

# Solid-Phase Parallel Synthesis of Phosphite Ligands

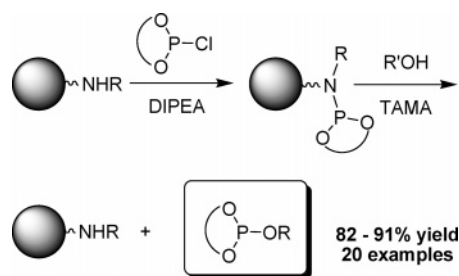
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## ABSTRACT



Various routes for the synthesis of polymer-bound phosphites and phosphoramidites have been investigated. In the presence of a suitable activator the supported phosphoramidites react cleanly with alcohols to give the corresponding monodentate phosphite ligands in solution. We have applied this novel solid-phase route in the parallel synthesis of several monodentate chiral and achiral phosphite ligands.

In the past decade (chiral) phosphite and phosphoramidite ligands have found wide applications in asymmetric catalysis.<sup>1,2</sup> In several transition-metal-catalyzed (asymmetric) reactions these ligands proved superior with respect to activity and enantioselectivity. Most notable is the successful application of monodentate ligands in the rhodium-catalyzed hydrogenation of alkenes and carbon-element double bonds.<sup>2</sup> The high-speed generation of chemical libraries offered by solid-phase organic synthesis is highly efficient, as workup and purification can be achieved by simple washing and

filtration. Moreover the site-isolation, resulting from the immobilization of the reactant on the support, can stabilize reactive intermediates and thus reduce byproduct formation. Polymer-supported ligands allow the recycling of the catalyst, and as a result of the swelling of the polymer, good mixing with the reactants is maintained.<sup>3</sup> Several groups have prepared polystyrene-supported phosphites and phosphoramidites.<sup>4</sup> Waldmann and co-workers have shown that polymer-bound phosphoramidites in copper-catalyzed enantioselective conjugate addition reactions mirrored the per-

(1) See for instance: (a) Baker, M.; Pringle, P. G. *J. Chem. Soc. Chem. Commun.* **1991**, 1292. (b) Buisman, G. J. H.; Kamer, P. C. J.; van Leeuwen, P. W. M. N. *Tetrahedron: Asymmetry* **1993**, *4*, 1625. (c) Seebach, D.; Hayakama, M.; Sakaki, J.; Schweizer, B. *Tetrahedron* **1993**, *49*, 1711. (d) Alexakis, S.; Burton, J.; Vastra, J.; Benhaim, C.; Fournioux, X.; van den Heuvel, A.; Leveque, J.-M.; Maze, F.; Rosset, S. *Eur. J. Org. Chem.* **2000**, 4011–4027. (e) Boele, M. D. K.; Kamer, P. C. J.; Lutz, M.; Spek, A. L.; de Vries, J. G.; van Leeuwen, P. W. N. M.; van Strijdonck, G. P. F. *Chem. Eur. J.* **2004**, *10*, 24, 6232–6246.

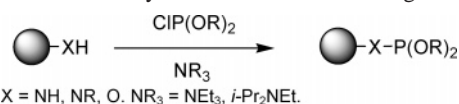
(2) (a) Minnaard, A. J.; Feringa, B. L.; Lefort, L.; de Vries, J. G. *Acc. Chem. Res.* **2007**, *40*, 1267–1277. (b) Reetz, M. T.; Mehler, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 3889–3890. (c) Ansell, J.; Wills, M. *Chem. Soc. Rev.* **2002**, *31*, 259–268.

(3) (a) McNamara, C. A.; Dixon, M. J.; Bradley, M. *Chem. Rev.* **2002**, *102*, 3275–3300. (b) Bergbreiter, D. E. *Chem. Rev.* **2002**, *102*, 3345–3384. (c) Leadbeater, N. E.; Marco, M. *Chem. Rev.* **2002**, *102*, 3217–3274. (d) Clapham, B.; Reger, T. S.; Janda, K. D. *Tetrahedron* **2001**, *57*, 4637–4662.

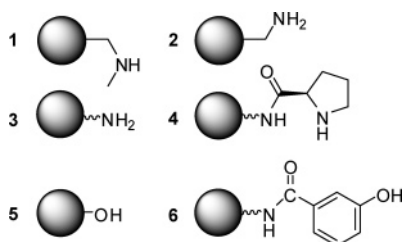
(4) (a) Jiang, Z.-D.; Meng, Z.-H. *Chin. J. Chem.* **2007**, *25*, 542–545. (b) Chen, W.; Roberts, S. M.; Whittall, J. *Tetrahedron Lett.* **2006**, *47*, 4263–4266. (c) Hu, X.-P.; Huang, J.-D.; Zeng, Q.-H.; Zheng, Z. *Chem. Commun.* **2006**, 293–295. (d) Doherty, S.; Robins, E. G.; Pal, I.; Newman, C.; Hardacre, C.; Rooney, D.; Mooney, D. A. *Tetrahedron: Asymmetry* **2003**, *14*, 1517–1527. (e) Mandoli, A.; Calamante, M.; Feringa, B. L.; Salvadoria, P. *Tetrahedron: Asymmetry* **2003**, *14*, 3647–3650. (f) Huttenloch, O.; Laxman, E.; Waldmann, H. *Chem. Eur. J.* **2002**, *8*, 4767–4780.

formance of the soluble analogues, albeit with lower activities and selectivities.<sup>4f</sup> Lefort and de Vries reported the parallel synthesis of a library of 96 phosphoramidite ligands in solution and its application in asymmetric hydrogenation.<sup>5</sup> Combinatorial solid-phase techniques can thus speed up both the synthesis and the testing of libraries of ligands, provided that efficient synthetic protocols to structural diversity exist. The reported phosphoramidites and phosphites are, however, almost exclusively binol (1,1'-binaphthalene-2,2'-diol)-based, prepared by reacting the corresponding chlorophosphites with, respectively, amino- or hydroxy-functionalized resins (Scheme 1).

**Scheme 1.** Synthesis of Solid-Phase Ligands



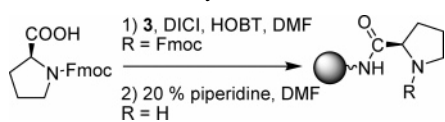
Here we report efficient routes for the solid-phase synthesis of monodentate phosphoramidites and phosphites, as well as the application of resin-bound phosphoramidites as intermediates in the combinatorial synthesis of (chiral) homogeneous monodentate phosphite ligands. Figure 1



**Figure 1.** Resins used in this study. The balls represent the polystyrene supports (DVB-PS), and the wavy lines (~~~) represent poly(ethylene glycol) linkers (TentaGel); **1** is *N*-methyl aminomethylated polystyrene, **2** is aminomethylated polystyrene, **3** is TentaGel-S-NH<sub>2</sub>, **4** is **3** functionalized with a proline moiety, **6** is **3** functionalized with a phenol moiety, and **5** is 4-hydroxyphenol polymer-bound.

depicts the resins used in this study, which were prepared by standard peptide coupling reactions (Scheme 2).

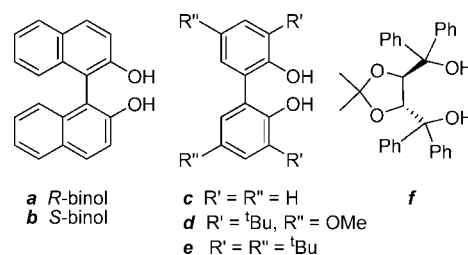
**Scheme 2.** Synthesis of Resin **4**



Reaction of the resins with an excess (1.2–3 equiv) of chlorophosphites, in the presence of a tertiary amine as a

(5) Lefort, L.; Boogers, J. A. F.; de Vries, A. H. M.; de Vries, J. G. *Org. Lett.* **2004**, *6*, 1733–1735.

base in DCM, toluene, or THF as a solvent, allowed the straightforward synthesis of a variety of (chiral) immobilized phosphoramidites and phosphites (Scheme 1). Figure 2



**Figure 2.** Diols used in the synthesis of supported ligands.

depicts the diols applied in the synthesis of the supported ligands.<sup>6</sup> The presence of phosphorus-based compounds on the resin was monitored with <sup>31</sup>P gel-phase NMR,<sup>7,8</sup> and the observed chemical shifts were in accordance with their homogeneous analogues. The bis-aryl-based phosphoramidites supported on resin **1** and **2** showed two fairly broad signals around 148 and 139 ppm, respectively, in a 10:6 (**1**) or 10:2 ratio (**2**).<sup>9,10</sup> On the basis of the chemical shifts, the downfield signals are assigned to the anticipated phosphoramidites, while the upfield signals remain unidentified, although the values suggest the presence of supported phosphites.<sup>11</sup>

This thus suggests the presence of a second type of functionality, possibly an alcohol, on the resin. The primary amine-functionalized TentaGel resin **3** yielded *S*-binol (**b**)-based phosphoramidite **3b**, but it proved very prone to hydrolysis; next to the main signal at 152 ppm, several signals between 15 and –8 ppm were observed (~40%). Phosphoramidites supported on pyrrolidine-functionalized **4** showed a higher stability. The ligands were formed in good purity, with small amounts (<2%) of hydrolysis products as the major byproduct. The *R*-binol (**a**), bisphenol (**c**) and the aliphatic taddol (1,1,4,4-tetraphenyl-2,3-*O*-isopropylidene-*L*-threitol, **f**) based phosphoramidites showed single resonances at 152 (**4a**), 151 (**4c**), and 143 ppm (**4f**). Applying hydroxy-functionalized resin **5** in this reaction yielded supported phosphites cleanly, displaying typical phosphite resonances in the <sup>31</sup>P NMR (128–146 ppm). Since the purification of the resins can be achieved by a simple washing procedure, the use of an excess of partially hydrolyzed (~30%) chlorophosphite does not compromise the purity of the resulting immobilized ligands.

(6) The supported ligands are referred to with a code, in which the numbers indicate the support, and the letters refer to the diol or alcohol moiety.

(7) Bardella, F.; Eritja, R.; Pedroso, E.; Giralt, E. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2193–2196.

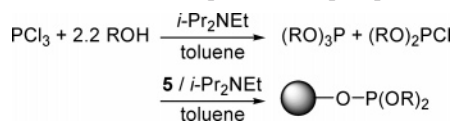
(8) The use of THF resulted in considerably sharper signals than C<sub>6</sub>D<sub>6</sub>, which we attribute to an increased swelling. Similarly TentaGel gave sharper signals than unmodified polystyrene.

(9) For **1f** a similar pattern was observed at 140 and 132 ppm.

(10) During the preparation of this manuscript Jiang et al. reported the synthesis of **1a** and **1f**.<sup>4a</sup>

The synthesis of chlorophosphites from phenols and  $\text{PCl}_3$  is not trivial, as it frequently leads to mixtures containing additional species such as dichlorophosphites and phosphites. We therefore investigated solid-phase routes that can overcome these problems. We anticipated that by pushing the equilibrium toward the formation of a mixture of chlorophosphite and phosphite, the formation of dichlorophosphite, and thus of resin-bound byproducts, could be repressed. Indeed reacting  $\text{PCl}_3$  with 2.2 equiv of 2-phenylphenol (**j**), which should lead to a chlorophosphite/phosphite ratio of 77:23, and the subsequent reaction with the hydroxy-functionalized resin **5** lead to the clean formation of **5j**<sub>2</sub> (Scheme 3). Next we investigated the use of resin bound

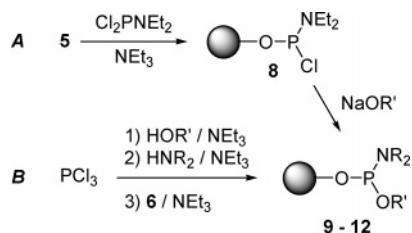
**Scheme 3.** Use of Phosphite/Chlorophosphite Mixture



dichlorophosphites. Reaction of **5** with an excess  $\text{PCl}_3$  leads to the clean formation of the corresponding dichlorophosphite (**7**), as indicated by a single resonance at 180 ppm observed with  $^{31}\text{P}$  gel-phase NMR. Subsequent reaction of **7** with 2,4,6-trimethylphenol (**k**) yielded the corresponding phosphite **5k**<sub>2</sub> as the sole product. The approach is not limited to phenols; reaction with bisphenol (**c**) yielded **5c**.

To allow maximum structural diversity (“bottom up” approach), we explored routes to synthesize solid-phase phosphoramidites containing two different alcohol moieties (Scheme 4). After reaction of **5** with  $\text{Et}_2\text{NPCl}_2$ , a single

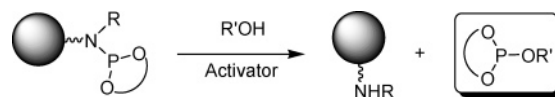
**Scheme 4.** Solid-Phase Synthesis of Phosphoramidites



resonance at 168 ppm was observed with  $^{31}\text{P}$  gel-phase NMR spectroscopy, which we assign to the supported chlorophosphoramidite (**8**, Route A). Subsequent reaction with the sodium salt of 2-phenylphenol or 2-(pyridine-2-yl)ethanol yielded the corresponding racemic phosphoramidites (**9** and **10**) as the sole products, displaying characteristic resonances at 143 and 146 ppm, respectively. Alternatively homogeneous in situ formed chlorophosphoramidites based on 2-*tert*-butyl-4-methylphenol were reacted with resin **6**, leading to the clean formation of the supported phosphoramidites (Route B). By variation of the secondary amine applied in the synthesis (*i*-Pr<sub>2</sub>HN or pyrrolidine), two different racemic phosphoramidites (**11** and **12**) were synthesized in situ.

Inspired by the efficiency of fully automated DNA synthesis,<sup>12</sup> we investigated the potential of our phosphoramidites as synthetic intermediates for phosphites. By applying phosphoramidites linked to the solid support via the amido functionality, acid-catalyzed substitution of the P–N bond by alcohols should thus yield monophosphites liberated from the resin (Scheme 5). This route would therefore allow the combinatorial solid-phase synthesis of phosphites. First we

**Scheme 5.** Solid-Phase Phosphoramidites as Intermediates in the Synthesis of Phosphites



investigated the efficiency of several activators. In the absence of an acid activator, no reaction was observed for any of the phosphoramidites with methanol. 1*H*-Tetrazole, universally applied as activator in DNA synthesis, proved inactive for the di-aryl phosphoramidites **4a** and **4c**, whereas with the aliphatic **4f** it gave rise to approximately 10% conversion in 12 h (Table 1, entry 1). Other activators like

**Table 1.** Combinatorial Solid-Phase Synthesis of Phosphites

entry	resin	alcohol (1.5 equiv)	activator (1 equiv)	time (min)	yield <sup>a</sup> (%)
1	<b>4f</b>	MeOH	tetrazole	720	10
2	<b>4f</b>	MeOH	TAMA	30	82
3	<b>4f</b>	(–)-menthol	TAMA	60	84
4	<b>4a</b>	BnOH	TAMA	60	84
5	<b>4d</b>	MeOH	TAMA	30	91
6	<b>1f</b>	MeOH	TAMA	30	88
7	<b>1f</b>	MeOH	TAMA	30	85 <sup>b</sup>
8	<b>1c</b>	MeOH	TAMA	30	0

<sup>a</sup> Yields based on the loading of **4** and **1**, respectively. <sup>b</sup> **1** recovered from entry 6 was applied as support for **1f**.

*N*-methyl-imidazolium trifluoroacetate and pyridinium-tetrafluoroborate were tested but proved unsatisfactory, as conversion to product was slow or incomplete and the prolonged reaction times promoted side product formation via oxidation and hydrolysis. *N*-Methylanilinium trifluoroacetate<sup>13</sup> (TAMA) (1 equiv) was found to be the most suitable activator, resulting in fast product formation (within 30 min) in good yields (>80%) for both the aliphatic and the bis-aryl phosphoramidites immobilized on resin **4** (entries 2–5). A short plug filtration over silica proved sufficient to remove the TAMA. Applying catalytic amounts of TAMA slowed down the reaction considerably.

(11) Peña, D.; Minnaard, A. J.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 14552–14553.

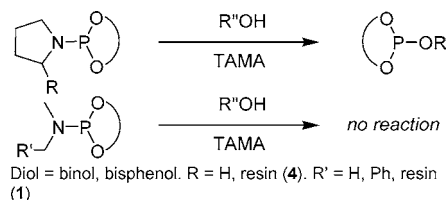
(12) Beaucage, S. L.; Iyer, R. P. *Tetrahedron* **1992**, *48*, 2223–2311. This process is based on the protonation of the nitrogen of a phosphoramidite by an acid activator, followed by reaction with an alcohol to give the corresponding phosphite

(13) Fourrey, J.-L.; Varenne, J. *Tetrahedron Lett.* **1984**, *25*, 4511–4514.

We applied the optimized reaction conditions to in situ generated resins **4a–4f** in the synthesis of 20 (chiral) monophosphites using various alcohols. This approach proves the potential for a parallel synthesis of a monodentate phosphite library. All phosphites were obtained in high yields (82–91%) and purities (>97%). Both primary alkyl and more sterically hindered alcohols can be applied, although the latter need slightly longer reaction times to reach full conversion (entries 3 and 4). To find the optimal combination of stability and reactivity for phosphite release, we also tested supported phosphoramidites with different amido groups. For the commercially available *N*-methylaminomethyl resin (**1**), phosphite formation depended highly on the diol moiety. The aliphatic taddol based phosphoramidite **1f** gave the corresponding monophosphites in good yields (80–89%, entry 6). This result indicates that the presence of the second functionality on the resin, as observed by <sup>31</sup>P NMR (vide supra), does not hamper the overall reaction significantly. Resin **1** could be successfully reused as support for the solid-phase synthesis of taddol-based phosphites, with only a slight drop in yield between successive runs (88% to 85%, entries 6–7), indicating the regeneration of the amino functionality on the resin. No products were observed when phosphoramidites **1a** and **1c** were applied (entry 8).<sup>14</sup> We attribute the difference in reactivity to an insufficient basicity of the *N*-methyl-benzylamine moiety ( $pK_a = 9.7$ ) in bis-aryl phosphoramidites. Since the pyrrolidine linker in **4** has a higher basicity ( $pK_a = 11.3$ ), it yields reactive phosphoramidites with both aliphatic and aromatic diols. The use of more acidic activators in combination with **1a** or **1c** led to mainly phosphite hydrolysis products. Homogeneous model compounds showed similar behavior; bisphenol, binol, and taddol phosphoramidites with a pyrrolidine amido substituent gave the corresponding phosphites, whereas for *N*-methyl-benzyl-

amine and dimethylamino based phosphoramidites, only the taddol derivative was found to be reactive (Scheme 6).

**Scheme 6.** Effect of the Leaving Group in Di-aryl Phosphoramidites



In summary, facile synthetic routes to structural diverse solid-phase (chiral) monodentate phosphite and phosphoramidite ligands have been developed. In addition the polymer-supported phosphoramidites proved valuable intermediates for the combinatorial synthesis of homogeneous (chiral) monodentate phosphites. We found that the acidity of the activator, the leaving group capacity of the amino-functionalized resin, and the nature of the resin and the diol are all important. The easy preparation of the solid-phase phosphoramidites and the excellent yields allowed the preparation of a ligand library in a very efficient manner. A report on the performance of the solid-phase ligands in asymmetric transition-metal-catalyzed reactions is in preparation.

**Acknowledgment.** This work was supported by the NWO Combinatorial Chemistry program and DSM.

**Supporting Information Available:** Analytical data and experimental procedures for the synthesis of the resins, the solid-phase ligands and the homogeneous phosphites. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(14) Brill, W. K.-D.; Nielsen, J.; Caruthers, M. H. *J. Am. Chem. Soc.* **1991**, *113*, 3972–3980.