Stereoselective Synthesis of *vic*-Halohydrins via L-*tert*-Leucine-Catalyzed *syn*-Selective Aldol Reaction

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Received 9 November 2011

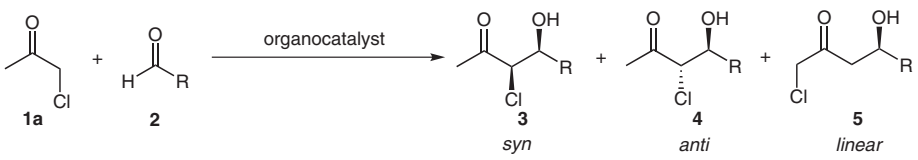
Abstract: L-*tert*-Leucine was found to be an effective organocatalyst for the asymmetric aldol reaction of chloroacetone. The stereoselective synthesis of *vic*-halohydrins was accomplished with excellent regioselectivity (>99%) to generate α-chloro-β-hydroxy ketones with high *syn* selectivity (*syn*/*anti* = 16:1) and enantioselectivity (up to 95% ee).

Key words: aldol reaction, amino acids, asymmetric synthesis, chloroacetone, organocatalysis

Optically active *vic*-halohydrins are versatile building blocks and key intermediates for the synthesis of biologically active compounds and natural products such as β-agonists,[1] substituted pyrrolidines,[2] a polychlorosulfolipid,[3] and insect sex pheromones.[4] Thus, the development of effective synthetic methods for the production of these compounds has attracted much attention. The most common procedure for the preparation of optically active *vic*-halohydrins is the ring opening of enantiomerically pure epoxides,[5] but this approach results in a mixture of regioisomers. On the other hand, asymmetric reductions of prochiral α-halo ketones by chiral oxazaborolidine catalysts with borane[1b,c,2,6] and asymmetric hydrogenation using chiral Ru[1a,7] or Rh[7c,8] catalysts have shown excellent enantioselectivity to afford a variety of *vic*-halohydrins. Moreover, organocatalyzed direct asymmetric aldol reaction of chloroacetone with aldehydes has been reported by several groups.[9] We have been interested in an alternate approach, which provides α-chloro-β-hydroxy ketones, for obtaining *vic*-chlorohydrins. The development of an organocatalyst for the asymmetric aldol reaction of chloroacetone with aldehydes is a formidable task, since the reaction can lead to the formation of regio- and diastereomeric isomers and their enantiomers (Scheme 1). Nájera and co-workers reported an L-proline-derivative-catalyzed direct asymmetric aldol reaction of chloroacetone, which afforded *anti*-*vic*-chlorohydrins in high regio-, diastereo-, and enantioselectivity.[9b] Although Gong and co-worker have reported that primary amine catalyzed direct asymmetric aldol reactions of chloroacetone primarily provide *syn* products, the *syn* diastereoselectivity was very low.[9e] Despite recent advances in the area of catalytic asymmetric aldol reactions,[10] high regioselective, *syn*-diastereoselective, and enantioselective synthesis of α-chloro-β-hydroxy ketones remains challenging. In this paper, we report the highly *syn*-selective direct asymmetric aldol reaction of chloroacetone catalyzed by L-*tert*-leucine to afford *syn*-*vic*-harohydrins.

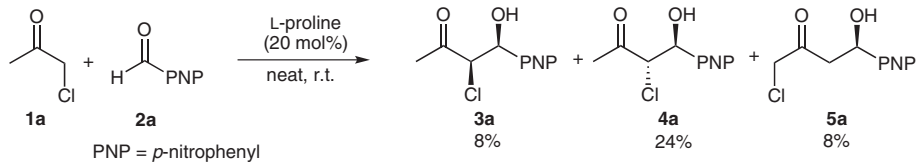
Initially, a test reaction was carried out using L-proline as a catalyst (20 mol%). The reaction of chloroacetone (**1a**) with 4-nitrobenzaldehyde (**2a**) at room temperature gave the *anti*-selective product **4a** in low yield with low regioselectivity (Scheme 2). This *anti* selectivity was in agreement with literature data.[9b] Next, we examined the utility of a series of primary amino acids as catalysts for *syn*-selective aldol reaction of chloroacetone (**1a**). Natural primary amino acids and commercially available unnatural amino acids were used as catalysts in the reaction of chloroacetone (**1a**) with 4-nitrobenzaldehyde (**2a**) at room temperature (Table 1).

L-*tert*-Leucine exhibited much higher efficiency than the other primary amino acids, providing *syn*-aldol product **3a** in high yield (89%) with excellent regioselectivity (>99:1), and high diastereo- (*syn*/*anti* = 7:1), and enantioselectivity (83% ee, Table 1, entry 1). Although L-alanine, L-valine, L-leucine, L-threonine, and L-phenylglycine exhibited excellent regioselectivity, only low reaction yields were obtained (Table 1, entries 2–4, 9, and 11). L-Isoleucine, L-phenylalanine, L-tryptophan, and L-methionine gave the *syn* product **3a** in moderate yields and diastereoselectivities (Table 1, entries 5, 7, 8, and 10). L-Tyrosine and L-penicillamine showed no catalytic activity in this reaction (Table 1, entries 6 and 12). All the primary amino



Scheme 1 Organocatalyzed asymmetric aldol reaction of chloroacetone (**1a**)

SYNLETT 2012, 23, 453–457
Advanced online publication: 19.01.2012
DOI: 10.1055/s-0031-1290316; Art ID: U64911ST



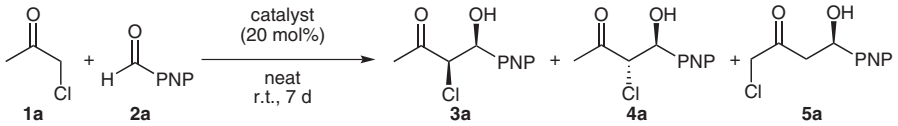
Scheme 2 L-Proline-catalyzed asymmetric aldol reaction of chloroacetone (**1a**)

acids, except L-tyrosine and L-penicillamine, afforded perfect regioselectivity and the desired aldol product **3a** with *syn* selectivity; of these amino acids, L-*tert*-leucine was the most effective catalyst in the aldol reaction with chloroacetone (**1a**).[11] We previously reported that L-*tert*-leucine exhibits high catalytic activity compared to other amino acids due to the stability of an enamine derived from L-*tert*-leucine in the presence of aromatic aldehydes.[12]

Next, to investigate the generality of this reaction, a variety of aromatic aldehydes **2a–i** were used as substrates for the L-*tert*-leucine-catalyzed aldol reaction (Table 2).[11] In all cases, *syn*-*vic*-chlorohydrins **3a–i** were obtained with excellent regioselectivity. When aldehydes with an electron-withdrawing substituent were employed, the reaction proceeded smoothly to afford desired *syn* adducts **3a–g** with high stereoselectivities (Table 2, entries 1–7). In particular, 2-nitrobenzaldehyde afforded the *syn* product **3c** with excellent yield (99%) and enantioselectivity (95% ee, Table 2, entry 3). The reaction of 2-bromobenzaldehyde resulted in the *syn* product **3f** with high diastereoselectivity (*syn*/*anti* = 10:1) (Table 2, entry 6). 2-Trifluoromethylbenzaldehyde gave the product **3g** with high diastereoselectivity (*syn*/*anti* = 7:1) and excellent enantioselectivity (94% ee, Table 2, entry 7). On the other hand, benzaldehyde and 1-naphthaldehyde were less reactive and gave **3h** and **3i** in low yield, but the enantioselectivities remained high (Table 2, entries 8 and 9).

We then examined L-*tert*-leucine-catalyzed asymmetric aldol reactions of 4-nitrobenzaldehyde (**2a**) with α-heteroatom-substituted ketones, 2-butanone, or 4-hydroxy-2-butanone (Table 3).[11] Although hydroxyacetone smoothly underwent the reaction to give *syn* adduct **3j** with excellent regioselectivity, the enantioselectivity was low

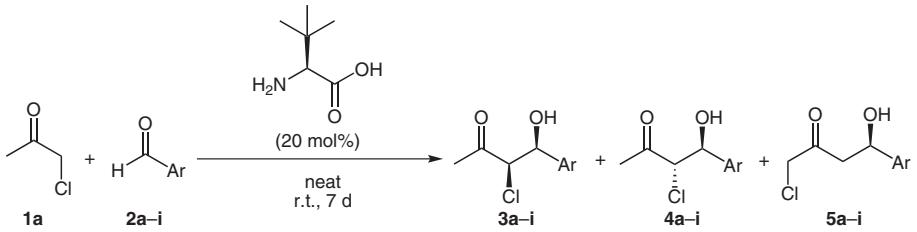
Table 1 L-Amino Acid Catalyzed Asymmetric Aldol Reaction of Chloroacetone (**1a**)



Entry[a]	Catalyst	Yield (%)[b]	(**3a** + **4a**)/**5a**[c]	**3a**/**4a**[c]	ee of **3a** (%)[d]
1	L-*tert*-leucine	89	>99:1	7:1	83
2	L-alanine	7	>99:1	6:1	70
3	L-valine	14	>99:1	5:1	80
4	L-leucine	30	>99:1	7:1	73
5	L-isoleucine	71	>99:1	2:1	38
6	L-tyrosine	trace	n.d.[e]	n.d.[e]	n.d.[e]
7	L-phenylalanine	66	>99:1	4:1	69
8	L-tryptophan	64	>99:1	2:1	68
9	L-threonine	6	>99:1	5:1	n.d.[e]
10	L-methionine	66	>99:1	4:1	72
11	L-phenylglycine	13	>99:1	3:1	18
12	L-penicillamine	trace	n.d.[e]	n.d.[e]	n.d.[e]

[a] The reaction was performed with 4-nitrobenzaldehyde (**2a**, 1 equiv), chloroacetonene (**1a**, 10 equiv), and L-amino acid (0.2 equiv) at r.t. for 7 d.
[b] The combined isolated yield of the diastereomers.
[c] Determined by ^{1}H NMR.
[d] Determined by HPLC.
[e] Not determined.

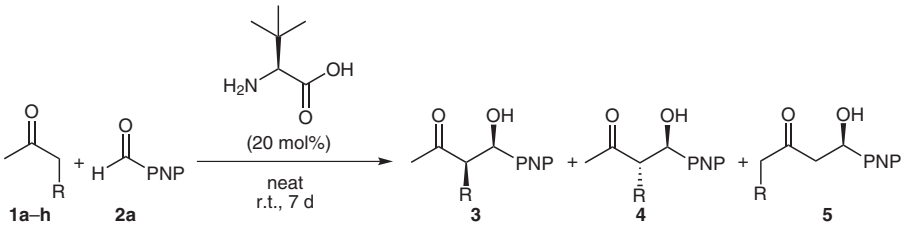
Table 2 L-*tert*-Leucine-Catalyzed Asymmetric Aldol Reaction of Chloroacetone (**1a**)



Entry[a]	Ar	Product (*syn*)	Yield (%)[b]	(**3** + **4**)/**5**[c]	**3**/**4**[c]	ee of **3** (%)[d]
1	4-$O_2NC_6H_4$	**3a**	89	>99:1	7:1	83
2	3-$O_2NC_6H_4$	**3b**	87	>99:1	6:1	87
3	2-$O_2NC_6H_4$	**3c**	99	>99:1	8:1	95
4	4-NCC_6H_4	**3d**	81	>99:1	5:1	80
5	4-$O_2CMeC_6H_4$	**3e**	72	>99:1	7:1	83
6	2-BrC_6H_4	**3f**	84	>99:1	10:1	89
7	2-$F_3CC_6H_4$	**3g**	80	>99:1	7:1	94
8	Ph	**3h**	33	94:6	5:1	87
9	1-naphthyl	**3i**	29	>99:1	16:1	90

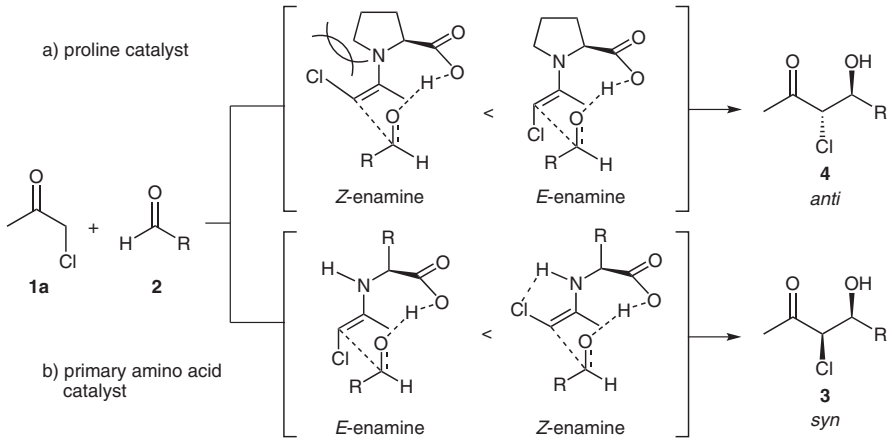
[a] The reaction was performed with arylaldehyde **2** (1 equiv), chloroacetonene (**1a**, 10 equiv), and L-*tert*-leucine (0.2 equiv) at r.t. for 7 d.
[b] The combined isolated yield of the diastereomers.
[c] Determined by ^{1}H NMR.
[d] Determined by HPLC.

Table 3 L-*tert*-Leucine-Catalyzed Asymmetric Aldol Reaction of α-Substituted Acetone **1a–h**



Entry[a]	R	Product (*syn*)	Yield (%)[b]	(**3**+**4**)/**5**[c]	**3**/**4**[c]	ee of **3** (%)[d]
1	Cl	**3a**	89	>99:1	7:1	83
2	OH	**3j**	85	>99:1	2:1	46
3	OMe	**3k**	74	19:1	2:1	60
4[e]	F	**3l**	23	4:1	3:1	85
5	SMe	**3m**	88	14:1	4:1	64
6	Br	**3n**	trace	n.d.[f]	n.d.[f]	n.d.[f]
7	Me	**3o**	83	5:1	2:1	68
8	CH_2OH	**3p**	68	2:6	1:1	n.d.[f]

[a] Unless otherwise stated, the reaction was performed with 4-nitrobenzaldehyde (**2a**, 1 equiv), α-substituted acetone **1** (10 equiv), and L-*tert*-leucine (0.2 equiv) at r.t. for 7 d.
[b] The combined isolated yield of the diastereomers.
[c] Determined by ^{1}H NMR.
[d] Determined by HPLC.
[e] The reaction was performed in the presence of 0.35 equiv of L-*tert*-leucine.
[f] Not determined.



Scheme 3 A proposed mechanism for the organocatalyzed asymmetric aldol reaction of chloroacetone (**1a**)

(Table 3, entry 2). Methoxyacetone and methylthioacetone gave *syn* adducts **3k** and **3m**, respectively, as a major product with good regioselectivities, but the stereoselectivities were moderate (Table 3, entries 3 and 5). The use of fluoroacetone resulted in high enantioselectivity, but the chemical yield was low (Table 3, entry 4). In the case of bromoacetone, only trace amounts of the desired product **3n** were obtained (Table 3, entry 6). Furthermore, the reactions of 2-butanone and 4-hydroxy-2-butanone, which lack a functional group at the α-position, afforded *syn* adducts **3o** and **3p** with low and no diastereoselectivity, respectively (Table 3, entries 7 and 8).

In previous reports, direct asymmetric aldol reaction of α-hydroxy ketones catalyzed by a secondary amine such as L-proline or its derivatives provided *anti*-selective aldol adducts,[13] whereas the reaction catalyzed by a chiral primary amine provided *syn*-selective aldol adducts.[9e,14] According to the model proposed by Barbas,[14a] in the case of a secondary amine, *E*-enamine intermediates predominate because of steric repulsion. As a result, secondary amine catalyzed aldol reactions of α-hydroxy ketone **1b** afford *anti*-aldol adducts **4**. In contrast, *Z*-emanine intermediates predominate in the case of a primary amine because of stabilization of the intermediate due to the formation of an intramolecular hydrogen bond. Therefore, primary amine catalyzed reactions afford *syn*-aldol adducts **3**. For the reaction of chloroacetone (**1a**), we propose a mechanism similar to the case of α-hydroxy ketone (Scheme 3).[15] According to the results in Table 2, a hydrogen bond can be formed in an enamine generated from a primary amine and chloroacetone (**1a**). The asymmetric aldol reaction provides *syn* adducts **3** with high *syn* diastereoselectivities in the presence of appropriate chiral primary amine catalysts. In addition, the results in Table 3 suggest that intramolecular hydrogen bonding is necessary for the reaction to proceed in high regio- and stereoselectivity, and only chloro and methylthio groups at the α-position can effectively bond with the neighboring hydrogen. Thus, sufficient electronegativity and an appropriate atomic radius might be prerequisite for the formation of the intramolecular hydrogen bonds necessary to afford *syn* selectivity.

In summary, we have developed a protocol for the highly stereoselective organocatalyzed synthesis of *vic*-halohydrins. Using L-*tert*-leucine as the catalyst, the aldol reactions of chloroacetone with aromatic aldehydes were accomplished with excellent regioselectivity (>99%) to generate the corresponding α-chloro-β-hydroxy ketones with high *syn* selectivity (up to *syn*/*anti* = 16:1) and high enantioselectivity (up to 95% ee). Thus, L-*tert*-leucine-catalyzed reactions hold promise for the synthesis of optically active *vic*-chlorohydrins. Further applications of this approach to total synthesis are currently under investigation in our laboratory.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

This work was supported in part by a Grant for the High-Tech Research Center Project from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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(11) **Optimized Procedure for the Synthesis of 3a**
To a mixture of chloroacetone (**1a**, 400 μL, 5 mmol) and L-*tert*-leucine (13 mg, 0.1 mmol), 4-nitrobenzaldehyde (**2a**, 76 mg, 0.5 mmol) was added, and the mixture was stirred at r.t. The reaction was monitored by TLC analysis. After 7 d, H_2O was added and extracted with CH_2Cl_2 (3×), dried over $MgSO_4$, and concentrated in vacuo. To determine the regioselectivity and the diastereomeric ratio, the remaining residue was analyzed by ^1H NMR. Moreover, the ee value of the product **3a** was determined by chiral-phase HPLC analysis of the residue. Then, the residue was purified by column chromatography on silica gel in gradient elution with hexane–EtOAc to give a 7:1 inseparable mixture of the desired products **3a** and **4a** (108 mg, 89%).
Analytical Data for Compound 3a
^1H NMR (400 MHz, $CDCl_3$): δ = 8.24–8.20 (m, 2 H), 7.61–7.58 (m, 2 H), 5.47 (t, *J* = 3.6 Hz, 1 H), 4.46 (d, *J* = 3.2 Hz, 1 H), 3.43 (d, *J* = 4.0 Hz, 1 H), 2.40 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.4, 147.6, 146.2, 127.3, 123.5, 72.0, 67.3, 28.3. HPLC: 83% ee [Daicel CHRALCEL OJ-H, hexane–iPrOH (9:1), flow rate 1.0 mL/min, λ = 254 nm]: t_R(major) = 34.7 min; t_R(minor) = 39.1 min.
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