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Direct Asymmetric Aldol Reaction of 5*H*-Oxazol-4-ones with Aldehydes Catalyzed by Chiral Guanidines

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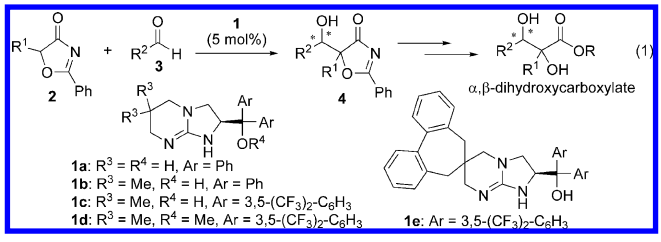
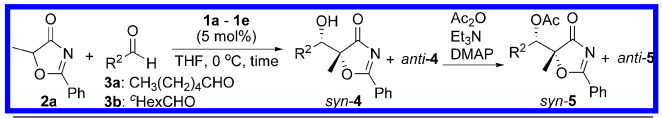
Chiral α,β-dihydroxycarboxylic acids and their derivatives possessing a quaternary stereogenic center at the α-carbon atom are considered to be important chiral synthons[1] and also serve as partial structures of many biologically active natural products.[2] These features have stimulated the development of preparative methods for these compounds. However, effective methods are limited by the difficulty of achieving highly stereoselective construction of the chiral quaternary carbon atom.[3−5] The asymmetric aldol reaction of α-hydroxycarboxylate analogues with aldehydes is regarded as an influential reaction for the preparation of α,β-dihydroxycarboxylates that bear a quaternary α-carbon atom. Most of the reported aldol reactions of this type are diastereoselective reactions utilizing chiral auxiliaries,[3a−c] with the exception of several Mukaiyama-type catalytic asymmetric aldol reactions that require the preconversion of donor substrates into reactive silyl enolates.[3d] However, a direct catalytic asymmetric version[6] of these quaternary α-carbon atom-constructing aldol reactions has not yet been reported.[7] Using as donor substrates α-hydroxy ketones, which may be transformed to carboxylate analogues by Baeyer−Villiger reaction, Shibasaki and co-workers achieved a direct catalytic aldol reaction involving chiral quaternary α-carbon atom construction.[8,9] Here we report a direct asymmetric aldol reaction of 5*H*-oxazol-4-ones (donors) with aldehydes (acceptors) catalyzed by new chiral guanidines **1** for the preparation of α,β-dihydroxycarboxylates bearing a quaternary α-carbon atom (eq 1).



The construction of a quaternary α-carbon atom using an aldol reaction demands a highly reactive system for the sterically hindered donor substrates. To achieve this aldol reaction, we selected 5*H*-oxazol-4-ones **2** as pronucleophiles, since it was anticipated that the compactly cyclized enolates of **2** would have high nucleophilicity. 5*H*-Oxazol-4-ones were first introduced by Trost and co-workers as useful pronucleophiles in asymmetric allylic alkylation,[10] but they have not been used since that report. In contrast, the structurally similar 4*H*-oxazol-5-ones (azlactones) are widely used in various reactions.[11] New chiral guanidines were also developed as Brønsted base catalysts for the present system to achieve high levels of stereocontrol.[12] We designed bicyclic chiral guanidines[13] **1** bearing a hydroxy group at the appropriate position with the expectation that the hydroxy group would coordinate with the aldehyde through a hydrogen bond, achieving activation and position control.[14] Additionally, we assumed that the enolate anions generated by deprotonation of **2** in the initial step of the reaction would also have their position and direction controlled through hydrogen bonds with two acidic hydrogen atoms lined up on the bicyclic guanidium moiety.

Table 1. Evaluation of Catalysts **1a**−**e** in the Direct Aldol Reaction of **2a** and **3**[a]



entry	catalyst **1**	acceptor **3**	time (h)	product **5**	yield (%)[b]	syn:anti ratio[c]	ee (%) (syn/anti)[d]
1	**1a**	**3a**	4	**5a**	63	45:55	64/53
2	**1b**	**3a**	5.5	**5a**	60	51:49	69/38
3	**1c**	**3a**	5	**5a**	58	61:39	94/80
4	**1e**	**3a**	5	**5a**	84	70:30	94/73
5	**1a**	**3b**	2	**5b**	73	90:10	81/12
6	**1c**	**3b**	5	**5b**	84	>98:2	96/26
7	**1e**	**3b**	9	**5b**	75	>98:2	96/11
8	**1d**	**3b**	31	**5b**	29[e]	63:37	3/9

[a] Reactions were performed on a 0.3 mmol scale in 1.0 mL of anhydrous THF using 2 equiv of aldehyde **3** and 5 mol % catalyst **1** at 0 °C. [b] Combined isolated yield of *syn*/*anti*-**5**. [c] Determined by 600 MHz ^{1}H NMR analysis of the crude mixture. [d] Determined by chiral HPLC analysis. [e] Low conversion yield (<50%) caused the low isolated yield.

We initiated our studies with steric and electronic tuning of the chiral guanidine catalysts **1** using **2a** and linear aldehyde **3a** or α-branched aldehyde **3b** as model substrates. The aldol reaction proceeded smoothly at 0 °C in the presence of **1** (5 mol %) to give the aldol adducts **4**, which were converted in situ to the acetate analogues **5**. A retro-aldol reaction was observed during silica-gel column chromatographic purification of **4**. The reasons for the difficulties associated with aldol reactions involving quaternary α-carbon atom construction appear to be not only the forcible use of sterically hindered donor substrates but also a possible retro-aldol reaction. Fortunately, the retro-aldol reaction was not observed during the present aldol reaction (for confirmation of the retro-aldol reaction, see the Supporting Information). As shown in Table 1, appreciable enantioselectivity was attained using **1a** or **1b**, but no syn/anti selectivity was observed (entries 1 and 2). Use of electron-deficient 3,5-bis(trifluoromethyl)phenyl groups as aromatic substituents (Ar) on catalyst **1** improved the enantioselectivity, but the syn/anti selectivity was still low (entry 3). Through further investigation, we found that the syn/anti selectivity was enhanced to 70:30 using **1e** (entry 4). Although the syn/anti selectivity was still moderate, the two isomers were easily separable through purification by simple column chromatography. In the case of the α-branched aldehyde **3b**, the aldol reaction proceeded with both high syn/anti selectivity and well-controlled enantioselectivity using either **1c** or **1e**, while sterically smaller **1c** was more reactive than bulky **1e** (entries 6 and 7). It should be noted that the aldol reaction with **1d**, whose hydroxy group was protected as a methyl ether, proceeded remarkably slowly and with quite low stereoselectivity (entry 8).

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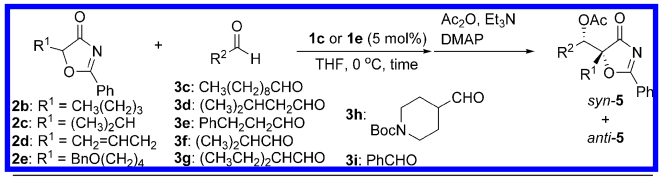
Various combinations of 5*H*-oxazol-4-ones **2** and aldehydes **3** were applied to the aldol reaction using catalyst **1c** or **1e** (Table 2). For linear (non-α-branched) aldehydes, **1e** was used (entries 1−6), whereas **1c** was used for α-branched aldehydes and benzaldehyde (entries 7−14). As a result, product **5** was obtained with uniformly high enantioselectivity, and moderate (entries 1−6) to excellent (entries 7−14) syn/anti selectivities were observed. Even in the case of non-α-branched aldehydes, relatively high syn/anti selectivities were observed in the reaction of a bulky donor substrate **2c** (entries 5 and 6). Several functionalities in **2** or **3** were tolerated during the reaction (entries 10, 11, and 13), and benzaldehyde (**3i**) was also applicable (entry 14). Although the isolated yield of bulky **5k** was relatively low, the stereoselectivities were similarly high (entry 9).

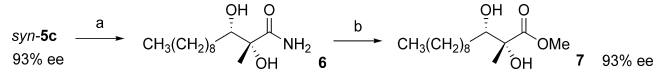
Table 2. Direct Aldol Reaction of Various 5*H*-Oxazol-4-ones **2** and Aldehydes **3** Catalyzed by **1c** or **1e**[a]



		substrates						
entry	catalyst **1**	**2**	**3**	time (h)	product **5**	yield (%)[b]	syn:anti ratio[c]	syn ee (%)[d]
1	**1e**	**2a**	**3c**	12	**5c**	71	67:33	94
2	**1e**	**2a**	**3d**	4	**5d**	67	75:25	93
3	**1e**	**2a**	**3e**	6	**5e**	72	77:23	95
4	**1e**	**2b**	**3a**	4.5	**5f**	65	76:24	92
5	**1e**	**2c**	**3a**	11.5	**5g**	83	80:20	92
6	**1e**	**2c**	**3d**	24	**5h**	81	83:17	95
7	**1c**	**2a**	**3f**	3.5	**5i**[e]	92	98:2	97
8	**1c**	**2b**	**3f**	6.5	**5j**	66	98:2	96
9	**1c**	**2c**	**3f**	24	**5k**	43	>98:2	96
10	**1c**	**2d**	**3f**	8.5	**5l**	79	97:3	95
11	**1c**	**2e**	**3f**	13.5	**5m**	72	98:2	95
12	**1c**	**2a**	**3g**	30	**5n**	74	>98:2	96
13	**1c**	**2a**	**3h**	72	**5o**	68	95:5	97
14[f]	**1c**	**2a**	**3i**	28	**5p**[g]	84	97:3	96

[a−d]See corresponding footnote in Table 1. [e] The absolute configuration of **5i** was determined by X-ray analysis of the corresponding compound having a bromo substituent at the 4-position of the phenyl group.[15] [f] Reactions were carried out at −40 °C. [g] The absolute configuration of **5p** was determined by conversion into the known α,β-dihydroxyester.[15,16]

Scheme 1. Derivatization of Aldol Product *syn*-**5c** to Methyl Ester **7**[a]



[a] Conditions: (a) 2.5 M NaOH(aq), EtOH, 0 °C, 3 h (84%); (b) conc. HCl, 80 °C, 3 h, then cat. H_2SO_4, MeOH, reflux, 6 h (84%). Optical rotation value of **7**: $[\alpha]_D^{20} = -30.6$ (*c* 1.0, $CHCl_3$) {lit.:[3b] $[\alpha]_D^{20} = -25.0$ (*c* 1.0, $CHCl_3$) (2*R*,3*S*)}.

The aldol products **5** can easily be converted into α,β-dihydroxycarboxylic amides or esters without loss of enantiopurity. As shown in Scheme 1, hydrolysis through treatment of diastereomerically pure *syn*-**5c** (93% ee) with aqueous NaOH in EtOH readily afforded the corresponding amide **6**, which was converted to methyl ester **7** by simple acidic hydrolysis and subsequent H_2SO_4-catalyzed esterification. The absolute configuration of **7** was assigned as (2*R*,3*S*)[15] after comparison of the optical rotation value of the obtained **7** with the reported value.[3b] The enantiopurity of **7** was also confirmed as 93% ee by HPLC analysis of the corresponding monobenzoate of **7**.

In conclusion, we have developed a direct catalytic aldol reaction of 5*H*-oxazol-4-ones **2** with aldehydes **3** and achieved high stereoselectivities using new chiral guanidines **1** bearing a hydroxy group at the appropriate position. This reaction is the first direct catalytic asymmetric aldol reaction of α-oxygen atom-substituted carboxylate analogues with aldehydes involving quaternary α-carbon atom construction.

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Supporting Information Available: Representative experimental procedures; spectral data for chiral guanidine catalysts **1**, pronucleophile **2e**, aldol products **5**, and derivatized products **6** and **7**; and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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