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# One-pot-synthesis of novel cinchonine-based phosphites

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**Abstract**

Cinchonine was employed as backbone for the synthesis of novel phosphite compounds with diol substituents. These monophosphinites were provided in one pot with the yields ranged from 63% to 75%. Their structures were confirmed by NMR spectroscopy and HRMS.


*Keywords:* Cinchona alkaloids; Diols; Chiral phosphite; Asymmetric reaction; Ligand

Readily accessible cinchona alkaloids are known to be widely used in the pharmaceutical and chemical industries [1]. They are also catalysts or co-catalysts in a variety of enantioselectivity reactions due to their general structure of five stereogenic centers and of an aromatic quinoline ring connected to an aliphatic quinuclidinebicycle [2,3]. In recent years, phosphite ligands have emerged as suitable ones for many metal-catalyzed asymmetric processes [4]. Most of them achieved excellent results, such as the monophosphinite reported by Oscar et al. [5], which gave an enantiomeric excess up to 99%*ee* in Pd-catalyzed substitution reactions. Besides, phosphites are also attractive in catalysis as they are easy to prepare from readily available alcohols and less sensitive to oxidation than phosphines [4]. Taking advantage of the high modularity, with cinchona alkaloids as highly versatile and cheap raw chiral materials, in this paper we describe the synthesis of a new family of chiral phosphites **1**–**3** (Fig. 1) derived from cinchonine.

## 1. Experimental

The synthesis of phosphites **1**–**3** is straightforward. They are easily produced in one pot from the corresponding diols and cinchonine. With the unique steric properties of the two basic donor sites (quinuclidine N atom and P atom), **1**–**3** are anticipated to coordinate with transition metals to catalyze asymmetric reactions. In general, chiral ligands possessing two different coordinating atoms should allow more regiocontrol, such as the successful ligand–*PHOX* [6].

Starting from (*S*,*S*)-1,2-bis(2-bromophenyl)ethane-1,2-diol [7] and cinchonine, phosphite **1** was obtained under the mild conditions (Scheme 1). In the first step, the optical pure 1,2-diol was completely converted to corresponding chiral phosphorochloridite **4** in a clear system. Notably, it is crucial to control the molar ratio of chiral diol with the phosphorus trichloride to 1:1 in order to achieve a good overall yield. Then, without being isolated in pure form, the

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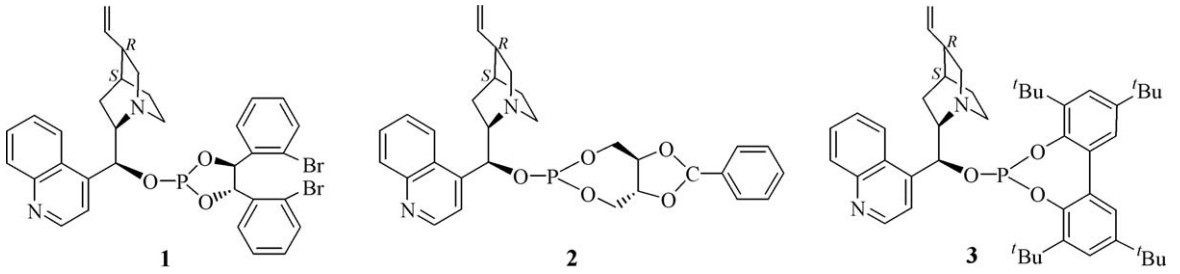
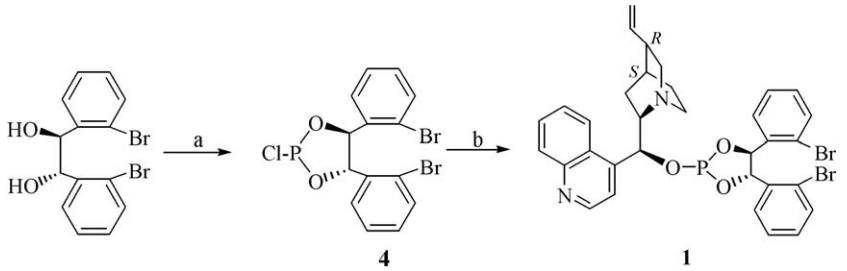


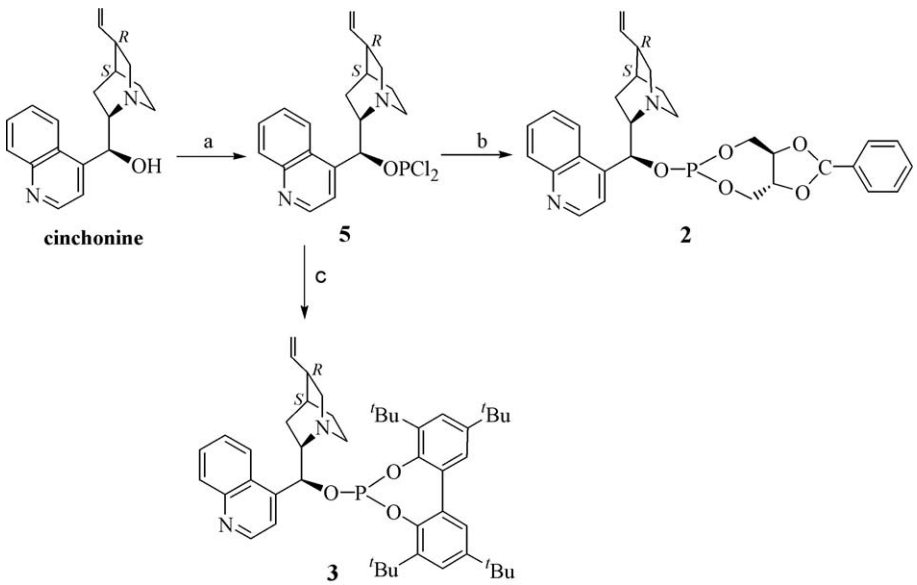

Fig. 1. The structure of novel phosphites **1–3**.




Scheme 1. Synthetic route of phosphite **1**. Reagents and conditions: (a) $PCl_3$, THF, rt, $N_2$, 5 h, 100%; (b) cinchonine, $Et_3N$, THF, 60 °C, $N_2$, 20 h, 72%.

intermediate **4** was directly treated with cinchonine to give the desired phosphite **1** in total yield of 72%. Phosphite **1** can be purified as a white solid by silica gel column chromatography.

The route shown in Scheme 1 was also considered to construct the chiral phosphites **2** and **3**. However, all the attempts to achieve them in the same manner have failed. Probably it has suffered from the backbone rigidity and steric hindrance of (*R*,*R*)-(+)-2,3-*O*-benzylene-1,4-butanediol [8] and 4,4′,6,6′-tetra-*t*-butyl-2,2′-bisphenol [9]. So a reverse approach was employed to prepare phosphites **2** and **3** (Scheme 2). Firstly, the hydroxyl group at $C_9$ in cinchonine was substituted by phosphorus trichloride in the presence of triethylamine and the corresponding cinchonine-P-Cl




Scheme 2. Synthetic route of phosphites **2** and **3**. Reagents and conditions: (a) $PCl_3$, $CHCl_3$, rt, $N_2$, 5 h, 100%; (b) (*R*,*R*)-(+)-2,3-*O*-benzylene-1,4-butanediol, $Et_3N$, $CHCl_3$, rt, $N_2$, 13 h, 63%; (c) 4,4′,6,6′-tetra-*t*-butyl-2,2′-bisphenol, $Et_3N$, $CHCl_3$, rt, $N_2$, 13 h, 75%.

intermediate **5** was yielded. Similarly **5** was not isolated in pure form and directly treated with (*R*,*R*)-(+)-2,3-*O*-benzylene-1,4-butanediol or 4,4′,6,6′-tetra-*t*-butyl-2,2′-bisphenol to give the goal compound **2** or **3**. The overall yields were 63% and 75%, respectively. Compounds **2** and **3** can also be purified by silica gel column chromatography.

## 2. Results and discussion

Phosphites **1** and **2** are characterized by several stereogenic centers and the 'privileged' [10] structure backbone of cinchona alkaloids. The chiral cooperativity among sterocenters and the steric cavity make them possible to lead to a better chiral induction. Different from the above two phosphites, **3** contains biaryl moieties with bulky substituents, besides the above two unique skeleton properties. Noteworthy is the fact that two resonances at $\delta$ 157.22 and $\delta$ 156.77 were observed in the $^{31}$P NMR spectrum of phosphite **3**, which suggested that **3** may be a mixture of diastereoisomers. This must be caused by the rotation about the single bond connecting the two aryl rings (the chiral axis) of bisphenol. The separation of the isomer mixture was not successful. For all that, due to the special structure skeleton of phosphites **1**–**3**, they will open up a rather unexplored field of ligand design.

In summary, a novel family of phosphites **1**–**3** was developed from diols and cinchonine in one pot. These compounds are fully characterized using $^{1}$H, $^{13}$C and $^{31}$P NMR spectroscopy as well as by HRMS [11]. Their applications in asymmetric reactions are in progress in our laboratory.

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[11] Phosphite **1**: m.p. 40–42 °C; $[\alpha]_D^{25}$ − 92 (*c* 1.0, $CHCl_3$); $^{1}$H NMR (300 MHz, $CDCl_3$, $\delta$ ppm): 8.87 (d, 1H, *J* = 3.93, Ar–H), 8.22 (d, 1H, *J* = 8.19, Ar–H), 8.12 (d, 1H, *J* = 6, Ar–H), 7.94 (d, 1H, *J* = 7.41, Ar–H), 7.71–7.09 (m, 10H, Ar–H), 6.15–6.02 (m, 3H, =$CH_2$, =CH–), 5.44–5.07 (m, 3H, HC–O), 3.42 (m, 2H), 3.13–1.57 (m, 9H). $^{13}$C NMR (75 MHz, $CDCl_3$, $\delta$ ppm): 149.5 (ArC), 148.2, 145.9, 139.8, 135.2 (=CH–), 134.2, 132.3, 132.2, 130.1, 129.5, 129.4, 129.3, 128.6, 128.5, 128.4, 128.3, 128.1, 127.2, 126.1, 125.1, 122.9, 118.7 (ArC), 114.4 (=$CH_2$), 84.2 (Ar–C–O), 81.0 (Ar–C–O), 60.4 (CH–O–P), 49.5, 48.8, 45.6, 39.4, 27.6, 26.0, 25.7. $^{31}$P NMR (202 MHz, $CDCl_3$, $\delta$ ppm): 142.8; ESI-MS: 695(*m/z* +1); HRMS (ESI): calcd. for $C_{33}H_{31}Br_2N_2O_3P$, 694.39, found 695.03. Phosphite **2**: m.p. 43–44 °C; $[\alpha]_D^{25}$ + 78 (*c* 1.0, $CHCl_3$); $^{1}$H NMR (300 MHz, $CDCl_3$, $\delta$ ppm): 8.75 (d, 1H, *J* = 3.45, Ar–H), 8.10 (m, 1H, Ar–H), 7.90–7.65 (m, 4H, Ar–H), 7.43–7.27 (m, 5H, Ar–H), 5.92 (m, 2H, =CH–, $O_2$–CH–Ar), 5.06–5.01 (m, 3H, $CH_2$=), 3.49–3.44 (m, 6H), 2.74–1.25 (m, 11H). $^{13}$C NMR (75 MHz, $CDCl_3$, $\delta$ ppm): 149.1 (ArC), 139.7, 139.6, 139.3 (=$CH_2$–), 129.9, 129.0, 128.6, 128.5, 127.9, 127.9, 126.5, 126.3, 126.1, 126.0, 125.0, 122.6 (ArC), 114.4 (=$CH_2$), 103.4 ($O_2$–CH–Ar), 79.3 (CH–O–P), 78.9, 78.3, 61.9, 61.8, 59.8, 49.4, 48.5, 45.6, 39.2, 27.3, 25.6. $^{31}$P NMR (202 MHz, $CDCl_3$, $\delta$ppm): 143.5; ESI-MS: 533 (*m/z* +1); HRMS (ESI): calcd. for $C_{30}H_{33}N_2O_5P$ 533.53, found 533.22. Phosphite **3**: m.p. 112–114 °C. $[\alpha]_D^{25}$ − 45 (*c* 1.0, $CHCl_3$). $^{1}$H NMR (300 MHz, $CDCl_3$, $\delta$ ppm): 8.96–8.79 (br, 2H, Ar–H), 8.13–8.10 (br, 2H, Ar–H), 7.68–6.88 (m, 6H, Ar–H), 5.9–5.7 (m, 1H, =CH–), 4.95–4.82 (m, 3H, =$CH_2$, –CH–O–P), 2.99–2.38 (m, 11H), 1.64–1.01 (m, 36H). $^{13}$C NMR (75 MHz, $CDCl_3$, $\delta$ ppm): 149.1 (ArC), 147.6, 144.2, 139.4, 138.7, 129.8, 128.5, 128.1, 127.3, 126.9, 126.8, 126.2, 125.6, 125.4, 124.3, 123.3, 123.1, 122.8, 121.9, 121.7, 120.2, 114.0 (=CH–), 113.7 (=$CH_2$), 59.7 (–CH–O–P), 57.7, 49.2, 48.7, 46.4, 45.7, 39.6, 39.1, 35.1, 34.9, 34.7, 34.5, 33.9, 31.4, 31.2, 31.1, 31.0, 29.8, 29.5, 29.3, 27.3, 27.0, 25.5 24.7. $^{31}$P NMR (202 MHz, $CDCl_3$, $\delta$ ppm): 156.77, 157.22; ESI–MS: 733 (*m/z* +1); HRMS (ESI): calcd. for $C_{47}H_{61}N_2O_3P$ 733.44, found 733.45.