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Development of Tartaric Acid Derived Chiral Guanidines and Their Application to Catalytic Enantioselective α-Hydroxylation of β-Dicarbonyl Compounds

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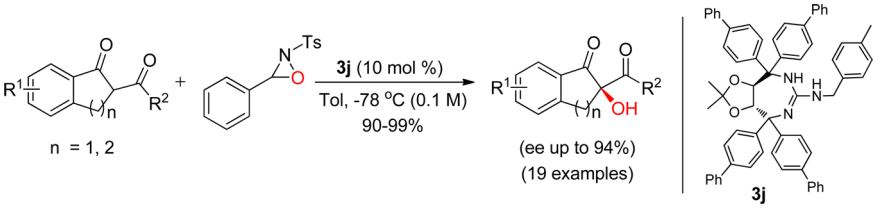
ABSTRACT



A novel library of chiral guanidines featuring a tartaric acid skeleton was developed from diethyl L-tartrate. These guanidines are easily accessed with tunable steric and electronic properties. The utilities of the guanidines were highlighted by their ability to catalyze the α-hydroxylation of β-ketoesters and β-diketones with remarkable efficiency and excellent enantioselectivity.

Tartaric acid has played a prominent role in the development of chiral auxiliaries and chiral catalysts for use in asymmetric organic synthesis due to its rich abundance and ready diversification.[1] In the context of the flourishing development of asymmetric organocatalysis with small chiral organic molecules as catalysts over the past decade,[2] a number of tartaric acid derivatives have been introduced as organic catalysts including, for example, TADDOLs,[3] TADDOL-based phosphoric acids,[4] and TADDOL-derived phase transfer catalysts.[5] Despite these sporadic reports, the potential of tartaric acid as a parent scaffold for the development of chiral organic catalysts is far from being fully exploited.

In the field of asymmetric organocatalysis, chiral guanidines represent a preeminent catalyst class, which have enabled a broad spectrum of asymmetric organic reactions.[6] Although a wide array of structurally diverse chiral guanidines have been developed, there still exists a paucity in this field of more general guanidine catalysts capable of catalyzing a broader scope of asymmetric transformations. As a consequence, the development of chiral guanidines

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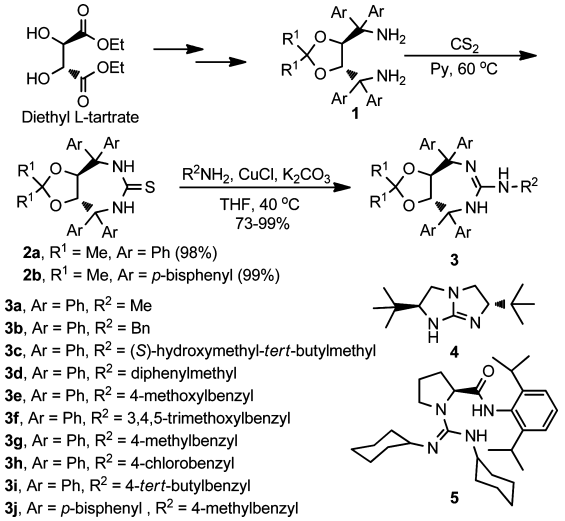
from simple precursors with readily tunable steric and electronic factors for more asymmetric applications is highly desirable. Since its first introduction by Seebach and co-workers two decades ago, the TADDOL derived diamine **1** and derivatives thereof have found very few catalytic asymmetric applications.[7] Given the readily tunable nature of the TADDOL backbone, we envisioned that diamine **1** (Scheme 1) could serve as a promising precursor for the construction of a library of guanidine catalysts.

Scheme 1. Tartaric Acid Derived Chiral Guanidines and the Known Catalysts Used in This Work



On the other hand, the α-hydroxy-β-dicarbonyl moiety is an intriguing structural motif commonly found in a variety of biologically active natural products, agrochemicals, pharmaceuticals, and advanced synthetic intermediates thereof.[8] Consequently, much effort has been devoted to the construction of this architecture over the past decade, including the stoichiometric use of chiral oxaziridine initiated by Davis[9] and asymmetric catalysis by chiral metal or organic catalysts in conjunction with appropriate oxygenating agents.[10,11] In the case of asymmetric organocatalysis toward this goal, only the cinchona alkaloid[11a,d,e] and chiral phosphoric acid[11b] have been reported as efficient catalysts, while other organocatalysts include the natural alkaloid lappaconitine[11c] and a synthetic analogue of *S*-timolol,[11f] but with moderate results. To the best of our knowledge, there is no literature precedent with guanidine catalysis on this project. Herein, we report the development of a novel library of chiral guanidines featuring a tartaric acid skeleton and their efficient application to the enantioselective α-hydroxylation of β-dicarbonyl compounds.

Our studies commenced with the construction of the library of guanidine catalysts starting from diethyl L-tartrate. The key diamine intermediate was readily obtained according to the literature procedure,[7a] which was transformed into thiourea **2** almost quantitatively upon treatment with carbon disulfide.[12] The reaction of the thiourea **2** with primary amines smoothly occurred under the mediation of CuCl,[13] affording the guanidines **3a**–**j** in good to excellent yield.[14] By varying R^1, Ar, and R^2, a library of chiral guanidines with different steric and electronic properties was constructed (Scheme 1).

With the guanidine library established, we evaluated the catalytic activity and enantioselectivity on the α-hydroxylation of β-dicarbonyl compounds. To this end, the α-hydroxylation of indanone derived β-ketoester was selected as a model reaction to identify the optimal reaction conditions. With the hydroxylation of **6a** in toluene under the catalysis of 10 mol % **3b**, the oxidants were first screened. While the reactions with H_2O_2 and *tert*-butyl hydroperoxide (TBHP) were very sluggish with low enantioselectivity, *m*-chloroperoxybenzoic acid (*m*CPBA) reacted much faster but afforded a racemic product (Table 1, entries 1–3). When oxaziridine **7a** was used, to our delight, the reaction was complete in 5 min with full conversion and a promising enantioselectivity of 48% ee (Table 1, entry 4). Further investigation on the use of chloro substituted oxaziridine **7b** and saccharin-based **7c** and **7d** afforded inferior ee values (Table 1, entries 5–7).[15]

(7) (a) Seebach, D.; Hayakawa, M.; Sakaki, J.; Schweizer, W. B. *Tetrahedron* **1993**, *49*, 1711. (b) Seebach, D.; Pichota, A.; Beck, A. K.; Pinkerton, A. B.; Litz, T.; Karjalainen, J.; Gramlich, V. *Org. Lett.* **1999**, *1*, 55. (c) Kretzschmar, E. A.; Kipke, J.; Sundermeyer, J. *Chem. Commun.* **1999**, 2381. (d) Lauber, M. B.; Fröhlich, R.; Paradies, J. *Synthesis* **2012**, 3209.

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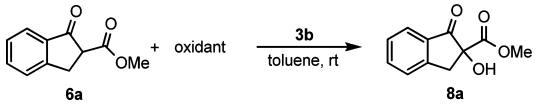
(14) The X-ray crystal structure of **3a** hydrochloride was shown in the Supporting Information. CCDC 934885 of this compound contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk /data_request/cif.

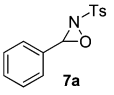
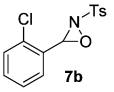
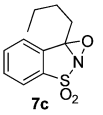
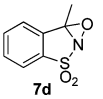
(15) For the preparation of oxaziridines **7a**–**d**, see: (a) Davis, F. A.; Towson, J. C.; Vashi, D. B.; ThimmaReddy, R.; McCauley, J. P., Jr.; Harakal, M. E.; Gosciniak, D. J. *J. Org. Chem.* **1990**, *55*, 1254. (b) Ruano, J. L. G.; Alemán, J.; Fajardo, C.; Parra, A. *Org. Lett.* **2005**, *7*, 5493.

With **7a** as the oxidant and **3b** as the catalyst other solvents were surveyed, and the result indicated that toluene maintained the solvent of choice (see the Supporting Information Table S-1).

Table 1. Survey of the Oxidant[a]



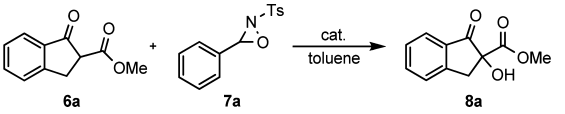
6a 8a

entry	oxidant	time	yield (%)[b]	ee (%)[c]
1[d]	H_2O_2	50 h	29	26
2[d]	*t*-BuOOH	67 h	48	8
3	*m*CPBA	15 min	81	0
4	 **7a**	5 min	99	48
5	 **7b**	5 min	99	42
6	 **7c**	2 min	99	34
7	 **7d**	2 min	99	36

[a] Unless otherwise noted, reactions were conducted with β-ketoester **6a** (0.2 mmol), catalyst **3b** (0.02 mmol, 10 mol %), and oxidant (0.26 mmol, 1.3 equiv) in toluene (1 mL) at room temperature. [b] Isolated yield. [c] Determined by chiral HPLC analysis (Chiralcel OD-H). [d] The conversion was not complete.

With the optimal oxidant and solvent identified, other reaction parameters were examined including the guanidine catalyst, temperature, and concentration. It was found that the amine moiety, which was introduced at the final stage as an integral component of the guanidine catalyst, has a marked influence on the enantioselectivity of the hydroxylation reaction. While benzyl amine derived guanidine **3b** exhibited promising enantioselectivity at rt, other alkyl amine based guanidine catalysts generally showed poor enantiocontrol except for the methylamine derived guanidine which afforded 40% ee (Table 2, entries 1−4). When the reaction was run at −20 °C, to our delight, the enantioselectivity was improved to 67% ee (Table 2, entry 5). Dilution of the reaction to 0.1 M resulted in a slight increase of the enantioselectivity to 69% ee (Table 2, entry 6). Further lowering of the temperature to −60 and −78 °C gave 81% and 85% ee values, respectively (Table 2, entries 7−10). To further improve the enantioselectivity, we then focused our attention on the modification of the benzyl moiety of the guanidine (Table 2, entries 11−15). Substitution with a *p*-methoxy group on the phenyl ring of the benzyl unit led to a slight increase of the enantioselectivity

Table 2. Optimization of the Reaction Conditions[a]



6a 7a 8a

entry	cat.	temp (°C)	time (min)	yield (%)[b]	ee (%)[c]
1	**3a**	rt	5	99	40
2	**3b**	rt	5	99	48
3	**3c**	rt	1	99	0
4	**3d**	rt	10	99	2
5	**3b**	−20	10	99	67
6[d]	**3b**	−20	10	99	69
7[d]	**3b**	−60	40	99	81
8[d]	**3b**	−78	120	99	84
9[d,e]	**3b**	−78	120	99	84
10[d−f]	**3b**	−78	120	99	85
11[d−f]	**3e**	−78	50	99	87
12[d−f]	**3f**	−78	40	99	83
13[d−f]	**3g**	−78	30	99	90
14[d−f]	**3h**	−78	60	99	82
15[d−f]	**3i**	−78	120	99	86
16[d−f]	**3j**	−78	60	99	93
17[d−g]	**3j**	−78	150	99	92
18	**4**	rt	1	99	26
19	**5**	rt	1	99	−28

[a] Unless otherwise noted, reactions were conducted with β-ketoester **6a** (0.2 mmol), catalyst (0.02 mmol, 10 mol %), and oxaziridine **7a** (0.26 mmol, 1.3 equiv) in toluene (1 mL). [b] Isolated yield. [c] Determined by chiral HPLC analysis (Chiralcel OD-H). [d] Toluene (2 mL). [e] Oxaziridine **7a** (0.24 mmol, 1.2 equiv). [f] Under a nitrogen atmosphere. [g] Catalyst (5 mol %).

to 87% ee at −78 °C (Table 2, entry 11), but the guanidine with a 3,4,5-trimethoxybenzyl group gave a slightly lower ee of 83% (Table 2, entry 12). Interestingly, the use of the guanidine with a *p*-methylbenzyl group delivered the product with 90% ee (Table 2, entry 13). Further variation of the aryl groups at 1,4-position of the tartaric acid backbone with *p*-bisphenyl functionality finally gave rise to an enantioselectivity of 93% ee (Table 2, entry 16). Notably, the catalyst loading could be reduced to 5 mol % without erosion of the yield and enantioselectivity, albeit at the expense of an extended reaction time (Table 2, entry 17). For comparison, some amino acid based guanidine catalysts were tested. The result indicated that both L-*tert*-leucine and L-proline based guanidines[16] showed inferior asymmetric induction at rt compared to **3b**, affording 26% and 28% ee, respectively (Table 2, entries 18 and 19).

With the optimized conditions established, we next explored the substrate scope of the α-hydroxylation process (Figure 1). Initially, esters of different steric bulk were investigated (**6a**−**e**). The substrate displaying a methyl ester proved the most effective. As the steric bulk of the ester group increased, the reactivity and enantioselectivity

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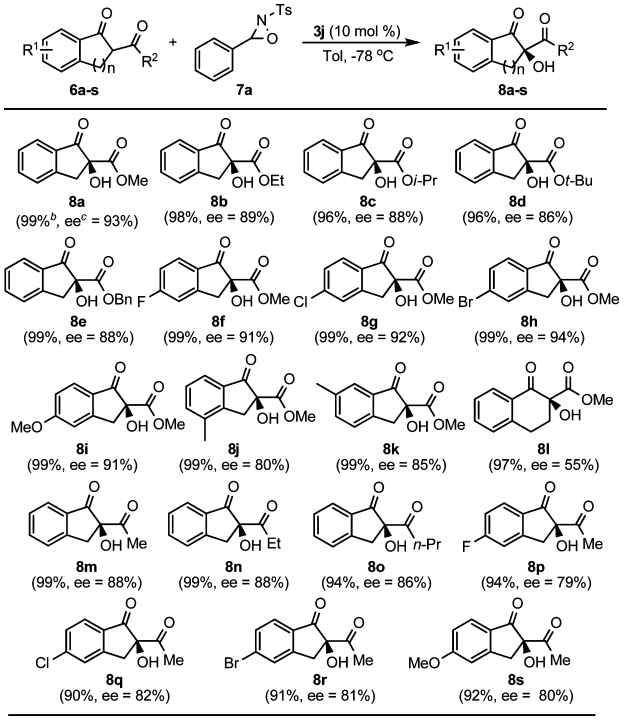
decreased accordingly, albeit to a small extent in terms of enantioselectivity. As exemplified in the case of the sterically hindered *tert*-butyl ester, the reaction reached completion after 13 h giving 86% ee (**8d**). The benzyl ester afforded a comparable result to ethyl ester with 88% and 89% ee, respectively, in 2 h (**8b** and **8e**).



[a] Unless otherwise noted, reactions were conducted under nitrogen atmosphere with substrate (0.2 mmol), catalyst **3j** (0.02 mmol, 10 mol %) and oxaziridine **7a** (0.24 mmol, 1.2 equiv) in toluene (2 mL) at -78 °C. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

Figure 1. Substrate scope of the α-hydroxylation process.

The effect of the substituent identity and substitution pattern on the phenyl ring was then studied. Substrates halogenated at the 5-position all gave the desired products in quantitative yield with excellent enantioselectivity (Figure 1). In particular, in the case of the brominated substrate, the hydroxylation occurred very fast which was completed in 30 min with 94% ee (**8h**). The presence of the bromo atom provides a versatile handle for further elaboration of the product through, for example, coupling reactions. The occurrence of a methoxy group at the 5-position also afforded an excellent result with 91% ee and 99% yield (**8i**). Notably, the substitution at the 4- and 6-position was found to be deleterious to the asymmetric induction. For example, the 4- and 6-methyl substituted substrates afforded decreased enantioselectivities to 80% and 85% ee values (**8j** and **8k**), respectively. The substrate with a six-membered ring also underwent the hydroxylation reaction, but with lowered enantioselectivity (**8l**).

In sharp contrast to β-ketoesters as common hydroxylation substrates, the asymmetric α-hydroxylation of β-diketone compounds has been much less explored, although the α-hydroxy-β-diketone moiety is of pharmaceutical and synthetic relevance.[17] To date, there is only one literature precedent that documented the α-hydroxylation of β-diketone compounds which built upon the use of chiral phosphoric acid catalysis in combination with nitroso arene as the oxidant.[11b] To further highlight the utility of our guanidine catalysts, the hydroxylation procedure was extended to β-diketone compounds. Gratifyingly, a variety of indanone based β-diketones were found to smoothly undergo the α-hydroxylation with excellent yield and synthetically useful enantioselectivity (Figure 1, **6m**–**s**). The steric character of the exocyclic acyl group does not exert an appreciable effect on the reactivity and enantioselectivity, as evidenced by the observation that diketones displaying acetyl, propionyl, and butionyl groups gave the same levels of yield and enantioselectivity (**8m**–**o**). Substitution on the phenyl ring led to a slight erosion of the enantioselectivity regardless of the electronic character of the substituent, but synthetically useful ee values were still maintained (**8p**–**s**).

The absolute configurations of α-hydroxy β-ketoesters **8a**–**e** and **8g** and α-hydroxy β-diketones **8l** and **8p** were determined to be *S* and *R*, respectively, by comparison of their optical rotations with literature data,[11b] and the absolute stereochemistry of other products was assigned by analogy.

In summary, we have developed a novel library of guanidines starting from ethyl L-tartrate as the chiral source. The guanidines are easily accessed with a tunable steric environment and basicity. The utilities of the guanidines were highlighted by their ability to catalyze the α-hydroxylation of β-ketoesters and β-diketones with remarkable efficiency and excellent enantioselectivity. Studies toward extending the catalytic applications of this novel chiral guanidine library for other asymmetric transformations are currently underway in our laboratory.

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Supporting Information Available. Experimental procedures, full characterization data for all new compounds, and crystallographic data in cif format. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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