Highly Selective Catalytic Cross-Aldol Reactions of Chloral with Aliphatic Aldehydes

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Abstract: An efficient synthetic method for β-trichloromethyl-β-hydroxy aldehydes is described. Using piperidine or L-prolinamide as the catalyst, direct cross-aldol reactions of chloral with aliphatic aldehydes occur smoothly at room temperature. The cross-aldol condensation products are isolated in high yields (up to 95%), and a moderate to high enantioselectivity (up to 88% ee) is observed in the case of L-prolinamide.

Key words: β-trichloromethyl-β-hydroxy aldehydes, cross-aldol reaction, chloral, piperidine, L-prolinamide

Preparation of α-trichloromethyl alcohols is of great importance because this skeleton is one of the most versatile precursors for the synthesis of various useful products such as α-hydroxy acids,[1] α-amino acids,[2] α-fluoro acids,[3] terminal alkynes,[4] and vinyl dichlorides.[5] Nowadays, synthetic routes to the α-trichloromethyl alcohols from chloral mainly involve the individual aldol reactions with ketones,[6] enamines,[7] or enol ethers,[8] the ene reactions,[9] and nucleophilic addition with terminal alkynes.[10] Among the known α-trichloromethyl alcohols, β-trichloromethyl-β-hydroxy aldehydes are not only important intermediates in the synthesis of biologically important compounds and natural products;[11] they can also be easily transformed to a variety of functional arrays.[11a,12] To the best of our knowledge, however, no report was referred to their synthesis via direct cross-aldol reaction between chloral and aliphatic aldehydes hitherto, though they could be prepared via the ring-opening reaction of 4-trichloromethyl-2-oxetanone.[11a]

Recently, we noticed that the aldol reactions of aldehydes can be efficiently promoted by some organocatalysts, especially by L-proline.[13] However, few work was focused on the direct cross-aldol reactions between different aliphatic aldehydes.[14] First proline-catalyzed aldol reaction between different aldehydes was reported by MacMillan and co-workers, in which the cross-aldol products were afforded in synthetically useful yields and selectivity. In this case, controlling the rate of addition of aliphatic aldehyde was necessarily required. This pioneering work aroused our interest in preparing β-trichloromethyl-β-hydroxy aldehydes by direct catalytic cross-aldol reactions of reactive chloral with other aliphatic aldehydes.

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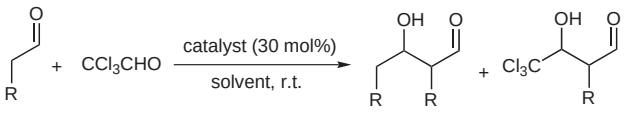
In this paper, the catalytic cross-aldol reactions between chloral and some simple aliphatic aldehydes were studied. We found that the yield of the desired β-trichloromethyl-β-hydroxy aldehydes was not satisfactory when L-proline was used as the catalyst, but could be markedly improved using other catalysts like piperidine or L-prolinamide (Scheme 1).



1 R = Et

2 R = Et
3 R = Me
4 R = *i*-Pr
5 R = Pent

Scheme 1 Cross-aldol reactions of chloral with aliphatic aldehydes

First catalytic aldol reaction was carried out by mixing chloral (148 mg, 1.0 mmol) and butanal (72 mg, 1.0 mmol) in the presence of L-proline (35 mg, 30 mol%) in DMSO at room temperature. Product analysis by GC clearly indicated that the main product was the self-aldol product **1** rather than the cross-adduct **2**[15] under these conditions (Table 1, entry 1). Considering the marked influence of reaction media used,[16] we next examined the reactions in different solvents. The results observed were

Table 1 Effect of Solvents on the Reactions of Chloral with Butanal[a]

Entry	Solvents	Yield of **2** (%)	Molar ratio (**2**:**1**)	dr for **2** *anti*:*syn*[b]	ee (%)[c] *anti*:*syn*
1	DMSO	21	1:3	73:27	53:3
2	DMF	27	1:2	61:29	47:1
3	Dioxane	35	2:3	83:17	75:57
4	THF	52	3:2	85:15	78:42
5	MeCN	56	5:3	64:36	68:53
6	CH_2Cl_2	64	3:1	70:30	83:54
7	Hexane	<5	–	–	–

[a] Butanal (1 mmol) was added to chloral (1 mmol) and L-proline (0.3 mmol) in a solvent (8 mL), and the mixture was stirred at r.t.
[b] Determined by GC.
[c] Determined by chiral GC analysis.

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given in Table 1. Apparently, the yield of **2** was somewhat related to the property of the solvents (entry 2–6). Among the solvents used, dichloromethane was the most suitable to promote cross-aldol condensation reaction (entry 6).

In addition, it was noticed that the structure identities of *anti* and *syn* isomers of **2** could not be determined by ^{1}H NMR spectroscopy as there was no coupling between the H-2 and H-3 signals, thus the isomeric ratio of **2** was determined by GC analysis as described.[18] Under the GC conditions, the *anti* isomer of **2** possessed an earlier retention time than its *syn* isomer. This result was further confirmed by comparing with the corresponding retention times and the coupling constants of other cross-adducts **3**–**5**. The ee value of **2** was determined by chiral GC, and a moderate to high diastereoselectivity and enantioselectivity was observed.

The main problem remained for the above catalytic processes is the competitive self-aldol reaction of butanal, though its proportion can be decreased to some extent by choosing an appropriate solvent. Our further effort was therefore directed to improve the yield of the cross-aldol product **2** by choosing a more efficient catalyst than L-proline. The catalytic role of several well-known catalysts has been assessed below for this purpose.

Sodium hydroxide, a common catalyst for aldol reaction, was first examined to catalyze the cross-aldol reaction in aqueous solution (Table 2, entry 1). However, the predominant products were the self-aldol product **1** and its corresponding α,β-unsaturated aldehyde generated by subsequent dehydration. Only a very little amount of the cross-aldol product **2** was detected. The low yield of **2** might be attributed to the low reactivity of hydrated chloral. For this reason, we turned our attention to the catalytic reactions in organic solvents.

Table 2 Effect of Catalysts on the Reactions of Chloral with Butanal[a]

Entry	Catalyst	Yield (%) of **2**	dr for **2** *anti*:*syn*[b]	ee (%)[c] *anti*:*syn*
1	NaOH	<5	–	–
2	Piperidine	89	69:31	–
3	Glycine	Trace	–	–
4	L-Tyrosine	Trace	–	–
5	L-Alanine	15	77:23	65:29
6	L-Phenylalanine	18	64:36	45:66
7	L-Proline	64	70:30	83:54
8	L-Prolinamide	96	85:15	75:65

[a] The reaction was done by mixing butanal (1 mmol), chloral (1 mmol) and catalyst (0.3 mmol) in CH_2Cl_2 (8 mL), and stirred for 24 h at r.t.
[b] Determined by GC and ^{1}H NMR.
[c] Determined by chiral GC.

As we know, some amino acids and secondary amines can act as efficient catalysts for the aldol reactions of aldehydes in organic solvents.[17] Thus we utilized three other natural amino acids, piperidine and L-prolinamide to catalyze the aldol condensation between chloral and butanal. All the reactions were performed in the presence of 30 mol% of the catalyst in dichloromethane at room temperature, and the yield and *anti*:*syn* ratio of **2** was determined by GC and ^{1}H NMR.

With glycine or L-tyrosine as the catalyst, the conversion was extremely low and only trace amounts of **2** and the self-aldol product **1** were detected by GC (Table 2, entries 3, 4). In the cases of L-alanine or L-phenylalanine, the desired cross-aldol product **2** was generated in low yield with moderate enantioselectivity (Table 2, entries 5, 6). In contrast, **2** was generated in high yield (89%) when piperidine was used as the catalyst, and only about 5% of **1** was detected by GC (Table 2, entry 2). Among the catalysts used, L-prolinamide was identified to be the best as it provided the desired product **2** in 96% yield and a trace amount of self-aldol product **1** (Table 2, entry 8). Moreover, the *anti*:*syn* ratio of **2** determined by ^{1}H NMR was further conformed by GC, and the formation of *anti* isomer was favored in all the cases. These results clearly indicated that cyclic secondary amines were much more efficient catalysts for the above cross-aldol reaction.

Encouraged by these results, we further explored the scope of this cross-aldol reactions with other aliphatic aldehydes containing a-hydrogen using piperidine or L-prolinamide as the catalyst. All the reactions were carried out according to the typical procedures described below.[18] Product analysis showed that the expected cross-aldol products **3**–**5**[19] were afforded in high yields in the respective reactions with propanal, 3-methylbutanal and heptanal in the presence of piperidine as the catalyst (Table 3). In the case of L-prolinamide, the reactions afforded good

Table 3 Direct Cross-Aldol Reactions between Chloral and Aliphatic Aldehydes

Entry	R	Catalyst[a]	Products (yield, %)	dr *anti*:*syn*[b]	ee (%)[c] *anti*:*syn*
1	Me	A	**3** (81)	58:42	–
2	Et	A	**2** (87)	60:40	–
3	*i*-Pro	A	**4** (83)	83:17	–
4	*n*-Pent	A	**5** (76)	71:29	–
5	Me	B	**3** (92)	45:55	88:78
6	Et	B	**2** (95)	85:15	75:65
7	*i*-Pro	B	**4** (35)	80:20	70:65
8	*n*-Pent	B	**5** (81)	69:31	68:40

[a] A: piperidine; B: L-prolinamide.
[b] Determined by ^{1}H NMR.
[c] Determined by chiral GC.

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to excellent yields of the desired cross-aldol products except for 3-methylbutanal. Moreover, the *anti*:*syn* ratios of **3**–**5** could be easily determined by ^{1}H NMR because the *anti* isomers of **3**–**5** showed larger coupling constants J_{2-3} than those of the *syn* isomers. These ratios were well consistent with those determined by GC analysis according to their different retention times, and the formation of *anti* isomer was favored in most cases except for propanal (Table 3, entry 5).

This cross-aldol reaction was also applicable to produce **3**–**5** on a large scale. For example, the reaction of chloral with propanal on a 50 mmol scale affording 8.65 g (81% yield) of 4,4,4-trichloro-3-hydroxy-2-methylbutanal (Table 3, entry 1), a useful intermediate for preparing vinyl dichloride and trisubstituted olefins.[12b]

In conclusion, we reported that piperidine and L-prolinamide were efficient catalysts for the cross-aldol reaction between chloral and aliphatic aldehydes. This catalytic process was suitable for preparing β-trichloromethyl-β-hydroxy aldehydes in high yields under mild conditions, in which aliphatic aldehyde could be added in one portion without the necessity of slow addition. Further studies on improving the reaction enantioselectivity are currently under investigation.

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(15) Compound **2**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.08 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3), 1.82 (dq, *J* = 7.2 Hz, 2 H, CH_2CH_3), 1.93 (dq, *J* = 7.2 Hz, 2 H, CH_2CH_3), 3.03 (t, *J* = 7.2 Hz, 1 H, $CHCH_2$), 3.17 (t, *J* = 7.2 Hz, 1 H, $CHCH_2$), 4.16 (s, 1 H, CHOH), 4.29 (s, 1 H, CHOH), 4.30 (s, 1 H, CHOH), 9.75 (d, *J* = 2.4 Hz, 1 H, CHO), 9.94 (d, *J* = 2.8 Hz, 1 H, CHO). IR (film): ν = 3435, 2968, 2936, 2843, 2769, 1713, 1124, 808 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 55.22 (100), 73.05 (90), 136.69 (95), 191.82 (30), 218.90 (15) $[M]^+$.
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(18) **A Typical Procedure.**
To a suspension of chloral (148 mg, 1.0 mmol) and a catalytic amount of L-prolinamide (34 mg, 0.3 mmol) in CH_2Cl_2 (8 mL) was added freshly distilled butanal (72 mg, 1.0 mmol) in one portion at 0 °C. The reaction mixture was first stirred at 0 °C for 1 h, then for additional 24 h at r.t. The reaction mixture was treated with H_2O (10 mL). Then the solution was extracted with EtOAc (3 × 10 mL). The combined organic layer was dried over anhyd $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using 6:1 (v/v) hexane–EtOAc as eluent, collecting 209 mg of product **2** in 95% yield (R_f = 0.43 for **1**; R_f = 0.31 for **2**). The ee was determined by chiral GC analysis with a DIKMA Chirasil-DEX CB (25 m × 0.25 mm) column. Temperature program: from 70 °C to 170 °C at a rate of 10 °C/min, then isotherm for 20 min at 170 °C; t_R(major) = 16.6 min; t_R(minor) = 17.2 min for *anti* isomer; t_R = 17.5 min, 18.3 min for *syn* isomer. $[\alpha]_D^{20}$ –2.9 (*c* 1.0, $CHCl_3$).
(19) Compound **3**: R_f = 0.21, 6:1 (v/v) hexane–EtOAc. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (d, *J* = 7.6 Hz, 3 H, $CHCH_3$), 1.41 (d, *J* = 7.6 Hz, 3 H, $CHCH_3$), 3.12–3.18 (m, 1 H, $CHCH_3$), 3.19–3.23 (m, 1 H, $CHCH_3$), 4.15 (br s, 1 H, CHOH), 4.23 (s, 1 H, CHOH), 4.75 (d, *J* = 3.2 Hz, 1 H, CHOH), 9.67 (s, 1 H, CHO), 9.95 (d, *J* = 2.8 Hz, 1 H, CHO). IR (film): ν = 3438, 2982, 2941, 2844, 2734, 1722, 1124, 808 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 121.92 (100), 140.79 (43), 204.47 (15) $[M]^+$. $[\alpha]_D^{20}$ +4.9 (*c* 1.0, $CHCl_3$).
Compound **4**: R_f = 0.36, 6:1 (v/v) hexane–EtOAc. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.08, 1.18 [d, *J* = 7.2 Hz, 6 H, $CH(CH_3)_2$], 1.11, 1.12 [d, *J* = 7.2 Hz, 6H, $CH(CH_3)_2$], 2.35–2.40 [m, *J* = 7.2 Hz, 1 H,$CH(CH_3)_2$], 2.52–2.56 [m, *J* = 7.2

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Hz, 1 H, C*H*(CH_3)$_2$], 2.87 (dd, *J* = 6.8, 3.2 Hz, 1 H, C*H*CHO), 2.98 (dd, *J* = 6.0, 2.4 Hz, 1 H, C*H*CHO), 3.04 (br s, 1 H, CHO*H*), 4.37 (d, *J* = 6.8 Hz, 1 H, C*H*OH), 4.82 (d, *J* = 7.2 Hz, 1 H, C*H*OH), 9.87 (d, 1 H, *J* = 2.8 Hz, C*H*O), 9.96 (q, 1 H, *J* = 1.2 Hz, C*H*O). IR (film): ν = 3437, 2953, 2935, 2852, 2734, 1713, 1126, 813 cm^{-1}.

Compound **5**: R_f = 0.49, 6:1 (v/v) hexane–EtOAc. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 6.4 Hz, 3 H, CH_2CH_3), 1.32–1.45 (m, 6 H, $CH_2CH_2CH_2CH_3$), 1.73–1.87 (m, 2 H, $CHCH_2$), 4.16 (s, 1 H, C*H*OH), 4.56 (d, *J* = 2.8 Hz, 1 H, C*H*OH), 4.28 (s, 1 H, CHO*H*), 9.74 (d, *J* = 2.4 Hz, 1 H, C*H*O), 9.94 (d, *J* = 2.8 Hz, 1 H, C*H*O). IR (film): ν = 3436, 2958, 2930, 2862, 2734, 1713, 1128, 816 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 73.08 (100), 121.94 (35), 142.99 (43), 189.79 (25), 260.96 (5) $[M]^+$. $[\alpha]_D^{20}$ –4.0 (*c* 1.0, $CHCl_3$).

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