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Catalytic aldol-transfer reactions with Al-alkoxide trapping

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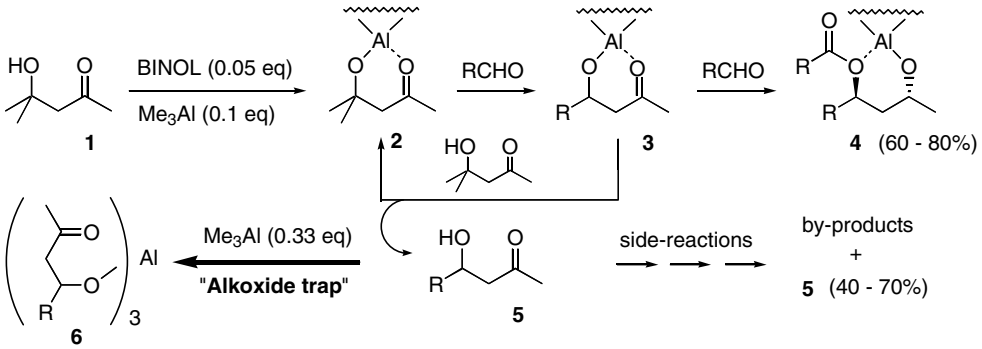
Abstract—Al-BINOL catalyzed aldol-transfer reactions of aldehydes with diacetonealcohol conducted with Al-alkoxide trapping gave aldol adducts in good yields. The best yields were obtained with electron-rich aromatic aldehydes (e.g., 83% yield with 3,4,5-trimethoxybenzaldehyde).

Nucleophile-transfer reactions have been shown to offer great potential for organic transformations.[1–9] They are analogous to hydride-transfer reactions found by pioneers Meerwein, Ponndorf, Verley, and Oppennauer.[1] During recent years, several publications considering new transfer reactions of nucleophiles other than hydride have appeared. Inoue et al. have described the use of Al- and Ti-based promotors (stoichiometric)[2] and La-alkoxides (catalytic)[3] for cyanohydrin transfer reactions. Maruoka et al. have described an alkynyl-transfer reaction mediated by an Al-*o*,*o*′-biphenyldioxy species[4] and Zr-alkoxides.[5] Allyl and homopropargyl-transfer reactions have been reported by Nokami et al. and by Loh et al.[6] (including an enantioselective allyl-transfer by Loh et al.[6d–6g]). Aldol-transfer reactions catalyzed by Al-BINOL (Scheme 1) were discovered by Nevalainen et al.[7] In this reaction aldol **1** is converted through **2** and **3** to a diolmonoester **4** or aldol **5**. Later Schneider et al. reported[8] the related Zr-BINOL catalyzed process (including enantioselective[8c] formation of analogs of **4**). Chandrasekhar et al. described the first L-proline catalyzed enantioselective aldol-transfer reaction for aldols **5**.[9]

Tandem reactions leading to **4** (Scheme 1) give better yields than those of **5**. This indicates that intermediate **3** is formed. However, the newly formed **5** (via **3**+**1**→**2**+**5**) may undergo side reactions, which lower the isolated yield of **5** (several by-products detected by TLC). In tandem reactions intermediate **3** is 'trapped' by the conversion of **3** to stable **4**. This is posing a question: Can the newly formed **5** be trapped so that it survives until the isolation step? For example, if 0.33 equiv extra trimethylaluminum is used, all **5** would



Scheme 1. Catalytic aldol-transfer reactions of diacetonealcohol **1** with RCHO.[7]

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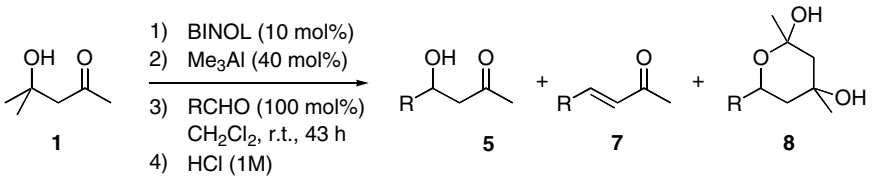

Scheme 2. Aldol-transfer reactions conducted with alkoxide trapping.

Table 1. Aldol-transfer reactions of aldehydes RCHO with diacetonealcohol **1**[a]

Entry	R	Derivative	Yield of **5** (%)[b]	Yield of **7** (%)[b]	Yield of **8** (%)[b]
1	C_6H_5	**a**	29	10	3
2	*p*-Cl–C_6H_4	**b**	18	33	5
3	*p*-NO_2–C_6H_4	**c**	38	—	12
4	*p*-CH_3O–C_6H_4	**d**	63	—	—
5	3-CH_3O,4-C_2H_5O–C_6H_3	**e**	84	—	—
6	3,4,5-$(CH_3O)_3C_6H_2$	**f**	83	—	—
7	1-Naphthyl	**g**	20	—	—
8	Pyridine-2	**h**	74	—	—
9	Furan-2	**i**	30	—	—
10	Thiophene-2	**j**	40	—	—

[a] See Scheme 2. The products were characterized by spectral data.
[b] Isolated yields (relative to RCHO) after flash chromatography.

be converted to **6** (Scheme 1). Converting BINOL (10 mol %) to its aluminum chelate would require $2/3 \times 10$ mol % = 0.06 equiv trimethylaluminum. Therefore, the total amount of trimethylaluminum needed is 0.4 equiv or 40 mol %. In order to test this trapping concept 10 (hetero)aromatic aldehydes were reacted with **1** and 40 mol % trimethylaluminum (Scheme 2) to obtain **5**. In three cases by-products **7** and **8** were also isolated. The results are summarized in Table 1.

Yields of reactions of chloro-, nitro-, and alkoxy-substituted benzaldehydes (Table 1, entries 1–6) indicate that, in contrast to that observed earlier,[7] the parent benzaldehyde is now a worse substrate. For *p*-chlorobenzaldehyde the aldol-transfer step occurs modestly but the yield is low because of water elimination (enone **7b** isolated in 33% yield, Table 1, entry 2). A small amount (10%) of enone **7a** was obtained also with benzaldehyde. With *p*-nitrobenzaldehyde the yield of **5c** was lowered because a second aldol-transfer reaction took place converting **3c** to a novel compound **8c** (Scheme 2) characterized by ^{1}H NMR, ^{13}C NMR, MS (FAB), and HRMS methods.[10] From the crude of **5a** and **5b** derivatives **8a** and **8b** were also found but in very low abundance (3% and 5%). The formation of **8** was expected, because ketones are known to undergo aldol-transfer reactions, although in very poor yields. For example, acetophenone reacted with **1** (instead of RCHO, conditions as depicted in Scheme 1), to give 2-hydroxy-2-phenyl-4-pentanone in 6% yield.[7a] Furthermore, the purification of **5a–c** was hampered by the formation of **8a–c**. Namely the R_f values of **5a–c** and **8a–c** were very similar.

With electron-rich benzaldehydes the new concept worked much better. For example, the *p*-methoxy derivative **5d** was obtained in 63% yield whereas the other method (Scheme 1, with 10 mol % BINOL, 22 h) gave[7a] **5d** only in 47% yield. Interestingly, an organocatalytic version of this aldol-transfer reaction gave **5d** only in 40% yield (30 mol % L-proline with 2 equiv of **1** in DMSO, 120 h at rt).[9] With di- and trialkoxybenzaldehydes the new method (Scheme 2) gave still significantly better results. Aldols **5e** and **5f** were obtained in 84% and 83% yields (Table 1, entry 5 and 6), respectively. Furthermore, in the crude of **5d–f** much less by-products were detected than in the case of **5a–c**. The new method was also checked with 1-naththaldehyde and *o*-chlorobenzaldehyde to see whether *o*-substitution would have any effect. However, aldol **5g** was isolated only in 20% yield and the corresponding reaction of *o*-chlorobenzaldehyde gave a bad mixture not worth purification.

When 2-heteroarylcarbaldehydes were used as substrates there was not a clear trend in the results. For example, the reaction of 2-pyridylcarbaldehyde with diacetonealcohol **1** under the standard conditions (Scheme 2) rendered the desired aldol **5h** in 74% yield whereas **5i** and **5j** were isolated only in 30% and 40% yields. For **5h** the method of isolation required modifications. By working in accord to the isolation method of Marvel and Stille[11] it was possible to isolate **5h** in 41% yield, but 12 extractions with $CHCl_3$ were necessary. The method of Chimni and Mahajan[12] (extracting a water solution of **5h** three times with CH_2Cl_2 to obtain **5h** in 98% yield) did not give satisfactory results either. For the isolation of **5h** the crude product was neutralized with aqueous NaOH (10%), saturated with NaCl and extracted several times with EtOAc. Another good method was the following: the neutralized crude reaction mixture is evaporated to dryness and the resulting semisolid is washed with $CHCl_3$. Filtration followed by evaporation of the filtrate to dryness renders crude **5h** (for purification by flash chromatography).

Aldol-transfer reaction of 2-thiophenecarbaldehyde gave **5j** in 40% yield. Aldol **5j** was simultaneously pre-

pared also by Chimni and Mahajan[12] in 30% yield using an organocatalytic direct aldol method (reactions conducted in water with 30 mol % pyrrolidine added as a catalyst). As regarding side reactions Chimni and Mahajan report extensive water elimination to accompany the formation of **5j**.[12] The yield of **5j** (Table 1, entry 10) was lowered because of extensive polymerization (a broad hump with numerous sharp signals in it was observed in the area of aromatic and enone protons in the ^{1}H spectrum of the crude). Very similar conclusions were drawn in the case of aldol **5i**, which was obtained in 30% yield only (Table 1, entry 9). Interestingly, Chimni and Mahajan[12] report a slightly better yield (44%) for **5i**.

For comparison the 2-heteroaryl aldols **5h–j** were synthesized using the conventional base-catalyzed method:[11] the aldehydes were reacted with acetone in aqueous NaOH (10%) at −20 °C for 40 min. The resulting mixture, which was first neutralized and evaporated to dryness, was washed with $CHCl_3$ and filtered. Evaporation of the filtrate to dryness rendered aldol **5h** in 72% yield after recrystallization from methanol. Aldols **5i** and **5j** were prepared accordingly in 20% and 24% yields (after flash chromatography with EtOAc:hexane from 1:8 to 1:3), respectively. Interestingly, the yields were better with the new method (Table 1).

In conclusion, using the new alkoxide trapping method electron-rich alkoxy-substituted benzaldehydes gave the best yields of desired aldols **5**. In contrast, electron-poor aldehydes gave low yields of **5** and the formation of either enones **7** or tetrahydropyran diols **8**, or both, was observed. Therefore, the purification of aldols derived from electron-poor aldehydes was tedious. When comparing the aldol-transfer (Scheme 2) and the base-catalyzed method similar yields were obtained with 2-pyridin-carbaldehyde whereas for 2-furan and 2-thiophenecarbaldehyde the new methods worked better. Finally, the new method gave the best yields for Al-catalyzed aldol-transfer reactions published so far.

Typical procedure for the aldol-transfer reaction of aromatic aldehydes is as follows: At room temperature under argon, trimethylaluminum (0.64 mmol, 0.32 mL, 2 M in toluene or heptane) was added to a suspension of 1,1′-bi-2-naphthol (0.32 mmol, 0.93 mg) in dry CH_2Cl_2 (1 mL) and stirred for 20 min. Then 3,4,5-trimethoxybenzaldehyde (3.33 mmol, 654.7 mg) and 4-hydroxy-4-methyl-2-pentanone (3.4 mmol, 399 mg) were added simultaneously. After stirring for 1 h trimethylaluminum (0.64 mmol, 0.32 mL) was again added. After further stirring for 42 h the mixture was quenched with aqueous HCl (1 M, 10 mL). After adding 10 mL EtOAc the mixture was stirred until homogeneous. The organic layer was separated. The aqueous layer was extracted with EtOAc (2×10 mL). The combined extracts were washed with aqueous $NaHCO_3$, dried over $MgSO_4$, and filtered. Evaporation of the filtrate gave 973.3 mg crude product. Flash chromatographic purification of 320 mg of the crude gave 4-hydroxy-4-(3′,4′,5′-trimethoxyphenyl)-2-butanone (227.6 mg, 0.895 mmol, 83%) as light yellow solid. $R_f = 0.17$ (EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C, $CHCl_3$, 7.26 ppm): δ 6.58 (s, 2H), 5.07 (d, 1H, $J = 7.2$ Hz), 3.87 (m, 6H), 3.83 (m, 3H), 3.26 (s, 1H), 2.83–2.87 (m, 2H) 2.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 77.0 ppm): δ 208.75, 153.17, 138.28, 137.21, 102.39, 69.83, 60.60, 55.92, 51.90, 30.54. These spectral values match well with the literature data.[13]

All compounds were characterized using ^{1}H NMR, ^{13}C NMR, and IR spectroscopy. The spectral data of known **5a–d**, **5f–j**, and **7a**,**b** were well consistent with the literature values.[7,12,13] New aldol **5e**[14] and the novel by-product **8c**[10] gave satisfactory analyses.

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14. Characterization of **5e**: $R_f = 0.15$ (EtOAc/hexane 1:2); ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C, $CHCl_3$, 7.26 ppm): δ 6.92 (s, 1H), 6.83 (s, 2H), 5.09 (d, 1H, $J = 8.0$ Hz), 4.09 (q, 2H,

$J = 6.97$ Hz), 3.88 (s, 3H), 3.30 (s, 1H), 2.90 (dd, 1H, $J =$ 9.05 Hz, $J' = 17.42$ Hz), 2.79 (dd, 1H, $J = 8.48$ Hz, $J' = 17.42$ Hz), 2.20 (s, 3H), 1.45 (t, 3H, $J = 2.8$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 77.0 ppm): δ 209.07, 149.34, 147.73, 135.37, 117.75, 112.52, 109.09, 69.69, 64.32, 55.86, 51.99, 30.73, 14.74; MS (*m*/*z*) BP: 238.2 (M), 221.1, 181.1, 57.4; HRMS (FAB) calcd for $C_{13}H_{18}O_4$ [M^+]: 238.1205, found: 238.1216.