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Asymmetric protonation of lithium enolates of α-amino acid derivatives with α-amino acid-based chiral Brønsted acids†

Kentaro Futatsugi‡,[a] Akira Yanagisawa[b] and Hisashi Yamamoto‡*[a]

[a] *Graduate School of Engineering, Nagoya University, SORST, Japan Science and Technology Corporation (JST), Chikusa 464-8603, Japan*

[b] *Department of Chemistry, Faculty of Science, Chiba University, Inage, Chiba 263-8522, Japan. E-mail: yamamoto@uchicago.edu*

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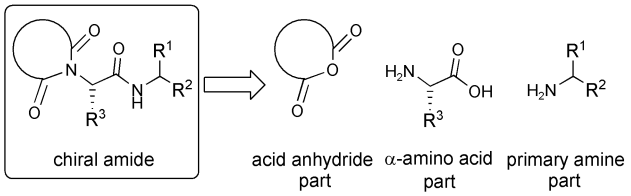
The reaction of lithium enolates of α-amino acid derivatives with chiral amides, easily synthesized from L-*tert*-leucine, gives corresponding optically active unnatural α-amino acid derivatives with up to 87% ee.

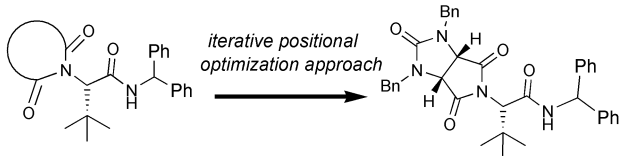
The establishment of an effective synthetic method to supply optically active α-amino acids with desirable absolute configurations is one of the most important challenges for organic chemists.[1] The construction of an asymmetric α-carbon of an α-amino acid by asymmetric protonation[2,3] is a conceptually simple but effective route to this target molecule, and is particularly useful for the conversion from natural L-amino acids to unnatural D-amino acids. There are few reports however, on the protonation of prochiral metal enolates of α-amino acid derivatives that give high enantioselectivity.[4] Here we wish to report on new types of chiral Brønsted acids based on optically active α-amino acids and their application to the asymmetric protonation of the lithium enolates of α-amino acid derivatives.

The design of the asymmetric protonation approach depends on the structure and acidity of the chiral proton source. We envisaged that the use of combinatorial and related strategies[5] would make the design and optimization of effective chiral Brønsted acids more facile. From this point of view, we prepared a new chiral amide, an α-amino acid derivative possessing an acidic amide proton as a chiral proton source, which is readily optimized by changing the acid anhydride part, the α-amino acid part, and/or the primary amine part (Scheme 1).

To optimize the structure of α-amino acid-based chiral amide, lithium enolate of 2,2,6-trimethylcyclohexanone **3** was chosen as a model substrate for the asymmetric protonation.[6] Initially, the structure of the imide part was optimized based on the chiral amide **1** by an iterative positional optimization approach.[7] Several derivatives possessing a phthalimide or related units, which have a relatively planar structure, were examined but they gave **4** (<9% ee). In contrast, the use of chiral amide **1a**, possessing a unique bicyclic structure derived from a synthetic intermediate of biotin,[8] led to a dramatic increase in the enantioselectivity with excellent yield (59% ee, 98% yield, Scheme 2).



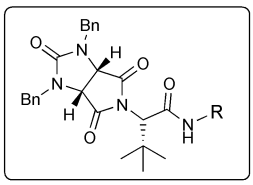
Scheme 1 Design of new chiral proton source.



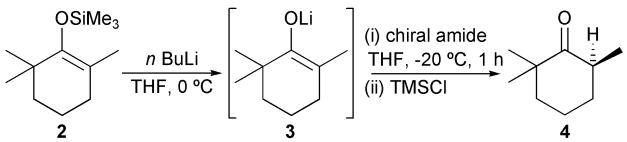
Scheme 2

At the next stage, we performed further optimization of the amide part of **1a** using a variety of primary amines (Table 1). Use of chiral amides having a secondary carbon adjacent to the nitrogen atom of the amide group gave better results than chiral amides with a primary or tertiary carbon (entries 4–7 and 9 *vs.* entries 1–3 and 12). Bulky chiral amides, such as **1ah** in entry 8, could hardly discriminate the enantioface of lithium enolate **3** in spite of having a secondary carbon. This result may be attributable to their sterically hindered structure, which precludes the formation of the preferable transition state. As a

Table 1 Structural optimization of the amide part of chiral amide **1a**[a]



1aa: R=Me
1ab: R=Et
1ac: R=Bn
1ad: R=*i*Pr
1ae: R=*c*Hex
1af: R=*c*Hep
1ag: R=*c*-dodecyl
1ah: R=2-adamantyl
1a: R=Ph_2CH
1ai: R=$(1\text{-Nap})_2CH$
1aj: R=$(t\text{Bu})_2CH$
1ak: R=*t*Bu



Entry	Chiral amide	Yield (%)[b]	Ee (%)[c]
1	**1aa**	89	26
2	**1ab**	>99	15
3	**1ac**	>99	42
4	**1ad**	98	69
5	**1ae**	>99	71
6	**1af**	88	53
7	**1ag**	62	78
8	**1ah**	26	3
9	**1a**	98	59
10	**1ai**	56	13
11	**1aj**	64	<1
12	**1ak**	31	17

[a] Unless otherwise specified, the lithium enolate **3** was generated from the corresponding silyl enol ether **2** (1 equiv.) and a solution of *n*BuLi–hexane (1.1 equiv.) in THF at 0 °C for 1.5 h. The following protonation was carried out using a chiral amide (1.1 equiv.) in THF at −20 °C for 1 h. The reaction was quenched by TMSCl at −78 °C to exclude the unreacted enolate **3**. [b] Isolated yield. [c] Determined by GC analysis with chiral column (astec, Chiraldex G-TA). See also ref. 6

† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b2/b211523a/

‡ Present address: Department of Chemistry, University of Chicago, 5735 South Ellis Avenue, Chicago, IL 60637, USA.

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result, among a variety of primary amines tested, the highest enantioselectivity (78% ee) was obtained when cyclododecyl amine-derived chiral amide **1ag** was used (entry 7).

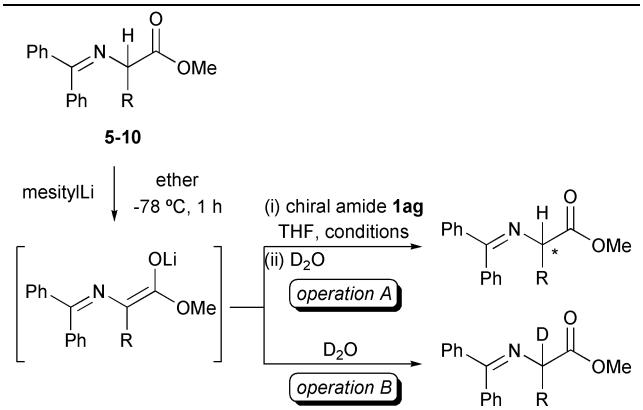
With the chiral amide optimized in a model system (**1ag**), we focused on the asymmetric protonation of lithium enolate of α-amino acid derivatives, which was generated from the corresponding racemic amino acid derivatives and mesityllithium in ether (Table 2). To evaluate precisely the capacity for the asymmetric induction of **1ag**, '*corrected ee*' was applied to our system, which is a corrected value based on the *actual rate* of the protonated product by **1ag**.[9] The rate of protonated product was determined by quenching both the deprotonation stage (*operation B*) and the protonation stage (*operation A*) with D_2O at −78 °C. Optimization of the reaction conditions with a racemic alanine derivative **5** as a starting substrate showed that the unnatural alanine derivative **5** was obtained with the highest enatioselectivity (87% ee, entry 2) when the reaction was performed at −20 °C. This high level of asymmetric induction clearly shows that this α-amino acid derived chiral amide **1ag** could be an effective chiral proton source for the asymmetric protonation of the lithium enolate of α-amino acid derivatives, *i.e.*, "*deracemization*" of α-amino acid derivatives.

These successful results encouraged us to apply the chiral proton source **1ag** to a variety of lithium enolates of α-amino acid derivatives. Moderate to high asymmetric induction occurred in the protonation of lithium enolates of α-amino acid derivatives **5**-**8** with good yield (entries 2, 4–6), even in the presence of a hetero atom in the alkyl side chain such as **8** (entry 6). The highest enantioselectivity (87% ee) was obtained with the enolate of alanine derivative **5** (entry 2). Protonation with the enolate of leucine derivative **7** also gave rise to significant induction (85% ee, entry 5). The reaction with the enolate of phenylalanine derivative **9** also afforded moderate optical purity, though the chemical yield of the reaction was somewhat low (entry 7). However, use of phenylglycine derivative **10**, which has a phenyl ring at the α position, gave an unsatisfactory result (entry 8). From this result, it is assumed that the basicity of the corresponding enolate would be critical to the enantioface discrimination.

In summary, we developed a new chiral proton source that is effective for deracemization of α-amino acid derivatives. This type of chiral proton source, which consists of an acid anhydride part, an amino acid part, and an amine part, has the great advantage of optimizing its structure easily for the strict face discrimination of prochiral enolates. Further study on asymmetric protonation with this type of chiral amide and its precise reaction mechanism is currently underway.

We gratefully acknowledge Sumitomo Chemical Co., Ltd. for a gift of biotin precursor, and helpful advice on its preparation.

Table 2 Enantioselective protonation of various lithium enolates of α-amino acid derivatives **5**–**10** with chiral amide **1ag**[a]



Entry	Conditions	R		Yield (%)[b]	Ee (%)[c]	Configuration
1	−78 °C, 3 h	Me	(**5**)	57	13[d]	*S*[d]
2	−20 °C, 2.5 h	Me	(**5**)	73	87[d]	*R*[d]
3	0 °C, 1.5 h	Me	(**5**)	89	79[d]	*R*[d]
4	−20 °C, 2.5 h	Et	(**6**)	77	64[e]	—
5	−20 °C, 2.5 h	Isobutyl	(**7**)	66	85[f]	*R*[h]
6	−20 °C, 2.5 h	$(CH_2)_2SMe$	(**8**)	79	78[g]	—
7	−20 °C, 2.5 h	Bn	(**9**)	27	65[g]	*R*[h]
8	−20 °C, 2.5 h	Ph	(**10**)	87	23[g]	—

[a] For the details of the experimental procedure, see ESI.† [b] Isolated yield. [c] Corrected value based on the actual rate of the protonated product. See also note 9 and ESI.† [d] Ref. 4. [e] Determined by HPLC analysis (Chiralcel AD-H, Daicel Chemical Industries, Ltd.). [f] Determined by HPLC analysis (Chiralcel AS, Daicel Chemical Industries, Ltd.). [g] Determined by HPLC analysis (Chiralcel OD-H, Daicel Chemical Industries, Ltd.). [h] Determined by comparison of its retension time with that of the authentic sample synthesized from the corresponding L-α-amino acid.

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9 For example, 87% ee (entry 2, Table 2) was calculated using the following data: 79% ee, >99% enolization (from *operation B*), 10% deuteration in quench (from *operation A*). Therefore the *actual rate* of the protonated product should be 90%, and corrected ee should be obtained by dividing the observed ee by the *actual rate* of the protonated product. Further details about these operations are described in the ESI†.