The use of phosphonium anhydrides for the synthesis of 2-oxazolines, 2-thiazolines and 2-dihydrooxazine under mild conditions†

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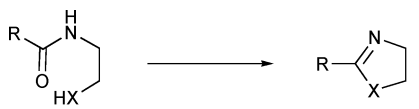
β-Hydroxy amides **6** and **7** were treated with triphenylphosphonium anhydride trifluoromethane sulfonate (**3**), or the cyclic analogue **4**, to generate 2-oxazolines **5** and **8** under mild conditions. The reaction was optimised by examining the number of equivalents of reagents **3** or **4**, or diisopropylethyl amine required to best effect cyclisation. The effects of altering the reaction temperature, reaction time, concentration, solvent, and addition rate also were investigated. However, it was found that use of a trityl group to block reaction at the hydroxyl or thiol group of the starting amides, and subsequent *in situ* detritylation, in the absence of base, led to greatly improved yields. Reagent **4** offered significant advantages in the purification of products and was used to dehydrate a range of trityl derivatives to form simple oxazolines, thiazolines, and a dihydro-1,3-oxazine, in high yield (85–99%), as well as a tetrahydro-1,3-oxazepine (31%).

Introduction

2-Oxozalines and 2-thiazolines are heterocycles that have attracted a wide range of interest from synthetic and medicinal chemists over the last 20 years. Oxazoline and thiazoline rings occur in natural products and in drug like compounds,[1–7] and derivatives have been identified as anti-HIV,[6,8] antimitotic,[4,5] anti-cancer,[4,7] and antibiotic agents.[9,10] In synthesis, 2-oxazolines and 2-thiazolines have been used as building blocks,[9,11,12] protecting groups for β-amino alcohols,[13] and as auxiliaries and ligands[14,15] in a number of applications. Synthetic procedures to 2-oxazolines and 2-thiazolines have been developed from a range of precursors.[3,15–17] One of the more common approaches is the synthesis of oxazolines and thiazolines from acylamino alcohols or acylamino thiols, respectively (Scheme 1). A variety of reagents[1,12,17–23] have been used to carry out such transformations, however, typically harsh conditions {as with [bis(2-methoxylethyl)amino]sulfur trifluoride (Deoxo-Fluor)[20] or DAST[17,21]} and low to moderate yields (as with PPh_3/DIAD[12,18,22] or Burgess' reagent[12,18,19]) are observed.



1 X = S, O **2** X = S, O

Scheme 1 General synthesis of thiazolines and oxazolines from acylamino thiols or acylamino alcohols.

One of the mildest reagents for this type of cyclisation/cyclodehydration appears to be the Hendrickson 'POP' reagent (triphenylphosphonium anhydride trifluoromethane sulfonate **3**), which has been used to convert *N*-acyl serines[24] and *N*-acyl cysteines,[25]‡ into the corresponding heterocyclic analogues under very mild conditions with little or no racemisation. This paper reports that phosphonium anhydride **3**[26,27] and the cyclic analogue, 1,1,3,3-tetraphenyl-2-oxa-1,3-phospholanium bis(trifluoro methanesulfonate) (**4**),[28] can be used for the synthesis of simple oxazolines and thiazolines, as well as a dihydrooxazine and a tetrahydro-1,3-oxazepine. The use of the cyclic analogue **4** offers significant advantages in some cases. The importance of protection of the terminal hydroxyl or thiol group in the starting amide, by a group that can be deprotected *in situ* (i.e. trityl) by the expelled triflic acid in the absence of base, was established.

Results and discussion

The Hendrickson reagent (**3**), brings about dehydrations and coupling reactions (such as ester and amide formation[29]), in a similar manner to the Mitsunobu reaction,[30] and along with the cyclic analogue **4**, is useful for the synthesis of simple esters and amides, and conversion of primary alcohols to azides.[28,29] Reagent **3** was prepared as previously reported,[27,29] by treatment of triphenylphosphine oxide with triflic anhydride at 0 °C under an atmosphere of nitrogen. Likewise, the cyclic analogue **4** was prepared under the same conditions by reaction of the corresponding bis-phosphine oxide with triflic anhydride.[28] Initially, we examined the use of reagent **3**, and the cyclic analogue **4** for oxazoline synthesis using *in situ* formation of the benzamide intermediate and subsequent cyclisation (Scheme 2). Accordingly, the acyloxyphosphonium intermediate $C_6H_5COOP^+Ph_3$ was generated by stirring a mixture of **3** (2 equiv.) and benzoic acid for 60 minutes in dry dichloromethane (DCM) at room temperature, followed by addition of 2-amino-1-ethanol and diisopropylethylamine

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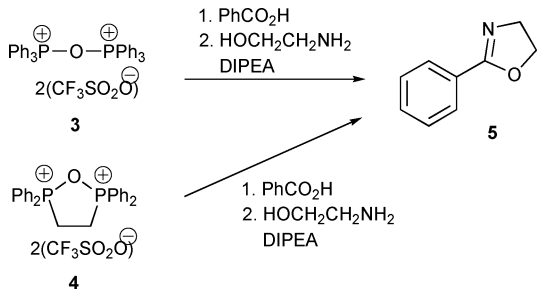
† Electronic supplementary information (ESI) available: General procedures; further experimental procedures; ^{1}H NMR spectra of compounds **17**–**22**, **25**, **27**, **29**. See DOI: 10.1039/b818310d

‡ Although the literature states that Hendrickson reagent (**3**), converts a *N*-acyl cysteine into the corresponding thiazoline, no experimental evidence is reported.

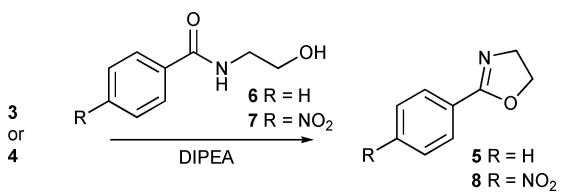


Scheme 2 Formation of oxazoline **5** from benzoic acid.

(DIPEA). Oxazoline **5** was isolated (54%). Similarly, use of reagent **4** also gave oxazoline **5** (50%). When reagent **3** or **4** was used in excess, oxazoline **5** was formed in reduced yields (2.4 equiv. of **3**, 47%; 2.4 equiv. of **4**, 38%; 2.8 equiv. of **4**, 15%).

The moderate yields suggested that in the two-step process reagent **3** (or **4**) was reacting with not only the benzoic acid, but also the amino group of the amino alcohol. Cyclisation of amide **6** potentially would circumvent this. Reaction of benzoyl chloride or nitrobenzoyl chloride with 2-amino-1-ethanol in the presence of triethylamine, gave amide **6** (73%) and amide **7** (99%), respectively.

Treatment of one equivalent of reagent **3** or **4** with amide **6** and DIPEA gave oxazoline **5**§ in 60% or 57% isolated yield, respectively (Scheme 3). In a similar manner, treatment of **3** or **4** with nitroamide **7** gave the corresponding nitrooxazoline **8** in 56% or 52% isolated yield, respectively (Scheme 3). Compared to oxazoline **5**, the oxazoline **8** offered the advantage of separation of the aromatic peaks in the ^{1}H NMR spectra for crude product analysis. Thus, amide **7** was extensively used in subsequent studies.



Scheme 3 Formation of oxazolines **5** and **8** from amides **6** and **7**.

Firstly, the effect of altering the number of equivalents of reagent **3** was examined. Thus, between 0.5 and 2.0 equivalents of **3** were reacted with amides **6** or **7** (Fig. 1). The best conversion of amides **6** and **7** to oxazolines **5** and **8**, respectively, was achieved when only one equivalent of reagent **3** was used.

As an example, oxazoline **8** (56%) was isolated along with recovered amide **7** (42%), giving an adjusted yield of 97% for oxazoline **8** based on reacted amide **7** (Fig. 1). Reduced yields of oxazolines **5** and **8** were obtained when excess reagent **3** was used. This correlated with an increase in decomposition products, as observed in the ^{1}H NMR spectra of the crude products, along with reduced isolated yields [e.g. use of 1.2 equivalents of **3** or **4**, gave **5** (33% and 37%, respectively) or **8** (49% and 39%, respectively), not adjusted for recovery of **6** or **7**.

§ The stability of oxazoline **5** to acid conditions was tested by stirring oxazoline **5** with silica gel in DCM for 16 hours, or with aqueous hydrochloric acid (2M) for 1 hour. In the silica experiment, no significant decomposition of oxazoline **5** was observed by ^{1}H NMR analysis of the crude mixture. The hydrochloric acid test showed some decomposition, a 91:9 ratio of oxazoline **5** and amide **6** was observed.

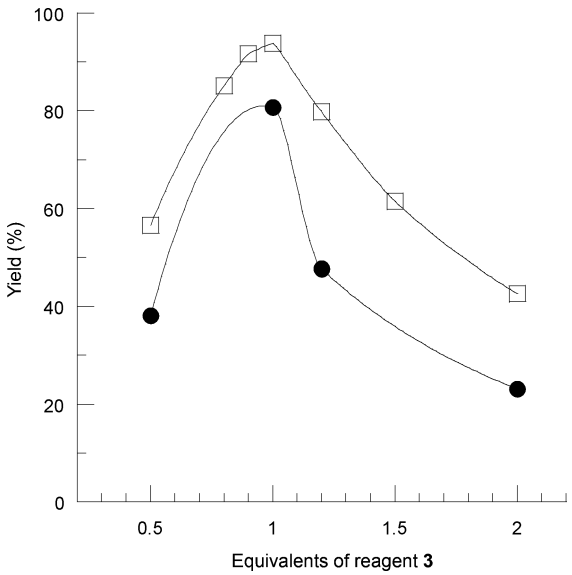


Fig. 1 Equivalents of reagent **3** *versus* % yield of oxazoline **5** (filled circles), or **8** (open squares) based on recovery of unreacted amide **6** or **7** respectively.

Next, reagent **3** was generated at 0 °C and subsequent reaction with amide **7** in the presence of DIPEA, was carried out at 0, 10, 22 and 40 °C. The optimal reaction temperature was found to be 22 °C which gave the best yield of oxazoline **8** (56%) and best overall recovery of mass (97% mass recovery).

The influence of the solvent was examined by carrying out the reaction of reagent **3** with amide **7** in the presence of DIPEA (at 22 °C, with 1 equivalent of **3**) in either DCM, CH_3CN or THF as the solvent. A complex mixture was obtained with THF and a reduced yield of product **8** (30%) with 67% recovery of amide **7** was obtained with CH_3CN. DCM gave the best yield of **8** (56%) with the least amount of recovered amide **7** (40%). The chlorinated solvent appears to be best for the formation and use of **3**.[27]

Using DCM, the effect of reaction concentration on the formation of **8** was examined (Table 1). Dilution (entries 4 and 5, Table 1) or increased concentration (entries 1 and 2, Table 1) of the reactants **3** and **7**, led to decreased yields of **8**. The optimal concentration was around 0.05 mM, which gave moderate yields of **8** (entry 3, Table 1).

Next, the reaction time was altered. Reagent **3** was reacted with amide **7** in the presence of DIPEA. At 2 and 24 hours an aliquot of the reaction mixture was analysed by ^{1}H NMR spectroscopy. Oxazoline **8** was present in 56% and 57% yield,

Table 1 Reaction of **7** with reagent **3** with variation in solvent (DCM) volume

Entry	Conc. of **7** and **3** (mM)	Reaction volume (mL)	Yield **8**[a] (%)	Recovered **7** (%)
1	0.095	2.5	42	47
2	0.095	2.5	46[b]	42
3	0.048	5.0	56	40
4	0.024	10.0	13	78
5	0.005	50.0	13	84

[a] Yield from analysis of ^{1}H NMR spectra of crude product. [b] Isolated yield; separate reaction from entry 1.

Table 2 Reaction of **7** with reagent **3** with variation in equivalents of DIPEA

Entry	Equiv. of **7** and **3**	Equiv. of DIPEA	Yield **8** (%)	Recovered **7** (%)
1	1.0	1.1	47	42
2	1.0	2.2	56	40
3	1.0	3.0	19	67
4	1.0	4.4	0	88

respectively. Complete reaction workup at 2 hours gave 57% of **8**, indicating that 2 hours is sufficient for reaction.

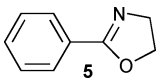
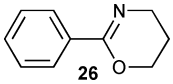
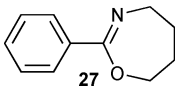
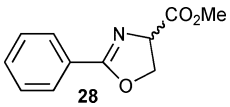
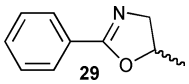
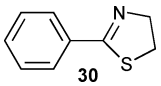
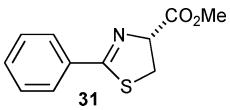
The effect of excess DIPEA was considered. Reagent **3** was reacted with amide **7** and 1.1, 2.2, 3.0 or 4.4 equivalents of DIPEA then the solvent removed. The ratio of **7** and **8** was analysed by ^{1}H NMR spectroscopy (Table 2). These results indicate that the use of 2.2 equivalents of DIPEA was preferred for formation of oxazoline **8**. Amide **7** was generally recovered during the course of the above studies. Inverse addition of reagent **3** was also investigated. Generation of reagent **3** at 0 °C and addition of the suspension of **3** to a solution of amide **7** in the presence of DIPEA at 0 °C over 30 minutes, gave oxazoline **8** (25%) and amide **7** (33%), as determined by ^{1}H NMR analysis of the crude product. Difficulties in the control of temperature and transfer of reagent **3** could account for the reduced recovery of **7** and yield of **8**.

Reaction conditions that allowed easy isolation of oxazoline **5** were also investigated. When reagent **3** is used, the triphenylphosphine oxide by-product ($R_f = 0.54$; EtOAc:Hexane, 3:1) co-elutes with a significant amount of **5** during chromatography leading to lower isolated yields of oxazoline **5**, unless a second chromatography step is carried out. By comparison, the corresponding bis-phosphine oxide by-product from reagent **4** is significantly more polar ($R_f = 0.11$; EtOAc:Hexane, 3:1) and thus more easily removed by chromatography. Thus, amide **6** was treated with reagent **4** using the optimized reactions conditions (1.0 equiv. reagent **4**, 22 °C, DCM, 0.05 mM of **6**, 2 hours, 2.2 equiv. DIPEA) and oxazoline **5** was easily isolated in 57% yield.

Finally, the rate of addition of the amide was varied, using **6** as the example. Direct addition of amide **6** as a solid to reagent **4** gave oxazoline **5** in moderate yield (56%). However, co-addition of amide **6** with DIPEA in DCM to reagent **4** dropwise over 5 minutes gave oxazoline **5** in an increased yield (70%). Delivery of **6** and DIPEA in DCM *via* syringe pump over 30 or 60 minutes, gave **5** in 72% (entry 2, Table 3) or 64% yields, respectively. The optimal mode of addition was as a pre-made solution of **6** and DIPEA with a rate of addition of between 5 and 30 minutes. These conditions led to improved yields of **5** (72% *cf* ~57%) as compared to the previous experiments.

During the course of the optimisation work we considered that the reduced yields of oxazoline **8** (and **5**) and the recovery of amide **7** (or **6**) may be due to a side reaction where aziridine **9** (Fig. 2) is formed, which is then hydrolysed upon workup to give amide **7** (or **6**). In an attempt to trap the proposed by-product **9**, amide **7** was treated with reagent **4** (1.0 equiv. of **4**, 22 °C, DCM, 0.05 mM of **7**, 16 hours, 2.2 equiv. DIPEA) followed by addition of propyl amine. *In situ* trapping of an intermediate such as aziridine **9** with propyl amine should generate amide **10** (Fig. 2). Upon workup, amide **7** (46%) and oxazoline **8** (51%) were isolated, confirming the absence of aziridine **9**.

Table 3 Heterocycles generated from amides **6**, **13**, **14**, **17–23** with reagent **4**

Entry	Starting material	Product	Yield
1	benzoic acid	 **5**	50%
2	**6**		72%
3	**17**		94%
4	benzoic acid	 **26**	55%
5	**13**		71%
6	**20**		99%
7	**14**	 **27**	11%
8	**21**		31%
9	**18**	 **28**	85%
10	**19**	 **29**	98%
11	**15**	 **30**	57%
12	**22**		95%
13	**23**	 **31**	88%

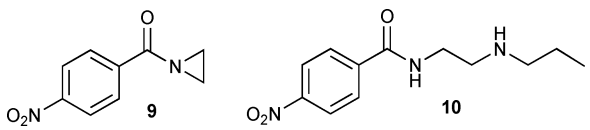


Fig. 2 Structures **9** and **10**.

A plausible explanation for the recovery of amide **7** (or **6**) in the optimisation reactions is that both the hydroxyl and amide groups are blocked as oxyphosphonium salts and therefore the cyclisation reaction cannot take place. Upon workup these phosphonium salts would be hydrolysed back to amide **7** (or **6**).

Using the optimized conditions and reagent **4** we sought to extend this reaction to the preparation of other heterocycles. Benzoyl chloride was reacted with 3-amino-1-propanol, 4-amino-1-butanol or cysteamine in the presence of triethylamine to give amides **13**, **14** and **15** (99%, 81% and 93% yield respectively). Cyclisation of amides **13** and **14** with reagent **4** in the presence of DIPEA with slow addition of amide and DIPEA gave dihydro-1,3-oxazine **26**, and tetrahydro-1,3-oxazepine **27** (entries 5 and 7, Table 3). In contrast, cyclisation of amide **15** with reagent **4** generated thiazoline **30** (57%, entry 11, Table 3) in conjunction with disulfide **24** (8%, Fig. 3). Disulfide **24** was formed through mono reduction of the bis-phosphine oxide, as reported elsewhere.[31]

To improve the yields we considered the use of an acid-labile protecting group on the hydroxyl or thiol group of amides **6**, **13**, **14** and **15**, which would be deprotected *in situ* by the expelled triflic acid if no base is present in the reaction. There is a literature report of the formation of a thiazoline ring within peptides from

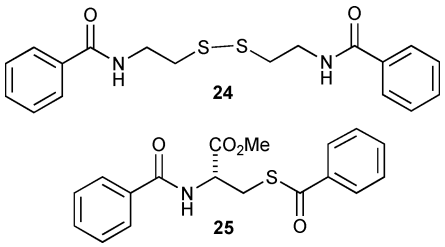
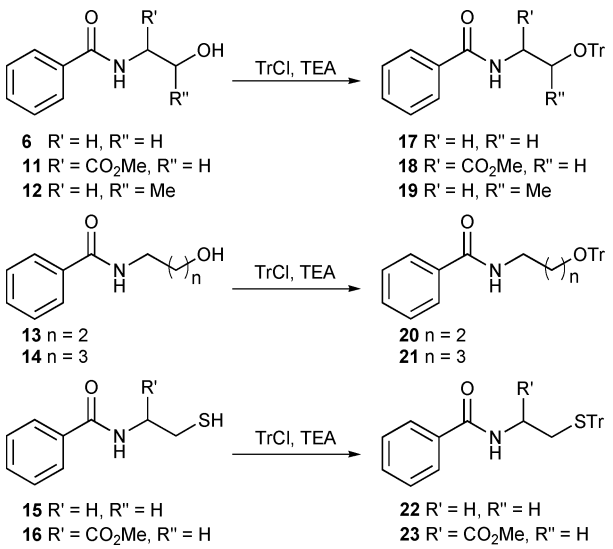


Fig. 3 Structures **24** and **25**.

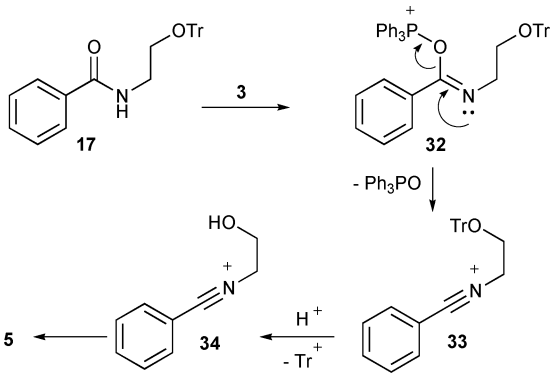
cyclisation of Tr-S-cysteine peptides.[32] We therefore applied the trityl protecting group to our hydroxy and thiol amides. Treatment of amides **6**, **13**, **14** and **15**, with trityl chloride and DIPEA or triethylamine gave trityl derivatives **17**, **20**, **21** and **22** (93%, 99%, 65% and 84% respectively, Scheme 4). Trityl derivatives **17** and **20** were stable upon standing in $CDCl_3$ for 24 hours, whereas trityl derivative **21** converted to a 62:38 mixture of amide **14** and **21**, as determined by ^{1}H NMR spectroscopy. However, trityl derivative **21** was stable in the solid form.



Scheme 4 Synthesis of trityl derivatives **17–23**.

Cyclisation of trityl derivatives **17**, **20**, **21** and **22** with reagent **4**, in the absence of base, gave oxazoline **5** (94%), dihydro-1,3-oxazine **26** (99%), tetrahydro-1,3-oxazepine **27** (31%; perhaps due to the instability of **21** as noted before) and thiazoline **30** (95%) (entries 3, 6, 8 and 12, Table 3). Further examples, using commercially available starting materials, were considered. 1-Amino-2-propanol, and D,L-serine methyl ester were converted to amides **11** (95%) and **12** (94%), respectively, with benzoyl chloride in the presence of triethylamine. However, treatment of L-cysteine methyl ester with benzoyl chloride and triethylamine gave unwanted dibenzoyl product **25** (98%, Fig. 3). Instead, treatment of L-cysteine methyl ester with benzoic anhydride, and triethylamine at –78 °C, gave both amide **16** (67%) and amide **25** (30%). Amides **11**, **12**, and **16** were converted to trityl derivatives **18** (97%), **19** (97%), and **23** (72%), as described above (Scheme 4). Cyclisation of **18**, **19** and **23** with reagent **4**, in the absence of base, gave oxazolines **28** and **29**, and thiazoline **31** in excellent yields (entries 9, 10, 13; Table 3).

A mechanism for these cyclodehydrations is suggested in Scheme 5 (illustrated for the reaction of **17** with reagent **3**). Attack of the amide carbonyl in **17** on the phosphonium anhydride **3** would result in formation of the oxyphosphonium intermediate **32** with expulsion of Ph_3PO and triflic acid. Expulsion of a second molecule of Ph_3PO from **32** would generate the nitrilium intermediate **33** (analogous to the formation of benzonitrile when benzamide is treated with **3**).[33] Detritylation of **33** would generate **34**, which would undergo a (favoured) *5-endo-dig* cyclisation to give the oxazoline **5**.



Scheme 5 Suggested mechanism for the cyclodehydration of **17**.

Alternatively, if detritylation of **32** were to occur, this intermediate could also undergo loss of Ph_3PO to generate **34** (a *5-endo-trig* cyclisation at this stage is possible, but this is disfavoured by Baldwin's rules).[34] Another possibility is that intermediate **33** could form **5** directly (attack by the trityl oxygen on the nitrilium carbon, followed by loss of the trityl cation). However, based on related work on the synthesis of cyclic amidines (e.g., using **3**, X = NTr, R = Ph),[35] it was found that the reaction failed when carried out in the presence of DIPEA. This suggests that detritylation is required for the reaction to proceed.

Conclusions

In summary, the versatility of reagent **4** as a general dehydrating-type reagent to access simple heterocycles has been demonstrated by the synthesis of oxazolines, thiazolines, a dihydro-1,3-oxazine and a tetrahydro-1,3-oxazepine. The preferred conditions for dehydration (1.0 equiv. reagent **3** or **4**, 22 °C, DCM, 0.05 mM of **6** or **7**, 2 hours, 2.2 equiv. DIPEA) were established, using the reaction between β-hydroxy amides **6** or **7** and reagents **3** or **4**. Oxazolines **5** and **8** were obtained in moderate to good yields (typically 50–72%). Use of the acid-labile trityl protecting group on the hydroxyl or thiol group of the amide precursor significantly improved the yield of heterocycle obtained. Using reagent **4**, a range of trityl derivatives (such as **17–23**) were converted to the above mentioned heterocycles, in high yields (85–99%, apart from tetrahydro-1,3-oxazepine **27**). This identifies reagent **4** as an effective mild dehydrating reagent, with further potential for the synthesis of other heterocycles. Reagent **4** has the advantage over reagent **3** of much easier removal of the bis-phosphine oxide by-product.

Experimental

For general experimental procedures see ESI.† Preparation of reagents **3**[29] and **4**[28] are described elsewhere.

Representative example for the preparation of 2-phenyl-4,5-dihydro-1,3-oxazole (5) from benzoic acid and 2-amino-1-ethanol using reagent 4

Freshly distilled triflic anhydride (276 μL, 1.64 mmol) was added slowly to a solution of 1,2-bis(diphenylphosphinyl)ethane (980 mg, 2.46 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C under a nitrogen atmosphere. A thick white precipitate was formed and left to stir at 0 °C for 30 minutes. Benzoic acid (100 mg, 0.82 mmol) was added and the mixture was warmed to room temperature and then stirred for 1 hour. 2-Amino-1-ethanol (49 μL, 0.82 mmol) and DIPEA (426 μL, 2.46 mmol) were added simultaneously to the reaction mixture (over 5 minutes). The pale yellow mixture was stirred for 16 hours. The reaction mixture was washed with sodium hydrogen carbonate (5% aqueous solution, 2 × 30 mL), dried (anhydrous Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography (ethyl acetate/hexane, gradient from 25:75 to 100:0). Compound **5**[36,37] (61 mg, 50%) was obtained as a colourless oil.

Representative example for the preparation of amides: synthesis of *N*-(2-hydroxyethyl)benzamide (6)

Benzoyl chloride (1.65 mL, 14.2 mmol) was added dropwise to 2-amino-1-ethanol (859 μL, 14.2 mmol) and triethylamine (1.9 mL, 14.2 mmol) in dry CH_2Cl_2 (100 mL), and the mixture stirred at room temperature under a nitrogen atmosphere for 16 hours. The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography (ethyl acetate/hexane, gradient from 10:90 to 100:0). Compound **6**[38] (1.71 g, 73%) was obtained as an amorphous white solid. Mp 56–58 °C (lit.,[38] mp 56–57 °C).

Representative example for the cyclisation of amides *via* direct addition: synthesis of 2-phenyl-4,5-dihydro-1,3-oxazole (5)

Triflic anhydride (102 μL, 0.61 mmol) and 1,2-bis(diphenylphosphinyl)ethane (313 mg, 0.73 mmol) were reacted in dry CH_2Cl_2 (10 mL) according to the representative procedure above. *N*-(2-Hydroxyethyl)benzamide (**6**) (100 mg, 0.61 mmol) and DIPEA (231 μL, 1.33 mmol) were added to the reaction mixture. The pale yellow mixture was warmed to room temperature and then stirred for 16 hours. The reaction mixture was washed with sodium hydrogen carbonate (5% aqueous solution, 2 × 30 mL), dried (anhydrous Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography (ethyl acetate/hexane, gradient from 25:75 to 100:0). Compound **5**[36,37] (51 mg, 57%) was obtained as a colourless oil, identical by TLC and ^{1}H NMR spectroscopy to that obtained previously.

Representative example for the cyclisation of amides with slow addition time: synthesis of 2-phenyl-4,5-dihydro-1,3-oxazole (5)

Triflic anhydride (306 μL, 1.82 mmol) and 1,2-bis(diphenylphosphinyl)ethane (938 mg, 2.2 mmol) were reacted in dry CH_2Cl_2 (30 mL) according to the representative procedure above. *N*-(2-hydroxyethyl)benzamide (**6**) (300 mg, 1.82 mmol) and DIPEA (692 μL, 4.0 mmol) in dry CH_2Cl_2 (5 mL) were added dropwise (over 5 minutes) to the reaction mixture. The pale yellow mixture was warmed to room temperature and then stirred for 2 hours. The reaction mixture was washed with sodium hydrogen carbonate (5% aqueous solution, 2 × 30 mL), dried (anhydrous Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography (ethyl acetate/hexane, gradient from 10:90 to 100:0). Compound **5**[36,37] (188 mg, 70%) was obtained as a colourless oil, identical by TLC and ^{1}H NMR spectroscopy to that obtained previously. Amide **6**[38] (88 mg, 29%) was also recovered.

Representative example for the preparation of trityl derivatives: synthesis of *N*-[(2-trityloxy)ethyl] benzamide (17)

Tritylchloride (1.69 g, 6.05 mmol) was added to *N*-(2-hydroxyethyl)benzamide (**6**) (500 mg, 3.03 mmol) and DIPEA (1.58 mL, 9.08 mmol) in dry CH_2Cl_2 (25 mL), and the mixture stirred at room temperature under a nitrogen atmosphere for 16 hours. The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography (ethyl acetate/hexane, gradient from 10:90 to 50:50). Compound **17**[39] (1.15 g, 93%) was obtained as an amorphous white solid. Mp 139–141 °C. (lit.,[39] mp 135–136 °C); ν_{max}/cm^{-1} 3270, 3070, 2917, 1642, 1556 and 1317. δ_H(400 MHz; $CDCl_3$) 3.37 (2 H, t, *J* 5.3, H-2), 3.67 (2 H, dt, *J* 5.3 and 5.3, H-1), 6.45 (1 H, br s, NH), 7.22–7.32 [9 H, m, *m*-C(C_6H_5)$_3$ and *p*-C(C_6H_5)$_3$], 7.43–7.47 [8 H, m, *m*-C_6H_5 and *o*-C(C_6H_5)$_3$], 7.50–7.54 (1 H, m, *p*-C_6H_5), 7.73–7.76 (2 H, m, *o*-C_6H_5); δ_C(100 MHz; CD_3OD) 41.2 (C-1), 63.7 (C-2), 87.9 [*C*(C_6H_5)$_3$], 128.1 [*p*-C(C_6H_5)$_3$], 128.3 (*o*-C_6H_5), 128.8 [*m*-C(C_6H_5)$_3$], 129.6 (*m*-C_6H_5), 129.8 [*o*-C(C_6H_5)$_3$], 132.7 (*p*-C_6H_5), 135.8 (*i*-C_6H_5), 145.5 [*i*-C(C_6H_5)$_3$], 170.4 (C=O); *m*/*z* (ES+) 430.1756 (M + Na^+ $C_{28}H_{25}NO_2Na$ requires 430.1777), 430.2 (M + Na^+, 100%), 414.3 (M + Li^+, 100%), 243.0 [C(C_6H_5)$_3^+$, 76%].

N-Benzoyl-*O*-tritylserine methyl ester (18)

Tritylchloride (936 mg, 3.36 mmol), *N*-benzoylserine methyl ester (**11**) (500 mg, 2.24 mmol) and triethylamine (624 μL, 4.48 mmol) were reacted in dry CH_2Cl_2 (30 mL) according to the representative procedure above. Compound **18** (1.01 g, 97%) was obtained as an amorphous white solid. Mp 132–134 °C; ν_{max}/cm^{-1} 3248, 3060, 2942, 1746, 1635 and 1207. δ_H(400 MHz; $CDCl_3$) 3.53 (1 H, dd, *J* 2.9 and 9.2, CH_2), 3.68 (1 H, dd, *J* 2.9 and 9.2, CH_2), 3.81 (3 H, s, CH_3), 4.92 (1 H, ddd, *J* 2.9, 5.4 and 8.0, α-CH), 7.01 (1 H, br d, *J* 8.0, NH), 7.20–7.29 [9 H, m, *p*-C(C_6H_5)$_3$ and *m*-C(C_6H_5)$_3$], 7.36–7.39 [6 H, m, *o*-C(C_6H_5)$_3$], 7.44–7.48 (2 H, m, *m*-C_6H_5), 7.52–7.55 (1 H, m, *p*-C_6H_5), 7.77–7.79 (2 H, m, *o*-C_6H_5); δ_C(100 MHz; $CDCl_3$) 52.6 (CH_3), 53.1 (α-CH), 63.7 (CH_2), 86.6 [*C*(C_6H_5)$_3$], 127.1 (*o*-C_6H_5), 127.2 [*p*-C(C_6H_5)$_3$], 127.9 [*m*-C(C_6H_5)$_3$], 128.5 [*o*-C(C_6H_5)$_3$], 128.6 (*m*-C_6H_5), 131.8 (*p*-C_6H_5), 134.0 (*i*-C_6H_5), 143.4 [*i*-C(C_6H_5)$_3$], 166.9 [C(O)N], 171.1 [C(O)O]; *m*/*z* (ES+) 488.1819 (M + Na^+ $C_{30}H_{27}NO_4Na$ requires 488.1832), 488.3 (M + Na^+, 58%), 243.0 [C(C_6H_5)$_3^+$, 100%].

N-[(2-Trityloxy)propyl]benzamide (19)

Trityl chloride (1.63 g, 5.86 mmol), *N*-(2-hydroxypropyl) benzamide (**12**) (700 mg, 3.91 mmol) [with approximately 6% of *N*-(2-hydroxy-1-methylethyl)benzamide present] and triethylamine (1.1 mL, 7.8 mmol) were reacted in dry CH_2Cl_2 (40 mL) according to the representative procedure above. Compound **19** (1.59 g, 97%) was obtained as an amorphous white solid containing 6% of *N*-(2-triphenylmethoxy-1-methylethyl)benzamide. Mp 110–112 °C (decomposed); ν_{max}/cm^{-1} 3322, 3047, 2929, 1639, 1541 and 1075. δ_H(400 MHz; $CDCl_3$) 1.05 (3 H, d, *J* 6.0, CH_3), 2.87–2.93 (1 H, m, H-1), 3.29–3.36 (1 H, m, H-1), 3.79–3.85 (1 H, m, H-2), 6.35 (1 H, br s, NH), 7.23–7.32 [9 H, m, *p*-C(C_6H_5)$_3$ and *m*-C(C_6H_5)$_3$], 7.38–7.42 (2 H, m, *m*-C_6H_5), 7.44–7.53 [7 H, m, *p*-C_6H_5 and *o*-C(C_6H_5)$_3$], 7.65–7.67 (2 H, m, *o*-C_6H_5); δ_C(100 MHz; $CDCl_3$) 19.9 (CH_3), 45.0 (C-1), 69.0 (C-2), 87.0 [*C*(C_6H_5)$_3$], 126.8 (*o*-C_6H_5), 127.3 [*p*-C(C_6H_5)$_3$], 127.9 [*m*-C(C_6H_5)$_3$], 128.5 (*m*-C_6H_5), 128.7 [*o*-C(C_6H_5)$_3$], 131.3 (*p*-C_6H_5), 134.6 (*i*-C_6H_5), 144.8 [*i*-C(C_6H_5)$_3$], 167.2 (C=O); *m/z* (ES+) 444.1924 (M + Na^+ $C_{29}H_{27}NO_2Na$ requires 444.1934), 444.2 (M + Na^+, 39%), 243.0 [C(C_6H_5)$_3^+$, 100%].

N-[(3-Trityloxy)propyl]benzamide (20)

Trityl chloride (1.85 g, 6.64 mmol), *N*-(3-hydroxypropyl) benzamide (**13**) (793 mg, 4.42 mmol) and triethylamine (1.24 mL, 8.90 mmol) were reacted in dry CH_2Cl_2 (40 mL) according to the representative procedure above. Compound **20** (1.84 g, 99%) was obtained as an amorphous white solid. Mp 111–113 °C; ν_{max}/cm^{-1} 3365, 3047, 2934, 2868, 1634, 1534 and 1090. δ_H(400 MHz; $CDCl_3$) 1.91 (2 H, tt, *J* 5.6 and 5.6, H-2), 3.31 (2 H, t, *J* 5.6, H-3), 3.57 (2 H, dt, *J* 5.6 and 6.4, H-1), 6.70 (1 H, br s, NH), 7.22–7.32 [11 H, m, *m*-C_6H_5, *m*-C(C_6H_5)$_3$, and *p*-C(C_6H_5)$_3$], 7.41–7.46 [7 H, m, *o*-C(C_6H_5)$_3$ and *p*-C_6H_5], 7.59–7.62 (2 H, m, *o*-C_6H_5); δ_C(100 MHz; $CDCl_3$) 29.0 (C-2), 38.9 (C-1), 62.8 (C-3), 87.2 [*C*(C_6H_5)$_3$], 126.9 (*o*-C_6H_5), 127.1 [*p*-C(C_6H_5)$_3$], 127.9 [*m*-C(C_6H_5)$_3$], 128.3 (*m*-C_6H_5), 128.6 [*o*-C(C_6H_5)$_3$], 131.1 (*p*-C_6H_5), 134.6 (*i*-C_6H_5), 143.8 [*i*-C(C_6H_5)$_3$], 167.3 (C=O); *m/z* (ES+) 444.1935 (M + Na^+ $C_{29}H_{27}NO_2Na$ requires 444.1934), 444.2 (M + Na^+, 46%), 243.0 [C(C_6H_5)$_3^+$, 100%].

N-[(4-Trityloxy)butyl]benzamide (21)

Trityl chloride (995 mg, 3.57 mmol), *N*-(4-hydroxybutyl) benzamide (**14**) (230 mg, 1.19 mmol) and triethylamine (497 μL, 3.57 mmol) were reacted in dry CH_2Cl_2 (20 mL) according to the representative procedure above. TLC indicated complete conversion of compound **14** to the desired product **21**, however upon purification by silica gel column chromatography (ethyl acetate/hexane with 0.5% triethylamine, gradient from 5:95 to 50:50) part of the product decomposed and compound **21** (335 mg, 65%) was therefore obtained only in moderate yield as an amorphous white solid. Amide **14**[40] (161 mg, 31%) was also isolated.

N-[(4-Trityloxy)butyl]benzamide (21)

Mp 153–154 °C; ν_{max}/cm^{-1} 3287, 3056, 2946, 2856, 1629, 1537 and 1070. δ_H(300 MHz; $CDCl_3$) 1.66–1.77 (4 H, m, H-2 and H-3), 3.14 (2 H, t, *J* 5.8, H-4), 3.46 (2 H, dt, *J* 5.8 and 6.8, H-1), 6.20 (1 H, br s, NH), 7.20–7.32 [9 H, m, *m*-C(C_6H_5)$_3$ and *p*-C(C_6H_5)$_3$], 7.37–7.52 [9 H, m, *o*-C(C_6H_5)$_3$, *p*-C_6H_5 and *m*-C_6H_5], 7.69–7.73 (2 H, m, *o*-C_6H_5); δ_C(100 MHz; $CDCl_3$) 26.1 (C-2), 27.1 (C-3), 39.9 (C-1), 62.8 (C-4), 85.8 [*C*(C_6H_5)$_3$], 126.9 [*p*-C(C_6H_5)$_3$], 127.1 (*o*-C_6H_5), 127.9 [*o*-C(C_6H_5)$_3$], 128.2 [*m*-C(C_6H_5)$_3$], 128.2 (*m*-C_6H_5), 131.0 (*p*-C_6H_5), 134.7 (*i*-C_6H_5), 144.1 [*i*-C(C_6H_5)$_3$], 166.1 (C=O); *m/z* (ES+) 458.2076 (M + Na^+ $C_{30}H_{29}NO_2Na$ requires 458.2091), 458.3 (M + Na^+, 40%), 243.0 [C(C_6H_5)$_3^+$, 100%].

N-[2-(Triphenylmethylsulfanyl)ethyl] benzamide (22)

Tritylchloride (308 mg, 1.10 mmol), *N*-(2-sulfanylethyl) benzamide (**15**) (100 mg, 0.55 mmol) and DIPEA (288 μL, 1.66 mmol) were reacted in dry CH_2Cl_2 (5 mL) according to the representative procedure above. Compound **22** (195 mg, 84%) was obtained as an amorphous white solid. Mp 134–136 °C; ν_{max}/cm^{-1} 3326, 3273, 3044, 2921, 1632, 1541 and 1310. δ_H(400 MHz; $CDCl_3$) 2.53 (2 H, t, *J* 6.2, H-2), 3.30 (2 H, dt, *J* 6.2 and 6.2, H-1), 6.24 (1 H, br s, NH), 7.18–7.28 [9 H, m, *p*-C(C_6H_5)$_3$ and *m*-C(C_6H_5)$_3$], 7.40–7.44 [8 H, m, *o*-C(C_6H_5)$_3$ and *m*-C_6H_5], 7.47–7.52 (1 H, m, *p*-C_6H_5), 7.69–7.72 (2 H, m, *o*-C_6H_5); δ_C(100 MHz; $CDCl_3$) 32.1 (C-2), 38.5 (C-1), 66.8 [*C*(C_6H_5)$_3$], 126.8 [*p*-C(C_6H_5)$_3$], 126.9 (*o*-C_6H_5), 127.9 [*m*-C(C_6H_5)$_3$], 128.5 (*m*-C_6H_5), 129.5 [(*o*-C(C_6H_5)$_3$)], 131.4 (*p*-C_6H_5), 134.4 (*i*-C_6H_5), 144.6 [*i*-C(C_6H_5)$_3$], 167.2 (C=O); *m/z* (ES+) 446.1555 (M + Na^+ $C_{28}H_{25}NOSNa$ requires 446.1549), 446.2 (M + Na^+, 100%), 430.3 (M + Li^+, 44%), 243.0 [C(C_6H_5)$_3^+$, 100%].

***N*-Benzoyl-*S*-tritylcysteine methyl ester (23)**

Tritylchloride (365 mg, 1.31 mmol), *N*-benzoylcysteine methyl ester (**16**) (209 mg, 0.87 mmol) and triethylamine (243 μL, 1.75 mmol) were reacted in dry CH_2Cl_2 (15 mL) according to the representative procedure above. Compound **23**[41] (301 mg, 72%) was obtained as an amorphous white solid. Mp 130–133 °C (lit.,[41] mp 132–134 °C). δ_H(300 MHz; $CDCl_3$) 2.78 (2 H, m, CH_2), 3.75 (3 H, s, CH_3), 4.84 (1 H, dt, *J* 6.7 and 10.4, CH), 6.72 (1 H, br d, *J* 10.4, NH), 7.19–7.28 [8 H, m, *m*-C(C_6H_5)$_3$ and *m*-C_6H_5], 7.37–7.56 [9 H, m, *o*-C(C_6H_5)$_3$, *p*-C(C_6H_5)$_3$ and *p*-C_6H_5], 7.76–7.79 (2 H, m, *o*-C_6H_5); *m/z* (ES+) 482.3 (M + H^+, 8%), 504.2 (M + Na^+, 8%), 488.2 (M + Li^+, 100%), 243.0 [C(C_6H_5)$_3^+$, 100%].

Representative example for the cyclisation of trityl derivatives: synthesis of 2-phenyl-4,5-dihydro-1,3-oxazole (5)

Triflic anhydride (186 μL, 1.10 mmol) was added slowly to a solution of 1,2-bis(diphenylphosphinyl)ethane (539 mg, 1.25 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C under a nitrogen atmosphere. *N*-(2-Triphenylmethoxyethyl)benzamide (**17**) (300 mg, 0.74 mmol) in dry CH_2Cl_2 (15 mL) was added dropwise to the reaction mixture. The reaction was stirred at room temperature for 2 hours. The reaction mixture was washed with sodium hydrogen carbonate (5% aqueous solution, 2 × 20 mL), dried (anhydrous Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography (ethyl acetate/hexane, gradient from 10:90 to 100:0). Compound **5**[36,37] (102 mg, 94%) was obtained as a colourless oil, identical by TLC and ^{1}H NMR spectroscopy to that obtained previously.

2-Phenyl-5,6-dihydro-4H-1,3-oxazine (26)

Triflic anhydride (180 μL, 1.07 mmol), 1,2-bis(diphenylphosphinyl)ethane (521 mg, 1.21 mmol) and *N*-(3-triphenylmethoxypropyl)benzamide (**20**) (300 mg, 0.71 mmol) were reacted in dry CH_2Cl_2 (15 mL) according to the representative procedure above. Compound **26**[42] (113 mg, 99%) was obtained as a colourless oil.

2-Phenyl-4,5,6,7-tetrahydro-1,3-oxazepine (27)

Triflic anhydride (55 μL, 0.33 mmol), 1,2-bis(diphenylphosphinyl)ethane (160 mg, 0.37 mmol) and *N*-(4-triphenylmethoxybutyl)benzamide (**21**) (95 mg, 0.22 mmol) were reacted in dry CH_2Cl_2 (5 mL) according to the representative procedure above. Compound **27** (12 mg, 31%) was obtained as a colourless oil. ν_{max}/cm^{-1} 3436, 3052, 2974, 2880, 1626, 1426 and 1266. δ_H(400 MHz; $CDCl_3$) 1.91 (4 H, br s, H-5 and H-6), 3.44 (2 H, br s, H-7), 3.65 (2 H, br s, H-4), 7.38–7.42 (3 H, m, *m*-C_6H_5 and *p*-C_6H_5), 7.50–7.53 (2 H, m, *o*-C_6H_5); δ_C(100 MHz; $CDCl_3$) 24.5 (C-5 or C-6), 26.1 (C-5 or C-6), 46.1 (C-4), 49.6 (C-7), 127.1 (*o*-C_6H_5), 128.2 (*m*-C_6H_5), 129.7 (*p*-C_6H_5), 137.2 (*i*-C_6H_5), 169.7 (C-2); *m*/*z* (ES+) 175.0997 (M + H^+ $C_{11}H_{13}NO$ requires 175.0997), 175.8 (M + H^+, 100%), 181.9 (M + Li^+, 100%).

Methyl 2-phenyl-4,5-dihydro-1,3-oxazole-4-carboxylate (28)

Triflic anhydride (163 μL, 0.97 mmol), 1,2-bis(diphenylphosphinyl)ethane (472 mg, 1.10 mmol) and methyl *N*-benzoyl-*O*-(triphenylmethylethyl)serinate (**18**) (300 mg, 0.64 mmol) were reacted in dry CH_2Cl_2 (13 mL) according to the representative procedure above. Compound **28**[43] (112 mg, 85%) was obtained as a pale yellow oil. δ_H(400 MHz; $CDCl_3$) 3.83 (3 H, s, CH_3), 4.61 (1 H, dd, *J* 8.3 and 10.7, H-5), 4.71 (1 H, dd, *J* 8.3 and 8.3, H-5), 4.97 (1 H, dd, *J* 8.3 and 10.7, H-4), 7.40–7.44 (2 H, m, *m*-C_6H_5), 7.49–7.53 (1 H, m, *p*-C_6H_5), 7.98–8.00 (2 H, m, *o*-C_6H_5); *m*/*z* (ES+) 206.0803 (M + H^+ $C_{11}H_{12}NO_3$ requires 206.0812), 205.9 (M + H^+, 52%).

5-Methyl-2-phenyl-4,5-dihydro-1,3-oxazole (29)

Triflic anhydride (180 μL, 1.07 mmol), 1,2-bis(diphenylphosphinyl)ethane (521 mg, 1.21 mmol) and *N*-(2-triphenylmethoxypropyl)benzamide (**19**) (300 mg, 0.71 mmol) [with approximately 6% of *N*-(2- triphenylmethoxy-1-methylethyl)benzamide present] were reacted in dry CH_2Cl_2 (15 mL) according to the representative procedure above. Compound **29**[44] (112 mg, 98%) was obtained as a colourless oil containing approximately 6% 4-methyl-2-phenyl-4,5-dihydro-1,3-oxazole.[44]

5-Methyl-2-phenyl-4,5-dihydro-1,3-oxazole (29). δ_H(400 MHz; $CDCl_3$) 1.43 (3 H, d, *J* 6.4, CH_3), 3.60 (1 H, dd, *J* 7.2 and 14.4, H-4), 4.14 (1 H, dd, *J* 9.6 and 14.4, H-4), 4.80–4.88 (1 H, m, H-5), 7.39–7.43 (2 H, m, *m*-C_6H_5), 7.46–7.49 (1 H, m, *p*-C_6H_5), 7.94–7.96 (2 H, m, *o*-C_6H_5); δ_C(100 MHz; $CDCl_3$) 21.1 (CH_3), 61.6 (C-4), 76.2 (C-5), 128.1 (*o*-C_6H_5), 128.2 (*i*-C_6H_5), 128.3 (*m*-C_6H_5), 131.2 (*p*-C_6H_5), 163.7 (C-2); *m*/*z* (ES+) 162.0907 (M + H^+ $C_{10}H_{12}NO$ requires 162.0913), 161.8 (M + H^+, 100%).

4-Methyl-2-phenyl-4,5-dihydro-1,3-oxazole. δ_H(400 MHz; $CDCl_3$) 1.43 (3H, d *J* 6.4, CH_3), 3.60 (1H, dd, *J* 7.2, 14.4, H-4), 4.14 (1H, dd, *J* 9.6, 14.4, H-4), 4.80–4.88 (1H, m, H-5), 7.39–7.43 (2H, m, *m*-C_6H_5), 7.46–7.49 (1H, m, *p*-C_6H_5), 7.94-7.96 (2H, m, *o*-C_6H_5); δ_C(100 MHz; $CDCl_3$) 21.4 (CH_3), 62.0 (C-4), 74.0 (C-5), 128.1 (*o*-C_6H_5), 128.2 (*i*-C_6H_5), 128.3 (*m*-C_6H_5), 131.2 (*p*-C_6H_5), 163.7 (C-2).

2-Phenyl-4,5-dihydro-1,3-thiazole (30)

Triflic anhydride (179 μL, 1.06 mmol), 1,2-bis(diphenylphosphinyl)ethane (518 mg, 1.20 mmol) and *N*-[2-(triphenylmethylsulfanyl)ethyl]benzamide (**22**) (300 mg, 0.71 mmol) were reacted in dry CH_2Cl_2 (15 mL) according to the representative procedure above. Compound **30**[45,46] (110 mg, 95%) was obtained as a pale yellow oil.

Methyl 2-phenyl-4,5-dihydro-1,3-thiazole-4-carboxylate (31)

Triflic anhydride (89 μL, 0.53 mmol), 1,2-bis(diphenylphosphinyl)ethane (257 mg, 0.60 mmol) and *N*-[2-(triphenylmethylsulfanyl)ethyl]benzamide (**23**) (169 mg, 0.35 mmol) were reacted in dry CH_2Cl_2 (10 mL) according to the representative procedure above. Compound **31**[46,47] (68 mg, 88%) was obtained as a pale yellow oil.

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