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Chiral Tetraaminophosphonium Salt-Mediated Asymmetric Direct Henry Reaction

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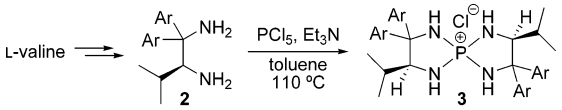
Quaternary phosphonium salts are widely employed in organic synthesis and normally regarded as the precursors of ylides, the reagents developed by Georg Wittig for carbonyl olefination.[1,2] Despite the prevailing applications as stoichiometric reagents and ionic liquid solvents, however, the challenges associated with the catalytic use of phosphonium salts are rather limited.[3] Especially, chiral, nonracemic phosphonium salts have received little attention and were left behind in the evolution of asymmetric organic molecular catalysis.[3b,4]

Tetraaminophosphonium salts bearing four primary amino groups [$(RNH)_4P^+X^-$, **1**] have been studied as broad-spectrum biocides,[5] and also used as precursors of P-1 phosphazenes in organic chemistry.[6] In contrast to phosphorus acid esters, the amino series are generally insusceptible to the P−N bond cleavage by a nucleophilic anion, such as a halide, and thus the salts are relatively stable even in the presence of excess anions. It is noteworthy that deprotonation from a nitrogen of **1** generates triaminoiminophosphorane, which is known as a nucleophilic component of aza-Wittig reaction as well as a strongly basic reagent.[7−9] In addition, the secondary interaction between the cation and anion moieties of **1** via double hydrogen-bonding has been documented.[6a,d] Although the judicious combination of these characteristics would provide a new and fruitful opportunity for the design and utilization of chiral phosphonium salts as a catalyst for synthetically relevant, stereoselective transformations, this possibility has remained unexplored. Herein, we disclose the development and application of a chiral tetraaminophosphonium chloride of type **3**, demonstrating its inherent potential to exert efficient asymmetric catalysis.

Scheme 1. Molecular Design and Synthesis of Chiral Tetraaminophosphonium Salts **3**



Our tactics for the molecular design was to introduce a phosphorus-centered [5.5]-spirocyclic core using the readily accessible chiral 1,2-diamine **2**[10] as the requisite subunit (Scheme 1). The advantage of this structural motif is that the directions of not only the alkyl and geminal aromatic substituents on the rigid diazaphosphacycles but also the N−H protons would be rigorously regulated, making it feasible to fully appreciate the intrinsic hydrogen-bonding capability for anion recognition. The actual synthesis of the desired *P*-spirocyclic aminophosphonium salt **3** was implemented in a single step from L-valine-derived diamine **2** and phosphorus pentachloride.[6a] Interestingly, **3** was obtained as a diastereomeric mixture on the phosphorus stereogenic center. Purification by simple silica gel column chromatography and single recrystallization fortunately gave the major diastereomer in an essentially pure form.[11] The three-dimensional molecular structure of the chiral *P*-spiro tetraaminophosphonium salt **3a** (major diastereomer) was successfully verified by a single-crystal X-ray diffraction analysis, thus establishing its (*M*,*S*) configuration (Figure 1). Importantly, the chloride anion is located in proximity to two of the N−H protons, being able to interact with them via double hydrogen-bonding.[12] The two diazaphosphacycles linked through the P(V) center are nearly perpendicular, and this conformational information is transmitted to each substituent, creating an attractive chiral environment around the anion.

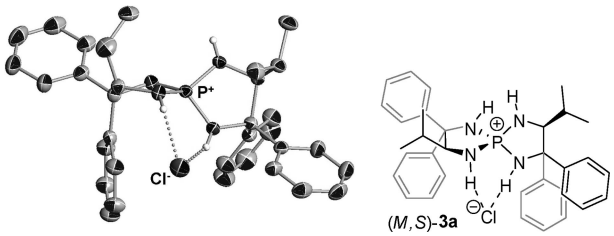


Figure 1. X-ray crystal structure of (*M*,*S*)-**3a** (all calculated hydrogens and solvent molecules are omitted for clarity).

With the exact structure of **3a** in hand, we next focused on the evaluation of its own ability as a catalytic stereocontroller for valuable carbon−carbon bond-forming reactions. For this purpose, we chose a Henry reaction[13,14] as an ideal probe on the basis of the following considerations: (1) nitroalkanes would be deprotonated by triaminoiminophosphorane (**I**)[7,9d] generated in situ from **3** and a strong base, such as KO^{t}Bu; (2) since nitronate anions are bidentate hydrogen-bonding acceptors, the resulting chiral phosphonium nitronate could form a structured ion pair (**II**), allowing the highly stereoselective addition to aldehydes (Figure 2). Preliminary ^{31}P NMR studies revealed that the original signal of the phosphonium salt (*M*,*S*)-**3a** at δ 34.7 ppm in DMF underwent a downfield shift to δ 47.1 ppm upon the addition of KO^{t}Bu at −40 °C, and it shifted upfield back to δ 37.9 ppm by the subsequent treatment with nitromethane.[15] This observation suggests that the iminophosphorane of type **I** can indeed be derivatized from **3** and could promote a Henry reaction in a manner illustrated in Figure 2.

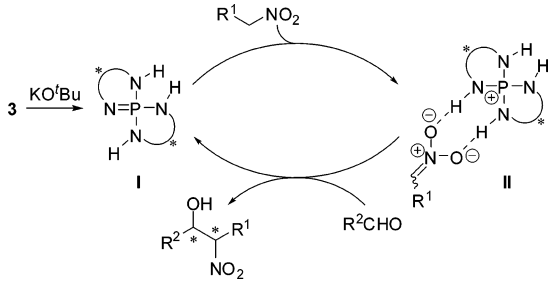


Figure 2. Working hypothesis for the phosphonium salt **3**-mediated asymmetric direct Henry reaction.

In the experiments to examine this hypothesis, (*M*,*S*)-**3a** was initially neutralized in the presence of nitromethane (**4a**) by the treatment with a solution of KO^{t}Bu in THF at −78 °C for 30 min, and then benzaldehyde was successively added. As expected, the

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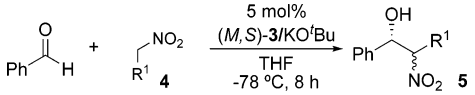
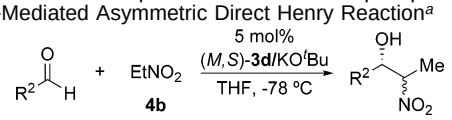
Table 1. Effect of Aromatic Substituent (Ar) of **3** and Scope of the Nitroalkanes[a]



entry	(*M*,*S*)-**3**	**4** (R^1)	yield[b] (%)	dr[c] (anti:syn)	ee[d] (%)
1	**3a**	H (**4a**)	86		89
2	**3b**	**4a**	36		45
3	**3c**	**4a**	84		88
4	**3d**	**4a**	90		94
5	**3d**	Me (**4b**)	93	>19:1	97
6	**3d**	Et (**4c**)	78	13:1	96
7[e]	**3d**	**4b**	90	>19:1	97

[a] See Supporting Information for details. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of crude reaction mixtures. [d] Determined by chiral HPLC analysis. Enantiomeric excess of anti isomer (entries 5−7). [e] Reaction was performed for 48 h with 1 mol % of (*M*,*S*)-**3d**/KO^{t}Bu.

Table 2. Substrate Scope of Chiral Tetraaminophosphonium Salt (*M*,*S*)-**3d**-Mediated Asymmetric Direct Henry Reaction[a]



entry	R^2	time (h)	yield[b] (%)	dr[c] (anti:syn)	ee[d] (%)
1	*o*-F−C_6H_4	5	94	>19:1	96
2	*p*-F−C_6H_4	9	91	>19:1	97
3	*p*-Cl−C_6H_4	9	95	>19:1	97
4	*p*-Me−C_6H_4	24	90	>19:1	97
5	1-naphthyl	8	84	>19:1	96
6	2-furyl	6	96	>19:1	97
7	(*E*)-PhCH=CH	21	74	>19:1	99
8	$Ph(CH_2)_2$	24	76	4:1	93
9	$Me(CH_2)_7$	24	77	4:1	94

[a] See Supporting Information for details. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of crude reaction mixtures. [d] Enantiomeric excess of anti isomer that was determined by chiral HPLC analysis.

reaction proceeded smoothly even at −78 °C to furnish the corresponding nitro alcohol **5** (R^1 = H) in 86% yield with 89% ee (entry 1, Table 1). Here, we found that the choice of the aromatic substituent (Ar) on the diazaphosphacycle of **3** had a significant effect on the catalyst efficiency (entries 1−4). While the use of (*M*,*S*)-**3b** having *m*-xylyl groups caused a substantial decrease in the reactivity and selectivity (entry 2), the *p*-tolyl substitution [(*M*,*S*)-**3c**] scarcely affected the performance of the catalyst (entry 3). Eventually, introduction of an electron-deficient *p*-trifluoromethylphenyl functionality [(*M*,*S*)-**3d**] led to the formation of **5** (R^1 = H) in 90% yield with 94% ee (entry 4). This system was applicable to other nitroalkanes, in which a high level of diastereo- and enantioselectivities was attained (entries 5−6). It should be added that the catalyst loading could be reduced to 1 mol % without any detrimental effect on the selectivity albeit a longer reaction time was required (entry 7).

Further investigation of the ability of (*M*,*S*)-**3d** to control the relative and absolute configurations was conducted with nitroethane (**4b**) as a representative nucleophilic component and various aldehydes, and these results are summarized in Table 2. A virtually complete stereochemical control was achieved with a series of aromatic aldehydes including fused and heteroaromatic ones (entries 1−6). Notably, α,β-unsaturated and aliphatic aldehydes also appeared to be good candidates (entries 7−9), which clearly demonstrated the broad generality of this asymmetric direct Henry protocol.

In conclusion, we have designed a chiral tetraaminophosphonium salt **3** possessing the *P*-spirocyclic structure, and its potential as an organic molecular catalyst has been demonstrated in the application to the asymmetric direct Henry reaction. We believe that the present study offers a new axis of chiral onium salt catalyses.

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Supporting Information Available: Representative experimental procedures, physical characterization data of (*M*,*S*)-**3a-d** including the X-ray analysis, and the details of the low-temperature NMR study; crystallographic data for (*M*,*S*)-**3a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) See Supporting Information for details of the NMR experiment.

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