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PS-IIDQ: a supported coupling reagent for efficient and general amide bond formation

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Abstract—Polystyrene-IIDQ, a polymer-supported coupling reagent, was synthesized in three steps from Merrifield resin in 86% overall conversion. This reagent efficiently coupled carboxylic acids to amines in good yields and high purities, required no pre-activation step, and was tolerant of the order of reagent addition. PS-IIDQ was observed to be more efficient than polymer-supported carbodiimides (PS-EDC and PS-DCC) and gave higher yields than HATU for general amide bond formation, including the coupling of anilines and hindered substrates. When evaluated with five carboxylic acids and nine amines (including anilines and secondary amines) PS-IIDQ gave an average isolated yield of 73%.

1. Introduction

Over the past decade, interest in the development of new solid-supported reagents has increased,[1] predominantly because these reagents combine the traditional advantages of solution-phase chemistry, such as reaction monitoring, with the solid-phase advantages of being able to drive reactions by mass action, and the associated ease of parallel synthesis. Ideally, when using solid-supported materials, unreacted reagents and by-products should remain on the resin and be easily removed by filtration at the end of the reaction. However, although the scope of polymer-supported reagents, such as oxidants, reductants, and catalysts has broadened considerably in recent years, relatively few coupling reagents have been immobilized. This is probably because peptides are usually synthesized directly on a polymer support with the coupling reagent being in solution. However, amide bonds are found in large numbers of pharmaceutically relevant compounds, and supported coupling reagents would therefore be of great interest for general amide bond formation, especially when it is necessary to produce libraries of compounds by parallel synthesis.

Currently available supported coupling reagents include a number of immobilized carbodiimides such as PS-EDC[2] **1** and PS-DCC **2**,[3] although PS-TBTU[4] **3** and PS-BOP[5] **4** have also been immobilized (Fig. 1). However, these two latter reagents imply the release of uronium or phosphonium salts into solution during coupling, clearly an undesirable occurrence for an immobilized reagent as these by-products have to be removed following synthesis.

Solution-phase coupling reagents cover a broad range of chemistries and include carbodiimides, HOBt/HOAt based uronium or phosphonium salts such as HATU[6] **5** and PyAOP[7b] **6**, reagents that generate acid halides in situ such as BOP-Cl[8] **7**, and EEDQ **8** (Fig. 2).[9] The huge choice of coupling reagents available provides the chemist with numerous possibilities, however many of the coupling reagents reported have serious drawbacks or are simply not efficient. In addition, many of the reagents have been designed for peptide synthesis, which involves predominantly coupling with primary amines.

In the synthesis of diverse small molecules, the medicinal chemist faces the challenges of finding a method to couple efficiently a broad range of anilines, primary and secondary

Keywords: Coupling reagent; Polymer-supported reagent; Immobilized reagent; IIDQ; Parallel synthesis; Amide bond formation; Amidation; Amide.
Abbreviations: BOP, benzotriazolyl-*N*-oxytrisdimethylaminophosphonium hexafluorophosphate; BOP-Cl, *N*,*N*′-bis(2-oxo-3-oxazolidinyl)-phosphinic chloride; DCC, dicyclohexyl-carbodiimide; DCE, dichloroethane; DCM, dichloromethane; DIPEA, *N*,*N*-diisopropylethylamine; DMA, dimethylacetamide; DMAP, 4-dimethylaminopyridine; DMF, *N*,*N*-dimethylformamide; DMSO, dimethyl-sulfoxide; EDC, 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide; EEDQ, *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline; HOAt, 1-hydroxy-7-azabenzotriazole; HOBt, 1-hydroxy-1*H*-benzotriazole; HATU, *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; IIDQ, *N*-isobutoxycarbonyl-2-isobutoxy-1,2-dihydroquinoline; MP, microporous; MTBD, 7-methyl-1,5,7-triaza-bicyclo[4.4.0]dec-5-ene; NMM, *N*-methyl-morpholine; PS, polystyrene; PyAOP, [(7-azabenzotriazol-1-yl)oxy]tris-(pyrrolidino)-phosphonium hexafluorophosphate; SPE, solid-phase extractor; TBTU, *O*-benzotriazol-1-yl-1,1,3,3-tetramethyluronium tetrafluoroborate; TEA, triethylamine; THF, tetrahydrofuran.

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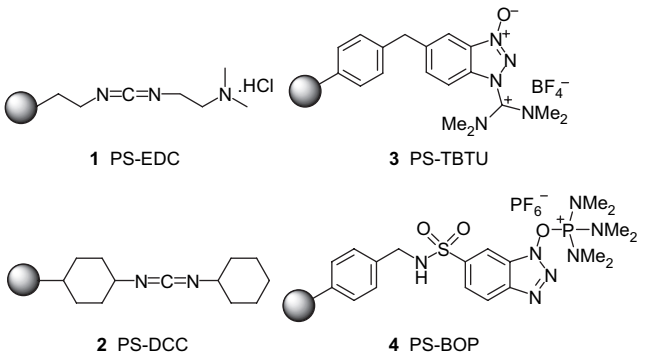


Figure 1. Structures of some supported coupling reagents.

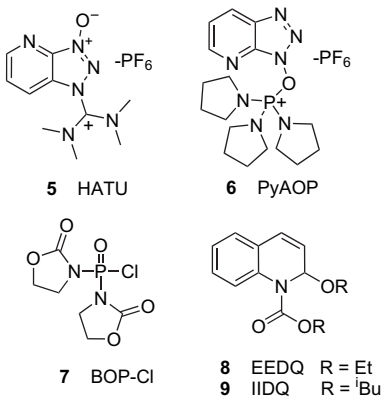


Figure 2. Structures of coupling reagents.

amines, and bulky substrates whose reactivities should (in order to achieve a diverse range of products) be widely variable. However, none of the reagents reported to date can achieve this routinely with good conversion, and most coupling reagents have one or more of the following drawbacks. (1) The structure of the reagent means that side-reactions will occur in the presence of nucleophiles. This is particularly the case with uronium-type reagents, which can yield guanidinium species in the presence of amines. (2) A pre-activation step is often necessary: the carboxylic acid has to be added to the coupling reagent prior to the addition of the amine. This has an impact particularly in parallel synthesis where the pre-activated species may decompose. (3) Many reagents require the use of a base in order to activate the coupling agent, however many reagents exhibit poor stability in the presence of the base. For example, only 36% of the coupling reagent HATU **5** remains after 1 h in the presence of 1 equiv of DIPEA in DMF.[7a]

The ideal coupling reagent should therefore have the following characteristics. (1) No pre-activation step should be necessary, with the added flexibility of being able to add the reactants in any order and at any time. (2) No particular specificity for amino-acids, the reagent should be useful for general amide bond formation. (3) There should be no need of any other additive such as a base to achieve efficient coupling. (4) No racemization when coupling chiral amines or acids. (5) No non-volatile by-products left behind in solution.

2. Results and discussion

EEDQ **8** and IIDQ **9**[35] are interesting, yet under-used, coupling reagents, which have the advantages of being inert toward amines (no pre-activation needed) while also generating a base during the reaction, which makes the use of an additional base redundant. Their lack of use can perhaps be explained by the fact that the by-product of the reaction, quinoline, is often hard to separate from the product.

2.1. Comparison of EEDQ and IIDQ

Their potential was initially assessed by investigating the relative solution coupling reactivities of EEDQ **8** and IIDQ **9** with three amines (4-*tert*-butylaniline, benzylamine, and morpholine) and two carboxylic acids (benzoic acid and phenylacetic acid). The results are presented in Table 1. Yields were good with benzylamine and anilines, but only moderate when using morpholine. Overall these results showed that IIDQ was slightly more efficient than EEDQ, and IIDQ was therefore selected for comparison tests against other common coupling reagents.

2.2. Comparison of IIDQ, HATU, BOP-Cl, and PyAOP

In order to compare the coupling efficiency of IIDQ with three other widely used coupling reagents (HATU **5**, PyAOP **6**, and BOP-Cl **7**) (without pre-activation) four amines and three carboxylic acids were tested. The synthesis was carried out in CH_3CN (because of its ability to dissolve carboxylic acids and its ease of evaporation which is important for use in parallel synthesis) with 1 equiv of each reactant/reagent. After the reaction, the mixtures were passed through an SPE cartridge containing a mixed bed of sulfonic acid/quaternary ammonium hydroxide ion-exchange resins, in order to scavenge any unreacted materials. The results are

Table 1. Coupling comparison of EEDQ and IIDQ

Entry	Amide	Amine	Acid	IIDQ		EEDQ	
				Yield[a]	Purity[b]	Yield[a]	Purity[b]
1	**10**	4-*tert*-Butyl-aniline	Phenylacetic acid	96	100	94	100
2	**11**	Benzylamine	Phenylacetic acid	91	100	87	100
3	**12**	Morpholine	Phenylacetic acid	38	100	32	93
4	**13**	4-*tert*-Butyl-aniline	Benzoic acid	88	100	85	100
5	**14**	Benzylamine	Benzoic acid	85	100	66	100
6	**15**	Morpholine	Benzoic acid	50	99	41	95
			Average	76	100	67	98

[a] Isolated yield.
[b] Purity determined by ELSD.

shown in Table 2 and clearly demonstrated that IIDQ **9** generally gave highly pure products. It was interesting to note that quinoline was removed via filtration through the SPE. For the other coupling reagents, their many products of decomposition remained in the reaction mixture yielding much less pure products. However, HATU **5** performed surprisingly well considering its poor stability, but this could be explained by the absence of a tertiary base during coupling. In fact, in terms of purities HATU **5** performed as well as IIDQ **9**. Due to the high purities obtained when using IIDQ **9** or HATU **5**, the isolated yields obtained when using these two coupling reagents were compared (Table 3). Most of the substrates chosen were coupled in good yields but morpholine gave relatively poor conversion, emphasizing the usual difficulty of coupling secondary amines. Overall, IIDQ performed better than HATU **5** in terms of yield. These studies showed that IIDQ **9** could potentially be used as a coupling reagent for efficient, general amide bond formation without requiring a pre-activation step. Attachment of IIDQ **9** onto a resin would allow immobilization of the quinoline by-product, obtained during the reaction process eliminating the need for SPE purification.[10] A simple filtration would therefore yield the pure product and isobutanol (boiling point: 108 °C) that could be removed in vacuo.

Table 3. Comparison of the yields obtained using IIDQ and HATU

Entry	Amide	Amine	Acid	IIDQ	HATU
1	**16**	4-*tert*-Butyl-aniline	Z-Ala-OH	93	38
2	**17**	Benzylamine	Z-Ala-OH	86	53
3	**18**	1,2,3,4-Tetrahydro-naphthalen-1-ylamine	Z-Ala-OH	71	37
4	**19**	Morpholine	Z-Ala-OH	69	54
5	**10**	4-*tert*-Butyl-aniline	Phenylacetic acid	80	31
6	**11**	Benzylamine	Phenylacetic acid	58	55
7	**20**	1,2,3,4-Tetrahydro-naphthalen-1-ylamine	Phenylacetic acid	59	37
8	**12**	Morpholine	Phenylacetic acid	33	53
9	**13**	4-*tert*-Butyl-aniline	Benzoic acid	89	33
10	**14**	Benzylamine	Benzoic acid	88	52
11	**21**	1,2,3,4-Tetrahydro-naphthalen-1-ylamine	Benzoic acid	67	37
12	**15**	Morpholine	Benzoic acid	48	50
			Yield average	70	44

2.3. Synthesis of PS-IIDQ

The coupling of commercially available 6-hydroxyquinoline **23** onto Merrifield resin **22** (Polymer Laboratories, 3.99 mmol/g, microporous, 150–300 μm) was performed in DMA at reflux in the presence of a large excess of potassium carbonate as shown in Scheme 1. After 6 h, the IR spectrum revealed almost complete conversion, while leaving the reaction mixture for a longer reaction time was disadvantageous as insoluble by-products started to form (leading to clogging of the resin). Nitrogen and chlorine analysis of the resin after 6 h revealed a 98% conversion with a loading of 2.74 mmol/g (the 'apparent' reduction in loading is due to the mass increase in the resin as the chloride is displaced by the 6-hydroxyquinoline). The structure of PS-quinoline **24** was confirmed by Magic-Angle Spinning NMR and the spectrum obtained compared favorably to the solution NMR of 6-benzyloxy-quinoline **25** (Fig. 3).

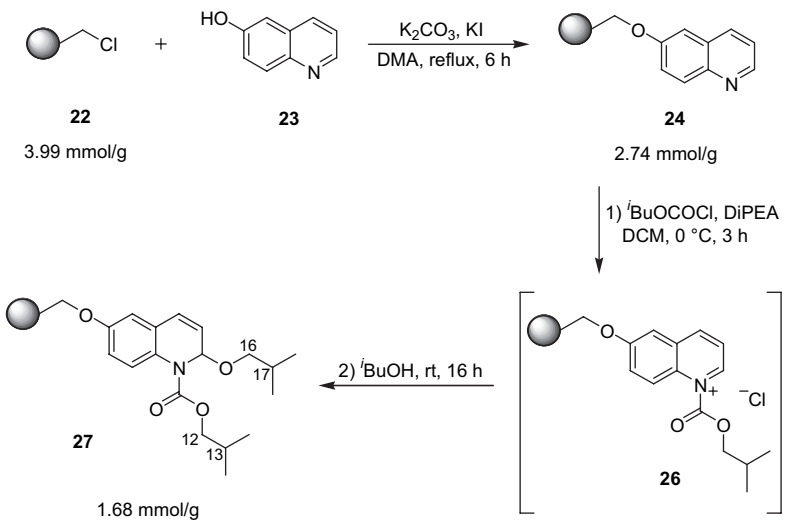
The reaction of isobutyl chloroformate with the supported quinoline in the presence of Hünig's base yielded a reactive intermediate **26**, which could be quenched with isobutanol to form polymer-supported IIDQ **27** (Scheme 1). The transformation appeared to be successful by IR (Fig. 4, conversion was evaluated via integration of the carbamate band using one of the resin backbone bands at 1490 cm^{-1} as a reference) and was confirmed by MAS-NMR. Figure 5 shows the ^1H NMR spectrum of IIDQ **9** in solution and the ^1H MAS-NMR spectrum of polymer-supported IIDQ **27**, while a ^1H–^1H COSY spectra confirmed the correlation between H-12 and H-13 and H-16 and H-17.

Other bases (TEA, NMM, pyridine, 2,6-lutidine, *N*-methyl-piperidine, 2,6-di-*tert*-butyl-4-methyl-pyridine, DMAP, MTBD, 2-*tert*-butyl-1,1,3,3-tetramethylguanidine) and solvents (DCM, THF, dioxane, CH_3CN, DMSO, DMF) were investigated in this step but DIPEA and DCM outperformed then all.

As only carbon, hydrogen, and oxygen atoms were added during the conversion of PS-quinoline into PS-IIDQ elemental analysis was not a suitable method for determination of the final loading of the reagent (the resin dominates the C/H balance). Therefore, a known mass of IIDQ resin was used to couple an excess of phenylacetic acid and benzylamine and the product isolated and quantified. The yield of the reaction thus gave the practical and accessible loading of the resin. Using this method, a loading of 1.68 mmol/g was determined corresponding to a conversion of 88%

Table 2. Comparison of the compound purities obtained (determined by ELSD) using the coupling reagents IIDQ, PyAOP, BOP-Cl, and HATU

Entry	Amide	Amine	Acid	IIDQ	PyAOP	BOP-Cl	HATU
1	**16**	4-*tert*-Butyl-aniline	Z-Ala-OH	100	85	3	100
2	**17**	Benzylamine	Z-Ala-OH	100	97	89	100
3	**18**	1,2,3,4-Tetrahydro-naphthalen-1-ylamine	Z-Ala-OH	100	99	94	100
4	**19**	Morpholine	Z-Ala-OH	100	95	92	100
5	**10**	4-*tert*-Butyl-aniline	Phenylacetic acid	100	84	0	100
6	**11**	Benzylamine	Phenylacetic acid	100	95	12	100
7	**20**	1,2,3,4-Tetrahydro-naphthalen-1-ylamine	Phenylacetic acid	100	96	80	100
8	**12**	Morpholine	Phenylacetic acid	87	8	2	100
9	**13**	4-*tert*-Butyl-aniline	Benzoic acid	100	84	0	100
10	**14**	Benzylamine	Benzoic acid	100	90	27	100
11	**21**	1,2,3,4-Tetrahydro-naphthalen-1-ylamine	Benzoic acid	100	91	83	100
12	**15**	Morpholine	Benzoic acid	39	7	0	42
			Purity average	94	78	53	95



Scheme 1. Synthesis of polymer-supported IIDQ (PS-IIDQ).

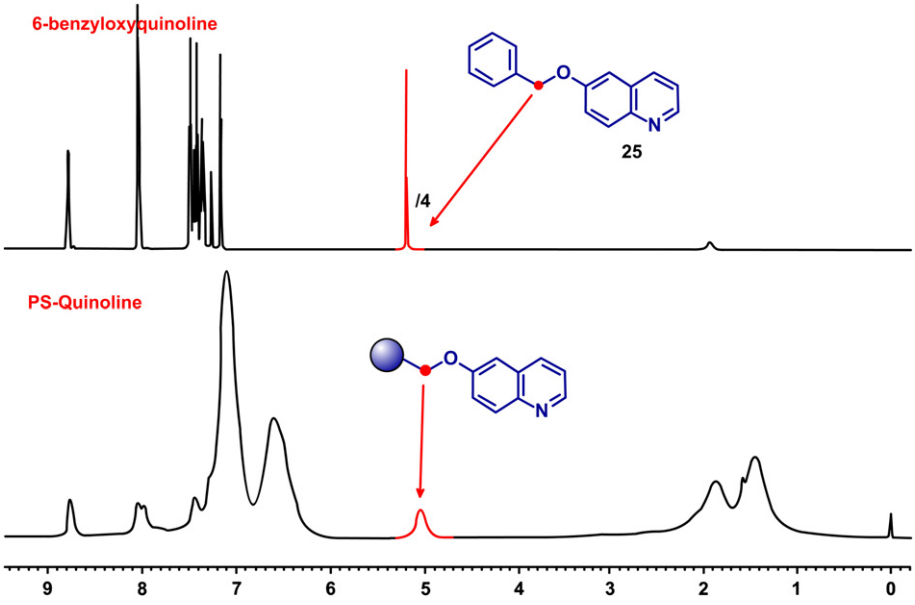


Figure 3. Comparison of the ^{1}H NMR spectra of 6-benzyloxyquinoline and ^{1}H PS-quinoline (MAS).

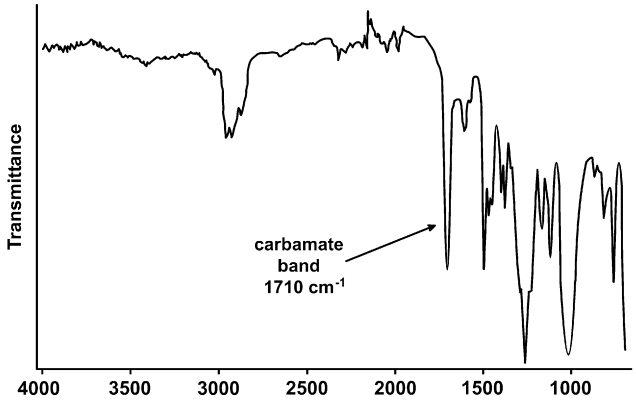


Figure 4. IR spectrum of PS-IIDQ.

from the supported quinoline **24** into the supported IIDQ **27** (assuming complete reaction of the immobilized reagent with phenylacetic acid and benzylamine).

In order to determine the optimal coupling conditions for PS-IIDQ, the coupling between benzylamine and phenylacetic acid was performed in different solvents. DCM was the first solvent tested and this proved to work efficiently as shown in Table 4 (entry 1). However, the choice of DCM was not optimal, because many carboxylic acids are insoluble in it, while it is too volatile for parallel synthesis use. In order to solve these problems, DMF, DMA, CH_3CN, THF, dioxane, and DCE were also evaluated. The results shown in Table 4 showed that DMF (entry 2) or DMA (entry 3) performed worse than DCM (entry 1). DCE (entry 7) gave similar results to DCM, but its choice was again not optimal in

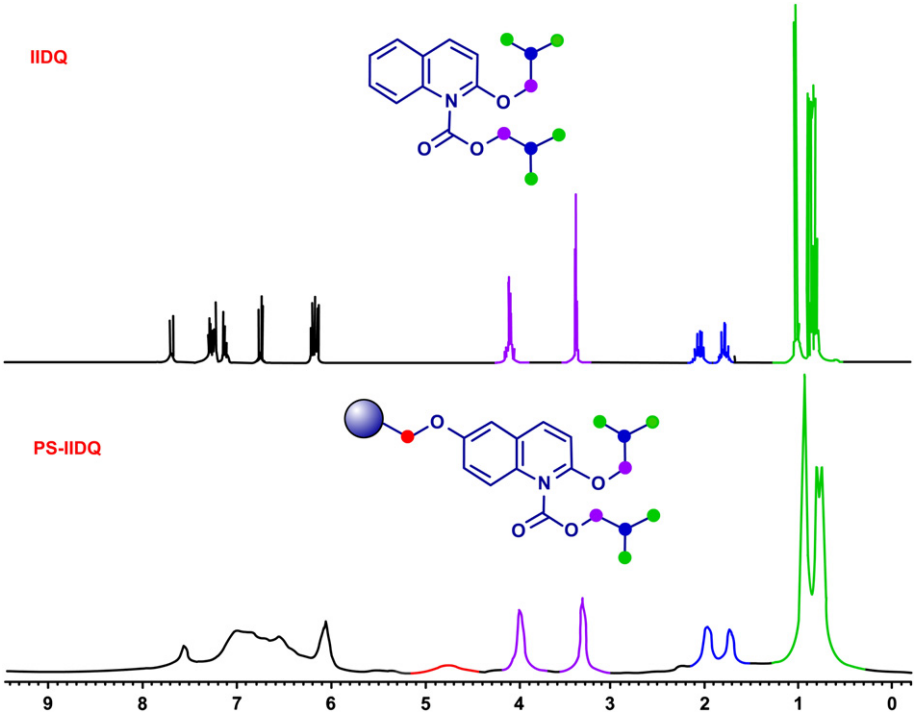


Figure 5. Comparison of the ^{1}H NMR spectra of IIDQ and PS-IIDQ (MAS).

Table 4. Solvent optimization for the coupling of benzylamine (1 equiv) and phenylacetic acid (1 equiv) with PS-IIDQ (3 equiv)

Entry	Solvent	Yield
1	DCM	98
2	DMF	32
3	DMA	37
4	CH_3CN	91
5	THF	64
6	Dioxane	87
7	DCE	94

terms of acid solubility. THF (entry 5) was not efficient, while dioxane (entry 6) also gave acceptable results. The best compromise was acetonitrile, which gave comparable conversion to DCM but with better acid solubility and reduced volatility. Therefore, acetonitrile was chosen as the coupling solvent, although it is known generally as having poor swelling properties for polystyrene supports.[11] The quantity of coupling reagent required for efficient coupling was also investigated: 1.5 equiv of PS-IIDQ only gave 67% yield, while 2 or 3 equiv typically gave 80–85% yields.

2.4. Comparison of PS-IIDQ with commercial coupling reagents

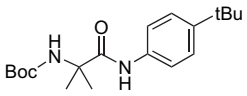
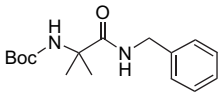
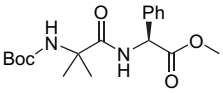
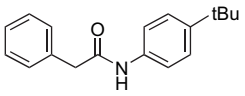
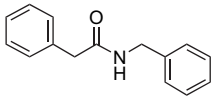
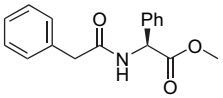
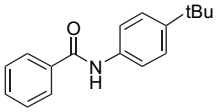
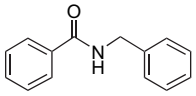
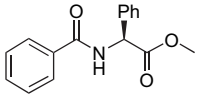
PS-IIDQ **27** was compared to some commercially available coupling reagents: HATU **5** and two polymer-supported carbodiimides PS-EDC **1** and PS-DCC **2** (Table 5). The coupling was realized using CH_3CN as solvent, 2 equiv of coupling reagent and 1 equiv of amine and acid, and a coupling time of 24 h in order to enable difficult substrates to react. This time-frame contrasts with many coupling reagents, which usually have very high reactivity but are unstable in solution with most of the reagent being degraded after an hour, a characteristic, which is unsuitable for hindered substrates or if the coupling is slow. In this respect, PS-IIDQ **27** offered a good balance between reactivity and stability.

HATU **5** (5 min pre-activation) gave lower yields than PS-IIDQ **27**. In particular couplings with HATU **5** using aminoisobutyric acid (entries 1–3) and/or anilines (entries 1, 4, and 7) were significantly poorer. Results were quite poor for the supported carbodiimides. PS-EDC gave an average yield of 41% while PS-DCC gave only 26%, in comparison to the average 71% yield obtained with PS-IIDQ. Both supported carbodiimides were less efficient than PS-IIDQ, making PS-IIDQ a reagent of choice for parallel solution-phase libraries.

2.5. Scope and limitations of PS-IIDQ

Polymer-supported IIDQ was efficient even when using hindered substrates and to explore this in more detail a comprehensive study of the scope and limitations of the reagent was carried out (Table 6). All building blocks were commercially available, except H-Aib-OMe **33**, which was prepared following a literature procedure.[12] Coupling was realized using the optimized conditions, and any unreacted amine and carboxylic acid were removed either by ion-exchange resins (Amberlyst 15 and 26) or by an aqueous workup (entries 3, 9, 15, 21, 26, 29, and 34), depending on the presence of acidic or basic labile protecting groups on the amine and/or carboxylic acid. PS-IIDQ succeeded, in almost all cases, in coupling the amine to the acid in excellent purities. Yields were good even when coupling hindered substrates such as aminoisobutyric acid methyl ester to any of the different acids (entries 3, 9, 15, 21, and 29). Similarly, phenylglycine methyl ester was coupled to Z-Ala-OH or phenoxyacetic acid in high yield (entries 26 and 34). In addition secondary

Table 5. Comparison of PS-IIDQ with some commonly utilized coupling reagents

Entry		Amide	PS-IIDQ		HATU[c]		PS-EDC		PS-DCC	
			Yield[a]	Purity[b]	Yield[a]	Purity[b]	Yield[a]	Purity[b]	Yield[a]	Purity[b]
1	**28**		69	100	42	100	15	100	16	100
2	**29**		66	100	45	93	39	87	17	94
3	**30**		64	100	48	100	24	95	24	86
4	**10**		60	100	43	100	68	100	41	100
5	**11**		80	100	69	100	48	100	25	100
6	**31**		61	100	77	92	49	100	35	100
7	**13**		89	100	45	100	44	100	28	100
8	**14**		85	100	68	100	48	81	24	95
9	**32**		75	100	54	100	33	100	24	100
		Average	72	100	55	98	41	96	26	97

[a] Isolated yield.
[b] Purity determined by ELSD.
[c] A 5 min activation time was applied when using HATU.

amines were successfully coupled, including morpholine (entries 1, 7, 13, 19, and 27) and proline (entries 6, 12, and 18). PS-IIDQ did fail to couple 4-nitroaniline to any of the acids, which is perhaps not surprising as nitroanilines are some of the hardest amines to couple in view of the electron withdrawing nitro group. The yield was also very low when coupling aminoisobutyric acid to proline benzyl ester **61** (entry 6). Similarly, the amides obtained when coupling proline benzyl ester to phenylacetic acid and benzoic acid needed purification due to the formation of a carbamate by-product. However, the global library was successful as two thirds of the substrates gave the expected amides in yields over 67%, with an average yield of 73% for the reactions yielding the expected products (Fig. 6).

The formation of a carbamate by-product can occur during the PS-IIDQ mediated coupling once the carbonic anhydride **60** has been generated. The amine (proline benzyl ester **61**) can react at either of the two electrophilic centers, the carbon of the carboxylic acid, yielding the expected amide **62**, or at the carbon of the carbonic anhydride itself, yielding a carbamate **63** (Scheme 2). Compound **61** was coupled to 15 carboxylic acids with various groups in the α and β positions (Table 7) and the expected amide and the carbamate by-products **63** were separated by column chromatography after aqueous workup of the reaction mixtures. When the α-carbon

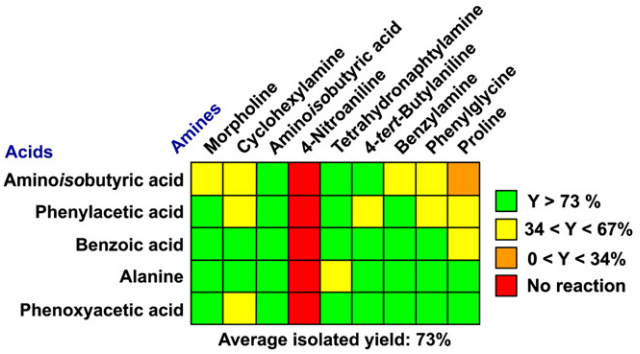
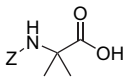
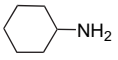
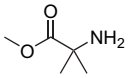
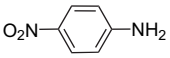
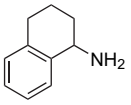
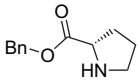
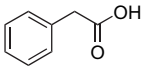
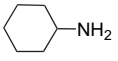
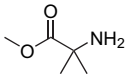
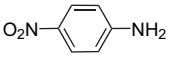
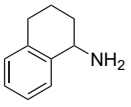
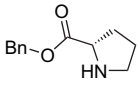
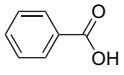
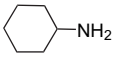
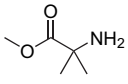
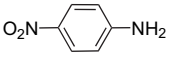
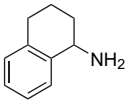
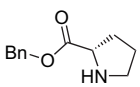
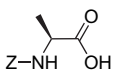
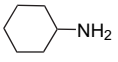
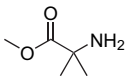


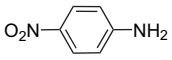
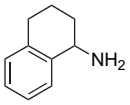
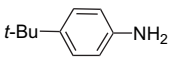
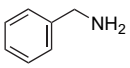
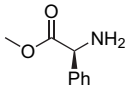
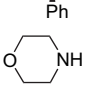
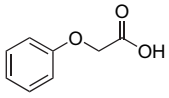
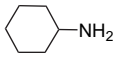
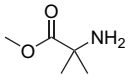
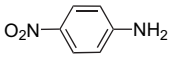
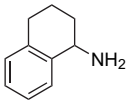
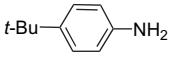
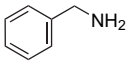
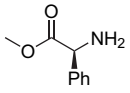
Figure 6. Library synthesis and overview of yields when using PS-IIDQ as the coupling reagent.

Table 6. Scope and limitation of PS-IIDQ

Entry	Amide	Amine	Carboxylic acid	Yield
1	**34**			44
2	**35**			61
3	**36**			67
4	**37**			0
5	**38**			74
6	**39**			3
7	**12**			77
8	**40**			44
9	**41**			73
10	**42**			0
11	**20**			74
12	**43**			60
13	**15**			77
14	**44**			84
15	**45**			91
16	**46**			0
17	**21**			83
18	**47**			34
19	**19**			79
20	**48**			71
21	**49**			82

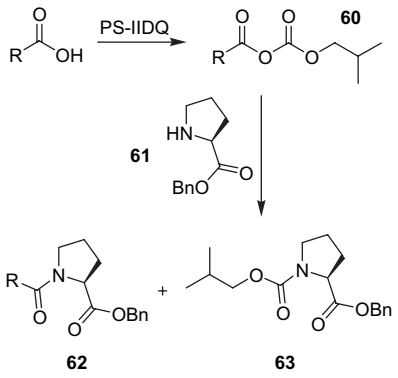
(*continued*)

Table 6. (*continued*)

Entry	Amide	Amine	Carboxylic acid	Yield
22	**50**			0
23	**18**			64
24	**16**			70
25	**17**			76
26	**51**			83
27	**52**			80
28	**53**			52
29	**54**			70
30	**55**			0
31	**56**			74
32	**57**			83
33	**58**			82
34	**59**			82

of the acid was not sterically too hindered, that is to say, when it was linked to just one group and two hydrogens, the major product obtained was the expected amide (entry 14). On the other hand when the α-carbon was more hindered (such as two methyl groups) the carbamate **63** was almost the exclusive product (entry 13). Benzoic acid (entry 15) gave intermediate results. The presence of bulky groups at the α position clearly increased the quantity of by-product (entry 5). One of the dominant effects seemed to be the presence of a methyl group in the α position, which increased dramatically by-product generation (compare entries 9 and 14), although two phenyl groups in the α position had little effect (entry 4).

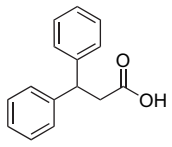
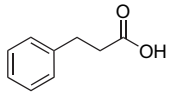
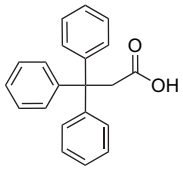
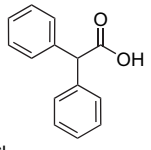
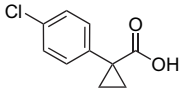
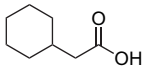
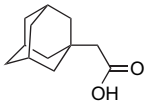
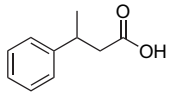
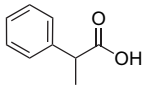
When going from a cyclohexyl to a cyclopentyl carboxylic acid group the percentages inverted (entries 10 and 11). This study showed a limitation of PS-IIDQ but no real rule could be established for the influence of groups on the carboxylic acid. However, this side-reaction was observed only with proline, other secondary amines were unaffected and we hypothesize that interactions with the proline ester with the mixed anhydride may be responsible for this alternative pathway.



Scheme 2. Side-reaction observed when coupling a carboxylic acid to proline benzyl ester using PS-IIDQ.

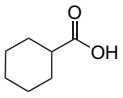
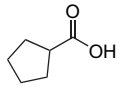
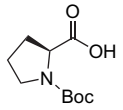
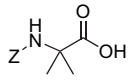
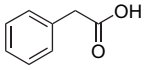
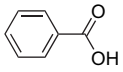
The above examples show that PS-IIDQ worked very efficiently for general amide bond formation. In order to apply PS-IIDQ for coupling amino-acids, the extent of epimerization during segment coupling had to be evaluated. The classic method to achieve this is to carry out the Anteunis test, via the coupling between Z-Gly–L-Phe-OH and H-L-Val-OMe.[13] This test is particularly robust as amide cyclization to give the oxazolone is a real issue for dipeptides. Coupling between Z-Gly–L-Phe-OH and H-L-Val-OMe with PS-IIDQ gave the expected tripeptide **76** in 65% yield without any epimerization detected by ^{1}H NMR (400 MHz) (the other isomer **77** was synthesized separately). This unambiguously confirmed the absence of epimerization with PS-IIDQ (Fig. 7).

Table 7. Evaluation of the influence of various carboxylic acids on the side-reaction observed with H-Pro-OBn **61**

Entry	Amide	Carboxylic acid	Amide yield	Carbamate yield	Relative percentage
1	**64**		43	24	64/36
2	**65**		76	13	85/15
3	**66**		18	74	20/80
4	**67**		50	20	71/29
5	**68**		35	51	41/59
6	**69**		66	22	75/25
7	**70**		48	37	56/44
8	**71**		57	17	77/23
9	**72**		35	24	59/41

(*continued*)

Table 7. (*continued*)

Entry	Amide	Carboxylic acid	Amide yield	Carbamate yield	Relative percentage
10	**73**		30	55	35/65
11	**74**		55	26	68/32
12	**75**		49	47	51/49
13	**39**		3	38	8/92
14	**43**		60	4	94/6
15	**47**		34	53	39/61

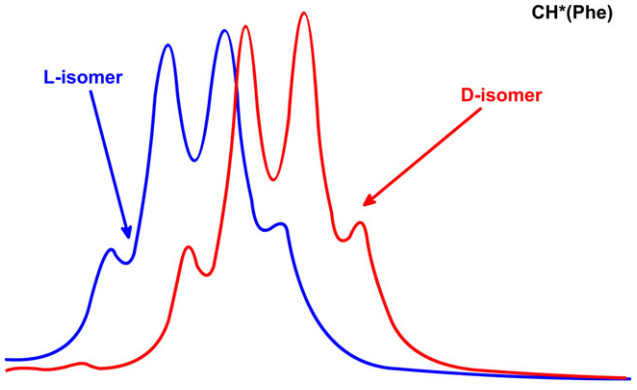


Figure 7. NMR evidence showing the absence of epimerization when using PS-IIDQ. The NMR resonances shown correspond to the CH-α group of the phenylalanine residue in the peptide Z-Gly-L-Phe-L-Val-OMe.

The possibility of recycling/regenerating PS-IIDQ was investigated. Thus the resin used for couplings was washed extensively with various solvents (THF/H_2O 1/1, MeOH, DCM, Et_2O). Then the procedure used previously to transform PS-quinoline into PS-IIDQ was applied, and the loading evaluated by coupling phenylacetic acid to benzylamine. The same regeneration process was carried out three times with little variation in loading levels (Table 8).

Table 8. Recycling of PS-IIDQ (loading was determined by saturation coupling of benzylamine with phenylacetic acid with a known mass of resin and thus sets the lower limit on available or practical resin loading)

Cycle	Loading (mmol/g)
1	≥1.68
2	≥1.71
3	≥1.65
4	≥1.64

3. Conclusion

PS-IIDQ is a high loading, efficient polymer-supported coupling reagent for general amide bond formation, including hindered substrates and anilines. It is also suitable for coupling of amino-acids as the epimerization levels were low. PS-IIDQ proved to be more efficient than other commercially available polymer-supported coupling reagents (PS-EDC, PS-DCC) and also better than the powerful and widely used HATU. One limitation of this new reagent was observed, but this was noticed only with proline. Stability, ease of recycling, convenient procedures for parallel amide bond formation, good yields, and high purities make PS-IIDQ a reagent of choice for N-acylation in organic chemistry, especially for parallel synthesis.[14]

4. Experimental

4.1. General

The reagents commercially available were used without further purification. Solvents were not dried or distilled except where specified. NMR spectra were recorded on Bruker DPX 400 and 300, or ARX 250 spectrometers in the solvents indicated at 298 K. Chemical shifts are reported on the δ scale in parts per million and are referenced to residual non-deuterated solvent resonances. All ^{13}C NMR experiments were supported with DEPT. IR spectra were obtained on a Thermo Mattson Satellite FTIR spectrometer or a Bruker Tensor 27 Spectrometer, with 16 scans, at a resolution of $\pm 4\ cm^{-1}$. The FTIR spectrometers were fitted with a Specac single reflection diamond ATR Golden Gate, and neat compounds or resins were used for analysis. Frequencies are reported in cm^{-1} and only frequencies corresponding to significant functional groups are reported. LC–mass spectra were recorded either on a Waters ZMD single quadrupole MS, with a 2700 Autosampler and a 600 Pump, or an Agilent Technologies LC/MSD 1100 Quadrupole Mass Spectrometer (QMS), both with an electrospray ion source. HPLC spectra were obtained on an Agilent 1100 coupled to a Polymer Lab 100 ES Evaporative Light Scattering Detector (ELSD), with a Phenomenex Luna C18, 5 μm, 10 cm column (column 1), a Phenomenex Gemini C18, 5 μm, 10 cm column (column 2), or a Phenomenex Luna C18, 5 μm, 15 cm column (column 3). HPLC grade water, MeOH or CH_3CN with 0.1% formic acid were used as eluants, at a flow rate of 1 mL/min, with samples prepared to a concentration of about 30 $\mu g\ mL^{-1}$ (ZMD) or 1 $mg\ mL^{-1}$ (Agilent) and filtered prior to injection. The following methods were used. Method A (column 1, H_2O/MeOH, 12 min): 0 min (95/5), 7 min (5/95), 9 min (5/95). Method B (column 2, H_2O/MeOH, 10 min): 0 min (95/5), 7 min (5/95), 9 min (5/95). Method C (column 3, H_2O/MeOH, 15 min): 0 min (95/5), 12 min (5/95), 14 min (5/95). Melting points (Pyrex capillaries) are uncorrected. HRMS analyses were performed by the Mass Spectrometry Service of the University of Southampton, UK. Elemental analyses were carried out by Medac Ltd, UK.

4.1.1. Synthesis of a library for comparison of IIDQ and EEDQ. The following mother solutions were prepared: *tert*-butyl aniline: 207 μL (0.5 mmol) in 5 mL CH_3CN (0.1 mmol/mL), benzylamine: 143 μL (0.5 mmol) in 5 mL CH_3CN (0.1 mmol/mL), morpholine: 114 μL (0.5 mmol) in 5 mL CH_3CN (0.1 mmol/mL), phenylacetic acid: 95 mg (0.7 mmol) in 7 mL CH_3CN (0.1 mmol/mL), benzoic acid: 85 mg (0.7 mmol) in 7 mL CH_3CN (0.1 mmol/mL), IIDQ: 212 mg (0.7 mmol) in 7 mL CH_3CN (0.1 mmol/mL), EEDQ: 172 mg (0.7 mmol) in 7 mL CH_3CN (0.1 mmol/mL). *Procedure*. In each vial, a solution of an amine (1 mL, 0.1 mmol, 1 equiv) and carboxylic acid (1 mL, 0.1 mmol, 1 equiv) were added, followed by the addition of a solution of a coupling reagent (1 mL, 0.1 mmol, 1 equiv). The 12 vials were shaken at room temperature for 16 h. The contents of the vials were filtered through an SPE cartridge containing a mixed bed of MP acidic/basic ion-exchange resins (Polymer Lab, 500 mg). The filtrates were concentrated in vacuo to afford the compounds listed below.

4.1.1.1. *N*-(4-*tert*-Butyl-phenyl)-2-phenyl-acetamide (10). The title compound was obtained as an off-white solid (25 mg, 96%). HPLC (method B): t_R=7.32 min. Purity (ELSD): 100%. ^1H NMR (250 MHz, $CDCl_3$): 7.48 (s, 1H, N*H*), 7.39–7.25 (m, 9H, Ar–*H*), 3.69 (s, 2H, CH_2), 1.28 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): 169.16 (C=O), 147.32 (C–Ar), 135.02 (C–Ar), 134.61 (CH–Ar), 129.38 (CH–Ar), 129.02 (CH–Ar), 127.42 (CH–Ar), 125.63 (CH–Ar), 119.71 (CH–Ar), 44.60 (CH_2), 34.27 ($C(CH_3)_3$), 31.27 (C(CH_3)$_3$). FTIR (neat): 3285 (m), 1655 (s). Mp: 146–148 °C (methanol). HRMS (ES): calcd for $C_{18}H_{21}NO$: 268.1696 $(M+H)^+$. Found: 268.1696.

4.1.1.2. *N*-Benzyl-2-phenyl-acetamide[15] (11). The title compound was obtained as a white solid (20 mg, 91%). HPLC (method A): t_R=7.66 min. Purity (ELSD): 96%. ^1H NMR (300 MHz, $CDCl_3$): 7.29–7.08 (m, 10H, Ar–*H*), 5.71 (br s, 1H, N*H*), 4.32 (d, *J*=5.7 Hz, 2H, NHCH_2), 3.53 (s, 2H, CH_2). *m/z* (ESMS): 226 $(M+H)^+$ (85%), 248 $(M+Na)^+$ (100%). Mp: 119–121 °C (ethanol, lit.:[15] 118–120 °C).

4.1.1.3. 4-Phenylacetyl-morpholine[16] (12). The title compound was obtained as a colorless oil (8 mg, 38%). HPLC (method C): t_R=8.11 min. Purity (ELSD): 100%. ^1H NMR (250 MHz, $CDCl_3$): 7.36–7.23 (m, 5H, Ar–*H*), 3.74 (s, 2H, Ar–CH_2), 3.65–3.46 (m, 8H, CH_2). *m/z* (ESMS): 206 $(M+H)^+$ (46%), 228 $(M+Na)^+$ (100%). Mp: 60–63 °C (ethanol, lit.:[16] 60–62 °C).

4.1.1.4. *N*-(4-*tert*-Butyl-phenyl)-benzamide[17] (13). The title compound was obtained as a white solid (22 mg, 88%). HPLC (method B): t_R=7.29 min. Purity (ELSD): 100%. ^1H NMR (250 MHz, $CDCl_3$): 7.96 (br s, 1H, N*H*), 7.87–7.84

(m, 2H, OC–C–CH), 7.59–7.35 (m, 7H, Ar–*H*), 1.32 (s, 9H, C(CH_3)$_3$). *m*/*z* (ESMS): 254 (M+H)$^+$ (65%), 276 (M+Na)$^+$ (61%), 529 (2M+Na)$^+$ (100%). Mp: 142–143 °C (ethanol, lit.:[18] 143–144 °C).

4.1.1.5. *N*-Benzyl-benzamide[19] (14). The title compound was obtained as a white solid (18 mg, 85%). HPLC (method A): t_R=7.52 min. Purity (ELSD): 100%. ^{1}H NMR (300 MHz, $CDCl_3$): 7.74–7.71 (m, 2H, OC–C–CH), 7.46–7.19 (m, 8H, Ar–H), 6.51 (br s, 1H, N*H*), 4.56 (d, *J*=5.7 Hz, 2H, CH_2). *m*/*z* (ESMS): 212 (M+H)$^+$ (72%), 234 (M+Na)$^+$ (100%). Mp: 106–107 °C (ethanol, lit.:[20] 105–106 °C).

4.1.1.6. 4-Benzoyl-morpholine[21] (15). The title compound was obtained as a white solid (9 mg, 50%). HPLC (method C): t_R=7.59 min. Purity (ELSD): 100%. ^{1}H NMR (300 MHz, $CDCl_3$): 7.42–7.37 (m, 5H, Ar–*H*), 3.85–3.44 (m, 8H, CH_2). *m*/*z* (ESMS): 192 (M+H)$^+$ (100%). Mp: 73–74 °C (ethanol, lit.:[21] 72 °C).

4.1.2. Synthesis of the library and comparison of IIDQ, PyAOP, BOP-Cl and HATU. The following mother solutions were prepared: *tert*-butyl aniline: 207 μL (1.3 mmol) in 13 mL CH_3CN (0.1 mmol/mL), benzylamine: 143 μL (1.3 mmol) in 13 mL CH_3CN (0.1 mmol/mL), 1,2,3,4-tetrahydro-naphthalen-1-ylamine: 137 μL (1.3 mmol) in 13 mL CH_3CN (0.1 mmol/mL), morpholine: 114 μL (1.3 mmol) in 13 mL CH_3CN (0.1 mmol/mL), Z-Ala-OH: 469 mg (2.1 mmol) in 21 mL CH_3CN (0.1 mmol/mL), phenylacetic acid: 285 mg (2.1 mmol) in 21 mL CH_3CN (0.1 mmol/mL), benzoic acid: 257 mg (2.1 mmol) in 21 mL CH_3CN (0.1 mmol/mL), IIDQ: 485 mg (1.6 mmol) in 16 mL CH_3CN (0.1 mmol/mL), PyAOP: 836 mg (1.6 mmol) in 16 mL CH_3CN (0.1 mmol/mL), BOP-Cl: 407 mg (1.6 mmol) in 16 mL CH_3CN (0.1 mmol/mL), HATU: 608 mg (1.6 mmol) in 16 mL CH_3CN (0.1 mmol/mL). *Procedure*. In each vial, a solution of an amine (1 mL, 0.1 mmol, 1 equiv) and of a carboxylic acid (1 mL, 0.1 mmol, 1 equiv) were added, followed by the addition of a coupling reagent (1 mL, 0.1 mmol, 1 equiv). The 48 vials were shaken at room temperature for 16 h. The contents of the vials were then filtered through an SPE cartridge containing a mixed bed of MP acidic/basic ion-exchange resins (Polymer Lab, 500 mg). The filtrates were concentrated in vacuo to afford the compounds listed below.

4.1.2.1. [(*S*)-1-(4-*tert*-Butyl-phenylcarbamoyl)-ethyl]-carbamic acid benzyl ester (16). The title compound was obtained as a pale orange solid (33 mg, 93%). HPLC (method C): t_R=10.96 min. Purity (ELSD): 100%. ^{1}H NMR (250 MHz, $CDCl_3$): 8.38 (br s, 1H, Ar–N*H*), 7.49–7.28 (m, 9H, Ar–*H*), 5.62 (br d, *J*=7.5 Hz, 1H, CH–N*H*), 5.12 (AB-d, *J*=12.25 Hz, 2H, OCH_2), 4.49–4.38 (m, 1H, C*H*), 1.45 (d, *J*=7.2 Hz, 3H, CH_3), 1.29 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): 170.44 (C=O), 156.33 (C=O), 147.40 (C–Ar), 135.99 (C–Ar), 134.96 (C–Ar), 128.54 (CH–Ar), 128.22 (CH–Ar), 127.97 (CH–Ar), 125.70 (CH–Ar), 119.77 (CH–Ar), 67.22 (CH_2), 51.21 (CH), 34.33 (*C*(CH_3)$_3$), 31.32 (C(*C*H_3)$_3$), 18.296 (CH_3). FTIR (neat): 3294 (w), 3264 (w), 1689 (s), 1661 (s). Mp: 85–88 °C (methanol). HRMS (ES): calcd for $C_{21}H_{26}N_2O_3$: 355.2016 (M+H)$^+$. Found: 355.2016.

4.1.2.2. ((*S*)-1-Benzylcarbamoyl-ethyl)-carbamic acid benzyl ester (17). The title compound was obtained as a white solid (27 mg, 86%). HPLC (method C): t_R=9.77 min. Purity (ELSD): 100%. ^{1}H NMR (300 MHz, $CDCl_3$): 7.38–7.21 (m, 10H, Ar–*H*), 6.61 (br s, 1H, N*H*), 5.46 (br d, *J*=7.2 Hz, 1H, NH), 5.03 (AB-d, *J*=12.5 Hz, 2H, OCH_2), 4.40 (dd, *J*=2.2 Hz and 5 Hz, 2H, NHCH_2), 4.35–4.22 (m, 1H, C*H*), 1.39 (d, *J*=7.0 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 172.34 (C=O), 155.97 (C=O), 137.88 (C–Ar), 136.05 (C–Ar), 128.57 (CH–Ar), 128.43 (CH–Ar), 128.10 (CH–Ar), 127.88 (CH–Ar), 127.49 (CH–Ar), 127.37 (CH–Ar), 66.87 (OCH_2), 50.52 (CH), 43.36 ($NHCH_2$), 18.71 (CH_3). FTIR (neat): 3297 (w), 3279 (m), 1684 (s), 1640 (s). Mp: 129–131 °C (methanol). HRMS (ES): calcd for $C_{18}H_{20}N_2O_3$: 313.1547 (M+H)$^+$. Found: 313.1547.

4.1.2.3. [(*S*)-1-(1,2,3,4-Tetrahydro-naphthalen-1-yl-carbamoyl)-ethyl]-carbamic acid benzyl ester (18). The title compound was obtained as a white solid (25 mg, 71%). HPLC (method C): t_R=10.55 min. Purity (ELSD): 100%. ^{1}H NMR (300 MHz, $CDCl_3$): 7.37–7.05 (m, 9H, Ar–*H*), 6.44 (br s, 1H, N*H*), 5.48 (br s, 1H, NH), 5.12 (m, 1H, NHC*H* naphthyl), 4.99 (s, 2H, OCH_2), 4.26 (m, 1H, C*H**), 2.78–2.69 (m, 2H, Ar–CH_2 naphthyl), 2.02–1.97 (m, 1H, CH naphthyl), 1.82–1.78 (m, 3H, CH naphthyl), 1.42 (dd, *J*=6.9 Hz and 3.3 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 171.49 (C=O), 155.84 (C=O), 137.50 (C–Ar), 136.32 (C–Ar), 136.18 (C–Ar), 129.14 (CH–Ar), 128.47 (CH–Ar), 128.41 (CH–Ar), 128.14 (CH–Ar), 127.96 (CH–Ar), 127.30 (CH–Ar), 127.26 (CH–Ar), 126.26 (CH–Ar), 66.91 (OCH_2), 50.68 (CH naphthyl), 47.54 (CH*), 30.10 (CH_2), 29.16 (CH_2), 19.99 (CH_2), 18.94 (CH_3). FTIR (neat): 3289 (m), 1687 (s), 1639 (s). Mp: 130–132 °C (methanol). HRMS (ES): calcd for $C_{21}H_{24}N_2O_3$: 353.1865 (M+H)$^+$. Found: 353.1862.

4.1.2.4. ((*S*)-1-Methyl-2-morpholin-4-yl-2-oxo-ethyl)-carbamic acid benzyl ester (19). The title compound was obtained as a white solid (20 mg, 69%). HPLC (method C): t_R=8.72 min. Purity (ELSD): 100%. ^{1}H NMR (300 MHz, $CDCl_3$): 7.34–7.29 (m, 5H, Ar–*H*), 5.83 (d, *J*=6.9 Hz, 1H, N*H*), 5.09 (s, 2H, Ar–CH_2), 4.64 (quint., *J*=6.0 Hz, 1H, C*H*), 3.73–3.43 (m, 8H, CH_2 morpholine), 1.32 (d, *J*=6.9 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 170.89 (C=O), 155.51 (C=O), 136.35 (C–Ar), 128.46 (CH–Ar), 128.06 (CH–Ar), 127.99 (CH–Ar), 66.73 (OCH_2 morpholine), 66.47 (OCH_2Ph), 46.49 (CH), 45.882 (N–CH_2), 19.23 (CH_3). FTIR (neat): 3307 (w), 3289 (w), 1711 (s), 1638 (s). Mp: 134–136 °C (ethanol). HRMS (ES): calcd for $C_{15}H_{20}N_2O_4$: 293.1496 (M+H)$^+$. Found: 293.1494.

4.1.2.5. 2-Phenyl-*N*-(1,2,3,4-tetrahydro-naphthalen-1-yl)-acetamide (20). The title compound was obtained as a white solid (16 mg, 59%). HPLC (method C): t_R=10.36 min. Purity (ELSD): 100%. ^{1}H NMR (400 MHz, $CDCl_3$): 7.33–7.04 (m, 9H, Ar–*H*), 5.63 (br s, 1H, N*H*), 5.20–5.15 (m, 1H, NHC*H* naphthyl), 3.62 (s, 2H, Ar–CH_2–CO), 2.74–2.72 (m, 2H, Ar–CH_2 naphthyl), 2.07–2.00 (m, 1H, CH naphthyl), 1.82–1.63 (m, 3H, CH naphthyl). ^{13}C NMR (75 MHz, $CDCl_3$): 170.30 (C=O), 137.49 (C–Ar), 136.54 (C–Ar), 134.86 (C–Ar), 129.28 (CH–Ar), 129.08 (CH–Ar), 128.96 (CH–Ar), 128.16 (CH–Ar),

127.28 (CH–Ar), 127.16 (CH–Ar), 126.17 (CH–Ar), 47.68 (CH), 43.99 (Ph–CH_2), 30.17 (CH_2), 29.14 (CH_2), 20.12 (CH_2). *m/z* (ESMS): 266 $(M+H)^+$ (43%), 288 $(M+Na)^+$ (100%). FTIR (neat): 3264 (m), 1631 (s). Mp: 124–125 °C (methanol). Anal. Calcd for $C_{18}H_{19}NO$: C: 81.48, H: 7.22, N: 5.28. Found: C: 81.23, H: 7.22, N: 5.30.

4.1.2.6. *N*-(1,2,3,4-Tetrahydro-naphthalen-1-yl)-benzamide (21). The title compound was obtained as a white solid (18 mg, 67%). HPLC (method C): t_R=10.33 min. Purity (ELSD): 100%. ^{1}H NMR (300 MHz, $CDCl_3$): 7.78 (m, 2H, OC–C–CH), 7.52–7.12 (m, 7H, Ar–*H*), 6.38 (br s, 1H), 5.43–5.36 (m, 1H, NHC*H* naphthyl), 2.90–2.75 (m, 2H, Ar–CH_2 naphthyl), 2.20–2.13 (m, 1H, CH naphthyl), 1.99–1.85 (m, 3H, CH naphthyl). ^{13}C NMR (75 MHz, $CDCl_3$): 166.65 (C=O), 137.69 (C–Ar), 136.63 (C–Ar), 134.65 (C–Ar), 131.41 (CH–Ar), 129.22 (CH–Ar), 128.73 (CH–Ar), 128.52 (CH–Ar), 127.34 (CH–Ar), 126.90 (CH–Ar), 126.32 (CH–Ar), 47.94 (CH), 30.18 (CH_2), 29.26 (CH_2), 20.05 (CH_2). FTIR (neat): 3301 (m), 1632 (s). Mp: 122–125 °C (ethanol). HRMS (ES): calcd for $C_{17}H_{17}NO$: 274.1202 $(M+H)^+$. Found: 274.1206.

4.1.3. Polymer-supported quinoline (24). Merrifield resin (25 g, Polymer Lab, 3.99 mmol/g, 99.8 mmol, 1 equiv) was swollen in DMA (250 mL). K_2CO_3, (69 g, 499 mmol, 5 equiv), 6-hydroxyquinoline (36.2 g, 249 mmol, 2.5 equiv), and a catalytic amount of KI were added and the reaction mixture was heated at reflux with mechanical agitation for 6 h. The resin was collected by filtration and washed successively with THF/H_2O (1/1, 3×250 mL), THF (3×250 mL), DCM (3×250 mL), MeOH (3×250 mL), DCM (3×250 mL), MeOH (3×250 mL), Et_2O (3×250 mL). ^{1}H MAS-NMR+^{1}H–^{1}H COSY (400 MHz, $CDCl_3$): 8.75 (N–C*H*), 8.05–7.96 (N–CH–CH–C*H* and N–C–C*H*), 5.04 (OCH_2). FTIR (neat): 1622 (w), 1223 (m), 1016 cm^{-1} (w). Loading of polymer-supported quinoline: determined by nitrogen elemental analysis (C: 88.6, H: 7.18, N: 1.54, Cl: 0.20): 2.74 mmol/g (98%).

4.1.4. 6-Benzyloxyquinoline (25). 6-Hydroxyquinoline (5 g, 1 equiv, 34.4 mmol) was dissolved in DMF (30 mL). K_2CO_3 (23.8 g, 5 equiv, 172 mmol) was introduced and the reaction mixture was stirred for 1 h. Benzyl chloride (4 mL, 1 equiv, 34.4 mmol) was added and the mixture was stirred at 80 °C for 24 h. DMF was evaporated under reduced pressure yielding a dark brown solid. This solid was suspended in water (150 mL) and DCM (250 mL) and the insoluble impurities were filtered off. The water phase was extracted three times with DCM (50 mL). The combined organic phases were washed with brine (100 mL), dried over Na_2SO_4, and evaporated in vacuo. The brown solid obtained was extracted with petroleum ether at 50 °C. Evaporation of the petroleum ether yielded 6-benzyloxyquinoline as a pale yellow powder (3.78 g, 47%). HPLC (method B): t_R=7.24 min. Purity (ELSD): 98%. ^{1}H NMR (400 MHz, $CDCl_3$): 8.79 (dd, 1H, *J*=4.4 Hz and 1.5 Hz, N–C*H*), 8.05 (dd, 1H, *J*=8.1 Hz and 1.5 Hz, N–CH–CH–C*H*), 8.04 (d, 1H, *J*=8.8 Hz, N–C–C*H*), 7.52–7.34 (m, 7H, Ar–*H*), 7.17 (d, 1H, *J*=2.9 Hz, O–C–C*H*–C), 5.20 (s, 2H, OCH_2). ^{13}C NMR (100 MHz, $CDCl_3$): 157.3 (O–C–Ar), 148.5 (N–CH–Ar), 144.9 (C–Ar), 136.9 (C–Ar), 135.3 (CH–Ar), 131.4 (CH–Ar), 129.7 (CH–Ar), 129.1 (C–Ar), 128.6 (CH–Ar), 127.9 (CH–Ar), 123.0 (CH–Ar), 121.8 (CH–Ar), 107.0 (CH–Ar), 70.7 (OCH_2). *m/z* (EIMS): 235.13 (M^+) (100%). FTIR (neat): 1618 (m), 1225 (m), 1019 (m). Mp: 66–68 °C (ethanol). Anal. Calcd for $C_{16}H_{13}NO$: C: 81.68, H: 5.57, N: 5.95. Found: C: 81.46, H: 5.63, N: 5.95.

4.1.5. Polymer-supported IIDQ (27). PS-quinoline (20 g, 2.74 mmol/g, 54.8 mmol, 1 equiv) was swollen in dry DCM (200 mL). DIPEA (27 mL, 164 mmol, 3 equiv) was added and the mixture was mechanically stirred and cooled to 0 °C. Isobutyl chloroformate (21.4 mL, 164 mmol, 3 equiv) was added dropwise to the reaction mixture. After 3 h, isobutanol (100 mL) was added, the mixture allowed to warm to room temperature, and stirred mechanically for 16 h. The resin was then collected by filtration and washed successively with three cycles of DCM, DCM/Et_2O, Et_2O (200 mL each). ^{1}H MAS-NMR (400 MHz, $CDCl_3$): 7.80 (N–C–C*H*), 6.22 (N–CH–C*H*), 4.80 (OCH_2–PS), 4.00 (CO_2CH_2), 3.32 (OCH_2CH), 1.97 ($CO_2CH_2CH(CH_3)_2$), 1.74 ($OCH_2CH(CH_3)_2$), 0.95 ($CO_2CH_2CH(CH_3)_2$), 0.83 ($OCH_2CH(CH_3)_2$). FTIR (neat): 1709 (s), 1265 (s), 1018 (m). *Determination of IIDQ loading*. Phenylacetic acid (765 mg, 5.62 mmol, 3 equiv) and benzylamine (614 μL, 5.62 mmol, 3 equiv) were dissolved in DCM (5 mL). PS-IIDQ (maximum loading 1.87 mmol/g, 1.0 g, 1.87 mmol) was added and the reaction mixture was shaken at room temperature for 16 h. The resin was removed by filtration and washed with DCM/MeOH (three cycles of 5 mL). The filtrates were combined and concentrated in vacuo. The residue was taken up in EtOAc (50 mL), washed with 1 M HCl (3×20 mL), 1 M $NaHCO_3$ (3×20 mL), brine (1×20 mL), dried over $MgSO_4$, and concentrated in vacuo to give 2-phenyl-benzylacetamide as a white powder (370 mg, 88%). The yield of the reaction was related to the loading of the resin (*loading=yield×theoretical loading=0.88×1.87=1.68 mmol/g*) and assumes no losses during the reaction and its workup and thus represents the lower limit of resin loading.

4.1.6. General procedure for using PS-IIDQ as coupling reagent. To a solution of amine (1 equiv) and carboxylic acid (1 equiv) in CH_3CN was added PS-IIDQ (2 equiv). The reaction mixture was shaken at room temperature for 24 h. The resin was then removed by filtration, and washed with DCM/MeOH (three cycles). The filtrates were concentrated in vacuo and the unreacted amine and carboxylic acid removed either by an aqueous workup (EtOAc, 1 M HCl, 1 M $NaHCO_3$) or by using SPE cartridges containing a mixed bed of acidic/basic MP ion-exchange resin (Polymer Lab, 500 mg).

4.1.6.1. [1-(4-*tert*-Butyl-phenylcarbamoyl)-1-methyl-ethyl]-carbamic acid *tert*-butyl ester (28). The title compound was prepared according to the general procedure of coupling with PS-IIDQ and obtained as a white solid (62 mg, 69%). HPLC (method A): t_R=9.13 min. Purity (ELSD): 100%. ^{1}H NMR (250 MHz, $CDCl_3$): 7.47–7.30 (m, 4H, Ar–*H*), 4.93 (br s, 1H, N*H*), 1.55 (s, 6H, $C(CH_3)_2$), 1.44 (s, 9H, Ar–$C(CH_3)_3$), 1.30 (s, 9H, $OC(CH_3)_3$). ^{13}C NMR (62.5 MHz, $CDCl_3$): 172.55 (C=O), 155.27 (C=O), 146.93 (C–Ar), 135.54 (C–Ar), 125.72 (CH–Ar), 119.53 (CH–Ar), 80.27 ($OC(CH_3)_3$), 57.64 (NH–$C(CH_3)_2$), 34.32 (Ar–$C(CH_3)_3$), 31.35 (Ar–$C(CH_3)_3$), 28.25 ($OC(CH_3)_3$),

25.73 ($C(CH_3)_2$). FTIR (neat): 3315 (m), 1686 (s), 1596 (m). Mp: 148–151 °C (methanol). HRMS (ES): calcd for $C_{19}H_{30}N_2O_3$: 335.2329 $(M+H)^+$. Found: 335.2328.

4.1.6.2. (1-Benzylcarbamoyl-1-methyl-ethyl)-carbamic acid *tert*-butyl ester (29). The title compound was prepared according to the general procedure of coupling with PS-IIDQ and obtained as a white solid (52 mg, 66%). HPLC (method B): t_R=7.47 min. Purity (ELSD): 99%. ^{1}H NMR (300 MHz, $CDCl_3$): 7.26–7.17 (m, 5H, Ar–*H*), 6.70 (br s, 1H, NH), 4.86 (br s, 1H), 4.37 (d, *J*=5.4 Hz, 2H, CH_2), 1.44 (s, 6H, $C(CH_3)_2$), 1.33 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (75 MHz, $CDCl_3$): 174.45 (C=O), 154.69 (C=O), 138.36 (C–Ar), 128.57 (CH–Ar), 127.62 (CH–Ar), 127.29 (CH–Ar), 80.23 ($OC(CH_3)_3$), 56.83 ($C(CH_3)_2$), 43.69 (CH_2), 28.23 ($OC(CH_3)_3$), 25.77 ($C(CH_3)_2$). FTIR (neat): 3350 (m), 3292 (m), 1682 (s), 1654 (s). Mp: 135–138 °C (methanol). HRMS (ES): calcd for $C_{16}H_{24}N_2O_3$: 293.1860 $(M+H)^+$. Found: 293.1862.

4.1.6.3. (*R*)-(2-*tert*-Butoxycarbonylamino-2-methyl propionylamino)-phenyl-acetic acid methyl ester (30). The title compound was prepared according to the general procedure of coupling with PS-IIDQ and obtained as a white solid (60 mg, 64%). HPLC (method A): t_R=8.02 min. Purity (ELSD): 100%. ^{1}H NMR (300 MHz, $CDCl_3$): 7.50 (br s, 1H, NH), 7.38–7.29 (m, 5H, Ar–*H*), 5.54 (d, *J*=7.2 Hz, 1H, C*H*), 4.92 (br s, 1H, NH), 3.71 (s, 3H, CH_3), 1.48 (d, *J*=6.0 Hz, 6H, $C(CH_3)_2$), 1.39 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (75 MHz, $CDCl_3$): 173.96 (C=O), 171.27 (C=O), 154.64 (C=O), 136.57 (C–Ar), 128.82 (CH–Ar), 128.34 (CH–Ar), 127.17 (CH–Ar), 80.32 ($OC(CH_3)_3$), 56.75 ($C(CH_3)_2$), 56.52 (CH), 52.64 (OCH_3), 28.18 ($OC(CH_3)_3$), 25.32 ($C(CH_3)_2$). FTIR (neat): 3320 (m), 1748 (m), 1684 (s), 1657 (s). Mp: 104–108 °C (methanol). HRMS (ES): calcd for $C_{18}H_{26}N_2O_5$: 351.1915 $(M+H)^+$. Found: 351.1918.

4.1.6.4. (*S*)-Phenyl-phenylacetylamino-acetic acid methyl ester (31). The title compound was prepared according to the general procedure of coupling with PS-IIDQ and obtained as a white solid (46 mg, 61%). HPLC (method B): t_R=6.50 min. Purity (ELSD): 100%. ^{1}H NMR (300 MHz, $CDCl_3$): 7.31–7.15 (m, 10H, Ar–*H*), 6.41 (d, *J*=6.3 Hz, 1H, N*H*), 5.48 (d, *J*=7.2 Hz, 1H, C*H*), 3.60 (s, 3H, CH_3), 3.53 (s, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): 171.18 (C=O), 170.21 (C=O), 136.32 (C–Ar), 134.39 (C–Ar), 129.31 (CH–Ar), 128.93 (CH–Ar), 128.87 (CH–Ar), 128.45 (CH–Ar), 127.36 (CH–Ar), 127.07 (CH–Ar), 56.40 (CH), 52.71 (OCH_3), 43.39 (CH_2). FTIR (neat): 3303 (m), 1740 (s), 1647 (s). Mp: 96–98 °C (methanol). HRMS: calcd for $C_{17}H_{17}NO_3$: 284.1281 $(M+H)^+$. Found: 284.1283.

4.1.6.5. (*S*)-Benzoylamino-phenyl-acetic acid methyl ester[22] (32). The title compound was prepared according to the general procedure of coupling with PS-IIDQ and obtained as a white solid (54 mg, 75%). HPLC (method C): t_R=9.38 min. Purity (ELSD): 100%. ^{1}H NMR (250 MHz, $CDCl_3$): 7.85–7.80 (m, 2H, OC–C–CH), 7.55–7.30 (m, 8H, Ar–H), 7.19 (br d, *J*=6.3 Hz, 1H, N*H*), 5.78 (d, *J*=7.2 Hz, 1H, C*H*), 3.77 (s, 3H, CH_3). *m/z* (ESMS): 270 $(M+H)^+$ (27%), 292 $(M+Na)^+$ (100%). Mp: 104–105 °C (ethanol, lit.:[22] 104–105 °C).

4.1.6.6. Aminoisobutyric acid methyl ester hydrochloride[12] (33). To a solution of aminoisobutyric acid (5 g, 48.5 mmol, 1 equiv) in MeOH (50 mL) was added dropwise at 0 °C thionyl chloride (5.5 mL, 242 mmol, 5 equiv). After completion of the addition, the solution was allowed to warm up to room temperature and stirred for 5 h. The volatiles were then evaporated in vacuo. The residue was taken up in MeOH and crystallized upon addition of Et_2O. The solid collected by filtration, washed with Et_2O, and dried in vacuo to afford the title compound as white crystals (6.46 g, 87%). ^{1}H NMR (300 MHz, DMSO-d_6): 8.70 (br s, 2H, NH_2), 3.76 (s, 3H, CH_3), 1.63 (s, 6H, $C(CH_3)_2$). *m/z* (ESMS): 118 $(M+H)^+$ (100%). Mp: 183–185 °C (ethanol, lit.:[28] 185–185.5 °C).

4.1.6.7. (1,1-Dimethyl-2-morpholin-4-yl-2-oxo-ethyl)-carbamic acid benzyl ester (34). The title compound was prepared according to the general procedure of coupling with PS-IIDQ and obtained as a white solid (40 mg, 44%). HPLC (method B): t_R=7.918 min. Purity (ELSD): 100%. ^{1}H NMR (250 MHz, $CDCl_3$): 7.36–7.30 (m, 5H, Ar–*H*), 5.49 (br s, 1H, N*H*), 5.06 (s, 2H, Ar–CH_2), 3.64–3.42 (m, 8H, CH_2 morpholine), 1.52 (s, 6H, $C(CH_3)_2$). ^{13}C NMR (62.5 MHz, $CDCl_3$): 171.17 (C=O), 154.18 (C=O), 136.20 (C–Ar), 128.47 (CH–Ar), 128.35 (CH–Ar), 128.27 (CH–Ar), 66.53 (CH_2OCH_2, Ar–CH_2–O), 56.76 ($C(CH_3)_2$), 45.59 (N–CH_2), 25.98 ($C(CH_3)_2$). FTIR (neat): 3306 (w), 3265 (m), 1714 (s), 1605 (s). Mp: 135–141 °C (methanol). HRMS (ES): calcd for $C_{16}H_{22}N_2O_4$: 307.1652 $(M+H)^+$. Found: 307.1650.

4.1.6.8. [1-(Cyclohexylmethyl-carbamoyl)-1-methyl-ethyl]-carbamic acid benzyl ester (35). The title compound was prepared according to the general procedure of coupling with PS-IIDQ and obtained as a white solid (58 mg, 61%). HPLC (method C): t_R=10.32 min. Purity (ELSD): 100%. ^{1}H NMR (400 MHz, $CDCl_3$): 7.28–7.24 (m, 5H, Ar–H), 6.03 (s, 1H, NH), 5.26 (s, 1H, NH), 5.01 (s, 2H, Ar–CH_2), 3.64 (m, 1H, C*H*), 1.74–0.99 (m, 10H, CH_2 *c*-Hex), 1.43 (s, 6H, $C(CH_3)_2$). ^{13}C NMR (100 MHz, $CDCl_3$): 173.21 (C=O), 155.03 (C=O), 136.30 (C–Ar), 128.50 (CH–Ar), 128.15 (CH–Ar), 128.09 (CH–Ar), 66.66 (OCH_2), 56.86 ($C(CH_3)_2$), 48.23 (CH), 32.77 (CH_2), 25.69 ($C(CH_3)_2$), 25.52 (CH_2), 24.66 (CH_2). *m/z* (ESMS): 319 $(M+H)^+$ (30%), 341 $(M+Na)^+$ (100%). FTIR (neat): 3341 (w), 3296 (m), 1699 (s), 1649 (s). Mp: 121–122 °C (methanol). Anal. Calcd for $C_{18}H_{26}N_2O_3$: C: 67.90, H: 8.23, N: 8.79. Found: C: 67.78, H: 8.28, N: 8.78.

4.1.6.9. 2-(2-Benzyloxycarbonylamino-2-methyl-propionylamino)-2-methyl-propionic acid methyl ester[23] (36). The title compound was prepared according to the general procedure of coupling with PS-IIDQ and obtained as a white solid (67 mg, 67%). HPLC (method C): t_R=9.35 min. Purity (ELSD): 100%. ^{1}H NMR (300 MHz, $CDCl_3$): 7.36–7.26 (m, 5H, Ar–*H*), 6.90 (br s, 1H, NH), 5.32 (br s, 1H, NH), 5.09 (s, 2H, CH_2), 3.71 (s, 3H, OCH_3), 1.50 (s, 12H, $C(CH_3)_2$). *m/z* (ESMS): 337 $(M+H)^+$ (20%), 359 $(M+Na)^+$ (100%). Mp: 108–109 °C (ethanol, lit.:[23] 109–110 °C).

4.1.6.10. [1-Methyl-1-(1,2,3,4-tetrahydro-naphthalen-1-ylcarbamoyl)-ethyl]-carbamic acid benzyl ester (38).

The title compound was prepared according to the general procedure of coupling with PS-IIDQ and obtained as a white solid (81 mg, 74%). HPLC (method C): t_R=10.63 min. Purity (ELSD): 100%. ^{1}H NMR (300 MHz, $CDCl_3$): 7.32–7.08 (m, 9H, Ar–*H*), 6.40 (br d, *J*=7.8 Hz, 1H, N*H*–CH), 5.34 (br s, 1H, N*H*), 5.14–5.09 (m, 1H, NHC*H* naphthyl), 5.07 (s, 2H, OCH_2), 2.84–2.68 (m, 2H, Ar–CH_2 naphthyl), 2.02–1.99 (m, 1H, CH naphthyl), 1.80–1.69 (m, 3H, CH naphthyl), 1.55 (s, 6H, C(CH_3)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$): 173.42 (C=O), 154.85 (C=O), 137.59 (C–Ar), 136.62 (C–Ar), 136.14 (C–Ar), 129.09 (CH–Ar), 128.50 (CH–Ar), 128.150 (CH–Ar), 128.08 (CH–Ar), 127.17 (CH–Ar), 126.23 (CH–Ar), 66.71 (OCH_2), 56.92 (*C*(CH$_3$)$_2$), 47.67 (CH), 30.00 (CH_2), 29.23 (CH_2), 25.53 (C(*C*H$_3$)$_2$), 20.04 (CH_2). FTIR (neat): 3351 (w), 3286 (m), 1694 (s), 1645 (s). Mp: 119–121 °C (ethanol). HRMS (ES): calcd for $C_{22}H_{26}N_2O_3$: 367.2016 (M+H)$^+$. Found: 367.2018.

4.1.6.11. (*S*)-1-(2-Benzyloxycarbonylamino-2-methyl-propionyl)-pyrrolidine-2-carboxylic acid benzyl ester (39). The title compound was prepared according to the general procedure of coupling with PS-IIDQ, separated from the carbamate by-product by column chromatography (hexane/EtOAc 6/4), and was obtained as a colorless oil (4 mg, 3%). In the case of amides derived from proline, the presence of multiple rotamers[24] made the NMR spectra poorly significant to report. However, compound **63** was fully characterized using NMR at higher temperature. HPLC (method B): t_R=6.32 min. Purity (ELSD): 100%. FTIR (neat): 3277 (m), 1739 (s), 1702 (s), 1621 (s). HRMS (ES): calcd for $C_{21}H_{30}N_2O_5$: 391.2228 (M+H)$^+$. Found: 391.2231.

4.1.6.12. *N*-Cyclohexylmethyl-2-phenyl-acetamide (40). The title compound was prepared according to the general procedure of coupling with PS-IIDQ and obtained as a white solid (29 mg, 44%). HPLC (method C): t_R= 9.96 min. Purity (ELSD): 100%. ^{1}H NMR (300 MHz, $CDCl_3$): 7.27–7.16 (m, 5H, Ar–*H*), 5.22 (br s, 1H, NH), 3.73–3.63 (m, 1H, C*H*), 3.46 (s, 2H, Ar–CH_2), 1.79–0.88 (m, 10H, CH_2 *c*-Hex). ^{13}C NMR (75 MHz, $CDCl_3$): 169.93 (C=O), 135.16 (C–Ar), 129.29 (CH–Ar), 128.89 (CH–Ar), 127.17 (CH–Ar), 48.12 (Ph–CH_2), 43.96 (CH), 32.85 (CH_2), 25.42 (CH_2), 24.64 (CH_2). FTIR (neat): 3267 (m), 1665 (s). Mp: 125–127 °C (methanol). HRMS (ES): calcd for $C_{14}H_{19}NO$: 218.1540 (M+H)$^+$. Found: 218.1540.

4.1.6.13. 2-Methyl-2-phenylacetylamino-propionic acid methyl ester[25] (41). The title compound was prepared according to the general procedure of coupling with PS-IIDQ and obtained as a white solid (51 mg, 73%). HPLC (method C): t_R=8.66 min. Purity (ELSD): 100%. ^{1}H NMR (300 MHz, $CDCl_3$): 7.31–7.19 (m, 5H, Ar–*H*), 5.93 (br s, 1H, N*H*), 3.64 (s, 3H, OCH_3), 3.47 (s, 2H, CH_2), 1.42 (6H, C(CH_3)$_2$). *m*/*z* (ESMS): 236 (M+H)$^+$ (33%), 258 (M+Na)$^+$ (100%). Mp: 103–104 °C (ethanol, lit.:[25] 102–103.5 °C).

4.1.6.14. (*S*)-1-Phenylacetyl-pyrrolidine-2-carboxylic acid benzyl ester (43). The title compound was prepared according to the general procedure of coupling with PS-IIDQ, separated from the carbamate by-product by column chromatography (hexane/EtOAc 6/4), and was obtained as a colorless oil (52 mg, 60%). HPLC (method A): t_R=8.19 min. Purity (ELSD): 100%. FTIR (neat): 1740 (s), 1642 (s). HRMS (ES): calcd for $C_{20}H_{21}NO_3$: 324.1594 (M+H)$^+$. Found: 324.1592.

4.1.6.15. *N*-Cyclohexylmethyl-benzamide[26] (44). The title compound was prepared according to the general procedure of coupling with PS-IIDQ and obtained as a white solid (51 mg, 84%). HPLC (method C): t_R=9.77 min. Purity (ELSD): 100%. ^{1}H NMR (300 MHz, $CDCl_3$): 7.77–7.75 (m, 2H, OC–C–CH), 7.51–7.39 (m, 3H, OC–C–CH–C*H*–C*H*), 6.09 (br s, 1H, NH), 4.05–3.92 (m, 1H, NHC*H*), 2.06–2.01 (m, 2H, CH naphthyl), 1.80–1.59 (m, 3H, CH naphthyl), 1.51–1.34 (m, 2H, CH naphthyl), 1.32–1.14 (m, 3H, CH naphthyl). *m*/*z* (ESMS): 204 (M+H)$^+$ (100%). Mp: 152–154 °C (ethanol, lit.:[27] 152–153 °C).

4.1.6.16. 2-Benzoylamino-2-methyl-propionic acid methyl ester (45). The title compound was prepared according to the general procedure of coupling with PS-IIDQ and obtained as a white solid (60 mg, 91%). HPLC (method C): t_R=8.35 min. Purity (ELSD): 100%. ^{1}H NMR (400 MHz, $CDCl_3$): 7.77 (d, *J*=6.8 Hz, 2H, OC–C–CH), 7.51–7.39 (m, 3H, OC–C–CH–C*H*–C*H*), 6.81 (br s, 1H, N*H*), 3.78 (s, 3H, OCH_3), 1.68 (s, 6H, C(CH_3)$_2$). ^{13}C NMR (100 MHz, $CDCl_3$): 175.86 (C=O), 166.57 (C=O), 134.51 (C–Ar), 131.50 (CH–Ar), 128.49 (CH–Ar), 126.91 (CH–Ar), 56.90 (*C*(CH$_3$)$_2$), 52.73 (OCH_3), 24.74 (C(*C*H$_3$)$_2$). FTIR (neat): 3223 (m), 1732 (s), 1627 (s). Mp: 116–119 °C (ethanol). HRMS (ES): calcd for $C_{12}H_{15}NO_3$: 244.0944 (M+Na)$^+$. Found: 244.0943.

4.1.6.17. (*S*)-1-Benzoyl-pyrrolidine-2-carboxylic acid benzyl ester (47). The title compound was prepared according to the general procedure of coupling with PS-IIDQ, separated from the carbamate by-product by column chromatography (hexane/EtOAc 6/4), and was obtained as a colorless oil (26 mg, 34%). HPLC (method A): t_R= 7.88 min. Purity (ELSD): 100%. FTIR (neat): 1740 (s), 1629 (s). HRMS (ES): calcd for $C_{19}H_{19}NO_3$: 310.1438 (M+Na)$^+$. Found: 310.1434.

4.1.6.18. [(*S*)-1-(Cyclohexylmethyl-carbamoyl)-ethyl]-carbamic acid benzyl ester (48). The title compound was prepared according to the general procedure of coupling with PS-IIDQ and obtained as a white solid (69 mg, 71%). HPLC (method C): t_R=10.20 min. Purity (ELSD): 100%. ^{1}H NMR (300 MHz, $CDCl_3$): 7.26 (m, 5H, Ar–H), 5.96 (br s, 1H, NH), 5.39 (br s, 1H, NH), 5.03 (s, 2H, Ar–CH_2), 4.10 (m, 1H, CH*), 3.64 (m, 1H, CH *c*-Hex), 1.86–0.97 (m, 10H, CH_2 *c*-Hex), 1.26 (d, *J*=7.2 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 171.18 (C=O), 155.92 (C=O), 136.21 (C–Ar), 128.49 (CH–Ar), 128.14 (CH–Ar), 127.96 (CH–Ar), 66.91 (OCH_2), 50.62 (CH*), 48.23 (CH *c*-Hex), 32.85 (CH_2), 25.43 (CH_2), 24.69 (CH_2), 18.76 (CH_3). FTIR (neat): 3277 (m), 1688 (s), 1642 (s). Mp: 153–156 °C (methanol). HRMS (ES): calcd for $C_{17}H_{24}N_2O_3$: 327.1679 (M+H)$^+$. Found: 327.1677.

4.1.6.19. 2-((*S*)-2-Benzyloxycarbonylamino-propionyl-amino)-2-methyl-propionic acid methyl ester[28] (49). The title compound was prepared according to the general procedure of coupling with PS-IIDQ and obtained as a white solid (79 mg, 82%). HPLC (method C): t_R=9.24 min. Purity

(ELSD): 100%. ^{1}H NMR (300 MHz, $CDCl_3$): 7.34–7.29 (m, 5H, Ar–*H*), 6.725 (br s, 1H, NH), 5.44 (br s, 1H, NH), 5.10 (s, 2H, CH_2), 4.24–4.20 (m, 1H, C*H*), 3.70 (s, 3H, OCH_3), 1.50 (d, *J*=3 Hz, 6H, C(CH_3)$_2$), 1.35 (d, *J*=7 Hz, 3H, CH–CH_3). *m*/*z* (ESMS): 345 (M+Na)$^+$ (100%). Mp: 118–120 °C (ethanol, lit.:[28] 120 °C).

4.1.6.20. (*S*)-((*S*)-2-Benzyloxycarbonylamino-propionylamino)-phenyl-acetic acid methyl ester (51). The title compound was prepared according to the general procedure of coupling with PS-IIDQ and obtained as a white solid (92 mg, 83%). HPLC (method C): t_R=9.76 min. Purity (ELSD): 100%. ^{1}H NMR (300 MHz, $CDCl_3$): 7.32 (m, 10H, Ar–*H*), 7.19 (br s, 1H, NH), 5.54 (d, *J*=7.2 Hz, 1H, C*H*–Ph), 5.40 (br s, 1H, NH), 5.07 (s, 2H, Ar–CH_2), 4.33 (m, 1H, C*H*–CH_3), 3.71 (s, 3H, OCH_3), 1.38 (d, *J*=6.9 Hz, 3H, CH–CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 171.69 (C═O), 171.05 (C═O), 155.93 (C═O), 136.17 (C–Ar), 136.11 (C–Ar), 128.99 (CH–Ar), 128.60 (CH–Ar), 128.53 (CH–Ar), 128.17 (CH–Ar), 128.06 (CH–Ar), 127.21 (CH–Ar), 67.03 (OCH_2), 56.49 (*C*H–Ph), 52.82 (OCH_3), 50.35 (*C*HCH_3), 18.61 (CH_3). FTIR (neat): 3301 (m), 1734 (s), 1692 (s), 1650 (s). Mp: 121–123 °C (methanol). HRMS (ES): calcd for $C_{20}H_{22}N_2O_5$: 371.1602 (M+H)$^+$. Found: 371.1601.

4.1.6.21. 4-Phenoxyacetyl-morpholine[29] (52). The title compound was prepared according to the general procedure of coupling with PS-IIDQ and obtained as a white solid (53 mg, 80%). HPLC (method C): t_R=8.21 min. Purity (ELSD): 100%. ^{1}H NMR (300 MHz, $CDCl_3$): 7.32–7.27 (m, 2H, O–C–CH–C*H*), 7.02–6.93 (m, 3H, O–C–C*H*–CH–C*H*), 4.69 (s, 2H, Ar–O–CH_2), 3.64 (m, 8H, CH_2 morpholine). *m*/*z* (ESMS): 222 (M+H)$^+$ (23%), 244 (M+Na)$^+$ (100%). Mp: 95–97 °C (ethanol, lit.:[29] 94–96 °C).

4.1.6.22. *N*-Cyclohexylmethyl-2-phenoxy-acetamide (53). The title compound was prepared according to the general procedure of coupling with PS-IIDQ and obtained as a white solid (36 mg, 52%). HPLC (method C): t_R=10.36 min. Purity (ELSD): 100%. ^{1}H NMR (300 MHz, $CDCl_3$): 7.34–7.29 (m, 2H, O–C–CH–CH), 7.02 (t, *J*=7.5 Hz, 1H, O–C–CH–CH–CH), 6.91 (d, *J*=7.8 Hz, 2H, O–C–CH), 6.45 (br s, 1H, NH), 4.46 (s, 2H, Ar–O–CH_2), 3.92–3.82 (m, 1H, CH), 1.95–1.10 (4m, 10H, CH_2 *c*-Hex). ^{13}C NMR (75 MHz, $CDCl_3$): 167.150 (C═O), 157.22 (C–Ar), 129.72 (CH–Ar), 122.06 (CH–Ar), 114.70 (CH–Ar), 67.44 (OCH_2), 47.78 (CH), 32.95 (CH_2), 25.42 (CH_2), 24.74 (CH_2). FTIR (neat): 3335 (m), 1647 (s). Mp: 75–78 °C (methanol). HRMS (ES): calcd for $C_{14}H_{19}NO_2$: 256.1308 (M+Na)$^+$. Found: 256.1305.

4.1.6.23. 2-Methyl-2-(2-phenoxy-acetylamino)-propionic acid methyl ester (54). The title compound was prepared according to the general procedure of coupling with PS-IIDQ and obtained as a white solid (53 mg, 70%). HPLC (method C): t_R=9.14 min. Purity (ELSD): 100%. ^{1}H NMR (300 MHz, $CDCl_3$): 7.32 (t, *J*=7.5 Hz, 2H, O–C–CH–C*H*), 7.15 (br s, 1H, N*H*), 7.02 (t, *J*=7.5 Hz, 1H, O–C–CH–CH–C*H*), 6.94 (d, *J*=7.8 Hz, 2H, O–C–CH), 4.44 (s, 2H, CH_2), 3.76 (s, 3H, OCH_3), 1.60 (s, 6H, C(CH_3)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$): 174.64 (C═O), 167.47 (C═O), 157.19 (C–Ar), 129.70 (CH–Ar), 122.09 (CH–Ar), 114.76 (CH–Ar), 67.49 (OCH_2), 56.40 (*C*(CH$_3$)$_2$), 52.69 (OCH$_3$), 24.67 (C(*C*H$_3$)$_2$). *m*/*z* (ESMS): 252 (M+H)$^+$ (22%), 274 (M+Na)$^+$ (100%). FTIR (neat): 3209 (w), 1738 (s), 1649 (s). Mp: 61–62 °C (methanol). Anal. Calcd for $C_{13}H_{17}NO_4$: C: 62.14, H: 6.82, N: 5.57. Found: C: 61.98, H: 6.85, N: 5.52.

4.1.6.24. 2-Phenoxy-*N*-(1,2,3,4-tetrahydro-naphthalen-1-yl)-acetamide (56). The title compound was prepared according to the general procedure of coupling with PS-IIDQ and obtained as a white solid (62 mg, 74%). HPLC (method C): t_R=10.76 min. Purity (ELSD): 100%. ^{1}H NMR (400 MHz, $CDCl_3$): 7.31 (t, *J*=8.8 Hz, 2H, O–C–CH–C*H*), 7.22–7.10 (m, 4H, Ar–H naphthyl), 7.02 (t, *J*=7.2 Hz, 1H, O–C–CH–CH–C*H*), 6.90 (d, *J*=8.0 Hz, 2H, O–C–CH), 6.79 (d, *J*=7.6 Hz, 1H, NH), 5.32–5.28 (m, 1H, NHC*H*), 4.57 (AB-d, *J*=14.8 Hz, 2H, OCH_2), 2.87–2.74 (m, 2H, Ar–CH_2 naphthyl), 2.14–2.09 (m, 1H, CH naphthyl), 1.87–1.77 (m, 3H, CH naphthyl). ^{13}C NMR (75 MHz, $CDCl_3$): 167.60 (C═O), 157.10 (C–Ar), 137.58 (C–Ar), 136.15 (C–Ar), 129.70 (CH–Ar), 129.18 (CH–Ar), 128.36 (CH–Ar), 127.33 (CH–Ar), 126.28 (CH–Ar), 122.08 (CH–Ar), 114.67 (CH–Ar), 67.38 (OCH_2), 47.20 (CH), 30.23 (CH_2), 29.16 (CH_2), 20.11 (CH_2). *m*/*z* (ESMS): 304 (M+Na)$^+$ (100%). FTIR (neat): 3309 (m), 1649 (s). Mp: 79–82 °C (ethanol). Anal. Calcd for $C_{18}H_{19}NO_2$: C: 76.84, H: 6.81, N: 4.98. Found: C: 76.69, H: 6.81, N: 4.97.

4.1.6.25. *N*-(4-*tert*-Butyl-phenyl)-2-phenoxy-acetamide (57). The title compound was prepared according to the general procedure of coupling with PS-IIDQ and obtained as a white solid (70 mg, 83%). HPLC (method C): t_R=11.09 min. Purity (ELSD): 100%. ^{1}H NMR (300 MHz, $CDCl_3$): 8.25 (br s, 1H, N*H*), 7.53–7.50 (m, 2H, HN–C–CH), 7.40–7.33 (m, 2H, HN–C–CH–C*H*, 2H, O–C–CH–C*H*), 7.09–6.99 (m, 3H, O–C–C*H*–CH–C*H*), 4.61 (s, 2H, CH_2), 1.33 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): 166.15 (C═O), 157.03 (C–Ar), 147.86 (C–Ar), 134.14 (C–Ar), 129.84 (CH–Ar), 125.85 (CH–Ar), 122.37 (CH–Ar), 119.95 (CH–Ar), 114.82 (CH–Ar), 67.62 (OCH_2), 34.37 (*C*(CH$_3$)$_3$), 31.30 (C(*C*H$_3$)$_3$). *m*/*z* (ESMS): 306 (M+Na)$^+$ (47%), 589 (2M+Na)$^+$ (100%). FTIR (neat): 3264 (w), 1657 (s). Mp: 80–82 °C (methanol). Anal. Calcd for $C_{18}H_{21}NO_2$: C: 76.30, H: 7.47, N: 4.94. Found: C: 76.09, H: 7.50, N: 4.97.

4.1.6.26. *N*-Benzyl-2-phenoxy-acetamide[30] (58). The title compound was prepared according to the general procedure of coupling with PS–IIDQ and obtained as a white solid (59 mg, 82%). HPLC (method C): t_R=9.85 min. Purity (ELSD): 100%. ^{1}H NMR (300 MHz, $CDCl_3$): 7.36–7.25 (m, 7H, Ar–H), 7.04 (t, *J*=7.5 Hz, 1H, O–C–CH–CH–C*H*), 6.90 (d, *J*=7.5 Hz, 2H, O–C–CH), 4.54 (d, *J*=5.7 Hz, 2H, NHCH_2), 4.46 (s, 2H, OCH_2). *m*/*z* (ESMS): 242 (M+H)$^+$ (22%), 264 (M+Na)$^+$ (100%). Mp: 84–85 °C (ethanol, lit.:[31] 84–86 °C).

4.1.6.27. (*S*)-(2-Phenoxy-acetylamino)-phenyl-acetic acid methyl ester[32] (59). The title compound was prepared according to the general procedure of coupling with PS-IIDQ and obtained as a white solid (73 mg, 82%). HPLC (method C): t_R=9.94 min. Purity (ELSD): 99%. ^{1}H NMR (300 MHz, $CDCl_3$): 7.58 (d, *J*=6.6 Hz, 1H, NH), 7.37–7.29 (m, 7H, Ar–H), 7.06–7.01 (m, 1H, O–C–CH–CH–

CH), 6.97–6.92 (m, 2H, O–C–CH), 5.67 (d, J=7.5 Hz, 1H, C*H*), 4.53 (AB-d, J=15 Hz, 2H, CH_2), 3.74 (s, 3H, CH_3). *m/z* (ESMS): 300 $(M+H)^+$ (19%), 322 $(M+Na)^+$ (100%). Mp: 94–96 °C (ethanol, lit.:[32] 95–96 °C).

4.1.6.28. (*S*)-Pyrrolidine-1,2-dicarboxylic acid 2-benzyl ester 1-isobutyl ester (63). Isobutylchloroformate (54 μL, 0.41 mmol, 1 equiv) was added to a mixture of proline benzyl ester hydrochloride (100 mg, 0.41 mmol, 1 equiv) and DIPEA (137 μL, 0.82 mmol, 2 equiv) in DCM (10 mL). The mixture was stirred at room temperature for 2 h and concentrated in vacuo. The residue was taken up in EtOAc (50 mL) and washed with 1 M $NaHCO_3$ (3× 25 mL), 1 M HCl (3×25 mL), brine (1×25 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give the title compound as a pale yellow oil (109 mg, 85%). HPLC (method A): t_R=9.02 min. Purity (ELSD): 100%. ^{1}H NMR (400 MHz, 373 K, DMSO-d_6): 7.38–7.33 (m, 5H, Ar–*H*), 5.15 (s, 2H, Ar–CH_2), 4.34 (dd, J=3.5 Hz and 8.5 Hz, 1H, CH*), 3.78 (d, J=6.4 Hz, 2H, OCH_2CH), 3.44 (m, 2H, N–CH_2), 2.26 (m, 1H, C*H*$(CH_3)_2$), 1.94–1.84 (m, 4H, CH*CH_2CH_2), 0.87 (d, J=6.75 Hz, 6H, CH(CH_3)$_2$). ^{13}C NMR (100 MHz, 363 K, DMSO-d_6): 172.01 (C═O), 154.00 (C═O), 135.9 (C–Ar), 128.23 (CH–Ar), 127.84 (CH–Ar), 127.56 (CH–Ar), 70.60 (Ph–CH_2), 65.85 (O*C*H_2CH), 58.75 (CH*), 46.28 (CH_2), 29.80 (CH_2), 27.44 (*C*H$(CH_3)_2$), 23.28 (CH_2), 18.56 (CH(*C*H_3)$_2$). FTIR (neat): 1745 (m), 1702 (s). HRMS (ES): calcd for $C_{17}H_{23}NO_4$: 306.1700 $(M+H)^+$. Found: 306.1699.

4.1.6.29. (*S*)-1-(3,3-Diphenyl-propionyl)-pyrrolidine-2-carboxylic acid benzyl ester (64). The title compound was prepared according to the general procedure of coupling with PS-IIDQ, separated from the carbamate by-product by column chromatography (petroleum ether/EtOAc 6/4), and obtained as a pale yellow oil (48 mg, 43%). HPLC (method A): t_R=9.44 min. Purity (ELSD): 94%. FTIR (neat): 1740 (s), 1645 (s). HRMS (ES): calcd for $C_{27}H_{27}NO_3$: 414.1907 $(M+H)^+$. Found: 414.1905.

4.1.6.30. (*S*)-1-(3-Phenyl-propionyl)-pyrrolidine-2-carboxylic acid benzyl ester[33] (65). The title compound was prepared according to the general procedure of coupling with PS-IIDQ, separated from the carbamate by-product by column chromatography (petroleum ether/EtOAc 6/4), and obtained as a pale yellow oil (69 mg, 76%). HPLC (method A): t_R=8.72 min. Purity (ELSD): 100%. FTIR (neat): 3222 (w), 1739 (s), 1642 (s). HRMS (ES): calcd for $C_{21}H_{23}NO_3$: 338.1751 $(M+H)^+$. Found: 338.1758.

4.1.6.31. (*S*)-1-(3,3,3-Triphenyl-propionyl)-pyrrolidine-2-carboxylic acid benzyl ester (66). The title compound was prepared according to the general procedure of coupling with PS-IIDQ, separated from the carbamate by-product by column chromatography (petroleum ether/EtOAc 6/4), and obtained as a pale yellow oil (24 mg, 18%). HPLC (method B): t_R=8.22 min. Purity (ELSD): 100%. FTIR (neat): 3218 (w), 1738 (s), 1643 (s). HRMS (ES): calcd for $C_{33}H_{31}NO_3$: 490.2377 $(M+H)^+$. Found: 490.2385.

4.1.6.32. (*S*)-1-Diphenylacetyl-pyrrolidine-2-carboxylic acid benzyl ester (67). The title compound was prepared according to the general procedure of coupling with PS-IIDQ, separated from the carbamate by-product by column chromatography (petroleum ether/EtOAc 6/4), and obtained as a pale yellow oil (54 mg, 50%). HPLC (method A): t_R=9.19 min. Purity (ELSD): 100%. FTIR (neat): 1740 (s), 1645 (s). HRMS: calcd for $C_{26}H_{25}NO_3$: 400.1907 $(M+H)^+$. Found: 400.1905.

4.1.6.33. (*S*)-1-[1-(4-Chloro-phenyl)-cyclopropanecarbonyl]-pyrrolidine-2-carboxylic acid benzyl ester (68). The title compound was prepared according to the general procedure of coupling with PS-IIDQ, separated from the carbamate by-product by column chromatography (petroleum ether/EtOAc 6/4), and obtained as a pale yellow oil (44 mg, 43%). HPLC (method A): t_R=9.31 min. Purity (ELSD): 96%. FTIR (neat): 1740 (s), 1637 (s). HRMS: calcd for $C_{22}H_{22}NO_3Cl$: 384.1361 $(M+H)^+$. Found: 284.1362.

4.1.6.34. (*S*)-1-(2-Cyclohexyl-acetyl)-pyrrolidine-2-carboxylic acid benzyl ester (69). The title compound was prepared according to the general procedure of coupling with PS-IIDQ, separated from the carbamate by-product by column chromatography (petroleum ether/EtOAc 6/4), and obtained as a pale yellow oil (58 mg, 66%). HPLC (method A): t_R=9.26 min. Purity (ELSD): 100%. FTIR (neat): 1742 (s), 1642 (s). HRMS: calcd for $C_{20}H_{27}NO_3$: 330.2064 $(M+H)^+$. Found: 330.2062.

4.1.6.35. (*S*)-1-(2-Adamantan-1-yl-acetyl)-pyrrolidine-2-carboxylic acid benzyl ester (70). The title compound was prepared according to the general procedure of coupling with PS-IIDQ, separated from the carbamate by-product by column chromatography (petroleum ether/EtOAc 6/4), and obtained as a pale yellow oil (49 mg, 48%). HPLC (method A): t_R=10.10 min. Purity (ELSD): 100%. FTIR (neat): 1742 (s), 1638 (s). HRMS: calcd for $C_{24}H_{31}NO_3$: 382.2382 $(M+H)^+$. Found: 382.2383.

4.1.6.36. (*S*)-1-(3-Phenyl-butyryl)-pyrrolidine-2-carboxylic acid benzyl ester (71). The title compound was prepared according to the general procedure of coupling with PS-IIDQ, separated from the carbamate by-product by column chromatography (petroleum ether/EtOAc 6/4), and obtained as a pale yellow oil (54 mg, 57%). HPLC (method B): t_R=7.14 min. Purity (ELSD): 100%. FTIR (neat): 1742 (s), 1644 (s). HRMS (ES): calcd for $C_{22}H_{25}NO_3$: 374.1726 $(M+Na)^+$. Found: 374.1728.

4.1.6.37. (*S*)-1-(2-Phenyl-propionyl)-pyrrolidine-2-carboxylic acid benzyl ester (72). The title compound was prepared according to the general procedure of coupling with PS-IIDQ, separated from the carbamate by-product by column chromatography (petroleum ether/EtOAc 6/4), and obtained as a pale yellow oil (32 mg, 35%). HPLC (method B): t_R=7.11 min. Purity (ELSD): 99%. FTIR (neat): 1742 (s), 1644 (s). HRMS (ES): calcd for $C_{21}H_{23}NO_3$: 338.1751 $(M+H)^+$. Found: 338.1748.

4.1.6.38. (*S*)-1-Cyclohexanecarbonyl-pyrrolidine-2-carboxylic acid benzyl ester[34] (73). The title compound was prepared according to the general procedure of coupling with PS-IIDQ, separated from the carbamate by-product by column chromatography (petroleum ether/EtOAc 6/4), and obtained as a pale yellow oil (25 mg, 30%). HPLC (method

A): t_R=8.80 min. Purity (ELSD): 100%. FTIR (neat): 1741 (s), 1639 (s). HRMS (ES): calcd for $C_{19}H_{25}NO_3$: 316.1907 $(M+H)^+$. Found: 316.1910.

4.1.6.39. (*S*)-1-Cyclopentanecarbonyl-pyrrolidine-2-carboxylic acid benzyl ester (74). The title compound was prepared according to the general procedure of coupling with PS-IIDQ, separated from the carbamate by-product by column chromatography (petroleum ether/EtOAc 6/4), and obtained as a pale yellow oil (44 mg, 55%). HPLC (method A): t_R=8.42 min. Purity (ELSD): 100%. FTIR (neat): 1741 (s), 1639 (s). HRMS (ES): calcd for $C_{18}H_{23}NO_3$: 302.1751 $(M+H)^+$. Found: 302.1746.

4.1.6.40. Boc-Pro–Pro-OBn[24] (75). The title compound was prepared according to the general procedure of coupling with PS-IIDQ, separated from the carbamate by-product by column chromatography (petroleum ether/EtOAc 6/4), and obtained as a pale yellow oil (53 mg, 49%). HPLC (method A): t_R=8.46 min. Purity (ELSD): 100%. FTIR (neat): 3222 (w), 1741 (m), 1693 (s), 1656 (s). HRMS (ES): calcd for $C_{22}H_{30}N_2O_5$: 403.2228 $(M+H)^+$. Found: 403.2229.

4.1.7. Z-Gly-L-Phe-Val-OMe[23] (76). To a solution of H-Val-OMe hydrochloride (29 mg, 0.175 mmol, 1 equiv), DIPEA (29 μL, 0.175 mmol, 1 equiv), and Z-Gly–Phe-OH (60 mg, 0.175 mmol, 1 equiv) in CH_3CN (5 mL) was added PS-IIDQ (250 mg, 0.350 mmol, 2 equiv). The reaction mixture was shaken at room temperature for 24 h, filtered and the resin washed with DCM/MeOH (three cycles of 5 mL). The filtrates were concentrated in vacuo and the unreacted amine and carboxylic acid removed using an SPE cartridge containing a mixed bed of acidic/basic MP ion-exchange resin (Polymer Lab, 500 mg). The title compound was obtained as a pale yellow oil (82 mg, 65%). HPLC (method B): t_R=8.25 min. Purity (ELSD): 100%. ^{1}H NMR (300 MHz, $CDCl_3$): 7.27–7.09 (m, 10H, Ar–H), 6.76 (br s, 1H), 6.40 (br s, 1H), 5.42 (br s, 1H), 5.03 (s, 2H, Ph–CH_2–O), 4.66–4.63 (m, 1H, CH^*_{Phe}), 4.34 (dd, J= 8.4 Hz and 5.2 Hz, 1H, CH^*_{Val}), 3.77 (m, 2H, NH–CH_2), 3.60 (s, 3H, OCH_3), 2.97 (d, J=4.4 Hz, 2H, $CHCH_2Ph$), 2.02–1.96 (m, 1H, $CH(CH_3)_2$), 0.77 (d, J=6.8 Hz, 3H, CH_3), 0.74 (d, J=6.8 Hz, 3H, CH_3). *m/z* (ESMS): 470 $(M+H)^+$ (5%), 492 $(M+Na)^+$ (100%).

4.1.8. Z-Gly-D-Phe-Val-OMe[23] (77). The title compound was prepared similar to compound **76** and obtained as a pale yellow oil (78 mg, 63%). HPLC (method B): t_R= 8.26 min. Purity (ELSD): 100%. ^{1}H NMR (300 MHz, $CDCl_3$): 7.29–7.12 (m, 10H), 6.64 (br s, 1H), 6.28 (br s, 1H), 5.34 (br s, 1H), 5.05 (s, 2H, Ph–CH_2–O), 4.68–4.62 (m, 1H, CH^*_{Phe}), 4.36 (dd, J=8.4 Hz and 5.2 Hz, 1H, CH^*_{Val}), 3.79 (m, 2H, $NHCH_2$), 3.63 (s, 3H, OCH_3), 3.05–2.95 (m, 2H, $CHCH_2Ph$), 2.06–1.98 (m, 1H, $CH(CH_3)_2$), 0.79 (d, J=6.8 Hz, 3H, CH_3), 0.76 (d, J=6.8 Hz, 3H, CH_3). *m/z* (ESMS): 470 $(M+H)^+$ (5%), 492 $(M+Na)^+$ (100%).

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References and notes

1. (a) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815–4195; (b) Kirschning, A.; Monenschein, H.; Wittenberg, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 650–679; (c) Bhalay, G.; Dunstan, A.; Glen, A. *Synlett* **2000**, 1846–1859.
2. See for example: Desai, M. C.; Stephens Stramiello, L. M. *Tetrahedron Lett.* **1993**, *34*, 7685–7688.
3. See for example: Zhang, M.; Vedantham, P.; Flynn, D. L.; Hanson, P. R. *J. Org. Chem.* **2004**, *69*, 8340–8344.
4. Chinchilla, R.; Dodsworth, D. J.; Najera, C.; Soriano, J. M. *Tetrahedron Lett.* **2000**, *41*, 2463–2466.
5. Filip, S. V.; Lejeune, V.; Vors, J.-P.; Martinez, J.; Cavelier, F. *Eur. J. Org. Chem.* **2004**, *9*, 1936–1939.
6. Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397–4398.
7. (a) Albericio, F.; Bofill, J. M.; El-Faham, A.; Kates, S. A. *J. Org. Chem.* **1998**, *63*, 9678–9683; (b) Albericio, F.; Cases, M.; Alsina, J.; Triolo, S. A.; Carpino, L. A.; Kates, S. A. *Tetrahedron Lett.* **1997**, *38*, 4853–4856.
8. Tung, R. D.; Rich, D. H. *J. Am. Chem. Soc.* **1985**, *107*, 4342–4343.
9. (a) Belleau, B.; Martel, R.; Lacasse, G.; Menard, M.; Weinberg, N. L.; Perron, Y. G. *J. Am. Chem. Soc.* **1968**, *90*, 823–824; (b) Belleau, B.; Malek, G. *J. Am. Chem. Soc.* **1968**, *90*, 1651–1652.
10. Valeur, E.; Bradley, M. *Chem. Commun.* **2005**, 1164–1166.
11. Delgado, M.; Janda, K. D. *Curr. Org. Chem.* **2002**, *6*, 1031–1043.
12. Boissonnas, R. A.; Guttmann, S.; Jaquenoud, P. A.; Waller, J. P. *Helv. Chim. Acta* **1955**, *38*, 1491–1501.
13. Van der Auwera, C.; Van Damme, S.; Anteunis, M. J. O. *Int. J. Pept. Protein Res.* **1987**, *29*, 464–471.
14. PS-IIDQ is now commercially available from Novabiochem (01-64-0469) and Polymer Laboratories (PL-IIDQ).
15. Perreux, L.; Loupy, A.; Volatron, F. *Tetrahedron* **2002**, *58*, 2155–2162.
16. Heyde, C.; Zug, I.; Hartmann, H. *Eur. J. Org. Chem.* **2000**, 3273–3278.
17. Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101–1104.
18. Acheson, R. M.; Harvey, C. W. C. *J. Chem. Soc., Perkin Trans. 1* **1976**, 465–470.
19. Park, S.-D.; Oh, J.-H.; Lim, D. *Tetrahedron Lett.* **2002**, *43*, 6309–6311.
20. Badr, M. Z. A.; Aly, M. M.; Mahgoub, S. A.; Fahmy, A. M.; Atallah, A. A. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1779–1783.
21. Tillack, A.; Rudloff, I.; Beller, M. *Eur. J. Org. Chem.* **2001**, 523–528.
22. Dondoni, A.; Perrone, D.; Semola, T. *Synthesis* **1995**, *2*, 181–186.
23. Albericio, F.; Bailen, M. A.; Chinchilla, R.; Dodsworth, D. J.; Najera, C. *Tetrahedron* **2001**, *57*, 9607–9613.
24. Zhang, R.; Madalengoita, J. S. *Tetrahedron Lett.* **1996**, *37*, 6235–6239.
25. Obrecht, D.; Heimgartner, H. *Helv. Chim. Acta* **1987**, *70*, 102–115.
26. Wintner, E. A.; Conn, M. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1994**, *116*, 8877–8884.
27. Lee, C. K.; Yu, J. S.; Ji, Y. R. *J. Heterocycl. Chem.* **2002**, *39*, 1219–1227.
28. Wipf, P.; Heimgartner, H. *Helv. Chim. Acta* **1987**, *70*, 354–368.
29. Ogawa, T.; Hikasa, T.; Ikegami, T.; Ono, N.; Suzuki, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3473–3478.

30. Koh, H. J.; Kim, T. H.; Lee, B.-S.; Lee, I. *J. Chem. Res.* **1996**, *11*, 2741–2751.
31. Baker, B. R.; Hurlbut, J. A. *J. Med. Chem.* **1967**, *10*, 1129–1133.
32. Frkanec, L.; Visnjevac, A.; Kojic-Prodic, B.; Zinic, M. *Chem.—Eur. J.* **2000**, *6*, 442–453.
33. Abraham, D. J.; Gazze, D. M.; Kennedy, P. E.; Mokotoff, M. *J. Med. Chem.* **1984**, *12*, 1549–1559.
34. Yoshikawa, K.; Achiwa, K. *Chem. Pharm. Bull.* **1995**, *43*, 2048–2053.
35. Kiso, Y.; Yajima, H. *Chem. Commun.* **1972**, 942–943.