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Catalytic Enantioselective Aldol Reactions of Unprotected Carboxylic Acids under Phosphine Oxide Catalysis

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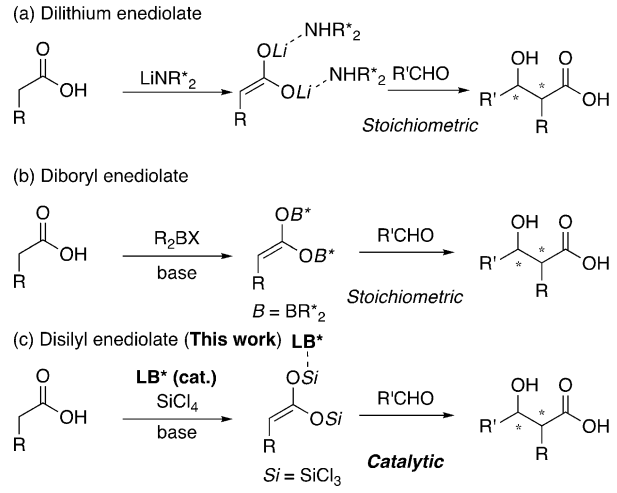
Abstract: *The first catalytic enantioselective aldol reaction of various unprotected carboxylic acids is described. In the presence of a chiral bis(phosphine oxide) as a Lewis base catalyst, carboxylic acids were activated with silicon tetrachloride to form the corresponding bis(trichlorosilyl)enediolates in situ, which subsequently underwent an aldol reaction with an aldehyde or a ketone to produce β-hydroxycarboxylic acids in high enantioselectivities of up to 92 % ee.*

The carboxylic acid functional group is fundamentally important in the biochemistry of living systems as well as in a wide range of biologically significant substances, including amino acids, prostanoids, and nonsteroidal anti-inflammatory drugs (NSAIDs).[1] Recently, much attention has been paid to the development of direct transformations of carboxylic acids to simplify synthetic sequences. However, owing to their inherent Brønsted acidity, the reactivity of carboxylic acids is markedly different from that of other carbonyl compounds.[2] Generating enolates of carboxylic acids, known as enediolates, is rather difficult and usually requires more than two equivalents of a strong base.[3] Thus the direct application of carboxylic acids in aldol-type reactions is often problematic and difficult to control. Whereas "masked" derivatives of carboxylic acids, such as esters and amides, have been frequently employed in stereoselective aldol reactions, asymmetric variants employing unprotected carboxylic acids have been rare.[4–9] While the groups of Mulzer,[4] Zakarian,[5] and Fringuelli[6] developed asymmetric aldol reactions of carboxylic acids, their procedures required stoichiometric amounts of chiral reagents to realize enantioselectivity (Scheme 1 a, b). To the best of our knowledge, catalytic variants of asymmetric aldol reactions of carboxylic acids have not been reported to date. Considering the high demand for carboxylic acids, their direct catalytic aldol reaction represents a new tool in complex molecule synthesis. Recently, Kanai and co-workers developed an asymmetric Mannich-type reaction of carboxylic acids by using a combination of catalytic borane and a chiral binol,[10] but the reaction was limited to imine electrophiles, and the use of carbonyl electrophiles as aldol acceptors has remained difficult.[9] In this work, we report the first catalytic enantioselective aldol reaction of unprotected carboxylic acids. In the presence of a chiral Lewis base organocatalyst, carboxylic acids were activated with silicon tetrachloride to form the corresponding bis(trichlorosilyl)-enediolates, which subsequently underwent an aldol reaction with an aldehyde or ketone to give β-hydroxycarboxylic acids in up to 92 % *ee* (Scheme 1 c).[11]



Scheme 1. Enantioselective aldol reactions of carboxylic acids.

Our strategy for activating carboxylic acids is shown in Scheme 2. Carboxylic acid **1** reacts with silicon tetrachloride to form trichlorosilyl carboxylate **2**. Subsequently, intermediate **2** reacts with another molecule of silicon tetrachloride to generate bis(trichlorosilyl)enediolate **3** in the presence of a chiral Lewis base catalyst. The silicon atom in **2** is electron-deficient owing to the presence of the three chlorine atoms, which makes the α-CH_2 moiety more acidic and facilitates the formation of **3**. Enediolate **3**, coordinated to the chiral Lewis base, reacts with aldehyde **4** to produce silyl β-hydroxycar-

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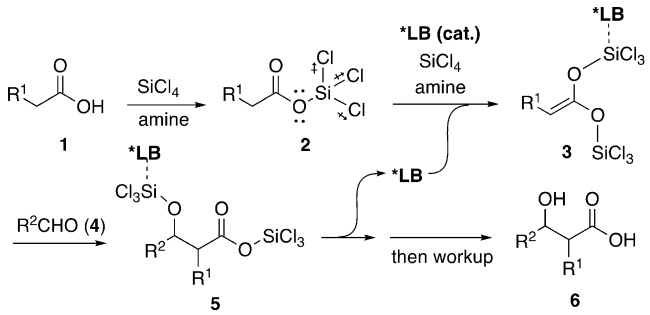


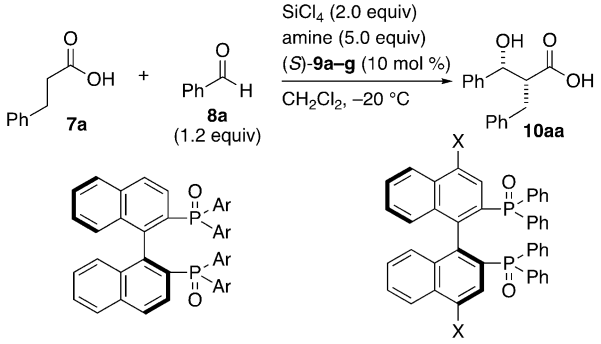
Scheme 2. Strategy for the $SiCl_4$-assisted catalytic asymmetric aldol reaction of carboxylic acids.

boxylate **5** in an enantioselective fashion and to release the Lewis base, which is available to another catalytic cycle.[12,13]

At the outset, the reaction of carboxylic acid **7a** with aldehyde **8a** was examined in the presence of silicon tetrachloride (2 equiv relative to **7a**), excess triethylamine, and (*S*)-BINAPO (**9a**, 10 mol%) in dichloromethane at −20°C for 6 hours (Table 1, entry 1). As expected, the reaction proceeded smoothly to yield aldol adduct **10aa** in 51% yield, albeit in low stereoselectivity (*syn*/*anti* 52:48, 18% *ee* for the *syn* isomer).[14,15] The presence of Lewis base **9a** was essential; the reaction did not proceed without **9a** under otherwise identical reaction conditions (entry 2). Among the amine bases surveyed, sterically demanding *N*,*N*-diisopropylisobutylamine showed the best result (entry 4).[16] A longer reaction time (15 h) improved the yield to 93% with retention of the stereoselectivity (entry 5). The use of 1 equiv of silicon tetrachloride reduced the yield to 49% (entry 6). This result is consistent with our hypothesis, in which two equivalents of silicon tetrachloride are necessary to activate the carboxylic acid (Scheme 2).

Next, several chiral phosphine oxide catalysts were screened to enhance the enantioselectivity.[17] Modifying the diarylphosphine moieties of chiral phosphine ligands is a common tactic to improve their performance in metal-catalyzed reactions; however, analogous modifications of BINAPOs did not improve the enantioselectivity in the present reaction; the 4-tolyl and 3,5-xylyl BINAPO derivatives (**9b** and **9c**) gave lower enantioselectivities than BINAPO (entries 7 and 8).[18] Recently, we reported that modifications of BINAPO at the 4- and 4′-positions of the binaphthyl skeleton enhanced the enantioselectivity of Lewis base catalyzed reactions.[19] Whereas 4,4′-Br_2-BINAPO (**9d**) gave a lower enantioselectivity than **9a** (entry 9), the 4,4′-bis(trialkylsilyl) derivatives **9e–g** were more enantioselective than **9a** (entries 10–12). Among the three 4,4′-bis(trialkylsilyl)-BINAPO derivatives, 4,4′-$TIPS_2$-BINAPO (**9g**), which contains the bulkiest silyl groups, showed the highest enantioselectivity of 56% *ee* (entry 12). Lowering the temperature to −60°C further increased the enantioselectivity to 72% *ee* (entry 13). The sodium salt of **7a** could be used as the substrate of the aldol reaction, affording **10aa** in nearly identical yield and selectivity as from free acid **7a** (entry 14). It should be mentioned that catalyst **9g** could be easily recovered from the reaction mixture and reused.

Table 1: Optimization of the reaction conditions.[a]

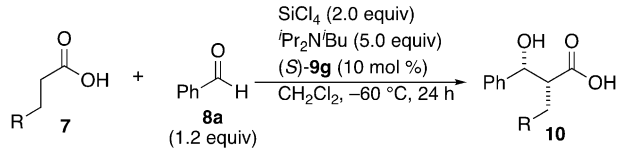


Entry	Amine	9	Time [h]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	Et_3N	**9a**	6	51	52:48	18
2	Et_3N	–	6	–	–	–
3	$^iPr_2NEt$	**9a**	6	67	78:22	22
4	$^iPr_2N^tBu$	**9a**	6	67	78:22	25
5	$^iPr_2N^tBu$	**9a**	15	93	80:20	25
6[e]	$^iPr_2N^tBu$	**9a**	15	49	80:20	24
7	$^iPr_2N^tBu$	**9b**	15	92	83:17	23
8	$^iPr_2N^tBu$	**9c**	15	93	85:15	−7
9	$^iPr_2N^tBu$	**9d**	15	84	79:21	18
10	$^iPr_2N^tBu$	**9e**	15	94	81:19	43
11	$^iPr_2N^tBu$	**9f**	15	94	82:18	45
12	$^iPr_2N^tBu$	**9g**	15	91	80:20	56
13[f]	$^iPr_2N^tBu$	**9g**	24	82	76:24	72
14[f,g]	$^iPr_2N^tBu$	**9g**	24	76	76:24	72

[a] Unless otherwise noted, reactions were carried out in the presence of **7a** (0.5 mmol), **8a** (0.6 mmol), $SiCl_4$ (1.0 mmol), an amine (2.5 mmol), and **9** (0.05 mmol) in dichloromethane (5.0 mL) at −20°C. [b] Yield of the isolated diastereomeric mixture. [c] Determined by ^1H NMR analysis. [d] For the *syn* isomer, determined by HPLC analysis on a chiral stationary phase. [e] With $SiCl_4$ (0.5 mmol). [f] At −60°C. [g] Using the sodium salt of **7a** instead of **7a**.

With optimized reaction conditions and a suitable Lewis base catalyst in hand, the scope of the present reaction was examined using various carboxylic acids (Table 2).[20] Both the diastereo- and enantioselectivities were improved in the reaction with *ortho*-bromohydrocinnamic acid (**7b**; entry 2). The reactions with ω-halogenated carboxylic acids **7c–7e** afforded the aldol products in excellent enantioselectivities (entries 3–5); δ-bromocarboxylic acid **7d** showed the highest enantioselectivity of 92% *ee* (entry 4). The aldol reaction was applicable to acids with an ether (**7f**), a sulfide (**7g**), or a nitro (**7h**) group, and the corresponding aldol adducts were obtained in 80–85% *ee* (entries 6–8). Carboxylic acid **7i**, bearing a nitrile group, features two acidic methylene groups, one is adjacent to the carboxyl group, and the other one is next to the nitrile group. The present aldol reaction of **7i** proceeded with excellent regioselectivity at the α-position to the carboxylic acid to give **10ia** exclusively in 92% *ee* (entry 9). As summarized in Table 2, the present protocol tolerates a wide range of carboxylic acids, affording aldol adducts bearing various functional groups in good enantiose-

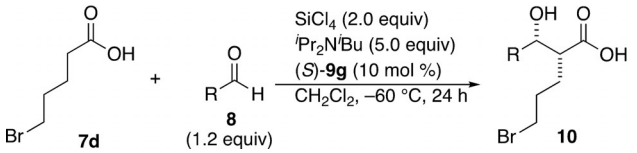
Table 2: Substrate scope: carboxylic acids.[a]



Entry	7	R	10	Yield [%][b]	d.r.[c]	ee [%][d]
1	**7a**	Ph	**10aa**	77	81:19	72
2	**7b**	2-BrC_6H_4	**10ba**	78	91:9	80
3	**7c**	$(CH_2)_2Cl$	**10ca**	80	88:12	90
4	**7d**	$(CH_2)_2Br$	**10da**	77	89:11	92
5	**7e**	$(CH_2)_2I$	**10ea**	79	91:9	91
6	**7f**	$(CH_2)_2OMe$	**10fa**	62	75:25	80
7	**7g**	$(CH_2)_2SBn$	**10ga**	77	82:18	85
8	**7h**	CH_2NO_2	**10ha**	84	91:9	81
9	**7i**	$(CH_2)_2CN$	**10ia**	73	92:8	92

[a] Reactions were carried out in the presence of **7** (0.5 mmol), **8a** (0.6 mmol), $SiCl_4$ (1.0 mmol), $^iPr_2N^tBu$ (2.5 mmol), and **9g** (0.05 mmol) in dichloromethane (5.0 mL) at −60 °C for 24 h. Yields and selectivities were determined after conversion into the corresponding methyl esters. [b] Yield of the isolated diastereomeric mixture. [c] Determined by ^1H NMR analysis. [d] For the *syn* isomer, determined by HPLC analysis on a chiral stationary phase.

Table 3: Substrate scope: aldehydes.[a]



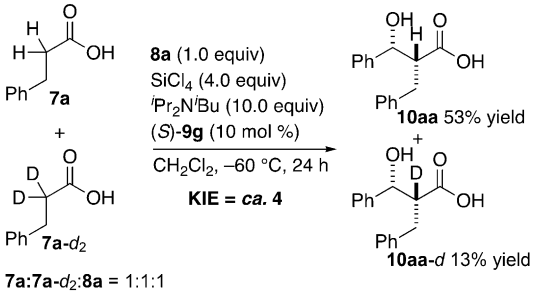
Entry	8	R	10	Yield [%][b]	d.r.[c]	ee [%][d]
1	**8a**	Ph	**10da**	77	89:11	92
2	**8b**	4-MeC_6H_4	**10db**	70	92:8	92
3	**8c**	4-$MeOC_6H_4$	**10dc**[e]	73	92:8	92
4	**8d**	4-BrC_6H_4	**10dd**	73	91:9	92
5	**8e**	4-$CF_3C_6H_4$	**10de**	72	86:14	91
6	**8f**	4-$NO_2C_6H_4$	**10df**	77	84:16	89
7[f]	**8g**	4-HOC_6H_4	**10dg**	60	90:10	88
8	**8h**	3-BrC_6H_4	**10dh**	82	88:12	89
9	**8i**	2-BrC_6H_4	**10di**	84	99:1	76
10	**8j**	2-naphthyl	**10dj**	84	86:14	89
11	**8k**	2-furyl	**10dk**[e]	76	85:5	86
12	**8l**	CH=CHPh	**10dl**[e]	77	60:40	86
13	**8m**	cyclopropyl	**10dm**	78	71:29	82
14[g]	**8a**	Ph	**10da**	75	90:10	92

[a] Unless otherwise noted, reactions were carried out in the presence of **7d** (0.5 mmol), **8** (0.6 mmol), $SiCl_4$ (1.0 mmol), $^iPr_2N^tBu$ (2.5 mmol), and **9g** (0.05 mmol) in dichloromethane (5.0 mL) at −60 °C for 24 h. Yields and selectivities were determined after conversion into the corresponding methyl esters. [b] Yield of the isolated diastereomeric mixture. [c] Determined by ^1H NMR analysis. [d] For the *syn* isomer, determined by HPLC analysis on a chiral stationary phase. [e] Isolated as the carboxylic acid. [f] With $SiCl_4$ (3.2 equiv). [g] With 5.5 mmol of **7d**; all other amounts were changed accordingly.

lectivity. Recrystallization of the methyl ester of **10ba** (**11ba**) from hexane/2-propanol provided enantiomerically pure compound. X-ray crystallographic analysis of **11ba** disclosed its absolute configuration to be 2*R*,3*R*.[21] The configurations of the other products were assigned by analogy or by comparison of the sign of the optical rotation with reported data.

Reactions of carboxylic acid **7d** with various aldehydes **8** were examined next (Table 3). The reactions of the 4-substituted benzaldehydes **8b**–**8f** gave high enantioselectivities of 89–92 % *ee* (entries 2–6). Aldehyde **8g** with phenol moiety could be used without protection to give **10dg** in 88 % *ee* (entry 7). Whereas 3-bromobenzaldehyde (**8h**) gave the corresponding aldol adduct in 89 % *ee*, 2-bromobenzaldehyde (**8i**) reacted with a slightly lower enantioselectivity of 76 % *ee* (entries 8 and 9). Both 2-naphthaldehyde (**8j**) and 2-furfural (**8k**) were also amenable to the present reaction (entries 11 and 12). The reaction of cinnamaldehyde (**8l**) was less diastereoselective (*syn*/*anti* 60:40) while the enantioselectivity remained at a high level of 86 % *ee* (entry 12). Aliphatic cyclopropanecarboxaldehyde (**8m**) also reacted well, producing **10dm** in 78 % yield with 82 % *ee* (entry 13). To further demonstrate the practicality and efficiency of the developed reaction, the reaction was scaled up (entry 14). β-Hydroxycarboxylic acids can be synthesized on gram scale, as exemplified by the synthesis of **10da** (75 % yield, 90:10 d.r., 92 % *ee* for the *syn* isomer).

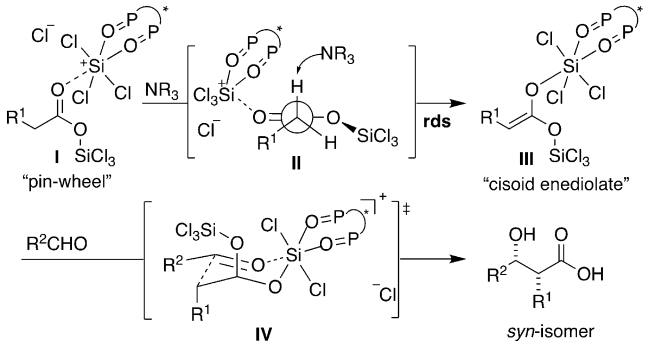
We next turned our attention to the elucidation of the reaction mechanism. Unfortunately, the crucial bis(trichlorosilyl)enediolate intermediate **3** could not be detected in the mixture of the carboxylic acid and an aldehyde either by NMR measurements or by MS analysis. These observations implied that the reaction of **3** with an aldehyde was faster than its formation. To clarify the rate-determining step of the aldol reaction, a deuterium labelling experiment was conducted (Scheme 3). Treatment of an equimolar mixture of **7a**/**7a**-d_2 with **8a** (0.5 equiv with respect to the mixture of **7a**/**7a**-d_2) under the standard conditions gave a mixture of the aldol



Scheme 3. Deuterium isotope effect studies.

adducts **10aa** and **10aa**-*d* in 53 % and 13 % yield, respectively (determined by ^1H NMR analysis), and the KIE for this reaction was estimated to be approximately 4:1. The preferential consumption of protio-aldehyde **7a** indicates that the rate-determining step is the formation of **3**, and this is consistent with the inability to detect of enediolate **3**.

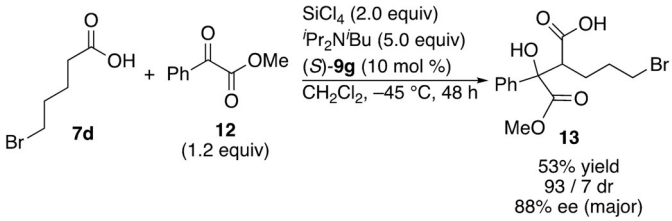
The stereochemical pathway of the reaction is explained in Scheme 4; the conformation of enediolate **III** is important because Lewis base catalyzed aldol reactions generally proceed via a cyclic transition state.[22] The most stable



Scheme 4. Plausible stereochemical pathway.

conformation of complex **I** might be the "pinwheel" form, in which the steric repulsion between the bulky peripheral groups is minimized. Deprotonation by a base preferably takes place via **II** to afford "*cisoid*" *Z*-bis(trichlorosilyl)enediolate **III**,[23] which is associated with the chiral phosphine oxide. The *Z*-enediolate subsequently reacts with an aldehyde via a six-membered transition state **IV** to achieve the high diastereo- and enantioselectivities.

The present procedure could be extended to the reaction with an α-ketoester (Scheme 5). Carboxylic acid **7d** reacted smoothly with methyl benzoylformate (**12**) in dichloromethane at −45 °C to furnish adduct **13** in 53 % yield with good diastereoselectivity (93:7 d.r.). The enantiomeric purity of the major diastereomer was 88 % *ee*.



Scheme 5. Asymmetric aldol reaction with α-ketoester **12**.

In conclusion, we have developed the first catalytic asymmetric aldol reaction of unprotected carboxylic acids. Key to success was the use of inexpensive silicon tetrachloride as an activator. The carboxylic acids readily reacted with silicon tetrachloride in the presence of the catalytic chiral phosphine oxide to form the corresponding bis(trichlorosilyl)enediolates, which reacted with an aldehyde or ketone to give the corresponding β-hydroxycarboxylic acids in high diastereo- and enantioselectivities. We are undertaking studies to disclose the reaction mechanism in detail and to extend the protocol of activating carboxylic acids to other stereoselective reactions.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: aldol reaction · carboxylic acids · hypervalent silicon · organocatalysis · phosphine oxides

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