Organocatalysis

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Enantioselective Addition of a 2-Alkoxycarbonyl-1,3-dithiane to Imines Catalyzed by a Bis(guanidino)iminophosphorane Organosuperbase

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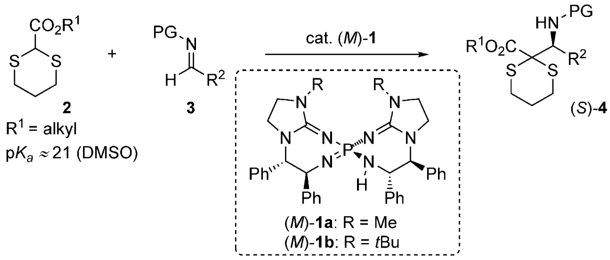
Abstract: *A chiral bis(guanidino)iminophosphorane catalyzes enantioselective addition reactions of a 1,3-dithiane derivative as a pronucleophile. The chiral uncharged organosuperbase facilitates the addition of benzyloxycarbonyl-1,3-dithiane to aromatic N-Boc-protected imines to provide optically active α-amino-1,3-dithiane derivatives, which are valuable versatile building blocks in organic synthesis.*

In recent years, much attention has been paid to the development of chiral uncharged strong organobase catalysts and their application in a variety of enantioselective reactions.[1] Many efficient catalysts, such as chiral guanidines and P1 phosphazenes, have been developed to date, and they have enabled many useful transformations that cannot be achieved with conventional chiral tertiary amine catalysts, including cinchona alkaloids.[2,3] However, the application of these catalysts is still limited to pronucleophiles bearing a rather acidic proton, such as 1,3-dicarbonyl compounds and nitroalkanes, because of their inherent basicity. Thus, the development of much stronger organobases, namely chiral organosuperbases, is desirable to overcome these intrinsic limitations and to pave the way to enantioselective transformations that have never been achieved before. Recently, we have developed novel chiral bis(guanidino)iminophosphorane **1** as a chiral uncharged organosuperbase catalyst that facilitates the activation of less acidic pronucleophiles.[4] Its usability was demonstrated in the enantioselective amination of 2-alkyltetralone derivatives as less acidic pronucleophiles. To extend the utility of the newly developed catalyst, particularly in synthetically useful transformations, we focused our attention on 2-alkoxycarbonyl-1,3-dithiane **2** as a less acidic pronucleophile. The addition reaction of 1,3-dithianes is one of the most important umpolung reactions in organic synthesis.[5,6] The anion of 1,3-dithiane is regarded as an acyl anion equivalent, and its reaction with various electrophiles, such as carbonyl compounds, imines, and Michael acceptors, furnishes the corresponding protected carbonyl compounds. In general, a stoichiometric amount of a strong base, such as *n*-butyllithium, is required for generating the dithiane anion prior to the reaction with electrophiles. The direct addition reaction using a catalytic amount of a Brønsted base is rather limited because of the low acidity at the 2-position, even if it is α to an electron-withdrawing group, such as an alkoxycarbonyl group.[7–9] In particular, enantioselective variants are rare.[10] We envisioned that the enantioselective addition reaction of 2-alkoxycarbonyl-1,3-dithianes **2** as less acidic pronucleophiles with imines **3** by using our newly developed catalyst **1** would afford optically active α-amino-1,3-dithiane derivatives, which are known as valuable versatile building blocks (Scheme 1). Currently, the synthesis of those compounds relies on the asymmetric addition of 2-lithio-1,3-dithianes to chiral *N*-sulfinyl- and *N*-phosphoryl imines where a stoichiometric amount of a Brønsted base as well as a chiral auxiliary are required.[11,12] We herein report the realization of the catalytic enantioselective addition reaction of 1,3-dithiane derivatives to aromatic imines by using a chiral bis(guanidino)iminophosphorane organosuperbase catalyst.



Scheme 1. Enantioselective addition of 2-alkoxycarbonyl-1,3-dithianes to imines catalyzed by (*M*)-**1**. PG = protecting group.

We began our investigation by evaluating the reaction of 2-benzyloxycarbonyl-1,3-dithiane (**2a**) as a pronucleophile with *N*-Boc imine **3a**. The catalyst was generated in situ by treating (*M*)-**1**·HX, which possesses helical chirality because of the spirocyclic structure and the central chirality of the (1*S*,2*S*)-1,2-diphenyl-1,2-ethanediamine unit, with $NaN(SiMe_3)_2$ prior to use. An initial attempt was made by reacting 11 mol% of (*M*)-**1a**·HBr with 10 mol% of $NaN(SiMe_3)_2$ in toluene at −40°C. As a result, the desired adduct **4a** was obtained in moderate yield, but with only 3% *ee* (Table 1, entry 1). Replacing the solvent with an ethereal solvent, such as THF or diethyl ether, improved the chemical yield, but the enantioselectivity was still low (entries 2 and 3). The solvent

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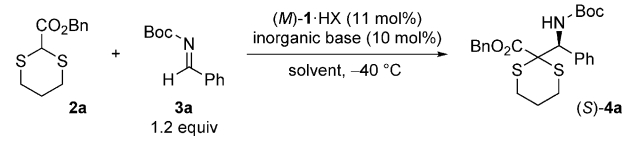
Table 1: Initial screening.[a]



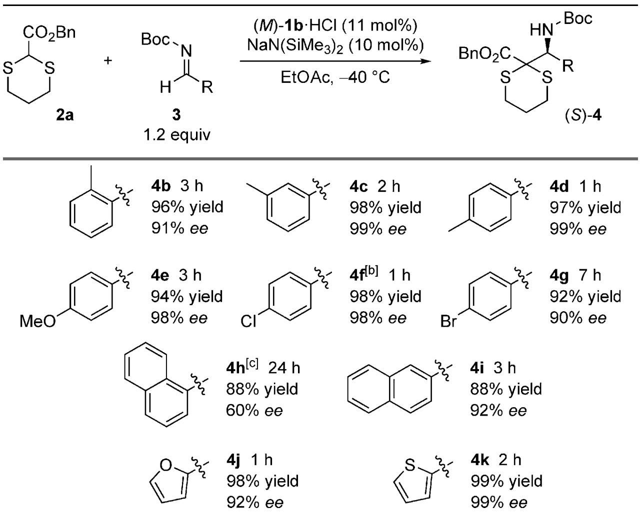
Entry	1·HX	Inorganic base[b]	Solvent	Time [h]	Yield[b] [%]	*ee*[c] [%]
1	**1a**·HBr	$NaN(SiMe_3)_2$	toluene	24	41	3
2	**1a**·HBr	$NaN(SiMe_3)_2$	THF	2	92	18
3	**1a**·HBr	$NaN(SiMe_3)_2$	Et_2O	24	93	13
4	**1a**·HBr	$NaN(SiMe_3)_2$	EtOAc	1	94	97
5	**1b**·HCl	$NaN(SiMe_3)_2$	EtOAc	1	98	99
6	**1b**·HCl	$LiN(SiMe_3)_2$	EtOAc	24	40	24
7	**1b**·HCl	$KN(SiMe_3)_2$	EtOAc	24	42	25
8	**1b**·HCl	*t*BuONa	EtOAc	24	56	56
9[d]	**1b**·HCl	$NaN(SiMe_3)_2$	EtOAc	2	96	98
10[e]	**1b**·HCl	$NaN(SiMe_3)_2$	EtOAc	1	93	97

[a] Reaction conditions: **2a** (0.10 mmol), **3a** (0.12 mmol), (*M*)-**1**·HX (0.011 mmol), inorganic base (0.010 mmol), solvent (0.50 mL), −40 °C. [b] Yields of isolated products. [c] The *ee* values were determined by HPLC analysis on a chiral stationary phase. [d] 0.015 mmol of **1b**·HCl (15 mol%) and 0.010 mmol of $NaN(SiMe_3)_2$ (10 mol%). [e] 0.010 mmol of **1b**·HCl (10 mol%) and 0.020 mmol of $NaN(SiMe_3)_2$ (20 mol%). Boc = *tert*-butoxycarbonyl.

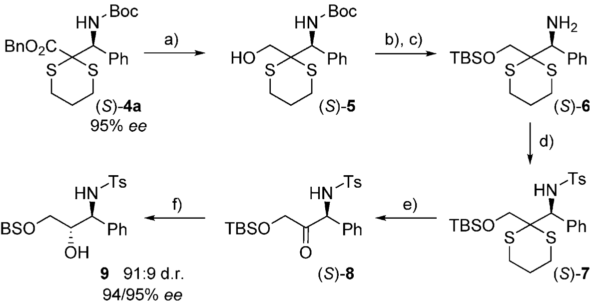
effect became evident when ethyl acetate was employed (entry 4). The reaction reached completion within one hour, and the product was obtained in high yield with excellent enantioselectivity. Further improvement of both chemical yield and the *ee* value was achieved by using (*M*)-**1b**·HCl as the precatalyst (entry 5). The choice of the inorganic base for the generation of the catalyst from precatalyst **1**·HX was found to be critical (entries 5–8). The use of $LiN(SiMe_3)_2$, $KN(SiMe_3)_2$, and *t*BuONa resulted in lower yields with lower enantioselectivity. This is presumably due to the detrimental effects of LiCl, KCl, and *t*BuOH, which are generated during the catalyst activation in situ. Whereas in our previous report, the use of excess inorganic base relative to precatalyst **1**·HX was essential to achieve high yields,[4] the use of a slight excess of **1**·HX relative to $NaN(SiMe_3)_2$ was optimal in the present reaction (entries 5, 9, and 10). The absolute configuration of product **4a** was unambiguously determined to be *S* by single-crystal X-ray diffraction analysis.[13]

With the optimized conditions in hand, the scope of imines was investigated (Table 2). At first, *ortho*-, *meta*-, and *para*-tolyl imines were tested, and the corresponding products **4b**–**4d** were obtained in high yields with high enantioselectivities. Imines with an electron-donating group, such as a methoxy group, or an electron-withdrawing group, such as a chloro or a bromo group, at the *para* position of the benzene ring underwent the reaction smoothly to provide products **4e**–**4g** in high yields with high enantioselectivities. The reaction of 2-naphthyl imine proceeded without any problems, whereas the reaction of 1-naphthyl imine resulted in moderate enantioselectivity. Heteroaromatic imines were also applicable to this reaction. 2-Furyl and 2-thienyl imines were compatible with the reaction conditions and afforded the corresponding products **4j** and **4k**, respectively, in high yields and with high enantioselectivity.[14,15]

Table 2: Imine scope.[a]



[a] Reaction conditions: **2a** (0.10 mmol), **3** (0.12 mmol), (*M*)-**1b**·HCl (0.011 mmol), $NaN(SiMe_3)_2$ (0.010 mmol), EtOAc (0.50 mL), −40 °C. [b] Conducted at −60 °C. [c] 1.0 mL of EtOAc.



Scheme 2. Derivatization of (*S*)-**4a**. Reagents and conditions: a) $NaBH_4$ (10.0 equiv), THF/MeOH, 0 °C to RT, 14 h, 92%, 94% *ee*; b) 47% HBr (aq.), MeOH, 40 °C, 2 h; c) TBSCl (1.5 equiv), imidazole (5.0 equiv), CH_2Cl_2, RT, 6 h, 91% (over 2 steps), 95% *ee*; d) TsCl (1.5 equiv), Et_3N (5.0 equiv), DMAP (50 mol%), CH_2Cl_2, RT, 6 h, 92%, 95% *ee*; e) NIS (8.0 equiv), acetone/H_2O, 0 °C, 10 min; f) $NaBH_4$ (6.0 equiv), THF, −78 °C, 1 h, 89% (over 2 steps), 91:9 d.r., 94/95% *ee*. DMAP = dimethylaminopyridine, NIS = *N*-iodosuccinimide, TBS = *tert*-butyldimethylsilyl, Ts = *para*-toluenesulfonyl.

Finally, the derivatization of the product, including the conversion of the 1,3-dithiane moiety into a ketone group, was attempted (Scheme 2). The reduction of the benzyl ester moiety of (*S*)-**4a** into a hydroxy group with $NaBH_4$ as the reducing agent yielded (*S*)-**5**. After protecting the primary hydroxy group with a TBS group, removal of the 1,3-dithiane moiety was investigated. However, all attempts failed because of the incompatibility of the *N*-Boc-protected amino moiety with the conditions. Therefore, we decided to convert the protecting group on the nitrogen atom into a tosyl group prior to the 1,3-dithiane deprotection. Cleavage of the Boc group under acidic conditions followed by chemoselective protection of the primary hydroxy group with TBSCl provided primary amine (*S*)-**6** in high yield. Tosylation of the amino group proceeded smoothly to afford (*S*)-**7**. The conversion of the 1,3-dithiane moiety of (*S*)-**7** was achieved by treatment with an excess amount of NIS in acetone/H_2O. Finally, the reduction of the resulting keto moiety with $NaBH_4$ proceeded in a diastereoselective manner to afford 3-amino-1,2-diol **9** in high yield.[16] In the course of the derivatization, the optical purity was not reduced.

In conclusion, we have developed a catalytic enantioselective addition reaction of a 1,3-dithiane derivative as a less acidic pronucleophile by using a chiral bis(guanidino)iminophosphorane organosuperbase catalyst. The addition of benzyloxycarbonyl-1,3-dithiane to *N*-Boc-protected aromatic imines proceeded in a highly enantioselective manner to provide optically active α-amino-1,3-dithiane derivatives, which are valuable versatile building blocks in organic synthesis. Ongoing studies are focused on the development of novel enantioselective transformations using chiral bis(guanidino)iminophosphorane catalysts as well as on the elucidation of the origin of the stereoselectivity.

Experimental Section

The reaction of **2a** with **3a** as a representative example: (*M*)-**1b**·HCl (8.1 mg, 0.011 mmol) was placed in a dried test tube and suspended in EtOAc (1.0 mL), and the solvent was evaporated once. EtOAc (0.50 mL) was added again, and the resulting suspension was degassed under reduced pressure. A solution of $NaN(SiMe_3)_2$ in THF (1.9 M, 5.3 μL, 0.010 mmol) was added to the suspension at room temperature. After stirring for ca. 1 min, 1,3-dithiane **2a** (25 mg, 0.10 mmol) was added, and the mixture was stirred for ca. 1 min. The solution was then cooled to −40 °C, and *N*-Boc imine **3a** (25 mg, 0.12 mmol) was added. The resulting mixture was stirred at that temperature for 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution (ca. 0.50 mL). The aqueous phase was extracted with EtOAc. The combined organic phase was dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 6:1) to afford **4a** (46 mg, 0.098 mmol, 98 %) as a white solid.

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[13] CCDC 1403953 (**4a**) and 1403954 (derivatized **9**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

[14] Aliphatic imines were also examined. However, the reactions showed poor reproducibility in terms of chemical yield, and the *ee* values were low in all cases (< 20% *ee*).

[15] The Boc group on the nitrogen atom was essential for this reaction. Imines with a tosyl group on the nitrogen atom did not undergo the reaction whereas imines with a diphenylphosphoryl group provided the corresponding products in low yield and as racemates.

[16] The relative configuration of the major diastereomer of **9** was determined by single-crystal X-ray diffraction analysis after benzoylation of the secondary hydroxy group of **9**; see Ref. [13].

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