Thiourea-Catalyzed Enantioselective Hydrophosphonylation of Imines: Practical Access to Enantiomerically Enriched α-Amino Phosphonic Acids

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α-Amino phosphonic acids, their phosphonate esters, and short peptides incorporating this unit are excellent inhibitors of a wide range of proteolytic enzymes.[1] In addition, α-amino phosphonate derivatives have broad application due to their antibacterial[2] and antifungal[3] activity, and as inhibitors of phosphatase activity.[4] The biological activity of compounds incorporating the α-amino phosphonic acid moiety depends on their absolute configuration. Therefore, the synthesis of enantiomerically enriched α-amino phosphonates has received considerable attention, and there are numerous reports of resolution and chiral auxiliary-based approaches.[5] However, there are few catalytic enantioselective methods available to access this class of compounds.[6,7] Of these methods, the most direct approach involves the addition of phosphites to imines. While significant advances have been made in the development of asymmetric hydrophosphonylation methodology, the highest selectivities are generally restricted to cyclic imine substrates, and an excess of the nucleophilic phosphite is required.[8] Furthermore, there have been no reports of the asymmetric catalytic synthesis of α-aryl-α-amino phosphonates. Herein, we describe a highly enantioselective hydrophosphonylation of *N*-benzyl imines promoted by a chiral thiourea catalyst (Figure 1). A mild procedure for the global deprotection of the hydrophosphonylation products is also demonstrated, providing straightforward access to enantiomerically enriched α-amino phosphonic acids.

Chiral ureas and thioureas have recently emerged as highly enantioselective catalysts for the addition of carbon nucleophiles to activated π-systems.[9] Preliminary exploratory experiments with phosphorus-based nucleophiles revealed that thiourea catalyst **1a** (10 mol %) promoted the addition of dimethyl phosphite **3a** to aryl imine **2a** at 23 °C with promising enantioselectivity (80% ee) but poor reaction rate (35% conversion in 22 h).[10] Attempts to improve yield by raising the reaction temperature or increasing the concentration of the nucleophile **3a** led to dramatically reduced enantioselectivities.

Variation of catalyst structure revealed that **1b**, which provides the highest enantioselectivities in the asymmetric hydrocyanation of imines,[9d] is also optimal for imine hydrophosphonylation.[11,12] In addition, the electronic nature of the nucleophilic phosphite was identified as a key parameter, with electron-withdrawing ester substituents providing superior reaction rates (Table 1). Although diphenyl phosphite **3b** and bis-(2,2,2-trifluoroethyl) phosphite **3c** underwent rapid and moderately enantioselective reaction, the resulting products were found to be configurationally unstable.[13] Further optimization of the nucleophile revealed that slightly less electron-deficient phosphites provided configurationally stable adducts, albeit at the expense of reaction rate. In particular, the additions of di-(2-chloroethyl) phosphite **3e** and di-(2-nitrobenzyl) phosphite **3h** proceeded with high enantioselectivity. The reactivity of phosphite **3h** was investigated further, with the expectation that its addition products would be susceptible to hydrogenolysis and
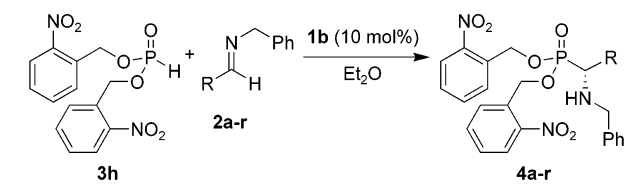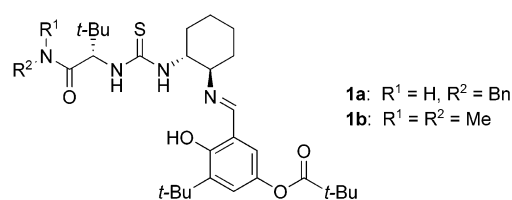
Figure 1. Thiourea catalysts.

1a: R[1] = H, R[2] = Bn
1b: R[1] = R[2] = Me

Table 1. Phosphite Optimization[a]

2a: R[2] = Ph
2b: R[2] = 3-pentyl

phosphite	R[1]	imine	time (h)	conv (%)[b]	ee (%)[c]
3b[d]	phenyl	**2a**	1	100	77
		2b[g]	1	100	80[f]
3c[d]	2,2,2-trifluoroethyl	**2a**	1	100	72[f]
		2b	1	100	53[f]
3d	2-cyanoethyl	**2a**[d]	2	83	68
		2b[e]	2	85	77
3e	2-chloroethyl	**2a**	8	89	90
		2b	8	91	84
3f	2-methoxyethyl	**2a**	32	50	43
		2b	8	65	59
3g[h]	*p*-nitrobenzyl	**2a**	24	86	78
		2b	18	90	73
3h[i]	*o*-nitrobenzyl	**2a**	26	99	93
		2b	24	100	90

[a] Reactions were carried out with 0.13 mmol of imine and phosphite in 100 μL of toluene. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC. [d] Slow addition of phosphite over 1 h. [e] Slow addition of phosphite over 2 h. [f] Product is not configurationally stable and slowly racemizes upon standing at 23 °C. [g] Reaction carried out using 100 μL of EtOAc as solvent. [h] Reactions carried out using 600 μL of EtOAc as solvent. [i] Reactions carried out using 300 μL of EtOAc as solvent.

thereby serve as convenient precursors to unprotected α-amino phosphonic acids.[14]

The addition of phosphite **3h** to *N*-benzyl imines **2** catalyzed by **1b** proved to be remarkably general under optimized conditions (Table 2).[15] High enantioselectivities were obtained across a wide range of both aliphatic and aromatic substrates.[16] Only imine **2f** bearing an alkenyl side chain and pyrrole derivative **2r** afforded modest ee's (81−82%). However, the optical purity of addition product **4f** was enhanced to 99% ee after two recrystallizations (64% overall yield from **2f**). In general, the best reaction rates were realized with aliphatic imines, while electron-poor aromatic substrates required longer reaction times and, in certain cases, elevated temperatures. The absolute configuration of products **4** obtained using catalyst **1b** was found to be consistent with the sense of stereoinduction observed in the asymmetric Strecker and Mannich reactions.[9a−e]

**Table 2.** Enantioselective Hydrophosphonylation of Imines[a]

product	R	temp (°C)	time (h)	yield (%)[b]	ee (%)[c]
4a[d]	Ph	4	72	87	98
4b	3-pentyl	4	24	90	96
4c	*i*-Pr	4	24	93	90
4d	*c*-hex	4	24	91	90
4e	*t*-Bu	4	72	83	93
4f[e,f]	$(CH_3)_2C\!=\!CH$	4	7	91 (64)	82 (99)
4g	p-FC_6H_4	4	72	89	98
4h	p-$OMeC_6H_4$	4	48	90	96
4i	p-$CO_2CH_3C_6H_4$	23	48	78	96
4j	o-MeC_6H_4	4	72	81	92
4k[g]	o-ClC_6H_4	4	72	52	96
4l	m-ClC_6H_4	23	48	83	98
4m	p-ClC_6H_4	4	72	87	99
4n	2-naphthyl	4	72	86	98
4o	3-pyridyl	23	48	77	96
4p	2-furyl	4	72	89	92
4q	2-thienyl	23	48	89	94
4r	2-pyrrolyl	4	18	86	81

[a] Reactions were carried out on a 0.5 mmol scale unless noted otherwise using unpurified commercial diethyl ether under ambient atmosphere. [b] Isolated yield after silica gel chromatography; yield in parentheses was obtained after recrystallization. [c] Determined by chiral HPLC; ee in parentheses was obtained after recrystallization (see Supporting Information). [d] Absolute configuration determined by conversion to the known α-amino phosphonic acid **5a**. [e] Absolute configuration determined by conversion to the known α-amino phosphonic acid **5f**. The absolute configurations of all other products **4** were assigned by analogy. [f] Reaction carried out on a 2.19 mmol scale. [g] Reaction employed 20 mol % **1b**.

Scheme 1. Synthesis of α-Amino Phosphonic Acids
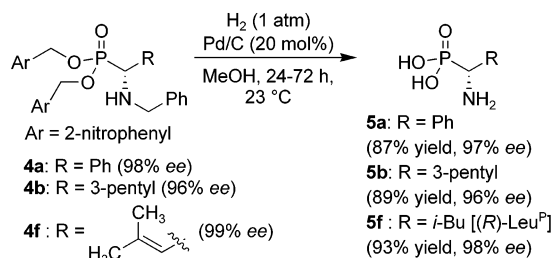
Hydrophosphonylation products **4** were examined as candidates for global deprotection under mild hydrogenolytic conditions. Treatment of adduct **4b** with 20 mol % Pd/C under an atmosphere of hydrogen afforded enantiomerically enriched α-amino phosphonic acid **5b** (Scheme 1). Deprotection of phenyl glycine derivative **4a** yielded **5a** via selective hydrogenolysis of the three protecting groups with no detectable cleavage of the more sterically demanding phosphorus-substituted benzylic position. Finally, α-amino phosphonate **4f** was prepared on a one-gram scale and recrystallized to 99% ee. Subjecting adduct **4f** to the deprotection conditions resulted in concomitant hydrogenation of the olefin to provide (*R*)-Leu[P] **5f**, the α-amino phosphonic acid analogue of leucine and a known inhibitor of leucine amino peptidase.[17]

This new methodology provides general and convenient access to a wide range of highly enantiomerically enriched α-amino phosphonates. The deprotection of these products under mild conditions yields the corresponding α-amino phosphonic acids.

Current efforts are directed toward developing synthetic applications and a mechanistic understanding of this promising hydrophosphonylation reaction.

Supporting Information Available: Representative experimental procedures, characterization data, and chiral chromatographic analyses of racemic and enantiomerically enriched products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Other nucleophilic phosphorus reagents examined included diethyl phosphite (6% conversion, 22 h), trimethyl phosphite (0% ee), and dimethyl *tert*-butyldimethylsilyl phosphite (no reaction, 16 h). The poor reactivity of dimethyl *tert*-butyldimethylsilyl phosphite implies a critical role for the proton of the dialkyl phosphites. This is further supported by the somewhat counterintuitive increase in reaction rate with less electron-rich dialkyl phosphite nucleophiles. A correlation between reactivity and the acidity of the phosphite proton is suggested.
(11) For example, **1a** catalyzes the addition of diphenyl phosphite **3b** to imine **2a** in 59% ee under the same conditions employed using **1b** to provide product in 77% ee (Table 1). Also, catalyst **1a** affords **4c** in 85% ee as compared to 90% ee using catalyst **1b** under the conditions described in Table 2. Additional urea and thiourea catalysts were examined. See the Supporting Information.
(12) These studies were guided by the hypothesis that catalysts **1** activate imines to nucleophilic addition via hydrogen bonding to the thiourea protons. See ref 9d.
(13) A crossover experiment revealed that racemization occurred via a retro-addition pathway.
(14) For the preparation of **3h**, see the Supporting Information.
(15) Optimization revealed very little solvent dependence; nonpolar ethereal solvents give the highest enantioselectivities, with diethyl ether providing optimal results. The reaction also displays a minimal dependence upon concentration, but best results are achieved at 0.4 M. When possible, lowering the temperature to 4 °C has a beneficial effect upon enantioselectivity.
(16) Unbranched aliphatic imines are not useful substrates due to their rapid decomposition under the reaction conditions.
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