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Development of a Chiral Bis(guanidino)iminophosphorane as an Uncharged Organosuperbase for the Enantioselective Amination of Ketones

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Supporting Information

ABSTRACT: Chiral bis(guanidino)iminophosphoranes were designed and synthesized as chiral uncharged organosuperbase catalysts that facilitate activation of less-acidic pro-nucleophiles. The newly developed bis(guanidino)-iminophosphoranes, which possess the highest basicity among chiral organocatalysts reported to date, were proven to be a superb class of chiral organosuperbases by reaction of azodicarboxylates with 2-alkyltetralones and their analogues as the less acidic pro-nucleophiles.

During the past decade, intensive interest has been devoted to the development of chiral uncharged strong organobase catalysts.[1] Among these reported organobase catalysts, chiral guanidine and P1-phosphazene bases have emerged as efficient enantioselective catalysts, and tremendous progress has been made in the development of a wide variety of enantioselective reactions using these catalysts.[2,3] However, the applications of these catalysts have been limited to pro-nucleophiles having a rather acidic proton, such as 1,3-dicarbonyl compounds and nitroalkanes. They have been seldom used for activation of less acidic pro-nucleophiles. The development of much stronger chiral organobases is demanded to overcome these intrinsic limitations. In general, the basicity of the organobases increases with increasing resonance stability of their conjugate acids, the protonated form of the organobases. For instance, introduction of phosphazene or guanidine subunit(s) to the iminophosphorane core stabilizes its conjugate acid, aminophosphonium cation, to afford a series of phosphazene organosuperbases.[4] However, no iminophosphoranes modified by additional phosphazene or guanidine subunits to develop chiral organosuperbases have been reported so far. We hence designed pseudo-C_2-symmetric bis(guanidino)iminophosphoranes **1** as a novel family of chiral phosphazene organosuperbases (Figure 1). In this catalyst design, two guanidine subunits were introduced to the central iminophosphorane core to enhance the basicity of the iminophosphorane moiety, where the guanidine subunits enable resonance extension to further stabilize the central aminophosphonium cation generated through the deprotonation of a pro-nucleophile.[5] It can be predicted that the newly designed pseudo-C_2-symmetric bis(guanidino)iminophosphoranes **1** allow activation of less acidic pro-nucleophiles and open up a new avenue in enantioselective catalysis using a chiral organosuperbase. Herein, we report the development of optically pure bis(guanidino)iminophosphoranes **1** as a superb class of chiral organosuperbases for catalytic enantioselective transformation.

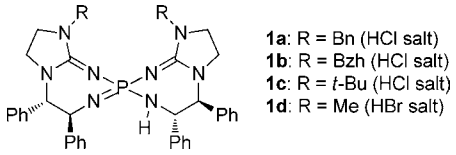

Figure 1. Structure of newly designed bis(guanidino)iminophosphorane catalyst in an optically active form.

The characteristic feature of the newly designed bis(guanidino)-iminophosphorane catalysts **1** is underscored by their helical chirality based on the 7,7-membered spirocyclic system. When (1*S*,2*S*)-1,2-diphenyl-1,2-ethanediamine ((*S*,*S*)-DPEN) is introduced to the catalyst molecule, the central chirality of the DPEN combined with the helical chirality of the spirocycle results in the formation of diastereomeric catalysts. In fact, the two diastereomers of bis(guanidino)iminophosphoranes **1a**−**d** were formed with moderate to high diastereoselectivity[6] when **1a**−**d** were prepared from commercially available (*S*,*S*)-DPEN in four steps and then isolated as HCl or HBr salts. In this catalyst design, we arranged the hydrogen bond donor and acceptor sites around the central phosphorus atom: the nitrogen atom of the iminophosphorane moiety (N═P) functions as the hydrogen bond acceptor, while the N−H moiety attached to the iminophosphorane core functions as the hydrogen bond donor. Indeed, the side-by-side arrangement of the donor and acceptor sites has been proven to be a fundamental approach to designing efficient chiral organobase catalysts such as chiral guanidines and P1-phosphazenes to achieve high enantioselectivities.[2]

At the outset of our studies, to determine the structural features of the newly designed chiral organosuperbases, single-crystal X-ray diffraction analysis of both diastereomeric HCl salts, bis(guanidino)aminophosphonium **1a**·HCl (R = benzyl), was conducted (Figure 2).[7] As shown in Figure 2a, (*M*)-**1a**·HCl, which was obtained as the major diastereomer, possesses nearly entirely C_2-symmetric structure. In addition, the two N−H moieties attached at the central phosphorus atom are

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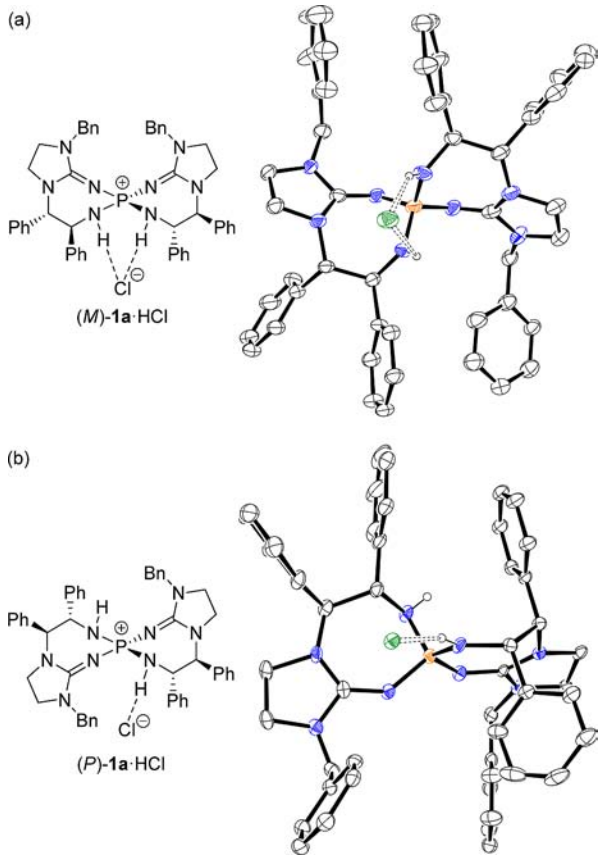


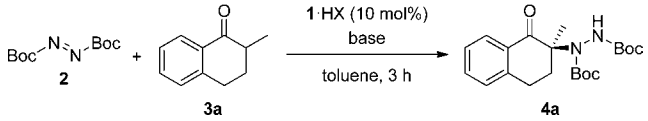
Figure 2. ORTEP drawings of (a) (*M*)-**1a**·HCl and (b) (*P*)-**1a**·HCl with probability ellipsoids drawn at the 50% level. The solvent molecules and hydrogen atoms, except N−H protons, are omitted for clarity.

arranged approximately in parallel to interact with the chloride anion through two hydrogen bonds. It can be considered that these two N−H moieties would function as efficient hydrogen-bond-forming sites to direct the orientation of both a nucleophile and an electrophile in the transient assembly. In sharp contrast, in the crystalline state of (*P*)-**1a**·HCl, obtained as the minor diastereomer, C_2-symmetry was seriously impaired, and the formation of two hydrogen bonds to the chloride anion was also invalidated (Figure 2b). Furthermore, the conformation of the phenyl rings of two DPENs was different in each DPEN unit: the two phenyl rings of one of the DPENs occupied pseudoequatorial positions, while those of the other occupied pseudoaxial positions, presumably due to the relatively flexible 7-membered ring spirocycle.

Next, in order to validate the catalytic performance of bis(guanidino)iminophosphoranes **1** as chiral organosuperbases, we selected electrophilic amination of 2-alkyltetralones **3** with azodicarboxylate **2** as an ideal probe. In principle, the activation of 2-alkyltetralones **3** as a nucleophile would be difficult using conventional chiral organobase catalysts because of their low acidity and steric congestion at the reaction site.[8]

The results are shown in Table 1. Bis(guanidino)iminophosphoranes **1** were generated in situ from **1**·HX salts.[9] Namely, the mixture of **1**·HX and tetralone **3** was treated with *t*-BuOK before the addition of azodicarboxylate **2**. An initial attempt was performed using 10 mol% of (*M*)-**1a**·HCl with 10 mol% of *t*-BuOK at 0 °C. Fortunately, the corresponding product **4a** was obtained in fairly good enantioselectivity (80% ee), albeit in low

Table 1. Electrophilic Amination of 2-Methyltetralone with Azodicarboxylate[a]



entry	**1**	base (mol%)	*T* (°C)	yield (%)[b]	ee (%)[c]
1	(*M*)-**1a**	*t*-BuOK (10)	0	34	80
2	(*P*)-**1a**	*t*-BuOK (10)	0	96	3
3	(*M*)-**1b**	*t*-BuOK (10)	0	23	82
4	(*M*)-**1c**	*t*-BuOK (10)	0	20	86
5	(*M*)-**1d**	*t*-BuOK (10)	0	37	91
6	(*M*)-**1d**	*t*-BuOK (15)	0	>99	92
7	(*M*)-**1d**	*t*-BuOK (20)	0	98	90
8	(*M*)-**1d**	*t*-BuOK (30)	0	97	80
9	(*M*)-**1d**	*t*-BuOK (15)	−40	55	94
10	(*M*)-**1d**	*t*-BuOK (20)	−40	66	94
11	(*M*)-**1d**	$KN(SiMe_3)_2$ (20)	−40	53	94
12	(*M*)-**1d**	$NaN(SiMe_3)_2$ (20)	−40	>99	95
13	(*M*)-**1d**	$LiN(SiMe_3)_2$ (20)	−40	nr	–

[a]Reactions were conducted with 1 equiv of **2** and 5 equiv of **3a** in the presence of 10 mol% of **1**·HX and the indicated base in toluene (0.1 M) for 3 h under an argon atmosphere. [b]Isolated yield. [c]Determined by chiral stationary phase HPLC.

chemical yield (entry 1). The absolute configuration of product **4a** was determined to be the (*S*)-form.[10] On the basis of the X-ray crystallographic analysis of **1a**·HCl (Figure 2), it could be predicted that the helical chirality of **1** should be influential in the stereochemical outcomes. As expected, (*P*)-**1a**·HCl afforded **4a** in nearly racemic mixtures despite the excellent chemical yield (entry 2). Further screening of the substituent introduced at the cyclic guanidine units was continued using (*M*)-**1**·HX (entries 3−5). The introduction of sterically hindered substituents such as benzhydryl and *tert*-butyl, giving (*M*)-**1b**·HCl and (*M*)-**1c**·HCl, respectively, led to a slight increase in the enantioselectivities (entries 3 and 4), albeit with a reduction of the chemical yield. (*M*)-**1d**·HBr, having the sterically less hindered methyl substituent, enhanced the enantioselectivity, although no marked improvement was detected in the chemical yield (entry 5). In an effort to enhance the chemical yield, we attempted to add an excess amount of *t*-BuOK to (*M*)-**1d**·HBr. It is noteworthy that the yield was drastically improved without compromising the enantioselectivity despite using excess *t*-BuOK (entries 6 and 7). However, a further increase in the amount of *t*-BuOK to 30 mol% resulted in a slight decrease in ee (entry 8). As expected, reducing the reaction temperature to −40 °C enhanced the enantioselectivity, but with a marked decrease in the yield (entries 9 and 10). Interestingly, the yield was affected by the countercations of the bases employed. $NaN(SiMe_3)_2$ was found to be the superior base for this reaction (entries 11−13), and the optimal reaction conditions were established as 10 mol% of (*M*)-**1d**·HBr and 20 mol% of $NaN(SiMe_3)_2$ in toluene at −40 °C.[11]

With the optimal reaction conditions in hand, we investigated the substrate scope of this reaction (Table 2). The positional effect of the methoxy substituent on the tetralone aromatic ring was searched for thoroughly (entries 2−7). Introduction of the substituent at either the 5- or 7-position exhibited yields and enantioselectivities similar to those obtained with the unsubstituted tetralone (entry 1 vs entries 2 and 5). Meanwhile, in the reaction of the 6- and 8-substituted tetralones **3c** and **3e**, higher temperature was required for

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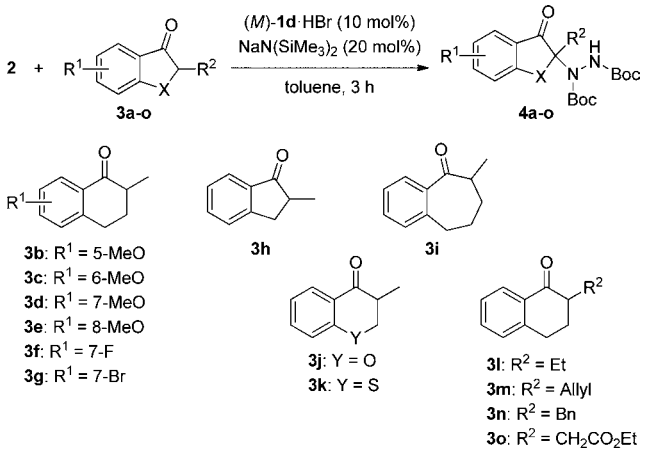
Table 2. Substrate Scope[a]



entry	3	4	T (°C)	yield (%)[b]	ee (%)[c]
1	**3a**	**4a**	−40	>99 (97)[d]	95 (97)[d]
2	**3b**	**4b**	−40	98	96
3	**3c**	**4c**	−40	18	90
4	**3c**	**4c**	25	83	88
5	**3d**	**4d**	−40	94	93
6	**3e**	**4e**	−40	7	34
7	**3e**	**4e**	25	78	10
8	**3f**	**4f**	−40	>99	93
9	**3g**	**4g**	−40	>99	82
10	**3h**	**4h**	−40	>99	91
11	**3i**	**4i**	−40	77	84
12	**3j**	**4j**	−40	>99	89
13	**3k**	**4k**	−40	>99	82
14	**3l**	**4l**	−40	93	94
15	**3m**	**4m**	−40	95	98
16	**3n**	**4n**	−40	92	97
17	**3o**	**4o**	−40	82	68

[a]Reactions were conducted with 1 equiv of **2** and 5 equiv of **3** in the presence of 10 mol% of (*M*)-**1d**·HBr and 20 mol% of $NaN(SiMe_3)_2$ (0.6 M toluene solution) in toluene (0.1 M) for 3 h under argon atmosphere. [b]Isolated yield. [c]Determined by chiral stationary phase HPLC. [d]In parentheses, 2.5 equiv of **3a** was used.

sufficient conversion (entries 3, 4, 6, and 7). More importantly, the 8-substituted tetralone **3e** showed much lower enantioselectivity, presumably due to the conformational change in the ion pairs between protonated (*M*)-**1d** and the enolate of **3e**, where the methoxy group exists in close proximity to the anionic oxygen atom of the enolate (entries 6 and 7). The tetralones bearing electron-withdrawing groups (**3f** and **3g**) underwent the reaction with good yields and slightly decreased enantioselectivities (entries 8 and 9). Next, the structural effect on the cyclic ketones was examined. Indanone (**3h**), benzosuberone (**3i**), chromanone (**3j**), and thiochromanone (**3k**) derivatives are also useful substrates in the present enantioselective amination, giving rise to the corresponding products **4h**−**k** in good to excellent yields without marked reduction in the enantioselectivities (entries 10−13). A variety of alkyl substituents can be introduced to the 2-position of the tetralone derivatives. Excellent enantioselectivities were achieved in the reactions of tetralones **3l**−**n** (entries 14−16), but not with tetralone **3o**, having a coordinatable substituent (entry 17). It should be pointed out that the reaction can be operated using 2.5 equiv of **3** without compromising chemical yield and enantioselectivity (entry 1).

In conclusion, we have developed novel chiral bis(guanidino)iminophosphoranes as a superb class of the uncharged chiral organosuperbase catalyst that facilitates the reaction of less-acidic pro-nucleophiles, 2-alkyltetralone derivatives and their analogues, with azodicarboxylate. The method provides efficient access to construct a quaternary chiral center at the α-position of tetralone derivatives and their analogues in a highly enantioselective manner. Further studies are in progress to extend the range of applicable nucleophiles and to discover catalytic enantioselective variants of other processes.

■ ASSOCIATED CONTENT

Supporting Information

Representative experimental procedures and spectral data for bis(guanidino)iminophosphorane catalysts and the amination products; X-ray crystallographic data for bis(guanidino)iminophosphoranes and determination of the configuration of product (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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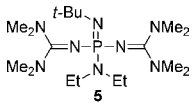
(5) The pK_a of the achiral bis(guanidino)iminophosphorane **5**, which has a backbone similar to that of the newly designed bis(guanidino) iminophosphorane catalysts **1**, was reported to be 26.8 (in THF) (see ref 4e).



5

p*K*a = 26.8 (THF)

(6) The diastereomeric ratio was roughly estimated to range from 7:3 to 9:1 ((*M*)-form was major). The exact diastereomeric ratio could not be determined because of the considerable amount of byproducts.

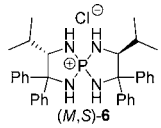
(7) The configurations of (*M*)-**1d** was also determined by a single-crystal X-ray diffraction analysis of (*M*)-**1d**·HBr. The configurations of (*M*)-**1b** and (*M*)-**1c** were determined by the chemical shift of ^{31}P NMR spectra by analogy.

(8) For examples of the amination of activated tetralone derivatives, see: (a) Xu, X.; Yabuta, T.; Yuan, P.; Takemoto, Y. *Synlett* **2006**, 137. (b) Terada, M.; Nakano, M.; Ube, H. *J. Am. Chem. Soc.* **2006**, *128*, 16044. (c) Liu, T.-Y.; Cui, H.-L.; Zhang, Y.; Jiang, K.; Du, W.; He, Z.-Q.; Chen, Y.-C. *Org. Lett.* **2007**, *9*, 3671. (d) Jung, S. H.; Kim, D. Y. *Tetrahedron Lett.* **2008**, *49*, 5527. (e) Kim, S. M.; Lee, J. H.; Kim, D. Y. *Synlett* **2008**, 2659. (f) Konishi, H.; Lam, T. Y.; Malerich, J. P.; Rawal, V. H. *Org. Lett.* **2010**, *12*, 2028. (g) Zhao, Y.; Pan, Y.; Liu, H.; Yang, Y.; Jiang, Z.; Tan, C.-H. *Chem.—Eur. J.* **2011**, *17*, 3571. (h) Inokuma, T.; Furukawa, T.; Uno, T.; Suzuki, Y.; Yoshida, K.; Yano, Y.; Matsuzaki, K.; Takemoto, Y. *Chem.—Eur. J.* **2011**, *17*, 10470.

(9) Neutralization of **1**·HX was conducted in accordance with Ooi's procedure, see: Uraguchi, D.; Sakaki, S.; Ooi, T. *J. Am. Chem. Soc.* **2007**, *129*, 12392. Observation of the free base form of bis(guanidino) iminophosphorane (*M*)-**1d** was attempted by ^{31}P NMR. See Supporting Information for details.

(10) The absolute configuration of product **4a** was determined by single-crystal X-ray diffraction analysis of the HBr salt of the Boc-deprotected compound of **4a**. See Supporting Information for details.

(11) Applying (*M*,*S*)-**6** (Ooi's catalyst, see refs 2f and 9) instead of (*M*)-**1d**·HBr resulted in low yield (18%, −57% ee) under the same reaction conditions as in Table 1, entry 12.



(*M*,*S*)-**6**

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