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Practical Asymmetric Synthesis of β-Trichloromethyl-β-hydroxy Ketones by the Reaction of Chloral or Chloral Hydrate with Chiral Imines

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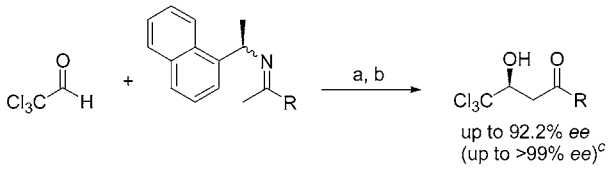
ABSTRACT



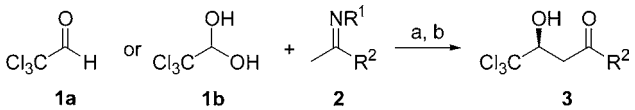
(a) -78 °C to rt, overnight, toluene. (b) 10% HCl, rt, 1 h.

Chloral or its hydrate undergoes the carbon−carbon bond-formation reaction with various optically active imines in the absence of any additive, followed by hydrolysis, to produce the corresponding β-trichloromethyl-β-hydroxy ketones in good yields with high enantioselectivities. In addition, the products with higher ee values were obtained by a simple recrystallization process.

The asymmetric syntheses of α-trichloromethyl alcohols are of great importance in organic synthesis, because this skeleton is one of the most versatile precursors for the synthesis of various enantiopure organic molecules such as α-hydroxy,[1] α-amino,[2] and α-fluoro acids[3] and monosubstituted oxiranes.[4] In particular, optically active β-trichloromethyl-β-hydroxy phenyl ketone (4,4,4-trichloro-3-hydroxy-1-phenyl-1-butanone) is a promising chiral building block for the asymmetric synthesis of enalapril, which is an angiotensin-converting enzyme (ACE) inhibitor.[5,6] However, to the best of our knowledge, there are only a few reports on the asymmetric synthesis of β-trichloromethyl-β-hydroxy ketones, which completely rely on the reaction of enantiopure β-trichloromethyl-β-propiolactone.[5,7,8]

We describe here a reaction of chloral with various chiral imines[9] in the absence of any additives, which provides the first practical, simple, and asymmetric entry to β-trichloro-β-hydroxy ketones (Scheme 1).

Scheme 1. Asymmetric Synthesis of β-Trichloromethyl-β-hydroxy Ketones[a]



[a] (a) Various conditions. (b) 10% HCl, rt, 1 h.

The reaction of **1a** with an equimolar amount of the imine **2a**, derived from acetophenone and (*R*)-1-phenylethylamine, in hexane at room temperature for 1 h, followed by

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Table 1. Screening of the Reaction Conditions[a]

entry	R^1	solvent	temp (°C)	time (h)	yield (%)[b]	(*S*:*R*)[c]	ee[c]
1	(*R*)-1-PhCH(Me)−	hexane	rt	1	79	80.1:19.9	60.2
2	(*R*)-1-PhCH(Me)−	hexane	0	3	83	86.9:13.1	73.7
3	(*R*)-1-PhCH(Me)−	hexane	−78 to rt	overnight	72	85.2:14.8	70.4
4	(*R*)-1-PhCH(Me)−	CH_2Cl_2	0	3	74	76.1:23.9	52.2
5	(*R*)-1-PhCH(Me)−	CH_2Cl_2	−78 to rt	overnight	59	82.8:17.2	65.6
6	(*R*)-1-PhCH(Me)−	Et_2O	0	3	48	78.2:21.8	56.4
7	(*R*)-1-PhCH(Me)−	Et_2O	−78 to rt	overnight	53	87.3:12.7	74.6
8	(*R*)-1-PhCH(Me)−	toluene	0	3	79	84.8:15.2	69.6
9	(*R*)-1-PhCH(Me)−	toluene	−78 to rt	overnight	64	90.2:9.8	80.4
10	(*R*)-1-(*c*-Hex)CH(Me)−	toluene	−78 to rt	overnight	36	67.7:32.3	35.4
11	(*R*)-1-(1-Nap)CH(Me)−	toluene	−78 to rt	overnight	77	96.1:3.9	92.2

[a] All reactions were carried out with chloral **1a** (1 mmol) and chiral imine **2** (1 mmol) derived from acetophenone (R^2 = Ph) in solvent (4 mL). [b] Yields of isolated products. [c] Determined by HPLC analysis with a DAICEL CHIRACEL OD column (hexane/*i*-PrOH = 95/5).

hydrolysis, gave 4,4,4-trichloro-3-hydroxy-1-phenyl-1-butanone (**3a**) in 79% yield with 60.2% ee (Table 1, entry 1). The results of these reactions under various conditions are summarized in Table 1.

To improve the enantioselectivity, the reactions were examined at lower temperatures such as 0 °C or −78 °C to room temperature. The product **3a** was produced with a higher enantioselectivity when the reactions were performed from −78 °C to room temperature overnight, except for the use of hexane as the solvent (entries 2−9). Among the examined solvents such as hexane, CH_2Cl_2, Et_2O, and toluene, employing toluene gave **3a** in 64% yield with the highest selectivity (entry 9). The treatment of **1a** with an imine **2b**, derived from (*R*)-1-cyclohexylethylamine, resulted in a significantly decreased yield as well as selectivity (entry 10). On the contrary, when the reaction of the imine **2c** with the (*R*)-1-(1-naphthyl)ethyl group was carried out, the product **3a** was obtained in 77% yield with the highest enantioselectivity (*S*:*R* = 96.1:3.9), together with the recovery of (*R*)-1-(1-naphthyl)ethylamine (76%) (entry 11).

Table 2 summarizes the reactions of chloral **1a** or its hydrate **1b** with various chiral imines **2** derived from (*R*)-1-(1-naphthyl)ethylamine under the optimized conditions.

Chiral imines **2d**−**f**, prepared from aromatic methyl ketone derivatives with 4-chloro- or 4-methoxy-substituted phenyl groups as well as a thienyl one, smoothly underwent a reaction with **1a** to produce the corresponding *β*-trichloromethyl-*β*-hydroxy ketones **3b**−**f** in good yields with high enantioselectivities (entries 2−4). The reaction of chiral imines **2g**,**h** carrying a *c*-hexyl and *tert*-butyl group, respectively, also gave the corresponding aliphatic ketones **3e**,**f** in 56 and 40% yields with good enantioselectivities, respectively (entries 5 and 6).

Table 2. Enantioselective Synthesis of Various *β*-Trichloromethyl-*β*-hydroxy Ketones **3**[a]

entry	**1**	imine	R^2	product	yield (%)[b]	(*S*:*R*)[c]	ee[c]
1	**1a**	**2c**	Ph	**3a**	77	96.1:3.9	92.2
2	**1a**	**2d**	4-ClC_6H_4	**3b**	76	94.8:5.2	89.6
3	**1a**	**2e**	4-$MeOC_6H_4$	**3c**	51	92.4:7.6	84.8
4	**1a**	**2f**	2-thienyl	**3d**	45	90.3:9.7	80.6
5	**1a**	**2g**	*c*-Hex	**3e**	56	94.0:6.0[d]	88.0[d]
6	**1a**	**2h**	*t*-Bu	**3f**	40	90.4:9.6[d]	80.8[d]
7	**1b**	**2c**	Ph	**3a**	80	93.9:6.1	87.8
8	**1b**	**2d**	4-ClC_6H_4	**3b**	60	92.3:7.7	84.6
9	**1b**	**2e**	4-$MeOC_6H_4$	**3c**	35	90.9:9.1	81.8
10	**1b**	**2g**	*c*-Hex	**3e**	34	95.0:5.0[d]	90.0[d]

[a] All reactions were carried out with chloral **1a** (1 mmol) or its hydrate **1b** (1 mmol) and chiral imine **2** (1 mmol) derived from (*R*)-1-(1-naphthyl)ethylamine in toluene (4 mL) from −78 °C to room temperature overnight. [b] Yields of isolated products. [c] Determined by HPLC analysis with a DAICEL CHIRACEL OD column (hexane/*i*-PrOH = 95/5). [d] After benzoylation of **3**, the isomer ratios were determined by HPLC analysis with a DAICEL CHIRACEL OD column (hexane/*i*-PrOH = 95/5).

The treatment of chloral hydrate **1b** in place of chloral **1a** with imines **2c**−**e**,**g** gave moderate to good yields (34−80%) of ketones **3a**−**c**,**e** with good enantioselectivities (entries 7−10). Compared with the reaction of chloral, most of the enantioselectivities of the products were slightly lower.

The absolute configurations of **3a**,**c** can be assigned as (*S*)- by comparison with the reported values of the optical rotations.[5] The configurations of the other products **3b**,**d**−**f** should be the same, since their optical rotations equally showed a negative value. The reaction may proceed via the enamines, which are tautomers of the imines.[10] However, the mechanism for the diastereoselective carbon−carbon bond-forming reaction leading to the enantioselective formation of **3** is not clear at this time.

The reaction of acetaldehyde **4** with chiral imine **2a** did not proceed at all, and acetophenone was recovered in

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(6) For another recent example, see. Huffman, M. A.; Reider, P. J. *Tetrahedron Lett.* **1999**, *40*, 831.

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Table 3. Recrystallization of the Obtained β-Trichloromethyl-β-hydroxy Ketones **3**

entry	R^2	**3**	solvent (mL/g of **3**)	ee[a] of parent compd	ee[a] of crystal	ee[a] of mother liquor
1	Ph	**3a**	hexane (60)	91.6	>**99.9** (61)[b]	66.8 (15)[b]
2	4-$MeOC_6H_4$	**3c**	hexane (120)	84.8	85.3 (61)[b]	87.4 (6)[b]
3	4-$MeOC_6H_4$	**3c**	hexane:AcOEt = 50/3 (90)	83.2	**98.6** (55)[b]	55.0 (25)[b]
4	4-ClC_6H_4	**3b**	hexane:AcOEt = 50/3 (90)	92.6	4.6 (3)[b]	**98.2** (70)[b]
5	2-thienyl	**3d**	hexane:AcOEt = 50/3 (90)	77.0	70.2 (44)[b]	**95.4** (54)[b]
6	*c*-Hex	**3e**	hexane (90)	86.2[c]	85.6[c] (5)[b]	86.2[c] (83)[b]

[a] Determined by HPLC analysis with a DAICEL CHIRACEL OD column (hexane/*i*-PrOH = 95/5). [b] Values in parentheses stand for the recovery of **3**. [c] After benzoylation of **3e**, the isomer ratio was determined by HPLC analysis with a DAICEL CHIRACEL OD column (hexane/*i*-PrOH = 95/5).

quantitative yield. Furthermore, the treatment of freshly prepared ethyl glyoxylate **5** or commercially available methyl 2-hydroxy-2-methoxyacetate (**6**) with **2c** gave ethyl 1-hydroxy-3-oxo-4-phenylpropanate (**7a**) in 36% yield with only 9.8% ee or methyl 1-hydroxy-3-oxo-4-phenylpropanate (**7b**) in 44% yield with only 1.6% ee.

To obtain the enantioenriched title compounds **3**, simple recrystallization was carried out as shown in Table 3. The crystal of **3a** with >99.9% ee was obtained in 61% yield by simple recrystallization with hexane (60 mL/g of **3a**). The highest ee of **3c** was also recovered in 55% yield as the crystal using the mixed solvents (hexane/AcOEt = 50/3) (90 mL/g) (entry 5). However, the procedure using hexane/AcOEt = 50/3 (90 mL/g) gave **3b**,**d** with the best optical purities and recovery from the mother liquor (entries 4 and 6).[11]

In conclusion, the reaction of chloral **1a** or its hydrate **1b** with various chiral imines **2** proceeded smoothly in the absence of any additives to give the corresponding β-trichloromethyl-β-hydroxy ketones **3** in good yields with high enantioselectivity. Furthermore, the ee values of these products can be improved by a simple recrystallization method. We believe that this reaction provides the first simple and practical route to the enantioenriched β-trichloromethyl-β-hydroxy ketones. Further studies on the catalytic version of this reaction are now in progress.

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Supporting Information Available: Experimental details and characterization data for **2a**−**h**, **3a**−**f**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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