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Article

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Ethyl 2-cyano-2-(2-nitrobenzenesulfonyloxyimino)acetate (*o*-NosylOXY): A Recyclable Coupling Reagent for Racemization free Synthesis of Peptide, Amide, Hydroxamate and Ester

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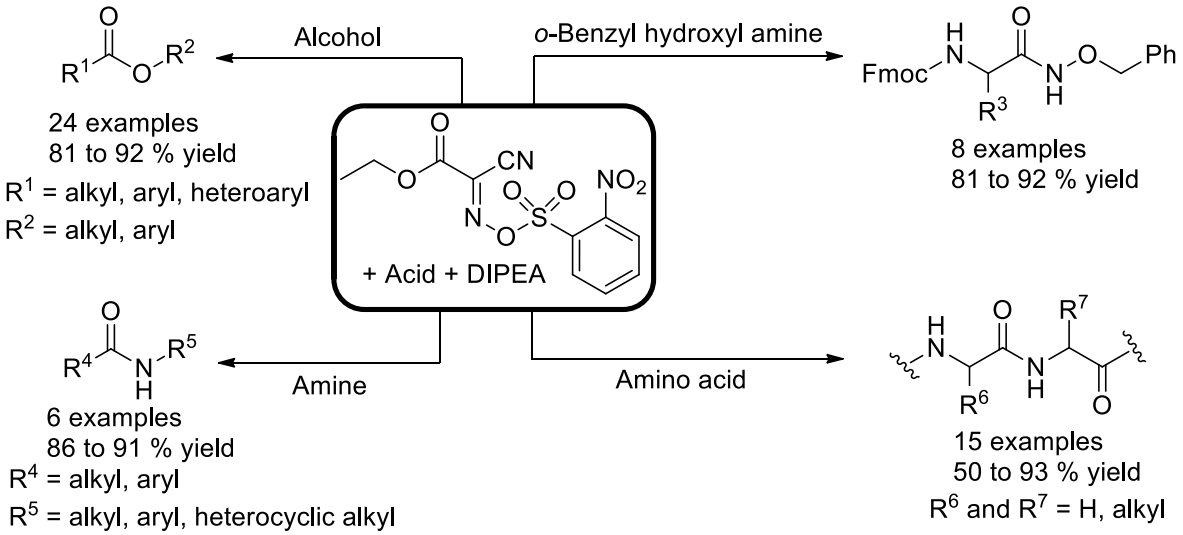


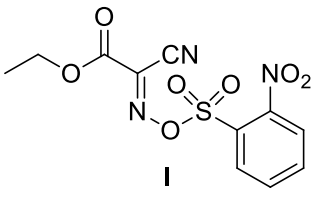
ABSTRACT: Ubiquitousness of amide and ester functionality makes coupling reactions extremely important. Although numerous coupling reagents are available, methods of preparation of the common and efficient reagents are cumbersome. Those reagents generate substantial amount of chemical waste and lack recyclability. Ethyl 2-cyano-2-(2-nitrobenzenesulfonyloxyimino)acetate (*o*-NosylOXY), the first member of a new generation of

coupling reagents, is found for which byproducts can be easily recovered and reused for the synthesis of the same reagent making the method more environment friendly and cost effective. Synthesis of amides, hydroxamates, peptides, and esters using this reagent is described. Synthesis of the difficult sequences, for example, islet amyloid polypeptide (22-27) fragment (with a C-terminal Gly, H-Asn-Phe-Gly-Ala-Ile-Leu-Gly-NH_2) and acyl carrier protein (65-74) fragment (H-Val-Gln-Ala-Ala-Ile-Asp-Tyr-Ile-Asn-Gly-OH), following solid phase peptide synthesis (SPPS) protocol and Amyloid β (39-42) peptide (Boc-Val-Val-IIe-Ala-OMe) following solution phase strategy is demonstrated. The remarkable improvement is noticed with respect to reaction time, yield, and retention of stereochemistry. A mechanistic investigation and recyclability are also described.

INTRODUCTION

Amide and ester functionality are present in most of the natural products as well as pharmaceutical compounds.[1] Therefore, coupling reactions, which comprise activation of carboxylic acids into an activated form that undergo acylation to produce esters, amides, and peptides, are extremely important for academia and industry. Numerous coupling reagents have been developed and commercialized including carbodiimides, phosphonium, and uronium/ aminium salts.[2] Most of them engage the benzotriazole or azabenzotriazole ring system as an important fragment of their structure, which is subsequently transformed into a good leaving group.[3] After two decades of domination of benzotriazole-based chemistry, with the pioneering work of Albericio et al., a new class of peptide coupling reagents, that is, ethyl 2-cyano-2-(hydroxyimino)acetate (Oxyma) based reagents, have been introduced.[4] Oxyma is superior to its

counterparts as racemisation suppressant and environment friendly reagent.[5] Nevertheless, existing popular coupling reagents (HOBt based coupling reagents as well as Oxyma based coupling reagents) still suffer from three major drawbacks: (a) They generate lot of chemical waste. For example, carcinogenic hexamethylphosphoramide (HMPA) and explosive hydroxybezotriazole (HOBt) are generated as by-products, when benzotriazol-1-yloxytris(dimethylamino)phos-phoniumhexafluorophosphate (BOP) is used as coupling reagent.[6] Similarly, a urea derivative as well as HOBt is generated when *N*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluroniumhexafluoro phosphate (HBTU) is used.[7] (b) Preparation protocols of these reagents involve harsh conditions and toxic reagents. For example, HBTU is synthesized using phosgene (inflammable, causes skin damage) and HOBt (explosive) in carbon tetrachloride, a carcinogenic solvent.[7] Similarly, 1-[(1-(cyano-2-ethoxy-2-oxoethylideneamino-oxy)-dimethylamino-morpholinomethylene)] methanaminium hexafluorophosphate (COMU), an Oxyma based coupling reagent, is also synthesized using phosgene. (c) Furthermore, recycling those reagents may be cumbersome. Thus, they are not environment friendly and cost effective. Therefore, invention of an ideal coupling reagent with highest level of efficacy but devoid of epimerization tendency at the same time environment friendly and recyclable still remains a challenge. We described herein a coupling reagent, Ethyl 2-cyano-2-(2-nitrobenzene sulfonyloxyimino)acetate (*o*-NosylOXY, **I**), which have similar efficiency but devoid of the said drawbacks.



I

Figure 1. Ethyl 2-cyano-2-(2-nitrobenzenesulfonyloxyimino)acetate (*o*-NosylOXY, **I**)

RESULTS AND DISCUSSION

The reagent **I**, *o*-NosylOXY, was synthesized easily by the reaction between *ortho*-nitrobenzenesulfonyl chloride and Oxyma in presence of diisopropylethylamine (DIPEA) under nitrogen atmosphere.[8] Reagent **I** is stable at room temperature (25 °C) and can be stored for long time. A time dependent HPLC and ^{1}HNMR studies of **I** indicated no change until 20 days (Supporting Information, Figure S112-S117). Its coupling efficiency was investigated using the reaction between phenyl acetic acid and benzyl amine, DCM as a solvent (Scheme 1). Very good yield (91 %) of the product, *N*-benzyl-2-phenylacetamide, was obtained in 2 h at room temperature. Sulfonamide formation is an expected side reaction for such reagents. We performed a model reaction between phenylacetic acid and benzyl amine using *o*-NosylOXY in presence of DIPEA in DCM without pre-activation. After completion of the reaction, we found 40 % yield of *N*-benzyl-2-nitrobenzenesulfonamide and 50 % yield of *N*-benzyl-2-phenylacetamide. To avoid such sulfonamide formation, we used 3-5 min pre-activation.

R^1 = aryl, alkyl, *N*-protected amino acid
R^2 = aryl, alkyl, heterocyclic alkyl or *C*-protected amino acid

Scheme 1. Synthesis of amides and peptides using reagent **I**.

For solvent optimization we screened several solvents for the coupling reaction between phenyl acetic acid and benzyl amine employing reagent **I**, and DCM was found to be the best solvent (Table 1). Therefore, DCM was used for amidation, esterification and hydroxamate synthesis.

Table 1. Solvent screening experiments

Entry[a]	Solvent	Yield (%)[b]	Time (h)
1	Acetonitrile	67	8
2	DMSO	56	11
3	THF	48	13
4	DMF	85	3
5	DCM	91	2.2
6	Ethyl acetate	70	5
7	Chloroform	78	3

[a]Performed with phenylacetic acid (136 mg 1 equiv), Reagent **I** (1 equiv), DIPEA (2.2 equiv), benzyl amine (1 equiv), room temperature (25 °C). [b]Yields refer to the isolated yield after column chromatography.

For racemization studies, we synthesized Z-DL-Phe-L-Ala-OMe and Z-L-Phe-L-Ala-OMe using **I** and compared their HPLC profiles (Figure 2) to estimate the amount of racemization caused by the coupling reagent. Appearance of the twin peak in the HPLC profile of Z-DL-Phe-L-Ala-OMe corresponds to the two diastereomeric products, whereas, presence of the single peak in that of Z-L-Phe-L-Ala-OMe demonstrates virtually no racemization occurred during the synthesis. Comparison of the ^{1}H and ^{13}C NMR spectra of these dipeptides also supports the hypothesis (supporting information, Figure S29-S32). We found two doublets in ^{1}H NMR at δ = 1.32 and 1.21 ppm and similarly four peaks at δ = 173.0, 172.9, 170.9 and 170.7 ppm in ^{13}C NMR of Z-DL-Phe-L-Ala-OMe, which indicate the presence of two diastereomers. Whereas, we found one doublet at δ = 1.32 ppm in the ^{1}H NMR and two peaks at δ = 173.0 and 170.7 ppm in ^{13}C NMR for Z-L-Phe-L-Ala-OMe indicating the presence of one diastereomer.

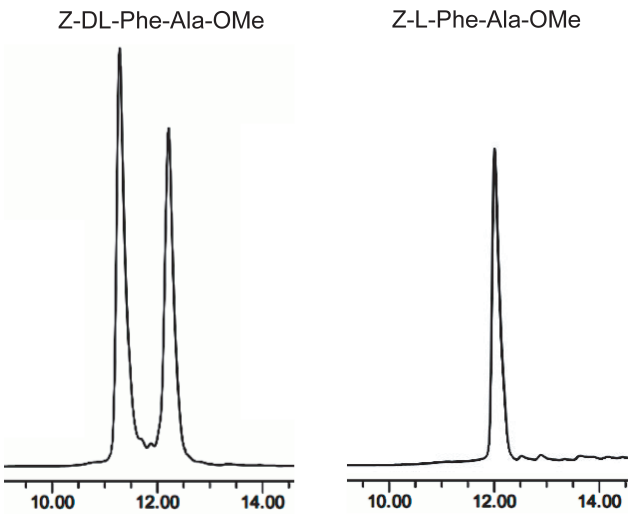


Figure 2. Comparison of the HPLC profiles of Z-DL-Phe-L-Ala-OMe (left panel) and Z-L-Phe-L-Ala-OMe (right panel) (C18 reverse phase analytical column, 5 μm, 25 cm× 4.6 mm, linear gradient of 0-80 %, 0-7 min. then 80-100 % upto 20 min., CH_3CN in H_2O with 0.1% formic acid**)**

However, supression of epimerization is known to occur for the presence of the *N*-terminal urethane protecting group.[9] To remove that doubt, we synthesized a tripeptide, Z-Gly-Phe-Val-OMe (entry 18, Table 3), via coupling of Z-Gly-Phe-OH and H-Val-OMe in solution using **I**, estimated the amount of racemization and compared that with reported data obtained for the synthesis of the same tripeptide using other coupling reagents, such as, HBTU (*N*-[(1*H*-benzotriazol-1-yl)(dimethylamino) methylene] *N*-methylmethanaminiumhexafluorophosphate*N*-oxide), HATU (*N*-[(dimethylamino)-1*H*-1,2,3-triazolo[4,5-b]pyridin-1-yl-methylene)-*N*-methylmethanaminium hexafluorophosphate-*N*-oxide), HDMB (1-((dimethylamino)(morpholino)methylene)-1*H*-benzotriazoliumhexafluorophosphate-3-oxide) and HDMA (1-((dimethylamino)-(morpholino)methylene)-1*H* [1,2,3]triazolo[4,5-

b]pyridiniumhexafluorophosphate3-oxide).[10] No racemization could be observed, when reagent **I** was used, however, epimerization was noted for other reagents (Table 2).

Table 2. Comparison of yield and racemization tendency for the formation of Z-Gly-Phe-Val-OMe using *o*-NosylOXY (**I**) with the reported[10] results using various coupling reagents.

Entry	Coupling Reagent	Yield (%)	Racemization (%)
1	HBTU	89	5.9
2	HATU	90	1.6
3	HDMB	90	2.9
4	HDMA	90	0.7
5	*o*-NosylOXY	91	n. d.[a]

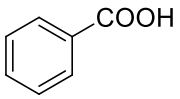
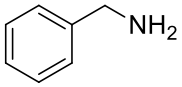
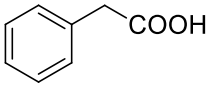
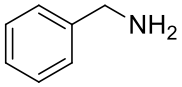
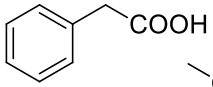
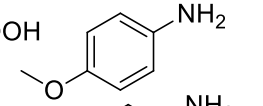
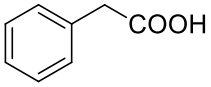
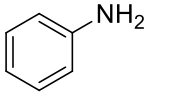
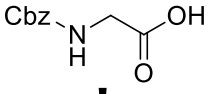
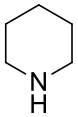
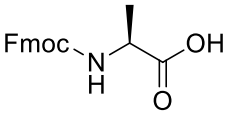
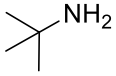
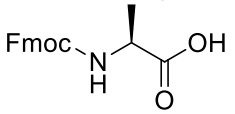
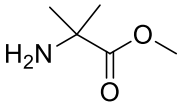
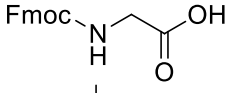
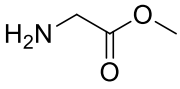
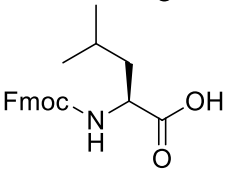
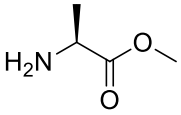
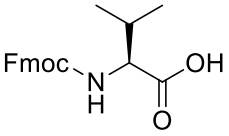
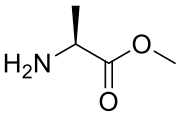
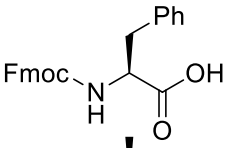
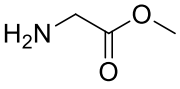
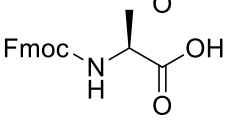
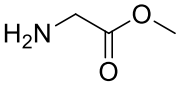
[a]No racemization could be detected by the ^{1}H and ^{13}C NMR spectra and the HPLC profile (Supporting Information, Figures S39- S40 and S128) within the limit of our experimental condition.

With the suitable conditions in hand, applicability of this method was explored with various carboxylic acids and amines (Table 3). Interestingly, the reaction worked well with aromatic and aliphatic carboxylic acids (entry 1-4, Table 3) as well as amino acids (entry 5-18). Even in case of less nucleophilic amine, aniline (entry 4), the yield was found to be remarkably good. However, repeated attempt of the reaction with 4-nitroaniline failed. It tolerates common amine protecting groups including Fmoc and Cbz. Furthermore, the reaction worked well for sterically hindered amino acids, e.g. Val (entries 10) and Aib (entries 16 and 17), as carboxylic acid component as well as tertiary butyl amine (entry 6), Aib (entry 7), and Val (entry 18) as amine component, which are known to be difficult for coupling. In all the cases, the yields were

excellent and comparable with other reported common coupling reagents[11] with no observed racemization.

We also performed the reaction between Fmoc-Phe-OH and NH_2-Ala-OMe in the presence of *o*-nitrobenzenesulfonyl chloride as a coupling reagent. In this case, we obtained dipeptide, Fmoc-Phe-Ala-OMe, with 65 % yield and sulfonamide, *o*-nitrobenzenesulfonamide of methyl ester of alanine, with 10% yield. About 10 % racemization was observed in the HPLC profile of the dipeptide (Supporting Information, Figure S130-S132). This demonstrates the utility of the Oxyma part in reagent **I**.

Table 3. Synthesis of various amides and peptides under optimized condition using reagent **I**.

Entry[a]	Acid	Amine	Yield (%)[b]
1			88
2			91
3			82
4			86
5			89
6			81
7			80
8			91
9			89
10			87
11			93
12			87

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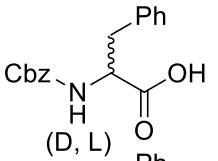
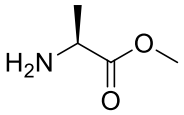
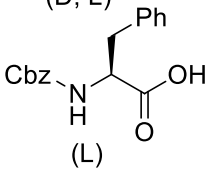
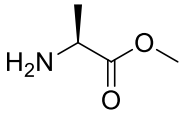
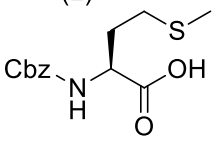
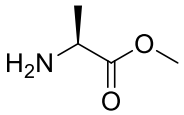
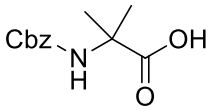
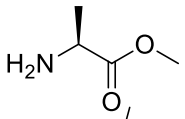
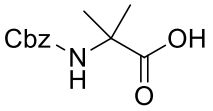
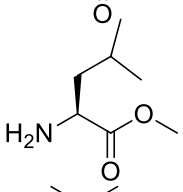
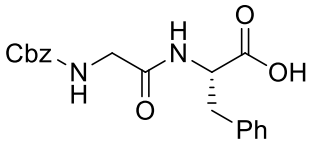
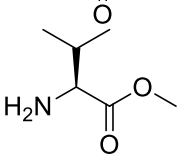
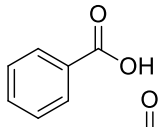
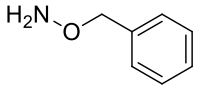
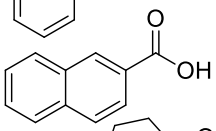
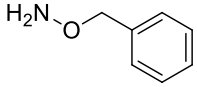
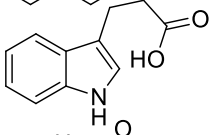
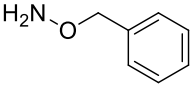
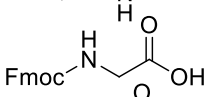
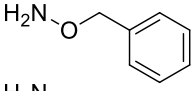
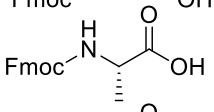
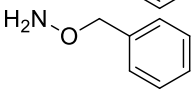
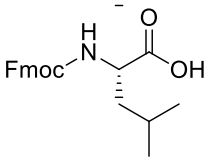
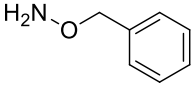
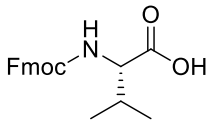
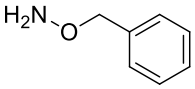
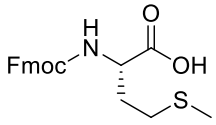
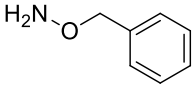
13			90
14			91
15			89
16			81
17			78
18			91

[a]Performed with Acid (1 equiv), Reagent I (1 equiv), DIPEA (2.2 equiv), Amine (1 equiv), room temperature (25 °C), 2-3 h. [b]Yields were referred to the isolated yields after column chromatography.

Hydroxamates of amino acids are another interesting class of compounds which possess a broad spectrum of medicinal properties.[12] Therefore, we wanted to adopt the present methodology for the synthesis of such important drug candidates.

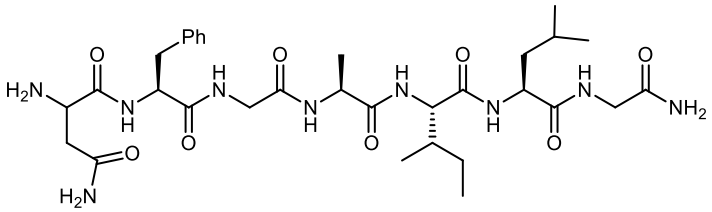
Table 4. Synthesis of hydroxamates using **I**

R^1 = aryl, alkyl or fmoc-amino acid

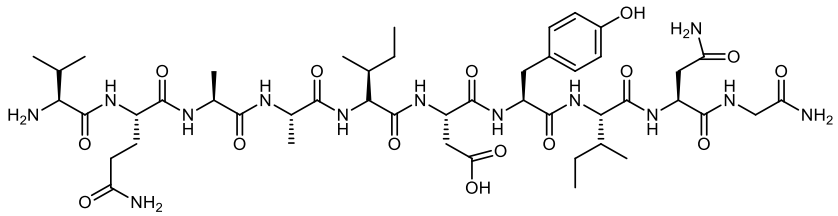
Entry[a]	Acid	O-benzylhydroxylamine	Yield (%)[b]
1			92
2			90
3			89
4			91
5			88
6			84
7			82
8			81

[a]Performed with Acid (1 equiv), Reagent I (1 equiv), DIPEA (2.2 equiv), *O*-benzylhydroxylamine (1 equiv), room temperature (25 °C), 2-3 h. [b]Yields were referred to the isolated yields after column chromatography.

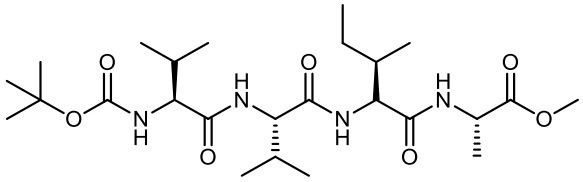
Our intial trials of coupling with model substrate, i.e. benzoic acid with *O*-benzyl hydroxyl amine using reagent **I** yielded the desired product in very good yield (91%, entry 1, Table 4). Then it was further extended to a variety of amino acids with varying side chain complexity (entry 4-8, Table 4). Very good yields (81 to 92 %) were obtained on stirring at room temperature (25 ^{o}C) for 2-3 hours.



(a)



(b)



(c)

Figure 3. Sequences of peptides synthesised: (a) NFGAILG and (b) VQAAIDYING using SPPS, HPLC and ESI-MS spectra (see supporting information, Figure S167-168); (c) Boc-VVIA-OMe in solution.

We further envisaged to use reagent **I** for long chain peptide synthesis. As target, we took IAPP (22-27) peptide (IAPP, Islet Amyloid Poly Peptide: H-Asn-Phe-Gly-Ala-Ile-Leu-Gly-NH_2, Figure 3a)[13] and ACP (65-74) peptide fragment (ACP, Acyl Carrier Protein: H-Val-Gln-Ala-Ala-Ile-Asp-Tyr-Ile-Asn-Gly-OH, Figure 3b).[11] Both of them are known as difficult sequences for synthesis as they contain many hydrophobic amino acids and undergo conformational change resulting in aggregation during the synthesis.

We achieved the synthesis of these peptides in very good yield (40% for the IAPP (22-27) and 50 % for the ACP (65-74) fragment after chromatographic purification, with respect to resin loading) by stepwise coupling of constituent amino acids on rink amide MBHA resin using **I** as a coupling reagent following Fmoc/tBu orthogonal protection technique based SPPS (Solid Phase Peptide Synthesis) method. 3.2 fold excess of the Fmoc amino acids and 3 fold excess of the coupling reagents were used for each coupling step and gently rotated. Care should be taken not to take more amount of the coupling reagent than that of the *N*-protected amino acid, unlike other coupling reagents, for avoiding truncation by sulfonamide formation. Although reagent **I** generates higher yield in DCM than in DMF (Table 1), we used DMF as solvent for SPPS, as DMF is more commonly used in SPPS. Couplings were accomplished smoothly in 2 hours, which were confirmed by Kaiser test. A small amount of resin was taken after each coupling and cleaved the peptide from resin using TFA/DCM/H_2O mixture, precipitated using cold ether and injected in analytical HPLC for examining the purity at each step. Each time single peak was observed; eluent was collected and injected in ESI-MS for confirming the mass of the peptide fragment. The HPLC retention times and ESI-MS data for each fragment during the synthesis of IAPP (22-27) are mentioned in Table S1 in Supporting Information. The HPLC profiles and ESI-MS spectra of the purified peptides are also provided in supporting information (Figure S153 and 154). Quality of the crude peptide also was excellent. As an example, that for peptide ACP (65-74) was compared with the reported data (Table 5).[11] Quality of the crude IAPP (22-27) peptide fragment synthesized using **I** as coupling reagent was also very good (Supporting Information, Figure S151). We also synthesized Boc-Val-Val-IIe-Ala-OMe, the C-terminal fragment of the Amyloid β peptide.[14] This is also a hydrophobic difficult sequence bearing huge steric

hinderance (Figure 3c). A Boc-chemistry based stepwise coupling was performed in DCM following solution phase methodology. Yield was good (78%, after five steps with respect to starting Boc-Ile-OH) and HPLC chromatogram of the crude peptide (Supporting Information, Figure S137) was as good as a purified peptide.

Table 5. Comparative study of the purity of crude ACP (65-74) by TBTU, HATU, TBCR and *o*-NosylOXY

Coupling reagent	Purity of crude ACP (65-74) [%]
TBTU	69
HATU	87
TBCR	84
o-NosylOXY	90[a]

[a]90% purity of the crude peptide could be detected by HPLC (supporting information Figure S165).

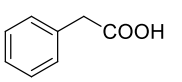
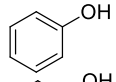
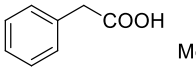
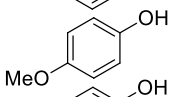
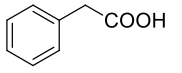
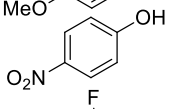
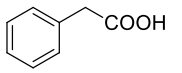
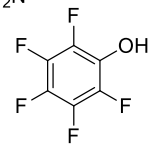
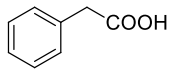
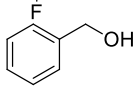
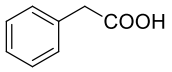
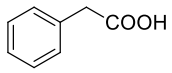
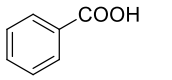
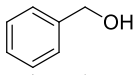
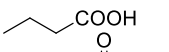
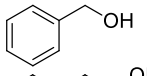
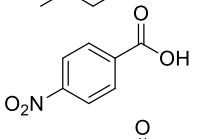
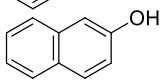
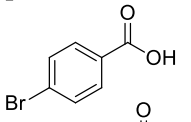
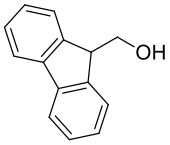
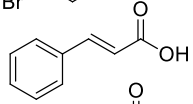
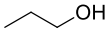
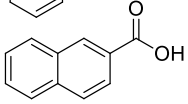
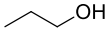
Soon completion of the establishment of the applicability of the coupling reagent **I** for the synthesis of amides, hydroxamates and peptides, we investigated its efficiency for esterification (Scheme 2). In spite of the numerous methodologies for the coupling reaction of alcohols and carboxylic acids, it is still desired to develop an efficient coupling reagent for the said transformation that is racemization free, with high yields for complicated substrates, clean isolation of the products and most importantly, recyclable. Esterification using **I** addressed most of these difficulties that were associated with the rest of the methodologies.

R^1 = aryl or alkyl
R^2 = aryl or alkyl

Scheme 2. Synthesis of ester under optimized condition

As a model reaction, we took phenyl acetic acid (1 mmol), in dichloromethane and added diisopropyl ethyl amine (1.1 mmol) to it. *o*-NosylOXY (1 mmol) was added to this mixture at room temperature (25 ^{o}C) with stirring. After 5 min, benzyl alcohol (1 mmol) and DIPEA (1.1 mmol) was added. After 2 h, the reaction was found to be complete and furnished the desired product in very good yield (92 %).

Table 6. Scope of esterification using reagent **I**

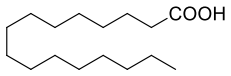
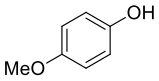
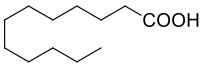
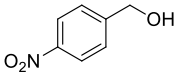
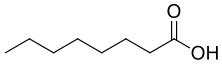
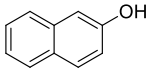
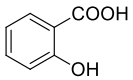
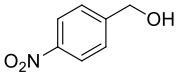
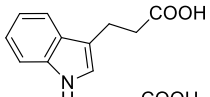
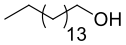
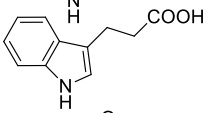
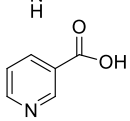
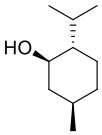
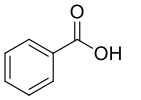
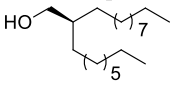
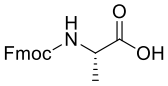
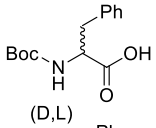
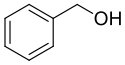
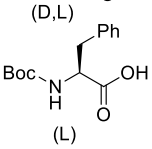
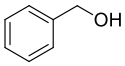
Entry[a]	Acid	Alcohol	Yield(%)[b]
1			87
2			82
3			90
4			81
5			92
6			84
7			89
8			85
9			91
10			90
11			89
12			91
13			87

[a]Performed with Acid (1 equiv), Reagent **I** (1 equiv), DIPEA (2.2 equiv), Alcohol (1 equiv), room temperature (25 °C), 2-3.5 h. [b]Yields refer to the isolated yields after column chromatography.

After standardization of the reaction conditions, we investigated the generality of the present protocol applying it to various alcohols and carboxylic acids. The reaction of phenyl acetic acid with varieties of aromatic (entry 1-4, Table 6) and aliphatic (entry 5-7) alcohols worked well. From the observation of the yields of entries 1-4, it was evident that the presence of electron donating group on phenol retards the reaction and thereby yields lesser product than its counterparts, which is in agreement with the stability of the phenoxide ions. The reaction went well with secondary (entry 7) and tertiary alcohol (entry 6).

The present protocol was successfully applied for the synthesis of biologically active esters also. The aliphatic carboxylic acids (entry 1-3, Table 7) worked well. The mentioned electromeric affect holds true for these reactions as well. In case of salicylic acid, i.e. entry 4, the reaction was chemoselctive and produced 4-nitro-benzyl ester of salicylic acid as a major product; although two nucleophilic attacks were logically possible. Self-condensation was very less due to the lesser nuclephilicity of the hydroxyl group of the salicylic acid than that of the *p*-nitrobenzyl alcohol. Phenolic acids have been esterified with excellent chemoselectivity in presence of strong protic acids (Fischer esterification), but harsh reaction conditions and excess of alcohol was required to drive the reaction to a satisfactory degree of conversion,[15] whereas, it worked smoothly in the present protocol, which is milder. Furthermore, in case of entry 5 and 6 (Table 7) the product observed was the ester alone, not the corresponding amide. Various aliphatic primary alcohols (entries 4-11, Table 7) and a secondary alcohol (entry 7) were subjected to the reaction conditions and the yield was good (82-90 %).

Table 7. Synthesis of various carboxylic esters using **I**.

Entry[a]	Acid	Alcohol	Time (h)	Yield (%)[b]
1			4.0	86
2			2.5	92
3			3.0	91
4			2.0	82
5			2.5	86
6			3.0	90
7			3.0	90
8			3.15	89
9		CH_3OH	3.0	87
10	 (D,L)		2.5	90
11	 (L)		2.5	89

[a]Performed with Acid (1 equiv), Reagent I (1 equiv), DIPEA (2.2 equiv), Alcohol (1 equiv), room temperature (25 °C). [b]Yields refer to the isolated yields after column chromatography.

Even amino acids (entry 9-11, Table 7) retained the same reactivity towards this reaction. In order to estimate the extent of racemization, we initially synthesized Boc-DL-Phe-OBn using our

protocol and passed through a chiral column. Two distinct peaks, corresponding to the two enantiomers, were observed in HPLC chromatogram (Figure 4, Left panel). Next, we synthesized Boc-L-Phe-OBn following the same strategy. Chromatographic signature of Boc-L-Phe-OBn reveals only one peak corresponding to the enantiopure product (Figure 4, Right panel). Therefore, it was inferred that the present protocol does not cause any detectable racemization.

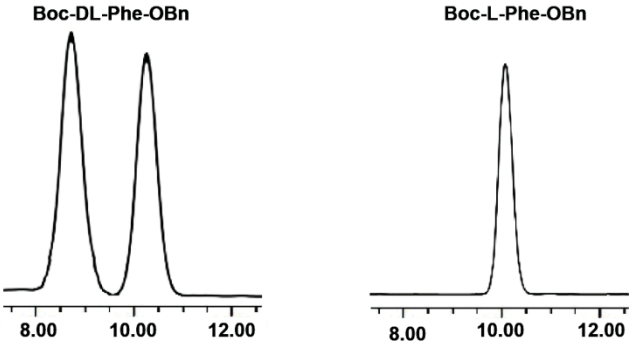
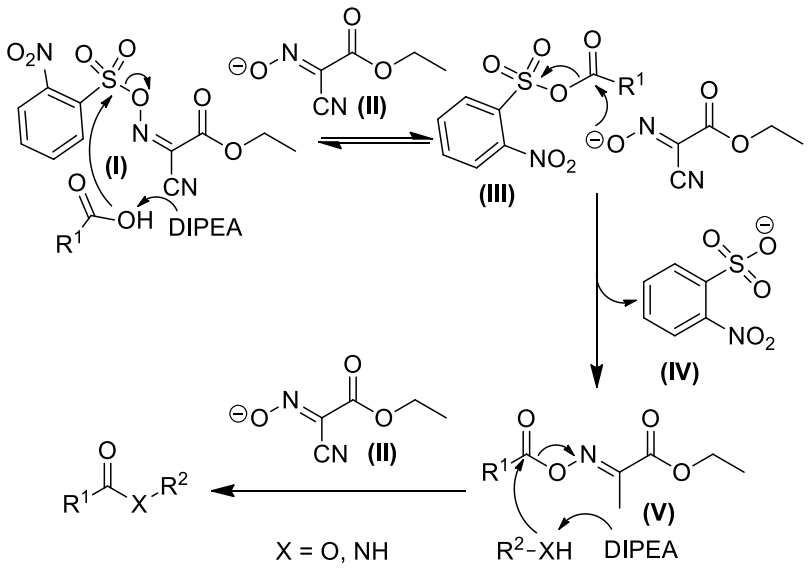


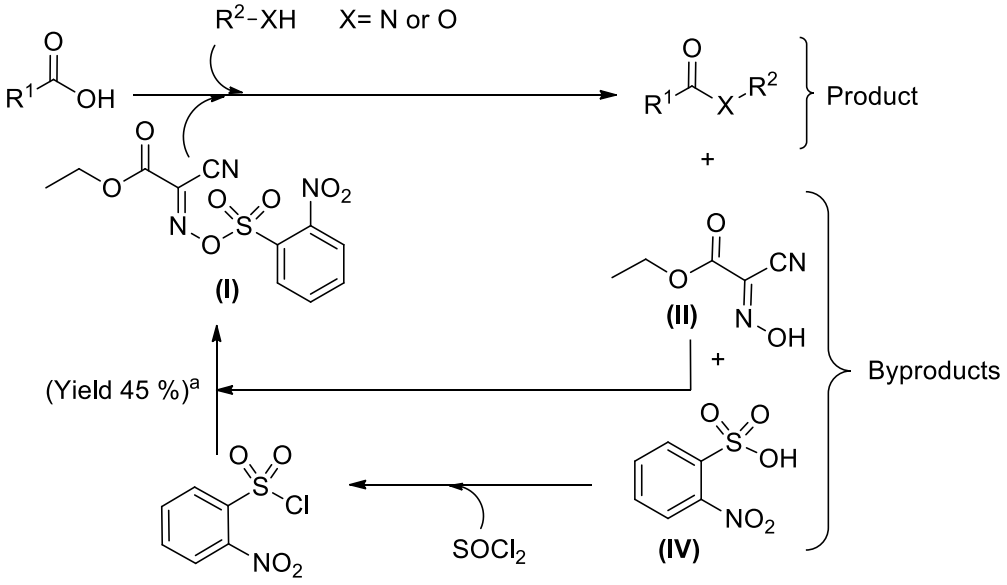
Figure 4. HPLC chromatogram of Boc-D,L-Phe-OBn (Left panel) and Boc-L-Phe-OBn (Right panel, CHIRAL PAK^{R} AS-H column, 5 μm, 2.1×150 mm, an isocratic gradient of 10% isopropanol in hexane was used).



Scheme 3. Plausible pathways for the condensation

A plausible mechanism is depicted in Scheme 3. Initially, the nucleophile generated by the deprotonation of the carboxylic acid in presence of DIPEA attacks the sulfonyl centre of **I**. Expulsion of the resonance stabilized Oxyma anion **II** results in the mixed anhydride **III**. Further nucleophilic attack of **II** on the carbonyl carbon of **III** and expulsion of the sulfonic acid **IV** results in the formation of the intermediate **V**, the activated Oxyma ester of the carboxylic acid. **V** undergoes nucelophilic substitution to produce the corresponding ester or amide. Isolation and complete characterization using ^{1}H NMR and ^{13}C NMR (Supporting Information, Figure S1-S2) and XRD analysis of the intermediate **V** was achieved (Supporting Information, Figure S169). However, the added nucleophile (amine or alcohol) may also react with the intermediate **III**. But, in that case, sulfonamide also may get generated as byproduct and racemization of the product is expected, as it was observed when the reaction was performed without pre-activation or using *o*-nitrobenzenesulfonyl chloride. A 3-5 min pre-activation precludes that possibility by increasing the population of the intermediate **V** in the reaction mixture.

The product as well as by-products Oxyma (II) and 2-nitrobenzene sulfonic acid (IV) were recovered easily. After completion of the reaction (entry 2, Table 4), the reaction mixture was diluted with ethyl acetate and washed with 5% citric acid solution (3×5 ml). Concentrated organic layer was directly purified by a silica gel column chromatography. The product and byproducts were eluted with specific eluents. Purity of the recovered II and IV was as good as the commercial samples (supporting information Figure S103-S105). The recovered sulfonic acid was chlorinated by heating on 60 ^{o}C for 1.5 h in toluene with a small amount of DMF using thionyl chloride. Pure sulfonyl chloride, obtained in this way, was transformed to **I** by stirring with Oxyma in basic medium (DIPEA).



Scheme 4. Recyclability of coupling reagent **I**. [a]Yield of the regenerated **I** from the recovered **II** and **IV** was calculated with respect to the initial amount of **I** used in the reaction.

To the best of our knowledge, only one such recyclable coupling reagent is reported, which is a hypervalent iodine-III reagent, iodosodilactone, and it works in association with DMAP and PPh_3.[16] Dipeptide formation with this combination of reagents usually takes 8 h under heating condition (60 °C). On the other hand, it takes only 1 h at room temperature (25 °C) by our method. Moreover, stoichiometric amount of triphenyl phosphine oxide is generated with iodosodilactone/DMAP/PPh_3, whereas the present method does not leave any solid waste to the environment.

CONCLUSION

We have introduced a new and efficient coupling reagent, *o*-NosylOXY (**I**), for the synthesis of amide, hydroxamate, peptide and ester. The present method is associated with the following important features: 1) apparently complete retention of stereochemistry, 2) applicability to both solution and solid phase synthesis of large peptides with difficult sequences, 3) ease of preparation of the reagent, 4) works under ambient and milder conditions. A plaussible mechanism is suggested and an intermediate could be isolated and fully characterized which supports that. Most importantly, the reagent is recyclable, therefore, cost effective and environment friendly. All these features makes this reagent useful for industry and academia in the context of condensation chemistry.

EXPERIMENTAL SYSTEM

General consideration:

All reagents were purchased from commercial sources and were used without any further purification unless mentioned otherwise. *o*-nitrobenzenesulfonyl chloride is freshly recrystallized before use. Dichloromethane is distilled and dried using standard procedure. Melting points were uncorrected. Thin layer chromatograms were run on glass plates coated with silica gel G for TLC, using solvent systems EtOAc/Hexane. Compounds were purified by column chromatography using Silica Gel (60-120 mesh) with EtOAc/Hexane (of specific proportion as required) as an eluent. ^{1}H NMR (400 MHz and 600 MHz) and ^{13}C NMR (100 MHz and 150 MHz) were recorded using $CDCl_3$ as solvent. Chemical shifts (δ) are reported in parts per million (ppm), internal reference (0.05% to 1 %) tetramethylsilane. Coupling constants (*J*) are reported in Hz singlet (s), doublet (d), triplet (t), doublet of doublet (dd), multiplet (m), or broad (br).

High resolution mass spectra were recorded on a Q-TOF ESI-MS instrument and a Q-TOF LC/MS system; HPLC analysis was carried out with either a C8 (5 μm, 3.5 × 150 mm) or a C18 (5 μm, 4.6 × 250 mm) reverse phase column and a chiral column (5 μm, 2.1×150 mm) coupled to a UV detector. HPLC grade solvents were used for HPLC analysis. IR spectra were recorded on a IR spectrometer; X-ray data were collected on a diffractometer equipped with a CCD area detector using Mo. Data for previously reported compounds (cited) matched well with our observed data.

Procedure for Synthesis of Coupling Reagent Ethyl 2-cyano-2-(2-nitrobenzenesulfonyloxy imino) acetate (*o*-NosylOXY, I):

DIPEA (0.87 ml, 5 mmol, 1 equiv) was added to a solution of Oxyma (710 mg, 5 mmol, 1 equiv) in 2 ml of DCM under nitrogen. The reaction mixture was cooled up to 0 ^{o}C and followed by dropwise addition of 2-nitrobenzenesulfonyl chloride (1108 mg, 1 mmol, 1 equiv) for 30 min. The reaction mixture was stirred for another 2 h at room temperature (25 °C). After completion of the reaction, the reaction mixture was diluted with 10 ml of DCM and washed with 5% of HCl (3×5 ml). Finally organic layer dried by anhydrous $CaCl_2$ and recrystallized with hexane. R_f = 0.50 (EtOAc:Hexane, 1:4), Yield 1308 mg, 80 %; colorless crystalline solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26-8.24 (d, J = 8.0 Hz, 1H), 7.95-7.90 (m, 1H), 7.89-7.84 (m, 2H), 4.45-4.40 (q, 2H), 1.39-1.36 (t, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5, 148.6, 137.3, 133.3, 132.9, 132.7, 126.7, 125.5, 105.9, 65.0, 13.8; IR (KBr) 3103, 2988, 2224, 1748, 1544.89, 928, 742 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{11}H_{10}N_3O_7S$ 328.0239, found 328.0235.

General Procedure for the Synthesis of Ester and Amide:

o-NosylOXY (1 equiv) was added to a solution of acid (1 equiv) and DIPEA (1 equiv) in 2 ml of DCM. The reaction mixture was stirred for 3-5 min. for preactivation followed by the addition of alcohol or amine (1.0 equiv). The reaction mixture was stirred at room temperature for 2-3 h. After completion of the reaction, the reaction mixture was diluted with 50 ml of ethyl acetate; the organic phase was washed with 5% citric acid (3×20 ml), 5% $NaHCO_3$ (3×20 ml) and dried by anhydrous Na_2SO_4. Finally, Na_2SO_4 was filtered off and the solvent was evaporated to obtain the product which was purified by column chromatography.

General Procedure for the Synthesis of Dipeptides:

To a solution of *N*-protected amino acid (1 equiv) and *o*-NosylOXY (1 equiv) in 2 ml of DCM, DIPEA (1.1 equiv) was added. The reaction mixture was stirred for 5 min. for preactivation followed by the addition of methyl ester of the second amino acid (1.1 equiv) and DIPEA (1.1 equiv) in 1 ml of DCM. The reaction mixture was stirred at room temperature for more 2-3 h. After completion of the reaction, the reaction mixture was diluted with 50 ml of ethyl acetate, the organic phase was washed with 5% citric acid (3×20 ml), 5% $NaHCO_3$ (3×20 ml), brine and dried over anhydrous Na_2SO_4. Finally, Na_2SO_4 was filtered and the solvent was evaporated. The product was purified by silica gel column chromatography.

General Procedure for the Synthesis of Hydroxamate:

To a solution of acid or *N*-protected amino acid (1 equiv) and *o*-NosylOXY (1 equiv) in 2 ml of DCM, DIPEA (1.1 equiv) was added. The reaction mixture was stirred for 3-5 min. for preactivation followed by the addition of O-benzylhydroxylamine (1.1 equiv) and DIPEA (1.1 equiv) in 1 ml of DCM. The reaction mixture was stirred at room temperature (25 °C) for more

2-3 h. After completion of the reaction, the reaction mixture was diluted with 50 ml of ethyl acetate, the organic phase was washed with 5% citric acid (3×20 ml), 5% $NaHCO_3$ (3×20 ml), brine and dried over Na_2SO_4 anhydrous. Finally, Na_2SO_4 was filtered and the solvent was evaporated. The product was purified by silica gel column chromatography.

Solution Phase Synthesis of Boc-VVIA-OMe:

Boc-isoleucine (750 mg, 3.24 mmol, 1 equiv,) and *o*-NosylOXY (1059 mg, 3.24 mmol, 1 equiv) was taken in a 25 ml RB, after that DIPEA (0.85 ml, 4.86 mmol, 1.5 equiv) was added and kept 5 min for pre-activation. In another oven dried 50 ml RB, methyl ester of alanine (675 mg, 4.86 mmol, 1.5 equiv) was taken in DCM and DIPEA was added to it until basic pH was reached. Finally, this solution was added in first RB and stirring continued until completion of the reaction. Then, the reaction mixture was diluted by 50 ml of EtOAc, washed by 5% $NaHCO_3$ solution (2 × 5 ml) and washed by 5% citric acid solution (2 × 5 ml). Finally, combined organic layer was dried using anhydrous Na_2SO_4. Solid product (Boc-IA-OMe) was obtained after evaporation of EtOAc by rotary vacuum evaporator.

In an oven dried 50 ml RB, Boc-IA-OMe was taken and 70% TFA solution in DCM was added to it. Starring continued up to 2.5 h. After that, TFA was evaporated by rotary evaporator and washed 3 times with diethyl ether and finally white solid (IA-OMe) was obtained.

After Boc deprotection, resulted IA-OMe was coupled with Boc-V-OH following the above mentioned procedure to obtain Boc-VIA-OMe. Another cycle of Boc-deprotection and coupling with Boc-V-OH, resulted white solid Boc-VVIA-OMe, which was characterized by reverse phase HPLC, retention time was 12.8 minutes on linear gradient of 20 to 100% CH_3CN/0.09% TFA in H_2O/0.09% TFA over 18 min, symmetry C8 analytical column and LRMS (ESI): m/z

$[M+H]^+$ calculated for $C_{25}H_{47}N_4O_7$ is 537.3264 found 537.3421. Yield was 1298 mg, 78% with respect to starting material Boc-isoleucine.

Solid Phase Synthesis of NFGAILG-NH_2 and VQAAIDYING-NH_2:

Specific amino acids were manually assembled on Fmoc-Rink Amide MBHA resin (loading 1.1 mmol/g) following Fmoc-^{t}But orthogonal protection strategy. Fmoc-amino acids (3.2 equiv), *o*-NosylOXY (3 equiv) and DIPEA (5 equiv) was kept for pre-activation for 5 min. Amino acid coupling was performed for 2 h. Fmoc deprotection was carried out with 25% piperidine/DMF (3 × 7 min). The peptide was cleaved from the resin using TFA/DCM/H_2O mixture for 2 h 30 min. Purification of the peptide was performed using semi-preparative HPLC using a linear gradient of 20 min (5 to 100 % ACN in water with 0.09% TFA) and characterized using ESI-MS.

For NFGAILG-NH_2, we took 300 mg of Fmoc-Rink Amide resin (loading 1.1 mmol/g), after final coupling, peptide was cleaved from resin and purified by semi-preparative HPLC. The purified yield of peptide was 90 mg, 40 %, HPLC profile and ESI-MS spectrum are shown in supporting information (S153-154).

And for VQAAIDYING-NH_2, we took 300 mg of Fmoc-Rink Amide resin (loading 1.1 mmol/g), after final coupling, this peptide was also cleaved from resin and purified by semi-preparative HPLC. Yield of the purified peptide was 175 mg, 50 %. HPLC profile and ESI-MS spectrum are provided in supporting information (S167-168).

Intermediate V (Scheme 3): Oxyma ester naphthanoic acid

White solid; R_f = 0.40 (EtOAc:Hexane, 1.0:9.0), ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.13-8.11 (t, *J* = 8.0 Hz, 1H), 8.00-7.98 (d, *J* = 12.0, Hz, 1H), 7.64-7.61 (t, *J* = 12.0 Hz, 2H), 7.64-7.61 (t, *J* = 6.5, Hz, 1H), 7.58-7.56 (t, *J* = 6.6, Hz, 1H), 4.46-4.43 (q, *J* = 6.0 Hz, 2H), 1.43-1.40 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.9, 157.1, 136.5, 133.1, 132.4, 129.9, 129.7, 129.2, 128.0, 127.4, 125.0, 122.8, 107.2, 64.7, 14.1; IR (KBr): 2924, 2853, 2224, 1715, 1646, 1593, 1541, 1398, 668, 544 cm^{-1}; HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{16}H_{12}N_2NaO_4$ 319.0695, found 319.0691. CCDC-936483 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Methyl 2-(2-((((9H-fluoren-9-yl)methoxy) carbonyl)amino)-3-phenylpropanamido) propanoate[17] (by *o*-nitrobenzenesulfonyl chloride). Yield: 307 mg (65%); white solid; R_f = 0.40 (EtOAc:Hexane, 3.0:7.0); m.p.178-180 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09-8.07 (m, 1H), 7.94-7.91 (m, 1H), 7.77-7.72 (m, 2H), 7.55-7.52 (t, *J* = 12.0 Hz, 2H), 7.42-7.38 (t, *J* = 12.0 Hz, 2H), 7.32-7.24 (m, 4H), 7.21-7.19 (m, 1H), 6.33 (br, 1H), 5.39 (br, 1H), 4.52-4.43 (m, 3H), 4.32-4.23 (m, 2H), 4.20-4.17 (t, *J* = 8.0 Hz, 1H), 3.52 (s, 3H), 3.12-3.05 (m, 1H), 1.50-1.48 (d, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 172.1, 170,67, 156.08, 143.9, 141.4, 136.4, 133.7, 132.9, 130.6, 129.5, 128.5, 127.8, 127.8, 127.2, 125.7, 120.1, 67.2, 56.1, 52.2, 48.3, 47.2, 19.7, 18.3; IR (KBr): 3304, 1738, 1690, 1652, 1534, 1262, 698 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{28}H_{29}N_2O_5$ 473.2076, found 473.2079.

(L) Methyl 2-(2-nitrophenylsulfonamido)propanoate (by *o*-nitrobenzenesulfonyl chloride)[18]: pale yellow solid; R_f = 0.50 (EtOAc:Hexane, 3.0:7.0); m.p.68-70 °C; ^{1}H NMR (400

MHz, $CDCl_3$): δ 8.29-8.27 (m, 1H), 8.07-8.05 (m, 1H), 7.92-7.90 (m, 1H), 7.74-7.71 (m, 1H), 6.18 (br, 1H), 4.23-4.19 (m, 1H), 3.50 (s, 3H), 1.50-1.48 (d, *J* = 8.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.1, 147.9, 134.4, 133.8, 133.0, 130.6, 125.7, 52.7, 48.8, 16.7; IR (KBr): 3330, 2921, 1746, 1691, 1536, 1261, 1184, 741 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{10}H_{12}N_2NaO_6S$ 311.0314, found 311.0317.

***N*-benzyl-2-nitrobenzenesulfonamide (byproduct of the reaction without pre-activation):** pale yellow solid; R_f = 0.52 (EtOAc:Hexane, 3.0:7.0); ^1H NMR (400 MHz, $CDCl_3$): δ 8.01-7.98 (m, 1H), 7.83-7.81 (m, 1H), 7.70-7.63 (m, 2H), 7.31-7.22 (m, 5H), 5.77 (br, 1H), 4.33-4.32 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.9, 135.8, 134.1, 133.6, 132.9, 131.1, 128.8, 128.0, 125.4, 48.0; IR (KBr): 3340, 2961, 1691, 1535, 1221, 1182, 933, 742 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{13}H_{12}N_2NaO_4S$ 315.0415, found 315.0420.

***N*-benzylbenzamide (entry 1, Table 3).[19]** Yield: 186 mg (88%); white solid; R_f = 0.50 (EtOAc:Hexane, 2.0:8.0) mp: 102-104 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.78-7.76 (m, 2H), 7.42-7.37 (m, 4H), 7.36-7.28 (m, 4H), 4.63-4.62 (d, *J* = 4.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 138.4, 134.4, 131.6, 128.8, 128.6, 127.9, 127.5, 127.1, 44.1; IR (KBr): 3290, 2924, 1637, 1551, 765, 565 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{14}NO$ 212.1075, found 212.1073.

***N*-benzyl-*2*-phenylacetamide (entry 2, Table 3).[19]** Yield: 205 mg (91%); white solid; R_f = 0.51 (EtOAc:Hexane, 2.0:8.0); mp: 76-78 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.36-7.27 (m, 5H), 7.24-7.16 (m, 5H), 5.76 (br, 1H), 4.42 (s, 2H), 3.62 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 138.3, 135.0, 129.4, 129.0, 128.7, 127.5, 127.4, 127.3, 43.7, 43.6; IR (KBr): 3289, 2925,

1638, 1552, 784, 634, 566 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{16}NO$ 226.1232, found 226.1231.

***N*-(4-methoxyphenyl)-2-phenylacetamide (entry 3, Table 3).** Yield: 198 mg (82%); pale yellowish solid; R_f = 0.40 (EtOAc:Hexane, 3.0:7.0); m.p.121-123°C; ^1H NMR (600 MHz, $CDCl_3$): δ 7.39-7.37 (m, 2H), 7.35-7.29 (m, 5H), 7.12 (br, 1H), 6.81-6.79 (d, *J* = 12.0 Hz, 2H), 3.75 (s, 3H), 3.70 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.3 156.7, 134.7, 130.8, 129.7, 129.3, 127.7, 122.0, 114.2, 55.6, 44.8; IR (KBr): 3330, 2930, 2832, 1751, 1519, 1262, 1188, 1016, 544 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{16}NO_2$ 242.1181, found 242.1183.

2-*N*-Diphenyl-acetamide (entry 4, Table 3).[20] Yield: 181 mg (86%); white solid; R_f = 0.40 (EtOAc:Hexane, 2.0:8.0); mp: 115-117 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.42- 7.36 (m, 5H), 7.35-7.06 (m, 5H), 3.73 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 137.9, 134.7, 129.5, 129.1, 128.9, 127.5, 124.5, 120.2, 44.6; IR (KBr): 3285, 2967, 1657, 1601, 865, 543 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{14}NO$ 212.1075, found 212.1071.

Benzyl 2-oxo-2-(piperidin-1-yl) ethylcarbamate (entry 5, Table 3).[21] Yield: 265 mg (89%); white solid; R_f = 0.30 (EtOAc:Hexane, 4.0:6.0); mp: 113-116 °C; ^1H NMR (400 MHz, $CDCl_3$): δ7.32-7.28 (m, 5H), 5.84 (br, 1H), 5.09 (s, 2H), 3.98-3.97 (d, *J* = 4.0 Hz, 2H), 3.54-3.52 (t, *J* = 5.2 Hz, 2H), 3.29-3.27 (t, *J* = 5.2 Hz, 2H), 1.70-1.68 (d, *J* = 4.0 Hz, 2H), 1.63-1.61 (d, *J* = 4.8 Hz, 2H), 1.54-1.52 (d, *J* = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 156.3, 136.6, 128.5, 128.1, 128.0, 66.8, 45.4, 43.1, 42.6, 34.0, 26.2, 25.7, 25.4, 25.0, 24.3; IR (KBr): 3293, 2936, 1707, 1641, 763, 541 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{15}H_{20}N_2NaO_3$ 299.1372, found 299.1368.

(9H-fluoren-9-yl)methyl (1-(tert-butylamino)-1-oxopropan-2-yl) carbamate (entry 6, Table 3). Yield: 296 mg (81%); yellowish solid; R_f = 0.40 (EtOAc:Hexane, 3.0:7.0); $[\alpha]_D^{25}$ = + 4.07 ($CHCl_3$, c = 0.54); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.76-7.75 (d, *J* = 12.0 Hz, 2H), 7.59-7.57 (d, *J* = 12.0 Hz, 2H), 7.41-7.38 (m, 2H), 7.32-7.29 (m, 2H), 4.43-4.37 (m, 3H), 4.24-4.19 (t, *J* = 6.0 Hz, 1H), 4.13 (br, 1H), 1.36-1.35 (d, *J* = 6.0 Hz, 3H), 1.34 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 171.6, 156.1, 144.0, 141.5, 127.9, 127.2, 125.2, 120.1, 67.2 51.5, 47.3, 28.8, 19.1; IR (KBr): 3330, 3231, 2984, 1754, 1243, 752, 542 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{22}H_{27}N_2O_3$ 367.2022, found 367.2025.

(L) Methyl 2-(2-((((9H-fluoren-9-yl)methoxy) carbonyl)amino) propanamido)-2-methylpropanoate (entry 7, Table 3). Yield: 328 mg (80%); white solid; R_f = 0.50 (EtOAc:Hexane, 3.0:7.0); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77-7.75 (d, *J* = 12.0 Hz, 2H), 7.62-7.58 (m, 2H), 7.42-7.38 (t, *J* = 12.0 Hz, 2H), 7.32-7.29 (t, *J* = 12.0 Hz, 2H), 5.42 (br, 1H), 4.43-4.37 (m, 2H), 4.24-4.21 (t, *J* = 8.0 Hz, 1H), 4.16-4.10 (m, 1H), 3.76 (s, 3H), 1.44-1.42 (d, *J* = 12.0 Hz, 3H), 1.25 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 155.8, 144.1, 141.5, 127.9, 127.2, 125.2, 124.9, 120.2, 76.9, 67.2, 52.7, 50.5, 49.8, 47.3, 29.7, 18.9; IR (KBr): 3341, 1722, 1654, 1650, 1231, 664 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{23}H_{27}N_2O_5$ 411.1920, found 411.1922.

Methyl 2-(2-(((9H-fluoren-9-yl) methoxy)carbonyl) acetamido)acetate (entry 8, Table 3). Yield: 321 mg (91%); white solid; R_f = 0.31 (EtOAc:Hexane, 4.0:6.0); mp: 162-163 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76-7.74 (d, *J*= 8.0 Hz, 2H), 7.58-7.56 (d, *J* = 8.0 Hz, 2H), 7.40-7.37 (t, *J*= 8.0 Hz, 2H), 7.31-7.27 (t, *J* = 8.0 Hz, 2H), 6.80 (br, 1H), 5.73 (br, 1H), 4.43-4.41 (d, *J* = 6.8 Hz, 2H), 4.22-4.19 (t, *J* = 7.2 Hz, 1H), 4.04-4.03 (d, *J* = 8.0 Hz, 2H), 3.92-3.91 (d, *J* = 6.8 Hz, 2H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 169.7, 156.8, 143.7, 141.2,

128.6, 128.5, 128.3, 127.1, 67.1, 47.0, 44.2, 41.2, 33.8; IR (KBr): 3316, 2931, 1734, 1692, 1654, 865, 523 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{20}H_{19}NNaO_5$ 376.1161, found 376.1165.

(L,L) Methyl 2-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)-4-methylpentanamido) propanoate (entry 9, Table 3) Yield: 390 mg (89%); white solid; R_f = 0.50 (EtOAc:Hexane, 3.0:7.0); mp: 161-163 °C; $[\alpha]_D^{25}$ = - 16.5 ($CHCl_3$, c = 0.35); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76-7.74 (d, *J* = 8.0 Hz, 2H), 7.59-7.57 (d, *J* = 8.0 Hz, 2H), 7.41-7.37 (t, *J* = 7.2 Hz, 2H), 7.32-7.28 (t, *J* = 7.2 Hz, 2H), 6.62 (br, 1H), 5.36-5.34 (d, *J* = 8.0 Hz, 1H), 4.58-4.52 (m, 1H), 4.41-4.35 (m, 1H), 4.22-4.19 (t, *J* = 6.4 Hz, 3H), 3.73 (s, 3H), 1.81-1.74 (m, 1H), 1.65-1.63 (m, 2H), 1.40-1.38 (d, *J* = 6.8 Hz, 3H), 1.01-0.98 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.2, 163.1, 156.6, 143.8, 141.1, 129.3, 128.6, 127.5, 126.9, 124.9, 66.6, 57.4, 52.2, 46.9, 38.2, 38.3, 28.1, 18.0; IR (KBr): 3307, 2925, 1754, 1694, 1654, 879, 534 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{25}H_{31}N_2O_5$ 439.2233, found 439.2235.

(L,L) Methyl 2-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)-3-methylbutanamido)propanoate (entry 10, Table 3).[22] Yield: 369 mg (87%); white solid; R_f = 0.50 (EtOAc:Hexane, 3.0:7.0); mp: 204-205 °C; $[\alpha]_D^{25}$ = - 14.5 ($CHCl_3$, c = 0.40); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76-7.75 (d, *J* = 8.0 Hz, 2H), 7.60-7.58 (d, *J* = 8.0 Hz, 2H), 7.41-7.37 (t, *J* = 8.0 Hz, 2H), 7.31-7.28 (t, *J* = 8.0 Hz, 2H), 6.54-6.52 (d, *J* = 8.0 Hz, 1H), 5.54-5.52 (d, *J* = 8.0 Hz, 1H), 4.60-4.58 (d, *J* = 8.0 Hz, 2H), 4.44-4.35 (m, 1H), 4.23-4.21(d, *J* = 8.0 Hz, 1H) 4.04-4.00 (t, *J* = 7.0 Hz, 1H), 3.73 (s, 3H), 2.11-2.08 (m, 1H), 1.41-1.39 (d, *J* = 8.0 Hz, 3H), 0.98-0.96 (d, *J* = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3, 171.2, 156.6, 144.0, 141.4, 127.8, 127.2, 125.2, 120.1, 67.2, 60.4, 52.6, 48.2, 47.3, 31.9, 29.8, 19.2, 18.2; IR (KBr): 3296, 2953, 1745, 1692, 1650, 765, 599 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{24}H_{28}N_2NaO_5$ 447.1896, found 447.1901.

(L) Methyl 2-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)-3-phenylpropanamido)acetate (entry 11, Table 3) Yield: 412 mg (93%); white solid; R_f = 0.52 (EtOAc:Hexane, 3.0:7.0); mp: 175-178 °C; $[\alpha]_D^{25}$ = - 6.5 ($CHCl_3$, c = 0.60); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77-7.75 (d, *J* = 8.0 Hz, 4H), 7.54-7.50 (t, *J* = 8.0 Hz, 2H), 7.42-7.38 (t, *J* = 8.0 Hz, 2H), 7.32-7.28 (m, 5H), 6.31 (br, 1H), 5.33 (br, 1H), 4.45-4.40 (t, *J* = 8.0 Hz, 2H), 4.40-4.32 (d, *J* = 8.0 Hz, 1H), 4.20-4.16 (t, *J* = 7.2 Hz, 1H), 4.00-3.99 (d, *J* = 4.0 Hz, 2H) 3.72 (s, 3H); 3.10-3.00 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 171.5, 170.0, 156.2, 143.8, 141.4, 136.5, 129.4, 128.8, 128.5, 127.8, 127.7, 127.3, 127.2, 125.1, 120.1, 67.2, 56.1, 52.5, 47.2, 41.3, 38.5; IR (KBr): 3300, 1749, 1692, 1651, 1539, 1260, 757; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{27}H_{26}NO_5$ 444.1811, found 444.1809.

(L) Methyl 2-(2-(((9H-fluoren-9-yl)methoxy)carbonyl) propanamido)acetate (entry 12, Table 3) Yield: 319 mg (87%); white solid; R_f = 0.40 (EtOAc:Hexane, 4.0:6.0); mp: 157-159 °C; $[\alpha]_D^{25}$ = - 12.4 ($CHCl_3$, c = 0.60); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75-7.73 (d, *J* = 8.0 Hz, 2H), 7.56-7.55 (d, *J* = 8.0 Hz, 2H), 7.39-7.35 (t, *J* = 8.0 Hz, 2H), 7.30-7.27 (t, *J* = 8.0 Hz, 2H), 6.63 (br, 1H), 5.54 (br, 1H), 4.39-4.38 (t, *J* = 4.0 Hz, 2H), 4.31-4.30 (t, *J* = 4.0 Hz, 1H), 4.20-4.17 (d, *J* = 4.0 Hz, 1H), 4.01-3.99 (d, *J* = 4.0 Hz, 2H), 3.71 (s, 3H), 1.40-1.38 (d, *J* = 8.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.9, 170.2, 156.2, 143.9, 141.4, 127.8, 127.2, 125.2, 120.1, 67.2, 52.5, 50.5, 47.2, 41.3, 18.7; IR (KBr): 3294, 1731, 1693, 1648, 1551, 1265, 758 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{21}H_{23}N_2O_5$ 383.1607, found 383.1609.

(DL) Methyl 2-(2-(benzyloxycarbonyl)-3-phenyl propanamido)propanoate (entry 13, Table 3).[23] Yield: 345 mg (90%); white solid; R_f = 0.51 (EtOAc:Hexane, 3.0:7.0); mp: 120-122 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.30 (m, 4H), 7.29-7.26 (m, 4H), 7.23-7.17 (m, 2H), 6.60 (br, 1H), 5.53 (br, 1H), 5.05 (s, 2H), 4.53-4.51 (d, *J* = 8.0 Hz, 1H), 4.47-4.45 (d, *J* = 8.0 Hz, 1H), 3.67 (s, 3H), 3.07-3.05 (d, *J* = 8.0 Hz, 2H), 1.32-1.30 (d, *J* =8.0 Hz, 3H), 1.21-1.19 (d, *J* = 8.0 Hz,

3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 172.9, 170.9, 170.7, 156.1, 136.6, 136.3, 129.3, 128.4, 128.1, 127.9, 126.9, 66.9, 56.1, 52.4, 38.9, 38.6, 17.8 ppm; IR (KBr): 3305, 1737, 1690, 1652, 1537, 1262, 698 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{21}H_{24}N_2NaO_5$ 407.1583, found 407.1588.

(L) Methyl 2-(2-(benzyloxycarbonyl)-3-phenyl propanamido)propanoate (entry 14, Table 3).[23] Yield: 349 mg (91%); white solid; R_f = 0.51 (EtOAc:Hexane, 3.0:7.0); mp: 120-122 °C. $[\alpha]_D^{25}$ = - 12.1 ($CHCl_3$, c = 0.32); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.31 (m, 4H), 7.30-7.24 (m, 4H), 7.22-7.17 (m, 2H), 6.47 (br, 1H), 5.42 (br, 1H), 5.07 (s, 2H), 4.51-4.52 (d, *J* = 4.0 Hz, 1H), 4.48-4.46 (d, *J* = 8.0 Hz, 1H), 3.70 (s, 3H), 3.07-3.05 (d, *J* = 8.0 Hz, 2H), 1.32-1.31 (d, *J* =4.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 173.0, 170.7, 156.2, 136.4, 129.5, 128.8, 128.7, 128.6, 128.3, 128.2, 127.2, 67.2, 56.2, 52.6, 49.3, 48.12, 38.7, 18.4; IR (KBr): 3305, 1737, 1690, 1652, 1537, 1262, 698 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{21}H_{24}N_2NaO_5$ 407.1583, found 407.1587.

(L, L) Methyl 2-(2-(benzyloxycarbonyl)-4-(methylthio) butanamido)propanoate (entry 15, Table 3) Yield: 327 mg (89%); white solid; R_f = 0.40 (EtOAc:Hexane, 3.0:7.0); mp: 107-110 °C. $[\alpha]_D^{25}$ = + 6.8 ($CHCl_3$, c = 0.70); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.32 (m, 3H), 7.30-7.27 (m, 2H), 6.69 (br, 1H), 5.55 (br, 1H), 5.08 (s, 2H), 4.55-4.52 (t, *J* = 8.0 Hz, 1H), 4.39-4.37 (t, *J* = 8.0 Hz, 1H), 3.71 (s, 3H), 2.59-2.56 (t, *J* = 8.0 Hz, 2H), 2.08 (s, 3H), 2.00-1.94 (q, *J* = 8.0 Hz, 2H), 1.38-1.37 (d, *J* =4.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 173.1, 170.8, 156.1, 136.3, 128.7, 128.4, 128.3, 67.3, 54.0, 527, 48.3, 31.9, 30.0, 18.3, 15.4 ppm; IR (KBr): 3299, 1735, 1688, 1647, 1538, 1265, 697 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{25}N_2O_5S$ 369.1484, found 369.1489.

(L) Methyl 2-(2-(benzyloxycarbonyl)-2-methyl propanamido)propanoate (entry 16, Table 3).[22] Yield: 260 mg (81%); yellowish solid; R_f = 0.50 (EtOAc:Hexane, 2.0:8.0); mp: 67-70 °C; $[\alpha]_D^{25}$ = - 1.8 ($CHCl_3$, c = 0.70); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28-7.22 (m, 3H), 7.21-7.15 (m, 2H), 6.89 (br, 1H), 5.82-5.76 (t, *J* = 8.0 Hz, 1H), 4.98 (s, 2H), 4.43 (br, 1H), 3.58 (s, 3H), 1.32 (s, 6H), 1.17-1.14 (d, *J* =4.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 174.2, 173.5, 155.1, 136.4, 128.5, 128.1, 128.0, 66.6, 56.8, 52.4, 48.2, 25.1, 25.1, 18.0; IR (KBr): 3316, 1734, 1692, 1654, 1234, 674 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{16}H_{23}N_2O_5$ 323.1607, found 323.1610.

(L) Methyl 2-(2-(benzyloxycarbonyl)-2-methyl propanamido)-4-methylpentanoate (entry 17, Table 3).[22] Yield: 283 mg (78%); white solid; R_f = 0.50 (EtOAc:Hexane, 2.0:8.0); mp: 77-80 °C; $[\alpha]_D^{25}$ = - 1.5 ($CHCl_3$, c = 1.64); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35-7.32 (m, 3H), 7.31-7.26 (m, 2H), 6.70 (br, 1H), 5.31 (br, 1H), 5.09 (s, 2H), 4.60-4.58 (t, *J* = 4.0 Hz, 1H), 3.71 (s, 3H), 1.65-1.61 (m, 3H), 1.50 (s, 3H), 1.49 (s, 3H), 0.95-0.92 (d, *J* = 4.0 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 174.3, 173.6, 155.3, 136.4, 128.7, 128.6, 128.9, 66.9, 57.2, 52.39, 51.9, 41.6, 25.9, 25.2, 25.0, 22.9, 22.0; IR (KBr): 3346, 1723, 1653, 1653, 1235, 664 cm^1; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{19}H_{29}N_2O_5$ 365.2076, found 365.2080.

(L,L) 2-[2-(2-Benzyloxycarbonylamino-acetylamino)-3-phenyl-propionylamino]-3-methyl-butyric acid methyl ester (entry 18, Table 3).[23] Yield: 426 mg (91%); white solid; R_f = 0.31 (EtOAc:Hexane, 3.0:7.0); mp 101 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35-7.27 (m, 5H), 7.23-7.11 (m, 5H), 5.88 (br, 1H), 5.11 (s, 2H), 4.78 (br, 1H), 443-4.40 (m, 2H), 3.88-3.84 (m, 2H), 3.60 (s, 3H), 304-299 (m, 2H), 2.06-2.03 (m, 1H), 0.87-0.84 (d, *J* = 8.0 Hz, 3H), 0.82-0.79 (d, *J* = 8.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 171.9, 171.4, 169.6, 156.7, 136.5, 136.4, 129.4, 129.0, 128.7, 128.6, 128.5, 128.1, 128.0, 126.8, 67.0, 57.5, 54.5, 52.0, 44.2, 38.5, 31.1, 18.8,

17.9; IR (KBr): 3406, 1728, 1677, 1651, 1646, 763, 543 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{25}H_{32}N_3O_6$ 470.2291, found 470.2294.

***N*-(benzyloxy)benzamide (entry 1, Table.4).[24]** Yield: 208 mg (92%), yellowish solid; R_f = 0.50 (EtOAc:Hexane, 2.0:8.0); m.p.107-110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12-8.10 (m, 2H), 7.69-7.51 (m, 2H), 7.49-7.35 (m, 6H), 5.02 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.76, 133.75, 132.14, 130.27, 129.67, 129.43, 128.83, 128.70, 128.67, 128.55, 127.34, 78.46; IR (KBr): 2963, 1626, 1522, 1145, 1001, 747, 638 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{14}NO_2$ 228.1025, found 228.1023.

***N*-(benzyloxy)-2-naphthamide (entry 2, Table.4).**Yield: 249 mg (90%); white solid; R_f = 0.50 (EtOAc:Hexane, 2.0:8.0); m.p 126-129 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.01 (s, br), 8.16 (s, 1H), 7.82-7.79 (d, *J* = 12.0 Hz, 2H), 7.70-7.68 (m, 1H), 7.53-7.46 (m, 2H), 7.43-7.42 (m, 3H), 7.38-7.34 (m, 3H), 5.04 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 135.2, 135.0, 132.8, 129.6, 129.3, 129.1, 128.9, 128.2, 128.0, 127.1, 123.56, 78.4; IR (KBr): 3208, 2920, 1647, 1501, 1123, 908, 752, 699, 533, 505 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{18}H_{16}NO_2$ 278.1181, found 278.1185.

***N*-(benzyloxy)-3-(1H-indol-3-yl)propanamide (entry 3, Table.4).[25]** Yield: 261 mg (89%), white solid; R_f = 0.50 (EtOAc:Hexane, 2.0:8.0); m.p. 145-147 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57-7.55 (d, *J* = 8.0 Hz, 1H), 7.37-7.35 (d, *J* = 8.0 Hz, 1H), 7.27-7.34 (m, 3H), 7.18-7.16 (m, 3H), 7.09-7.05 (m, 1H), 6.98 (s, 1H), 4.70 (s, 2H), 3.10-3.06 (t, *J* = 8.0 Hz, 2H), 2.42-2.38 (t, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.02, 136.36, 135.06, 129.00, 128.28, 128.11, 128.11, 126.84, 122.01, 121.26, 118.50, 118.13, 113.28, 111.15, 76.91, 33.67, 20.95; IR (KBr):

3402, 2922, 1656, 1502, 1145, 1001, 743, 698, 616, 516 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{18}H_{19}N_2O_2$ 295.1447, found 295.1443.

(9H-fluoren-9-yl)methyl 2-(benzyloxyamino)-2-oxoethyl carbamate (entry 4, Table.4) Yield: 366 mg (91%); white solid; R_f = 0.40 (EtOAc:Hexane, 4.0:6.0); m.p 114-118 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.34 (br, 1H), 7.76-7.73 (d, *J* = 12.0 Hz, 2H), 7.41-7.38 (m, 2H), 7.36-7.27 (m, 4H), 7.15-7.11 (m, 5H), 5.58 (br, 1H), 4.85 (s, 2H), 4.26-4.24 (d, *J* = 8.0 Hz, 2H), 4.07-4.06 (d, *J* = 4.0 Hz, 2H), 3.70-3.68 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 156.9, 143.8, 141.4, 129.4, 128.9, 128.7, 127.9, 127.2, 125.2, 120.1, 78.5, 67.5, 47.2, 42.6; IR (KBr): 3334, 2912, 1702, 1674, 1540, 1272, 1167, 756, 698, 534 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{24}H_{23}N_2O_4$ 403.1658, found 403.1654.

(9*H*-fluoren-9-yl)methyl 1-(benzyloxyamino)-1-oxopropan-2-ylcarbamate (entry 5, Table.4).[26] Yield: 366 mg (88%); white solid; R_f = 0.50 (EtOAc:Hexane, 4.0:6.0); m.p 142-144 °C; $[\alpha]_D^{25}$ = - 13.4 ($CHCl_3$, c = 0.10); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.27 (br, 1H), 7.75-7.73 (d, *J* = 8.0 Hz, 2H), 7.54-7.53 (d, *J* = 4.0 Hz, 2H), 7.38-7.32 (m, 4H), 7.31-7.25 (m, 5H), 5.51 (br, 1H), 4.86 (s, 2H, 2H), 4.30 (d, *J* = 4.0 Hz, 2H), 4.14-4.12 (m, 2H), 1.25 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.9, 156.2, 143.7, 141.4, 135.1, 129.3, 128.9, 128.7, 127.9, 127.2, 125.2, 120.1, 78.3, 67.3, 48.2, 47.1, 18.0; IR (KBr): 3294, 2923, 1690, 1664, 1537, 1260, 755, 739, 521 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{25}H_{25}N_2O_4$ 417.1814, found 417.1811.

(9H-fluoren-9-yl)methyl 1-(benzyloxyamino)-4-methyl-1-oxopentan-2-ylcarbamate (entry 6, Table.4) Yield: 385 mg (84%); white solid; R_f = 0.50 (EtOAc:Hexane, 3.0:7.0); m.p 157-160 °C; $[\alpha]_D^{25}$ = - 12.4 ($CHCl_3$, c = 0.41); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.59 (br, 1H), 7.73-7.71 (d, *J* = 8.0 Hz, 2H), 7.57-7.49 (m, 4H), 7.35-7.25 (m, 7H), 5.59 (d, *J* = 8.0 Hz, 1H), 4.85 (s, 2H), 4.29-

4.27 (d, *J* = 8.0 Hz, 2H), 4.23-4.20 (t, *J* = 8.0 Hz, 1H), 4.14-4.12 (t, *J*= 8.0 Hz, 1H), 1.57-1.54 (m, 2H), 0.92-0.91 (d, *J* = 4.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 156.4, 143.7, 141.3, 135.1, 129.3, 128.7, 128.5, 127.4, 127.1, 125.1, 120.0, 78.2, 67.3, 50.9, 47.0, 41.3, 24.7, 22.6, 22.4; IR (KBr): 3311, 2957, 1688, 1666, 1535, 1248, 1040, 765, 532, 458 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{28}H_{31}N_2O_4$ 459.2284, found 459.2279.

(9H-fluoren-9-yl)methyl 1-(benzyloxyamino)-3-methyl-1-oxobutan-2-ylcarbamate (entry 7, Table 4) Yield: 364 mg (82%); white solid; R_f = 0.40 (EtOAc:Hexane, 3.0:7.0); m.p 205-208 °C; $[\alpha]_D^{25}$ = - 18.7 ($CHCl_3$, c = 0.50); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.54 (br, 1H), 7.73-7.71 (d, *J* = 8.0 Hz, 2H), 7.53-7.51 (m, 2H), 7.36-7.35 (m, 3H), 7.27-7.24 (m, 6H), 5.72-5.70 (d, *J* = 8.0 Hz, 1H), 4.84 (s, 2H), 4.30-4.28 (d, *J* = 8.0 Hz, 2H), 4.22-4.19 (d, *J* = 4.0 Hz, 1H), 2.04-2.01 (m, 1H), 0.91 (d, *J* = 4.0 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.0, 156.7, 143.8, 141.4, 135.1, 129.4, 128.9, 128.6, 127.3, 127.2, 125.3, 120.1, 78.5, 67.4, 58.3, 47.2, 31.1, 19.2, 18.5; IR (KBr): 3281, 2961, 1698, 1657, 1544, 1294, 1251, 748, 742, 541 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{27}H_{29}N_2O_4$ 445.2127, found 445.2131.

(9H-fluoren-9-yl)methyl 1-(benzyloxyamino)-4-(methylthio)-1-oxobutan-2-ylcarbamate (entry 8, Table 4) Yield: 385 mg (81%); white solid; R_f = 0.50 (EtOAc:Hexane, 3.0:7.0); m.p 171-174 °C; $[\alpha]_D^{25}$ = - 15.3 ($CHCl_3$, c = 0.37); ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.05 (br, 1H), 7.76-7.74 (d, *J* = 8.0 Hz, 2H), 7.54-7.51 (m, 2H), 7.37-7.35 (m, 3H), 7.28-7.25 (m, 6H), 5.52 (br, 1H), 4.89 (s, 2H), 4.30-4.28 (d, *J* = 8.0 Hz, 2H), 4.22-4.19 (m, 2H), 2.59-2.56 (q, *J* = 4.0 Hz, 2H), 2.09 (s, 3H), 2.04-2.01 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 156.4, 143.7, 141.4, 135.1, 129.4, 128.9, 128.6, 127.3, 127.2, 125.3, 120.1, 78.5, 67.4, 51.3, 47.2, 31.6, 30.0, 15.5; IR (KBr): 3281, 2961, 1698, 1657, 1544, 1294, 1251, 748, 742, 541 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{27}H_{29}N_2O_4S$ 477.1848, found 477.1852.

Phenyl 2-phenylacetate (entry 1, Table 6).[27] Yield: 184 mg (87%); yellowish oil; R_f = 0.51 (EtOAc:Hexane, 1.0:9.0); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.30 (m, 7H), 7.22-7.18 (m, 1H), 7.05-7.04 (m, 2H), 3.85 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 151.2, 134.0, 129.8, 129.7, 129.1, 127.7, 126.2, 121.8, 41.7; IR (KBr): 2924, 2853, 1759, 1593, 1398, 1261, 1088, 1016, 696; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{13}O_2$ 213.091, found 213.0911.

4-Methoxyphenyl 2-phenylacetate (entry 2, Table 6) Yield: 198 mg (82%); clear oil; R_f = 0.50 (EtOAc:Hexane, 1.0:9.0); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.35 (m, 5H), 6.97-6.95 (d, *J* = 8.0 Hz, 2H), 6.86-6.84 (d, *J* = 8.0 Hz, 2H), 3.83 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.9, 157.48, 144.6, 133.7, 129.5, 128.9, 127.5, 122.4, 114.6, 55.7, 41.5 ppm; IR (KBr): 2930, 2837, 1754, 1509, 1267, 1188, 1016, 544 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{15}H_{14}NaO_3$ 265.0835, found 265.0832.

4-Nitrophenyl 2-phenylacetate (entry 3, Table 6) Yield: 231 mg (90%); clear oil; R_f = 0.50 (EtOAc/Hexane, 1.0:9.0); ^{1}H NMR(400 MHz, $CDCl_3$): δ 8.26-8.23 (d, *J* = 12.0 Hz, 2H), 7.39-7.37 (m, 5H), 7.26-7.24 (d, *J* = 8.0 Hz, 2H), 3.90 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.3, 155.6, 145.5, 130.5, 129.5, 128.8, 127.9, 125.5, 122.5, 41.5; IR (KBr): 2924, 2851, 1764, 1593, 1524, 1347, 1216, 1114 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{14}H_{11}NNaO_4$ 280.0586, found 280.0583.

Pentafluorophenyl 2-phenylacetate (entry 4, Table 6) [28] Yield: 245 mg (81%); clear oil; R_f = 0.51 (EtOAc:Hexane, 1.0:9.0); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.38 (m, 2H), 7.36-7.32 (m, 3H), 3.96 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7, 132.3, 129.4, 129.2, 129.0, 128.8, 128.0, 127.7, 40.1; IR (KBr): 3055, 2929, 1776, 1740, 1456, 1220, 1094, 1003, 732, 696, 557 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{14}H_7F_5NaO_2$ 325.0258, found 325.0256.

Benzyl 2-phenylacetate (entry 5, Table 6).[29] Yield: 229 mg (92%), colorless oil; R_f = 0.60 (EtOAc:Hexane, 1.0:9.0); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.31 (m, 5H), 7.28-7.26 (m, 5H), 5.13 (s, 2H), 3.67 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 171.4, 135.9, 134.0, 129.3, 128.6, 128.6, 128.2, 128.1, 127.2, 66.6, 41.3; IR (KBr): 3032, 1737, 1497, 1455, 1259, 1146, 725, 491 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{15}H_{14}NaO_2$ 249.0886, found 249.0889.

Tert-butyl 2-phenylacetate (entry 6, Table 6).[30] Yield: 161 mg (84%); clear oil; R_f = 0.50 (EtOAc:Hexane, 1.0:9.0); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.22 (m, 5H), 3.51 (s, 2H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 134.7, 129.2, 128.5, 126.8, 80.7, 42.6, 28.0; IR (KBr): 3230, 2989, 1754, 1243, 752, 543 cm^{-1}; HRMS (ESI): m/z$[M+Na]^+$ calcd for $C_{12}H_{16}NaO_2$ 215.1048, found 215.1051.

Isopropyl 2-phenylacetate (entry 7, Table 6). Yield: 158 mg (89%); clear oil; R_f = 0.51 (EtOAc:Hexane, 1.0:9.0); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.29 (m, 3H), 7.28-7.26 (m, 2H), 5.03-4.97 (m, 1H), 3.57 (s, 2H), 1.22 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 134.4, 129.3, 128.6, 127.0, 68.2, 41.8, 21.8; IR (KBr): 2934, 2827, 1754, 1522, 1436, 1266, 1126, 563 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{11}H_{14}NaO_2$ 201.0891, found 201.0894.

Benzyl benzoate (entry 8, Table 6).[27] Yield: 180 mg (85%); colorless oil; R_f = 0.50 (EtOAc:Hexane, 2.0:8.0); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09-8.06 (d, J = 12Hz, 2H), 7.57-7.53 (t, 1H), 7.45-7.42 (m, 3H), 7.40-7.33 (m, 4H), 5.39 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5, 136.2, 133.1, 130.3, 129.8, 128.7, 128.5, 128.4, 128.3, 66.8; IR (KBr): 2853, 1749, 1543, 1352, 1273, 1043, 654, 544 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{14}H_{12}NaO_2$ 235.0735, found 235.0738.

Benzyl butyrate (entry 9, Table 6) [31] Yield: 162 mg (91%); oily; R_f = 0.50 (EtOAc:Hexane, 0.5:9.5); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.34 (m, 1H), 7.31-7.30 (m, 4H), 5.10 (s, 2H), 2.34-2.31 (t, *J* = 8.0 Hz, 2H), 1.69-1.64 (q, 2H), 0.95-0.92 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5, 136.3, 128.6, 128.2, 66.1, 36.2, 18.5, 13.7; IR (KBr): 2928, 1738, 1754, 1381, 1253, 1171, 697 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{11}H_{14}NaO_2$ 201.0891, found 201.0889.

Naphthalen-2-yl 4-nitrobenzoate (entry 10, Table 6) Yield: 263 mg (90%); white solid; R_f = 0.51 (EtOAc:Hexane, 1.0:9.0); m.p.167-170 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.07 (s, 1H), 8.65-8.54 (d, *J* = 8.0 Hz, 1H), 8.50-8.48 (d, *J* = 8.0 Hz, 1H), 7.92-7.84 (m, 3H), 7.75-7.70 (m, 2H), 7.52-7.49 (m, 2H) 7.37-7.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 151.0, 148.3, 135.1, 133.9, 131.8, 131.4, 129.9, 128.0, 127.9, 127.8, 127.0, 126.8, 126.2, 126.0, 123.9, 120.8, 118.7; IR (KBr): 2922, 2852, 1724, 1593, 1424, 1347, 1299, 1096 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{17}H_{11}NNaO_4$ 316.0586, found 316.0583.

(9H-fluoren-9-yl)methyl 4-bromobenzoate (entry 11, Table 6).[32] Yield: 336 mg (89%); white crystalline solid; R_f = 0.50 (EtOAc:Hexane, 1.0:9.0); m.p.98-102 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91-7.89 (d, *J* = 8.0 Hz, 2H), 7.78-7.76 (d, *J* = 8.0 Hz, 2H), 7.61-7.59 (m, 4H), 7.42-7.48 (t, *J* = 8.0 Hz, 2H), 7.32-7.28 (t, *J* = 8.0 Hz, 2H), 4.61-4.59 (d, *J* = 8.0 Hz, 2H), 4.37-4.35 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 165.9, 143.8, 141.5, 132.1, 131.3, 129.2, 128.4, 128.0, 127.3, 125.1, 120.3, 67.4, 47.1; IR (KBr): 3030, 2890, 1727, 1590, 1452, 1241, 1118, 1010, 751, 551 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{21}H_{15}BrNaO_2$ 401.0153, found 401.0157.

Butyl cinnamate (entry 12, Table 6) Yield: 186 mg (91%); clear oil; R_f = 0.50 (EtOAc:Hexane, 1.0:9.0); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86-7.64 (d, *J* = 12.0 Hz, 1H), 7.51-7.49 (m, 2H), 7.37-7.35 (m, 3H), 6.44-6.40 (d, *J* = 12.0 Hz, 1H), 4.20-4.17 (t, *J* = 8.0 Hz, 2H), 1.70-1.63 (m, 2H), 1.44-1.39 (m, 2H), 0.96-0.92 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 167.2, 144.6, 134.6, 130.3, 129.0, 128.1, 118.47, 64.5, 30.9, 19.3, 13.8; IR (KBr): 2960, 2873, 1714, 1638, 1450, 1311, 1172, 980, 767, 684, 486 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{13}H_{16}NaO_2$ 227.1048, found 227.1045.

Butyl 2-naphthoate (entry 13, Table 6) Yield: 198 mg (87%); oily; R_f = 0.51 (EtOAc:Hexane, 1.0:8.0); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (s, 1H), 8.08-8.06 (d, *J* = 8.0 Hz, 2H), 8.93-8.91 (d, *J* = 8.0 Hz, 2H), 7.84-7.81 (m, 2H), 4.39-4.36 (t, *J* = 4.0 Hz, 2H), 1.82-1.75 (q, 2H), 1.53-1.47 (q, 2H), 1.01-0.98 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 135.5, 132.5, 130.9, 129.3, 128.2, 127.8, 126.6, 125.3, 65.0, 30.9, 19.4, 13.8; IR (KBr): 2959, 2873, 1716, 1632, 1466, 1286, 1196, 955, 779, 474 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{15}H_{16}NaO_2$ 251.1048, found 251.1051.

4-Methoxyphenyl palmitate (entry 1, Table 7).[33] Yield: 311 mg (86%); white solid powder; R_f = 0.50 (EtOAc:Hexane, 0.5:9.5); m.p.52-52 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.98-6.95 (d, *J* = 12.0 Hz, 2H), 6.87-6.85 (d, *J* = 8.0 Hz, 2H), 3.77 (s, 3H), 2.52-2.48 (t, *J* = 8.0 Hz, 2H), 1.72-1.70 (m, 2H), 1.26-1.21 (m, 24H), 0.87-0.84 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.8, 157.3, 144.5, 122.4, 114.5, 55.6, 34.5, 32.1, 29.8, 29.7, 29.6, 29.5, 29.4, 29.2, 25.1, 22.9 14.3; IR (KBr): 2916, 2849, 1746, 1552, 1509, 1463, 1213, 1033, 844 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{23}H_{38}NaO_3$ 385.2719, found 385.2716.

4-Nitrobenzyl tetradecanoate (entry 2, Table 7) Yield: 308 mg (92%); oily R_f = 0.51 (EtOAc:Hexane, 0.5:9.5); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20-8.18 (d, *J* = 8.0 Hz, 2H), 7.49-7.47 (d, *J* = 8.0 Hz, 2H), 5.17 (s, 2H), 2.38 (t, *J* = 8.0 Hz, 2H), 1.64-1.60 (m, 2H), 1.26-1.21 (m, 16H), 0.85-0.82 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 147.7, 143.6, 128.4, 123.8, 64.6, 34.3, 32.0, 29.7, 29.5, 29.4, 29.3, 29.2, 25.0, 22.8, 14.2; IR (KBr): 2926, 2853, 1743, 1607, 1524, 1347, 1015, 859, 738 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{19}H_{30}NO_4$ 336.2175 found 336.2171.

Naphthalen-2-yl octanoate (entry 3, Table 7) Yield: 246 mg (91%); white solid; R_f = 0.50 (EtOAc:Hexane, 1.0:9.0); m.p.42-43 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83-7.81 (m, 2H), 7.78-7.76 (d, *J* = 8.0 Hz, 1H), 7.53 (s, 1H), 7.46-7.43 (m, 2H), 7.22-7.19 (m, 1H), 2.61-2.57 (t, *J* = 8.0 Hz, 2H), 1.81-1.74 (m, 2H), 1.43-1.31 (m, 10H), 0.91-0.88 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.6, 148.6, 134.0, 131.6, 129.5, 127.9, 127.8, 126.7, 125.8, 121.4, 118.7, 34.6, 31.8, 29.3, 29.1, 25.2, 22.8, 14.2; IR (KBr): 2928, 2852, 1751, 1510, 1211, 1162, 812, 634, 483 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{18}H_{22}NaO_2$ 293.1517, found 293.1521.

4-nitrophenyl 2-hydroxybenzoate (entry 4, Table 7).[34] Yield: 224 mg (82%); colourless solid; R_f = 0.50 (EtOAc:Hexane, 1.0:9.0); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.53 (s, 1H), 8.25-8.23 (d, *J* = 8.0 Hz, 2H) 7.88-7.86 (d, *J* = 8.0 Hz, 1H), 7.60-7.58 (d, *J* = 8.0 Hz, 2H), 7.49-7.45 (t, *J* = 8.0 Hz, 1H), 6.99-6.97 (d, *J* = 8.0 Hz, 1H), 6.91-6.87 (t *J* = 8.0 Hz, 1H), 5.22 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 162.0, 148.0, 142.6, 136.4, 129.9, 128.6, 124.0, 119.5, 117.9, 112.0, 65.5; IR (KBr): 3427, 2967, 2851, 1725, 1524, 1339, 1253, 754, 532 cm^{-1}; HRMS (ESI): m/z $[M-H]^-$ calcd for $C_{14}H_{10}NO_5$ 272.0559, found 272.0557.

Hexadecyl 3-(1H-indol-3-yl)propanoate (entry 5, Table 7).[35] Yield: 355 mg (86%); yellowish crystalline solid; R_f = 0.50 (EtOAc:Hexane, 2.0:8.0); m.p. 60-62 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (br, 1H), 7.60-7.58 (d, *J* = 8.0 Hz, 1H), 7.34-7.32 (d, *J* = 8.0 Hz, 1H), 7.20-7.16 (t, *J* = 8.0 Hz, 1H), 7.13-7.09 (t, *J* = 8.0 Hz, H), 6.98 (s, 1H), 4.07-4.04 (t, 2H), 3.11-3.07 (t, *J* = 8.0 Hz, 2H), 2.72-2.68 (t, *J* = 8.0 Hz, 2H), 1.59-1.57 (m, 2H), 1.26-1.23 (m, 26H), 0.90-0.85 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 136.5, 127.3, 122.1, 121.6, 119.4, 118.8, 115.0, 111.3, 64.8, 35.2, 32.1, 29.8, 29.7, 29.5, 29.4, 28.8, 26.1, 25.8, 22.8, 20.8, 14.3; IR (KBr): 3342, 2916, 2848, 1718, 1471, 1279, 1186, 734, 552 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{27}H_{44}NO_2$ 414.3372, found 414.3368.

Ethyl 3-(indolin-3-yl)propanoate (entry 6, Table 7).[36] Yield: 195 mg (90%); yellowish solid; R_f = 0.50 (EtOAc:Hexane, 2.0:8.0); m.p. 39-41 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (br, 1H), 7.60-7.58 (d, *J* = 8.0 Hz, 1H), 7.30-7.28 (d, *J* = 8.0 Hz, 1H), 7.19-7.15 (t, *J* = 8.0 Hz, 1H), 7.12-7.08 (t, *J* = 8.0 Hz, H), 6.97 (s, 1H), 4.15-4.07 (q, 2H), 3.11-3.07 (t, *J* = 8Hz, 2H), 2.72-2.68 (t, *J* = 8.0 Hz, 2H), 1.23-1.19 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 136.4, 127.2, 122.0, 121.7, 119.2, 118.7, 114.6, 111.3, 60.5, 35.1, 20.7, 14.2; IR (KBr): 3345, 2926, 2841, 1728, 1472, 1272, 1183, 724, 562 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{16}NO_2$ 218.1181, found 218.1177.

(1S, 2R, 5S)-2-isopropyl-5-methylcyclohexyl nicotinate (entry 7, Table 7).[35] Yield: 235 mg (90%); oily R_f = 0.50 (EtOAc:Hexane, 1.0:9.0); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.18 (s, 1H, 1×ArH), 8.73-8.71 (d, *J* = 8.0 Hz, 1H), 8.26-8.24 (d, *J* = 8.0 Hz, 1H), 7.36-7.33 (t, *J* = 8.0 Hz, 1H), 4.96-4.89 (s, 1H), 2.10-2.05 (m, 1H), 1.91-1.87 (m, 1H), 1.72-1.67 (m, 2H), 1.56-1.49 (m, 2H), 1.12-1.06 (m, 2H), 0.93-0.88 (m, 6H), 0.76-074 (d, *J* = 8.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 164.9, 153.3, 151.0, 137.2, 126.8, 123.4, 75.7, 47.3, 41.0, 34.4, 31.6, 26.7, 23.8, 22.1,

20.9, 16.6 ppm; IR (KBr): 2957, 2870, 1719, 1591, 1289, 1121, 741 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{16}H_{24}NO_2$ 262.1807, found 262.1810.

2-Octyldodecyl benzoate (entry 8, Table 7). Yield: 358 mg (89%); oily R_f = 0.50 (EtOAc:Hexane, 0.5:9.5); ^1H NMR (400 MHz, $CDCl_3$): δ 8.03-8.01 (d, *J* = 8.0 Hz, 2H), 7.55-7.53 (m, 1H), 7.42-7.40 (m, 2H), 4.21-4.17 (m, 1H), 1.76-1.74 (m, 1H), 1.29-1.23 (m, 32H), 0.86-0.83 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 166.8, 132.8, 130.7, 129.8, 129.4, 128.4, 128.1, 67.8, 37.6, 37.3, 32.1, 31.8, 31.6, 31.3, 31.1, 30.1, 29.8, 29.7, 29.5, 27.0, 26.8, 26.6, 22.8, 22.6, 14.3, 14.0; IR (KBr): 2925, 2854, 1723, 1466, 1272, 1133, 710 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{27}H_{46}NaO_2$ 425.3319, found 425.3314.

Methyl 2-(((9H-fluoren-9-yl)methoxy)carbonyl) propanoate (entry 9, Table 7).[37] Yield: 283 mg (87%); white solid; R_f = 0.51 (EtOAc:Hexane, 2.0:8.0); m.p.106-108 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.75-7.73 (d, *J* = 8.0 Hz, 2H), 7.59-7.57 (m, 2H), 7.40-7.36 (t, *J* = 8.0 Hz, 2H), 7.31-7.28 (t, *J* = 8.0 Hz, 2H), 5.34 (br, 1H), 4.39-4.36 (m, 3H), 4.22-4.19 (t, *J* = 8.0 Hz, 1H), 3.74 (s, 3H), 1.42-1.41 (d, *J* = 4.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 155.8, 144.0, 141.4, 127.8, 127.2, 125.2, 120.1, 67.1, 52.6, 49.7, 47.2, 18.7; IR (KBr): 3330, 2924, 1747, 1690, 1536, 1267, 1084, 740 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{19}H_{19}NO_4$ 326.1392, found 326.1388.

(DL) Benzyl 2-(tert-butoxycarbonyl)-3-phenylpropanoate (entry 10, Table 7).[38] Yield: 319 mg (90%); yellowish solid; R_f = 0.50 (EtOAc:Hexane, 2.0:8.0); ^1H NMR (600 MHz, $CDCl_3$): δ 7.34-7.31 (m, 3H), 7.28-7.26 (d, *J* = 8.0 Hz, 2H), 7.24-7.21 (m, 3H), 7.05-7.01 (m, 2H), 5.16 (s, 2H), 5.05 (br, 1H), 4.54-4.59 (t, *J* = 4.0 Hz, 1H), 3.10-3.07 (d, *J* = 8.0 Hz, 2H), 1.42 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 171.9, 155.2, 136.1, 135.4, 129.5, 128.7, 127.1, 80.0, 67.3, 54.6,

38.4, 28.4; IR (KBr): 3456, 2923, 1732, 1688, 1521, 1223, 1087, 740 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{21}H_{26}NO_4$ 356.1862, found 356.1857.

(L) Benzyl 2-(tert-butoxycarbonyl)-3-phenylpropanoate (entry 11, Table 7).[38] Yield: 316 mg (89%); yellowish solid; R_f = 0.51 (EtOAc:Hexane, 2.0:8.0); ^1H NMR (600 MHz, $CDCl_3$): δ 7.36-7.33 (m, 3H), 7.29-7.27 (d, *J* = 8.0 Hz, 2H), 7.23-7.21 (m, 3H), 7.04-7.02 (m, 2H), 5.14 (s, 2H), 5.01 (br, 1H), 4.63-4.61 (t, *J* = 4.0 Hz, 1H), 3.11-3.09 (d, *J* = 8.0 Hz, 2H), 1.41 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 171.8, 155.19, 135.9, 135.5, 129.5, 128.7, 127.1, 80.1, 67.29, 54.6, 38.4, 28.4; IR (KBr): 3456, 2923, 1732, 1688, 1521, 1223, 1087, 740 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{21}H_{26}NO_4$ 356.1862, found 356.1857.

ASSOCIATED CONTENT

Supporting Information

NMR (^1H and ^{13}C) spectra of 2NBsOXY, the intermediate, and the products in table 3 (entry 1-18); table 4 (entry 1-8); table 6 (entry 1-13); table 7 (entry 1-11); HPLC profiles and ESI spectra of peptides and crystal data of the intermediate. This material is available free of charge via the internet at http://pubs.acs.org

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