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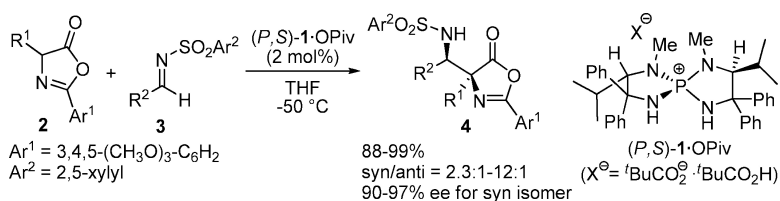
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Chiral Tetraaminophosphonium Carboxylate-Catalyzed Direct Mannich-Type Reaction

Daisuke Uraguchi, Yusuke Ueki, and Takashi Ooi*

Department of Applied Chemistry, Graduate School of Engineering, Nagoya University, Nagoya 464-8603, Japan

Received August 16, 2008; E-mail: tooi@apchem.nagoya-u.ac.jp

Organic ion pair catalysis, particularly that involving chiral, nonracemic onium salts, occupies a unique place in the recent development of organic molecular catalysis,[1] and its characteristic features have attracted significant attention from industrial and academic communities. In the catalysis of chiral quaternary onium salts, the cation structure is regarded as the most important element for controlling reactivity and selectivity. Accordingly, a catalyst manifold has been created for different types of reactions such as a phase-transfer-catalyzed bond formation by the modification of a cationic moiety.[2] Although the anion part of the salts is essential for neutralizing the charge, it is hardly associated with the overall efficiency and/or stereoselectivity in the targeted transformation because of the multiple ion-exchange processes. Even in the case of chiral onium salts bearing Lewis basic anions, their roles have been restricted to the activation of silyl nucleophiles for initiating the catalysis.[3,4] Thus, the inherent synthetic relevance of incorporating tunable, functional anions to the parent *quaternary* onium salts is yet to be explored.[5] In this context, we are interested in the possibility of establishing a novel catalysis of chiral quaternary onium salts possessing an appropriate organic anion, which can be controlled by not only the structural manipulation of the cation but also that of the initial anion through its continuous participation in the catalytic cycle. Here, we report such an asymmetric catalysis of chiral tetraaminophosphonium carboxylate **1·OCOR** and demonstrate its utility in the highly enantioselective direct Mannich-type reaction of azlactones (eq 1).
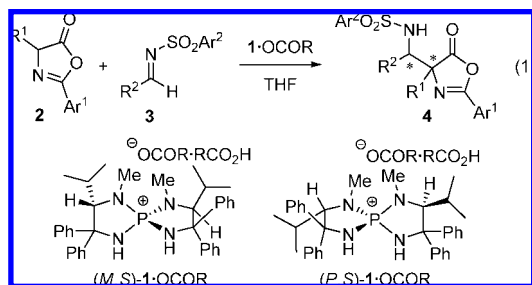
At the outset of our study, we sought to employ our recently developed [5,5]-*P*-spirocyclic tetraaminophosphonium framework as a primary structure of the key onium ion and carboxylate as an organic counteranion.[6] Considering the general basicity of the carboxylate anion,[7] we selected the direct and stereoselective Mannich-type reaction[8] of oxazol-5-(4*H*)-one (**2**), i.e., azlactone,[9] with sulfonyl imine **3** to evaluate the salt catalysis.[10] We also recognized that this particular Mannich-type protocol could provide new access to differently protected, optically active α,β-diamino acids with an α-tetrasubstituted carbon stereocenter.[11,12] In an illustration of the expected catalytic cycle (Figure 1), a basic carboxylate anion would abstract the active methine proton of azlactone to give the corresponding chiral phosphonium enolate. To achieve high levels of enantiocontrol, enforcing the geometrically identical ion pairing seemed to be important. This led us to presume that use of a partially yet selectively alkylated aminophosphonium cation such as **1** could minimize the mode of the secondary interaction between the phosphonium cation and the
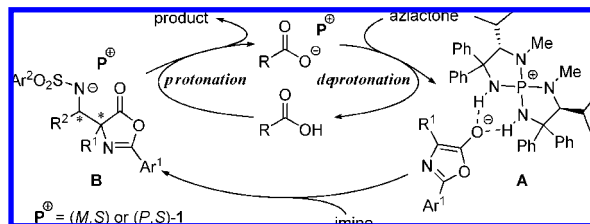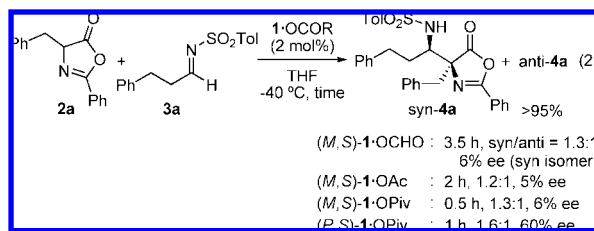

Figure 1. Working hypothesis for the salt catalysis of **1·OCOR**.

enolate anion, rendering the ion pair assembly with a defined hydrogen-bonding network (**A**). Subsequent stereoselective bond formations with imine would afford phosphonium sulfonamide **B** that could be rapidly protonated by carboxylic acid to regenerate the chiral phosphonium carboxylate.

Initial experiments to examine this hypothesis were conducted by treating phenylalanine-derived azlactone **2a** with *N*-tosyl imine **3a** in the presence of chiral aminophosphonium formate (*M,S*)-**1·OCHO** (2 mol%), readily prepared from (*M,S*)-**1·Cl** through ion exchange, in THF at −40 °C (eq 2). After 3.5 h of stirring, the desired Mannich adduct **4a** was obtained near quantitatively with a syn/anti ratio of 1.3:1 (6% ee for the major syn isomer). Interestingly, tuning the basicity of the anionic component by changing it to acetate [(*M,S*)-**1·OAc**] and then to pivalate [(*M,S*)-**1·OPiv**] led to a substantial rate enhancement though the stereoselectivities were virtually unaffected.[7] This observation strongly suggested the intervention of the expected protonation−deprotonation sequence. Another intriguing observation was that the enantioselectivity was dramatically improved by simply switching the chirality of the phosphorus center of the catalyst, and *syn*-**4a** was obtained in 60% ee under the influence of (*P,S*)-**1·OPiv**.[13] The origin of this quantum leap of the enantioselectivity could be ascribed to the difference in the hydrogen-bonding manner depending on the *P*-spiro chirality of **1** as revealed by the single crystal X-ray diffraction analyses of (*M,S*)- and (*P,S*)-**1·Cl** (Figure 2). While the two N−H protons of the (*M,S*)-isomer are mutually disposed in opposite directions and interact with Cl⁻ and a water molecule, respectively, those of the (*P,S*)-isomer are oriented on the same side, capturing the anion simultaneously. The latter, more structured ion pairing assisted by the double hydrogen bonding would be crucial for inducing high selectivity.

Further optimization was made by examining the effect of the aromatic substituents (Ar¹, Ar²) in the substrates **2** and **3**. With respect to azlactone **2**, the introduction of more electron-donating, methoxy-substituted phenyl groups enhanced enantioselectivity (entries 1−3, Table 1). This can be
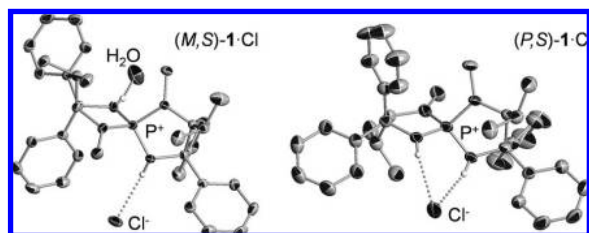
Figure 2. ORTEP diagrams of (M,S)- and (P,S)-**1**·Cl (all calculated hydrogens and a solvent molecule were omitted for clarity).

Table 1. Effect of Protective Groups (Ar^1, Ar^2) on Stereoselectivity^a (eq 1; R^1 = PhCH$_2$, R^2 = PhCH$_2$CH$_2$)

entry	Ar^1 (2)	Ar^2 (3)	time (h)	yield^b (%)	dr^c (syn/anti)	ee^d (%)	prod 4
1	4-CH$_3$O$-$C$_6$H$_4$	4-tolyl	7	97	2.2:1	64	4b
2	2-CH$_3$O$-$C$_6$H$_4$		30	89	2.2:1	65	4c
3	3,4,5-(CH$_3$O)$_3$$-C_6H_2$		5	98	2.6:1	75	4d
4		mesityl	9	99	2.9:1	93	4e
5		2,4-xylyl	9	99	4.5:1	93	4f
6		2,5-xylyl	9	95	6.7:1	95	4g
7^e			20	99	7.1:1	97	

^{a} Unless otherwise noted, reactions were performed at -40 °C using (P,S)-**1**·OPiv as a catalyst. See Supporting Information for details. ^{b} Isolated yield. ^{c} Determined by ^{1}H NMR analysis of crude reaction mixture. ^{d} Enantiomeric excess of syn isomer, which was determined by chiral HPLC analysis. Absolute configuration of **4g** was determined to be (2S,3R) by X-ray diffraction analysis after hydrolysis of azlactone, and the configurations of the other products were assigned on the analogy. ^{e} Reaction was conducted at -50 °C.

Table 2. Substrate Scope of the Direct Mannich-Type Reaction of Azlactone^a (eq 1; Ar^1 = 3,4,5-(CH$_3$O)$_3$$-C_6H_2$, Ar^2 = 2,5-xylyl)

| entry	R^1 (2)	R^2 (3)	time (h)	yield^b (%)	dr^c (syn/anti)	ee^d (%)	prod 4
1	PhCH$_2$	CH$_3$	12	91	4.5:1	92	4h
2		CH$_3$(CH$_2$)$_7$	20	92	6.6:1	96	4i
3		CH$_2$=CH(CH$_2$)$_8$	21	99	7.6:1	96	4j
4		PhCH$_2$OCH$_2$	14	98	5.3:1	95	4k
5		PhCO$_2$CH$_2$	24	88	12:1	93	4l
6		(CH$_3$)$_2$CHCH$_2$	17	94	4.4:1	95	4m
7		^{c}Hex	37	98	2.3:1	90	4n
8	(CH$_3$)$_2$CHCH$_2$	PhCH$_2$CH$_2$	15	99	7.8:1	96	4o
9	CH$_3$OCH$_2$		14	97	3.1:1	90	4p

^{a} Reactions were performed at -50 °C with (P,S)-**1**·OPiv as a catalyst. See Supporting Information for details. $^{b-d}$ See footnotes in Table 1.

understood by assuming the formation of a tighter ion pair as a consequence of the increased electron density on the oxygen of the enolate of **3**.[14] Moreover, the subsequent screening of the sulfonyl substituent on the imine nitrogen in the reactions with **3** possessing the 3,4,5-trimethoxyphenyl moiety revealed its significant impact on the stereoselectivity. A synthetically useful diastereoselectivity and an excellent enantioselectivity were attained when 2,5-xylylsulfonyl imine was employed (entries 3−6). Finally, decreasing the reaction temperature to −50 °C enabled the highest level of stereochemical control (entry 7).

Experiments were then conducted to probe the scope of the present (P,S)-**1**·OPiv-catalyzed, asymmetric direct Mannich-type protocol. The representative results are listed in Table 2. A variety of aliphatic imines having different substitution patterns are well accommodated,[15] and even the reaction with sulfonyl imine derived from acetaldehyde proceeds smoothly in a highly stereoselective manner (entries 1−7). Not only phenylalanine but also other α-amino acid derived azlactones are employable as nucleophilic reacting partners (entries 8 and 9).

The Mannich adduct **4** can easily be converted into the corresponding α,β-diamino acid dihydrochloride **6** in two steps without the loss of enantiopurity. For instance, the treatment of diastereomerically pure *syn*-

Scheme 1. Deprotection of *syn*-**4h** to α,β-Diamino Acid Dihydrochloride (Ar^1 = 3,4,5-(CH$_3$)$_3$$-C_6H_2$, Ar^2 = 2,5-xylyl)
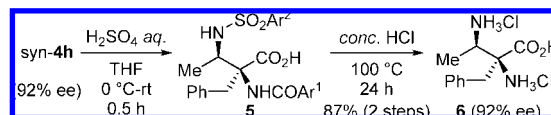
4h (92% ee) with aqueous H$_2$SO$_4$ in THF quantitatively afforded the corresponding carboxylic acid. Complete deprotection was then achieved by simple acidic hydrolysis with hydrochloric acid at 100 °C, and subsequent purification through an ion-exchange resin (Amberlite IR120, H$^+$ form) gave **6** in 87% yield (92% ee) (Scheme 1).[16]

In conclusion, the cooperative asymmetric catalysis of chiral tetraaminophosphonium carboxylate has been presented, and its synthetic utility has been successfully demonstrated by the application to the highly enantioselective direct Mannich-type reaction of azlactones with N-sulfonyl imines. Further studies based on this concept will be reported in due course.

Supporting Information Available: Representative experimental procedures and spectral data of **1**·OCOR and **2**−**6**. Crystallographic data for (M,S)- and (P,S)-**1**·Cl. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) The conservation of enantiomeric purity was confirmed by HPLC analysis after derivatization to the corresponding fully protected α,β-diamino acid ester. See Supporting Information for details.

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