Asymmetric Catalysis Hot Paper

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Construction of Vicinal Quaternary Stereogenic Centers by Enantioselective Direct Mannich-Type Reaction Using a Chiral Bis(guanidino)iminophosphorane Catalyst

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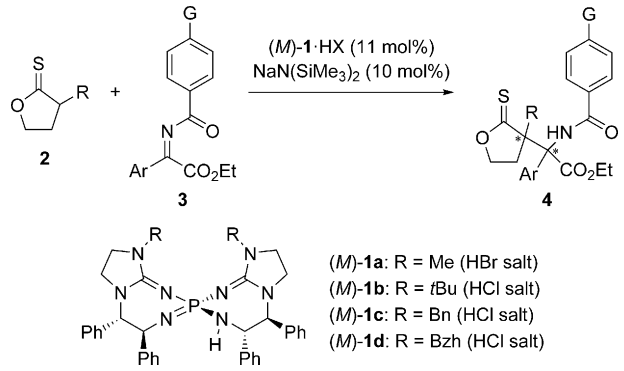
Abstract: *A novel asymmetric direct Mannich-type reaction of α-iminophenylacetate esters with thionolactones, bearing a substituent at the α-position, as a less acidic pronucleophile was developed. Using bis(guanidino)iminophosphorane as the chiral organosuperbase catalyst, the reaction afforded densely functionalized amino-acid derivatives having vicinal quaternary stereogenic centers, one of which is an all-carbon quaternary stereogenic center, in good yield with high diastereo- and enantioselectivities.*

The catalytic asymmetric construction of vicinal quaternary stereogenic centers, which are commonly found as a core structure in bioactive compounds, is a topic of profound interest in the fields of synthetic chemistry.[1–6] Intensive efforts have been devoted to the development of an efficient stereoselective method for the construction of vicinal quaternary stereogenic centers given the difficulties encountered in not only the formation of a carbon–carbon bond in the presence of steric congestion but also controlling the requisite stereochemical outcome. Asymmetric cycloadditions and intramolecular reactions which employ chiral metal catalysts[2] and organocatalysts[3] have been actively pursued in an effort to overcome these difficulties. In recent years, the nucleophilic 1,2-addition of trisubstituted carbon nucleophiles to ketones and ketimines has emerged as a potential method for constructing vicinal quaternary stereogenic centers.[4,5] Although several reliable approaches towards the construction of vicinal quaternary stereogenic centers are available in the field of asymmetric catalysis, those approaches are inherently limited to either the reaction of pronucleophiles having a relatively acidic proton at the α-position, such as 1,3-dicarbonyl and related compounds, or preformed nucleophiles, such as silylated derivatives. The direct use of less acidic pronucleophiles, which is expected to expand the scope of the reaction, is a formidable challenge in carbon–carbon bond formation to construct vicinal quaternary stereogenic centers. In an effort to activate the less acidic pronucleophiles, we recently developed the novel chiral bis(guanidino)iminophosphorane **1** as a superb class of uncharged chiral organosuperbase catalysts (Scheme 1).[7]



Scheme 1. Asymmetric Mannich-type reaction to construct vicinal quaternary stereogenic centers and structure of the chiral bis(guanidino)iminophosphorane **1**.

The catalytic efficiency of **1** has been demonstrated in the enantioselective 1,2-addition reactions of less acidic pronucleophiles, such as 2-alkyltetralone derivatives[7a,b] and 2-alkoxycarbonyl-1,3-dithiane,[7c] to azodicarboxylates and *N*-Boc imines, respectively. Considering the characteristic features of **1**, it is speculated to have the potential to circumvent the inherent limitation in the nucleophilic 1,2-addition of trisubstituted carbon pronucleophiles. To establish a system for constructing vicinal quaternary stereogenic centers, we envisaged a direct Mannich-type reaction of lactones or its derivatives, bearing a substituent at the α-position, as a less-acidic pronucleophile with α-iminophenylacetate esters. α-Iminophenylacetate esters have been employed in various nucleophilic addition reactions as a reactive ketimine, thus affording valuable precursors of α-quaternary phenylglycine derivatives.[8] Herein we report the novel asymmetric Mannich-type reaction of thionolactone derivatives (**2**) with α-iminophenylacetate esters (**3**) using a chiral organosuperbase catalyst (**1**), and it gives rise to densely functionalized amino acid derivatives (**4**) having vicinal quaternary stereogenic centers, one of which is an all-carbon quaternary stereogenic center, in a highly diastereo- and enantioselective manner (Scheme 1).

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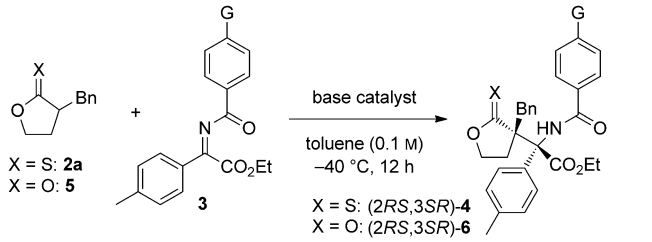
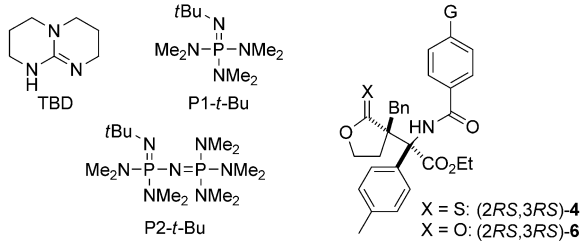
Initially, the Mannich-type reaction of the α-benzyl-substituted lactone **5** with the *N*-benzoyl-α-iminophenylacetate ester **3a** was investigated under the reaction conditions from our previous asymmetric α-amination of tetralones, in which two equivalents of $NaN(SiMe_3)_2$, relative to (*M*)-**1a**·HBr, were employed for the generation of the catalyst (Table 1, entry 1).[7a,b] However, **5** did not undergo the Mannich-type reaction under the influence of 10 mol% (*M*)-**1a**·HBr and 20 mol% $NaN(SiMe_3)_2$, presumably because of the low acidity at the α-position of **5**. We hence turned our attention to the thionolactone **2a** instead of **5**, in order to enhance the acidity at the α-position.[9] To our delight, the desired Mannich adduct **4aa** was obtained in high yield albeit with low stereoselectivity (entry 2). As shown in entries 3–5, in comparison with the reactions which use achiral bases having different basicities,[10] these results clearly indicate that the catalyst basicity is essential for promoting the present reaction. Whereas use of the less basic guanidine-derived TBD and P1-*t*Bu phosphazene (entries 3 and 4) resulted in the formation of **4aa** in only a trace amount, the use of P2-*t*Bu phosphazene, the basicity of which is stronger than those of TBD and P1-*t*Bu phosphazene, dramatically accelerated the reaction, thus affording **4aa** in good yield (entry 5). Subsequently, the reaction conditions, the catalyst substituent, and the *N*-protective group of ketimine **3** were explored to improve the stereochemical outcome.[11] The use of excess $NaN(SiMe_3)_2$ relative to (*M*)-**1a**·HBr, which was employed in the α-amination of tetralones,[7a,b] had a detrimental effect on the enantioselectivity (entry 2 versus entry 6). In the present Mannich reaction, the use of a slight excess of the salt form (*M*)-**1a**·HBr, relative to $NaN(SiMe_3)_2$, furnished a product with high enantioselectivity (entry 6). To improve diastereo- and enantioselectivities, the substituent R, attached to the nitrogen atom of the guanidine unit of **1**, was modified (entries 6–9). In contrast to the comparable enantioselectivities irrespective of the substituent, the diastereoselectivity was highly dependent on R. The introduction of a sterically hindered benzhydryl group led to a significant improvement of the diastereoselectivity (entry 9). Further improvement of the diastereoselectivity was achieved by a thorough screening of the benzoyl substituent introduced at the nitrogen atom of **3** (entries 10–14). The introduction of an electron-withdrawing substituent, such as a nitro, cyano, or trifluoromethyl group, to the *para*-position of the benzoyl group enhanced the diastereoselectivity (entries 12–14), although a slight reduction of the enantioselectivity was observed in the case of nitro and cyano substituents. In addition, electron-withdrawing substituents are essential to achieving a high chemical yield. Indeed, an electron-donating methoxy group resulted in a marked reduction of the chemical yield (entry 11). During the course of the screening, the 4-trifluoromethylbenzoyl group was found to be the substituent of choice (entry 14).[11] Further enhancement of the diastereo- and enantioselectivities was achieved by lowering the reaction temperature to −80 °C (entry 15). Finally, the optimum reaction conditions were established by reducing the amount of the pronucleophile **2a** from 2.5 equivalents to 1.2 equivalents without any detrimental effect on the chemical yield and stereoselectivity (entry 16). Furthermore, the absolute configuration of major product **4af** was determined to be (2*R*,3*S*) by single-crystal X-ray diffraction analysis of the ammonium salt **7**, which is composed of the stereochemically known amino diol and the carboxylic acid derivatized from **4af**. The corresponding carboxylic acid was isolated after oxidative desulfurization of the thiocarbonyl group and the hydrolysis of the ester moiety (Figure 1).[12]

With the optimum reaction conditions in hand, the substrate scope of this reaction was investigated (Table 2). In the reaction of the thionolactones **2c** and **2d**, bearing the small methyl and allyl groups, respectively (entries 2 and 3), high yields and diastereoselectivities were achieved and were similar to those obtained with **2a** and **2b**, bearing arylmethyl groups (Table 1, entry 16 and Table 2, entry 1), albeit with

Table 1: Enantioselective Mannich-type reaction of thionolactone **2a** (lactone **5**) and α-iminophenylacetate esters **3**.[a]





Entry	Base catalyst (mol%) salt of **1**/$NaN(SiMe_3)_2$	X	G	**4**/**6**	Yield [%][b]	d.r.[c]	*ee* [%][d]
1[e]	(*M*)-**1a**·HBr (10/20)	O	H	**6**	0	–	–
2	(*M*)-**1a**·HBr (10/20)	S	H	**4aa**	97	57:43	50
3[f]	TBD (10/–)	S	H	**4aa**	<1	–	–
4[f]	P1-*t*Bu (10/–)	S	H	**4aa**	<1	–	–
5[f]	P2-*t*Bu (10/–)	S	H	**4aa**	85	44:56	–
6	(*M*)-**1a**·HBr (11/10)	S	H	**4aa**	>99	52:48	78
7	(*M*)-**1b**·HCl (11/10)	S	H	**4aa**	97	67:33	85
8	(*M*)-**1c**·HCl (11/10)	S	H	**4aa**	98	76:24	87
9	(*M*)-**1d**·HCl (11/10)	S	H	**4aa**	>99	87:13	86
10	(*M*)-**1d**·HCl (11/10)	S	*t*Bu	**4ab**	>99	88:12	88
11	(*M*)-**1d**·HCl (11/10)	S	OMe	**4ac**	35	88:12	87
12	(*M*)-**1d**·HCl (11/10)	S	NO_2	**4ad**	94	94:6	83
13	(*M*)-**1d**·HCl (11/10)	S	CN	**4ae**	92	93:7	83
14	(*M*)-**1d**·HCl (11/10)	S	CF_3	**4af**	93	95:5	87
15[e,g]	(*M*)-**1d**·HCl (11/10)	S	CF_3	**4af**	95	99:1	95
16[e,g,h]	(*M*)-**1d**·HCl (11/10)	S	CF_3	**4af**	97	99:1	95

[a] Reactions were conducted with 1.0 equiv of **3** and 2.5 equiv of **2** in the presence of base catalyst in toluene (0.1 M) under argon atmosphere. [b] Yield of isolated product. [c] Ratio of (2*RS*,3*SR*)-**4** and (2*RS*,3*RS*)-**4**. Determined by NMR analysis and chiral stationary phase HPLC. [d] The *ee* value of (2*RS*,3*SR*)-**4** as determined by chiral stationary phase HPLC. [e] The reaction was conducted for 24 h. [f] The reaction was conducted at 0 °C. [g] The reaction was conducted at −80 °C. [h] 1.2 equiv of **2a** was used.

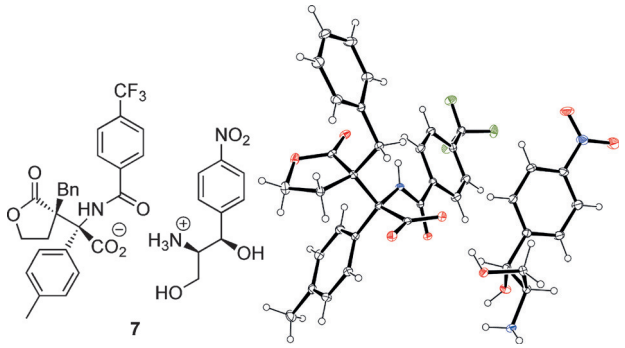
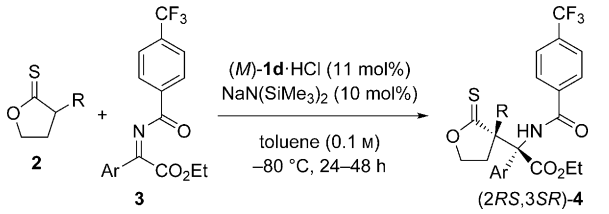


Figure 1. Single-crystal X-ray analysis of the ammonium salt **7**. Thermal ellipsoids shown at 30% probability.

Table 2: Substrate scope.[a]

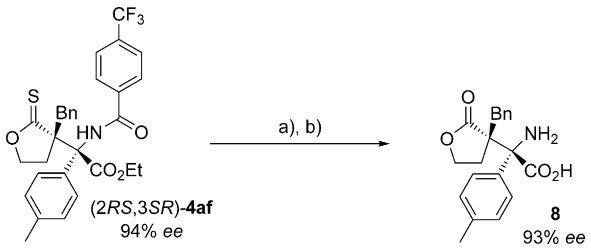


Entry	R	Ar	4	t [h]	Yield [%][b]	d.r.[c]	ee [%][d]
1	4-$BrC_6H_4CH_2$	4-MeC_6H_4	**4bf**	48	96	98:2	91
2	Me	4-MeC_6H_4	**4cf**	24	97	96:4	89
3	Allyl	4-MeC_6H_4	**4df**	24	93	99:1	88
4	$BnOCH_2CH_2$	4-MeC_6H_4	**4ef**	48	64	98:2	88
5[e]	*c*-$C_6H_{11}CH_2$	4-MeC_6H_4	**4ff**	48	56	95:5	83
6	Bn	4-$MeOC_6H_4$	**4ag**	24	91	97:3	93
7	Bn	4-ClC_6H_4	**4ah**	24	90	99:1	93
8	Bn	2-Naphthyl	**4ai**	24	>99	99:1	93
9	Bn	3,4,5-$(MeO)_3$-C_6H_2	**4aj**	48	64	99:1	92

[a] Reactions were conducted with 1.0 equiv of **3** and 1.2 equiv of **2** in the presence of 11 mol% (*M*)-**1d**·HCl and 10 mol% $NaN(SiMe_3)_2$ (0.6 M toluene solution) in toluene (0.1 M) under argon atmosphere. [b] Yield of the isolated product. [c] Ratio of (2*RS*,3*SR*)-**4** and (2*RS*,3*RS*)-**4** as determined by NMR analysis and chiral stationary phase HPLC. [d] The *ee* value of (2*RS*,3*SR*)-**4** as determined by chiral stationary phase HPLC. [e] The reaction was conducted at −20 °C.

a slight decrease in enantioselectivity. The benzyloxyethyl-substituted **2e** underwent the reaction in moderate yield with similar stereoselectivities to those of the small alkyl group substituted **2c** and **2d** (Table 2, entry 4). A significant decrease in reactivity was observed when **2f**, bearing a cyclohexylmethyl group was used, thus affording the desired product **4ff** in moderate yield even at an elevated temperature (−20 °C; entry 5). Further investigation of the substrate scope was performed by changing the aryl substituent of **3** (entries 6–9). A variety of aryl groups, such as 4-methoxyphenyl (**3g**), 4-chlorophenyl (**3h**), 2-naphthyl (**3i**), and 3,4,5-trimethoxyphenyl (**3j**), were applicable to the present reaction, thus giving rise to the corresponding products in moderate to good yields with high diastereo- and enantioselectivities.[13]

Finally, the derivatization of the Mannich-type reaction product **4af** into the amino-acid derivative **8** was demonstrated (Scheme 2). The thionolactone moiety of **4af** was desulfurized by AgOAc.[14] Subsequently, the hydrolysis of the benzoyl moiety attached to the amino group and the ethyl ester moiety was simultaneously conducted under the acidic conditions[15] to afford **8** in good yield. The newly developed asymmetric Mannich-type reaction enables efficient access to densely functionalized and complicated amino acid derivatives which are difficult to prepare by previous procedures.



Scheme 2. Derivatization of Mannich-type reaction product **4af** into the amino-acid derivative **8**. Reagents and conditions: a) AgOAc (2.4 equiv), H_2O, CH_3CN, RT, 2 h; b) HCl aq., AcOH, 100 °C, 20 h, 73% (in 2 steps), 93% *ee*.

In conclusion, we have developed a novel asymmetric Mannich-type reaction of α-iminophenylacetate esters with thionolactones, bearing a substituent at the α-position, using a chiral bis(guanidino)iminophosphorane organosuperbase catalyst which facilitated the construction of vicinal quaternary stereogenic centers in a highly diastereo- and enantioselective manner. Further studies are in progress toward the development of unprecedented enantioselective transformations using various pronucleophiles, with reduced acidity, under the influence of the bis(guanidino)iminophosphorane organosuperbase catalyst.

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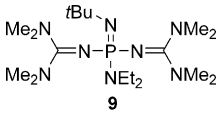
[11] The results of initial screening for reaction conditions were shown in the Supporting Information.



9

[12] See the Supporting Information for details of derivatization of **4af** into **7** and the X-ray diffraction analysis. CCDC 1450163 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre. Absolute configurations of other products were assigned by analogy.

[13] The desired products were not obtained when δ-thionovalerolactone, thionolactam, α-secondary-alkyl-substituted thionolactone, α-alkoxythionolactone, and *ortho*-substituted α-iminoarylacetate were used.

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