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Pentanidium-Catalyzed Enantioselective Phase-Transfer Conjugate Addition Reactions

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Supporting Information

ABSTRACT: A new chiral entity, pentanidium, has been shown to be an excellent chiral phase-transfer catalyst. The enantioselective Michael addition reactions of *tert*-butyl glycinate−benzophenone Schiff base with various α,β-unsaturated acceptors provide adducts with high enantioselectivities. A successful gram-scale experiment at a low catalyst loading of 0.05 mol % indicates the potential for practical applications of this methodology. Phosphoglycine ester analogues can also be utilized as the Michael donor, affording enantioenriched α-aminophosphonic acid derivatives and phosphonic analogues of (*S*)-proline.

Asymmetric phase-transfer catalysis has been recognized as a convenient and powerful methodology in organic chemistry.[1] The unique advantages of this synthetic approach include simple procedures, mild conditions, suitability for large-scale reactions, ease of catalyst recovery, and a safe and environmentally benign character. In the 1980s, chiral phase-transfer catalysts (PTCs) were mainly derived from *Cinchona* alkaloids.[1,2] Following the success of the "first- and second-generation catalysts",[1,2] the "third-generation catalyst" containing an *N*-anthracenylmethyl group was reported by Lygo and Corey independently.[3] In 1999, Maruoka[4] designed an *N*-spiro chiral ammonium salt that showed excellent catalytic activity toward a wide variety of phase-transfer reactions. Various PTCs based on other designs have been developed, such as C_2-symmetric chiral pentacyclic guanidine,[5] two-center tartrate,[6] and C_3-symmetric amine.[7a] It is still highly desirable to add to this list a catalyst that is highly efficient and also highly amenable to modification so that it is easy to accommodate substrates for a wide range of asymmetric reactions. The ability to work in nonchlorinated solvents is also important.

Despite the success of many chiral PTCs, almost all of them are sp^3-quaternized ammonium salts. The design and synthesis of sp^2-quaternized ammonium salts as PTCs is rare, with only one existing example.[8] The nitrogen of an sp^3-quaternized ammonium salt has an imaginary tetrahedron composed of four carbon atoms. Three faces of this tetrahedron are efficiently blocked by steric groups, leaving one face sufficiently open to allow close contact between the enolate of the substrate and the ammonium cation.[1c,3a,4a] However, sp^2-quaternized ammonium is freely accessible from two opposite directions (i.e., the "p orbital" directions). Thus, it is much more difficult to control the configurational ion pair consisting of the catalyst and the substrate. Besides Coulomb forces, other interactions, such as H-bonding[7a] or π interactions,[7b] are thus required to fix the ion pair more rigidly, so the electrophile can approach only from a fixed direction, leading to high stereoselectivity.

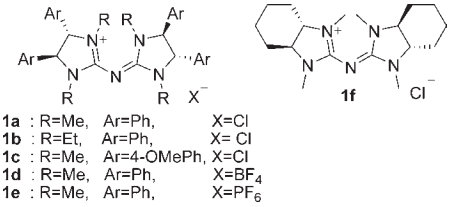

Figure 1. Various chiral pentanidium salts.

We have developed bicyclic guanidines as chiral Brønsted base catalysts for enantioselective reactions over the past several years.[9] As an extension of this work, we began a program to develop novel structures that are more basic than guanidines. We naively developed pentanidine, a structure containing five nitrogen atoms in conjugation, with the hypothesis that this may render it more basic than guanidine. Serendipitously, we found that its alkylated salt, pentanidium, is an excellent phase-transfer catalyst.[10] Herein we describe a novel C_2-symmetric chiral pentanidium (Figure 1) and its successful application to catalytic enantioselective Michael addition of *tert*-butyl glycinate−benzophenone Schiff base to various α,β-unsaturated acceptors, such as vinyl ketones, acrylates, and chalcones.

The synthesis of pentanidium chloride **1a** required five steps starting from commercially available (*S*,*S*)-diphenyldiaminoethane and other commonly available and inexpensive reagents (Scheme 1). The structure of the chiral pentanidium salt was confirmed by single-crystal X-ray diffraction analysis (see the Supporting Information). The preparation protocol required flash chromatography only once and a single recrystallization at the end of the synthesis.

Michael addition of *tert*-butyl glycinate−benzophenone Schiff base (**2**) has been evaluated previously by several groups under either phase-transfer or homogeneous conditions.[3c,3d,4b,4c,11] As a preliminary study, phase-transfer Michael addition of Schiff base **2** to ethyl vinyl ketone (**3a**) was catalyzed using pentanidium

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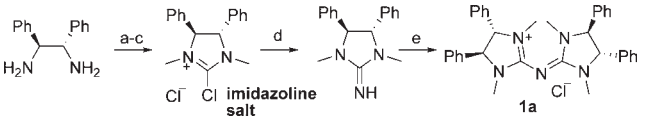
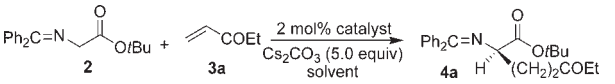
Scheme 1. Preparation of Pentanidium Chloride 1a[a]



[a] Conditions: (a) Triphosgene, Et_3N, CH_2Cl_2; (b) MeI, NaH, THF, 80% yield for two steps; (c) $(COCl)_2$, toluene, reflux 24 h, >99% yield; (d) NH_3, MeCN, sealed tube, reflux overnight, 99% yield; (e) Et_3N, imidazoline salt, MeCN, recrystallization, 48% yield.

Table 1. Michael Addition between Schiff Base 2 and Ethyl Vinyl Ketone[a]



entry	catalyst	temp/°C	solvent	yield (%)[b]	ee (%)[c]
1	**1a**	r.t.	Et_2O	81	81
2	**1a**	r.t.	CH_2Cl_2	80	<5
3	**1a**	r.t.	toluene	84	83
4	**1a**	0	toluene	89	86
5	**1b**	0	toluene	83	76
6	**1c**	0	toluene	87	85
7	**1d**	0	toluene	75	80
8	**1e**	0	toluene	72	57
9	**1f**	0	toluene	90	<5
10	**1a**	0	mesitylene	88	89
11[d]	**1a**	−20	mesitylene	85	93

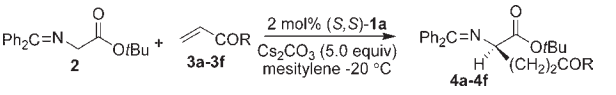
[a] Reactions were performed by using **2** (0.02 mmol) and **3a** (0.04 mmol) in 0.2 mL of solvent for 2 h. [b] Yield of isolated product. [c] Determined by HPLC analysis using a Chiralcel OD-H column. The absolute configuration was determined to be *R*.[11c] [d] Reaction time was 4 h.

1a. With 2 mol % of the catalyst (*S,S*)-**1a** and 50% KOH(aq) as the base, the reaction was complete in 5 min, affording adduct **4a** with 45% ee. After evaluation of several bases, the solid base Cs_2CO_3 (5 equiv) was found to provide the best enantioselectivity (83%; Table 1, entry 3). Diethyl ether (entry 1) afforded an ee value comparable to that of toluene, and dichloromethane (entry 2) led to almost racemic product. Decreasing the reaction temperature to 0 °C increased the ee value slightly (entry 4). Chiral pentanidiums **1b**−**1f** were also tested under these reaction conditions. Unfortunately, they did not improve the results further (entries 5−9). When mesitylene was used as the solvent and the reaction temperature decreased to −20 °C, the ee value improved to 93% (entries 10 and 11).

With the optimal reaction conditions established, we studied the phase-transfer Michael addition of **2** with various vinyl ketones and acrylates (Table 2). Both alkyl vinyl ketones **3a**−**c** and phenyl vinyl ketone **3d** gave excellent ee values (entries 1−4). The low yield of adduct **4d** (entry 4) might be due to double addition.[3d] Acrylates **3e** and **3f** also provided good yields and excellent enantioselectivities (entries 5−8). Remarkably, the catalyst loading could be lowered to 0.03 mol % without significantly affecting the enantioselectivity (entry 8).

The same conditions were successfully applied to chalcones and led to adducts **6a**−**q** with excellent yields, enantioselectivities, and diastereoselectivities (Table 3) regardless of the steric or electronic properties of the aromatic rings on the chalcones. All of the

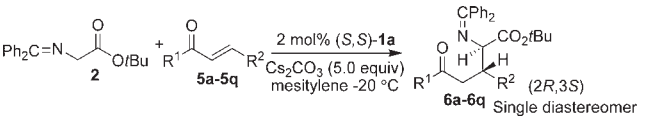
Table 2. Michael Addition of Schiff Base 2 to Vinyl Ketones and Acrylates[a]



entry	**3** [R]	**4**	time(h)	yield(%)[b]	ee (%)[c]
1	**3a** [Et]	**4a**	4	92	93
2	**3b** [Me]	**4b**	3	86	91
3	**3c** [*n*Bu]	**4c**	1	97	93
4	**3d** [Ph]	**4d**	1	50	88
5	**3e** [OEt]	**4e**	6	71	97
6	**3f** [OBn]	**4f**	4	80	96
7[d]	**3f** [OBn]	**4f**	6	77	93
8[e]	**3f** [OBn]	**4f**	12	75	91

[a] Reactions were performed by using **2** (0.06 mmol) and **3** (0.12 mmol) in 0.6 mL of mesitylene for the indicated time. [b] Yield of isolated product. [c] Determined by HPLC analysis using Chiralcel OD-H and Chiralpak AD-H columns. [d] 0.1 mol % catalyst was used. [e] 0.03 mol % catalyst was used.

Table 3. Michael Addition of Schiff Base 2 to 5[a]



entry	R^1, R^2	product	time (h)	yield (%)[b]	ee (%)[c]
1	Ph, Ph	**6a**	12	98	92
2	Ph, 1-naphthyl	**6b**	12	91	92
3	Ph, 2-naphthyl	**6c**	24	93	90
4	Ph, 4-PhC_6H_4	**6d**	21	88	91
5	Ph, 4-FC_6H_4	**6e**	18	89	90
6	Ph, 4-ClC_6H_4	**6f**	15	98	92
7	Ph, 4-BrC_6H_4	**6g**	15	96	92
8	Ph, 4-$NO_2C_6H_4$	**6h**	10	91	94
9	Ph, 2-ClC_6H_4	**6i**	12	93	94
10	Ph, 4-MeOC_6H_4	**6j**	36	89	85
11	4-ClC_6H_4, Ph	**6k**	12	90	92
12	4-$NO_2C_6H_4$, Ph	**6l**	12	91	91
13	4-MeOC_6H_4, Ph	**6m**	18	83	87
14	2-naphthyl, Ph	**6n**	11	80	91
15	2-fural, Ph	**6o**	12	95	90
16	2-thiophenyl, Ph	**6p**	12	92	90
17	Me, Ph	**6q**	16	71	87
18[d]	Ph, 4-ClC_6H_4	**6f**	24	89	92

[a] Reactions were performed by using **2** (0.06 mmol) and **5** (0.072 mmol) in 0.6 mL of mesitylene for the indicated time. [b] Yield of isolated product. [c] Determined by HPLC analysis using a Chiralcel OD-H column. Only one diastereomer was observed, and the absolute configuration was verified by single-crystal X-ray diffraction of **7**. [d] **2** (0.1 mmol), **5f** (0.12 mmol), and 2.5 equiv of Cs_2CO_3 were used with a catalyst loading of 0.05 mol %.

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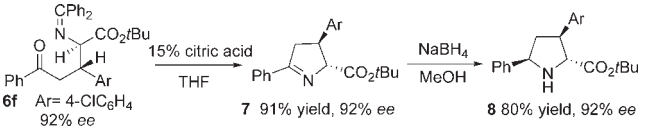
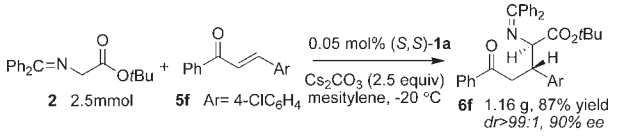
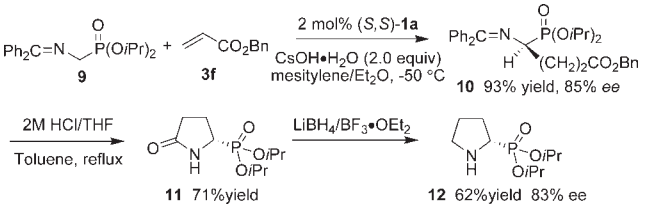
Scheme 2. Synthesis of Enantiopure Pyrrolidine Derivatives



Scheme 3. Gram-Scale Experiment with Low Catalyst Loading



Scheme 4. Michael Reaction between 9 and Benzyl Acrylate



reactions provided a single syn stereoisomer. Chalcones bearing electron-donating groups took a longer time for the reaction to reach completion (entries 10 and 13). It was also revealed that a low catalyst loading of 0.05 mol % was sufficient to provide excellent enantioselectivity (entry 18), albeit longer reaction time of 24 h was required.

The usefulness of adducts **6a**−**q** was clearly demonstrated through a simple and efficient synthesis of substituted pyrrolidines (Scheme 2). In the presence of citric acid, deprotection of the amino group of **6f** was followed by cyclization through imine formation, affording **7**. Reduction with $NaBH_4$ provided pyrrolidine **8** in good yield with no loss of enantioselectivity.[12] This methodology provides an efficient entry to enantiopure substituted pyrrolidines that cannot be prepared through [3 + 2] cycloaddition reactions.[13] Electron-rich alkenes usually do not undergo [3 + 2] cycloaddition reactions with glycinate imines. Considering the low catalyst loading (Table 2, entry 8; Table 3, entry 18), chiral pentanidium could be a highly efficient chiral PTC for practical asymmetric synthesis. To exploit the potential catalytic ability of chiral pentanidium **1a**, we scaled up the reaction in the presence of 0.05 mol % **1a** (Scheme 3). Excellent enantioselectivity was maintained with good yield.

In addition to Schiff base **2**, benzophenone imines of phosphoglycine ester **9** could also be utilized as donors in a related Michael addition reaction (Scheme 4). α-Aminophosphonic acid can easily be obtained through a one-step modification of adduct **10**.[14] α-Aminophosphonic acids and their phosphonate esters are transition-state analogues of amino acids.[15] A number of potent inhibitors of enzymes have been prepared from these amino acid mimics. Furthermore, **10** can also be transformed to phosphonic analogues of (*S*)-proline **12**, for which no general method of preparation exists.[16] A single recrystallization of **11** improved the ee value to 96%, as indicated using *N*-Cbz-**12**.

In summary, a new chiral entity, pentanidium, has been developed as an excellent chiral phase-transfer catalyst. Michael addition reactions of *tert*-butyl glycinate−benzophenone Schiff base with various α,β-unsaturated acceptors, such as vinyl ketones, acrylates, and chalcones, have been shown to provide adducts with high ee values. A successful gram-scale experiment at a low catalyst loading of 0.05 mol % indicates the potential for practical applications of this methodology. Adducts can be easily transformed to enantiopure pyrrolidines or α-aminophosphonic acid derivatives and phosphonic analogues of proline.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, spectroscopic data, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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