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Direct Enantioselective Amination of α-Ketoesters Catalyzed by an Axially Chiral Guanidine Base

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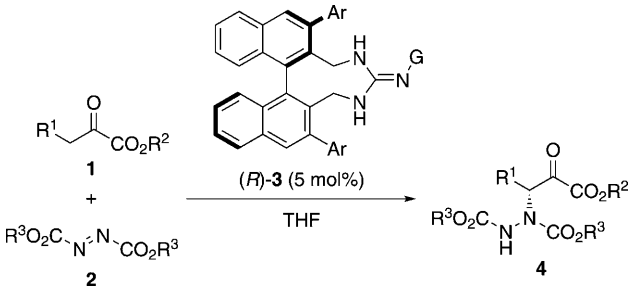
Pyruvate esters and related α-ketoesters are extensively utilized as multifunctional synthons in synthetic organic chemistry due to the fact that an electron-withdrawing ester moiety adjacent to a ketone functionality enhances the electrophilicity of the ketone carbonyl carbon. Indeed, α-ketoesters have been applied in a diverse array of organic transformations as an active ketone where the reaction of a carbon nucleophile affords a tertiary alcohol with an ester functionality.[1] In this context, the development of catalytic enantioselective reactions of α-ketoesters using chiral metal complexes[2] or organocatalysts[3] has stimulated much interest because the method provides an efficient route for the construction of a quaternary stereogenic center in an enantioenriched fashion. In contrast, the enol tautomer (or enolate form) of α-ketoesters have rarely been utilized as a nucleophilic component in catalytic enantioselective reactions,[4,5] despite the fact that these groups function as a homo-enolate equivalent to afford densely functionalized products in an optically active form. The lack of investigation of these reagents is presumably due to their high electrophilicity, which is prone to induce homo-aldol reactions. In fact, enantioselective homo-aldol reactions of pyruvate esters have been reported using chiral catalysts.[4c,6] Hence, the development of cross reactions of α-ketoesters as the pro-nucleophile is a challenging and attractive topic in asymmetric synthesis. Several excellent studies have been reported to date on enantioselective reactions of α-ketoesters using chiral metal complexes,[4] however organocatalytic approaches employing α-ketoesters as the pro-nucleophile in cross reactions have received little attention,[5] despite the tremendous growth in asymmetric organocatalysis during the past decade.[7] We therefore aimed to expand the synthetic potential of α-ketoesters **1** by means of organocatalysts. Herein, we report the enantioselective β-functionalization of α-ketoesters **1** with azodicarboxylates **2**[8] to prepare β-hydrazinyl-α-ketoesters **4** in high enantioselectivity using axially chiral guanidine **3**, which was developed by our group as a chiral Brønsted base catalyst[9,10] (Scheme 1). The enantioselective process thus developed is the first organocatalytic approach to the electrophilic amination of α-ketoesters **1**.[4b]



Scheme 1. Enantioselective amination of α-ketoesters catalyzed by axially chiral guanidine base **3**.

An initial investigation was conducted by exploring the appropriate ester substituents of both α-ketoesters **1** (R^2) and azodicarboxylates **2** (R^3) as well as the substituents Ar and G of guanidine catalyst **3** (Table 1). The screening of these substituents was performed using **3** (5 mol%) in THF at 0 °C, and the enantioselectivity of the amination products, β-amino-α-ketoesters **4**, was determined by chiral stationary phase HPLC analysis after reduction of the α-ketone to a hydroxy group using L-selectride, exclusively affording *syn* products **5**.[4b,11] Introduction of bulky *tert*-butyl moieties to the azodicarboxylate **2b**, led to an increase in the enantioselectivity without a detrimental effect on the reaction rate as compared to that obtained with the sterically less hindered ethyl-substituted azodicarboxylate **2a** (Table 1, entry 1 vs. 2). In contrast, the ester substituents of α-ketoesters did not display a significant effect on the enantioselectivity but did

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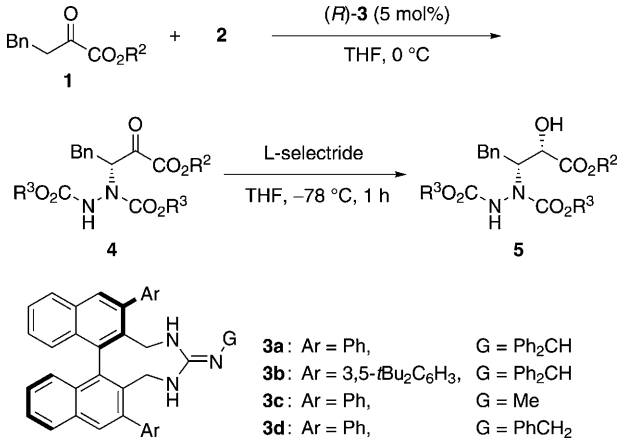
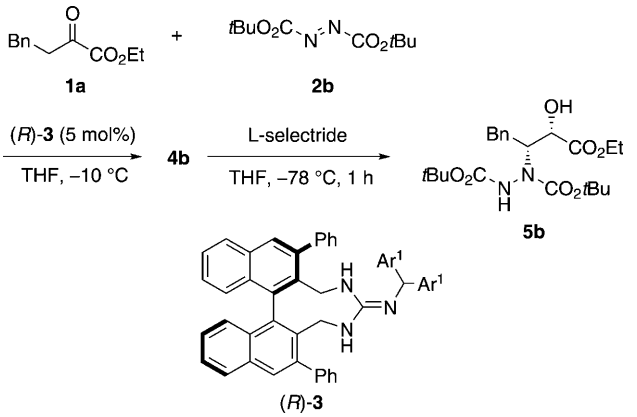
Table 1. Optimization of enantioselective amination of α-ketoesters **1** catalyzed by (*R*)-**3**.[a]



Entry	**1**	R^2	**2**	R^3	**3**	*t* [h]	**5**	Yield [%][b]	*ee* [%][c]
1	**1a**	Et	**2a**	Et	**3a**	7	**5a**	76	67
2	**1a**	Et	**2b**	*t*Bu	**3a**	6	**5b**	72	84
3	**1b**	Me	**2b**	*t*Bu	**3a**	4	**5c**	85	78
4	**1c**	*t*Bu	**2b**	*t*Bu	**3a**	22	**5d**	68	83
5	**1a**	Et	**2b**	*t*Bu	**3b**	26	**5b**	74	43
6	**1a**	Et	**2b**	*t*Bu	**3c**	26	**5b**	37	59
7	**1a**	Et	**2b**	*t*Bu	**3d**	24	**5b**	61	70

[a] Unless otherwise noted, all reactions were carried out using (*R*)-**3** (0.005 mmol, 5 mol%), **1** (0.11 mmol, 1.1 equiv), and **2** (0.10 mmol) in THF (1.0 mL) at 0°C. [b] Yield of isolated product **5**. [c] Determined by chiral stationary phase HPLC analysis after reduction of **4** to **5** (exclusive formation of *syn* isomer).

Table 2. Optimization of guanidine catalysts **3**.[a]



Entry	**3**	Ar^1	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**3a**	Ph	5	79	86
2	**3e**	3,5-$(CF_3)_2C_6H_3$	24	53	59
3	**3f**	3,5-$(CH_3)_2C_6H_3$	5	>99	83
4	**3g**	4-$MeOC_6H_4$	2	88	88
5	**3h**	3,5-$(MeO)_2C_6H_3$	4	80	91
6	**3i**	3,4,5-$(MeO)_3C_6H_2$	2	>99	93
7[d]	**3i**		2	>99	95
8[d,e]	**3i**		4	>99	96

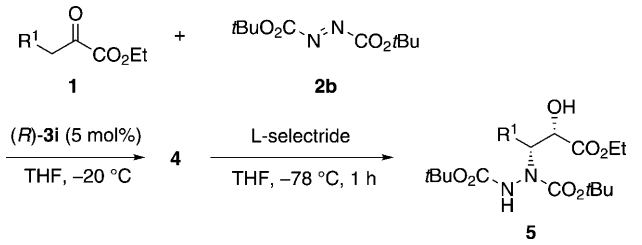
[a] Unless otherwise noted, all reactions were carried out using (*R*)-**3** (0.005 mmol, 5 mol%), compound **1a** (0.11 mmol, 1.1 equiv), and **2b** (0.10 mmol) in THF (1.0 mL) at −10°C. [b] Yield of isolated product **5b**. [c] Determined by chiral stationary phase HPLC analysis after reduction of **4b** to **5b**. [d] Carried out using **1a** (0.10 mmol) and **2b** (0.15 mmol, 1.5 equiv) in THF (0.2 mL). [e] At −20°C.

induce a marked change in the reaction rate (Table 1, entries 2–4), in which the sterically hindered *tert*-butyl ester **1c** retarded the reaction considerably (Table 1, entry 4). The highest enantioselectivity was achieved in the reaction of ethyl ester **1a** with di-*tert*-butyl azodicarboxylate (**2b**) without compromising the reaction rate (Table 1, entry 2). Screening of the catalyst was thus performed in the reaction of **1a** with **2b** by changing the substituents Ar and G introduced at the 3,3′-position of the binaphthyl backbone and at the nitrogen atom of the guanidine moiety, respectively (Table 1, entries 5–7). The substituent effects of Ar and G are notable in the efficient enantioselective catalysis. An increase in steric bulkiness of the Ar group by substituting the 3,5-di-*tert*-butylphenyl moiety resulted in a considerable loss of both catalytic activity and enantioselectivity (Table 1, entry 5). Further, substitution of G by methyl or benzyl instead of benzhydryl also exhibited a negative effect on catalytic performance (Table 1, entry 2 vs. entries 6 and 7).

As shown in Table 1, introduction of a benzhydryl moiety as the substituent G in the catalyst **3** is the key to gaining good catalytic performance. We therefore next focused our attention on modification of the benzhydryl substituent (Table 2). Further optimization of catalyst **3** was conducted using the reaction of **1a** with **2b** in THF by lowering the reaction temperature to −10°C. As shown in Table 2, the electronic effect of the aromatic rings (Ar^1) of the benzhydryl substituents exhibited a marked influence not only on enantioselectivity but also on catalytic activity (Table 2, entries 1–6). The catalyst bearing electron-withdrawing trifluoromethyl substituents, **3e**, exhibited low catalytic activity and significant loss of enantioselectivity (Table 2, entry 2). In contrast, the enantiomeric excess was improved when catalysts **3g–3i** having electron-donating methoxy groups were employed (Table 2, entries 4–6). Furthermore, the enantiomeric excess of **5b** was enhanced in accordance with the number of methoxy groups introduced. Further optimization of the reaction conditions by increasing the equivalents of **2b** (1.5 equiv) and lowering the reaction temperature to −20°C enhanced the enantioselectivity to 96% enantiomeric excess (*ee*)(Table 2, entry 8).

Having identified the optimal guanidine catalyst and reaction conditions, the scope of the present amination reaction was investigated with a series of α-ketoesters having aliphatic substituents using **3i** as the catalyst in THF at −20°C. As shown in Table 3, the amination reaction is well suited for a range of α-ketoesters, giving rise to products **5** in uniformly high enantioselectivities, although chemical yields were strongly dependent on the substituent employed. The reaction of α-ketoesters having primary substituents proceeded smoothly to afford products **5** in good yields (Table 3, entries 1–4) with the exception of α-ketoester **1e** bearing a methyl substituent, in which the homo-aldol reaction of **1e** occurred simultaneously (Table 3, entry 2). Secondary alkyl substituents (isopropyl) retarded the reaction with a consid-

Table 3. Substrate scope for the enantioselective amination catalyzed by (*R*)-**3i**.[a]

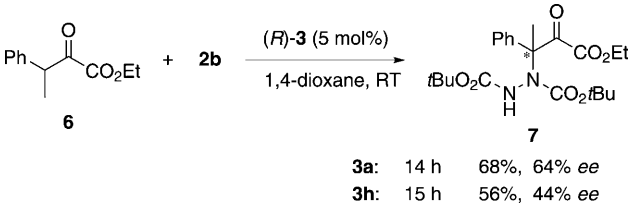


Entry	**1**	R^1	*t* [h]	**5**	Yield [%][b]	*ee* [%][c]
1	**1d**	*n*Pr	5	**5e**	76	96
2	**1e**	Me	13	**5f**	31	93
3	**1f**	allyl	4	**5g**	73	96
4	**1g**	*i*Bu	4	**5h**	90	96
5	**1h**	*i*Pr	13	**5i**	36	94

[a] Unless otherwise noted, all reactions were carried out using (*R*)-**3i** (0.005 mmol, 5 mol%), **1** (0.10 mmol), and **2b** (0.15 mmol, 1.5 equiv) in THF (0.2 mL) at −20 °C. [b] Yield of isolated product **5**. [c] Determined by chiral stationary phase HPLC analysis after reduction of **4** to **5**.

erable amount of starting α-ketoester **1h** recovered under the optimal reaction conditions (Table 3, entry 5).

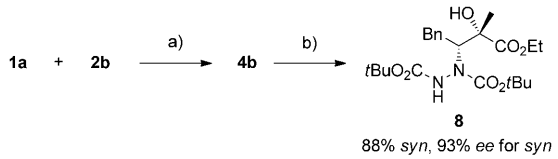
We next applied the present method to the construction of a quaternary stereogenic center with a nitrogen functionality by using unsymmetrically substituted α-ketoester **6**. The reaction of **2b** with **6** (phenyl and methyl substituents at the β-position) was conducted using (*R*)-**3** (5 mol%) in 1,4-dioxane at room temperature.[12] As shown in Scheme 2,



Scheme 2. Enantioselective amination of unsymmetrically substituted α-ketoester **6**.

catalyst **3a** accelerated the reaction efficiently to give the corresponding amination product **7** in fairly good yield with moderate enantioselectivity. The use of dimethoxy-substituted catalyst **3h**, however, resulted in a considerable decrease in the enantioselectivity.

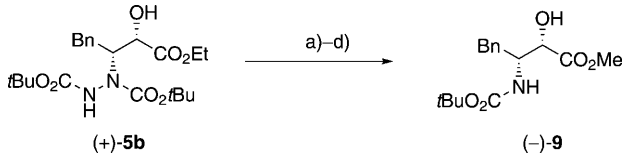
To demonstrate the synthetic potential of the present methodology, we further investigated the nucleophilic addition of an alkylation reagent such as a trialkylzinc(II) ate complex to β-hydrazinyl-α-ketoester **4b** at the reactive ketone functionality (Scheme 3). The nucleophilic addition to **4b** was conducted in a one-pot sequential manner. After the amination reaction of **1a** with **2b** was complete, the reaction mixture was directly introduced to a preformed solution of $Me_3ZnMgCl$ prepared from a methyl Grignard reagent and dimethylzinc.[13] The corresponding β-hydrazinyl-α-hydroxy ester **8**, possessing a quaternary stereogenic



Scheme 3. Transformation of amination product **4b** to β-hydrazinyl-α-hydroxy ester **8** (93% *ee*). Reagents and conditions: a) (*R*)-**3i** (5 mol%), THF, −20 °C, 4 h; b) MeMgCl (4 equiv), $ZnMe_2$ (4 equiv), THF, −78 °C, 6 h (93% from **1a**).

center at the α-position, was obtained with high *syn* diastereoselectivity without considerable loss of enantiomeric purity.

The absolute stereochemistry of (+)-**5b** was determined after the transformation to stereochemically known *N*-*tert*-butoxycarbonyl (*N*-Boc)-protected β-amino-α-hydroxy ester **9** by a four step transformation (Scheme 4). Derivatization



Scheme 4. Transformation of β-hydrazinyl-α-hydroxy ester (+)-**5b** (98% *ee*) to β-amino-α-hydroxy ester (−)-**9** (98% *ee*). Reagents and conditions: a) CF_3COOH, CH_2Cl_2, RT, 10 min; b) Raney-Ni (W-2), H_2, EtOH, RT, 12 h; c) Boc_2O, 4-(dimethylamino)pyridine, EtOH, 40 °C, 12 h; d) MeONa, MeOH, RT, 12 h (39% from **5b**).

of recrystallized (+)-**5b** (98% *ee*) was achieved by deprotection of the Boc groups under acidic conditions followed by hydrogenolysis of the hydrazine moiety using Raney-Ni (W-2). The amino group thus generated was protected by a Boc group, and subsequent transesterification yielded methyl ester **9**. The absolute stereochemistry of **9** was determined to be the (2*S*,3*R*)-configuration by comparison of the measured optical rotation with the literature value.[4b] Thus it was confirmed that the electrophilic amination catalyzed by (*R*)-**3i** gave (3*R*)-**4** as the major product.

We further attempted the X-ray crystallographic analysis of the guanidine catalyst (*R*)-**3i**. To our delight, an X-ray grade single crystal of the HBF_4 salt, $[(R)\text{-}\mathbf{3i}\cdot H]^+BF_4^-$, was successfully obtained (Figure 1a).[14] In the crystalline state, the guanidinium salt exists as contact ion pairs. The BF_4^- anion occupies the bottom side of the basal plane defined by the guanidinium moiety to avoid steric repulsion of both the modified benzhydryl moiety and one of the two phenyl rings attached to the binaphthyl backbone. Furthermore, electrostatic potential analysis of the crystal structure conformation of $[(R)\text{-}\mathbf{3i}\cdot H]^+$ indicated that both of the NH groups at positions 1 and 2 have a partial positive charge (blue in the electrostatic potential map) (Figure 1b). Of particular interest is the fact that position 1 is more positive than position 2, as clearly indicated in Figure 1b.[15] These

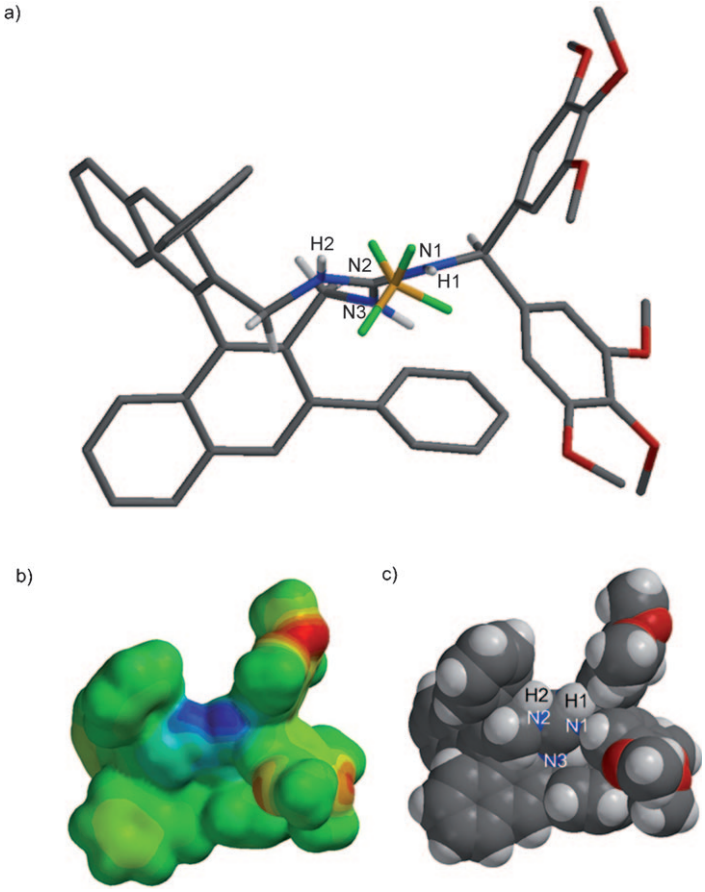


Figure 1. a) X-ray crystallographic analysis of the $[(R)\text{-}\mathbf{3i}\cdot H]^+BF_4^-$ salt (N = blue, O = red, C = gray, B = yellow, F = green). Hydrogen atoms of aromatic rings and methyl groups have been omitted for clarity. b) B3LYP/6-311 + g(d,p) 0.002 au isodensity surface with superimposed electrostatic potential using the crystal structure conformation of $[(R)\text{-}\mathbf{3i}\cdot H]^+$. c) A space-filling representation of the crystal structure of $[(R)\text{-}\mathbf{3i}\cdot H]^+$.

electronic properties suggest that anionic species are prone to interact with H1 rather than H2.

The structural and electronic properties of $[(R)\text{-}\mathbf{3i}\cdot H]^+$ coupled with the determination of the absolute stereochemistry of **4b** prompted us to propose a plausible transition-state (TS) model (Figure 2). Deprotonation of α-ketoester **1** by the chiral guanidine catalyst generates ion pairs of the guanidinium ion $[(R)\text{-}\mathbf{3i}\cdot H]^+$ and the enolate of **1a**, which would interact at H1 rather than H2 through hydrogen bonding as speculated based on the electrostatic potential analysis of $[(R)\text{-}\mathbf{3i}\cdot H]^+$. Because of the equilibrium conditions it seems likely that the geometry of the generated enolate is the thermodynamically stable *Z* form as an exclusive isomer.[16] Meanwhile, the H2 proton of the guanidinium ion would interact with the Lewis basic nitrogen atom of the azodicarboxylate **2b** through hydrogen bonding and thus activate **2b**.[9d,17] As illustrated in Figure 2, the transient structure would be located at the sterically less hindered side of the guanidinium moiety, as observed for BF_4^-, to avoid steric repulsion of both the modified benzhydryl moiety and

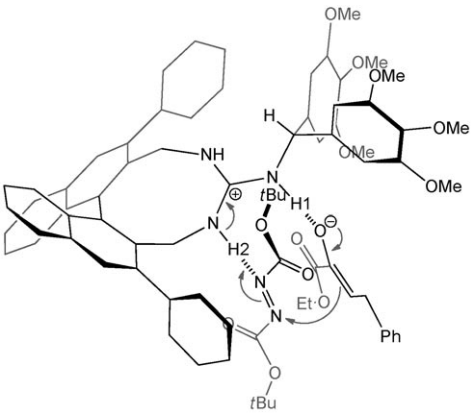


Figure 2. Plausible transition-state model for enantioselective amination catalyzed by (*R*)-**3i**.

the phenyl ring (Figure 1 a, c). According to this proposed TS model, the *re* face of the enolate form of **1a** is exposed to the electrophilic addition of azodicarboxylate **2b**, giving (3*R*)-**4b**, which is consistent with the major stereoisomer obtained experimentally.

In conclusion, we have demonstrated the direct enantioselective amination of α-ketoesters catalyzed by an axially chiral guanidine base. The present method enables an efficient access to enantioenriched multifunctionalized ketoesters, which can be readily derivatized to β-amino-α-hydroxy esters with an aliphatic substituent at the β-position with high *syn* diastereo- and enantioselectivities. Further studies of direct transformations through activation of α-ketoesters by chiral guanidine catalysts are currently underway in our laboratory.

Experimental Section

Representative procedure: To a solution of di-*tert*-butyl azodicarboxylate **2b** (34.5 mg, 0.15 mmol) and α-ketoester **1a** (20.6 mg, 0.10 mmol) in THF (200 μL) at −20 °C was added (*R*)-**3i** (4.18 mg, 0.005 mmol). After stirring at that temperature for 4 h, the reaction mixture was cooled to −78 °C and a 1.0 M solution of L-selectride in THF (200 μL) was added. The mixture was stirred for 1 h and then quenched with an aqueous NH_4Cl solution, followed by extraction with ethyl acetate. The organic phase was dried over Na_2SO_4 and filtered. After removal of solvents, the residue was purified by flash column chromatography (hexane/EtOAc = 10:1 to 2:1 as eluent) to afford the corresponding product **5b** (> 99 % yield, 96 % *ee*).

Acknowledgements

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Keywords: amino alcohols · asymmetric catalysis · enantioselectivity · guanidine · organocatalysis

[1] For a recent review, see: M. Shibasaki, M. Kanai, *Chem. Rev.* **2008**, *108*, 2853–2873.

[2] For selected examples, see: a) D. A. Evans, M. C. Kozlowski, C. S. Burgey, D. W. C. MacMillan, *J. Am. Chem. Soc.* **1997**, *119*, 7893–7894; b) D. A. Evans, D. W. C. MacMillan, K. R. Campos, *J. Am. Chem. Soc.* **1997**, *119*, 10859–10860; c) M. Johannsen, S. Yao, K. A. Jørgensen, *Chem. Commun.* **1997**, 2169–2170; d) S. Yao, M. Johannsen, H. Audrain, R. G. Hazell, K. A. Jørgensen, *J. Am. Chem. Soc.* **1998**, *120*, 8599–8605; e) D. A. Evans, S. W. Tregay, C. S. Burgey, N. A. Paras, T. Vojkovsky, *J. Am. Chem. Soc.* **2000**, *122*, 7936–7943; f) H. Audrain, K. A. Jørgensen, *J. Am. Chem. Soc.* **2000**, *122*, 11543–11544; g) P. I. Dalko, L. Moisan, J. Cossy, *Angew. Chem.* **2002**, *114*, 647–650; *Angew. Chem. Int. Ed.* **2002**, *41*, 625–628; h) H. Suga, K. Inoue, S. Inoue, A. Kakehi, *J. Am. Chem. Soc.* **2002**, *124*, 14836–14837; i) D. Yang, M. Yang, N.-Y. Zhu, *Org. Lett.* **2003**, *5*, 3749–3752; j) N. A. Caplan, F. E. Hancock, P. Bulman, C. Philip, G. J. Hutchings, *Angew. Chem.* **2004**, *116*, 1717–1720; *Angew. Chem. Int. Ed.* **2004**, *43*, 1685–1688; k) M. Langner, C. Bolm, *Angew. Chem.* **2004**, *116*, 6110–6113; *Angew. Chem. Int. Ed.* **2004**, *43*, 5984–5987; l) J. Cong-Dung Le, B. L. Pagenkopf, *Org. Lett.* **2004**, *6*, 4097–4099; m) L. C. Wieland, H. Deng, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2005**, *127*, 15453–15456; n) P. Rémy, M. Langner, C. Bolm, *Org. Lett.* **2006**, *8*, 1209–1211; o) K. Mikami, Y. Kawakami, K. Akiyama, K. Aikawa, *J. Am. Chem. Soc.* **2007**, *129*, 12950–12951; p) A. Yanagisawa, Y. Terajima, K. Sugita, K. Yoshida, *Adv. Synth. Catal.* **2009**, *351*, 1757–1762; q) M. Frings, I. Atodiresei, Y. Wang, J. Runsink, G. Raabe, C. Bolm, *Chem. Eur. J.* **2010**, *16*, 4577–4587; r) M. Frings, D. Goedert, C. Bolm, *Chem. Commun.* **2010**, *46*, 5497–5499.

[3] For recent examples, see: a) H. Li, B. Wang, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 732–733; b) Z. Tang, L.-F. Cun, X. Cui, A.-Q. Mi, Y.-Z. Jiang, L.-Z. Gong, *Org. Lett.* **2006**, *8*, 1263–1266; c) H. Li, Y.-Q. Wang, L. Deng, *Org. Lett.* **2006**, *8*, 4063–4065; d) C. Zheng, Y. Wu, X. Wang, G. Zhao, *Adv. Synth. Catal.* **2008**, *350*, 2690–2694; e) M. Raj, G. S. Parashari, V. K. Singh, *Adv. Synth. Catal.* **2009**, *351*, 1284–1288; f) V. B. Gondi, K. Hagihara, V. H. Rawal, *Chem. Commun.* **2010**, *46*, 904–906; g) X. Jiang, G. Zhang, D. Fu, Y. Cao, F. Shen, R. Wang, *Org. Lett.* **2010**, *12*, 1544–1547; h) M. Vecchione, L. Li, D. Seidel, *Chem. Commun.* **2010**, *46*, 4604–4606.

[4] For chiral metal catalysts. α-Ketoesters, see: a) K. Juhl, N. Gathergood, K. A. Jørgensen, *Angew. Chem.* **2001**, *113*, 3083–3085; *Angew. Chem. Int. Ed.* **2001**, *40*, 2995–2997; b) K. Juhl, K. A. Jørgensen, *J. Am. Chem. Soc.* **2002**, *124*, 2420–2421; c) N. Gathergood, K. Juhl, T. B. Poulsen, K. Thordrup, K. A. Jørgensen, *Org. Biomol. Chem.* **2004**, *2*, 1077–1085; d) A. Nakamura, S. Lectard, D. Hashizume, Y. Hamashima, M. Sodeoka, *J. Am. Chem. Soc.* **2010**, *132*, 4036–4037. α-Ketoanilides, see: e) G. Lu, H. Morimoto, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2008**, *120*, 6953–6956; *Angew. Chem. Int. Ed.* **2008**, *47*, 6847–6850.

[5] For organocatalysts, see: a) H. Torii, M. Nakadai, K. Ishihara, S. Saito, H. Yamamoto, *Angew. Chem.* **2004**, *116*, 2017–2020; *Angew. Chem. Int. Ed.* **2004**, *43*, 1983–1986; b) J.-M. Vincent, C. Morgottin, M. Berlande, D. Cavagnat, T. Buffeteau, Y. Landais, *Chem. Commun.* **2007**, 4782–4784.

[6] For chiral metal catalyst, see: a) K. Juhl, N. Gathergood, K. A. Jørgensen, *Chem. Commun.* **2000**, 2211–2212. For organocatalyst, see: b) P. Dambruoso, A. Massi, A. Dondoni, *Org. Lett.* **2005**, *7*, 4657–4660.

[7] For recent reviews, see: a) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*, Wiley-VCH, Weinheim, **2005**; b) *Enantioselective Organocatalysis: Reactions and Experimental Procedures* (Ed.: P. I. Dalko), Wiley-VCH, Weinheim, **2007**; c) *Hydrogen Bonding in Organic Synthesis* (Ed.: P. M. Pihko), Wiley-VCH, Weinheim, **2009**; d) *Topics in Current Chemistry, Vol. 291: Asymmetric Organocatalysis* (Ed.: B. List), Springer, Berlin, **2009**; e) H. Pellissier, *Recent Developments in Asymmetric Organocatalysis*, Royal Society of Chemistry Publishing, Cambridge, **2010**.

[8] For a review of electrophilic amination of carbonyl compounds, see: G. Guillena, D. J. Ramón, *Tetrahedron: Asymmetry* **2006**, *17*, 1465–1492.

[9] a) M. Terada, H. Ube, Y. Yaguchi, *J. Am. Chem. Soc.* **2006**, *128*, 1454–1455; b) M. Terada, T. Ikehara, H. Ube, *J. Am. Chem. Soc.* **2007**, *129*, 14112–14113; c) M. Terada, M. Nakano, *Heterocycles* **2008**, *76*, 1049–1055; d) H. Ube, N. Shimada, M. Terada, *Angew. Chem.* **2010**, *122*, 1902–1905; *Angew. Chem. Int. Ed.* **2010**, *49*, 1858–1861; e) M. Terada, H. Nii, *Chem. Eur. J.* **2011**, *17*, 1760–1763; f) M. Terada, K. Ando, *Org. Lett.* **2011**, *13*, 2026–2029. Also see: g) M. Terada, M. Nakano, H. Ube, *J. Am. Chem. Soc.* **2006**, *128*, 16044–16045; h) M. Nakano, M. Terada, *Synlett* **2009**, 1670–1674; i) M. Terada, D. Tsushima, M. Nakano, *Adv. Synth. Catal.* **2009**, *351*, 2817–2821; j) H. Ube, M. Terada, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3895–3898. For a personal research account, see: k) M. Terada, *J. Synth. Org. Chem. Jpn.* **2010**, *68*, 1159–1168.

[10] For reviews of chiral guanidine catalysts, see: a) T. Ishikawa, T. Isobe, *Chem. Eur. J.* **2002**, *8*, 552–557; b) T. Ishikawa, T. Kumamoto, *Synthesis* **2006**, 737–752; c) D. Leow, C.-H. Tan, *Chem. Asian J.* **2009**, *4*, 488–507.

[11] Epimerization of **4** was observed during purification by silica-gel column chromatography.

[12] When the reaction was performed using 5 mol% of (*R*)-**3h** in THF at 0 °C for 23 h, the corresponding product **7** was obtained in moderate yield (50%) with low enantioselectivity (27% *ee*).

[13] M. Hatano, S. Suzuki, K. Ishihara, *J. Am. Chem. Soc.* **2006**, *128*, 9998–9999.

[14] CCDC-722240 ($[(R)\text{-}\mathbf{3i}\cdot H]^+BF_4^-$) contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[15] An essentially identical result was obtained from the Mulliken population analysis, which indicates that the N1 atom is more positive than the N2 atom. See the Supporting Information for details.

[16] The relative stabilities of the enol forms of **1** were evaluated by DFT calculations at the B3LYP/6-311+g(d,p) level. The *Z* isomer is more stable than the *E* isomer by 3.98 kcal mol^{-1}. See the Supporting Information for details of the computational studies.

[17] a) E. J. Corey, M. J. Grogan, *Org. Lett.* **1999**, *1*, 157–160; b) Z. Jiang, Y. Pan, Y. Zhao, T. Ma, R. Lee, Y. Yang, K.-W. Huang, M. W. Wong, C.-H. Tan, *Angew. Chem.* **2009**, *121*, 3681–3685; *Angew. Chem. Int. Ed.* **2009**, *48*, 3627–3631.

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