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Organocatalytic Enantioselective Hydrophosphonylation of Sulfonylimines having a Heteroarenesulfonyl Group as a Novel Stereocontroller

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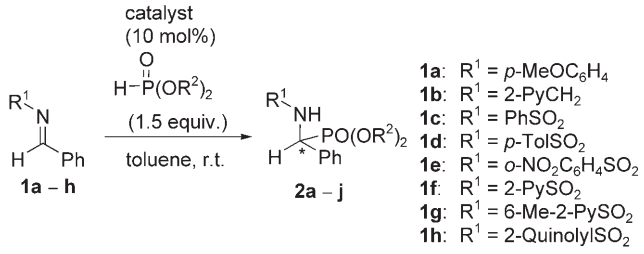
Abstract: Organocatalytic enantioselective hydrophosphonylation of imines having the a heteroarenesulfonyl group afforded the respective products with high enantioselectivity. Both enantiomers of α-amino phosphonates were obtained by using different *Cinchona* alkaloids with up to 98% *ee*.

Keywords: asymmetric synthesis; heteroarenesulfonyl group; hydrophosphonylation; organic catalysis; stereocontroller

Optically active α-amino phosphonic acids and their derivatives have proved to be useful building blocks for the preparation of pharmaceutical targets,[1] such as the antibacterial agent alafosfalin,[2] anti-HIV agents,[3] inhibitors of enzymes[4] and peptidic materials having unique structural properties. The diastereoselective addition of phosphite derivatives to chiral imines[5] and chiral Lewis acid-catalyzed enantioselective addition of phosphites to imines (aza-Pudovik reaction)[6,7] have been extensively investigated, whereas only a few studies exist on the organocatalytic enantioselective hydrophosphonylations of imines.[8] Jacobsen and his co-worker have reported highly enantioselective hydrophosphonylation using a highly elaborated thiourea catalyst prepared from a chiral diamine and L-*tert*-leucine.[8a] Recently, Pettersen and co-workers have reported the organocatalytic enantioselective hydrophosphonylation of *N*-Boc-imines with diethyl phosphite in the presence of quinine giving products with good enantioselectivity after 2–7 days. However, highly reactive *N*-tosylimines afforded products with low enantioselectivity.[8c] Recently, we[10] and others[11] have reported enantioselective reactions using bifunctional coordinative heteroarenesulfonyl groups to control the conformations and reactivities by chelation with chiral Lewis acids.[12] Herein, we report the first organocatalytic enantiocomplementary hydrophosphonylation of sulfonylimines catalyzed by commercially available pseudoenantiomeric *Cinchona* alkaloids.

The enantioselective hydrophosphonylation reaction of various sulfonylimines[13] with diethyl phosphite (1.5 equiv.) was carried out using 10 mol% of a variety of *Cinchona* alkaloids as organocatalysts (Table 1). The reaction of *N*-*p*-methoxyphenyl- and *N*-2-pyridylmethylimines (**1a**, **b**) with diethyl phosphite in the presence of quinine did not afford the products **2a**, **b** (entries 1,2), whereas the reaction of *N*-phenylsulfonyl-, *N*-*p*-tolylsulfonyl-, and *N*-(*o*-nitrophenylsulfonyl)imines (**1c–e**) gave the products (**2c–e**) in good yield but with low enantioselectivity (entries 3–5). On the other hand, the reaction of *N*-(2-pyridylsulfony)-, *N*-(6-methyl-2-pyridylsulfonyl)-, and *N*-(2-quinolylsulfonyl)imines **1f–h** afforded the hydrophosphonylated products **2f–h** with good enantioselectivity (entries 6–8). The reaction of **1f** with diethyl trimethylsilyl phosphite instead of diethyl phosphite gave the racemic product **2f** (entry 9). The reaction of **1f** with diphenyl phosphite showed higher enantioselectivity than with diethyl phosphite, although the reaction of **1g** with diphenyl phosphite showed slightly lower enantioselectivity (entries 10 and 11). Highly reactive diphenyl phosphite can react with **1g** at −40 °C for 1 h, and the reaction showed a marked increase in enantioselectivity (entry 12).[14] Performing optimization experiments with various organocatalysts, the reactions with hydroquinine and hydroquinidine were found to afford both enantiomers of **2j** with good enantioselectivity (entries 13-16, see also supporting Information). The reaction using acetylated

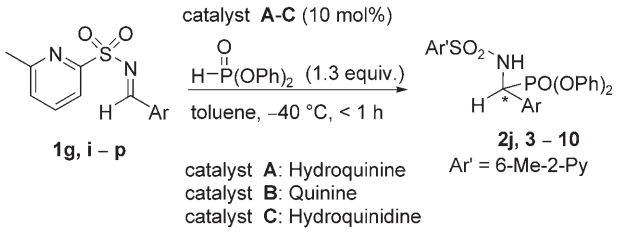
Table 1. Enantioselective addition of phosphites to aldimines **1a–h** using various *Cinchona* alkaloids.



Run	1	Catalyst	R^2	2	Yield [%]	*ee*[a] [%]
1	**1a**	Quinine	Et	**2a**	0	-
2	**1b**	Quinine	Et	**2b**	0	-
3	**1c**	Quinine	Et	**2c**	68[b]	49
4	**1d**	Quinine	Et	**2d**	65[b]	40
5	**1e**	Quinine	Et	**2e**	62[b]	30
6	**1f**	Quinine	Et	**2f**	98	65 (*S*)
7	**1g**	Quinine	Et	**2g**	98	64 (*S*)
8	**1h**	Quinine	Et	**2h**	70	51
9	**1f**	Quinine	Et[c]	**2f**	90	0
10	**1f**	Quinine	Ph	**2i**	94	61 (*S*)
11	**1g**	Quinine	Ph	**2j**	>99	71 (*S*)
12[d]	**1g**	Quinine	Ph	**2j**	>99	92 (*S*)
13[d]	**1g**	Hydroquinine	Ph	**2j**	>99	91 (*S*)
14[d]	**1g**	Hydroquinidine	Ph	**2j**	>99	92 (*R*)
15[e]	**1g**	Hydroquinine	Ph	**2j**	98	97 (*S*)
16[e]	**1g**	Hydroquinidine	Ph	**2j**	95	98 (*R*)
17[d]	**1g**	Acetylquinine	Ph	**2j**	50	36 (*S*)
18[d,f]	**1g**	Quinine	Ph	**2j**	>99	92 (*S*)
19[d,g]	**1g**	Quinine	Ph	**2j**	>99	92 (*S*)

[a] The *ee* was determined by HPLC analysis.
[b] Conversion yield.
[c] $TMSOP(OEt)_2$ was used as a phosphite.
[d] The reaction was carried out at −40 °C for 1 h.
[e] The reaction was carried out at −78 °C for 1 h.
[f] Quinine (5 mol%) was used.
[g] Under aerobic conditions.

Table 2. Enantioselective hydrophosphonylation to aldimines **1g**, **i–p** using various *Cinchona* alkaloids.



Entry	1	Ar	Cat.	Product	Yield [%]	*ee* [%][a]
1[b]	**1g**	Ph	**A**	(*S*)-**2j**	98	97 (99)
2[b]	**1i**	*p*-Tolyl	**A**	(*S*)-**3**	>99	92 (99)
3[b]	**1j**	*p*-$MeOC_6H_4$	**A**	(*S*)-**4**	>99	94 (98)
4[b]	**1k**	*o*-$MeOC_6H_4$	**A**	(*S*)-**5**	>99	85 (96)
5	**1l**	*m*-$MeOC_6H_4$	**B**	(*S*)-**6**	>99	81 (83)
6[b]	**1m**	*p*-ClC_6H_4	**A**	(*S*)-**7**	>99	87 (98)
7[b]	**1n**	1-Naphthyl	**A**	(*S*)-**8**	>99	82 (97)
8	**1o**	2-Naphthyl	**B**	(*S*)-**9**	>99	92 (95)
9	**1p**	*trans*-Cinnamyl	**B**	(*S*)-**10**	>99	85 (92)
10[b]	**1g**	Ph	**C**	(*R*)-**2j**	95	98 (99)
11	**1i**	*p*-Tolyl	**C**	(*R*)-**3**	>99	89 (97)
12[b]	**1j**	*p*-$MeOC_6H_4$	**C**	(*R*)-**4**	>99	93 (92)
13[b]	**1k**	*o*-$MeOC_6H_4$	**C**	(*R*)-**5**	>99	91 (98)
14	**1l**	*m*-$MeOC_6H_4$	**C**	(*R*)-**6**	>99	89 (93)
15[b]	**1m**	*p*-ClC_6H_4	**C**	(*R*)-**7**	>99	86 (99)
16[b]	**1n**	1-Naphthyl	**C**	(*R*)-**8**	>99	91 (99)
17	**1o**	2-Naphthyl	**C**	(*R*)-**9**	>99	92 (96)
18	**1p**	*trans*-Cinnamyl	**C**	(*R*)-**10**	>99	82 (92)

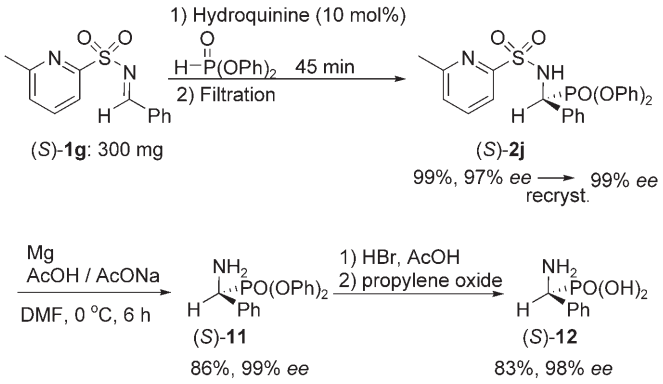
[a] The *ee* obtained after single recrystallization from hexane/ethyl acetate is shown in parenthesis.
[b] The reaction was carried out at −78 °C for 5–6 h.

quinine had a decreased enantioselectivity (entry 17). The catalyst loading could be reduced to 5 mol% in the case of quinine (entry 18). The reaction under aerobic conditions also afforded **2g** in high yield with good enantioselectivity (entry 19).

A series of sulfonylimines **1g**, **i–p** derived from aromatic aldehydes all proved to be excellent substrates with respect to enantioselectivity and chemical yield using quinine or hydroquinine (Table 2, entries 1–8). The reaction was completed within 1 h at −40 °C or within 6 h at −78 °C. The sulfonylimine **1p** having an unsaturated bond also afforded the product (*S*)-**10** with high enantioselectivity (entry 9). Furthermore, the reaction using hydroquinidine afforded the opposite enantiomer of the products **2j**, **3–10** with high enantioselectivity (entries 10–18). Since most of the products were crystalline, enantiomerically pure sulfonamides were easily obtainable by single recrystallization. For example, recrystallization of 97% *ee* of (*S*)-**2j** from hexane/ethyl acetate afforded enantiomerically pure (*S*)-**2j** in 76% yield (entry 1).

Larger scale synthesis starting with 300 mg of **1g** also gave 97% *ee* and 99% yield of (*S*)-**2j** by simple filtration without purification (Scheme 1). Recrystallization of the crude (*S*)-**2j**, followed by desulfonation afforded the optically pure α-amino phosphonate (*S*)-**11**, which was converted to the highly optically pure known α-amino phosphonic acid (*S*)-**12**. The optical purity of (*S*)-**12** was confirmed after conversion to the *N*-Cbz dimethylphosphonate derivative.[8a] The absolute configurations of other products **3–10** were tentatively assigned by analogy.

The enantioselective hydrophosphonylation of *N*-(heteroarenesulfonyl)imines **1f–h** gave products in good yield with good enantioselectivity, although the reaction of *N*-(arenesulfonyl)imines **1c–e** did not afford good results. These results show that the heteroarenesulfonyl group acts not only as an activating group but also as an efficient stereocontroller.



Scheme 1. Desulfonylation from (*S*)-**2j**.

Since protection of the hydroxy group in quinine decreases the enantioselectivity in comparison with the reaction using non-protected quinine (Table 1, entries 12 *vs.* 17), hydrogen bonding between the *Cinchona* alkaloid's hydroxy group and (heteroarenesulfonyl)imines plays a key role in exerting enantioselectivity. In addition, the reaction of **1g** with diethyl phosphite in toluene using 10 mol% of isopropyl alcohol did not afford the product, whereas the reaction with diethyl trimethylsilyl phosphite in the presence of quinine afforded the racemic product (Table 1, entry 8). These results imply that the nitrogen in *Cinchona* alkaloids, as a Brønsted base, activates phosphite by coordination with the acidic proton, and, hence, *Cinchona* alkaloids act as dual activating organocatalysts. From the above consideration, the assumed transition state for the enantioselective hydrophosphonylation using hydroquinine is shown in Figure 1 on the basis that the equilibrium would favor the active intermediate $(RO)_2POH$ over $(RO)_2P(=O)OH$ in the presence of hydroquinine. Further studies are required to fully elucidate the mechanistic detail of the hydrophosphonylation.

In conclusion, we found that the heteroarenesulfonyl group works as a good activating group of the imino group in hydrophosphonylation. The first organocatalytic highly enantiocomplementary hydrophosphonylation of *N*-(heteroarenesulfonyl)imines was achieved using a catalytic amount of commercially available organocatalysts. The 6-methyl-2-pyridinesulfonyl group was shown to be an easily removable, efficient protective group, having notable properties such as high chiral inducibility and activation of the imino group toward the addition of nucleophiles.

Experimental Section

General Procedure for the Enantioselective Hydrophosphonylation of Imines: (*S*)-Diphenyl (6-Methyl-2-pyridinesulfonylaminophenyl)methanephosphonate (2j)

To a solution of **1g** (40 mg, 0.154 mol) and (−)-hydroquinine (5.0 mg, 0.0154 mmol) in toluene (1.9 mL) was added diphenyl phosphite (39 μL, 0.200 mmol) at −78 °C. The reaction mixture was stirred for 60 min. Water was then added to the reaction mixture, and aqueous layer was extracted with $CHCl_3$. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product which was purified by column chromatography (silica gel, hexane/ethyl acetate = 50/50) to give **2j**; yield: 73.9 mg (99%, 98% *ee*). A single recrystallization of **2j** (98% *ee*) afforded 99.4% *ee* for **2j**.

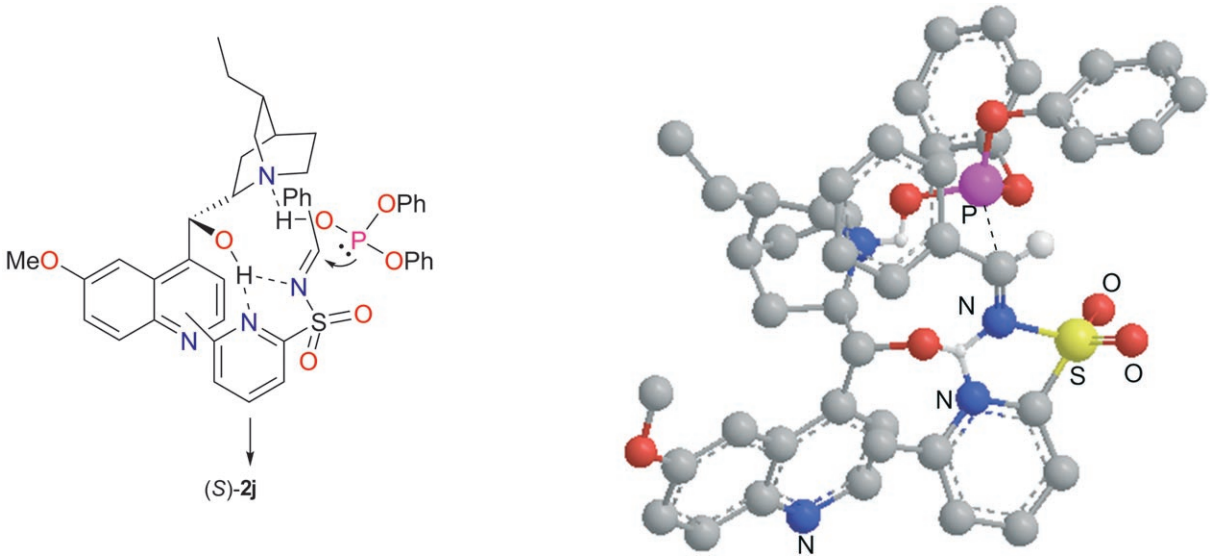


Figure 1. Assumed transition state for the hydrophosphonylation of **1g**.

Acknowledgements

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[14] We also examined various phosphorus nucleophiles, as shown in the Supporting Information.

