Racemization-free synthesis of dipeptide, amide and ester by oxalyl chloride and catalytic triphenylphosphine oxide

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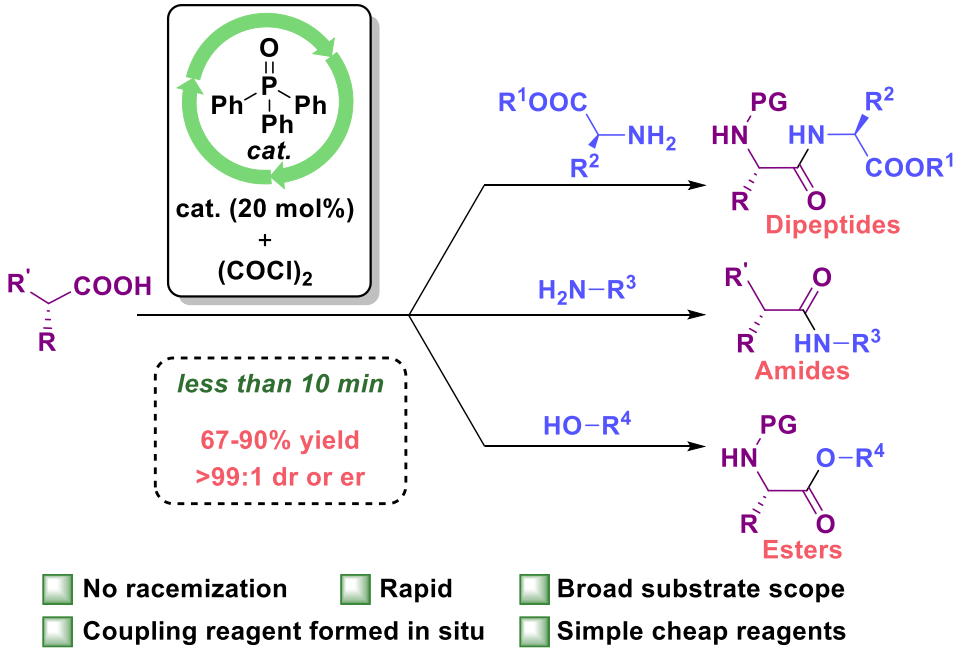
Supporting Information Placeholder

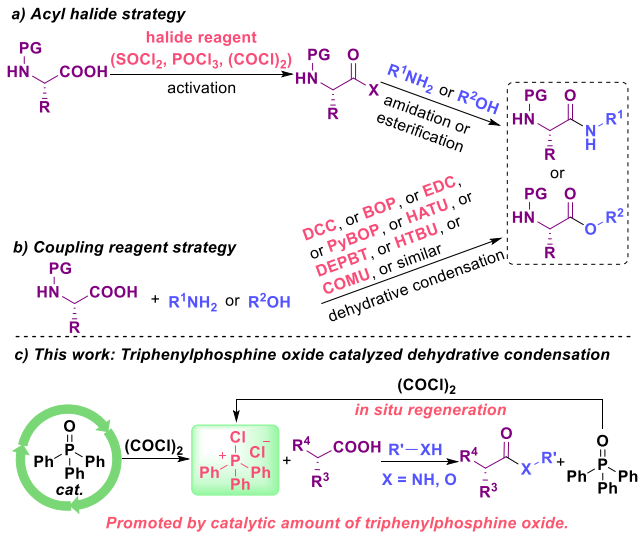


ABSTRACT: An efficient triphenylphosphine oxide (Ph_3PO) catalyzed amidation and esterification reaction for rapid synthesis of a series of dipeptides, amides and esters under mild condition is described. This reaction is applicable to challenging couplings of hindered carboxylic acid with low nucleophilic amine or alcohol, giving products in good yields (67-90%) without any racemization. This system employs highly reactive intermediate Ph_3PCl_2 as activator of carboxylate, in a catalytic manner, and drive the reaction to complete in short reaction time (less than 10 min). It has the advantages of good functional group tolerance, broad substrate scope and good atom-economy. A 100 mmol scale reaction with good yield shed light on its potential for industrial application. A plausible mechanism is proposed based on ^{31}P NMR monitor of reaction process.

Amide bond and ester bond formations are the most common reactions for the synthesis of pharmaceutical compounds and other organic transformations.[1] Due to the significant utilities of such structural motifs, the synthesis of amides and esters has become one of the hottest research areas in both academia and industry.[2] Early strategy to form amide and ester bonds is conversion of carboxylic acid moiety to a more reactive acyl halide (Scheme 1, eq a), which requires the harsh reagents such as $SOCl_2$, $POCl_3$, $(COCl)_2$.[3] In addition, this strategy brings potential racemization of α-chiral carboxylic acids. To mitigate these issues, coupling reagent strategy was developed for amide bond or ester bond formations (Scheme 1, eq b).[3,4] Numerous coupling reagents have been developed, such as carbodiimides[5], phosphoniums[6], uronium salts[7], immoniums[8], imidazolium salts[9] and pyridinium reagents[10]. Because of easy to handle, commercial reagents such as DCC, EDC, BOP, HATU are widely used in the activation of carboxylic acids. Meanwhile, novel types of activating strategies and coupling reagent systems have also been developed over the past few years, including ynamide-mediated esterification and amidation[11], 2,4-bis(trifluoromethyl)phenylboronic acid catalyzed dehydrative condensation[12], TCFH-NMI as coupling reagent[13], aminosilane-catalyzed amidation[14], visible light and DMAP/CCl_3Br assisted peptide coupling[15]. Unfortunately, preparation protocols of these coupling reagents involve harsh conditions and toxic reagents and it is not trivial to recycle

these coupling reagents. The formation of amide bond and ester bond avoiding poor atom economy reagents is recognized as one of the top challenges in synthetic chemistry.[1b] In accordance with the principles of atom economy and step economy, coupling reagent with a high efficacy and low molecular weight while being environmentally friendly and practical is essential for the green future of esterification and amidation.[16]

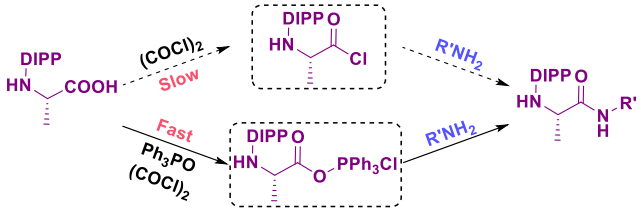
Scheme 1. Recent progresses in amidation and esterification reactions



In seeking for new coupling system, we noticed that triphenylphosphine (Ph_3P) is a versatile reagent. It was not only used in Wittig reaction[17], Mitsunobu reaction[18], Appel reaction[19] and Staudinger reaction[20], but also in amide and peptide synthesis in which the stoichiometric intermediate chlorophosphonium salt (Ph_3PCl^+/Cl^-) generated from triphenylphosphine and CCl_4 (or C_2Cl_6) can efficiently activate carboxylate group, and stoichiometric amount of triphenylphosphine oxide (Ph_3PO) was produced as intractable chemical waste. In order to apply Ph_3PCl^+/Cl^- species in a more cost-effective and easy-to-handle way, several studies adopt the cheaper Ph_3PO/oxalyl chloride ($(COCl)_2$) system for *in situ* formation of Ph_3PCl^+/Cl^-. It is worth mentioning that early in 1977 Masaki and Fukui[21] reported that the industrial byproduct Ph_3PO could be easily converted into Ph_3PCl^+/Cl^-, which was later applied in amide and ester synthesis via stoichiometric activation of non-chiral carboxylic acid[22], amide to nitrile dehydration[23], Appel reaction[24] and others[25]. Through analysis of an improved Appel reaction where catalytic Ph_3PO was continuously deoxygenated to the phosphonium Ph_3PCl^+/Cl^- by $(COCl)_2$[24a], and combined with the fact that phosphonium (e.g. BOP, PyBOP) are excellent coupling reagents in racemization-free activation of carboxylic acids, we hypothesized that Ph_3PO(cat.)/$(COCl)_2$ system generated Ph_3PCl^+/Cl^- could also be applied to α-chiral carboxylate activation and thus drives amide or ester bond formation. Herein, we reported an effective racemization-free amidation and esterification reaction of chiral carboxylic acids promoted by Ph_3PO(cat.)/$(COCl)_2$ system (Scheme 1, eq c).

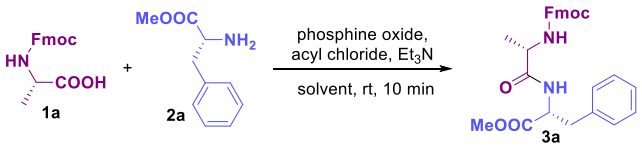
Before screening the reaction conditions, we first compared the activating rates of carboxylic acid by $(COCl)_2$ with and without presence of Ph_3PO. To facilitate assignment of activated species by ^{31}P NMR, model reactant alanine was N-protected by a phosphoryl moiety. In ^{31}P NMR spectra (see Fig S1~S3), we found that $(COCl)_2$ alone can only slowly converts N-protected alanine into corresponding acyl chloride, while $(COCl)_2$ and Ph_3PO combined instantly and predominantly converts the reactant to phosphonium adduct (Scheme 2).

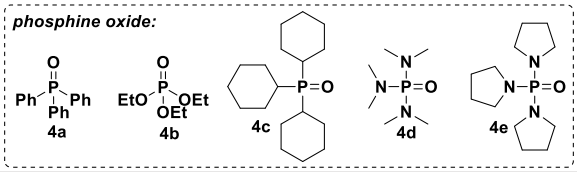
Scheme 2. Activation of N-protected alanine by $(COCl)_2$ and Ph_3PO



The investigation commenced with reaction conditions screening, the model reaction of N-protected amino acid **1a** and amino acid ester **2a** was initially evaluated (Table 1). Using stoichiometric quantity of Ph_3PO **4a** and 1.5 equiv of oxalyl chloride, dipeptide **3a** was formed in moderate yield (51%) with excellent diastereomeric purity (>99:1 dr) (Table 1, entry 1). Reduction of Ph_3PO **4a** to 20 mol % only resulted in a slightly lower yield (48%) (Table 1, entry 2). These results prove that catalytic amount of Ph_3PO is sufficed to accomplish the reaction. A series of solvents including toluene, tetrahydrofuran, 1,4-dioxane, acetonitrile, 1,2-dichloroethane, and dichloromethane were evaluated (Table 1, entries 3-7). It turns out that 1,2-dichloroethane was the favorite solvent and gave the dipeptide **3a** in 83% yield without racemization. It should be noted that this reaction completed in less than 10 min. Various phosphine oxides including triethyl phosphate **4b**, tricyclohexylphosphine oxide **4c**, hexamethylphosphoramide **4d**, and tris(pyrrolidinophosphine) oxide **4e** were briefly assessed and proved to be inferior (Table 1, entries 8-11). Replacement of oxalyl chloride with triphosgene did not produce the dipeptide **3a** (Table 1, entry 12). Further reduction of catalyst loading to 5 mol %, a significantly lower yield (43%) was observed (Table 1, entry 13). In the absence of Ph_3PO, the dipeptide **3a** was not obtained (Table 1, entry 14). Based on the above screening, the optimal reaction conditions were established as following: amino acids **1** (1.0 equiv.), amino acid esters **2** (1.2 equiv.) and triphenylphosphine oxide **4a** (20 mol %) were well mixed in 1,2-dichloroethane, oxalyl chloride (1.5 equiv.) and triethylamine (2.0 equiv.) were added in sequence at ambient temperature under argon atmosphere, the reaction mixture was stirred at ambient temperature for 10 min.

Table 1. Optimization of the peptide bond-forming reaction[a]



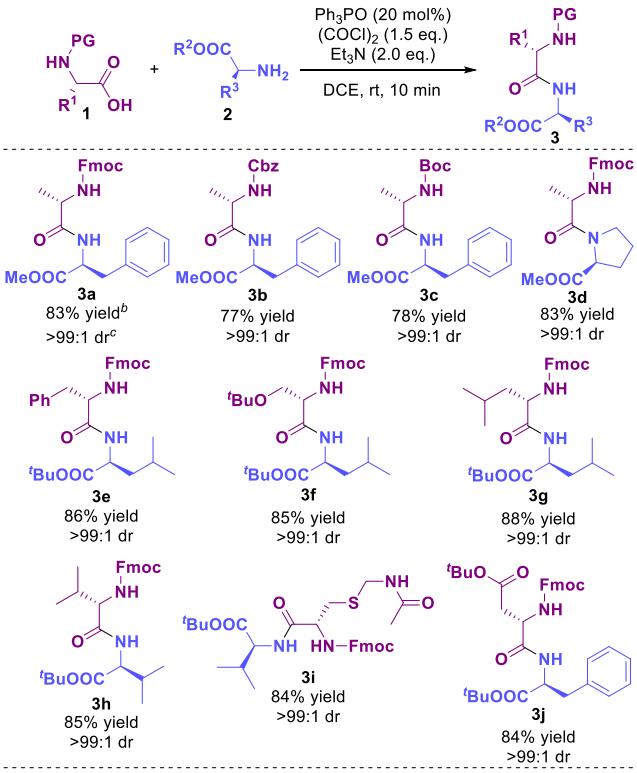


entry	solvent (1.0 mL)	phosphine oxide (mol %)	acyl chloride (1.5 eq.)	yield (%)[b]	dr[c]
1	PhMe	**4a** (100)	$(COCl)_2$	51	>99:1
2	PhMe	**4a** (20)	$(COCl)_2$	48	>99:1
3	THF	**4a** (20)	$(COCl)_2$	43	>99:1
4	1,4-dioxane	**4a** (20)	$(COCl)_2$	69	>99:1
5	MeCN	**4a** (20)	$(COCl)_2$	30	>99:1
6	**DCE**	**4a** (20)	**$(COCl)_2$**	**83**	**>99:1**
7	DCM	**4a** (20)	$(COCl)_2$	38	>99:1
8	DCE	**4b** (20)	$(COCl)_2$	53	96:4
9	DCE	**4c** (20)	$(COCl)_2$	41	96:4
10	DCE	**4d** (20)	$(COCl)_2$	trace	-
11	DCE	**4e** (20)	$(COCl)_2$	trace	-
12	DCE	**4a** (20)	triphosgene	NR	-
13	DCE	**4a** (5)	$(COCl)_2$	43	98:2
14	DCE	-	$(COCl)_2$	NR	-

[a]Unless otherwise noted, all reactions were carried out using amino acid **1a** (1.0 mmol, 1.0 equiv.), amino acid ester **2a** (1.2 mmol, 1.2 equiv.) and phosphine oxide **4** in solvent (1.0 mL) and acyl chloride (1.5 mmol, 1.5 equiv.) and triethylamine (2.0 mmol, 2.0 equiv.) were added in sequence at ambient temperature in argon. [b]Isolated yield. [c]Determined by HPLC on a chiral stationary phase.

Having the optimal conditions in hand, we sought to examine the substrate tolerance for dipeptide synthesis (Scheme 3). It is found that common amine protecting groups such as Boc, Cbz, and Fmoc could be tolerated (**3a**-**3c**). Different protecting groups had no noticeable influence on reaction yields (77-83%, >99:1 dr). Coupling reactions between secondary amine L-proline ester and *N*-Fmoc-L-Ala also provided the corresponding dipeptide **3d** in good yield (83%, >99:1 dr). Reactions between several of amino acid *tert*-butyl esters and a series of *N*-Fmoc amino acids provided the corresponding dipeptides **3e**-**3j** in good yields (84-88%). Notably, side-chain protected amino acids (Ser, Cys, Asp) also reacted smoothly to give the corresponding dipeptides in good yields without racemization.

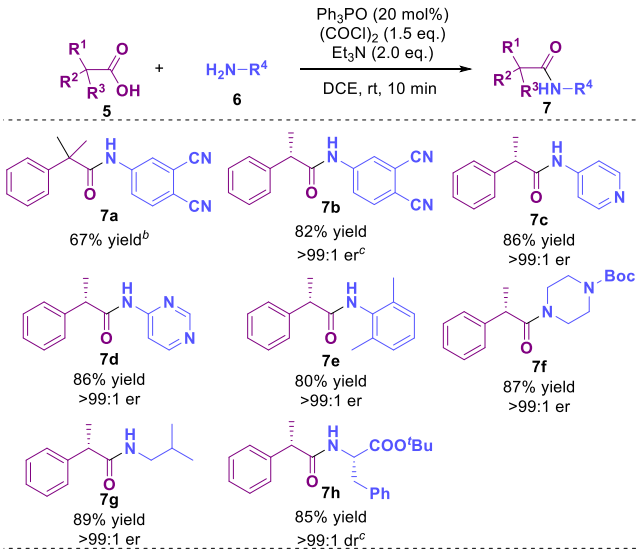
Scheme 3. Dipeptide synthesis[a]



[a]Unless otherwise noted, all reactions were carried out using amino acids **1** (1.0 mmol, 1.0 equiv.), amino acid esters **2** (1.2 mmol, 1.2 equiv.) and triphenylphosphine oxide **4a** in 1,2-dichloroethane (1.0 mL) and oxalyl chloride (1.5 mmol, 1.5 equiv.) and triethylamine (2.0 mmol, 2.0 equiv.) were added in sequence at ambient temperature in argon. [b]Isolated yield. [c]Determined by HPLC on a chiral stationary phase.

To test the reactivity of hindered carboxylic acid and low nucleophilic amine, 2-phenylisobutyric acid **5a** and 4-aminophthalonitrile **6a** were investigated. This challenging coupling gives moderate yield (**7a**, 67%). In addition, coupling reactions between (S)-phenylpropionic acid and a series of amines bearing both electron-donating and -withdrawing substituents, including pyridine and pyrimidine, gave the corresponding amides **7b**-**7h** in good yields (80-89%) without racemization (Scheme 4).

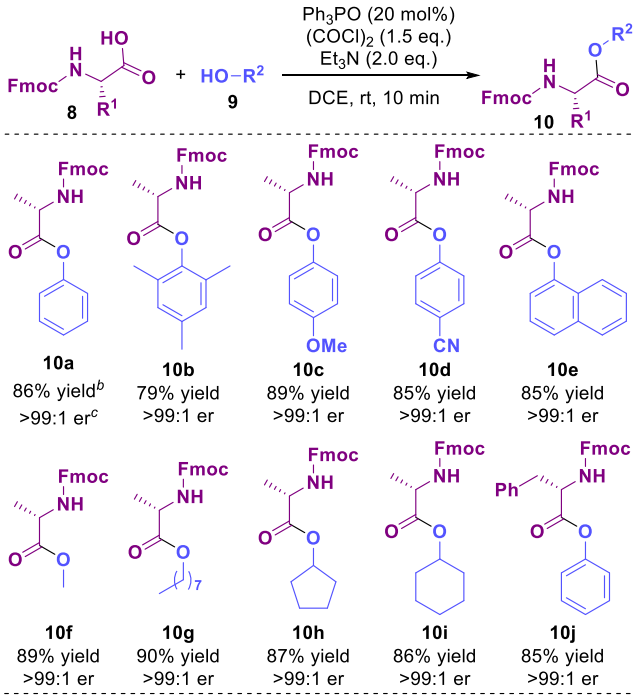
Scheme 4. Amide bond formation[a]



[a]Unless otherwise noted, all reactions were carried out using carboxylic acids **5** (1.0 mmol, 1.0 equiv.), amines **6** (1.2 mmol, 1.2 equiv.) and triphenylphosphine oxide **4a** in 1,2-dichloroethane (1.0 mL) and oxalyl chloride (1.5 mmol, 1.5 equiv.) and triethylamine (2.0 mmol, 2.0 equiv.) were added in sequence at ambient temperature in argon. [b]Isolated yield. [c]Determined by HPLC on a chiral stationary phase.

We next examined the coupling of N-protected amino acid **8** and alcohol **9** components under our optimal conditions. As shown in scheme 5, the esterification of *N*-Fmoc-L-Ala or *N*-Fmoc-L-Phe with various alcohols including phenols and aliphatic alcohols bearing both electron-donating and -withdrawing substituents proceeded smoothly to furnish the target esters **10a**-**10j** in good yields (79-90%, >99:1 er).

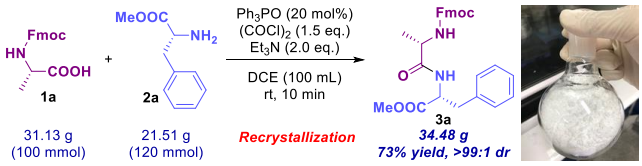
Scheme 5. Ester bond formation[a]



[a]Unless otherwise noted, all reactions were carried out using amino acids **8** (1.0 mmol, 1.0 equiv.), alcohols **9** (1.2 mmol, 1.2 equiv.) and triphenylphosphine oxide **4a** in 1,2-dichloroethane (1.0 mL) and oxalyl chloride (1.5 mmol, 1.5 equiv.) and triethylamine (2.0 mmol, 2.0 equiv.) were added in sequence at ambient temperature in argon. [b]Isolated yield. [c]Determined by HPLC on a chiral stationary phase.

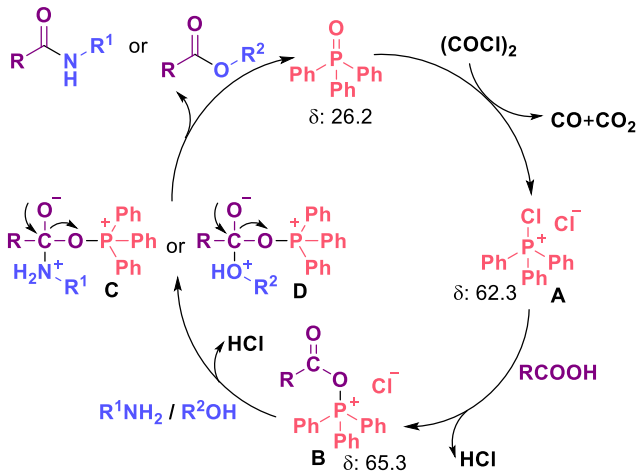
To test the scalability of this protocol, synthesis of **3a** at 100 mmol scale was carried out under the optimal reaction conditions. It gives isolated yield of 73% from simple recrystallization of product in dichloromethane, avoiding column chromatography (**Scheme 6**). Therefore, our protocol has potential value in industrial production of dipeptide.

Scheme 6. 100 mmol scale model reaction



In order to elucidate the role of Ph_3PO and $(COCl)_2$ and understand the nature of the catalytic cycle involved, ^{31}P NMR spectroscopy was used to monitor the reaction process. Based on the experimental results, a possible mechanism was proposed in Scheme 7. Initially, the solution of Ph_3PO in DCE showed a strong singlet at 26.2 ppm (Figure 1, a). A new signal appearance at 62.3 ppm after addition of oxalyl chloride (Figure 1, b), indicating triphenylphosphine oxide reacted with oxalyl chloride to generate chlorophosphonium **A**.[22,23,25d] Then the *in situ* generated intermediate **A** serves as activator of the carboxylic acid. **1a** converted it to a new resonance at 65.3 ppm (Figure 1, c), which is consistent with an acyl phosphonium salt **B**.[22] Finally, the addition of amino acid ester **2a** recovered a singlet at 26.2 ppm, the catalyst Ph_3PO (Figure 1, d). It is worthy to mention that, the singlet at about 26.2 ppm was mis-assigned to **C** or **D** in previous report.[22] Actually, **C** or **D** are transient intermediates that is impossible to accumulate at present of nucleophiles such as amines and alcohols.

Scheme 7. Proposed mechanism of amidation and esterification mediated by Ph_3PO and $(COCl)_2$



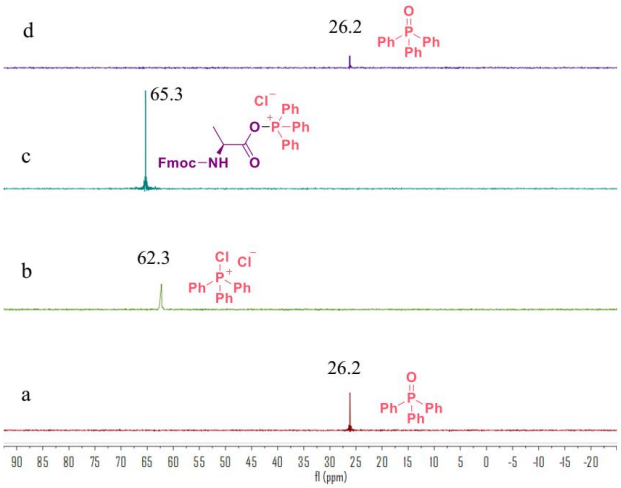


Figure 1. Monitored by ^{31}P NMR spectroscopy for synthesis dipeptide **3a**. a: the solution of Ph_3PO (0.2 mmol, 20 mol %) in DCE (1.0 mL). b: after addition of oxalyl chloride (1.5 mmol, 1.5 equiv.) to 1. c: amino acid **1a** (1.0 mmol, 1.0 equiv.) added to 2. d: amino acid ester **2a** (1.2 mmol, 1.2 equiv.) and triethylamine (2.0 mmol, 2.0 equiv.) were added to solution of 3.

In summary, we successfully developed an effective amidation and esterification reaction for α-chiral carboxylic acids. This reaction system employs catalytic amount of triphenylphosphine oxide and stoichiometric amount of oxalyl chloride under mild condition to *in situ* forming highly active and efficient phosphonium intermediate Ph_3PCl_2, which can drive even challenging couplings of hindered carboxylic acids and low nucleophilic amines or alcohols. The reaction is easy to operate and is able to synthesize dipeptides, amides and esters in good yields (67-90%) without racemization. Our system has the advantages of short reaction time (less than 10 min), using cheap and readily available reagents, good functionals tolerance, broad substrate scope and atom-economy (only CO, CO_2 and HCl as wastes in the end of reaction). A 100 mmol-scale reaction was successfully realized, showing its potential for industrial application.

ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures and characterization of new products; NMR spectra and HPLC chromatograms (PDF)

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Notes

The authors declare no competing financial interest.

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