Primary amino acid lithium salt as a catalyst for asymmetric Michael addition of isobutyraldehyde with β-nitroalkenes†

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Phenylalanine lithium salt was found to be an effective catalyst for asymmetric Michael addition of isobutyraldehyde with β-nitroalkenes to give quaternary carbon-containing nitroalkanes.

It is an undeniable fact that amino acids are extremely important organic compounds in nature, since they are constituent elements of proteins, which are the essence of life. Since the end of the last century, amino acids and their analogues have been attracting the attention of organic chemists as asymmetric catalysts, because organocatalysts have advantages in handling, environmental safety and operation costs compared with transition metal catalysts.[1] In organocatalysis based on the formation of iminiums or enamines from carbonyl compounds, secondary amines, especially proline and its derivatives or MacMillan's imidazolidinones, have been generally used as catalysts, while little attention has been paid to primary amines as catalysts.[2] Since a variety of optically active compounds can be obtained cheaply from a commercial source, we have studied the development of a new asymmetric catalyst using primary amino acids.

The Michael addition of enolates to nitroalkenes is a widely used method for obtaining enantioenriched nitroalkanes, and many successful organocatalytic methods have been reported in the past decade.[3,4] However, the construction of a quaternary carbon center by Michael addition of α-branched carbonyl compounds with nitroalkenes is still a challenging subject.[5] As a pioneering work, Tanaka and Barbas's group reported that Michael addition of isobutyraldehyde with *trans*-β-nitrostyrere was catalyzed by (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine/TFA to give the corresponding Michael adduct in 87% yield with 80% ee.[5e] Although several groups have attempted reaction of isobutyraldehyde with *trans*-β-nitrostyrene, only two groups succeeded in improving the enantioselectivity to over 90% ee: Jacobsen's group[5f] obtained 99% ee with a chiral primary amine thiourea catalyst and Wang's group[5l,m] obtained 90% ee with a pyrrolidine sulfonamide catalyst. We found that L-phenylalanine lithium salt, which can be readily prepared from L-phenylalanine and lithium hydroxide, was highly effective in the Michael addition of isobutyraldehyde with *trans*-β-nitrostyrene. Interestingly, we obtained the Michael adduct as an (*S*)-enriched enantiomer[5q] with a configuration opposite to that reported by Jacobsen, Wang, Tanaka and Barbas. In this communication, we report the details of our investigations.

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First, we attempted Michael addition of isobutyraldehyde (**1**) with *trans*-β-nitrostyrene (**2a**) using L-phenylalanine; however, no reaction was observed (Table 1, entry 1). We assumed that the addition of L-phenylalanine to **1** did not occur well, because L-phenylalanine firmly forms a zwitterion, $BnCH(NH_3^+)COO^-$, in the reaction conditions. Therefore, in order to increase the basicity, we treated L-phenylalanine with an equimolar base to prepare an L-phenylalanine metal salt, Phe-OM.[6] To our delight, we found that reaction of **1** with **2a** proceeded to give the Michael adduct **3a** with high enantioselectivity in the presence of L-phenylalanine alkaline metal salts or a magnesium salt (Table 1, entries 2–7).[6] The best result was obtained when L-phenylalanine lithium salt was used as a catalyst (92% yield with 94% ee); however, the reaction rate was reduced when a larger alkaline metal salt was used. L-Phenylalanine methyl ester was also employed as a catalyst; however, the starting material **2a** was recovered (Table 1, entry 8). These results can be explained as follows: the lithium cation behaves as a Lewis acid to aid the formation of enamine between the catalyst and **1** as shown in eqn (1).[7] Although an attack of an enolate of **1** can produce **3a**, the enamine mechanism seems to be preferable, since the use of a stronger base than the lithium salt resulted in a slow reaction rate.[2,4,8]

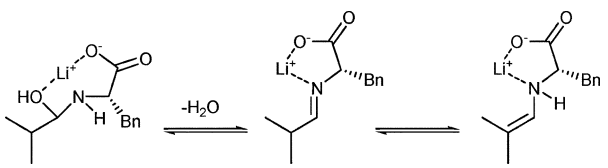

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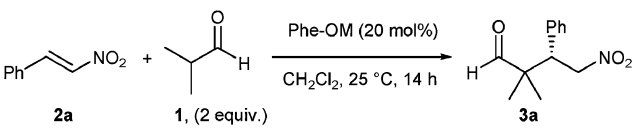
Table 1 Michael addition of **1** with **2a** in the presence of Phe-OM

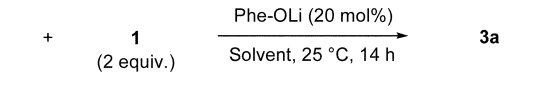


2a **1**, (2 equiv.) **3a**

Entry	M	Yield[a] (%)	ee[b] (%)
1	H	n.r.	—
2	Li	92	94
3	Na	84	83
4	K	73	88
5	Rb	60	84
6	Cs	22	92
7	MgBr	11	92
8[c]	Me	n.r.	—

[a] Isolated yield based on **2a**. [b] Determined by chiral HPLC analysis with a DAICEL CHIRALCEL OD–H column. [c] Freshly prepared Phe-OMe was used as a catalyst.

Table 2 Solvent screen for Michael addition of **1** with **2a**



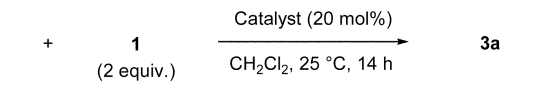
Entry	Solvent	Yield[a] (%)	ee[b] (%)
1	DMSO	14	43
2	DMF	18	58
3	CH_3CN	90	90
4	Acetone	82	85
5	AcOEt	96	86
6	THF	95	83
7	Et_2O	86	86
8	$CHCl_3$	93	92
9	CH_2Cl_2	92	94
10	$(CH_2Cl)_2$	88	94
11	Toluene	82	93
12	Hexanes	76	86

[a] Isolated yield based on **2a**. [b] Determined by chiral HPLC analysis with a DAICEL CHIRALCEL OD-H column.

Next, we examined a solvent screen with Phe-OLi as shown in Table 2. The Michael addition of **1** with **2a** in a strongly polarized solvent, DMSO or DMF, gave the Michael adduct **3a** in low yields with low enantioselectivity (Table 2, entries 1 and 2). In CH_3CN, acetone, AcOEt, THF and Et_2O, the Michael reaction gave **3a** in high yields with moderate enantioselectivity (Table 2, entries 3–7). When weakly polarized solvents, $CHCl_3$, CH_2Cl_2, 1,2-dichloroethane and toluene, were used, the enantioselectivity was improved to over 90% ee (Table 2, entries 8–11). Hexanes gave relatively poor results due to the low solubility of **2a** and the catalyst in the solvent (Table 2, entry 12). Since the best result was obtained in CH_2Cl_2 (92% yield with 94% ee), we chose CH_2Cl_2 as a solvent for further investigations.

As shown in Table 3, other readily obtainable amino acid lithium salts were evaluated for the Michael addition of **1** with **2a**. Relatively bulky amino acids, L-phenylalanine, L-valine, D-phenylglycine and L-*tert*-leucine, gave **3a** with over 90% ee (Table 3, entries 1–3 and 6). Interestingly, proline and its

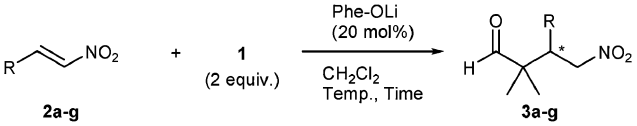
Table 3 Catalyst screen for Michael addition of **1** with **2a**



Entry	Catalyst	Yield[a] (%)	ee[b] (%)
1	Phe-OLi	92	94
2	Val-OLi	89	94
3	D-PhenylGly-OLi	92	94[c]
4	Leu-OLi	93	80
5	*iso*-Leu-OLi	95	88
6	*tert*-Leu-OLi	80	93
7	Ala-OLi	70	87
8	Try-OLi	90	84
9	Met-OLi	91	78
10	Ser-OLi	32	67
11	Pro-OLi	Trace	—
12	Pro	n.r.	—
13	*O*-TBS-Tyr-OLi	80	94

[a] Isolated yield based on **2a**. [b] Determined by chiral HPLC analysis with a DAICEL CHIRALCEL OD-H column. [c] (*R*)-**3a** was obtained.

Table 4 Optimization of reaction conditions



Entry	R	T/°C	t/h	Yield[a] (%)	ee[b] (%)
1	Ph	25	5	92, **3a**	94 (*S*)
2[c]	Ph	25	10	85, **3a**	93 (*S*)
3	Ph	0	72	82, **3a**	98 (*S*)
4	*p*-$MeOC_6H_4$	25	6	88, **3b**	93[d]
5	*p*-$MeOC_6H_4$	0	72	49, **3b**	98[d]
6	*p*-BrC_6H_4	25	4	86, **3c**	94 (*S*)
7	*p*-BrC_6H_4	0	72	81, **3c**	99 (*S*)
8	*p*-FC_6H_4	25	5	87, **3d**	95[d]
9	*p*-FC_6H_4	0	72	72, **3d**	99[d]
10	Furan-2-yl	0	72	71, **3e**	96 (*S*)
11	*cyclo*-C_6H_{11}	25	120	8,[e] **3f**	88[d]
12	$PhCH_2CH_2$	25	120	41,[f] **3g**	88[d]

[a] Isolated yield based on **2**. [b] Determined by chiral HPLC analysis with a DAICEL CHIRALCEL OD-H or CHIRALPAK AD-H column. In parentheses, absolute configuration of **3**. [c] The amount of **1** was reduced to 1.2 equiv. [d] The absolute configuration was not determined. [e] 59% of **2f** was recovered. [f] 18% of **2g** was recovered.

lithium salt did not show catalytic activity under the reaction conditions (Table 3, entries 11 and 12). We prepared an *O*-silylated tyrosine lithium salt and used it as a catalyst (Table 3, entry 13).[9] The silylated catalyst was very soluble in CH_2Cl_2; however, no enhancement of the reaction rate and enantioselectivity was observed.

By using Phe-OLi as a catalyst, we investigated more detailed reaction conditions as shown in Table 4. The reaction of **1** with **2a** completed within 5 h at 25 °C (Table 4, entry 1). Although a longer reaction time was required, the amount of **1** could be reduced to 1.2 equivalent to **2a** without considerable loss of yield and enantioselectivity of the product **3a** (Table 4, entry 2). When the reaction was carried out at 0 °C, the enantioselectivity was improved to 98% ee (Table 4, entry 3). Although the Michael addition of **1** with *p*-methoxy-*trans*-β-nitrostyrene (**2b**) did not complete within 72 h at 0 °C, the Michael adduct **3b** was obtained in 49% yield with 98% ee (Table 4, entry 5). When *p*-bromo- and *p*-fluoro-*trans*-β-nitrostyrene (**2c,d**) were used as starting materials, the Michael adducts **3c,d** were obtained in high yields with 99% ee, respectively (Table 4, entries 7 and 9). A heteroaromatic nitroalkene, 2-(*trans*-2-nitroethenyl)furan (**2e**), was also a good substrate (Table 4, entry 10). Unfortunately, the Michael addition reaction using aliphatic nitroalkenes **2f,g** were very slow even at 25 °C and gave the corresponding Michael adducts **3f,g** with many minor by-products (Table 4, entries 11 and 12).

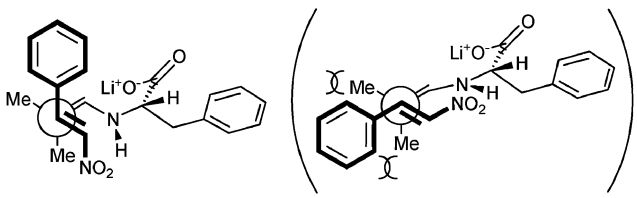


Fig. 1 Plausible transition state.

A plausible transition state is shown in Fig. 1. As shown in eqn (1), it is likely that Michael addition proceeds *via* an enamine mechanism.[2,4,8] The benzyl group of the enamine occupies the opposite side of the isobutenyl group to avoid a steric hindrance; therefore, the carboxylate group blocks one side of the enamine. The nitrostyrene approaches from the less hindered side of the enamine to occupy the most stable gauche conformation.[10] By an electrostatic interaction between the partially positive nitrogen atom of enamine and the partially negative nitro group, the enamine attacks the *Re* face of the nitrostyrene to generate the (*S*)-**3a**.[4a,c,5]

In summary, we found that readily obtainable L-phenylalanine lithium salt was very effective in the Michael addition of isobutyraldehyde with *trans*-β-nitroalkenes to form quaternary carbon-containing nitroalkanes in high yields with high enantioselectivity. Further study of asymmetric organosynthesis using amino acid salt by our group is under way.

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