido-L-phenylalanine beginning from L-phenylalanine is described. Investigations into the safety of the synthesis reveal that the Ullman-like Cu(I)-catalyzed azidation step does not represent a significant risk. The isolated 4-azido-L-phenylalanine product, however, exhibits previously undocumented explosive characteristics.



## ■ INTRODUCTION

The 64 possible three-letter codons of the genetic code map to the 20 proteinogenic amino acids and two punctuation marks (start and stop signals). The code is nearly universal; every cell on Earth performs protein synthesis according to the same translation of the genetic transcript.<sup>1</sup> The unnatural (or noncanonical) amino acids are not encoded by the universal genetic code. In contrast to the 20 proteinogenic amino acids, unnatural amino acids represent an essentially infinite chemical diversity and can potentially carry any structural motif or functional group, including those not found anywhere in biology.

Codon suppression and reassignment methods allow for redundant codons to be reprogrammed, resulting in an expanded genetic code.<sup>2</sup> Combined with carefully chosen tRNA/synthase pairs, organisms with an expanded genetic code can be trained to explicitly incorporate unnatural amino acids with high fidelity alongside their natural counterparts during ribosomal protein synthesis.<sup>3</sup> The identity of the unnatural amino acid included in the expanded genetic code is selectable, and its position inside a target protein can be programmed at the genetic level. Thus, the expanded genetic code represents an enormously powerful tool for site-specific introduction of exotic functional groups into proteins.

Protein-incorporated unnatural amino acids with bioorthogonal functional groups offer highly desirable reactive handles, and an extensive catalog of organic transformations has emerged to leverage this expanded chemical space.<sup>4</sup> For example, incorporation of 4-iodo-L-phenylalanine (**1**) into proteins allows synthetic post-translational modification by Suzuki–Miyaura reactions<sup>5</sup> and has been used for site-selective introduction of polyethylene glycol<sup>6</sup> and various fluorescent dyes.<sup>3a,7</sup> The phenyl azide functional group in 4-azido-L-phenylalanine (**4**) makes it one of the most versatile unnatural amino acids in common use. This wide usage reflects two

important properties. First, **4** is comparable in size to its natural analogs phenylalanine and tyrosine. Second, its exquisite bioorthogonal reactivity makes it suitable for use in photochemical applications and both Cu(I)-catalyzed and strain-promoted azide–alkyne cycloadditions. The exceptional utility of **4** in chemical biology and protein engineering applications is evident in its exploding popularity following the first demonstration of its ribosome-mediated incorporation into proteins via an orthogonal tRNA/synthase pair in *E. coli* by Peter Schultz in 2002 (Figure S1).<sup>8</sup>

Innovative use of **4** by the laboratories of D. Dafydd Jones (Cardiff, UK) and Gottfried Otting (Australian National University) are especially noteworthy. The Jones laboratory has demonstrated superb photochemical control of the fluorescent properties of the autofluorescent proteins GFP<sup>9</sup> and mCherry<sup>10</sup> through incorporation of **4** at specific sites inside the proteins. Irradiation of the phenyl azide with UV light furnishes a reactive nitrene species, which then causes structural rearrangement and cross-linking within the protein, resulting in altered fluorescence profiles.<sup>11</sup> Otting and co-workers developed several multidentate ligands that are synthesized *in situ* from protein-incorporated **4**.<sup>12</sup> In complex with appropriate metal ions, the approach allows for site-specific introduction of EPR- and NMR-active labels that provide powerful, long-range structural information about their tethered proteins.

The distinctive azide asymmetric stretch of **4** is also clearly visible in whole-protein IR spectra. Thus, **4** has been adopted as a vibrational probe for interrogation of local protein dynamics during folding and catalysis.<sup>13</sup> The “clickable” handle afforded by the phenyl azide of **4** has also empowered dozens of

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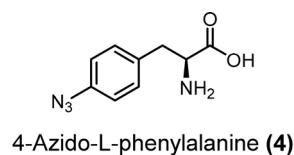
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fluorescence-tagging experiments and is featured heavily in FRET studies.<sup>14</sup>

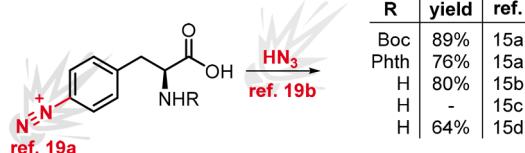
The unnatural amino acids **1** and **4** are premium reagents. Experiments with these compounds typically require high concentrations (5–10 mM) of the exogenous unnatural amino acid in the bacteria growth media for efficient incorporation. Consequently, even laboratory-scale protein production can be prohibitively expensive. Our interest in pursuing protein-labeling experiments using **4** led us to establish a reliable, scalable, and cost-effective synthesis of this compound from commodity precursors.

Three approaches have been reported for the synthesis of **4**: (1) azidodediazoniation of the corresponding phenyldiazonium species,<sup>15</sup> (2) a diazotransfer reaction performed with imidazole-1-sulfonyl azide<sup>16</sup> acting on a protected 4-amino-phenylalanine derivative,<sup>17</sup> and (3) an Ullman-type coupling of a protected 4-iodo-L-phenylalanine derivative directly to an azide anion (Figure 1).<sup>18</sup> The azidodediazoniation and



*Reported syntheses of the phenyl azide:*

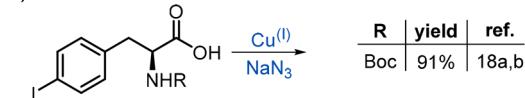
1) Azidodediazoniation



2) Diazotransfer



3) Ullman-like



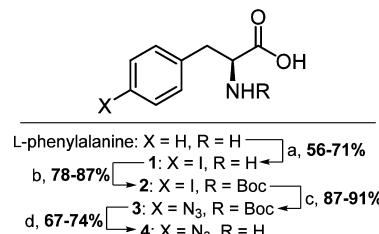
**Figure 1.** Literature precedents for the construction of the phenyl azide in **4**. Azidodediazoniation involves the use of explosive diazonium salts<sup>19a</sup> and poisonous and explosive hydrazoic acid.<sup>19b</sup> Detonation involving the diazotransfer reagent, imidazole-1-sulfonyl azide, has been reported by the Stick laboratory.<sup>16,19c</sup> Safety appraisal for the Ullman-like synthesis of phenyl azides has not previously appeared in the literature.

diazotransfer approaches are not appropriate for multigram-scale preparations owing to the well-documented explosion hazards of these transformations.<sup>19</sup> Thus, our attention turned to the only remaining literature precedent. The Ullman-type azidation can also be expected to represent an explosion hazard due to the probable formation of copper azide complexes *in situ*; however, this risk is more difficult to evaluate, owing to a relative lack of reliable documentation surrounding this transformation.

Herein, we report a procedure for the synthesis of **4** beginning from L-phenylalanine and demonstrate that the

conditions employed do not cause any detectable erosion of stereochemistry at the  $\alpha$ -carbon (Scheme 1). In addition, we

**Scheme 1. Synthesis of 4-Azido-L-phenylalanine<sup>a</sup>**



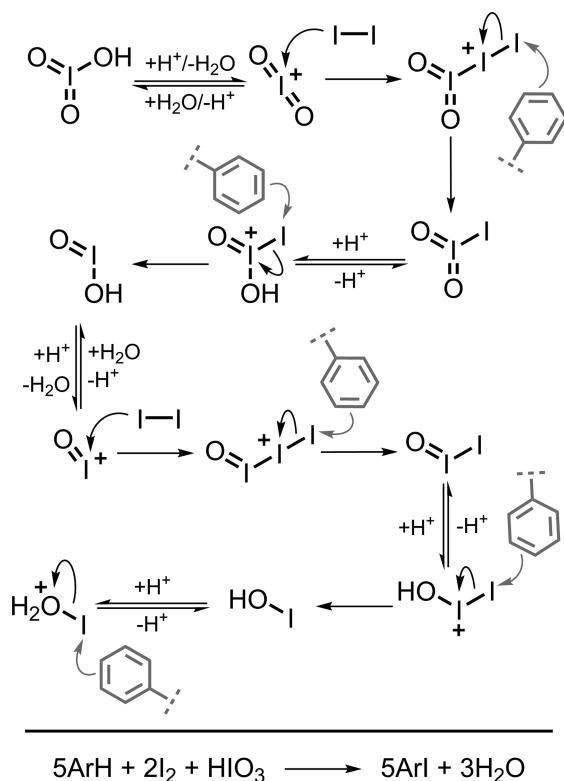
<sup>a</sup>Conditions: (a) (i) NaIO<sub>3</sub>, I<sub>2</sub>, AcOH/H<sub>2</sub>SO<sub>4</sub>, 70 °C, (ii) NaIO<sub>4</sub>; (b) Boc<sub>2</sub>O, Et<sub>3</sub>N, H<sub>2</sub>O/MeOH, 55 °C; (c) *N,N'*-dimethylethylenediamine, CuI, NaN<sub>3</sub>, KOH, sodium ascorbate, EtOH/H<sub>2</sub>O, 25 °C; (d) H<sub>2</sub>SO<sub>4</sub>/H<sub>2</sub>O, 1,4-dioxane, 25 °C.

provide an improved synthesis and characterization data for ethyl 2-(*tert*-butoxycarbonyloxyimino)-2-cyanoacetate (Boc-Oxyma) and re-establish its utility as a racemization-free coupling reagent for use in chiral derivatization analyses. Lastly, we present DSC and ARC data to establish the safety of performing the Ullman-type azidation step of the synthesis. During the investigation it was discovered that **4**, when isolated, exhibits explosive characteristics. Worryingly, and despite the widespread employment of this compound in chemical biology and biophysics laboratories, the explosive properties of **4** have not been previously documented.

## RESULTS AND DISCUSSION

**Iodination and Azidation of L-Phenylalanine.** Synthesis of **1** has a long history. The racemate was first prepared in 1908<sup>20</sup> via alkylation of *N*-phthalimidomalic ester according to the general method established by S. P. L. Sørensen.<sup>21</sup> The reported synthesis involved the preparation of an intermediate via nitration, reduction, and diazotization of toluene, followed by a Sandmeyer reaction.<sup>22</sup> This initial effort set a strong precedent for installation of the iodine atom in iodophenylalanine derivatives via Sandmeyer chemistry and was featured in the first synthesis of enantiopure **1** in 1969.<sup>23</sup> In 1994 the first direct oxidative iodination of L-phenylalanine was reported by Schwabacher.<sup>24</sup> The approach employs a mixture of iodic acid (generated *in situ* from NaIO<sub>3</sub>) and iodine (HIO<sub>3</sub>/I<sub>2</sub>, Suzuki's reagent),<sup>25</sup> and was the first example of an alternative to Sandmeyer chemistry for the synthesis of **1**.

The iodination mechanism is not trivial to understand, and the intermediates of the reaction have not been directly observed. It stands to reason that the acid-catalyzed dehydration of iodic acid could liberate a dioxoiodonium ion, which may participate directly as the electrophile in an S<sub>E</sub>Ar reaction (analogous to a nitration), or facilitate iodination indirectly via the formation of activated polar iodine intermediates. The formation of polarized iodine intermediates is consistent with similar Lewis acid-activated iodinations, such as those employing SbCl<sub>5</sub>. Moreover, the high para-regioselectivity observed in this iodination makes the presence of naked I<sup>+</sup> ions in the reaction mixture unlikely. These considerations permit the proposal of a hypothetical mechanism (Figure 2); however, it should be noted that the likely presence of coordinating bisulfate ions has been ignored for simplicity.<sup>26</sup>



**Figure 2.** Heuristic proposal for understanding the mechanism of iodination by Suzuki's reagent. Mechanism likely involves the formation of a polarized iodine intermediate, which then participates in S<sub>E</sub>Ar reactions.

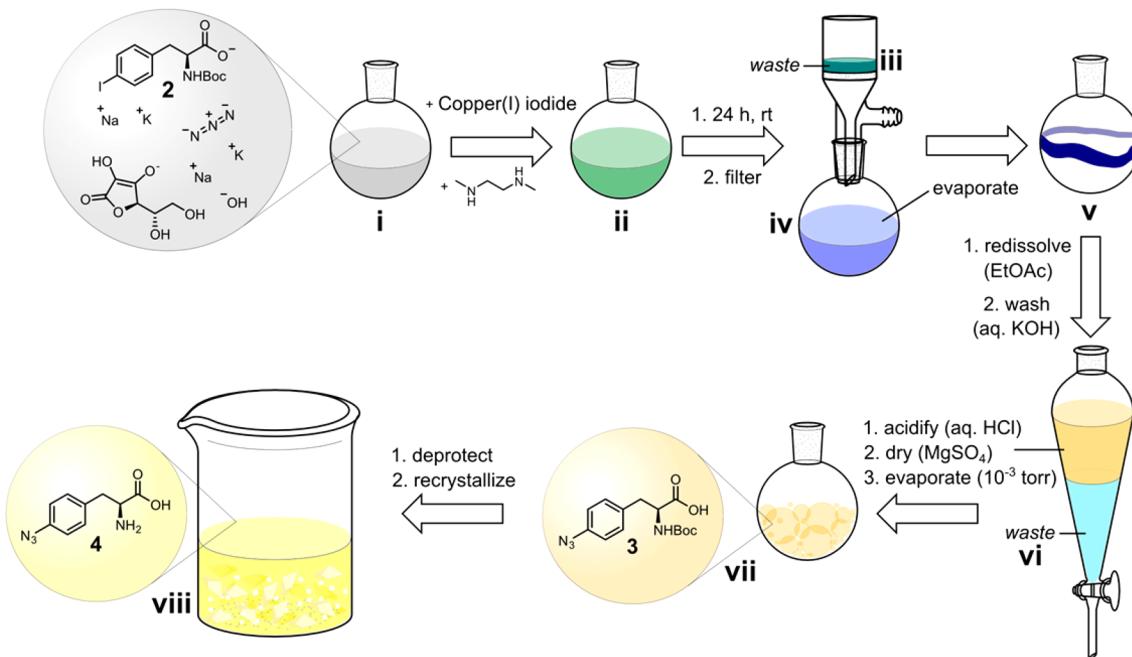
Consistent with Schwabacher's report, we observed some variability in the time required to observe complete consumption of the iodine and by inference the complete iodination of L-phenylalanine. Commonly, crystals of iodine appear on the inside surface of the reaction flask within the first 5 h of heating. However, their persistent formation after 6 h was generally a good indicator that the reaction had permanently stalled. Comparatively slow reaction rates and frequent stalling was observed when using older bottles of H<sub>2</sub>SO<sub>4</sub> and AcOH as solvents, suggesting that the reaction may prefer anhydrous conditions. Predrying the acids by treatment with small amounts of Ac<sub>2</sub>O was less likely to yield a favorable result than simply obtaining the acids from previously unopened bottles. In general, the iodination is virtually complete within 4 h, as indicated by changes in the color of the reaction mixture from dark purple, to red, and then to yellow. Stalled reactions can sometimes be recovered by adding NaIO<sub>4</sub> and additional H<sub>2</sub>SO<sub>4</sub> to the solution. Other than these minor quirks, the reaction is highly dependable and delivers good yields on 10–50 g scales. The product **1** is obtained after aqueous workup and crystallization from 50% EtOH/H<sub>2</sub>O, affording purities up to 99% by weight as judged by <sup>1</sup>H QNMR. The product is sometimes contaminated with up to ~5 mol % of a side product, presumed to be 3,4-diiodo-L-phenylalanine.

Masking the  $\alpha$ -NH<sub>2</sub> of **1** is necessary to suppress its arylation during the Ullman step. Thus, the N-Boc derivative (**2**) was prepared before installation of the azide. The Ullman-like transformation of **2** into the aryl azide **3** was first reported by Ma in 2004.<sup>18</sup> The reaction is performed under the agency of an appropriate Cu(I) complex in the presence of NaN<sub>3</sub> and sodium ascorbate in aqueous ethanol. Ma used L-proline as the

obligatory Cu(I) ligand; however, in our hands, this condition was sluggish and unreliable. In 2005, Liang re-evaluated the use of L-proline with a panel of other potential Cu(I) ligands, noting that *N,N'*-dimethylethylenediamine displays superior reactivity.<sup>27</sup> While we observed a dramatic improvement in product yields under Liang's conditions, the chances of executing a reaction uneventfully proved erratic. Thoroughly degassed solvents are essential, and reaction success is also highly dependent on the quality of the Cu(I) source. The Ma group has reported that washing commercial copper(I) iodide with refluxing THF in a Soxhlet extractor before use is critical to obtaining satisfactory catalytic activity.<sup>18b</sup> We also found that higher catalyst loadings (20 mol %) and longer reaction times (4–24 h) were generally required to achieve total product conversion than previous reports suggest. Estimating the reaction progress is nontrivial, as **2** and **3** have identical chromatographic mobilities as judged by TLC analysis. Instead, reaction progress can be monitored by removing small aliquots from the reaction mixture and conducting a miniworkup followed by NMR analysis; the disappearance of the doublet at  $\delta$  7.62 ppm signifies complete consumption of **2**. On occasion, the reaction can become permanently stalled without an obvious cause. Recovery of a stalled reaction is possible and requires isolation of the **2/3** mixture via aqueous workup, followed by immediate resubmission to the same conditions. Despite the difficulty encountered in forcing the reaction to completion, the isolated yields of **3** were consistently high, and it was obtained in up to 97% purity by weight after a simple aqueous workup.

In both Ma's and Liang's reports, a solution containing NaN<sub>3</sub> is combined with copper ions. The likely formation of copper azide complexes represents a credible explosion risk. The earliest reports on the characteristics of copper(II) azide (cupric azide) compounds noted that they are prone to explosion under heating, friction, and shock. In 1898, Curtius reported that cupric azides maintained their explosive properties even when wet with water.<sup>28</sup> In contrast, later reports by Cirulis noted that cupric azides do not appear to exhibit any explosive properties until after they have been thoroughly dried.<sup>29</sup> The sensitivity of dry cupric azide to friction is so great that it is prone to explosion during its removal from filter paper.<sup>30</sup> Copper(I) azide (cuprous azide) is similarly perilous, and explosions have been reported for this complex while completely submerged in water<sup>31</sup> and after being lightly touched with a feather in open air.<sup>30</sup> An intelligence bulletin from The National Institute for Occupational Safety and Health warned in 1976 that several explosions had occurred in the United States and Canada, apparently resulting from the accumulation of heavy-metal azides in hospital plumbing. These events were likely due to the routine disposal of NaN<sub>3</sub>-laced waste from automatic blood cell counting machines directly into hospital drains.<sup>32</sup> Since many of these incidents occurred while attempting to clear a blocked pipe, it seems unlikely that any metal azides present were dry.

While these reports attest to a general explosion risk, it is still unclear how the safety of Ma's Cu(I)-catalyzed azidation protocol should be evaluated and if the reaction can be performed without endangering the chemist. To address the ambiguity in the perceived safety of this transformation, we established an explicit protocol for the execution of this step and systematically investigated each of the chemical mixtures representing a potential explosion hazard obtained during reaction setup, workup, and isolation of the product. A detailed



**Figure 3.** Potential explosion hazards associated with the synthesis of 4. Roman numerals (i–viii) denote the eight discrete chemical mixtures chosen for explosion risk evaluation by DSC; hazards v–viii were further evaluated by ARC.

description of the procedure for this step is included in the [Experimental Section](#). In short, an aqueous ethanol solution containing the potassium salt of 2, KOH, NaN<sub>3</sub>, and sodium ascorbate is charged with CuI and *N,N'*-dimethylethylenediamine. The reaction mixture is stirred at rt for 24 h and then filtered. The filtrate is evaporated, and the residue is dissolved in EtOAc and submitted to an aqueous workup. During this procedure, there are seven chemically distinct mixtures that represent potential explosion hazards, which have been denoted with roman numerals (i–vii, [Figure 3](#)). For each of these hazards, samples were taken directly from the procedure, as it was being performed, and submitted to differential scanning calorimetry (DSC) analyses ([Table 1](#)). In addition to the

Compound 3 (hazard vii) exhibited the highest decomposition energy of any mixture obtained during the azidation protocol and may indicate that its isolation is in fact the most dangerous part of performing this reaction. The increased decomposition energy observed in v can therefore be attributed to the increased concentration of the product 3 (vii) after evaporation of the filtrate, rather than the presence of metal azides. Hazard v was also submitted to an isothermal DSC measurement at 100 °C for a period of 2 h. Only a tiny exotherm was observed after temperature equilibration, and then no exothermic behavior was exhibited for the remainder of the experiment.

The most concerning DSC datum is that of compound 4 (hazard viii). DSC measurements of both the  $\alpha$ - and the  $\beta$ -crystal polymorphs of cuprous azide have been reported previously; the decomposition is nonexplosive under N<sub>2</sub> atmosphere and with an enthalpy change of 1490 and 1160 J/g, respectively.<sup>33</sup> Therefore, weight for weight, the pre-eminent unnatural amino acid 4 exhibits a decomposition energy nearly on par with that of pure CuN<sub>3</sub>. Hazards v, vii, and viii were then further evaluated by accelerating rate calorimetry (ARC) experiments ([Table 2](#)).

The concentrated filtrate (v) shows a very mild exotherm beginning at 106 °C, which adiabatically self-heats to a maximum temperature of 132 °C. The isolated product 3

**Table 1. DSC Measurements**

| hazard         | first exotherm, J/g <sup>a</sup> | second exotherm, J/g <sup>a</sup> |
|----------------|----------------------------------|-----------------------------------|
| i              | 59 (152)                         |                                   |
| ii             | 4 (41)                           | 73 (85)                           |
| iii            | 49 (128)                         | 13 (176)                          |
| iv             | 4 (47)                           | 73 (124)                          |
| v              | 120 (136)                        | 7 (222)                           |
| v <sup>b</sup> | 13 (100)                         |                                   |
| vi             | 11 (129)                         |                                   |
| vii (3)        | 851 (124)                        |                                   |
| viii (4)       | 1145 (139)                       |                                   |

<sup>a</sup>Temperature (°C) where exothermic decomposition occurred appears in parentheses. <sup>b</sup>Isothermal DSC at 100 °C for 2 h.

mixtures obtained from the azidation step, the deprotected product 4 (hazard viii), isolated by crystallization, was also evaluated for potential explosion risks.

The observed total decomposition energies for the chemical mixtures i–iv and vi are sufficiently mild that the risk of an unexpected detonation occurring, due to the presence of CuN<sub>3</sub> or any compound, is virtually nil. The marked increase in decomposition exothermicities for v and vii is noteworthy.

**Table 2. ARC Measurements**

| hazard   | T <sub>d</sub> <sup>a</sup> °C | ΔT <sub>max</sub> °C/min | ΔP <sub>max</sub> bar/min | Φ-TMR <sup>c</sup> min | T <sub>D24</sub> <sup>d</sup> °C |
|----------|--------------------------------|--------------------------|---------------------------|------------------------|----------------------------------|
| v        | 106 (132)                      | 0.1                      | 0.09                      | 130                    | 91                               |
| vii (3)  | 111 (193)                      | 8                        | 4                         | 120                    | 79                               |
| viii (4) | 124 (>250) <sup>b</sup>        | 635                      | 660                       | 70                     | 102                              |

<sup>a</sup>The first number indicates the temperature where adiabatic self-heating occurred; the number in parentheses indicates the highest temperature observed under adiabatic self-heating. <sup>b</sup>Exceeded set temperature threshold. <sup>c</sup>Phi-corrected time to maximum rate. <sup>d</sup>Temperature at which Φ-TMR is 24 h.

(vii) shows a decomposition exotherm with an accelerating rate starting at 111 °C and running as high as 193 °C, with a concomitant increase in pressure. In both v and vii, the maximum rates of temperature and pressure increase are very mild. These observations together with the DSC data for hazards i–iv and vi firmly establish the low risk of detonation during the azidation step, up to and including isolation of the product 3. Compound 4 (hazard viii) is much more concerning. Compound 4 shows a decomposition exotherm with an accelerating rate beginning at 124 °C. A sharp temperature and pressure spike was observed after the sample reached 140 °C under self-heating (see Supporting Information). The measurement was stopped after the set maximum temperature threshold for the experiment was reached (250 °C). The massive temperature and pressure spikes observed for the decomposition of this material approach the behavior expected of a high explosive. Yoshida's correlation (eqs 1 and 2) can be used to estimate shock sensitivity (SS) and explosive propagation (EP) of a material directly from DSC data.<sup>34</sup> The test method evaluates the thermal behavior of a material from the total measured energy ( $Q$ , cal·g<sup>-1</sup>) and onset temperature ( $T$ , °C) of exothermic decomposition.

$$\text{SS} = \log_{10} Q - 0.72 \cdot \log_{10}(T - 25) - 0.98 \quad (1)$$

$$\text{EP} = \log_{10} Q - 0.38 \cdot \log_{10}(T - 25) - 1.67 \quad (2)$$

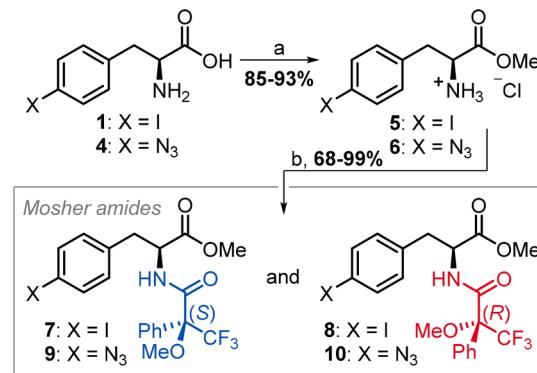
Compounds with SS or EP values equal to or greater than zero are predicted to be shock sensitive and exhibit explosive propagation properties, respectively. The DSC data for the deprotected amino acid 4 is alarmingly close to satisfying these criteria, attaining SS and EP values of -0.02 and -0.01, respectively. In our judgment, these values should qualify 4 for inclusion as an explosion hazard for the purposes of evaluating the safety of its handling and storage. The highest temperature involving 4 in the provided protocol is during recrystallization in aqueous ethanol at 85 °C (see Experimental Section). It should be noted that this temperature is below the measured exothermic decomposition point (124 °C) determined for this compound and that decomposition energies are usually greatly tempered in the presence of solvent. Regardless, there is a nonzero risk of an explosion occurring during any attempted isolation of 4, and both due diligence and standard safety precautions should be carefully followed when attempting this or any other procedure involving 4.<sup>35</sup>

**Double-Chiral Derivatization Analyses.** No literature consensus exists for the physical properties of 1 and 4. For example, previously reported optical rotation values for 1 are -20°, -10.6°, -9.1°, -6.2°, and +20°.<sup>3a,7,36</sup> We note that variation in both sign and magnitude is reported, despite each value being measured apparently from the same stereoisomer. The literature characterization data of 4 is similarly poor. The 1971 seminal articles from Caviezel and Birr provide a melting point, key IR and UV absorbances, and elemental analysis. While the synthesis of 4 has been reported more recently by Glass and Hashimoto, no additional information has been offered regarding its physical properties. From our reading, the optical rotatory power of 4 appears to have never been reported.<sup>15</sup> The lack of authoritative characterization of the physical properties of 1 and 4 is problematic. For example, the optical purity of these reagents obtained from commercial sources cannot be easily evaluated.

To alleviate the confusion surrounding these values, we report a thorough stereochemical characterization of com-

pounds 1–4 using double chiral derivatization techniques. Amino acids 1 and 4 were first converted into their methyl ester hydrochlorides and then derivatized with both (R)- and (S)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride<sup>37</sup> (MTPA-Cl) (Scheme 2). NMR analysis of the resultant Mosher amides

Scheme 2. Mosher Amide Synthesis<sup>a</sup>



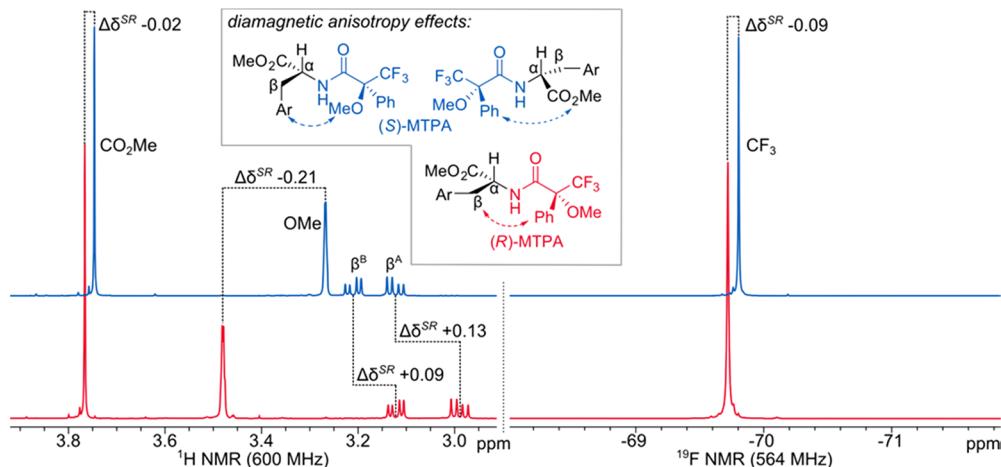
<sup>a</sup>Conditions: (a)  $\text{SOCl}_2$ ,  $\text{MeOH}$ , 50 °C, 2 h; (b) (S)- or (R)-MTPA-Cl,  $i\text{Pr}_2\text{NEt}$ , DMAP, DMF, rt, 16 h.

7–10 revealed pronounced diamagnetic anisotropy effects consistent with the expected L absolute configuration<sup>38</sup> of amino acids 1 and 4 (Figure 4, Table 3). Importantly, there is no evidence of contamination with the D-phenylalanine epimer in any of the <sup>1</sup>H, <sup>13</sup>C, or <sup>19</sup>F NMR spectra for these compounds and encourages a high level of confidence for the measured optical rotatory powers of 1 and 4.

The optical purity of N-Boc-protected intermediates 2 and 3 requires a different method of assessment, as Mosher analysis relies on the presence of a free amine or alcohol not present in either of these compounds. In an alternative approach, esterification of chiral acids with D- and L-menthol can generate diastereomeric products with different chromatographic mobilities, even in the absence of a chiral stationary phase.<sup>39</sup> Unfortunately, most esterification reactions employ the use of coupling agents in the presence of stoichiometric or excess base, which may not be conducive to maintaining stereochemistry at the α-carbon.<sup>40</sup>

This problem has been mitigated in the past through use of multistep synthetic routes that avoid exposing the chiral acid to the destructive conditions of direct esterification<sup>41</sup> and more recently through the use of an apparently racemization-free coupling agent, ethyl 2-(tert-butoxycarbonyloxyimino)-2-cyanoacetate (Boc-Oxyma).<sup>42</sup> Oxyma-based acylation protocols have become a welcomed advancement in synthetic chemistry, owing to the reclassification of N-hydroxybenzotriazole (HOBT) as a UN0508, class 1.3C explosive in 2005.<sup>43</sup> Despite the claimed success of Boc-Oxyma in racemization-free coupling, it has not appeared in the literature again since its first report in 2013. Motivated by its potential use in chiral derivatization of 2 and 3, we investigated the claims of the original article and uncovered several problems regarding the reported synthesis and physical properties.

In the original report, Boc-Oxyma is described as a red liquid and IR spectra are provided as part of an attempted time course experiment to better understand the coupling mechanism. Using the published protocol, we were able to reproduce the red liquid but found that it consists of a complex mixture of products. After optimization, we were able to synthesize Boc-



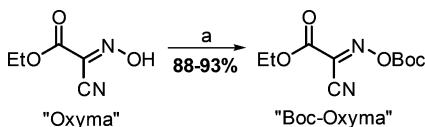
**Figure 4.** Mosher amide analyses.  $^1\text{H}$  NMR spectra of **9** (blue trace) and **10** (red trace) exhibit distinct  $\Delta\delta^{\text{SR}}$  values at the ester  $\text{CH}_3$ , the  $\alpha$ -proton, and both  $\beta$ -protons of the amino acid portion of the molecule. Mosher acyl group also exhibits an unusually high  $\Delta\delta^{\text{SR}}$  value at its etheric  $-\text{OCH}_3$ , apparently caused by diamagnetic shielding from the phenyl ring of the amino acid. Exquisite sensitivity of  $^{19}\text{F}$  NMR also provides high confidence in the optical purity, as no significant overlap is observed between the blue and the red traces.

**Table 3. Measured  $\Delta\delta^{\text{SR}}$  Values for Selected Resonances for Mosher Amides 7–10**

| nucleus         | $\delta$ (ppm)           |         |                            |                       |          |                            |
|-----------------|--------------------------|---------|----------------------------|-----------------------|----------|----------------------------|
|                 | 4-iodo Mosher amides     |         |                            | 4-azido Mosher amides |          |                            |
|                 | (S) (7)                  | (R) (8) | $\Delta\delta^{\text{SR}}$ | (S) (9)               | (R) (10) | $\Delta\delta^{\text{SR}}$ |
| $^1\text{H}$    | $\alpha$                 | 4.89    | 4.98                       | -0.09                 | 4.90     | 4.97                       |
|                 | $\beta^{\text{A}}$       | 3.09    | 2.93                       | +0.16                 | 3.12     | 2.99                       |
|                 | $\beta^{\text{B}}$       | 3.17    | 3.11                       | +0.06                 | 3.21     | 3.12                       |
|                 | $\text{CO}_2\text{CH}_3$ | 3.74    | 3.76                       | -0.02                 | 3.75     | 3.77                       |
|                 | $\text{OCH}_3$           | 3.27    | 3.47                       | -0.20                 | 3.27     | 3.48                       |
|                 | $\text{NH}$              | 7.35    | 7.01                       | +0.34                 | 7.36     | 7.00                       |
| $^{13}\text{C}$ | $\alpha$                 | 53.08   | 52.46                      | +0.62                 | 53.28    | 52.72                      |
|                 | $\beta$                  | 37.35   | 37.46                      | -0.11                 | 37.26    | 37.33                      |
|                 | $\text{CO}_2\text{CH}_3$ | 52.66   | 52.75                      | -0.09                 | 52.63    | 52.73                      |
|                 | $\text{OCH}_3$           | 54.97   | 55.36                      | -0.39                 | 54.97    | 55.38                      |
| $^{19}\text{F}$ | $\text{CF}_3$            | -69.79  | -69.74                     | -0.05                 | -69.81   | -69.72                     |

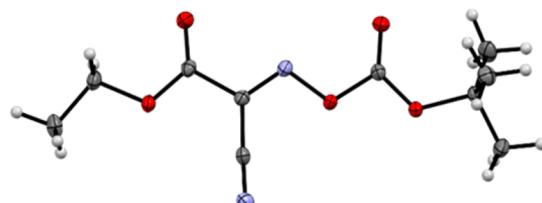
Oxyma in analytical purity on multigram scales (Scheme 3). The isolated product is a white, crystalline solid, and its identity

### Scheme 3. Synthesis of Boc-Oxyma<sup>a</sup>



<sup>a</sup>Conditions: (a)  $\text{Boc}_2\text{O}$ ,  $\text{iPr}_2\text{NEt}$  (cat.),  $\text{THF}$ ,  $35\text{ }^\circ\text{C}$ , 3.5 h.

was unambiguously assigned by single-crystal X-ray diffraction analysis (Figure 5). Comparison of the IR spectra in the region  $1600$ – $2000\text{ cm}^{-1}$  reveals a mismatch with the original report; the composition of the material used to perform coupling reactions by the original authors is unclear (Figure 6). The discussion of the mechanism in the original report also obscures an important difference between Boc-Oxyma and the prototypical aminium, uronium and phosphonium coupling agents. A base-regenerating catalytic cycle, afforded by the ejection of a *tert*-butoxide molecule at the activated ester-forming step, must be in operation (Figure 7). This may be an important omission, as the reagent can be used to generate activated esters in the presence of only catalytic quantities of base. This observation

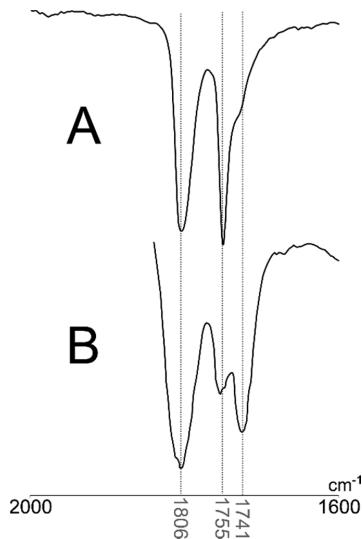


**Figure 5.** ORTEP representation of the molecular structure of Boc-Oxyma determined by single-crystal X-ray crystallography. Ellipsoids are shown at the 50% probability level. All hydrogens were discovered and are drawn as fixed-size spheres of radius 0.15 Å.

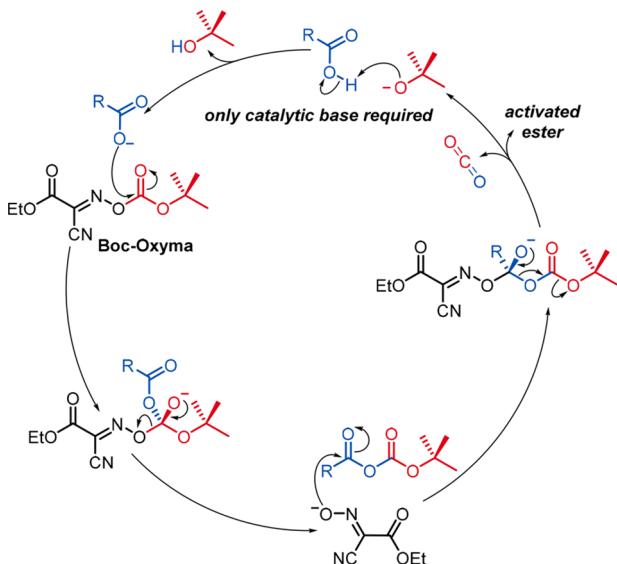
may help to explain the high observed coupling efficiencies in the presence of mild bases, such as  $\text{iPr}_2\text{NEt}$  (Hünig's base).<sup>42</sup>

Initial investigations into the utility of Boc-Oxyma in esterification reactions were very encouraging. In contrast to the Oxyma-based coupling agent COMU,<sup>44</sup> sterically demanding  $2^\circ$  alcohols were well tolerated in model reactions at rt in  $\text{EtOAc}$  and greatly accelerated in the presence of DMAP. The L- and D-menthol esters **11**–**14** were prepared directly from **2** and **3** using Boc-Oxyma to activate the carboxylic acid (Scheme 4).

The products were purified by flash chromatography, and diastereomeric mixtures were prepared by combining the D-



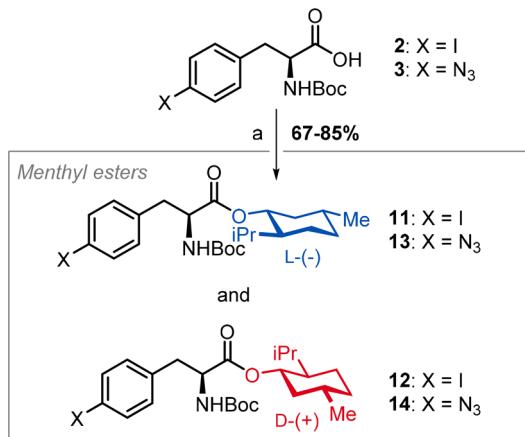
**Figure 6.** Comparison of IR spectra of Boc-Oxyma in the carbonyl stretch region. (A) IR spectrum of Boc-Oxyma (FT-IR/ATR). (B) Previously reported IR spectrum of the same compound (FT-IR/KBr disc). Image has been reproduced from ref 42 and has been altered as follows: spectrum has been reflected left-to-right.



**Figure 7.** Base-catalyzed formation of activated esters with Boc-Oxyma. Final step of the mechanism eliminates a *tert*-butoxide anion, allowing efficient activated ester generation in the presence of substoichiometric quantities of the added base.

and L-menthol ester pairs in approximately 1:1 ratios.  $^1\text{H}$  and  $^{13}\text{C}$  NMR analysis was performed separately on both the D- and the L-menthol esters and the diastereomeric mixtures. The diastereomeric mixtures can provide evidence that subtle differences in the measured chemical shifts are resolved under the conditions of the analysis. Several resonances were identified with substantial  $\Delta\delta^{\text{LD}}$  values and were sufficiently resolved in the diastereomeric mixture to be confident that each of the purified samples was free from D-phenylalanine epimers (Figure 8). Compounds 11–14 and their diastereomeric mixtures were then subjected to reverse-phase HPLC analysis. In all cases, HPLC analysis corroborated NMR data and provides high assurance that the stereochemical fidelity of 2 and 3 was maintained during the Boc-protection and Ullman-like

**Scheme 4. Synthesis of Menthyl Esters Using Boc-Oxyma as Coupling Agent<sup>a</sup>**



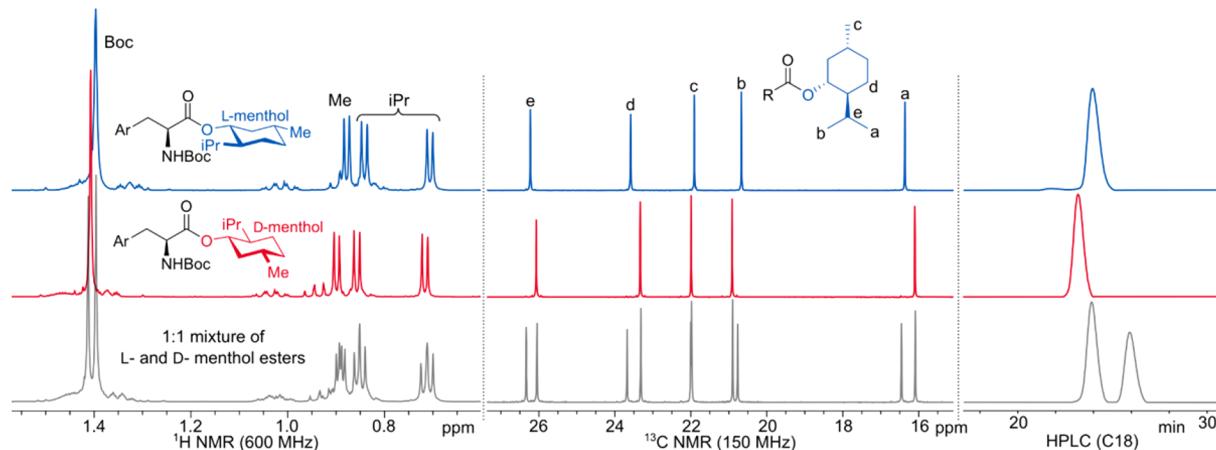
<sup>a</sup>Conditions: (a) Boc-Oxyma, iPr<sub>2</sub>NEt, DMAP, D- or L-menthol, EtOAc, rt, 24 h.

azidation steps of the sequence. Furthermore, the results of the analysis also validate the claim that Boc-Oxyma can be used in racemization-free esterification reactions.

In conclusion, we developed a scalable, cost-effective, and chromatography-free synthesis of 4 beginning from L-phenylalanine and without incurring any detectable erosion of stereochemistry at the  $\alpha$ -carbon. The search for a chiral derivatization analysis method for 2 and 3 led us to an improved synthesis of Boc-Oxyma. Further, we provide its corrected physical properties and re-establish its utility in racemization-free esterification reactions. A Cu(I)-catalyzed, Ullman-like azidation reaction was determined to be an unlikely candidate for accidental detonation and therefore may offer a safe alternative to diazotransfer and azidodediazoniation. While the Cu(I)-catalyzed process appears safe on its own, our results also serve as a sobering reminder that the target organic azides are high-energy materials and may represent a more urgent explosion hazard. The N-Boc-protected compound 3 was found to be relatively benign as an explosion risk; however, the deprotected amino acid, 4, does exhibit an explosive decomposition profile.

## EXPERIMENTAL SECTION

**General Experimental Methods.** DSC was performed using a Q2000 DSC from TA Instruments. Samples were heated in Swissi M20 high-pressure gold-plated pans at 5 °C/min. ARC was performed using an ARC-ES from Thermal Hazard Technology. Samples were heated in 10 mL hastelloy or titanium cells in a heat-wait-seek pattern at 5 °C increments. The exotherm threshold was 0.02 °C/min. High-resolution mass spectra (HRMS) were obtained by electrospray ionization (ESI) on a Waters (Micromass) LCT Premier equipped with a time-of-flight (TOF) mass analyzer. High-performance liquid chromatography (HPLC) analysis was performed on a Varian ProStar system, with an Agilent Eclipse Plus C18, 5  $\mu\text{m}$ , 4.6  $\times$  150 mm column, and UV detection at  $\lambda$  214 nm, with elution in  $\text{CH}_3\text{CN}/\text{H}_2\text{O}$  at a flow rate of 1.0 mL/min. Proton ( $^1\text{H}$ , 400 and 600 MHz), carbon ( $^{13}\text{C}$ , 100 and 150 MHz), and fluorine ( $^{19}\text{F}$ , 564 MHz) nuclear magnetic resonance (NMR) spectra were obtained on Bruker instruments equipped with a switchable QNP or BBFO probe. NMR samples were prepared in  $\text{CDCl}_3$  and  $\text{DMSO}-d_6$ , and residual protonated solvent was used as an internal chemical shift standard.  $^1\text{H}$  QNMR was performed with ethylene carbonate (Sigma-Aldrich) as an internal standard.  $^1\text{H}$  and  $^{13}\text{C}$  assignments were determined using HSQC and 10 Hz optimized HMBC 2D-NMR analyses. Optical



**Figure 8.** Menthyl ester analyses.  $^1\text{H}$  NMR spectra of **13** (blue trace) and **14** (red trace) exhibit subtle  $\Delta\delta^{\text{LD}}$  values at the three methyl groups on the menthol portion of the molecule and the *tert*-butyl of the Boc protecting group. These slight differences are clearly apparent in the sample comprising a ~1:1 mixture of both stereoisomers (gray trace).  $^{13}\text{C}$  NMR spectrum is less crowded, and signals assigned to the carbons of the menthol isopropyl group and a neighboring ring methylene display the greatest  $\Delta\delta^{\text{LD}}$  values. Lack of common peaks between the blue and the red traces indicates that no epimerization at the amino acid  $\alpha$ -carbon has occurred during the synthesis of **2** and **3** or during the esterification reaction.

rotatory powers were measured in the sodium D band (589 nm) on a Jasco P-1020 polarimeter. Fourier-transform infrared (FTIR) spectra were obtained as neat samples on a Jasco 4700 attenuated total reflectance instrument using a diamond-coated zinc selenide sample accessory. X-ray data was collected on a Bruker SMART APEX II diffractometer. Flash chromatography was carried out on silica gel 60 according to the procedure of Still et al.<sup>45</sup> Analytical thin layer chromatography (tlc) was conducted on aluminum-backed 2 mm thick silica gel 60 GF254, and chromatograms were visualized under a UV lamp (254 and 365 nm) or by chemical staining with ceric ammonium molybdate (Hanessian's stain) or KMnO<sub>4</sub>.

**Synthesis of 4-Azido-L-phenylalanine from L-Phenylalanine.** **4-Iodo-L-phenylalanine (1).** L-Phenylalanine (15.0 g, 90.8 mmol), NaIO<sub>3</sub> (3.59 g, 18.2 mmol), and I<sub>2</sub> (9.22 g, 36.3 mmol) were dissolved in a mixture of glacial AcOH (90.8 mL) and concentrated H<sub>2</sub>SO<sub>4</sub> (10.9 mL). The dark purple-colored solution was heated to 70 °C in an oil bath under an atmosphere of N<sub>2</sub> with vigorous stirring for 24 h. During this time the reaction mixture changed its color to red. NaIO<sub>4</sub> (583 mg, 2.72 mmol) was added, and the mixture was stirred at 70 °C under N<sub>2</sub> for a further 4 h until a clear, yellow-colored solution was obtained. The mixture was concentrated to approximately 50 mL at 80 °C on a rotary evaporator, and the orange-colored residue was dissolved with deionized H<sub>2</sub>O (250 mL), transferred to a separatory funnel, and then washed with Et<sub>2</sub>O (2 × 250 mL) and then CH<sub>2</sub>Cl<sub>2</sub> (1 × 250 mL). The aqueous phase was transferred to an Erlenmeyer flask and then cooled to 0 °C on an ice bath. The pH was adjusted to 7 by slow addition of a cold (0 °C) 5 M aq KOH solution with vigorous stirring. The cold, white, turbid mixture was filtered through a Büchner funnel, yielding a white solid with a mass more than 100 g due to the presence of residual water and K<sub>2</sub>SO<sub>4</sub>. The solid was transferred to an Erlenmeyer flask; then 50% aq EtOH solution was added (100 mL). The mixture was heated to 85 °C while stirring on a hot plate. Additional 100 mL aliquots of boiling 50% aq EtOH were added at 5 min intervals until a clear yellow-colored solution was obtained. The hot solution was filtered through glass wool, and the filtrate was left standing at rt for 12 h. Crystals were collected by filtration on a Büchner funnel, and the solid was washed with 100 mL of cold (0 °C) 50% aq EtOH solution. The product was dried overnight at 10<sup>-3</sup> Torr yielding 14.8–18.8 g (56–71%) of **1** as a brilliant white, pearlescent solid. The purity of **1** was determined to be 95–99% by weight as judged by  $^1\text{H}$  QNMR using ethylene carbonate as an internal standard; 3,4-diiodo-L-phenylalanine was identified as the major impurity. **1** is bench stable. Physical properties: mp = 265–270 °C (decomp.).  $[\alpha]_{D}^{23} -4.16^\circ$  (*c* 1.1 in 80% aq AcOH), +28.9° (*c* 1.1 in 1 M aq HCl/EtOH 1:1).  $^1\text{H}$  NMR (400 MHz, 1% TFA in DMSO-*d*<sub>6</sub>, 25 °C)  $\delta$ : 3.03 (1 H, dd, *J* 14.1, 6.5 Hz,  $\beta\text{-CH}_2$ ), 3.08 (1 H, dd, *J* 14.1, 6.2 Hz,  $\beta\text{-CH}_2$ ),

4.13–4.25 (1 H, m,  $\alpha\text{-CH}$ ), 7.07 (2 H, d, *J* 8.1 Hz, *ortho*-Ar), 7.69 (2 H, d, *J* 8.1 Hz, *meta*-Ar), 8.29 (3 H, br s, NH<sub>3</sub><sup>+</sup>), 14.18 (1 H, br s, CO<sub>2</sub>H).  $^{13}\text{C}$  NMR (100 MHz, 1% TFA in DMSO-*d*<sub>6</sub>, 25 °C)  $\delta$  35.4 ( $\beta\text{-CH}_2$ ), 53.1 ( $\alpha\text{-CH}$ ), 93.5 (*para*-Ar), 132.0 (2 C, *ortho*-Ar), 134.8 (*ipso*-Ar), 137.5 (2 C, *meta*-Ar), 170.4 (CO<sub>2</sub>H). IR  $\nu$  514, 798, 854, 1009, 1162, 1318, 1394, 1520, 1582, 2930 (br) cm<sup>-1</sup>. HRMS calcd for C<sub>9</sub>H<sub>10</sub>INNaO<sub>2</sub><sup>+</sup> [M + Na]<sup>+</sup> *m/z* 313.9648, found 313.9667.

**N-Boc-4-iodo-L-phenylalanine (2).** **1** (15.0 g, 51.5 mmol) and Boc<sub>2</sub>O (18.0 g, 82.4 mmol) were dissolved in a mixture of MeOH (25.8 mL), deionized H<sub>2</sub>O (25.8 mL), and Et<sub>3</sub>N (18.0 mL). The reaction mixture was heated to 55 °C in an oil bath under an atmosphere of N<sub>2</sub> with vigorous stirring for 16 h and then evaporated at 80 °C on a rotary evaporator. The thick, toffee-like residue was dried at 10<sup>-3</sup> Torr for 8 h, dissolved in EtOAc (150 mL), cooled to 0 °C on an ice bath, and then added to cold (0 °C) 250 mM aq HCl solution (250 mL) in a 1 L separatory funnel. The mixture was shaken vigorously for approximately 15 s, the organic phase was collected, and the aqueous phase was adjusted to pH 1 with cold 1 M aq HCl solution and then extracted again with EtOAc (2 × 100 mL). The combined organic phases were washed with 250 mM aq HCl in saturated NaCl solution (150 mL), dried (MgSO<sub>4</sub>), and then filtered through Celite in a sintered glass Büchner funnel. The clear, yellow-colored filtrate was evaporated to yield a solid white foam, which was then dried at 10<sup>-3</sup> Torr for 24 h. The foam was broken up with a spatula, then *n*-hexane (150 mL) was added, and the mixture was heated to 65 °C on a water bath. Et<sub>2</sub>O was added in 10 mL aliquots with gentle swirling until a clear yellow solution was obtained. The solution was decanted into a 500 mL beaker and then gently boiled at 55–65 °C on a hot plate until the volume decreased to 150 mL. Crystallization was initiated by cooling the solution on an ice bath. The crystal mass was broken up with a glass rod, and the cold suspension was filtered on a Büchner funnel. The solid was washed with 25 mL of cold (0 °C) *n*-hexanes and then dried overnight at 10<sup>-3</sup> Torr, yielding 15.8–17.6 g (78–87%) of **N**-Boc-4-iodo-L-phenylalanine (**2**) as a fine, white crystalline powder. The purity of **2** was determined to be >99% by weight as judged by  $^1\text{H}$  QNMR using ethylene carbonate as an internal standard. The product is bench stable. Physical properties: mp = 117–120 °C.  $[\alpha]_{D}^{21} +25.6^\circ$  (*c* 1.0 in MeOH), +23.6° (*c* 1.0 in EtOAc).  $^1\text{H}$  NMR (400 MHz, DMSO-*d*<sub>6</sub>, 84 °C)  $\delta$ : 1.34 (9 H, s, C(CH<sub>3</sub>)<sub>3</sub>), 2.84 (1 H, dd, *J* 13.9, 9.2 Hz,  $\beta\text{-CH}_2$ ), 3.01 (1 H, dd, *J* 13.9, 5.0 Hz,  $\beta\text{-CH}_2$ ), 4.15 (1 H, ddd, *J* 9.2, 8.5, 5.0 Hz,  $\alpha\text{-CH}$ ), 6.57 (1 H, br s, NH), 7.05 (2 H, d, *J* 8.3 Hz, *ortho*-Ar), 7.62 (2 H, d, *J* 8.3 Hz, *meta*-Ar), 12.25 (1 H, br s, CO<sub>2</sub>H).  $^{13}\text{C}$  NMR (100 MHz, DMSO-*d*<sub>6</sub>, 84 °C)  $\delta$  27.7 (3 C, C(CH<sub>3</sub>)<sub>3</sub>), 36.0 ( $\beta\text{-CH}_2$ ), 54.5 ( $\alpha\text{-CH}$ ), 77.8 (C(CH<sub>3</sub>)<sub>3</sub>), 91.2 (*para*-Ar), 131.1 (2 C, *ortho*-Ar), 136.4 (2 C, *meta*-Ar), 137.4 (*ipso*-Ar), 154.6 (NHCO<sub>2</sub>), 172.4

( $\text{CO}_2\text{H}$ ). IR  $\nu$  655, 812, 1006, 1053, 1162, 1252, 1520, 1685, 1737, 2976, 3342  $\text{cm}^{-1}$ . HRMS calcd for  $\text{C}_{14}\text{H}_{18}\text{INNaO}_4^+ [\text{M} + \text{Na}]^+$   $m/z$  414.0173, found 414.0178.

**N-Boc-4-azido-L-phenylalanine (3).** To abate the risks associated with possible formation of  $\text{HN}_3$  (a highly toxic and explosive gas), *N*-Boc-4-iodo-L-phenylalanine (2) (15.0 g, 38.3 mmol) was converted to its potassium salt by preparing a solution in EtOAc (150 mL), followed by mixing with cold (0 °C) 4 M aq KOH solution (150 mL) in a separatory funnel. The mixture was shaken vigorously for 10 s; then the organic phase was collected, and the remaining aqueous phase was extracted with additional EtOAc (100 mL). The combined clear, yellow-colored organic phases were evaporated at 50 °C on a rotary evaporator, yielding a white solid residue. The solid was dissolved in thoroughly degassed 70% aq EtOH solution (77 mL); then KOH (108 mg, 1.92 mmol), sodium ascorbate (380 mg, 1.91 mmol), and  $\text{NaN}_3$  (4.99 g, 76.7 mmol) were added. The mixture was heated at 65 °C under an atmosphere of  $\text{N}_2$  on a water bath with gentle stirring until a homogeneous solution was obtained (**Hazard i**). Then copper(I) iodide (1.46 g, 7.67 mmol) was added, followed by *N,N'*-dimethylethylenediamine (1.24 mL, 11.5 mmol) (**Hazard ii**), and the reaction mixture was stirred at rt under an atmosphere of  $\text{N}_2$  for 24 h. During the first 3–4 h, the reaction mixture changes color from blue to yellow. The reaction mixture was then filtered through Celite in a sintered glass Büchner funnel (**Hazards iii and iv**). During the filtering process, exposure to air causes the reaction mixture to change color to dark blue. The dark blue-colored filtrate was evaporated at 75 °C on a rotary evaporator, and the residue (**Hazard v**) was dissolved in a mixture of EtOAc (150 mL) and cold (0 °C) 2 M aq KOH solution (150 mL). The biphasic mixture was transferred to a 1 L separatory funnel, and the mixture was shaken vigorously, forming an intensely blue-colored aqueous phase (**Hazard vi**) and a pale green organic phase. The organic phase was collected, and the remaining aqueous phase was extracted with additional EtOAc (1 × 100 mL). The combined green-colored organic phases were washed with cold (0 °C) 250 mM aq HCl in saturated NaCl solution (200 mL), resulting in a color change of the organic phase from green to bright yellow. The organic phase was dried ( $\text{MgSO}_4$ ) and then filtered through Celite in a sintered glass Büchner funnel. The clear, yellow-colored filtrate was evaporated at 65 °C on a rotary evaporator and then dried at 10<sup>-3</sup> Torr for 4 h to yield a bright orange-colored viscous oil. The oil was dissolved in 19:1 *n*-hexane/CH<sub>2</sub>Cl<sub>2</sub> (150 mL) with gentle heating on a water bath at 65 °C; then the hot solution was filtered through glass wool. The clear, orange-colored solution was evaporated at 65 °C on a rotary evaporator and then dried at 10<sup>-3</sup> Torr for 24 h, yielding 10.2–10.7 g (87–91%) of 3 as a solid orange foam (**Hazard vii**). The purity of 3 was determined to be 95–97% by weight as judged by <sup>1</sup>H QNMR using ethylene carbonate as an internal standard. The product is light sensitive and should be stored in the dark at 4 °C. Physical properties: mp = 84 °C sharp.  $[\alpha]^{22}_D +49.5^\circ$  (c 1.2 in CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, 84 °C)  $\delta$ : 1.34 (9 H, s, C(CH<sub>3</sub>)<sub>3</sub>), 2.88 (1 H, dd, *J* 14.0, 9.2 Hz,  $\beta\text{-CH}_2$ ), 3.05 (1 H, dd, *J* 14.0, 5.0 Hz,  $\beta\text{-CH}_2$ ), 4.16 (1 H, ddd, *J* 9.2, 8.5, 5.0 Hz,  $\alpha\text{-CH}$ ), 6.56 (1 H, br s, NH), 7.02 (2 H, d, *J* 8.6 Hz, *ortho*-Ar), 7.28 (2 H, d, *J* 8.6 Hz, *meta*-Ar), 12.00 (1 H, br s, CO<sub>2</sub>H). <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>, 84 °C)  $\delta$  27.7 (3 C, C(CH<sub>3</sub>)<sub>3</sub>), 35.9 ( $\beta\text{-CH}_2$ ), 54.7 ( $\alpha\text{-CH}$ ), 77.8 ( $\text{C}(\text{CH}_3)_3$ ), 118.4 (2 C, *ortho*-Ar), 130.3 (2 C, *meta*-Ar), 134.7 (*para*-Ar), 137.2 (*ipso*-Ar), 154.7 (NHCO<sub>2</sub>), 172.5 (CO<sub>2</sub>H). IR  $\nu$  535, 680, 829, 1053, 1164, 1270, 1505, 1522, 1683, 1712, 2110, 2929, 2967, 3342  $\text{cm}^{-1}$ . HRMS calcd for  $\text{C}_{14}\text{H}_{18}\text{N}_4\text{NaO}_4^+ [\text{M} + \text{Na}]^+$   $m/z$  329.1220, found 329.1235.

**4-Azido-L-phenylalanine (4).** A 2 M aq H<sub>2</sub>SO<sub>4</sub> solution (82 mL) was added to a solution of 3 (10.0 g, 32.6 mmol) in 1,4-dioxane (82 mL), and the resulting cloudy, yellow mixture was stirred at rt for 2 h under an atmosphere of  $\text{N}_2$ . The reaction mixture was concentrated to approximately one-half its original volume at 70 °C on a rotary evaporator, and the clear, orange-colored residue was transferred to an Erlenmeyer flask and then cooled to 0 °C on an ice bath, causing a gray precipitate to appear. The pH was adjusted to 7 by slow addition of cold (0 °C) 4 M aq KOH solution with vigorous stirring. The cold, white, turbid mixture was filtered through a Büchner funnel, yielding a white solid with a mass of more than 30 g due to the presence of

residual water and K<sub>2</sub>SO<sub>4</sub>. The solid was dissolved in 50% aq EtOH solution (500 mL), and the mixture was heated to boiling with stirring on a hot plate for 15 min. The hot solution was filtered through glass wool, and the filtrate was boiled on a hot plate (85 °C) until the volume was reduced to 300 mL. The yellow-colored solution was left uncovered at rt for 12 h and then filtered on a Büchner funnel. The solid was washed with 50 mL of cold (0 °C) 50% aq EtOH solution and then was recrystallized via the same procedure. The solid was dried overnight at 10<sup>-3</sup> Torr to yield 4.50–4.97 g (67–74%) of 4 as a brilliant white, pearlescent solid. The purity of 4 was determined to >99% by weight as judged by <sup>1</sup>H QNMR using ethylene carbonate as an internal standard. The product is light sensitive and should be stored in the dark at 4 °C. Physical properties: mp = 186–191 °C (decomp.).  $[\alpha]^{22}_D -10.2^\circ$  (c 1.0 in 80% aq AcOH), +22.2° (c 1.0 in 1 M aq HCl/EtOH 1:1). <sup>1</sup>H NMR (400 MHz, 1% TFA in DMSO-d<sub>6</sub>, 25 °C)  $\delta$ : 3.07 (1 H, dd, *J* 14.3, 6.7 Hz,  $\beta\text{-CH}_2$ ), 3.11 (1 H, dd, *J* 14.3, 6.2 Hz,  $\beta\text{-CH}_2$ ), 4.12–4.22 (1 H, m,  $\alpha\text{-CH}$ ), 7.08 (2 H, d, *J* 8.5 Hz, *ortho*-Ar), 7.30 (2 H, d, *J* 8.5 Hz, *meta*-Ar), 8.28 (3 H, br s, NH<sub>3</sub>), 14.27 (1 H, br s, CO<sub>2</sub>H). <sup>13</sup>C NMR (100 MHz, 1% TFA in DMSO-d<sub>6</sub>, 25 °C)  $\delta$  35.4 ( $\beta\text{-CH}_2$ ), 53.4 ( $\alpha\text{-CH}$ ), 119.4 (2 C, *ortho*-Ar), 131.4 (2 C, *meta*-Ar), 132.0 (*para*-Ar), 138.7 (*ipso*-Ar), 170.6 (CO<sub>2</sub>H). IR  $\nu$  465, 523, 658, 787, 830, 867, 1129, 1282, 1399, 1506, 1579, 2112, 2917  $\text{cm}^{-1}$ . HRMS calcd for  $\text{C}_9\text{H}_{11}\text{N}_4\text{O}_2^+ [\text{M} + \text{H}]^+$   $m/z$  207.0876, found 207.0881.

**Synthesis of Mosher Amides and N-Boc Methyl Esters.** Methyl ester hydrochlorides 5 and 6 were prepared as follows: Amino acids 1 or 4 (7.00 mmol) were added to a stirring mixture of SOCl<sub>2</sub> (1.35 mL, 18.56 mmol) in methanol (10 mL) at 0 °C. The mixtures were stirred under an atmosphere of  $\text{N}_2$  at 0 °C for 10 min and then slowly heated to 50 °C and stirred for an additional 2 h. The reaction mixtures were evaporated at 50 °C on a rotary evaporator, and the solid residues were dissolved into hot methanol (30 mL) and then filtered on a Hirsch funnel. The filtrates were added to stirring Et<sub>2</sub>O (120 mL) at rt, the mixtures were stirred for 5 min, and then the precipitates were collected by filtration on a Büchner funnel. The solids were washed with diethyl ether (20 mL) and then dried at 10<sup>-3</sup> Torr for 24 h, yielding 5 and 6 as white powders.

**4-Iodo-L-phenylalanine Methyl Ester Hydrochloride (5).** Yield: 2.03 g (85%). Physical properties: mp 192–194 °C (decomp.).  $[\alpha]^{23}_D +17.1^\circ$  (c 1.0 in 1 M aq HCl/MeOH 1:1). <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>, 25 °C)  $\delta$ : 3.08 (1 H, dd, *J* 14.0, 7.2 Hz,  $\beta\text{-CH}_2$ ), 3.15 (1 H, dd, *J* 14.0, 5.9 Hz,  $\beta\text{-CH}_2$ ), 3.68 (3 H, s, CO<sub>2</sub>CH<sub>3</sub>), 4.22–4.28 (1 H, m,  $\alpha\text{-CH}$ ), 7.07 (2 H, d, *J* 8.3 Hz, *ortho*-Ar), 7.69 (2 H, d, *J* 8.3 Hz, *meta*-Ar), 8.71 (3 H, br s, NH<sub>3</sub>). <sup>13</sup>C NMR (125 MHz, DMSO-d<sub>6</sub>, 25 °C)  $\delta$  35.2 ( $\beta\text{-CH}_2$ ), 52.7 ( $\alpha\text{-CH}$ ), 52.9 (CO<sub>2</sub>CH<sub>3</sub>), 93.6 (*para*-Ar), 131.9 (2 C, *ortho*-Ar), 134.5 (*ipso*-Ar), 137.3 (2 C, *meta*-Ar), 169.3 (CHCO<sub>2</sub>). IR  $\nu$  480, 605, 712, 787, 835, 867, 937, 1005, 1056, 1142, 1211, 1243, 1446, 1496, 1738, 2826  $\text{cm}^{-1}$ . HRMS calcd for  $\text{C}_{10}\text{H}_{12}\text{INNaO}_2^+ [\text{M} + \text{Na}]^+$   $m/z$  327.9805, found 327.9825.

**4-Azido-L-phenylalanine Methyl Ester Hydrochloride (6).** Yield: 1.67 g (93%). Physical properties: mp 173–174 °C (decomp.).  $[\alpha]^{22}_D +23.3^\circ$  (c 1.0 in 1 M aq HCl/MeOH 1:1). <sup>1</sup>H NMR (600 MHz, DMSO-d<sub>6</sub>, 25 °C)  $\delta$ : 3.10 (1 H, dd, *J* 14.1, 7.3 Hz,  $\beta\text{-CH}_2$ ), 3.17 (1 H, dd, *J* 14.1, 5.9 Hz,  $\beta\text{-CH}_2$ ), 3.67 (3 H, s, CO<sub>2</sub>CH<sub>3</sub>), 4.23–4.27 (1 H, m,  $\alpha\text{-CH}$ ), 7.09 (2 H, d, *J* 8.5 Hz, *ortho*-Ar), 7.29 (2 H, d, *J* 8.5 Hz, *meta*-Ar). <sup>13</sup>C NMR (150 MHz, DMSO-d<sub>6</sub>, 25 °C)  $\delta$  35.1 ( $\beta\text{-CH}_2$ ), 52.6 ( $\alpha\text{-CH}$ ), 53.2 (CO<sub>2</sub>CH<sub>3</sub>), 119.3 (2 C, *ortho*-Ar), 131.1 (2 C, *meta*-Ar), 131.6 (*para*-Ar), 138.4 (*ipso*-Ar), 169.3 (CHCO<sub>2</sub>). IR  $\nu$  515, 634, 726, 802, 821, 830, 862, 901, 984, 1065, 1122, 1143, 1212, 1298, 1429, 1509, 1577, 1604, 1742, 2092, 2128, 2842  $\text{cm}^{-1}$ . HRMS calcd for  $\text{C}_{10}\text{H}_{12}\text{N}_4\text{NaO}_2^+ [\text{M} + \text{Na}]^+$   $m/z$  243.0852, found 243.0853.

Mosher amides 7–10 were prepared as follows: (S)- or (R)-MTPA-Cl (37  $\mu$ L, 0.20 mmol) was added to stirring solutions of 5 or 6 (0.19 mmol), iPr<sub>2</sub>NEt (35  $\mu$ L, 0.19 mmol), and DMAP (2.3 mg, 0.02 mmol) in anhydrous DMF (935  $\mu$ L) at 0 °C under an atmosphere of  $\text{N}_2$ . The mixtures were stirred at 0 °C for 15 min; then a second aliquot of iPr<sub>2</sub>NEt (35  $\mu$ L, 0.19 mmol) was added. The mixtures were warmed to rt and stirred in an atmosphere of  $\text{N}_2$  for 16 h. The reaction mixtures were then diluted with EtOAc (25 mL), washed with 2 × 25 mL of 1 M aq HCl solution, then 2 × 25 mL of saturated aq NaHCO<sub>3</sub> solution,

and then  $1 \times 25$  mL of saturated aq NaCl solution, then dried ( $\text{MgSO}_4$ ), filtered, and evaporated at  $40^\circ\text{C}$  on a rotary evaporator. The crude Mosher amides were purified by silica flash chromatography eluting with a gradient from 0% to 25% EtOAc in hexanes (product  $R_f = 0.55$  in 30% EtOAc/hexanes), yielding compounds **7–10** as colorless oils.

**4-Iodo-L-phenylalanine-(S)-Mosher Amide Methyl Ester (7).** Yield: 67.6 mg (68%). Physical properties:  $[\alpha]^{22}_{\text{D}} +14.9^\circ$  (*c* 1.0 in  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ , 25 °C)  $\delta$ : 3.09 (1 H, dd, *J* 14.1, 6.3 Hz,  $\beta\text{-CH}_2$ ), 3.17 (1 H, dd, *J* 14.1, 5.7 Hz,  $\beta\text{-CH}_2$ ), 3.25–3.28 (3 H, m,  $\text{OCH}_3$ ), 3.74 (3 H, s,  $\text{CO}_2\text{CH}_3$ ), 4.89 (1 H, ddd, *J* 8.1, 6.3, 5.7 Hz,  $\alpha\text{-CH}$ ), 6.90 (2 H, d, *J* 8.4 Hz, *ortho*-Ar), 7.35 (1 H, d, *J* 8.1 Hz, NH), 7.38–7.43 (3 H, m, *ortho*-Ph, *para*-Ph), 7.47–7.54 (2 H, m, *meta*-Ph), 7.64 (2 H, d, *J* 8.4 Hz, *meta*-Ar).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ , 25 °C)  $\delta$  37.4 ( $\beta\text{-CH}_2$ ), 52.7 ( $\text{CO}_2\text{CH}_3$ ), 53.1 ( $\alpha\text{-CH}$ ), 54.9–55.0 (m,  $\text{OCH}_3$ ), 84.1 (1 C, q, *J* 26.4 Hz,  $\text{CCF}_3$ ), 92.9 (*para*-Ar), 123.9 (1 C, q, *J* 290.3 Hz,  $\text{CCF}_3$ ) 128.0–128.1 (1 C, m, *para*-Ph), 128.7 (2 C, *ortho*-Ph), 129.7 (2 C, *meta*-Ph), 131.3 (2 C, *ortho*-Ar), 131.9 (*ipso*-Ph), 135.3 (*ipso*-Ar), 137.9 (*meta*-Ar), 166.2 ( $\text{CO}_2\text{CH}_3$ ), 171.3 ( $\text{NHC}=\text{O}$ ).  $^{19}\text{F}$  NMR (564 MHz, 1%  $\text{PhCF}_3$  in  $\text{CDCl}_3$ , 25 °C)  $\delta$  –69.79. IR:  $\nu$  505, 599, 631, 697, 719, 755, 800, 817, 950, 1007, 1079, 1102, 1163, 1219, 1261, 1359, 1447, 1485, 1511, 1689, 1743, 2952, 3404  $\text{cm}^{-1}$ . HRMS calcd for  $\text{C}_{20}\text{H}_{19}\text{F}_3\text{INNaO}_4^+$  [M + Na]<sup>+</sup> *m/z* 544.0203, found 544.0190.

**4-Iodo-L-phenylalanine-(R)-Mosher Amide Methyl Ester (8).** Yield: 80.5 mg (81%). Physical properties:  $[\alpha]^{22}_{\text{D}} +73.8^\circ$  (*c* 1.0 in  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ , 25 °C)  $\delta$ : 2.93 (1 H, dd, *J* 14.1, 7.4 Hz,  $\beta\text{-CH}_2$ ), 3.11 (1 H, dd, *J* 14.1, 5.2 Hz,  $\beta\text{-CH}_2$ ), 3.46–3.49 (3 H, m,  $\text{OCH}_3$ ), 3.76 (3 H, s,  $\text{CO}_2\text{CH}_3$ ), 4.98 (1 H, ddd, *J* 8.6, 7.4, 5.2 Hz,  $\alpha\text{-CH}$ ), 6.62 (2 H, d, *J* 8.4 Hz, *ortho*-Ar), 7.01 (1 H, d, *J* 8.6 Hz, NH), 7.34–7.40 (3 H, m, *ortho*-Ph, *para*-Ph), 7.40–7.44 (2 H, m, *meta*-Ph), 7.47 (2 H, d, *J* 8.4 Hz, *meta*-Ar).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ , 25 °C)  $\delta$  37.5 ( $\beta\text{-CH}_2$ ), 52.5 ( $\alpha\text{-CH}$ ), 52.8 ( $\text{CO}_2\text{CH}_3$ ), 55.3–55.5 (m,  $\text{OCH}_3$ ), 83.9 (1 C, q, *J* 26.4 Hz,  $\text{CCF}_3$ ), 92.8 (*para*-Ar), 123.6 (1 C, q, *J* 289.9 Hz,  $\text{CCF}_3$ ) 127.2–127.3 (1 C, m, *para*-Ph), 128.7 (2 C, *ortho*-Ph), 129.6 (2 C, *meta*-Ph), 131.2 (2 C, *ortho*-Ar), 132.7 (*ipso*-Ph), 135.2 (*ipso*-Ar), 137.7 (*meta*-Ar), 166.2 ( $\text{CO}_2\text{CH}_3$ ), 171.3 ( $\text{NHC}=\text{O}$ ).  $^{19}\text{F}$  NMR (564 MHz, 1%  $\text{PhCF}_3$  in  $\text{CDCl}_3$ , 25 °C)  $\delta$  –69.74. IR:  $\nu$  509, 631, 696, 719, 769, 801, 818, 951, 1007, 1078, 1103, 1162, 1219, 1262, 1357, 1448, 1485, 1514, 1689, 1743, 2953, 3405  $\text{cm}^{-1}$ . HRMS calcd for  $\text{C}_{20}\text{H}_{19}\text{F}_3\text{INNaO}_4^+$  [M + Na]<sup>+</sup> *m/z* 544.0203, found 544.0206.

**4-Azido-L-phenylalanine-(S)-Mosher Amide Methyl Ester (9).** Yield: 81.5 mg (99%). Physical properties:  $[\alpha]^{22}_{\text{D}} +12.7^\circ$  (*c* 1.0 in  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ , 25 °C)  $\delta$ : 3.12 (1 H, dd, *J* 14.0, 6.4 Hz,  $\beta\text{-CH}_2$ ), 3.21 (1 H, dd, *J* 14.0, 5.6 Hz,  $\beta\text{-CH}_2$ ), 3.25–3.29 (3 H, m,  $\text{OCH}_3$ ), 3.75 (3 H, s,  $\text{CO}_2\text{CH}_3$ ), 4.90 (1 H, ddd, *J* 8.1, 6.4, 5.6 Hz,  $\alpha\text{-CH}$ ), 6.98 (2 H, d, *J* 8.5 Hz, *ortho*-Ar), 7.14 (2 H, d, *J* 8.5 Hz, *meta*-Ar), 7.36 (1 H, d, *J* 8.1 Hz, NH), 7.38–7.42 (3 H, m, *ortho*-Ph, *para*-Ph), 7.48–7.53 (2 H, m, *meta*-Ph).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ , 25 °C)  $\delta$  37.3 ( $\beta\text{-CH}_2$ ), 52.6 ( $\text{CO}_2\text{CH}_3$ ), 53.3 ( $\alpha\text{-CH}$ ), 54.9–55.0 (m,  $\text{OCH}_3$ ), 84.2 (1 C, q, *J* 26.4 Hz,  $\text{CCF}_3$ ), 119.4 (2 C, *ortho*-Ar), 123.9 (1 C, q, *J* 289.8 Hz,  $\text{CCF}_3$ ) 128.0–128.1 (1 C, m, *para*-Ph), 128.7 (2 C, *ortho*-Ph), 129.7 (2 C, *meta*-Ph), 130.7 (2 C, *meta*-Ar), 131.9 (*ipso*-Ph), 132.4 (*para*-Ar), 139.3 (*ipso*-Ar), 166.1 ( $\text{CO}_2\text{CH}_3$ ), 171.4 ( $\text{NHC}=\text{O}$ ).  $^{19}\text{F}$  NMR (564 MHz, 1%  $\text{PhCF}_3$  in  $\text{CDCl}_3$ , 25 °C)  $\delta$  –69.81. IR:  $\nu$  513, 534, 637, 697, 718, 766, 800, 950, 994, 1017, 1079, 1102, 1161, 1220, 1262, 1284, 1359, 1448, 1505, 1692, 1742, 2114, 2954, 3407  $\text{cm}^{-1}$ . HRMS calcd for  $\text{C}_{20}\text{H}_{19}\text{F}_3\text{N}_4\text{NaO}_4^+$  [M + Na]<sup>+</sup> *m/z* 459.1251, found 459.1273.

**4-Azido-L-phenylalanine-(R)-Mosher Amide Methyl Ester (10).** Yield: 64.9 mg (80%). Physical properties:  $[\alpha]^{22}_{\text{D}} +80.6^\circ$  (*c* 1.0 in  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ , 25 °C)  $\delta$ : 2.99 (1 H, dd, *J* 14.1, 7.0 Hz,  $\beta\text{-CH}_2$ ), 3.12 (1 H, dd, *J* 14.1, 5.4 Hz,  $\beta\text{-CH}_2$ ), 3.47–3.50 (3 H, m,  $\text{OCH}_3$ ), 3.77 (3 H, s,  $\text{CO}_2\text{CH}_3$ ), 4.97 (1 H, ddd, *J* 8.5, 7.0, 5.4 Hz,  $\alpha\text{-CH}$ ), 6.80 (2 H, d, *J* 8.5 Hz, *ortho*-Ar), 6.84 (2 H, d, *J* 8.5 Hz, *meta*-Ar), 7.00 (1 H, d, *J* 8.5 Hz, NH), 7.33–7.39 (2 H, m, *ortho*-Ph), 7.39–7.44 (3 H, m, *para*-Ph, *meta*-Ph).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ , 25 °C)  $\delta$  37.3 ( $\beta\text{-CH}_2$ ), 52.72 ( $\alpha\text{-CH}$ ), 52.73 ( $\text{CO}_2\text{CH}_3$ ), 55.2–55.5 (m,  $\text{OCH}_3$ ), 83.8 (1 C, q, *J* 26.4 Hz,  $\text{CCF}_3$ ), 119.3 (2 C, *ortho*-Ar), 123.6 (1 C, q, *J* 289.9 Hz,  $\text{CCF}_3$ ), 127.2–127.4 (1 C, m, *para*-Ph),

128.6 (2 C, *ortho*-Ph), 129.6 (2 C, *meta*-Ph), 130.7 (2 C, *meta*-Ar), 132.2 (*para*-Ar), 132.8 (*ipso*-Ph), 139.0 (*ipso*-Ar), 166.1 ( $\text{CO}_2\text{CH}_3$ ), 171.4 ( $\text{NHC}=\text{O}$ ).  $^{19}\text{F}$  NMR (564 MHz, 1%  $\text{PhCF}_3$  in  $\text{CDCl}_3$ , 25 °C)  $\delta$  –69.72. IR:  $\nu$  534, 638, 697, 719, 768, 818, 996, 1018, 1078, 1105, 1120, 1164, 1219, 1274, 1357, 1449, 1507, 1692, 1744, 2115, 2954, 3411  $\text{cm}^{-1}$ . HRMS calcd for  $\text{C}_{20}\text{H}_{19}\text{F}_3\text{N}_4\text{NaO}_4^+$  [M + Na]<sup>+</sup> *m/z* 459.1251, found 459.1264.

Menthyl esters **11–14** were prepared as follows: iPr<sub>2</sub>NEt (523  $\mu\text{L}$ , 3.00 mmol) was added to a stirring solution of *N*-Boc amino acids **2** or **3** (3.00 mmol) in EtOAc (3.00 mL) at 0 °C. The mixtures were stirred under an atmosphere of  $\text{N}_2$  for 5 min; then a solution of Boc-Oxyma (1.16 g, 4.81 mmol) in EtOAc (3.00 mL) was added, and stirring was continued at 0 °C for a further 30 min. A solution of L- or D-menthol (516 mg, 3.30 mmol) and DMAP (92 mg, 0.75 mmol) in EtOAc (3.00 mL) was added, and the mixtures were warmed to rt and stirred in an atmosphere of  $\text{N}_2$  for 24 h. The reaction mixtures were then diluted with EtOAc (50 mL), washed with 2 × 50 mL of 5% w/v citric acid solution, then 2 × 50 mL of saturated aq  $\text{NaHCO}_3$  solution, and then 1 × 50 mL of saturated aq NaCl solution, then dried ( $\text{MgSO}_4$ ), filtered, and evaporated at 40 °C on a rotary evaporator. The crude menthyl esters were then purified twice by silica flash chromatography: first eluting with a gradient from 5% to 25% diethyl ether in hexanes (product  $R_f = 0.50$  in 25%  $\text{Et}_2\text{O}$ /hexanes), then second eluting with a gradient from 20% to 50%  $\text{CH}_2\text{Cl}_2$  in hexanes (product  $R_f = 0.33$  in 50%  $\text{CH}_2\text{Cl}_2$ /hexanes), affording compounds **11** and **13** as white crystalline solids and compounds **12** and **14** colorless oils.

**4-Iodo-L-phenylalanine-L-menthyl Ester (11).** Yield: 1.36 g (85%). Physical properties: mp = 106–107 °C.  $[\alpha]^{21}_{\text{D}} -22.7^\circ$  (*c* 1.0 in  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ , 55 °C)  $\delta$ : 0.70 (3 H, d, *J* 7.0 Hz,  $\text{CH}(\text{CH}_3)_2$ ), 0.77–1.07 (3 H, m, 3 × eq-H), 0.84 (3 H, d, *J* 7.2 Hz,  $(\text{CH}(\text{CH}_3)_2$ ), 0.88 (3 H, d, *J* 6.7 Hz, CyCH<sub>3</sub>), 1.30–1.48 (2 H, m, ax-H,  $\text{CH}(\text{CH}_3)_2$ ), 1.40 (9 H, s, C(CH<sub>3</sub>)<sub>3</sub>), 1.61–1.68 (2 H, m, 2 × ax-H), 1.68–1.77 (1 H, m, ax-H), 1.78–1.90 (1 H, m, ax-H), 2.94 (1 H, dd, *J* 13.5, 5.5 Hz,  $\beta\text{-CH}_2$ ), 3.02 (1 H, dd, *J* 13.5, 6.2 Hz,  $\beta\text{-CH}_2$ ), 4.46 (1 H, br s,  $\alpha\text{-CH}$ ), 4.67 (1 H, ddd, *J* 10.9, 10.9, 4.4 Hz, OCH), 4.99 (1 H, br s, NH), 6.89 (2 H, d, *J* 8.3 Hz, *ortho*-Ar), 7.56 (2 H, d, *J* 8.3 Hz, *meta*-Ar).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ , 55 °C)  $\delta$  16.4 (1 C,  $\text{CH}(\text{CH}_3)_2$ ), 20.7 (1 C,  $\text{CH}(\text{CH}_3)_2$ ), 22.0 (CyCH<sub>3</sub>), 23.6 ( $\text{CH}_2\text{CHiPr}$ ), 26.2 ( $\text{CH}(\text{CH}_3)_2$ ), 28.4 (3 C, C(CH<sub>3</sub>)<sub>3</sub>), 31.4 ( $\text{CH}_2\text{CHMe}$ ), 34.2 ( $\text{CH}_2\text{CH}_2\text{CHMe}$ ), 38.0 ( $\beta\text{-CH}_2$ ), 40.8 (OCH<sub>2</sub>CH<sub>2</sub>), 47.1 (CHiPr), 54.5 ( $\alpha\text{-CH}$ ), 75.7 (OCH), 79.8 (C(CH<sub>3</sub>)<sub>3</sub>), 92.2 (*para*-Ar), 131.6 (2 C, *ortho*-Ar), 136.1 (2 C, *meta*-Ar), 137.5 (*ipso*-Ar), 154.9 (NHCO<sub>2</sub>), 171.1 (CHCO<sub>2</sub>). IR:  $\nu$  461, 504, 648, 728, 906, 1008, 1163, 1218, 1367, 1485, 1705, 2956  $\text{cm}^{-1}$ . HRMS calcd for  $\text{C}_{24}\text{H}_{36}\text{INNaO}_4^+$  [M + Na]<sup>+</sup> *m/z* 552.1581, found 552.1591.

**4-Iodo-L-phenylalanine-D-menthyl Ester (12).** Yield: 1.07 g (67%). Physical properties:  $[\alpha]^{21}_{\text{D}} +76.9^\circ$  (*c* 1.0 in  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ , 55 °C)  $\delta$ : 0.68 (3 H, d, *J* 7.0 Hz,  $\text{CH}(\text{CH}_3)_2$ ), 0.77–1.05 (3 H, m, 3 × eq-H), 0.83 (3 H, d, *J* 7.1 Hz,  $(\text{CH}(\text{CH}_3)_2$ ), 0.88 (3 H, d, *J* 6.6 Hz, CyCH<sub>3</sub>), 1.30–1.48 (2 H, m, ax-H,  $\text{CH}(\text{CH}_3)_2$ ), 1.38 (9 H, s, C(CH<sub>3</sub>)<sub>3</sub>), 1.60–1.70 (3 H, m, 3 × ax-H), 1.91–1.98 (1 H, m, ax-H), 2.91 (1 H, dd, *J* 14.0, 6.1 Hz,  $\beta\text{-CH}_2$ ), 3.03 (1 H, dd, *J* 14.0, 6.4 Hz,  $\beta\text{-CH}_2$ ), 4.47 (1 H, br s,  $\alpha\text{-CH}$ ), 4.64 (1 H, ddd, *J* 10.9, 10.9, 4.4 Hz, OCH), 4.96 (1 H, br s, NH), 6.89 (2 H, d, *J* 8.3 Hz, *ortho*-Ar), 7.56 (2 H, d, *J* 8.3 Hz, *meta*-Ar).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ , 55 °C):  $\delta$  16.0 (1 C,  $\text{CH}(\text{CH}_3)_2$ ), 20.9 (1 C,  $\text{CH}(\text{CH}_3)_2$ ), 21.9 (CyCH<sub>3</sub>), 23.2 ( $\text{CH}_2\text{CHiPr}$ ), 26.0 ( $\text{CH}(\text{CH}_3)_2$ ), 28.3 (3 C, C(CH<sub>3</sub>)<sub>3</sub>), 31.4 ((CH<sub>2</sub>)<sub>2</sub>CHMe), 34.2 ((CH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>CHMe), 38.1 ( $\beta\text{-CH}_2$ ), 40.8 (OCH<sub>2</sub>CH<sub>2</sub>), 46.9 (CHiPr), 54.7 ( $\alpha\text{-CH}$ ), 75.9 (OCH), 79.8 (C(CH<sub>3</sub>)<sub>3</sub>), 92.3 (*para*-Ar), 131.4 (2 C, *ortho*-Ar), 136.1 (2 C, *meta*-Ar), 137.6 (*ipso*-Ar), 154.9 (NHCO<sub>2</sub>), 171.3 (CHCO<sub>2</sub>). IR:  $\nu$  465, 516, 648, 728, 906, 1008, 1164, 1219, 1367, 1486, 1708, 2956  $\text{cm}^{-1}$ . HRMS calcd for  $\text{C}_{24}\text{H}_{36}\text{INNaO}_4^+$  [M + Na]<sup>+</sup> *m/z* 552.1581, found 552.1577.

**4-Azido-L-phenylalanine-L-menthol Ester (13).** Yield: 1.04 g (78%). Physical properties: mp 86–87 °C.  $[\alpha]^{22}_{\text{D}} -37.7^\circ$  (*c* 1.0 in  $\text{CH}_2\text{Cl}_2$ ).  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ , 55 °C)  $\delta$ : 0.71 (3 H, d, *J* 7.0 Hz,  $\text{CH}(\text{CH}_3)_2$ ), 0.77–1.07 (3 H, m, 3 × eq-H), 0.84 (3 H, d, *J* 7.1 Hz,  $(\text{CH}(\text{CH}_3)_2$ ), 0.88 (3 H, d, *J* 6.6 Hz, CyCH<sub>3</sub>), 1.27–1.49 (2 H, m,

ax-H, CH(CH<sub>3</sub>)<sub>2</sub>). 1.40 (9 H, s, C(CH<sub>3</sub>)<sub>3</sub>), 1.61–1.68 (2 H, m, 2 × ax-H), 1.71–1.80 (1 H, m, ax-H), 1.82–1.90 (1 H, m, ax-H), 2.97 (1 H, dd, *J* 13.8, 6.0 Hz,  $\beta$ -CH<sub>2</sub>), 3.06 (1 H, dd, *J* 13.8, 6.3 Hz,  $\beta$ -CH<sub>2</sub>), 4.46 (1 H, br s,  $\alpha$ -CH), 4.68 (1 H, ddd, *J* 10.9, 10.9, 4.5 Hz, OCH), 5.01 (1 H, br s, NH), 6.90 (2 H, d, *J* 8.5 Hz, *ortho*-Ar), 7.13 (2 H, d, *J* 8.5 Hz, *meta*-Ar). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>, 55 °C):  $\delta$  16.4 (1 C, CH(CH<sub>3</sub>)<sub>2</sub>), 20.7 (1 C, CH(CH<sub>3</sub>)<sub>2</sub>), 21.9 (CyCH<sub>3</sub>), 23.6 (CH<sub>2</sub>CHiPr), 26.2 (CH(CH<sub>3</sub>)<sub>2</sub>), 28.3 (3 C, C(CH<sub>3</sub>)<sub>3</sub>), 31.4 ((CH<sub>2</sub>)<sub>2</sub>CHMe), 34.2 (CH<sub>2</sub>CH<sub>2</sub>CHMe), 37.8 ( $\beta$ -CH<sub>2</sub>), 40.9 (OCHCH<sub>2</sub>), 47.1 (CHiPr), 54.7 ( $\alpha$ -CH), 75.6 (OCH), 79.8 (C(CH<sub>3</sub>)<sub>3</sub>), 119.0 (2 C, *ortho*-Ar), 130.9 (2 C, *meta*-Ar), 133.3 (para-Ar), 138.9 (*ipso*-Ar), 155.0 (NHCO<sub>2</sub>), 171.2 (CHCO<sub>2</sub>). IR:  $\nu$  466, 534, 648, 729, 907, 1165, 1287, 1367, 1505, 1708, 2115, 2956 cm<sup>-1</sup>. HRMS calcd for C<sub>24</sub>H<sub>36</sub>N<sub>4</sub>NaO<sub>4</sub><sup>+</sup> [M + Na]<sup>+</sup> *m/z* 467.2629, found 467.2618.

**4-Azido-*l*-phenylalanine-*D*-methyl Ester (14).** Yield: 1.03 g (77%). Physical properties:  $[\alpha]^{22}_D$  +88.8° (*c* 1.0 in CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, 55 °C)  $\delta$ : 0.72 (3 H, d, *J* 7.0 Hz, CH(CH<sub>3</sub>)<sub>2</sub>), 0.77–1.07 (3 H, m, 3 × eq-H), 0.86 (3 H, d, *J* 7.0 Hz, (CH(CH<sub>3</sub>)<sub>2</sub>), 0.90 (3 H, d, *J* 6.6 Hz, CyCH<sub>3</sub>), 1.33–1.52 (2 H, m, ax-H, CH(CH<sub>3</sub>)<sub>2</sub>), 1.41 (9 H, s, C(CH<sub>3</sub>)<sub>3</sub>), 1.63–1.75 (3 H, m, 3 × ax-H), 1.94–2.01 (1 H, m, ax-H), 2.96 (1 H, dd, *J* 14.0, 6.2 Hz,  $\beta$ -CH<sub>2</sub>), 3.10 (1 H, dd, *J* 14.0, 6.2 Hz,  $\beta$ -CH<sub>2</sub>), 4.49 (1 H, br s,  $\alpha$ -CH), 4.67 (1 H, ddd, *J* 10.8, 10.8, 4.4 Hz, OCH), 4.92 (1 H, br s, NH), 6.94 (2 H, d, *J* 8.5 Hz, *ortho*-Ar), 7.15 (2 H, d, *J* 8.5 Hz, *meta*-Ar). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>, 55 °C):  $\delta$  16.1 (1 C, CH(CH<sub>3</sub>)<sub>2</sub>), 20.9 (1 C, CH(CH<sub>3</sub>)<sub>2</sub>), 22.0 (CyCH<sub>3</sub>), 23.3 (CH<sub>2</sub>CHiPr), 26.1 (CH(CH<sub>3</sub>)<sub>2</sub>), 28.4 (3 C, C(CH<sub>3</sub>)<sub>3</sub>), 31.5 ((CH<sub>2</sub>)<sub>2</sub>CHMe), 34.3 (CH<sub>2</sub>CH<sub>2</sub>CHMe), 38.0 ( $\beta$ -CH<sub>2</sub>), 40.9 (OCHCH<sub>2</sub>), 47.1 (CHiPr), 54.9 ( $\alpha$ -CH), 76.0 (OCH), 80.0 (C(CH<sub>3</sub>)<sub>3</sub>), 119.2 (2 C, *ortho*-Ar), 130.9 (2 C, *meta*-Ar), 133.3 (para-Ar), 139.0 (*ipso*-Ar), 155.1 (NHCO<sub>2</sub>), 171.5 (CHCO<sub>2</sub>). IR:  $\nu$  465, 534, 648, 729, 908, 1165, 1287, 1367, 1506, 1709, 2114, 2956 cm<sup>-1</sup>. HRMS calcd for C<sub>24</sub>H<sub>36</sub>N<sub>4</sub>NaO<sub>4</sub><sup>+</sup> [M + Na]<sup>+</sup> *m/z* 467.2629, found 467.2628.

**Synthesis of Boc-Oxyma.** A solution of ethyl (hydroxyimino)-cyanoacetate, “Oxyma” (10 g, 70.4 mmol), Boc<sub>2</sub>O (16.9 g, 77.4 mmol), and iPr<sub>2</sub>NEt (210  $\mu$ L, 1.20 mmol) in anhydrous THF (150 mL) was stirred at 35 °C under an atmosphere of N<sub>2</sub> for 3.5 h. Reaction progress was monitored by TLC (20% EtOAc in hexanes; product *rf* 0.4, Boc<sub>2</sub>O *rf* 0.65, Oxyma *rf* 0.0–0.2). After complete consumption of Oxyma, the reaction mixture was concentrated on a rotary evaporator at 35 °C, yielding a viscous orange-colored oil. The residue was dried at 10<sup>-3</sup> Torr for 12 h and then dissolved in Et<sub>2</sub>O (50 mL). The etheric solution was added dropwise to *n*-pentane (250 mL) at 0 °C with vigorous stirring. The resulting white precipitate was collected on a Büchner funnel and then dried at 10<sup>-3</sup> Torr for 12 h, yielding Boc-Oxyma as a white crystalline solid (15.0–15.9 g, 88–93%). Physical properties: mp 53–54 °C (decomp). <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  1.46 (3 H, t, *J* 7.1 Hz, CH<sub>2</sub>CH<sub>3</sub>), 1.59 (9 H, s, C(CH<sub>3</sub>)<sub>3</sub>), 4.46 (2 H, q, *J* 7.1 Hz, CH<sub>2</sub>CH<sub>3</sub>). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  14.1 (CH<sub>2</sub>CH<sub>3</sub>), 27.6 (C(CH<sub>3</sub>)<sub>3</sub>), 64.5 (CH<sub>2</sub>CH<sub>3</sub>), 87.7 (C(CH<sub>3</sub>)<sub>3</sub>), 106.8 (C≡N), 130.0 (C=N-O), 148.6 (CO<sub>3</sub>), 157.0 (CO<sub>2</sub>). IR:  $\nu$  438, 536, 589, 675, 756, 766, 831, 931, 961, 1010, 1046, 1149, 1237, 1301, 1371, 1398, 1472, 1581, 1751, 1805, 2942, 2990 cm<sup>-1</sup>. HRMS calcd for C<sub>10</sub>H<sub>14</sub>N<sub>2</sub>NaO<sub>5</sub><sup>+</sup> [M + Na]<sup>+</sup> *m/z* 265.0795; found 265.0791. Anal. Calcd for C<sub>10</sub>H<sub>14</sub>N<sub>2</sub>O<sub>5</sub>: C, 49.58; H, 5.83; N, 11.56. Found: C, 49.74; H, 6.03; N, 11.56.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b00270.

NMR and IR spectra for compounds 1–14 and Boc-

Oxyma, DSC and ARC plots (PDF)

Crystallographic data for Boc-Oxyma (CIF) (CIF)

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### Notes

The authors declare no competing financial interest.

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