$LiClO_4$-Induced Mannich Reaction − Diastereo- and Enantioselective Synthesis of β-Amino Ketones by Addition of Enamines, Imines or Silylenolethers to Aldehydes and Dialkyltrimethylsilylamines☆

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$LiClO_4$-mediated one-pot reactions of aldehydes with (trimethylsilyl)dialkylamines **2**, **5** or **19** and C nucleophiles such as enamines **3**, **10** and **12**, imines **7** and **11** or (trimethylsilyl)-enol ethers **8** and **9** afforded the corresponding aminoalkylation products in high yields. Whereas by using aromatic aldehydes, such as benzaldehyde, pyridine-3-carbaldehyde or thiophene-2-carbaldehyde, high diasteroselectivity was achieved, the aminoalkylation of aliphatic aldehydes such as isobutyraldehyde and pivalaldehyde lacked diastereoselectivity. Enantioselective Mannich reactions using chiral enamines **22** and **23** are reported.

The Mannich reaction is the most important multicomponent reaction in organic synthesis and biosynthesis.[1][2][3][4][5] The classical Mannich reaction is an aminoalkylation of aldehydes involving three components: (1) ammonia or a primary or secondary amine; (2) a non-enolizable aldehyde, usually formaldehyde; and (3) an acidic CH-bonding site. In the course of this reaction, the C−O double bond is replaced by a carbon−nitrogen and a carbon−carbon single bond. Although β-aminoketones (Mannich bases) can be obtained in good yield, the classical reaction has limited applications because of its restriction to non-enolizable aldehydes and its lack of diastereo- and regioselectivity.[1] Many attempts have been made to extend this reaction to enolizable aldehydes and to increase selectivity.[1][2][3][4][5][6] In this context, Mannich products have been synthesized from enolizable aldehydes in good to excellent yields, by the addition of nucleophiles to benzotriazole derivatives[7], as well as by the three-component addition of lithium enolates to (trimethylsilyl)dialkyl amines and aldehydes in concentrated ethereal $LiClO_4$ solutions.[8]

More recently, Risch et al. observed excellent diastereo- and regioselectivity with the addition of imines (Schiff bases) or enamines to preformed iminium salts.[9] Although this modification has broadened the scope of the Mannich reaction, the hygroscopicity of iminium salts and their susceptibility to hydrolysis (with the exception of Eschenmoser's salt, $H_2C{=}NMe_2^+\ I^-$ and the corresponding chloride) make the development of an alternative method desirable. In this paper, we describe a diastereo-and enantioselective one-pot three-component synthesis of β-amino ketones by the addition of enamines, imines or trimethylsilylenolethers to aldehydes (enolizable and non-enolizable) and (trimethylsilyl)dialkyl amines in concentrated ethereal $LiClO_4$ solutions.

Presumably due to the Lewis acidity of lithium ions and the high polarity of the medium, the reaction of the aldehyde and the (trimethylsilyl)dialkyl amine leads to an iminium ion as the intermediate,[8][10] which is trapped in situ by the nucleophilic imines, enamines or (trimethylsilyl)enolethers. Because of the mild reaction conditions, no undesired byproducts are formed, and the tedious preparation of preformed iminium salts is not necessary.

Results and Discussion

Although a solution of benzaldehyde **1**, amine **2** and enamine **3** in diethyl ether remains unchanged after 5 h at room temperature, the reaction in 5 M ethereal $LiClO_4$ solution, followed by hydrolysis, leads to the formation of pure crystalline *anti* amino ketone **4**, within 1.5 h, in 91% yield. No *syn* product could be detected in the crude material by the ^{1}H-NMR spectra.

Within the limits of our study, no significant differences are observed with regard to the diastereoselectivity and the yield of the reaction when imines or trimethylsilylenolethers are used instead of enamines. Addition of enamine **3**, imine **7** or silylenolether **8** to aldehyde **1** and amine **5** in 5 M $LiClO_4$/diethyl ether solution all lead to the formation of *anti* product **6** in 78−79% yield. However, the reaction of enamines proceeds more rapidly than the reaction of imines or silylenolethers.

Similarly, the addition of **9**−**12** to a solution of an aldehyde and a trimethylsilylamine in 5 M $LiClO_4$/diethyl ether

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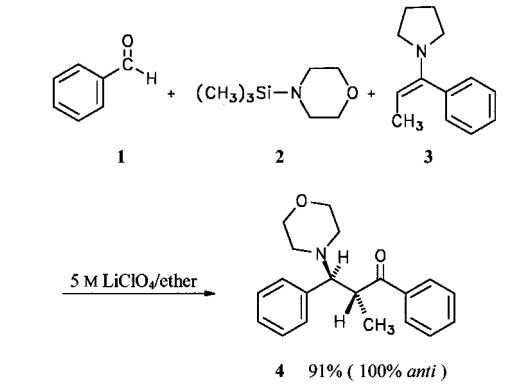
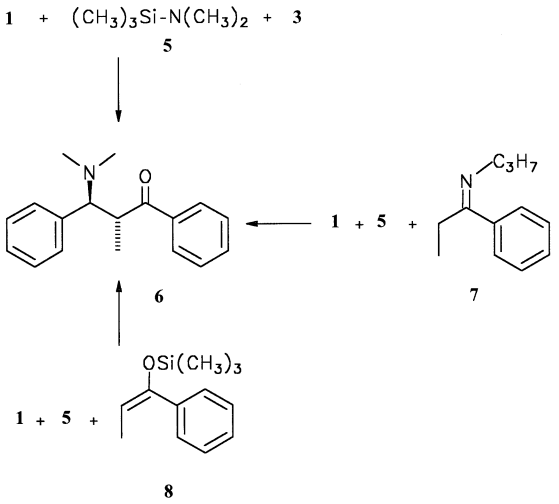
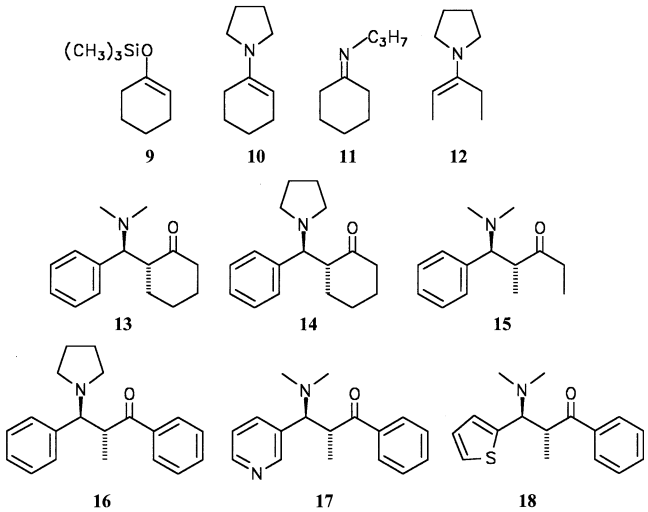
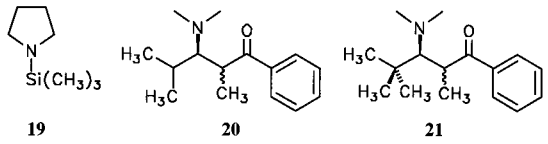






leads to the formation of the corresponding *anti* β-aminoketones **13**–**18** in high yields, with high diastereoselectivity.

This protocol can also be applied to aliphatic aldehydes such as isobutyraldehyde and pivalaldehyde, but the stereochemical outcome of the aminoalkylation reaction is disappointing. In both cases, the reaction with amine **5** and enamine **3** leads only to a 1:1 mixture of *anti*/*syn* isomers **20** and **21** after hydrolysis.



In Table 1, the β-amino ketones prepared in this investigation are listed.

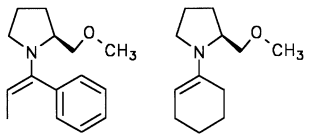
Table 1. Diastereoselective β-aminoalkylation of aldehydes

Aldehyde	Amine	Nucleophile	Product	Yield (%)	de (%)
1	**2**	**3**	**4**	90	100
1	**5**	**3**	**6**	93	100
1	**5**	**7**	**6**	84	100
1	**5**	**8**	**6**	78	100
1	**5**	**10**	**13**	89	90
1	**5**	**11**	**13**	81	100
1	**5**	**9**	**13**	76	100
1	**5**	**12**	**15**	90	90
1	**19**	**3**	**16**	89	100
1	**19**	**11**	**14**	80	100
$(CH_3)_2CHCHO$	**5**	**3**	**20**	56	0
$(CH_3)_3CCHO$	**5**	**3**	**21**	51	0
Pyridine-3-carbaldehyde	**5**	**3**	**17**	91	100
Thiophene-2-carbaldehyde	**5**	**3**	**18**	90	100

The stereochemical assignment of **6** is based on the comparison to an authentic sample.[9b] The *anti* configuration of **13**–**15** was unambiguously assigned by the comparison to those reported in the literature.[8][9c][11]

The stereochemical outcome of the reaction can be explained by a model described by Seebach and Golinski.[8][12] Based on this model, the transition state of the reaction is stabilized by electrostatic forces, and is analogous to the transition states in the reaction of lithium, sodium, magnesium and boron enolates of cyclohexanone with benzaldehyde.

In contrast to the well studied enantioselective aldol reaction, there is a lack of practical methods for the enantioselective synthesis of corresponding β-aminoketones. Only recently have a few examples of enantioselective Mannich reactions appeared in the literature.[9a][13] To test optical induction in this reaction, we studied the addition of chiral SMP-enamines **22** and **23** to benzaldehyde and thiophene-2-carbaldehyde in the presence of amine **5**. The results are summarized in Table 2. The range of reaction temperatures is limited by the solubility of $LiClO_4$ in ether. At −36°C and using 2.5 M $LiClO_4$, an enantiomeric excess of up to 86% can be achieved, but the chemical yield is unsatisfactory (20%). At higher $LiClO_4$ concentration (4.2 M) and higher temperature (−15°C), the chemical yield increases (55%) but the enantioselectivity decreases dramatically (22% ee).[14]



22 **23**

Table 2. Enantioselective β-aminoalkylation of aldehydes using enamines **22** and **23**

Product	M $LiClO_4$	Time (h)	Temp. (°C)	Yield (%)	ee (%)
6	2.5	8	−36	20	86
6	4.2	45	−15	55	22
13	4.2	16	−36	25	44
18	4.2	14	−36	15	86

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Experimental Section

Elemental Analysis: Carlo Erba Model 1104. − IR: Bruker IFS 25. − ^1H and ^{13}C NMR: Brucker AM400 and AC200, respectively. − MS: Varian MAT 311A or Varian MAT 111. $LiClO_4$ (Fluka) was dried at 140°C for 24 h at 10^{-2} Torr. − The following compounds were either purchased, or synthesized according to literature procedures: *N*-Trimethylsilyldimethylamine (Fluka), (*S*)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanole (98%, Aldrich), *N*-Trimethylsilylpyrrolidine and *N*-Trimethylsilylmorpholine,[15] enamines **3**, **10** and **12**,[16] imines **7** and **11**,[17] silylenolethers **8** and **9**,[18] and chiral enamines **22** and **23**[13a]. − All reactions were carried out under argon and anhydrous conditions.

General Procedure for the Preparation of β-Aminoketones by the Addition of Enamines: The aldehyde (2 mmol) and 4 ml of 5 M $LiClO_4$ in diethyl ether were placed in a 50 ml flask and stirred for 5 min. Dialkyltrimethylsilylamine (3 mmol) was then added via syringe. After 20 min, the enamine (2 mmol) was added. After stirring for 1.5 h at room temperature, water (30 ml) and diethyl ether (30 ml) were added. The organic phase was separated and hydrolysed with 3 N HCl (10 ml) for 15 min. After hydrolysis, the aqueous phase was separated, washed with diethyl ether (2 × 30 ml), and treated with dilute NH_3 solution (25 ml; $NH_3:H_2O$ = 1:4). This solution was then extracted with diethyl ether (2 × 50 ml). The organic phase was dried with $MgSO_4$, and the solvent was removed by means of a rotary evaporator.

General Procedure for the Preparation of β-Aminoketones by the Addition of Imines: The above procedure for enamines was used with the following modifications: The reaction mixture was stirred for 3 h at room temperature, and before hydrolysis with 3 N HCl, the organic phase was stirred with a 2 N acetic acid solution for 2 h.

General Procedure for the Preparation of β-Aminoketones by the Addition of Silylenolethers: The above procedure for enamines was used with the following modifications. The reaction mixture stirred for 6 h at room temperature. After the initial work-up with water/diethyl ether, the organic phase was treated with 0.2 N HCl. The aqueous phase was then neutralised with 2 N NaOH and extracted with diethyl ether. The product was obtained after drying, and removal of the solvent.

2-Benzoyl-1-morpholino-1-phenylpropane (**4**): M.p. 146−148°C (ref.[19] 149−150 °C).

2-Benzoyl-1-dimethylamino-1-phenylpropane (**6**): M.p. 152−153°C. − IR (KBr): $\tilde{\nu}$ = 1675 cm^{-1} (C=O). − ^1H NMR ($CDCl_3$): δ = 0.92 (d, 3 H), 2.06 (s, 6 H), 4.02 (d, 1 H), 4.21 (m, 1 H), 7.21 (d, 2 H), 7.28−7.65 (m, 6 H), 8.06 (d, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 15.72 (CH_3), 41.92 (CH_3), 42.09 (CH), 72.44 (CH), 127.29 (CH), 127.89 (CH), 128.09 (CH), 128.55 (C), 129.45 (CH), 132.49 (CH), 135.41 (CH), 137.97 (C), 203.72 (C=O).

2-[α-(Dimethylamino)benzyl]cyclohexanone (**13**): M.p. 129−130°C (ref.[20] 130.5−131.5°C).

2-(α-Pyrrolidinobenzyl)cyclohexanone (**14**): M.p. 65−66°C (ref.[21] 65−66°C).

2-[α-(N,N-Dimethylamino)benzyl]pentan-3-one (**15**): IR (neat): $\tilde{\nu}$ = 1708 cm^{-1} (C=O). − ^1H NMR ($CDCI_3$): δ = 0.85 (d, 3 H), 1.11 (m, 3 H), 2.08 (s, 6 H), 2.57 (m, 2 H), 3.24 (m, 1 H), 3.72 (d, 1 H), 7.12 (d, 2 H), 7.28-7.39 (m, 3 H).

2-Benzoyl-1-phenyl-1-pyrrolidinopropane (**16**): IR (KBr): $\tilde{\nu}$ = 1670 cm^{-1} (C=O). − ^1H NMR($CDC1_3$) δ = 0.92 (d, 3 H), 1.57 (m, 4 H), 2.37 (m, 4 H), 3.96 (d, 1 H), 4.12 (m, 1 H), 7.19−7.65 (m, 8 H), 8.04 (d, 2 H). − ^{13}C NMR ($CDC1_3$): δ = 15.08 (CH_3), 23.16 (CH_2), 44.71 (CH), 51.15 (CH_2), 70.07 (CH), 127.22 (CH), 127.95 (CH), 128.16 (CH). 128.48 (CH), 129.65 (CH), 132.53 (CH), 137.84 (C), 138.64 (C). 203.39 (C=O). − $C_{20}H_{23}NO$: calcd. 293.17796; found 293.18146 (HRMS).

2-Benzoyl-dimethylamino-1-(3-pyrridyl)propane (**17**): M.p. l40−142°C. − IR (KBr): $\tilde{\nu}$ = 1674 cm^{-1} (C=O). − ^1H NMR ($CDCl_3$): δ = 0.92 (d, 3 H), 2.08 (s, 6 H), 4.05 (d, 1 H), 4.21 (m, 1 H), 7.32 (m, 1 H), 7.48−7.62 (m, 4 H). 8.05 (d, 2 H), 8.49 (s, 1 H). 8.55 (d, 1 H). − ^{13}C NMR ($CDC1_3$): δ = 15.47 (CH_3), 41.61 (CH), 41.76 (CH_3), 70.10 (CH), 122.94 (CH), 128.07 (CH), 128.65 (CH), 130.80 (C), 132.73 (CH), 136.52 (CH), 137.61 (C), 148.86 (CH), 150.68(CH), 202.92 (C=O). − MS (70 ev): *m/z* (%) = 268 (6), 135 (100), 119 (35), 105 (65). − $C_{17}H_{20}N_2O$: calcd. 268.1576; found 268.1588 (HRMS). − $C_{17}H_{20}N_2O$ (268.2): calcd. C 76.08, H 7.51, N 10.43; found C 76.27, H 7.46, N 10.40.

2-Benzoyl-dimethylamino-1-(2-thienyl)propane (**18**): M.p. 108−110°C. − IR (KBr): $\tilde{\nu}$ = 1673 cm^{-1} (C=O). − ^1H NMR ($CDCl_3$,): δ = 0.92 (d, 3 H), 2.03 (s, 6 H), 3.98 (m, 1 H), 4.22 (d, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 16.10 (CH_3), 41.60 (CH_3), 43.95 (CH), 67.87 (CH), 124.40 (CH),126.33 (CH), 126.96 (CH), 128.12 (CH), 128.60 (CH), 132.62 (CH), 137.73 (C), 138.40 (CH), 203.25 (C=O). − MS (70 ev): *m/z* (%) = 273 (4), 228 (14), 166 (100), 140 (100), 105 (93). − $C_{16}H_{19}NOS$: calcd. 273.1187; found 273.1194 (HRMS). − $C_{16}H_{19}NOS$ (273.1): calcd. C 70.29, H 7.00, N 5.12; found C 70.52, H 6.98, N 5.06.

2-Benzoyl-3-dimethylamino-4-methylpentane (**20**): Two diastereoisomers in ratio of 1:1. − IR (neat): $\tilde{\nu}$ = 1682 cm^{-1} (C=O). − ^1H NMR ($CDCl_3$): δ = 0.88 (d, 3 H), 0.90 (d, H), 0.98 (d, 3 H), 1.00 (d, 3 H), 1.17 (d, 3 H), 1.22 (d, H), 1.91 (m, 1 H), 1.98 (m, 1 H), 2.21 (s, 6 H), 2.32 (s, 6 H), 2.88 (dd, 1 H), 3.02 (dd, 1 H), 3.70 (m, 1 H), 3.80 (m, 1 H), 7.42−7.59 (m, 2 × 3 H), 7.88−8.00 (m, 2 × 2 H). − MS (70 ev): *m/z* (%) = 190 (15), 105 (100), 100 (100), 43 (100).

4-Benzoyl-2,2-dimethyl-3-dimethylaminopentane (**21**)[6]: two diastereoisomers in ratio of 1:1. − ^1H NMR ($CDCl_3$): δ = 0.75 (s, 9 H), 0.95 (s, 9 H), 1.10 (d, 3 H), 1.20 (d, 3 H), 2.20 (s, 6 H), 2.60 (s, 6 H), 2.85 (d, 1 H), 2.95 (d, 1 H), 3.75−3.90 (m, 2 H), 7.30−7.50 (m, 6 H), 7.80 (d, 2 H), 7.90 (d, 2 H).

[☆] This paper is dedicated to the memory of Professor *William G. Dauben*.

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