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The phosphate–carboxylate mixed-anhydride method: a mild, efficient process for ester and amide bond construction

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ABSTRACT

A highly efficient carboxylate–phosphate anhydride pathway is described for the direct, economical synthesis of esters and amides from carboxylic acids and alcohols or amines. The reaction proceeds with retention of configuration with both chiral secondary alcohols and α-amino acid derivatives allowing access to useful chiral auxiliaries, ligands, and organocatalysts. Ester and amide products can be isolated directly in high yield due to the water soluble nature of the side products.

1. Introduction

Acylation reactions of carboxylic acids with alcohols or amines to form ester or amide derivatives represents one of the most important and commonly employed transformations in organic synthesis.[1,2] Large scale esterification processes are used for the synthesis of a variety of end-products including, monomers, polymers, plasticizers, and fragrance chemicals, many on an industrial scale. Classic methods, such as Fischer esterification or the use of activating agents, such as thionyl chloride proceed under highly acidic conditions, while alkylation of carboxylate anions to give esters can be performed under strongly basic conditions in dipolar solvents[2c] or ionic liquids.[2d] While these methods are appropriate for many simple carboxylate acylation reactions, the extreme acidity or basicity required limits the scope and these reactions are rarely employed in the synthesis of chiral and/or sensitive derivatives. Acylation processes leading to high-value fine chemicals, such as peptide derivatives, organocatalysts, pharmaceuticals, pheromones, and fragrances require milder and more stringent coupling protocols to achieve the desired chemo- and stereoselectivity. Situations that proceed with reliable stereocontrol involving either inversion or retention of stereochemistry, such as in the Mitsunobu[3] esterification process, are especially sought. Mild methods that achieve carboxylic acid activation resulting in retention of stereochemistry at the α-position of chiral carboxylic acids and retention coupled to the use of chiral amines or alcohols are also of great importance in amide and peptide bond forming reactions and in the synthesis of natural products (lactones, depsipeptides, lactams etc.). Several reagents are commonly employed to achieve these purposes, as shown in Scheme 1, notable examples being the use of carboxylate activating agents, such as DCC or EDC, and Mitsunobu-type reagents based on Ph_3P/DEAD or Bu_3P/DIAD. While effective in driving the acylation process, these reagents unfortunately produce stoichiometric quantities of unwanted hydrated side products, such as DCC–urea and $Ph_3P{=}O$/$DEADH_2$ (Scheme 1) that complicate work-up and purification processes and render the overall processes with low atom-economy.

The mixed-anhydride method for carboxylic group activation is also well known, typically involving activation with a reactive acid chloride, such as the Yamaguchi reagent.[4] Mixed carboxylate–phosphate anhydrides have also been employed in acylation reactions.[5–7] Surprisingly, this process does not appear to be well known and is rarely applied. The reactive reagent phenyl dichlorophosphate has been exploited in both ester[5] and thioester[6] bond forming processes. The use of less reactive, more selective monochloro-disubstituted phosphates has also been reported, mainly in the synthesis of macrocyclic lactones, through activation of the corresponding *seco*-acid derivatives via the mixed

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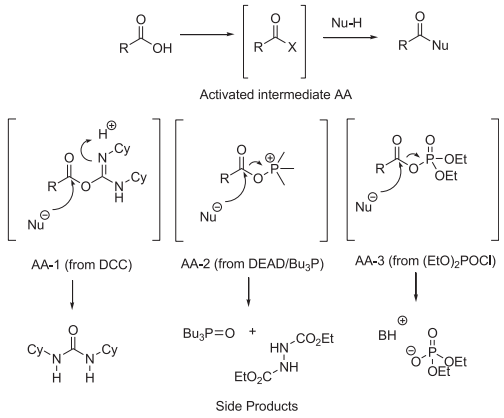
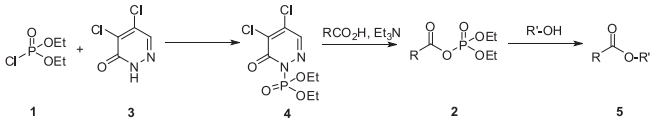


Scheme 1. Methods for mild carboxylate activation and the stoichiometric formation of side products (Cy=cyclohexyl-, DCC=dicyclohexylcarbodiimide, DEAD-=diethylazidodi-carboxylate).

phosphate–carboxylate anhydride in the presence of base.[7] This method has continued to escape attention[7a] despite the ready availability of the required reagents.

We have been interested in the development of novel carboxylic acid activating agents and conditions for controlled esterification over a number of years[2d,8] and were attracted to a publication[9] describing an activated derivative of the mild phosphorylating agent diethyl chlorophosphate **1**. This method, outlined in Scheme 2, was reported to require reagent **3** and the process based on the formation of an activated 6-oxo-6*H*-pyridazin-1-yl phosphorylating agent **4** from the reaction of **1** with **3**. This reagent reacts with the carboxylic acid to form the mixed anhydride **2**, subsequently proceeding to give the ester **5** upon addition of the desired alcohol derivative.



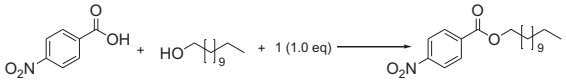
Scheme 2. Formation of phosphate–carboxylate mixed anhydride **2** via the use of reagent **3** and diethyl chlorophosphate.[9]

The requirement of the activated intermediate **4** in this chemistry drew our attention for two reasons, first of all the requirement of reagent **3** was not convincing mechanistically and secondly the situation appeared reminiscent of some of the lactonization difficulties encountered with the use of the Yamaguchi macrolactonization method. In problematic cases, Yonemitsu and coworkers[10] reported that the use of excess DMAP and mild heating, so as not to promote symmetrical carboxylic anhydride formation, was highly effective in promoting the mixed-anhydride pathway. In an initial communication from our group,[8e] we demonstrated that reagent **3** is not required, and that a pyridine base alone allowed formation of the mixed- anhydride **2** directly from **1** and the carboxylic acid. Herein we report our complete findings on the successful activation of this pathway using only pyridine. The method allows for the straightforward and direct synthesis of a range of esters and amides, with retention of stereochemistry at any stereogenic centers present when employing chiral alcohols or amines. Product purification can be achieved through simple aqueous/organic solvent partition. The relatively high atom-economy, ease of product isolation and low cost of reagents[11] make the phosphate–carboxylate method an attractive alternative in controlled ester and amide bond-forming processes.

2. Results and discussion

To begin, we studied the model reaction of 4-nitrobenzoic acid with the lipophilic alcohol n-dodecanol employing 1 equiv of diethyl chlorophosphate **1**. While no reaction occurred in dichloromethane at rt in the presence of triethylamine, a significant turnover was seen with the use of pyridine as a base at rt (Table 1, entry 2), and more so upon warming (Table 1, entry 3). Switching to neat pyridine as solvent allowed for complete conversion and isolation of the ester in very high yield (entry 4). Thus neither the more nucleophilic DMAP[10] nor reagent **3**[9] are required to effect efficient esterification using the monochloro phosphate **1**.

Table 1
Direct esterification of acids and alcohols with **1** in pyridine

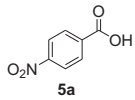
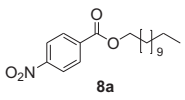
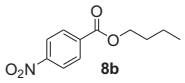
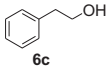
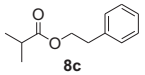
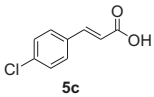
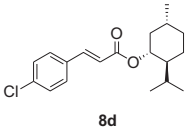
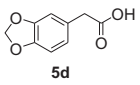
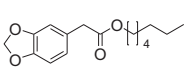
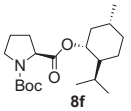
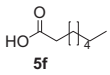
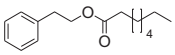
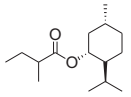
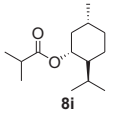
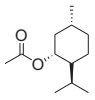
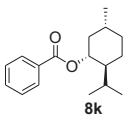
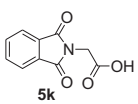
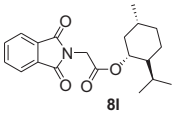
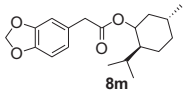


Entry	Base (equiv)	Reaction conditions	Isolated yield of **8a** (%)
1	Et_3N (2.5 equiv)	CH_2Cl_2, 20 °C, 12 h	0
2	Py (2.5 equiv)	CH_2Cl_2, 20 °C, 6 h	48
3	Py (2.5 equiv)	CH_2Cl_2, 40 °C, 6 h	55
4	Py (2.5 equiv)	70 °C, 6 h	91

From this initial process we developed a generally effective procedure for the esterification process and work-up protocol. In the general reaction, use of a 1:1 ratio of carboxylic acid and alcohol and 1.05 equiv of diethyl chlorophosphate **1** reacted in neat pyridine at 70 °C successfully and all reactions were complete within 3 h. The overall scope of this acylation method is presented in Table 2. The table reports isolated yields for the chromatographically purified esters. Under these conditions, a range of aromatic, α,β-unsaturated and aliphatic carboxylic acids, including α-hindered acids, could readily be condensed with alcohols (Table 2). For example, L-menthol readily reacted with the phosphate-activated cinnamic acid derivative giving the methyl cinnamate ester in good yield and with complete retention of stereochemistry (Table 2, entry 4). In addition, *N*-protected α-amino acids (Table 2, entry 6) could also be coupled with alcohols including L-menthol, yielding a single diastereomeric product. All of the results confirmed that the reaction proceeds with retention of stereochemistry on both the part of the chiral secondary alcohol and α-amino carboxylic acid stereogenic centers. The successful participation of 2-phenylethanol **6c** (entries 3 and 7, Table 2) in the reaction provided 2-phenylethylesters in good yield without styrene formation, again indicating that no activation of the alcohol occurs. The reaction was successful with primary and secondary alcohols, failing only in the case of tertiary butanol. The esterification of the protected α-amino acid **5k** and phenylacetate **5d** with L-menthol (entries 12 and 13) allowed access to the useful chiral auxiliary functionalized derivatives **8l** and **8m**. A further advantage in using the diethyl chlorophosphate **1** process is that the reagent can be employed directly in the presence of the alcohol in pyridine. Most likely, the more nucleophilic carboxylate anion attacks the activated derivative of **1** to form the mixed anhydride, in preference to the alcohol. No diethyl phosphate esters have been observed from the direct reaction of the alcohols with **1**.

The reaction of the same diethyl phosphate-activated carboxylic acid anhydrides with amines could also be carried out effectively, however the process required a small change to the procedure. The overall reaction was not successful when done in the initial presence of the amine as diethylphosphoramide side products were obtained, no doubt due to the higher nucleophilicity of the amine. This issue was easily resolved through sequential addition of the amine to the activated acid. This general protocol completely

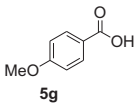
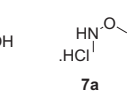
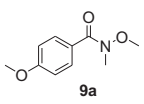
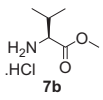
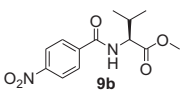
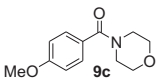
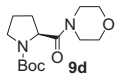
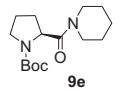
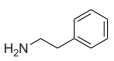
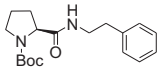
Table 2
Synthesis of ester derivatives using the phosphate–carboxylate mixed-anhydride method

Entry	R-CO_2H	R-OH **6**	Product **8**	Yield[a] (%) **8**
1	 **5a**	 **6a**	 **8a**	91
2	**5a**	 **6b**	 **8b**	88
3	 **5b**	 **6c**	 **8c**	80
4	 **5c**	 **6d**	 **8d**	86
5	 **5d**	 **6e**	 **8e**	79
6	 **5e**	**6d**	 **8f**	88
7	 **5f**	**6c**	 **8g**	82
8	 **5h**	**6d**	 **8h**	88
9	**5b**	**6d**	 **8i**	72
10	 **5i**	**6d**	 **8j**	67
11	 **5j**	**6d**	 **8k**	81
12	 **5k**	**6d**	 **8l**	77
13	**5d**	**6d**	 **8m**	75

[a] Isolated yields reported after silica-gel chromatography.

suppressed phosphoramide formation and resulted in high yields of the desired condensed amide products. This protocol proved to be general for all primary and secondary amines investigated and overall results are summarized in Table 3. The process allows rapid access to synthetically useful Weinreb[11a,b] amide derivatives as well as the amide adducts from both chiral α-amino ester derivatives as the amine component and with *N*-protected acids as the carboxylic acid component. In view of the current interest of prolinamide and derived products in asymmetric organocatalysis,[11c] we focussed on formation of amide derivatives from *N*-Boc-protected-L-proline **5e**. As shown in Table 3, a wide range of functionalized prolinamide derivatives are readily available using this method.

Table 3
Synthesis of amide derivatives using the phosphate–carboxylate mixed-anhydride method

Entry	R-CO_2H	R′-NH_2 **7**	Product **9**	Yield[a] (%) **9**
1	 **5g**	 **7a**	 **9a**	79
2	**5a**	 **7b**	 **9b**	80
3	**5g**	 **7c**	 **9c**	77
4	**5e**	**7c**	 **9d**	76
5	**5e**	 **7d**	 **9e**	79
6	**5e**	 **7e**	 **9f**	56
7	**5e**	**7f**	**9g**	79
8	**5e**	**7g**	**9h**	75
9	**5e**	**7h**	**9i**	79
10	**5e**	**7i**	**9j**	62

[a] Isolated yields reported after silica-gel chromatography.

While several reports on the preparation of *N*-Boc-protected prolinamide derivatives appear in the literature,[26,27] a considerable lack of NMR data appears in support of the characterization of these compounds. Not surprisingly, all of the *N*-Boc prolinamides **9d**–**j** (Table 3, entries 4–10) were observed by NMR to exist as a mixture of two rotamers in ratios varying from 50:50 to 70:30. This fact

complicates the full NMR spectral assignment of these derivatives particularly at low field (200–300 mHz). Nonetheless, we were able to fully resolve and characterize both amide rotamers in each instance (600 mHz) and report the ^{1}H and ^{13}C NMR data separately for each in the experimental section.

In terms of process-chemistry, a major advantage provided by the use of this phosphate–carboxylate mixed-anhydride method is that the ester and amide products can be isolated in all cases investigated so far by simple solvent removal and partition between ethyl acetate and aqueous sodium bicarbonate solution. The crude ester and amide products appear uncontaminated and can be used directly in subsequent reactions. In order to quantify yields, the data reported in Tables 2and 3 are of chromatographically pure ester and amide products and are considered to be minimum yields. In order to illustrate further from this process-chemistry view, Fig. 1 depicts the 'crude' and 'pure' ^{1}H NMR spectra obtained of the amide **9d** from the reaction of *N*-Boc-L-proline and morpholine via the phosphate–carboxylate process (Table 3, entry 4). Upon completion of the reaction, solvent removal and partition between ethyl acetate and aqueous bicarbonate (see experimental), the crude ^{1}H NMR obtained is recorded as shown (Fig. 1, top). Amide **9d** is observed as a 55:45 mixture of two rotamers as described, and very little else. Purification of 'crude' **9d** over silica-gel leads to isolation of the pure material in 76% yield the ^{1}H NMR of which is reproduced (Fig. 1, bottom) showing removal of only minor baseline contaminants. This process contrasts sharply to other coupling reagents commonly used to effect this transformation, such as DCC or Bu_3P/DIAD, which absolutely require chromatographic purification

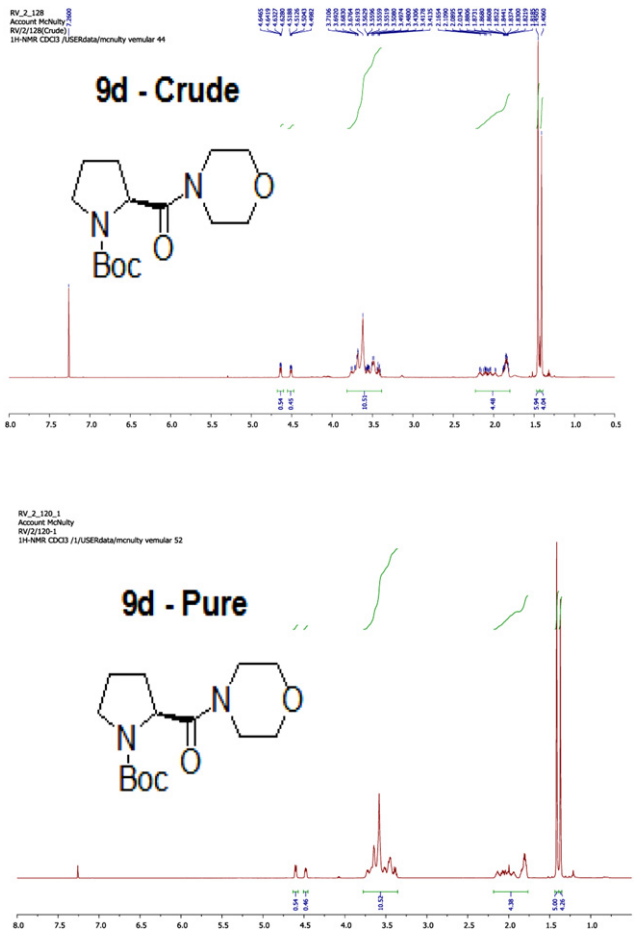
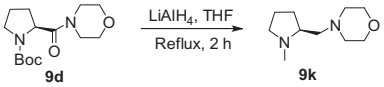


Fig. 1. Comparison of ^{1}H NMR spectrum (600 mHz) of *N*-Boc-morpholinyl-L-prolinamide **9d** obtained after aqueous/organic solvent partition (top) and subsequent purification over silica-gel chromatography (bottom).

to remove the hydrated side products shown at the bottom of Scheme 1.

Finally, in order to extend this method toward the synthesis of chiral tertiary amines, and, as further evidence that the NMR data reported for the prolinamide derivatives represents the amide conformers in each case, we investigated the reduction of the *N*-Boc-proline-morpholinamide derivative **9d**. As depicted in Scheme 3, reduction in THF using lithium aluminum hydride proceeded slowly to yield the single tertiary diamine **9k** as the sole product. In addition to confirming that the NMR complications are simply due to the existence of the rotamers, this overall process can now be extended to allow ready access to chiral tertiary amines. Such tertiary amines are of much interest in catalysis as ligands and directly as catalysts in Lewis-base mediated asymmetric organocatalysis, for example, in Baylis–Hilman and related reactions.[11d,e]



Scheme 3. Synthesis of chiral tertiary diamine.

3. Conclusion

In conclusion, we describe a general acylation process utilizing diethyl chlorophosphate in pyridine to mediate formation of a phosphate–carboxylate mixed-anhydride intermediate. This straightforward procedure contrasts with earlier phosphate–carboxylate protocols that required the use of adjuvants, such as **3**[9] (Scheme 1) and/or DMAP.[10] The process is applicable to the synthesis of a wide range of general ester and amide derivatives and allows rapid entry to useful chiral auxiliaries, ligands and amines suitable for organocatalysts. The reaction takes place selectively in the presence of an alcohol and sequentially in the presence of amines allowing access to useful ester, amide and peptide analogues. Purification is technically simple since there are no hydrated organic side products (such as $DEADH_2$, Ph_3PO, DCC–urea etc.) to contend with, all side products are either volatile or water soluble allowing for the straightforward isolation of high purity products. Simply removing solvents and work up from aqueous sodium bicarbonate/ethyl acetate yields the ester or amide product in relatively high purity (>95% in all cases so far investigated) without chromatographic purification. Diethyl chlorophosphate is readily available in quantity at approximately one-third the cost of the standard Yamaguchi reagent. In contrast to coupling reagents, such as DCC or DIAD, the reagent is stable indefinitely stored on the bench. The phosphate–carboxylate process is thus highly attractive in view of its simplicity as well as both economical and process-chemistry considerations. The use of phosphate–carboxylate mixed anhydrides is almost totally overlooked in acylation chemistry. We hope that the full description of this process and demonstration of its applicability and potential so far will result in adoption and consideration of the method by the wider synthetic community. Work in our laboratories continues with the exploration of the reactivity of the lesser reactive chlorophosphates with a view to expanding their chemical utility and in use of proline-derived secondary and tertiary amines described in organocatalytic reactions.

4. Experimental

4.1. General information

Reactions were carried out under an argon atmosphere in oven-dried glassware. Melting points (uncorrected) were measured on a Gallenkamp melting point apparatus. Diethyl chlorophosphate

was obtained from Cytec and Aldrich. All other fine chemicals were obtained from Aldrich and used without further purification. Pyridine, triethylamine and dichloromethane were distilled freshly over CaH_2. Silica-gel Merck (70–230 mesh) was used for column chromatography and silica-gel SIL G/UV254 for TLC (Macherey–Nagel). ^1H and ^{13}C NMR spectra were recorded on a Bruker AV 200 or AV 600 spectrometer using TMS as internal standard. Chemical shifts are reported in units of δ (parts per million) and coupling constants (J) are expressed in hertz. CIMS were run on a Micromass Quattro Ultima spectrometer fitted with a direct injection probe (DIP) with ionization energy set at 70 eV and HRMS (CI) were performed with a Micromass Q-Tof Ultima spectrometer. Optical rotations were determined on a Perkin–Elmer 241 polarimeter installed with a λ_{589} sodium lamp.

4.2. General procedures

4.2.1. General procedure for ester syntheses Table 2. (a) Typical procedure for the synthesis of L-menthol-4-chloro cinnamate, **8d**: to a mixture of 4-chlorocinnamic acid (0.365 g, 2.00 mmol) and L-menthol (0.312 g, 2.00 mmol) in pyridine (3.0 mL) was added diethyl chlorophosphate (0.320 mL, 2.10 mmol) slowly at rt in an atmosphere of argon, and the reaction mixture was stirred at rt for about 30 min. The heterogenous mixture was heated at 70 °C under argon atmosphere for 3 h, during which the reaction mixture became homogeneous. Pyridine was removed in vacuo, and the residue partitioned between ethyl acetate (15.0 mL) and saturated sodium bicarbonate (5.0 mL). After stirring well (10 min), the organic layer was separated, dried over anhyd Na_2SO_4 and the solvent evaporated in vacuo to yield the crude product. In all cases, crude products were >95% pure by ^1H NMR. Purification of **8d** over silica-gel (5% ethyl acetate in hexane) afforded 0.552 g, 86% yield of pure product **8d**.[12a]

4.2.2. General procedure for amide syntheses Table 3. (b) Typical procedure for the synthesis of L-*N*-(4-nitro-benzoyl)-Val-OMe, **9b**: to a mixture of 4-nitrobenzoic acid (0.334 g, 2.00 mmol) in pyridine (3.0 mL) was added slowly diethyl chlorophosphate (0.32 mL, 2.10 mmol) at rt in an atmosphere of argon, and the reaction mixture was stirred at rt for about 45 min. To this was then added L-valine methylester hydrochloride (0.335 g, 2.00 mmol) in one lot, and the reaction mixture was heated to 70 °C under argon atmosphere for 5 h. After completion of the reaction, pyridine was removed in vacuo and the residue partitioned between ethyl acetate (15.0 mL) and saturated sodium bicarbonate solution (5.0 mL) and stirred well for about 10 min. The organic layer was separated, dried over anhyd Na_2SO_4, and the solvent was evaporated in vacuo yielding the crude product. Purification of **9b** over silica-gel (5% ethyl acetate in hexane) afforded 0.448 g, 80% yield of pure product **9b**.[12b]

4.3. Characterization data for all ester and amide derivatives reported in Tables 2and 3

*4.3.1. Dodecyl 4-nitrobenzoate (**8a**).*[13] White solid (mp: 41–42 °C). ^1H NMR ($CDCl_3$): δ 0.84 (t, J=7.2 Hz, 3H), 1.26 (br s, 20H), 1.75–1.86 (m, 2H), 4.33 (t, J=7.2 Hz, 3H), 8.19–8.31 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 14.3, 22.9, 26.1, 28.8, 29.4, 29.5 (several overlapped peaks), 29.7, 29.8, 32.1, 66.3, 123.7, 130.8, 136.1, 164.9.

*4.3.2. Butyl 4-nitrobenzoate (**8b**).*[8a,14a] White solid (mp: 37–38 °C). ^1H NMR ($CDCl_3$): δ 0.96 (t, J=7.2 Hz, 3H), 1.43–1.51 (m, 2H), 1.72–1.86 (m, 2H), 4.35 (t, J=7.2 Hz, 3H), 8.18–8.32 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 13.4, 18.9, 29.4, 30.3, 65.5, 123.3, 130.4, 135.6, 150.2, 164.5.

*4.3.3. Phenethyl isobutyrate (**8c**).*[15] Colorless oil; ^1H NMR ($CDCl_3$): δ 1.12 (d, J=7.0 Hz, 6H), 2.41–2.60 (m, 1H), 2.91–3.04 (m, 2H), 4.22–4.32 (m, 2H), 7.21–7.30 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 18.9, 33.9, 36.6, 36.8, 64.7, 126.5, 126.6, 128.4, 128.5, 128.9, 129.0, 137.9, 177.1.

*4.3.4. (E)-((1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl) 3-(4-chlorophenyl)acrylate (**8d**).*[12a] Colorless oil; $[\alpha]_D^{25}$ −55.9 (*c* 0.47, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.75–1.30 (m, 11H), 1.40–2.09 (m, 6H), 4.76 (dt, 1H), 6.36 (dd, J=16 Hz, 1H), 7.34–7.49 (m, 4H), 7.58 (dd, J=16 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 16.3, 20.7, 22.0, 23.4, 26.3, 31.4, 34.2, 40.9, 47.2, 74.4, 119.3, 129.1, 129.2, 133.0, 142.9, 166.3.

*4.3.5. Heptyl 2-(benzo[d][1,3]dioxol-5-yl)acetate (**8e**).* Colorless liquid; ^1H NMR ($CDCl_3$): δ 0.80 (t, J=7.2 Hz, 3H), 1.19 (br s, 8H), 1.51 (m, 2H), 3.45 (s, 2H), 3.90 (t, J=7.2 Hz, 2H), 5.87 (s, 2H), 6.66–6.72 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 14.1, 22.6, 25.9, 28.6, 28.9, 31.8, 41.1, 65.1, 101.1, 108.3, 109.8, 122.4, 127.8, 146.7, 147.0, 171.9. EIMS (70 eV): m/z (%): 279 (15) [M+1], 278 (60) [M^+], 180 (10), 135 (100); HRMS (EI): m/z calcd for $C_{16}H_{22}O_4$: 278.1518; found: 278.1500.

*4.3.6. (S)-1-tert-Butyl-2-((1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl) pyrrolidine-1,2-dicarboxylate (**8f**).*[16] Viscous oil; $[\alpha]_D^{25}$ −92 (*c* 0.1, $CHCl_3$); ^1H NMR (600 MHz; $CDCl_3$, a mixture of two rotamers in the ratio 72:28): δ 0.75 (3H× 28/100, d, J=6.8 Hz, CMe), 0.80 (3H× 72/100, d, J=6.8 Hz, CMe), 0.83–1.15 (m, 15H), 1.31–1.38 (m, 6H), 1.42 (9H× 72/100, s, O^{t}Bu), 1.45 (9H× 28/100, s, O^{t}Bu), 1.63–1.72 (m, 4H), 1.81–2.02 (m, 5H), 2.12–2.30 (m, 2H), 3.34–3.57 (m, 2H), 4.06–4.19 (m, 3H), 4.23 (dd, 0.72H, J=3.2, 8.9 Hz), 4.28 (dd, 0.28H, J=3.2, 8.9 Hz), 4.67–4.73 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 15.7, 16.2, 20.8, 20.9, 22.0, 22.8, 23.2, 23.4, 25.5, 26.1, 28.3, 28.4, 31.1, 31.4, 31.5, 34.1, 34.2, 34.3, 40.8, 42.6, 46.4, 46.5, 46.8, 48.4, 48.6, 59.2, 63.4, 63.5, 74.7, 79.1, 79.2, 79.9, 154.3, 172.7.

*4.3.7. 2-Phenylethyl octanoate (**8g**).*[17] Colorless oil; ^1H NMR ($CDCl_3$): δ 0.85 (t, J=7.0 Hz, 3H), 1.25 (br s, 8H), 1.58 (m, 2H), 2.24–2.36 (m, 2H), 2.88–3.04 (m, 3H), 4.19–4.33 (m, 2H), 7.20–7.35 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 14.1, 22.7, 24.9, 24.98, 28.99, 29.1, 31.7, 34.4, 35.2, 63.8, 63.9, 126.6, 126.7, 128.6, 128.9, 129.1, 137.2, 174.1.

*4.3.8. (1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl-2-methyl-butanoate (**8h**).*[20] Colorless oil; $[\alpha]_D^{25}$ −42.3 (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.01–1.17 (m, 19H), 1.32–1.45 (m, 2H), 1.63–1.73 (m, 2H), 1.82–1.99 (m, 2H), 2.44–2.58 (m, 1H), 4.59 (dt, J=4.4, 10.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 16.2, 19.0, 19.1, 20.8, 22.1, 23.4, 26.2, 31.4, 34.3, 40.9, 47.1, 73.8, 176.8.

*4.3.9. (1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl isobutyrate (**8i**).*[21] Colorless oil; $[\alpha]_D^{25}$ −7.5 (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.73–1.15 (m, 16H), 1.38–2.00 (m, 8H), 2.28–2.38 (m, 1H), 4.60–4.73 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 11.6, 16.0, 16.1, 16.8, 20.8, 22.0, 23.2, 23.3, 26.1, 26.7, 26.9, 29.7, 31.3, 34.3, 40.8, 40.9, 41.4, 41.6, 46.9, 73.7, 176.3.

*4.3.10. (1R,2S,5R)-2-Isopropyl-5-methylcyclohexylacetate (**8j**).*[22] Colorless oil; $[\alpha]_D^{25}$ −7.5 (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.02–1.90 (m, 19H), 2.00 (s, 3H), 4.60–4.73 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 16.4, 20.8, 21.4, 22.1, 23.5, 26.3, 31.4, 34.3, 40.9, 47.0, 74.2, 170.7.

*4.3.11. (1R,2S,5R)-2-Isopropyl-5-methylcyclohexylbenzoate (**8k**).*[23] Colorless oil; $[\alpha]_D^{25}$ −86 (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.91–2.17 (m, 19H), 4.88 (dt, J=4.2, 10.6 Hz, 1H), 7.40–7.59 (m, 3H), 8.04 (d, J=8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 16.6, 20.9, 22.1, 23.7, 26.5, 31.5, 34.4, 41.0, 47.3, 74.9, 128.4, 129.6, 130.9, 132.8, 166.2.

*4.3.12. (1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl-1,3-dioxo-isoindoline-2-carboxylate (**8l**).*[24] White solid; mp: 69–71 °C; $[\alpha]_D^{25}$ −58 (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.78–2.06 (m, 18H), 4.42 (s, 2H),

4.68 (dt, *J*=4.4, 10.8 Hz, 1H), 7.73–7.92 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 16.3, 20.8, 22.0, 23.4, 26.3, 31.4, 34.1, 39.2, 40.7, 46.98, 76.3, 123.6, 132.1, 134.2, 166.9, 167.6. EIMS (70 eV): 344.185 (M+1).

*4.3.13. (1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl-2-(benzo[d]-[1,3] dioxol-5-yl)acetate (**8m**).* Colorless oil; $[\alpha]_D^{25}$ −63 (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.75–1.30 (m, 12H), 1.40–2.09 (m, 6H), 3.50 (s, 2H), 4.60 (dt, *J*=4.2, 10.8 Hz, 1H), 5.93 (s, 2H), 6.72–6.78 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 16.3, 20.8, 22.1, 23.4, 26.2, 31.4, 34.3, 40.8, 41.4, 47.1, 74.7, 101.0, 108.3, 109.7, 122.4, 128.0, 146.6, 147.7, 171.3. HRMS (EI): *m*/*z* calcd for $C_{19}H_{26}O_4$: 318.1831; found: 318.1841.

*4.3.14. N,4-Dimethoxy-N-methylbenzamide (**9a**).*[18] Pale yellow liquid; ^{1}H NMR ($CDCl_3$): δ 3.36 (s, 3H), 3.56 (s, 3H), 3.85 (s, 3H), 6.88 (d, *J*=8.0 Hz, 2H), 7.71 (d, *J*=8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 33.8, 55.3, 60.9, 113.2, 113.5, 125.9, 130.5, 132.1, 161.5, 169.4.

*4.3.15. (S)-Methyl-3-methyl-2-(4-nitrobenzamido)butanoate (**9b**).*[12b] Pale yellow liquid; $[\alpha]_D^{25}$ +17 (*c* 0.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.95–1.03 (m, 6H), 2.19–2.38 (m, 1H), 3.79 (s, 3H), 4.74–4.81 (m, 1H), 6.79 (d, 1H), 7.95 (d, *J*=8.0 Hz, 2H), 8.27 (d, *J*=8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 18.0, 19.0, 31.6, 52.5, 57.8, 123.9, 128.4, 139.7, 149.8, 165.4, 172.5.

*4.3.16. (4-Methoxyphenyl)(morpholino)methanone (**9c**).*[19] Colorless oil; ^{1}H NMR ($CDCl_3$): δ 3.67 (br s, 8H), 3.82 (s, 3H), 6.88 (d, *J*=8.0 Hz, 2H), 7.35 (d, *J*=8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 55.4, 66.9, 113.8, 127.3, 129.3, 160.9, 170.5.

*4.3.17. (S)-1-[tert-Butoxycarbonyl]-2-morpholinocarbonyl-pyrrolidine (**9d**).* White solid; $[\alpha]_D^{25}$ −53 (*c* 0.2, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) a mixture of two rotamers in the ratio 55:45; Rotamer A δ 1.42 (s, 9H), 1.77–1.85 (m, 2H), 1.93–2.15 (m, 2H), 3.36–3.72 (m, 10H), 4.60 (dd, *J*=8.3, 2.8 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 24.23, 29.81, 42.40, 45.97, 46.77, 56.16, 66.61, 66.97, 79.56, 154.50, 171.01; Rotamer B δ 1.37 (9H, s), 1.77–1.85 (m, 2H), 1.93–2.15 (m, 2H), 3.36–3.72 (m, 10H), 4.48 (dd, *J*=8.5, 3.5 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 23.54, 28.49, 30.53, 42.30, 45.70, 46.53, 56.68, 66.61, 67.07, 79.56, 153.84, 171.9 HRMS (EI): *m*/*z* calcd for $C_{14}H_{24}N_2O_4$: 284.1736; found: 284.1739.

*4.3.18. (S)-1-tert-Butyl-2-(piperidin-1-ylcarbonyl)pyrrolidine-1-carboxylate(**9e**).*[25] White solid; $[\alpha]_D^{25}$ −52 (*c* 0.2, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) a mixture of two rotamers in the ratio 55:45; Rotamer A δ 1.40 (9H, s), 1.48–1.64 (m, 6H), 1.78–1.82 (m, 2H), 1.91–1.97 (m, 1H), 2.06–2.14 (m, 1H), 3.05 (dd, *J*=10.7, 7.0 Hz, 1H), 3.26–3.74 (m, 5H), 4.51 (dd, *J*=8.6, 3.4 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 23.48, 24.64, 28.51, 26.54, 28.60, 30.61, 43.19, 46.38, 56.96, 79.34, 154.09, 170.69; Rotamer B δ 1.37 (9H, s), 1.48–1.64 (m, 6H), 1.78–1.82 (m, 2H), 1.91–1.97 (m, 1H), 2.06–2.14 (m, 1H), 3.32–3.57 (m, 5H), 3.94–4.01 (m, 1H), 4.65 (dd, *J*=8.6, 2.5 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 24.14, 26.54, 24.64, 28.51, 28.60, 29.87, 43.24, 46.24, 56.56, 79.34, 154.54, 170.45.

*4.3.19. (S)-1-tert-Butyl-2-[(2-phenylethyl)carbamoyl] pyrrolidine-1-carboxylate (**9f**).*[26] White solid; $[\alpha]_D^{25}$ −71.5 (*c* 0.2, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) a mixture of two rotamers in the ratio 55:45; Rotamer A δ 1.42 (9H, s), 1.72–2.30 (m, 4H), 2.74–2.82 (m, 2H), 3.32–3.50 (m, 4H), 4.24 (s, 1H), 6.84 (br s, 1H), 7.17–7.29 (m, 5H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 24.57, 28.47, 31.07, 35.84, 40.59, 47.15, 60.15, 80.46, 126.52, 128.78, 139.07, 155.87, 172.03; Rotamer B δ 1.42 (s, 9H), 1.72–2.30 (m, 4H), 2.74–2.82 (m, 2H), 3.32–3.50 (m, 4H), 4.17 (s, 1H), 6.04 (br s, 1H), 7.17–7.29 (m, 5H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 23.68, 28.47, 31.07, 35.84, 40.59, 47.15, 61.45, 126.52, 128.78, 138.62, 154.79, 172.67.

*4.3.20. (S)-1-tert-Butyl-2-(hexylcarbamoyl)pyrrolidine-1-carboxylate (**9g**).* White solid; $[\alpha]_D^{25}$ −50.5 (*c* 0.2, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) a mixture of rotamers in the ratio 60:40; Rotamer A δ 0.83 (t, *J*=6.8 Hz, 3H), 1.20–1.28 (m, 6H), 1.41–1.47 (m, 11H), 1.81–2.31 (m, 4H), 3.16–3.38 (m, 4H), 4.21 (s, 1H), 6.88 (br s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 14.04, 22.57, 23.77, 24.63, 26.57, 28.42, 29.54, 29.72, 31.11, 31.50, 39.40, 41.73, 59.88, 80.40, 155.89, 171.87; Rotamer B δ 0.83 t, *J*=6.8 Hz, 3H), 1.21–1.27 (m, 6H), 1.41–1.47 (m, 11H), 1.81–2.31 (m, 4H), 3.16–3.38 (m, 4H), 4.17 (s, 1H), 6.03 (br s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 14.04, 22.57, 23.77, 24.63, 26.57, 28.42, 29.54, 29.72, 31.11, 31.50, 39.40, 41.73, 61.42, 80.40, 154.84, 172.49. HRMS (EI): *m*/*z* calcd for $C_{16}H_{30}N_2O_3$: 298.2256; found: 298.2254.

*4.3.21. (S)-1-tert-Butyl-2-(cyclohexylcarbamoyl)pyrrolidine-1-carboxylate(**9h**).*[27] White solid; $[\alpha]_D^{25}$ −52.5 (*c* 0.2, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) a mixture of rotamers formed in the ratio 55:45; Rotamer A δ 1.12–1.32 (m, 5H), 1.40 (s, 9H), 1.51–1.80 (m, 8H), 2.05–2.30 (m, 1H), 3.26–3.39 (m, 2H), 3.70 (s, 1H), 4.13 (s, 1H), 5.84 (br s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 23.75, 24.61, 24.88, 25.55, 28.41, 31.16, 33.31, 47.09, 61.41, 80.46, 154.83, 171.50; Rotamer B δ 1.12–1.32 (m, 5H), 1.40 (s, 9H), 1.51–1.80 (m, 8H), 2.05–2.30 (m, 1H), 3.26–3.39 (m, 2H), 3.70 (s, 1H), 4.18 (s, 1H), 6.86 (br s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 23.75, 24.61, 24.88, 25.55, 28.41, 31.16, 32.81, 47.86, 61.41, 80.46, 155.75, 170.87. HRMS (EI): *m*/*z* calcd for $C_{16}H_{28}N_2O_3$: 296.2100; found: 296.2108.

*4.3.22. (S)-1-tert-Butyl-2-(benzylcarbamoyl)pyrrolidine-1-carboxylate(**9i**).*[26] White solid; $[\alpha]_D^{25}$ −51.5 (*c* 0.2, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) a mixture of rotamers formed in the ratio 60:40; Rotamer A δ 1.40 (s, 9H), 1.88–2.39 (m, 4H), 3.35–3.43 (m, 2H), 4.28–4.33 (m, 2H), 4.45 (s, 1H), 4.57 (s, 1H), 7.26–7.33 (m, 5H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 24.77, 28.41, 29.81, 43.44, 47.24, 80.61, 127.49, 128.76, 128.33, 155.72, 172.06; Rotamer B δ 1.37 (s, 9H), 1.88–2.39 (m, 4H), 3.35–3.43 (m, 2H), 4.28–4.33 (m, 2H), 4.45 (s, 1H), 6.37 (br s, 1H), 7.26–7.33 (m, 5H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 23.86, 28.41, 31.19, 43.44, 47.24, 80.61, 127.49, 128.76, 138.33, 154.64, 172.36.

*4.3.23. (S)-1-tert-Butyl (2S)-2-[(4-methoxyphenyl)carbamoyl] pyrrolidine-1-carboxylate (**9j**).* White solid; $[\alpha]_D^{25}$ −84 (*c* 0.2, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) a mixture of rotamers formed in the ratio 70:30; Rotamer A δ 1.46 (s, 9H), 1.86–2.42 (m, 4H), 3.34–3.44 (m, 2H), 3.73 (s, 3H), 4.45 (s, 1H), 6.76–6.77 (m, 2H), 7.37–7.39 (m, 2H), 9.32 (br s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 24.66, 27.71, 31.12, 42.74, 55.46, 60.44, 80.74, 114.03, 121.16, 131.79, 154.63, 156.32, 169.85; Rotamer B δ 1.46 (s, 9H), 1.86–2.01 (m, 4H), 3.34–3.44 (m, 2H), 3.73 (s, 3H), 4.28 (s, 1H), 6.76–6.77 (m, 2H), 7.37–7.39 (m, 2H), 7.81 (br s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 24.00, 27.71, 31.12, 42.74, 55.46, 61.86, 80.74, 114.03, 121.16, 130.68, 154.63, 155.98, 170.80. HRMS (EI): *m*/*z* calcd for $C_{17}H_{24}N_2O_4$: 320.1736; found: 320.1743.

*4.3.24. (S)-4[(1-Methyl-2-pyrrolidinyl)methyl]morpholine (**9k**).*[28] $LiAlH_4$ (0.053 g, 1.40 mmol) was suspended in dry THF (3.00 mL) and cooled to 0 °C under nitrogen. Compound **9d** (0.200 g, 0.70 mmol) dissolved in THF (3.00 mL) was slowly added and then heated to reflux for 2 h. Then the reaction mixture was cooled to 0 °C and quenched by dropwise addition of saturated aqueous Rochelle's salt. The organic and aqueous phases were separated and the aqueous phase was extracted with EtOAc (3×20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to provide the title compound as an yellow oil; $[\alpha]_D^{25}$ −45 (*c* 0.2, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.50–1.58 (m, 1H), 1.66–1.76 (m, 2H), 1.93–1.96 (m, 1H) 2.16 (td, *J*=9.6, 7.6 Hz, 1H), 2.24 (dd, *J*=12.0, 7.0 Hz, 1H), 2.30 (dt, *J*=7.3, 6.1 Hz, 1H), 2.40 (s, 3H), 2.44 (d, *J*=3.6 Hz, 4H), 2.50 (dd, *J*=12.0, 5.1 Hz, 1H), 3.04 (ddd, *J*=9.3, 7.6, 1.9 Hz, 1H), 3.68 (t, *J*=4.7 Hz, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 22.73, 30.92, 41.68, 54.54, 57.96, 62.62, 64.42, 61.74.

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