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Catalytic Enantioselective Hydrophosphonylation of Ketimines Using Cinchona Alkaloids

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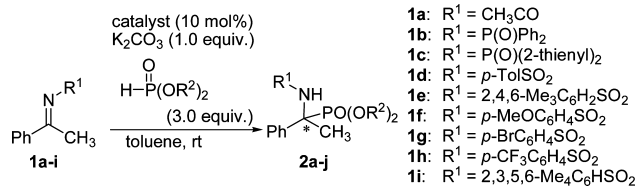
Optically active α-amino phosphonic acids and their derivatives are useful building blocks for the preparation of pharmaceutical targets[1] such as the antibacterial agent alafosfalin,[2] anti-HIV agents,[3] inhibitors of enzymes,[4] and peptidic materials having unique structural properties. The enantioselective addition of phosphite to imines (Pudovik reaction) is certainly one of the most versatile routes for the preparation of optically active α-amino phosphonic acids. Although high enantioselectivity and chemical yield have been achieved in the hydrophosphonylation of imines derived from aldehydes,[5] enantioselective addition of phosphite to imines derived from ketones (ketimines) is still challenging because of their lower reactivity and difficulty in enantiofacial discrimination.[6] To improve the bioactivity, stability, and utility of α-amino phosphonic acids, the asymmetric synthesis of optically active quaternary α-amino phosphonic acids is a significant objective. However, to date there are no reports of the enantioselective hydrophosphonylation of ketimines.[7] Recently, we reported the first organocatalytic enantiocomplementary hydrophosphonylation of *N*-sulfonylimines derived from aldehydes catalyzed by commercially available pseudoenantiomeric cinchona alkaloids.[8] We herein report the first catalytic enantioselective hydrophosphonylation of ketimines using cinchona alkaloids and a base.

The enantioselective hydrophosphonylation reaction of various ketimines with diphenyl phosphite (3.0 equiv) was carried out using 10 mol % catalyst loading of a variety of cinchona alkaloids along with K_2CO_3 (1.0 equiv) (Table 1). Although the reactions of *N*-acetyl- and *N*-diarylphosphonylketimines (**1a**−**c**) with diphenyl phosphite using quinine did not afford good results, the reaction of *N*-tosyl ketimine (**1d**) afforded the product **2d** in good yield with 31% ee (entries 1−4). After the optimization of various substituents on the nitrogen in the sulfonylimine, the 2,4,6-trimethylphenyl group was found to be the best substitution to obtain high yield and high enantioselectivity (entries 5−9). When the reaction was carried out without a base such as K_2CO_3, the reaction did not proceed (entry 10). Switching the base from K_2CO_3 to Na_2CO_3 enhanced the enantioselectivity (entry 5 vs 11). The enantioselectivity was improved when the reaction was performed at −20 °C, although the reactivity was lowered (entry 12). In optimization experiments using various cinchona alkaloids in the reaction of **1e**, a reaction with hydroquinine and hydroquinidine was found to afford the two enantiomers of **2e** with high enantioselectivity (entries 12−18). The reaction with a dialkyl phosphite, such as diethyl or dibenzyl phosphite, did not afford good results (entries 19 and 20).[9] The reaction of **1e** with diphenyl *tert*-butyldimethylsilylphosphite [TBSOP(OPh)$_2$] instead of diphenyl phosphite did not afford any product (entry 21). Importantly, lowering the catalyst loading to 2 and 0.5 mol % (entries 22 and 23), the latter of which represents the lowest catalyst loading employed in the asymmetric hydrophosphonylation of imine, resulted in no significant loss of enantioselectivity or yield. The reaction under aerobic conditions also afforded **2e** in high yield with good enantioselectivity (entry 24).

Table 1. Enantioselective Addition of Phosphites to Ketimines **1a**−**i** Using Various Cinchona Alkaloids and Bases



entry	1	catalyst	R^2	time (h)	2	yield (%)	ee (%)[a]
1	**1a**	quinine	Ph	36	**2a**	−	−
2	**1b**	quinine	Ph	36	**2b**	9	15
3	**1c**	quinine	Ph	24	**2c**	52	21
4	**1d**	quinine	Ph	12	**2d**	89	31
5	**1e**	quinine	Ph	36	**2e**	78	59
6	**1f**	quinine	Ph	60	**2f**	9	40
7	**1g**	quinine	Ph	20	**2g**	81	43
8	**1h**	quinine	Ph	20	**2h**	94	33
9	**1i**	quinine	Ph	36	**2i**	73	59
10[b]	**1e**	quinine	Ph	14	**2e**	−	−
11[c]	**1e**	quinine	Ph	27	**2e**	89	86
12[c,d]	**1e**	quinine	Ph	60	**2e**	86	90
13[c,d]	**1e**	quinidine	Ph	60	**2e**	88	−91
14[c,d]	**1e**	cinconine	Ph	60	**2e**	63	−58
15[c,d]	**1e**	cinconidine	Ph	60	**2e**	68	61
16[c,d]	**1e**	hydroquinine	Ph	60	**2e**	99	97
17[c,d]	**1e**	hydroquinidine	Ph	60	**2e**	99	−92
18[c,d]	**1e**	$(DHQ)_2PYR$	Ph	60	**2e**	72	14
19[c]	**1e**	hydroquinidine	Et	68	−	−	−
20[c]	**1e**	hydroquinidine	Bn	19	**2j**	95	61
21[c,d,e]	**1e**	hydroquinine	Ph	19	−	−	−
22[c,d,f]	**1e**	hydroquinine	Ph	72	**2e**	99	97
23[c,d,g]	**1e**	hydroquinine	Ph	68	**2e**	99	95
24[c,d,h]	**1e**	hydroquinine	Ph	63	**2e**	89	96

[a] Determined by HPLC analysis. [b] Without K_2CO_3. [c] Using Na_2CO_3 (1.5 equiv) instead of K_2CO_3. [d] The reaction was carried out at −20 °C. [e] Using TBSOP(OPh)$_2$ as a phosphite. [f] Using 2 mol % catalyst. [g] Using 0.5 mol % catalyst. [h] Under aerobic conditions.

With these optimized conditions, the reactions of a series of ketimines with diphenyl phosphite using hydroquinine or hydroquinidine were examined (Table 2). The reaction of ketimines derived from substituted acetophenone using hydroquinine afforded products **3**−**10** in high yield with high enantioselectivity (entries 1−9). Although the reaction of ketimine **1r** derived from 4-phenyl-2-butanone afforded product **11** with moderate enantioselectivity, the reactions of ketimine **1s** derived from the dialkyl ketone 1-cyclohexylethanone and ketimine **1t** derived from ethyl phenyl ketone also afforded the corresponding products **12** and **13** with a good level of enantioselectivity (entries 10−12). The reaction of a

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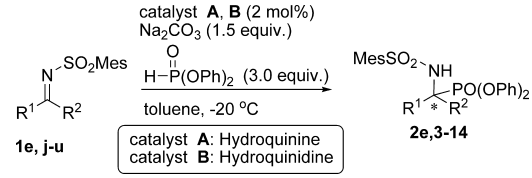
Table 2. Enantioselective Hydrophosphonylation of Ketimines **1e** and **1j**−**u** Using Hydroquinine or Hydroquinidine



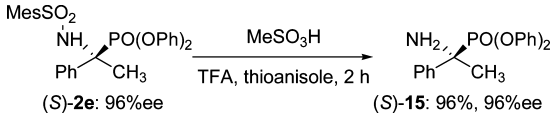
entry	1	R^1	R^2	cat.	product	yield (%)	ee (%)
1	**1e**	Ph	Me	**A**	(*S*)-**2e**	99	97
2	**1j**	*p*-tolyl	Me	**A**	(*S*)-**3**	97	96
3	**1k**	*p*-$MeOC_6H_4$	Me	**A**	(*S*)-**4**	99	97
4	**1l**	*p*-ClC_6H_4	Me	**A**	(*S*)-**5**	99	94
5	**1m**	*p*-BrC_6H_4	Me	**A**	(*S*)-**6**	98	93
6	**1n**	*p*-FC_6H_4	Me	**A**	(*S*)-**7**	99	97
7	**1o**	*m*-ClC_6H_4	Me	**A**	(*S*)-**8**	99	94
8	**1p**	*m*-BrC_6H_4	Me	**A**	(*S*)-**9**	99	94
9	**1q**	2-naphthyl	Me	**A**	(*S*)-**10**	99	96
10	**1r**	$PhCH_2CH_2$	Me	**A**	(*S*)-**11**	98	55
11	**1s**	cyclohexyl	Me	**A**	(*S*)-**12**	97	75
12	**1t**	Ph	Et	**A**	(*S*)-**13**	96	97
13	**1u**	1-indanone		**A**	(*S*)-**14**	93	89
14	**1e**	Ph	Me	**B**	(*R*)-**2e**	99	92
15	**1j**	*p*-tolyl	Me	**B**	(*R*)-**3**	90	92
16	**1k**	*p*-$MeOC_6H_4$	Me	**B**	(*R*)-**4**	91	94
17[a]	**1l**	*p*-ClC_6H_4	Me	**B**	(*R*)-**5**	99	95
18[a]	**1m**	*p*-BrC_6H_4	Me	**B**	(*R*)-**6**	99	92
19[a]	**1n**	*p*-FC_6H_4	Me	**B**	(*R*)-**7**	99	88
20[a,b]	**1o**	*m*-ClC_6H_4	Me	**B**	(*R*)-**8**	99	90
21[a,b]	**1p**	*m*-BrC_6H_4	Me	**B**	(*R*)-**9**	98	91
22	**1q**	2-naphthyl	Me	**B**	(*R*)-**10**	91	93
23	**1r**	$PhCH_2CH_2$	Me	**B**	(*R*)-**11**	97	52
24	**1s**	cyclohexyl	Me	**B**	(*R*)-**12**	86	80
25	**1t**	Ph	Et	**B**	(*R*)-**13**	92	92
26	**1u**	1-indanone		**B**	(*R*)-**14**	86	82

[a] Using 10 mol % catalyst. [b] The reaction was carried out at −40 °C.

cyclic ketimine **1u** derived from 1-indanone afforded **14** in high yield with good enantioselectivity (entry 13). Furthermore, the reaction using hydroquinidine instead of hydroquinine afforded the opposite enantiomers of products **3**−**14** with high enantioselectivity (entries 14−26). Since most of the products were crystalline, enantiomerically pure products were easily to obtain by single recrystallization. For example, recrystallization of 92% ee (*R*)-**3** from hexane/ethyl acetate afforded enantiomerically pure (*R*)-**3** (entry 15). To the best of our knowledge, these results are the first examples of catalytic enantioselective C−heteroatom bond formation involving ketimines.

The 2,4,6-trimethylbenzenesulfonyl group could be removed from optically active (*S*)-**2e** on treatment with methanesulfonic acid in trifluoroacetic acid (TFA)/anisole at room temperature to give chiral α-amino phosphonate (*S*)-**15** (Scheme 1).

Scheme 1. Desulfonylation of (*S*)-**2e**



The enantioselective hydrophosphonylation of **1e** with diphenyl phosphite gave products in good yield with good enantioselectivity, although the reaction with $TBSOP(OPh)_2$ did not afford product **2e** (Table 1, entry 21). Furthermore, the reaction without a base also did not afford a product (Table 1, entry 10). These results show that the formation of the sodium salt of phosphite is a key factor in the activation of phosphites. Therefore, the nitrogen in cinchona alkaloids as a Brønsted base would activate the nucleophilicity of sodium phosphite by coordination with sodium ion. On the other hand, protection of the hydroxyl group in hydroquinine also did not give a good result (Table 1, entry 18). This result implies that hydrogen bonding between the cinchona alkaloid hydroxyl group and the ketimine plays a key role in exerting enantioselectivity. Therefore, cinchona alkaloids act as dual-activating organocatalysts. From the above considerations, Figure 1 shows a proposed transition state for the enantioselective hydrophosphonylation using hydroquinine.

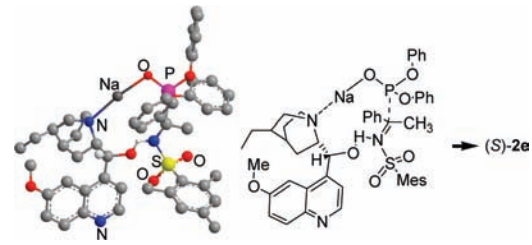


Figure 1. Proposed transition state for the hydrophosphonylation of **1e** using hydroquinine.

In conclusion, we have provided the first catalytic enantioselective hydrophosphonylations of ketimines using commercially available cinchona alkaloids. This approach provides direct access to both enantiomers of optically active quaternary α-amino phosphonic acids with satisfactory yields and enantioselectivities.

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Supporting Information Available: Experimental procedures and characterization data, including the X-ray crystal structure of (*S*)-**5** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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