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One-Pot Synthesis of Ureas from Boc-Protected Amines

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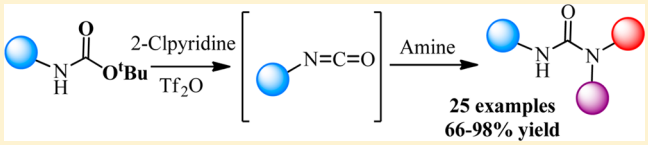
Supporting Information

ABSTRACT: A practical one-pot synthesis of ureas is described. Boc-protected amines can be transformed into nonsymmetrical and symmetrical disubstituted and trisubstituted ureas utilizing 2-chloropyridine and trifluoromethanesulfonyl anhydride for the in situ generation of an isocyanate, which reacts with an amine. A variety of amines can be employed successfully, leading to high yields of isolated ureas.

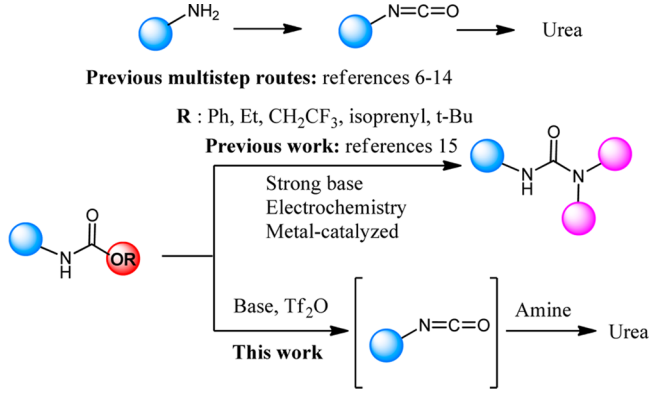


INTRODUCTION

Disubstituted and trisubstituted ureas are frequently encountered in biologically active compounds and constitute subunits of synthetic targets for a wide range of applications such as agrochemicals. In recent years, ureas have been employed as essential components in drug candidates including potent HIV protease inhibitors,[1a] CCK-B receptor antagonists,[1b] endothelin antagonists,[1c] CCR8 ligands,[1d] and p38-MAP kinase inhibitors.[1e] Furthermore, they have been employed in compounds that have been identified as potential antinociceptive,[1f] antiglycation,[1g] and anticancer agents.[1h] Apart from their presence in pharmaceuticals (such as sorafenib and cariprazine), they have also been employed as agrochemicals (such as monuron, isoproturon, diuron).[2] Oligoureas have also been introduced as scaffolds for the creation of artificial β-sheets[3] and as peptide backbone mimetics.[4] Even more recently, ureas have been used as substrates in materials science, as linkers in combinatorial chemistry, and in organocatalysis.[5]

Due to the numerous applications of ureas, a plethora of synthetic approaches exist in the literature. The traditional approach for their synthesis is the use of phosgene and its derivatives, such as triphosgene.[6] To replace the hazardous nature of phosgene by environmentally friendly substitutes, carbonates,[7] *N*,*N*′-carbonyldiimidazole,[8] 1,1′-carbonylbisbenzotriazole,[9] *S*,*S*-dimethylthiocarbonate,[10] *S*-methylthiocarbamate,[11] formamides,[12] chloroformates, and others[13] have been employed. However, in the above cases more than one step is required for the synthesis of ureas. Alternatively, metal-catalyzed processes, Curtius, Lossen, and Hoffman rearrangements, and metal-catalyzed reductive alkylations have been devised to give rise to urea derivatives, depending on the starting material in hand.[14] Among the most attractive transformations for the synthesis of ureas is the reaction of a carbamate with an amine (Scheme 1). Carbamate-type protecting groups are the most widely employed for the protection of amines and are particularly stable under a variety of conditions and inert toward nucleophilic reagents. Thus, the possibility of converting a protected amine to an urea is particularly attractive because in this manner two different amines could be used for the synthesis of the urea moiety. This straightforward approach has already been exploited by a number of researchers.[15] Unfortunately, in all these cases, a number of drawbacks are encountered. In some cases, the substrate scope is very narrow, limited to a handful of substrates,[15a,b] while in other cases strong bases are required which are not compatible with other functional groups on the molecule.[15c] Probably the main drawback though, of these methodologies, is the use of a variety of uncommon carbamates (R: phenyl, CH_2CF_3, isoprenyl, Scheme 1), because the most common *tert*-butyl (from Boc group) and benzyl (from Cbz group) are rather inert under the reaction conditions or have very low reactivity.[15a,d−f] By far, the Boc-protecting group is among the most commonly employed protecting groups for amines in organic chemistry, and only a few reports successfully utilize Boc-protected amines to furnish ureas.[15c,e] Unfortunately, a key problem in the above-mentioned methodologies is the epimerization occurring under the reaction conditions, which results in racemization of the substrates that possess chiral centers, such as those derived from amino acids.[15c]

Scheme 1. Approaches for the Synthesis of Nonsymmetrical Ureas



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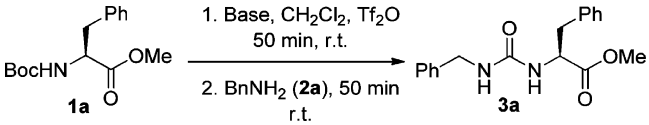
We have been actively involved in the application of ureas and thioureas as organocatalysts for a variety of transformations.[16] During the course of these studies, we have repeatedly encountered the problem of selective protection and deprotection of an amine, use of this amine and its conversion to an iso(thio)cyanate, and finally coupling with a second amine to form the (thio)urea. To decrease the number of steps required for such a transformation and coupled with recent literature findings,[17] we focused our attention to providing a mild, highly efficient one-pot synthesis of ureas from Boc-protected amines (Scheme 1). We postulated that instead of utilizing a nucleophilic base as used previously, we could employ a mild base in conjunction with trifluoromethanesulfonyl anhydride to form in situ the isocyanate, which in turn could react with an amine to afford the desired urea.

RESULTS AND DISCUSSION

To test our hypothesis, the methyl ester of Boc-protected phenylalanine (**1a**) was chosen as the model substrate (Table 1). The choice of this particular substrate had a dual role: first to check whether racemization would occur during this process and second if other functional groups, such as an ester, are compatible with this protocol. Initially, 2-chloropyridine was chosen as the base and trifluoromethanesulfonyl anhydride to form in situ the isocyanate. Benzylamine was used as the amine nucleophile and indeed the product was obtained, albeit in low yield (entry 1, Table 1). Optimization of the amount of both the base and the anhydride showed the optimum ratio of these reagents to afford the desired urea in 96% isolated yield (entries 1−4, Table 1). The amount of the amine nucleophile was then studied (entries 5−7, Table 1). Unfortunately, to have high yield in short reaction time, 9 equiv of benzylamine was necessary (entry 5, Table 1). To bypass this problem, after the completion of the reaction, the excess of the amine can be recycled via acid−base extractions; thus, expensive amines or amines that require alot of steps to be prepared can be recycled and used again. A variety of other anhydrides were then tested. Two of these attempts are included in Table 1 (entries 8 and 9). Acetic anhydride led to slightly inferior results (entry 9, Table 1), while trifluoroacetic anhydride led to a low yield (entry 8, Table 1). To further optimize the reaction conditions, a variety of bases were tested (entries 10−15, Table 1). Traditional bases such as triethylamine, DMAP, and pyridine led to poor results. Interestingly, 2-substituted pyridines, especially with a halogen, proved to be highly specific for this transformation (when 3-chloropyridine was used instead of 2-chloropyridine, the product was obtained in 66% yield). By far, the best results were obtained with 2-chloropyridine and then by 2-bromopyridine. The amount of the amine nucleophile was then studied again, because an efficient protocol with lower amounts of nucleophile would be highly desirable (entries 16−19, Table 1). It could be reduced to 3 equiv if the reaction time was extended to 20 h, leading to 96% yield of the product (entry 16, Table 1). Further reduction to 2 equiv led to moderate yield (entry 17, Table 1). To avoid extension of the reaction time and to use lower amounts of "more precious" amines, before the addition of benzylamine, triethylamine could be added and similar high yields could be obtained (entry 18, Table 1). Probably, triethylamine sequesters the acid generated, faster than 2-chloropyridine, and thus more benzylamine is "free" for the nucleophilic attack on the isocyanate. Unfortunately 3 equiv of amine is necessary for high yields, because further reduction of the amount of benzylamine led to low yield (entry 19, Table 1). Note that in the above cases the methyl ester functionality was left intact and no racemization occurred.

Table 1. Optimization of the Reaction Conditions for the One-Pot Synthesis of Ureas from Boc-Phe-OMe and Benzylamine



entry	base (equiv)	Tf_2O (equiv)	amine (equiv)	yield (%)[a]
1	2-Cl-pyridine (1)	1	12	21
2	2-Cl-pyridine (2)	1.5	12	71
3	2-Cl-pyridine (3)	1.5	12	96
4	2-Cl-pyridine (4)	2	12	96
5	2-Cl-pyridine (3)	1.5	9	96
6	2-Cl-pyridine (3)	1.5	6	83
7	2-Cl-pyridine (3)	1.5	3	59
8	2-Cl-pyridine (3)	1.5[b]	9	23
9	2-Cl-pyridine (3)	1.5[c]	9	81
10	Et_3N (3)	1.5	9	0
11	DMAP (3)	1.5	9	0
12	pyridine (3)	1.5	9	12
13	2-Me-pyridine (3)	1.5	9	28
14	2-F-pyridine (3)	1.5	9	69
15	2-Br-pyridine (3)	1.5	9	89
16	2-Cl-pyridine (3)	1.5	3[d]	96
17	2-Cl-pyridine (3)	1.5	2[d]	45
18	2-Cl-pyridine (3)	1.5	3[e]	93
19	2-Cl-pyridine (3)	1.5	2[f]	30

[a]Isolated yield after column chormatography. [b]Trifluoroacetic acid anhydride (TFAA) was used instead of Tf_2O. [c]Acetic acid anhydride (Ac_2O) was used instead of Tf_2O. [d]After addition of benzylamine, the reaction mixture was stirred for 20 h at rt. [e]Before addition of benzylamine (3 equiv), Et_3N (6 equiv) was added. [f]Before addition of benzylamine (2 equiv), Et_3N (7 equiv) was added.

Once the optimum reaction conditions were identified, the substrate scope was explored. Initially, a variety of amines were utilized (Scheme 2). In addition to benzylamine, other primary amines bearing long linear alkyl or alkenyl chains are well tolerated, leading from high to excellent yields (ureas **3b−d**). Not only were primary amines used but also primary amines on secondary alkyl chains were used, such as the symmetrical cyclohexylamine and isopropylamine and nonsymmetrical amines, which were employed successfully, leading to ureas **3e−h** in high yields. In the case of **3h**, an inseparable mixture of diastereomers (2:1) was obtained because racemic 2-methylbenzylamine was utilized. Anilines as well as the sterically hindered *tert*-butylamine were successfully used, leading to high yields. Finally, secondary amines can be employed, leading to trisubstituted ureas **3l−o**. Cyclic amines such as piperidine and morpholine and noncyclic secondary amines such as dibenzylamine led to high yields. Again, in all the above cases, racemization did not occur. Finally, a chiral secondary amine, H-Pro-OBn, was utilized, leading to urea peptidomimetic **3o**, which was isolated in excellent yield. To prove beyond doubt that no epimerization or racemization had occurred, urea **3a** was synthesized in its racemic form. Using chiral HPLC, we were able to confirm that no racemization was detected (for more details, see Supporting Information).

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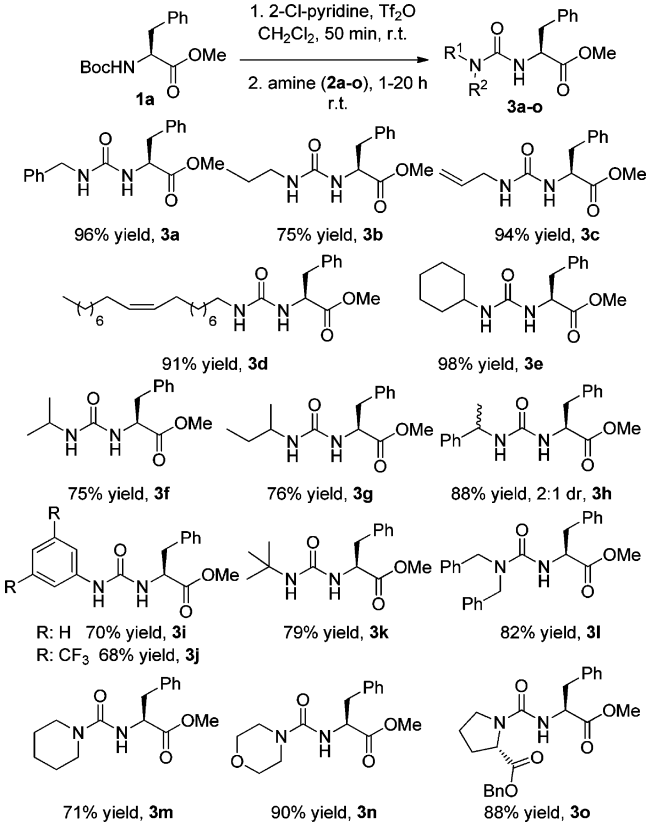
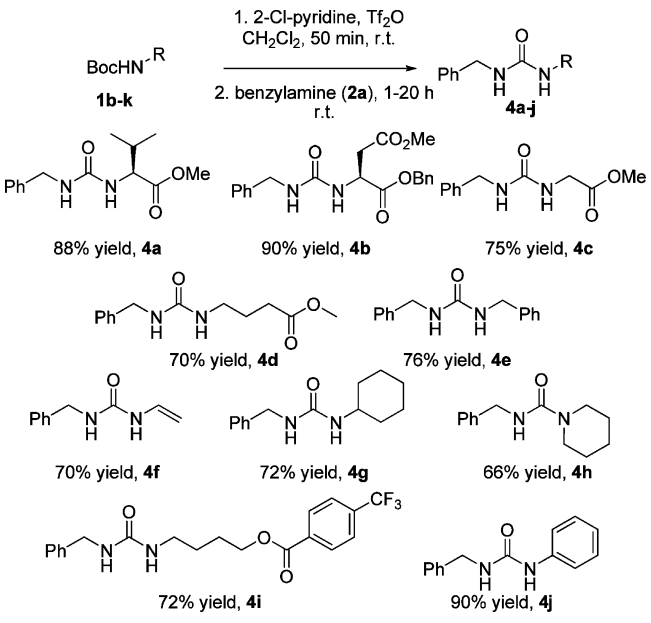
Scheme 2. One-Pot Synthesis of Ureas from Boc-Phe-OMe and Amines



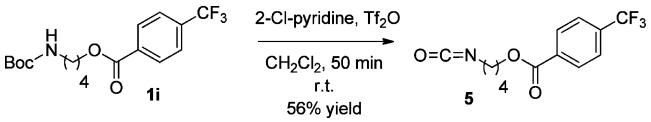
Because our main interest lies in the synthesis of chiral ureas,[16] we then explored the possibility of utilizing other Boc-protected amines (Scheme 3). Initially, a number of chiral and nonchiral protected amino acids were utilized, because the products could be employed as catalysts or could be further derivatized to be applied in organocatalytic reactions. Toward this end, Boc-protected derivatives of valine, aspartic acid, glycine, and 4-aminobutanoic acid (GABA) were successfully employed, leading to ureas **4a–d** in high yields. Symmetrical ureas can be also obtained, such as urea **4e**. Other Boc-protected aliphatic amines such as allylamine, cyclohexylamine, and even secondary amines such as piperidine can be utilized in this protocol, leading to ureas **4f–h**. Other functional groups such as protected alcohols are well tolerated, leading to high yield (urea **4i**). Finally, even Boc-aniline can be employed in this protocol, leading to urea **4j** in excellent yield.

Scheme 3. One-Pot Synthesis of Ureas from Boc-Protected Amines and Benzylamine



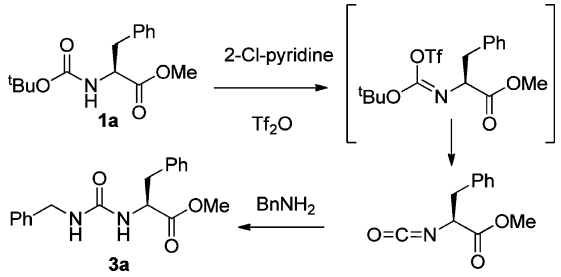
According to literature reports, when carbamates are used as the starting material, no matter which method is utilized, an intermediate isocyanate is postulated.[15,17] However, this intermediate was never isolated, but researchers have established its existence via monitoring the reaction by IR spectroscopy.[15e,17] We were able to isolate the intermediate isocyanate **5**, after treating the Boc-protected amine with 2-chloropyridine and trifluoromethanesulfonyl anhydride (Scheme 4).

Scheme 4. Isolation of the Intermediate Isocyanate



After identification of this crucial intermediate, the following mechanism can be proposed (Scheme 5). Initially, Boc-protected amine **1a** is treated with the dehydrating agents, leading to an intermediate imino triflate, which collapses to generate the corresponding isocyanate. Upon addition of the amine, urea **3a** is obtained.

Scheme 5. Proposed Reaction Mechanism



CONCLUSIONS

A mild and highly efficient one-pot process for the synthesis of ureas from Boc-protected amines is described. The substrate scope of the reaction is very general, and a variety of aliphatic primary and secondary amines, even aniline, can be tolerated. In addition, a number of Boc-protected amines can be employed, leading to ureas in high yields. This methodology enriches the literature knowledge, utilizes a widely accepted protecting group of amines (Boc) rather than some more reactive but rare carbamates and provides a shorter and efficient protocol to form ureas, and more importantly the use of chiral substrates is well tolerated, because no racemization or epimerization occurs. The mechanism of the reaction was studied, and the active intermediate was isolated.

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EXPERIMENTAL SECTION

General Remarks. Chromatographic purification of products was accomplished using forced-flow chromatography. Thin-layer chromatography (TLC) was performed on aluminum-backed silica plates (0.2 mm, 60 F_{254}). Visualization of the developed chromatogram was performed by fluorescence quenching using phosphomolybdic acid, anisaldehyde, or potassium permanganate stains. IR spectra were recorded on an FT-IR spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Melting points were determined on a hot stage apparatus and are uncorrected. Mass spectra (ESI) were recorded on a LC-MS spectrometer. HRMS spectra (ESI) were recorded on a QTOF spectrometer. ^1H, ^{19}F, and ^{13}C NMR spectra were recorded on 200, 188, and 50 MHz, respectively, and are internally referenced to residual solvent signals. Data for ^1H NMR are reported as follows: chemical shift (δ ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad signal, bs m = broad signal multiplet), and coupling constant. Data for ^{19}F NMR are internally referenced to trifluoroacetic acid. Data for ^{13}C NMR are reported in terms of chemical shift (δ ppm). All Boc-protected amines used were either commercially available or synthesized via literature procedures, and all data obtained matched literature data. Boc-protected amines were either commercially available or were synthesized using literature known procedures and all data matched literature data for **1c**,[18a] **1e**,[18b] and **1f**.[18c]

General Procedure for the One-Pot Synthesis of Ureas from Boc-Protected Amines. Boc-protected amine (0.30 mmol) was placed in a round-bottom flask followed by dry CH_2Cl_2 (10 mL). 2-Chloropyridine (0.09 mL, 0.90 mmol) was added, followed by trifluoromethanesulfonic anhydride (0.08 mL, 0.45 mmol), and the reaction mixture was stirred for 50 min at room temperature. Then amine (0.90 or 2.70 mmol) or Et_3N (1.80 mmol) followed by amine (0.90 mmol) was added, and the reaction mixture was stirred at room temperature for 1−20 h. The crude product was purified using column chromatography (30%−50% EtOAc in petroleum ether) to afford the desired product.

(*S*)-Methyl 2-(3-Benzylureido)-3-phenylpropanoate (3a).[19] Utilizing 3 equiv of amine, reaction time 20 h. White solid; 90 mg, 96% yield; mp 96−98 °C {lit. mp 94−96 °C};[19a] $[\alpha]_D$ = +56.5 (c = 1.0, $CHCl_3$) {lit. $[\alpha]_D$ = +57.4 (c = 1.0, $CHCl_3$)};[19b] IR (film) 3336, 3028, 2949, 2924, 1742, 1634, 1565, 1495, 1207; ^1H NMR (200 MHz, $CDCl_3$) δ 7.32−7.10 (8H, m), 7.10−6.99 (2H, m), 5.81−5.55 (2H, m), 4.75−4.60 (1H, m), 4.24 (1H, dd, J = 15.4 and 6.1 Hz), 4.13 (1H, dd, J = 15.4 and 5.8 Hz), 3.56 (1H, s), 2.98 (1H, dd, J = 14.6 and 6.6 Hz), 2.87 (1H, dd, J = 14.6 and 6.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.3, 157.5, 139.1, 136.2, 129.1, 128.3, 128.2, 127.1, 126.9, 126.6, 53.9, 51.9, 43.8, 38.3; MS 313 (M + H^+, 100).

(*S*)-Methyl 3-Phenyl-2-(3-propylureido)propanoate (3b). Utilizing 9 equiv of amine, reaction time 20 h. White solid; 59 mg, 75% yield; mp 84−86 °C; $[\alpha]_D$ = +61.2 (c = 1.0, $CHCl_3$); IR (film) 3341, 2960, 2873, 1744, 1635, 1566, 1210, 1096; ^1H NMR (200 MHz, $CDCl_3$) δ 7.44−6.94 (5H, m), 5.49−5.13 (1H, m), 4.99 (1H, t, J = 5.3 Hz), 4.75−4.67 (1H, m), 3.68 (3H, s), 3.35−2.73 (4H, m), 1.69−1.17 (2H, m), 0.85 (3H, t, J = 7.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.5, 157.5, 136.3, 129.2, 128.3, 126.8, 53.9, 52.0, 42.0, 38.4, 23.2, 11.2; MS 265 (M + H^+, 100); HRMS exact mass calculated for [M + Na] $^+$ ($C_{14}H_{20}O_3N_2Na$) requires m/z 287.1366, found m/z 287.1357.

(*S*)-Methyl 2-(3-Allylureido)-3-phenylpropanoate (3c). Utilizing 3 equiv of amine, reaction time 20 h. White solid; 74 mg, 94% yield; mp 73−75 °C; $[\alpha]_D$ = +74.7 (c = 1.0, $CHCl_3$); IR (film) 3322, 3061, 2353, 1744, 1633, 1565, 1217, 992, 919; ^1H NMR (200 MHz, $CDCl_3$) δ 7.35−7.15 (3H, m), 7.13−7.00 (2H, m), 5.87−5.67 (1H, m), 5.36 (1H, br s), 5.15 (3H, m), 4.80−4.67 (1H, m), 3,75−3.65 (2H, m), 3.67 (3H, s), 3.05 (1H, dd, J = 13.3 and 5.4 Hz), 2.96 (1H, dd, J= 13.3 and 5.9 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.3, 157.2, 136.2, 135.1, 129.2, 128.4, 126.8, 115.6, 53.9, 52.1, 42.8, 38.4; MS 263 (M + H^+, 100); HRMS exact mass calculated for [M + Na] $^+$ ($C_{14}H_{18}O_3N_2Na$) requires m/z 285.1210, found m/z 285.1201.

(*S,Z*)-Methyl 2-[3-(Octadec-9-en-1-yl)ureido]-3-phenylpropanoate (3d). Utilizing 3 equiv of amine, reaction time 20 h. Light yellow oil; 129 mg, 91% yield; $[\alpha]_D$ = +39.4 (c = 1.0, $CHCl_3$); IR (film) 3322, 2923, 2852, 2353, 1746, 1632, 1568, 1455, 1218, 1095; ^1H NMR (200 MHz, $CDCl_3$) δ 7.28−7.14 (3H, m), 7.12−7.04 (2H, m), 5.46−5.23 (3H, m), 5.11−4.98 (1H, m), 4.84−4.64 (1H, m), 3.64 (3H, s), 3.16−2.85 (4H, m), 2.22−1.78 (4H, m), 1.42−1.14 (24H, m), 0.84 (3H, t, J= 6.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.6, 157.5, 136.3, 129.8, 129.7, 129.2, 128.3, 126.8, 53.9, 52.0, 40.3, 38.4, 32.5, 31.8, 30.0, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 27.1, 26.9, 26.8, 22.6, 14.1; MS 473 (M + H^+, 100); HRMS exact mass calculated for [M + Na] $^+$ ($C_{29}H_{48}O_3N_2Na$) requires m/z 495.3557, found m/z 495.3537.

(*S*)-Methyl 2-(3-Cyclohexylureido)-3-phenylpropanoate (3e).[11] Utilizing 9 equiv of amine, reaction time 1 h. White solid; 89 mg, 98% yield; mp 83−85 °C; $[\alpha]_D$ = +66.5 (c = 1.0, $CHCl_3$); IR (film) 3342, 2928, 2852, 2372, 1773, 1627, 1498, 1490, 1218, 1100; ^1H NMR (200 MHz, $CDCl_3$) δ 7.35−7.00 (5H, m), 5.38 (1H, d, J = 8.1 Hz), 5.03 (1H, d, J = 7.9 Hz), 4.82−4.64 (1H, m), 3.64 (3H, s), 3.52−3.35 (1H, br m), 3.05 (1H, dd, J = 12.3 and 4.4 Hz), 2.97 (1H, dd, J = 12.3 and 4.6 Hz), 1.94−1.47 (5H, m), 1.42−0.91 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.5, 156.8, 136.3, 129.2, 128.3, 126.8, 54.0, 52.0, 48.9, 38.5, 33.6, 33.5, 25.5, 24.9, 24.8; MS 305 (M + H^+, 100).

(*S*)-Methyl 2-(3-Isopropylureido)-3-phenylpropanoate (3f).[19] Utilizing 9 equiv of amine, reaction time 20 h. White solid; 59 mg, 75% yield; mp 112−116 °C {lit. mp 115 °C};[19a] $[\alpha]_D$ = +72.8 (c = 1.0, $CHCl_3$); IR (film) 3448, 3372, 2968, 1736, 1637, 1560, 1218; ^1H NMR (200 MHz, $CDCl_3$) δ 7.28−7.16 (3H, m), 7.14−7.04 (2H, m), 5.33 (1H, d, J = 8.0 Hz), 4.92 (1H, d, J = 7.7 Hz), 4.79−4.61 (1H, m), 3.87−3.61 (1H, m), 3.66 (3H, s), 3.03 (1H, dd, J = 13.4 and 5.6 Hz), 2.94 (1H, dd, J = 13.4 and 5.5 Hz), 1.12−1.02 (6H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.5, 156.8, 136.3, 129.2, 128.3, 126.8, 53.9, 52.0, 42.0, 38.6, 23.2, 23.1; MS 265 (M + H^+, 100).

(*S*)-Methyl 2-(3-*sec*-Butylureido)-3-phenylpropanoate (3g). Utilizing 3 equiv of amine, reaction time 20 h. Yellow solid; 64 mg, 76% yield; mp 55−57 °C; $[\alpha]_D$ = +62.5 (c = 1.0, $CHCl_3$); IR (film) 3353, 2964, 1746, 1633, 1560, 1218; ^1H NMR (200 MHz, $CDCl_3$) δ 7.30−7.16 (3H, m), 7.14−7.06 (2H, m), 5.25 (1H, d, J = 7.8 Hz), 4.85−4.67 (2H, m), 3.66 (3H, s), 3.69−3.51 (1H, m), 3.06 (1H, dd, J = 13.3 and 5.5 Hz), 2.96 (1H, dd, J = 13.3 and 5.8 Hz), 1.48−1.31 (2H, m), 1.09−0.99 (3H, m), 0.91−0.79 (3H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.5, 157.0, 136.4, 129.2, 128.3, 126.8, 53.9, 52.0, 47.4, 38.5, 30.0, 20.8, 10.2; MS 279 (M + H^+, 100); HRMS exact mass calculated for [M + Na] $^+$ ($C_{15}H_{22}O_3N_2Na$) requires m/z 301.1523, found m/z 301.1512.

(2*S*)-Methyl 3-Phenyl-2-(3-(1-phenylethyl)ureido)-propanoate (3h).[20] Utilizing 3 equiv of amine, reaction time 20 h. Yellow oil; 86 mg, 88% yield; 2:1 mixture of diastereomers; $[\alpha]_D$ = +48.0 (c = 1.0, $CHCl_3$) {lit. $[\alpha]_D$ = +52.3 (c = 1.0, $CHCl_3$)};[19b] IR (film) 3331, 2968, 2352, 1744, 1631, 1559, 1494, 1217; ^1H NMR (200 MHz, $CDCl_3$) δ 7.37−7.12 (8H, m), 7.07−7.00 (1H, m), 7.00−6.90 (1H, m), 5.65−5.60 (1H, m), 5.59−5.45 (0.68H, m), 5.37−5.27 (0.32H, m), 4.84−4.62 (2H, m), 3.60 (3H, s), 3.06−2.84 (2H, m), 1.36−1.26 (3H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.3, 173.1, 156.9, 156.8, 144.3, 144.1, 136.2, 136.1, 129.2, 129.1, 128.5, 128.4, 128.3 128.2, 127.0, 126.9, 126.7, 126.6, 125.8, 125.7, 53.9, 53.8, 52.0, 51.9, 50.0, 49.8, 38.5, 38.4, 23.3, 23.0; MS 327 (M + H^+, 100).

(*S*)-Methyl 3-Phenyl-2-(3-phenylureido)propanoate (3i).[21] Utilizing 6 equiv of Et_3N and 3 equiv of amine, reaction time 1 h. White solid; 63 mg, 70% yield; mp 84−87 °C {lit. mp 81−82 °C};[21] $[\alpha]_D$ = +52.6 (c = 1.0, $CHCl_3$); IR (film) 3342, 2358, 1743, 1649, 1555, 1497, 1441, 1215; ^1H NMR (200 MHz, $CDCl_3$) δ 7.45 (1H, br s), 7.39−6.93 (10H, m), 5.96 (1H, d, J = 8.0 Hz), 4.86−4.75 (1H, m), 3.66 (3H, s), 3.09 (1H, dd, J = 13.8 and 5.7 Hz), 2.96 (1H, dd, J = 13.8 and 6.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 173.3, 155.3, 138.4, 136.1, 129.2, 128.9, 128.4, 126.9, 123.3, 120.3, 54.0, 52.2, 38.2; MS 299 (M + H^+, 100).

(*S*)-Methyl 2-[3-(3,5-Bis(trifluoromethyl)phenyl)ureido]-3-phenylpropanoate (3j).[22] Utilizing 6 equiv of Et_3N and 3 equiv of amine, reaction time 1 h. Light yellow solid; 89 mg, 68% yield; mp 80−82 °C; $[\alpha]_D$ = +64.8 (c = 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.70 (1H, s), 7.60 (2H, s), 7.35−7.21 (4H, m), 7.13−7.07 (2H, m), 5.92 (1H, d, J = 7.8 Hz), 4.83 (1H, ddd, J = 7.8, 7.1, and 5.2

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Hz), 3.85 (3H, s), 3.08 (1H, dd, J = 13.9 and 5.2 Hz), 2.96 (1H, dd, J = 13.9 and 7.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 175.1, 154.3, 140.0, 135.6, 131.6 (q, J = 33.2 Hz), 129.1, 128.8, 127.4, 122.9 (q, J = 272.7 Hz), 117.9 (m), 115.6 (m), 53.9, 52.9, 37.6; ^{19}F NMR (188 MHz, $CDCl_3$) δ −8.22 (3F, s); MS 435 (M + H$^+$, 100).

(*S*)-Methyl 2-(3-*tert*-Butylureido)-3-phenylpropanoate (3k).[23] Utilizing 9 equiv of amine, reaction time 20 h. Yellow low melting solid; 66 mg, 79% yield; $[\alpha]_D$ = +66.1 (c = 1.0, $CHCl_3$); IR (film) 3352, 2962, 1745, 1637, 1558, 1453, 1218; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.27−7.14 (3H, m), 7.12−7.05 (2H, m), 5.12 (1H, br s), 4.69 (1H, t, J = 5.8 Hz), 4.40 (1H, br s), 3.65 (3H, s), 3.01(1H, dd, J = 13.9 and 5.8 Hz), 2.91 (1H, dd, J = 13.9 and 5.8 Hz), 1.25 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.7, 156.6, 136.3, 129.3, 128.3, 126.8, 53.7, 52.0, 50.2, 38.6, 29.3; MS 279 (M + H$^+$, 100).

(*S*)-Methyl 2-(3,3-Dibenzylureido)-3-phenylpropanoate (3l). Utilizing 6 equiv of Et_3N and 3 equiv of amine, reaction time 1 h. Yellow solid; 99 mg, 82% yield; mp 84−86 °C; $[\alpha]_D$ = +29.6 (c = 1.0, $CHCl_3$); IR (film) 3353, 2964, 1746, 1633, 1560, 1454, 1218; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.39−7.24 (6H, m), 7.24−7.13 (7H, m), 7.02−6.94 (2H, m), 4.99−4.77 (2H, m), 4.49 (2H, d, J = 16.4 Hz), 4.39 (2H, d, J = 16.4 Hz), 3.68 (3H, s), 3.10 (1H, dd, J = 13.8 and 5.2 Hz), 3.00 (1H, dd, J = 13.8 and 6.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.7, 157.4, 137.0, 135.9, 128.9, 128.6, 128.3, 127.3, 127.0, 126.7, 54.3, 52.0, 50.0, 38.0; MS 417 (M + H$^+$, 100); HRMS exact mass calculated for [M + Na] $^+$ ($C_{25}H_{26}O_3N_2Na$) requires m/z 425.1836, found m/z 425.1855.

(*S*)-Methyl 3-Phenyl-2-(piperidine-1-carboxamido)-propanoate (3m). Utilizing 9 equiv of amine, reaction time 20 h. Yellow solid; 62 mg, 71% yield; mp 78−82 °C; $[\alpha]_D$ = +45.4 (c = 1.0, $CHCl_3$); IR (film) 3416, 2936, 1745, 1629, 1537, 1218; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30−7.15 (3H, m), 7.14−7.05 (2H, m), 4.88 (1H, d, J = 7.5), 4.78−4.69 (1H, m), 3.68 (3H, s), 3.36−3.16 (4H, m), 3.11 (1H, dd, J = 14.2 and 5.3 Hz), 3.04 (1H, dd, J = 14.2 and 5.4 Hz), 1.64−1.38 (6H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.2, 156.4, 136.3, 129.2, 128.3, 126.8, 54.3, 52.0, 44.7, 38.2, 25.4, 24.2; MS 291 (M + H$^+$, 100); HRMS exact mass calculated for [M + H] $^+$ ($C_{16}H_{23}O_3N_2$) requires m/z 291.1703, found m/z 291.1708.

(*S*)-Methyl 2-(Morpholine-4-carboxamido)-3-phenylpropanoate (3n).[24] Utilizing 9 equiv of amine, reaction time 20 h. Low melting point colorless solid; 79 mg, 90% yield; $[\alpha]_D$ = +60.3 (c = 1.0, $CHCl_3$); IR (film) 3180, 2924, 1744, 1632, 1533, 1454, 1263, 1218, 1116; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.39−7.16 (3H, m), 7.16−6.91 (2H, m), 4.97 (1H, d, J = 7.4 Hz), 4.84−4.63 (1H, m), 3.68 (3H, s), 3.65−3.52 (4H, m), 3.32−3.21 (4H, m), 3.12−3.02 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.0, 156.6, 136.0, 129.1, 128.4, 126.9, 66.3, 54.2, 52.2, 43.7, 38.1; MS 293 (M + H$^+$, 100).

(*S*)-Benzyl 1-{[(*S*)-1-Methoxy-1-oxo-3-phenylpropan-2-yl]-carbamoyl}pyrrolidine-2-carboxylate (3o). Utilizing 9 equiv of amine, reaction time 20 h. Yellow oil; 108 mg, 88% yield; $[\alpha]_D$ = +5.4 (c = 1.0, $CHCl_3$); IR (film) 3440, 2951, 1741, 1738, 1649, 1520, 1454, 1392, 1217, 1171; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.37−7.27 (5H, m), 7.27−7.15 (3H, m), 7.14−7.04 (2H, m), 5.20 (1H, d, J = 12.3 Hz), 5.10 (1H, d, J = 12.3 Hz), 4.88 (1H, br d, J = 7.8 Hz), 4.81−4.71 (1H, m), 4.48−3.38 (1H, m), 3.67 (3H, s), 3.42−3.20 (2H, m), 3.11 (1H, dd, J = 12.3 and 5.5 Hz), 3.06 (1H, dd, J = 12.3 and 5.5 Hz), 2.24−1.86 (4H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.7, 172.6, 155.3, 135.9, 135.5, 129.2, 128.4, 128.3, 128.1, 127.9, 126.8, 66.6, 58.9, 54.0, 52.0, 45.5, 38.0, 29.4, 24.2; MS 411 (M + H$^+$, 100); HRMS exact mass calculated for [M + H] $^+$ ($C_{23}H_{27}O_5N_2$) requires m/z 411.1914, found m/z 411.1931.

(*S*)-Methyl 2-(3-Benzylureido)-3-methylbutanoate (4a).[19] Utilizing 6 equiv of Et_3N and 3 equiv of amine, reaction time 1 h. White solid; 70 mg, 88% yield; mp 83−85 °C {lit. mp 82−84 °C};[19a] $[\alpha]_D$ = +16.8 (c = 1.0, $CHCl_3$) {lit. $[\alpha]_D$ = +16.0 (c = 1.0, $CHCl_3$)};[19b] IR (film) 3316, 2964, 2365, 1743, 1635, 1559, 1218, 1134; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.53−6.85 (5H, m), 5.95−5.59 (2H, m), 4.42−4.14 (3H, m), 3.57 (3H, s), 2.12−1.88 (1H, m), 0.86 (3H, d, J = 6.8 Hz), 0.79 (3H, d, J = 6.9 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.1, 158.2, 139.2, 128.4, 127.2, 127.0, 57.9, 51.8, 44.1, 31.2, 18.9, 17.6; MS 265 (M + H$^+$, 100).

(*S*)-1-Benzyl 4-Methyl 2-(3-benzylureido)succinate (4b). Utilizing 6 equiv of Et_3N and 3 equiv of amine, reaction time 1 h. Yellow solid; 100 mg, 90% yield; mp 64−66 °C; $[\alpha]_D$ = +16.3 (c = 1.0, $CHCl_3$); IR (film) 3356, 3319, 2348, 1732, 1627, 1219, 772; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35−7.12 (10H, m), 5.86 (1H, d, J = 8.3 Hz), 5.56 (1H, t, J = 5.5 Hz), 5.09 (1H, d, J = 12.3 Hz), 5.02 (1H, d, J = 12.3 Hz), 4.80 (1H, dt, J = 8.3 and 4.7 Hz), 4.35−4.25 (2H, m), 3.50 (3H, s), 2.96 (1H, dd, J = 17.1 and 4.7 Hz), 2.79 (1H, dd, J = 17.1 and 4.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.9, 171.8, 157.5, 139.0, 135.2, 128.5, 128.3, 128.1, 127.4, 127.2, 127.1, 67.3, 51.8, 49.5, 44.2, 36.9; MS 371 (M + H$^+$, 100); HRMS exact mass calculated for [M + H] $^+$ ($C_{20}H_{23}O_5N_2$) requires m/z 371.1601, found m/z 371.1605.

Methyl 2-(3-Benzylureido)acetate (4c). Utilizing 6 equiv of Et_3N and 3 equiv of amine, reaction time 1 h. Yellow oil; 50 mg, 75% yield; IR (film) 3338, 2347, 1743, 1619, 1433, 1219; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.27−7.15 (5H, m), 5.77 (2H, br s), 4.35−4.20 (2H, m), 3.90−3.80 (2H, m), 3.60 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.9, 158.5, 139.2, 128.4, 127.1, 127.0, 52.0, 44.0, 41.9; MS 223 (M + H$^+$, 100); HRMS exact mass calculated for [M + H]$^+$ ($C_{11}H_{15}O_3N_2$) requires m/z 223.1077, found m/z 223.1076.

Methyl 4-(3-Benzylureido)butanoate (4d). Utilizing 6 equiv of Et_3N and 3 equiv of amine, reaction time 1 h. Yellow solid, 53 mg, 70% yield; mp 62−66 °C; IR (film) 3346, 2347, 1733, 1634, 1568, 1437, 1219, 1030; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.36−7.09 (5H, m), 5.59 (1H, br s), 5.31 (1H, br s), 4.23 (2H, s), 3.62 (3H, s), 3.06 (2H, t, J = 6.2 Hz), 2.24 (2H, t, J = 7.2 Hz), 1.79−1.62 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.1, 158.8, 139.4, 128.4, 127.1, 127.0, 51.6, 44.0, 39.4, 31.1, 25.2; MS 251 (M + H$^+$, 100); HRMS exact mass calculated for [M + H]$^+$ ($C_{13}H_{19}O_3N_2$) requires m/z 251.1390, found m/z 251.1390.

1,3-Dibenzylurea (4e).[25] Utilizing 6 equiv of Et_3N and 3 equiv of amine, reaction time 1 h. White solid; 55 mg, 76% yield; mp 152−156 °C {lit. mp 166−169 °C}[24b]; IR (film) 3317, 2970, 5921, 2371, 1625, 1577, 1262, 1054, 1032, 1012; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35−7.11 (10H, m), 5.40−4.50 (2H, br s), 4.27 (4H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.2, 138.9, 128.6, 127.3, 127.2, 44.5; MS 241 (M + H$^+$, 100).

1-Allyl-3-benzylurea (4f).[26] Utilizing 6 equiv of Et_3N and 3 equiv of amine, reaction time 1 h. White solid; 40 mg, 70% yield; mp 90−93 °C {lit. mp 91 °C};[26] IR (film) 3319, 2351, 1621, 1555, 1217, 921; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35−7.08 (5H, m), 5.89−5.62 (1H, m), 5.52 (1H, br s), 5.33 (1H, br s), 5.17−4.94 (2H, m), 4.23 (2H, s), 3.76−3.58 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.7, 139.3, 135.4, 128.4, 127.2, 127.0, 115.3, 44.1, 42.7; MS 191 (M + H$^+$, 100).

1-Benzyl-3-cyclohexylurea (4g).[27] Utilizing 6 equiv of Et_3N and 3 equiv of amine, reaction time 1 h. Colorless solid, 50 mg, 72% yield; mp 151−154 °C {lit. mp 150−153 °C};[27b] IR (film) 3330, 2928, 2851, 1625, 1576, 1454, 1219; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.45−7.19 (5H, m), 5.05 (1H, br s), 4.65 (1H, br s), 4.27 (2H, s), 3.56−3.29 (1H, m), 1.95−1.77 (2H, m), 1.72−1.43 (3H, m), 1.39−0.90 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.5, 139.2, 128.6, 127.4, 127.3, 49.2, 44.5, 33.8, 25.5, 24.8; MS 233 (M + H$^+$, 100).

***N*-Benzylpiperidine-1-carboxamide (4h).**[25b,28] Utilizing 9 equiv of amine, reaction time 20 h. Colorless solid, 43 mg, 66% yield; mp 101−104 °C {lit. mp 103−105 °C};[28] IR (film) 3328, 2933, 2851, 1620, 1538, 1219; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.43−7.10 (5H, m), 4.82 (1H, br s), 4.42−4.36 (2H, m), 3.35−3.25 (4H, m), 1.65−1.42 (6H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.5, 139.6, 128.5, 127.7, 127.1, 45.0, 44.9, 25.5, 24.3; MS 219 (M + H$^+$, 100).

4-(3-Benzylureido)butyl 4-(trifluoromethyl)benzoate (4i). Utilizing 9 equiv of amine, reaction time 20 h. White solid; 85 mg, 72% yield; mp 128−130 °C; IR (film) 3323, 2348, 1729, 1621, 1328, 1218, 1121, 772; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.10 (2H, d, J = 8.2 Hz), 7.67 (2H, d, J = 8.2 Hz), 7.35−7.15 (5H, m), 4.35−4.25 (4H, m), 3.25−3.15 (2H, t, J = 6.7 Hz), 1.80−1.52 (4H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.4, 158.3, 138.9, 134.4 (q, J = 32.6 Hz), 133.4, 129.9, 128.6, 127.4, 127.3, 125.4 (q, J = 3.5 Hz), 123.6 (q, J = 272.7 Hz), 65.1, 44.5, 40.0, 26.7, 26.0; ^{19}F NMR (188 MHz, $CDCl_3$) δ −8.08 (3F, s); MS 395 (M + H$^+$, 100); HRMS exact mass calculated for [M + H]$^+$ ($C_{20}H_{22}F_3O_3N_2$) requires m/z 395.1577, found m/z 395.1591.

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1-Benzyl-3-phenylurea (4j).[29] Utilizing 9 equiv of amine, reaction time 20 h. Yellow solid; 61 mg, 90% yield; mp 148−152 °C {lit. mp 169−171 °C}[28b]; IR (film) 3307, 2303, 1633, 1594, 1558, 1219; ^{1}H NMR (200 MHz, CD_3OD) δ 7.42−7.18 (9H, m), 7.02−6.90 (1H, m), 4.37 (2H, s); ^{13}C NMR (50 MHz, CD_3OD) δ: 157.0, 139.8, 139.7, 128.6, 128.4, 127.0, 126.9, 122.3, 119.0, 43.3; MS 227 (M + H$^+$, 100).

Isolation of the Intermediate Isocyanate (5). Boc-protected amine (0.30 mmol) was placed in a round-bottom flask followed by CH_2Cl_2 (10 mL). 2-Chloropyridine (0.09 mL, 0.90 mmol) was added, followed by trifluoromethanesulfonic anhydride (0.08 mL, 0.45 mmol), and the reaction mixture was stirred for 50 min at room temperature. The crude product was purified using column chromatography (30%−50% EtOAc in petroleum ether) to afford the desired product. Low melting point yellow solid; 48 mg, 56% yield; IR (film) 2916, 2277, 1732, 1647, 1506, 1327, 1219, 772; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.14 (2H, d, J = 8.2 Hz), 7.71 (2H, d, J = 8.2 Hz), 4.39 (2H, t, J = 6.2 Hz), 3.41 (2H, t, J = 6.3 Hz), 1.98−1.58 (4H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.3, 134.5 (q, J = 32.6 Hz), 133.3, 129.9, 125.4 (q, J = 3.8 Hz), 123.6 (q, J = 272.8 Hz), 122.0, 64.7, 42.6, 27.8, 25.8; ^{19}F NMR (188 MHz, $CDCl_3$) δ −8.09 (3F, s); MS (ESI) 288 (M + H$^+$, 100%); HRMS exact mass calculated for [M + H]$^+$ ($C_{13}H_{13}F_3O_3N$) requires m/z 288.0842, found m/z 288.0854.

Recycling of the Amine Excess. After completion of the reaction, the reaction mixture was diluted with CH_2Cl_2 (15 mL). The organic layer was washed with aq HCl (2 × 10 mL, 1 N). The combined aqueous layers, that contain the salt of the amine, was basified with solid $NaHCO_3$ (pH = 9). The free amine was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried, and the solvent was removed in vacuo (78−85% recovery of amine). Alternatively, after purification of the urea by column chromatography, the column was flushed with CH_3OH until the amine was not observed by ninhydrin stain (72−81% recovery of amine).

Determination of Epimerization of the Urea Product. Following the same synthetic procedure, the racemic urea product **3a** was synthesized. Utilizing chiral HPLC (Chiralapak AD-H, hexane:^{i}PrOH 85:15, 1 mL/min flow rate, we separated the two enantiomers [(*R*)-enantiomer retention time: 15.87 min, (*S*)-enantiomer retention time: 28.26 min]. After running the synthesized **3a** under the identical conditions, we confirmed that negligible rate of epimerization had occurred (99.64:0.36).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR and HPLC data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For some examples of the use of urea derivatives in pharmaceuticals, see: (a) Lam, P. Y.; Jadhav, P. K.; Eyermann, C. J.; Hodge, C. N.; Ru, Y.; Bacheler, L. T.; Meek, J. L.; Otto, M. J.; Rayner, M. M.; Wong, Y. N.; Chang, C.-H.; Weber, P. C.; Jackson, D. A.; Sharpe, T. R.; Erickson-Viitanen, S. *Science* **1994**, *263*, 380−384. (b) Castro, J. L.; Ball, R. G.; Broughton, H. B.; Russell, M. G. N.; Rathbone, D.; Watt, A. P.; Baker, R.; Chapman, K. L.; Fletcher, A. E.; Patel, S.; Smith, A. J.; Marshall, G. R.; Ryecroft, W.; Matassa, V. G. *J. Med. Chem.* **1996**, *39*, 842−849. (c) von Geldern, T. W.; Kester, J. A.; Bal, R.; Wu-Wong, J. R.; Chiou, W.; Dixon, D. B.; Opgenorth, T. J. *J. Med. Chem.* **1996**, *39*, 968−981. (d) Petersen, T. P.; Mirsharghi, S.; Rummel, P. C.; Thiele, S.; Rosenkilde, M. M.; Ritzen, A.; Ulven, T. *Chem.—Eur. J.* **2013**, *19*, 9343−9350. (e) Regan, J.; Breitfelder, S.; Cirillo, P.; Gilmore, T.; Graham, A. G.; Hickey, E.; Klaus, B.; Madwed, J.; Morak, M.; Moss, N.; Pargellis, C.; Pav, S.; Proto, A.; Swinamer, A.; Tong, L.; Torcellini, C. *J. Med. Chem.* **2002**, *45*, 2994−3008. (f) dos Santos, L.; Lima, L. A.; Cechinel-Filho, V.; Correa, R.; de Campos Buzzi, F.; Nunes, R. J. *Bioorg. Med. Chem.* **2008**, *16*, 8526−8534. (g) Khan, K. M.; Saeed, S.; Ali, M.; Gohar, M.; Zhaid, J.; Khan, A.; Perveen, S.; Choudhary, M. I. *Bioorg. Med. Chem.* **2009**, *17*, 2447−2451. (h) Denoyelle, S.; Chen, T.; Wang, Y.; Klosi, E.; Halperin, J. A.; Aktas, B. H.; Chorev, N. *Bioorg. Med. Chem.* **2012**, *22*, 402−409.

(2) For a general review on ureas in drug design, see: Gallou, I. *Org. Prep. Proced. Int.* **2007**, *39*, 355−383.

(3) (a) Nowick, J. S.; Mahrus, S.; Smith, E. M.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 1066−1072. (b) Nowick, J. S.; Holmes, D. L.; Mackin, G.; Noronha, G.; Shaka, A. J.; Smith, E. M. *J. Am. Chem. Soc.* **1996**, *118*, 2764−2765. (c) Holmes, D. L.; Smith, E. M.; Nowick, J. S. *J. Am. Chem. Soc.* **1997**, *119*, 7665−7669.

(4) (a) Burgess, K.; Shin, H.; Linthicum, S. *Angew. Chem., Int. Ed.* **1995**, *34*, 907−909. (b) Burgess, K.; Ibarzo, J.; Linthicum, D. S.; Russell, D. H.; Shin, H.; Shitangkoon, A.; Totani, R.; Zhang, A. J. *J. Am. Chem. Soc.* **1997**, *119*, 1556−1564. (c) Wilson, M. E.; Nowick, J. S. *Tetrahedron Lett.* **1997**, *39*, 6613−6616. (d) Claudon, P.; Violette, A.; Lamour, K.; Decossas, M.; Fournel, S.; Heurtault, B.; Godet, J.; Mely, Y.; Jamart-Gregoire, B.; Averlant-Petit, M.-C.; Briand, J.-P.; Duportail, G.; Monteil, H.; Guichard, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 333−336. (e) Fischer, L.; Claudon, P.; Pendem, N.; Miclet, E.; Didierjean, C.; Ennifar, E.; Guichard, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 1067−1070.

(5) For selected reviews, see: (a) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713−5743. (b) Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187−1198. (c) Serdyuk, O. V.; Heckel, C. M.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2013**, *11*, 7051−7071. (d) Tsakos, M.; Kokotos, C. G. *Tetrahedron* **2013**, *69*, 10119−10222.

(6) (a) Majer, P.; Randal, R. S. *J. Org. Chem.* **1994**, *59*, 1937−1938. (b) Scialdone, M. A.; Shuey, S. W.; Soper, P.; Hamuro, Y.; Burns, D. M. *J. Org. Chem.* **1998**, *63*, 4802−4807. For a review on phosgene-free generation of isocyanates, see: (c) Kreve, O.; Mutlu, H.; Meier, M. A. R. *Green Chem.* **2013**, *15*, 1431−1455.

(7) (a) Izdebski, J.; Pawlak, D. *Synthesis* **1989**, 423−425. (b) Nagaraju, N.; Kuriakose, G. *Green Chem.* **2002**, *4*, 269−271. (c) Saliu, F.; Rindone, B. *Tetrahedron Lett.* **2010**, *51*, 6301−6304.

(8) (a) Zhang, X.; Rodrigues, J.; Evans, L.; Hinkle, B.; Ballantyne, L.; Pena, M. *J. Org. Chem.* **1997**, *62*, 6420−6423. (b) Batey, R. A.; Santhakumar, V.; Yoshina-Ishii, C.; Taylor, S. D. *Tetrahedron Lett.* **1998**, *39*, 6267−6270. (c) Padiya, K. J.; Gavade, S.; Kardile, B.; Tiwari, M.; Bajare, S.; Mane, M.; Gaware, V.; Varghese, S.; Harel, D.; Kurhade, S. *Org. Lett.* **2012**, *14*, 2814−2817. (d) Dusoare, P. A.; Islam, M. S.; Lough, A. J.; Batey, R. A. *J. Org. Chem.* **2012**, *77*, 10362−10368.

(9) Katritzky, A. R.; Pleynet, D. P. M.; Yang, B. *J. Org. Chem.* **1997**, *62*, 4155−4158.

(10) Leung, M.-K.; Lai, J.-L.; Lau, K.-H.; Yu, H.-H.; Hsiao, H.-J. *J. Org. Chem.* **1996**, *61*, 4175−4179.

(11) Anbazhagan, M.; Deshmukh, A. R. A. S.; Rajappa, S. *Tetrahedron Lett.* **1998**, *39*, 3609−3612.

(12) Kotachi, S.; Tsuji, Y.; Kondo, T.; Watanabe, Y. *J. Chem. Soc., Chem. Commun.* **1990**, 549−550.

(13) (a) Kittenringham, J.; Shipton, M. R.; Voyle, M. *Synth. Commun.* **2000**, *30*, 1937−1943. (b) Bogolubsky, A. V.; Ryabukhin, S. V.; Pipko, S. E.; Lukin, O.; Shivanyuk, A.; Mykytenko, D.; Tolmachev, A. *Tetrahedron* **2011**, *67*, 3619−3623. (c) Mateos-Caro, J.; Robin, Y.; Levacher, V.; Marsais, F. *Synlett* **2009**, 279−283. (d) Lee, H.-G.; Kim, M.-J.; Park, S.-E.; Kim, J.-J.; Kim, B. R.; Lee, S.-G.; Yoon, Y.-J. *Synlett* **2009**, 2809−2814. (e) Carafa, M.; Mele, V.; Quaranta, E. *Green Chem.*

2012, *14*, 217−225. (f) Ghazvini Zadeh, E. H.; Abo-Dya, N. E.; Sotuyo, A. C.; Ghiviriga, I.; Hall, C. D. *Tetrahedron Lett.* **2013**, *54*, 5467−5469.
(14) (a) Chong, P. Y.; Janicki, S. Z.; Petillo, P. A. *J. Org. Chem.* **1998**, *63*, 8515−8521. (b) Guichard, G.; Semetey, V.; Didierjean, C.; Aubry, A.; Briand, J.-P.; Rodriguez, M. *J. Org. Chem.* **1999**, *64*, 8702−8705. (c) El Dine, T. M.; Chapron, S.; Duclos, M.-C.; Duguet, N.; Popowycz, F.; Lemaire, M. *Eur. J. Org. Chem.* **2013**, 5445−5454.
(15) (a) Adamiak, R. W.; Stawinski, J. *Tetrahedron Lett.* **1977**, *22*, 1935−1936. (b) Basha, A. *Tetrahedron Lett.* **1988**, *29*, 2525−2526. (c) Lamothe, M.; Perez, M.; Colovray-Gotteland, V.; Halazy, S. *Synlett* **1996**, 507−508. (d) Matsumura, Y.; Satoh, Y.; Onomura, O.; Maki, T. *J. Org. Chem.* **2000**, *65*, 1549−1551. (e) Gastaldi, S.; Weinreb, S. M.; Stien, D. *J. Org. Chem.* **2000**, *65*, 3239−3240. (f) Gallou, I.; Eriksson, M.; Zeng, X.; Senanayake, C.; Farina, V. *J. Org. Chem.* **2005**, *70*, 6960−6963. (g) Lee, S.-H.; Matsushita, H.; Clapham, B.; Janda, K. D. *Tetrahedron* **2004**, *60*, 3439−3443. (h) Han, C.; Porco, J. A., Jr. *Org. Lett.* **2007**, *9*, 1517−1520.
(16) (a) Kokotos, C. G.; Kokotos, G. *Adv. Synth. Catal.* **2009**, *351*, 1355−1362. (b) Fotaras, S.; Kokotos, C. G.; Tsandi, E.; Kokotos, G. *Eur. J. Org. Chem.* **2011**, 1310−1317. (c) Kokotos, C. G. *J. Org. Chem.* **2012**, *77*, 1131−1135. (d) Tsakos, M.; Kokotos, C. G.; Kokotos, G. *Adv. Synth. Catal.* **2012**, *354*, 740−746. (e) Tsakos, M.; Kokotos, C. G. *Eur. J. Org. Chem.* **2012**, 576−580. (f) Fotaras, S.; Kokotos, C. G.; Kokotos, G. *Org. Biomol. Chem.* **2012**, *10*, 5613−5619. (g) Revelou, P.; Kokotos, C. G.; Moutevelis-Minakakis, P. *Tetrahedron* **2012**, *68*, 8732−8738.
(17) In, J.; Hwang, S.; Kim, C.; Seo, J. H.; Kim, S. *Eur. J. Org. Chem.* **2013**, 965−971.
(18) (a) Heredia-Moya, J.; Kirk, K. L. *Bioorg. Med. Chem.* **2008**, *16*, 5908−5913. (b) Barbayianni, E.; Fotakopoulou, I.; Schmidt, M.; Constantinou-Kokotou, V.; Bornscheuer, U. T.; Kokotos, G. *J. Org. Chem.* **2005**, *70*, 8730−8733. (c) Molander, G. A.; Shin, J. *Org. Lett.* **2012**, *14*, 3138−3141.
(19) (a) Sanders, M. L.; Donkor, I. O. *Synth. Commun.* **2002**, *32*, 1015−1021. (b) Knolker, H.-J.; Braxmeier, T. *Synlett* **1997**, 925−928.
(20) Davies, J. S.; Enjalbal, C.; Llewellyn, G. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1225−1231.
(21) Mu, Q. M.; Xue, C. H.; Zhang, Q. H.; Chen, S. H. *Synth. Commun.* **2003**, *33*, 3055−3061.
(22) Narenda, N.; Vishwanatha, T. M.; Sureshbabu, V. V. *Synthesis* **2011**, 3247−3254.
(23) Su, L.; Jia, Y.; Zhang, L.; Xu, Y.; Fang, H.; Xu, W. *Bioorg. Med. Chem.* **2012**, *20*, 3807−3815.
(24) Busacca, C. A.; Lorenz, J. C.; Grinberg, N.; Haddad, N.; Lee, H.; Li, Z.; Liang, M.; Reeves, D.; Saha, A.; Varsolona, R.; Senanayake, C. H. *Org. Lett.* **2008**, *10*, 341−344.
(25) (a) Aitken, R. A.; Armstrong, D. P.; Galt, R. H. B.; Mesher, S. T. E. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2139−2146. (b) Orito, K.; Miyazawa, M.; Nakamura, T.; Horibata, A.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Yamazaki, T.; Tokuda, M. *J. Org. Chem.* **2006**, *71*, 5951−5958.
(26) Sanna, M.; White, P. D.; Chan, W. C. *Tetrahedron Lett.* **2008**, *49*, 6160−6162.
(27) (a) Patonay, T.; Patonay-Peli, E.; Zolnai, L.; Mogyorodi, F. *Synth. Commun.* **1996**, *26*, 4253−4265. (b) Ramsden, C. A.; Rosen, H. L. *J. Chem. Soc., Perkin Trans. 1* **1997**, *16*, 2319−2327.
(28) Yagodkin, A.; Loschcke, K.; Weisell, J.; Azhayev, A. *Tetrahedron* **2010**, *66*, 2210−2221.
(29) (a) Viana, G. M.; de Sequeira Aguiar, L. C.; de Araujo Ferrao, J.; Simas, A. B. C.; Vasconcelos, M. G. *Tetrahedron Lett.* **2013**, *54*, 936−940. (b) Oh, H. K.; Park, J. E.; Sung, D. D.; Lee, I. *J. Org. Chem.* **2004**, *69*, 3150−3153.