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Convenient enol equivalents for catalytic aldol-transfer reactions

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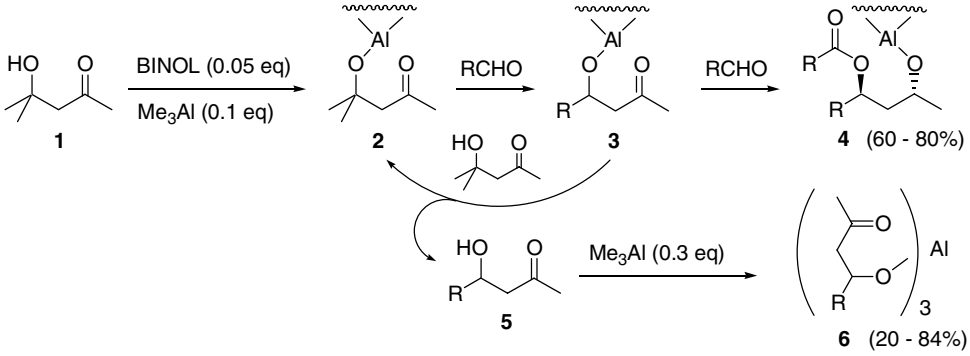
Abstract—Solid crystalline and stable 1,1-diphenyl-1-hydroxy-3-butanone was shown to serve as an excellent precursor of the Al-enolate of acetone generated in situ for Al-BINOL catalyzed aldol-transfer reactions of aldehydes. The best yields were obtained with electron rich aromatic aldehydes and 2-pyridine carbaldehyde of which the latter gave 1-hydroxy-1-(2-pyridyl)-3-butanone in 79% yield.

Nucleophile-transfer reactions offer great potential for organic transformations.[1–9] They are similar to MPV type of reactions[1] but the nucleophile transferred is other than hydride. For example, Inoue and co-workers described the use of Al- and Ti-based promotors[2] and La-alkoxide catalysts[3] for cyanohydrin transfer reactions. Maruoka and co-workers described alkynyl-transfer reactions mediated by Al-[4] and Zr-alkoxides.[5] Allyl and homopropargyl-transfer reactions have been reported by Nokami and co-workers, Loh et al., and Oshima and co-workers[6] Aldol-transfer reactions of aldehydes and diacetone alcohol **1** catalyzed by Al-BINOL (Scheme 1) were described by Nevalainen et al.[7] In this reaction **1** is converted via **2** and **3** to a diolmonoester **4** (R = alkyl) or aldol **5** (R = aryl, via **6**[7d]). Later Schneider et al. reported[8] the related Zr-BINOL process. Finally, Chandrasekhar et al. reported the first L-proline catalyzed enantioselective aldol-transfer reaction for aldols **5**.[9]

The most common enol equivalent for aldol-transfer reactions is diacetone alcohol **1**.[7–9] Recently Schneider et al. described Zr-BINOL catalyzed aldol-transfer reactions using other enol equivalents.[8a] They reported that 1,1-diphenyl-1-hydroxy-3-butanone (**7**, Scheme 2) performs poorly for the formation of Zr-analog of **4** (decomposition of **7** to acetone and benzophenone was claimed to be the main reaction instead of the desired



Scheme 1. Catalytic aldol-transfer reactions of **1** and RCHO. In parentheses are given typical isolated yields of diols (from **4**)[7c] and aldols (from **6**)[7d] obtained after acidic workup and flash chromatography.

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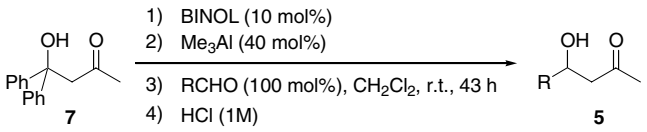

Scheme 2. Aldol-transfer reactions of 1,1-diphenyl-1-hydroxy-3-butanone **7**.

aldol-transfer pathway). In contrast to this, on the basis of one early experiment, compound **7** has been suggested[7a] to be a better enolate precursor than diacetone alcohol **1**. This poses a question: why do we care for the utility of **7** as an enol equivalent for aldol-transfer reactions? This is because **1** is a liquid, which slowly decomposes when stored. Therefore, compound **1** must always be distilled before use (Lewis acid-catalyzed aldol-transfer reactions require dry conditions). Compound **7**, however, is a crystalline solid and can be easily dried under vacuum. Furthermore, it can be stored for a longer time without decomposition (the sample used for the early experiment[7a] was a couple of decades old!). Therefore, aldol-transfer reactions, which employ **7** instead of **1**, would be easier to conduct and would facilitate the further development of aldol-transfer technology.

In order to determine the performance of **7** as an enol equivalent, we used our new method[7d] and reacted 10 (hetero)aromatic aldehydes with **7** in the presence of 40 mol % trimethylaluminum (Scheme 2) to obtain **5**. The results are summarized in Table 1. The results are compared with those obtained earlier[7d] using **1** (the reference method).

The yield of **5a** was only 26% (Table 1, entry 1). This value is only 3% lower than that obtained earlier[7d] using precursor **1** (entry 1, reference yield 29%). The same small difference of yields of **5b** was observed with 4-chlorobenzaldehyde (entry 2). Unfortunately, the main product with both **1** and **7** was the corresponding enone isolated in 39% and 33% yield, respectively. Interestingly, with electron-poor and more reactive 4-nitrobenzaldehyde, the yield of **5c** (entry 3) was significantly lower than that observed earlier using the reference method. With electron-rich benzaldehydes, **7** worked almost as well as did **1** (entries 4–6). Actually, with **7**, the *p*-methoxyl derivative **5d** was obtained in 70% yield (the yield of **5d** was 63% with **1**). Our new method[7d] was also checked with 1-naphthaldehyde and *o*-chlorobenzaldehyde to detect whether *o*-substitution would have any effect. However, aldol **5g** was isolated in 48% yield (entry 7). This value is 28% higher than that obtained earlier using **1**. Unfortunately, both **1** and **7**, when reacted with *o*-chlorobenzaldehyde, gave a bad mixture not worthy of purification.

When 2-pyridine carbaldehyde was reacted with **7**, aldol **5h** was obtained in 79% yield (entry 8). That is 5% better than the reference yield. On the other hand, the yields of **5i** and **5j** were only 24% and 30% and lower that the reference yields. Intensive polymerization, lowering the yield of **5j**, was observed for both reactions of 2-thiophene carbaldehyde (with **1** and **7**).

In conclusion, easy to handle enol equivalent **7** used according to our new alkoxide trapping method[7d] gives aldols **5** in yields closely similar to those obtained earlier with equivalent **1**. Only with 4-nitrobenzaldehyde and 2-thiophene carbaldehyde were the yields clearly lower (with **7**). Slightly better yields were obtained with **7** when it was reacted with *p*-methoxybenzaldehyde or 2-pyridine carbaldehyde. Only in the case of 1-naphthyl carbaldehyde did the yield improve a lot when precursor **7** was used instead of **1**. Finally, aldol **7** seems to be a much better enol equivalent for Al-BINOL catalyzed aldol-transfer reactions than for Zr-BINOL catalyzed ones.[8a] This study confirms the utility of this stable crystalline easy to dry and purify aldol **7** as an excellent precursor of metal enolates of acetone (for in situ generations) as well as the reactivity of the enolate toward aldehydes leading to the formation of aldol adducts. Further studies on structural modifications of aldol **7** to optimize it for aldol-transfer reactions are in progress.

Typical procedure for the aldol-transfer reaction of aromatic aldehydes is as follows: At room temperature under argon, trimethylaluminum (0.08 mmol, 0.04 mL, 2 M in toluene or heptane) was added to a suspension of 1,1′-bi-2-naphthol (0.041 mmol, 11.8 mg) in dry CH_2Cl_2 (0.5 mL) and stirred for 20 min. Then 2-pyridine

Table 1. Aldol-transfer reactions of aldehydes RCHO with 1,1-diphenyl-1-hydroxy-3-butanone **7**[a]

Entry	R	Derivative	Yield of **5**[b] (%)	Reference yield[c] (%)
1	C_6H_5	**a**	26	29
2	*p*-Cl–C_6H_4	**b**	15[d]	18[e]
3	*p*-NO_2–C_6H_4	**c**	22	38
4	*p*-CH_3O–C_6H_4	**d**	70	63
5	3-CH_3O, 4-C_2H_5O–C_6H_3	**e**	77	84
6	3,4,5-$(CH_3O)_3C_6H_2$	**f**	78	83
7	1-Naphthyl	**g**	48	20
8	Pyridine-2	**h**	79	74
9	Furan-2	**i**	24	30
10	Thiophene-2	**j**	30	40

[a] See Scheme 2. The products were characterized by spectral data.
[b] Isolated yields of **5** (relative to RCHO) after flash chromatography.
[c] The yield of **5** obtained when **1** was used instead of **7** (Ref. 7d).
[d] The corresponding enone was isolated in 39% yield.
[e] The corresponding enone was isolated in 33% yield.

carbaldehyde (0.41 mmol, 44.0 mg) and 1,1-diphenyl-1-hydroxy-3-butanone[10] (0.41 mmol, 98.5 mg) were added simultaneously in dry CH_2Cl_2 (0.5 mL). After stirring for 1 h, trimethylaluminum (0.08 mmol, 0.04 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 homogenized solution was neutralized with 10% NaOH and saturated with NaCl. The organic layer was separated and the aqueous layer was extracted with EtOAc (2×10 mL). The combined extracts (about 30 mL) were dried over $MgSO_4$ and filtered. Evaporation of the filtrate gave 150.9 mg crude product. Flash chromatographic purification of the crude gave 1-hydroxy-1-(2-pyridyl)-3-butanone (53.2 mg, 0.322 mmol, 79%) as white crystalline solid. $R_f = 0.72$ (CH_2Cl_2:MeOH 3:1); FTIR (neat, cm^{-1}): 3132, 1711, 1535; ^1H NMR (300 MHz, $CDCl_3$, 20 °C, $CHCl_3$, 7.26 ppm): δ 8.53 (m, 1H), 7.68–7.74 (m, 1H), 7.46 (d, $J = 7.90$ Hz, 1H), 7.19–7.23 (m, 1H), 5.18–5.22 (m, 1H), 4.18 (m, 1H), 3.00–3.07 (m, 1H), 2.98 (dd, $J = 8.31$, $J' = 17.10$ Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 77.0 ppm): δ 208.54, 161.25, 148.19, 136.82, 122.30, 120.24, 69.68, 50.59, 30.67. These spectral values match well with the literature data.[11] All compounds were characterized using ^1H NMR, ^{13}C NMR, and IR spectroscopy. The spectral data of known **5a**–**j** were well consistent with the literature values.[7c,d,11]

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