Aldehyde-Catalyzed Transition Metal-Free Dehydrative β-Alkylation of Methyl Carbinols with Alcohols

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Abstract: Different to the borrowing hydrogen strategy in which alcohols were activated by transition metal-catalyzed anaerobic dehydrogenation, the direct addition of aldehydes was found to be an effective but simpler way of alcohol activation that can lead to efficient and green aldehyde-catalyzed transition metal-free dehydrative C-alkylation of methyl carbinols with alcohols. Mechanistic studies revealed that the reaction proceeds via in situ formation of ketones by Oppenauer oxidation of the methyl carbinols by external aldehydes, aldol condensation, and Meerwein-Ponndorf-Verley (MPV)type reduction of α,β -unsatutated ketones by substrate alcohols, affording the useful long chain alcohols and generating aldehydes and ketones as the by-products that will be recovered in the next condensation to finish the catalytic cycle.

Keywords: alcohols; aldehyde catalysis; *C*-alkylation reaction; relay race mechanism; transition metal-free conditions

Developing efficient methods for C–C bond formation is a major research topic in synthetic chemistry. Current trends in the area have placed more and more emphasis on green catalytic methodologies such as organocatalytic reactions that use greener catalysts, cascade reactions like C–H activation that can use more available substrates and shorten the procedures, and those that can avoid the use of mutagenic and waste-producing reagents.^[1] For example, β -C-alkylation of methyl carbinols for the synthesis of the useful long chain alcohols, a reaction that used to be accomplished *via* tedious and wasteful multi-step processes [Eq. (1)],^[2] has recently been realized by the transition metal-catalyzed one-pot tandem dehydrative Calkylation of methyl carbinols by directly using alcohols as the alkylating reagents [Eq. (2)].^[3-6] This method is preferable from the synthetic point of view, because the alcohols, although less active, are much greener chemicals than the corresponding activated alkyl halides or carbonyl compounds,^[7,8] and because the reaction can afford the target alcohols with relatively high atom efficiency by producing water as the only by-product.

Firstly reported by Cho and co-workers with use of $RuCl_2(PPh_3)_3$,^[3] this reaction was later improved by other groups by using Ru,^[4] Ir,^[5] or other transition metal catalysts.^[6] These reactions, currently termed as the borrowing hydrogen or hydrogen autotransfer methodology,^[7] are believed to proceed *via* anaerobic dehydrogenative alcohol activation to aldehydes, dehydrative condensation, and reduction of the intermediates by the in situ generated hydridometal species [Eq. (2)]. However, these methods still suffer from the use of large amounts of hydrogen acceptors or bases, long reaction times, or low selectivity of the products.^[3-6] Besides, using preformed noble metal complexes or addition of capricious ligands for catalyst activation are not only expensive, not readily accessible and toxic, but are also severe drawbacks of the methods, especially in pharmaceutical, biochemical, and industrial applications.

While others are interested in developing catalysts or tuning ligands by employing the borrowing hydrogen strategy,^[3-7,9,10] we focused more on the reactions themselves and the mechanisms,^[8e,11-13] and developed the air-promoted metal-catalyzed aerobic N-^[11] and C-alkylation^[12] methods. During our ongoing studies, we found that the direct addition of external aldehydes can be a simpler way of alcohol activation, which then leads to aldehyde-catalyzed transition metal-free dehydrative N-^[14] and C-alkylation methods for a wide range of substrates. To the best of our knowledge, aldehyde-catalyzed reactions are still very rare up to date.^[15] Herein we report in detail the efficient and green aldehyde-catalyzed dehydrative β -C-



alkylation reaction of methyl carbinols with alcohols [Eq. (3)] and propose a mechanism for the reaction.^[16,17]

The reaction was firstly optimized under solventfree conditions using commercial benzyl alcohol (1a) and 1-phenylethanol (2a) as the substrates, KOH as the base, and benzaldehyde (3a) or acetophenone (4a) as the catalyst (Table 1). Initially, only a trace of product was detected in the blank reaction (run 1) and reactions using either KOH or 3a only;^[18,19] while addition of both 20 mol% of KOH and 3a could dramatically enhance the reaction rate to afford good yield and good selectivity of the target product **5aa** over by-product **7aa** (run 2). Notably, another possi-

Table 1. Screening and optimization of the reaction conditions.^[a]

Ph OH	cat. PhCHO (3a) cat. PhCOCH₃ (4a)	Ph +	Ph Ph
+ . OH 	cat. KOH, atm., <i>T, t</i>	5aa major O ↓	6aa not detected
Ph 2a		+ Ph 7aa minor	`Ph + H ₂ O

Run	KOH, 3a , 4a (mol%)	atm., <i>T</i> , <i>t</i>	$5+7[\%], 5/7^{[b]}$
1	0, 0, 0	air, 135°C, 8 h	trace, –
2	20, 20, 0	air, 135°C, 8 h	77, 89/11
3	33, 20, 0	air, 135°C, 8 h	93, 93/7
4	33, 0, 20	air, 135°C, 8 h	68, 93/7
5	100, 0, 0	air, 135°C, 8 h	54, -
6 ^[c]	30, 20, 0	N ₂ , 135 °C, 8 h	> 99, 97/3
7 ^[c]	30, 20, 0	N ₂ , 120 °C, 12 h	98, 97/3
		30 h	>99,>99/1
8 ^[c,d]	30, 20, 0	N ₂ , 120 °C, 30 h	>99, >99/1
9 ^[c]	30, 20, 0	$N_{2}, 110^{\circ}C, 32 h$	$>99'(92)^{[e]}, >99/1$
10 ^[c]	30, 20, 0	N ₂ , 100 °C, 50 h	91, >99/1
11 ^[c,f]	30, 20, 0	N ₂ , 110 °C, 32 h	63, >99/1
12 ^[c,g]	30, 20, 0	N ₂ , 110 °C, 32 h	90, 97/3

^[a] Unless otherwise noted, commercial **1a** (3.3 mmol, 1.1 equiv) and **2a** (3 mmol), absolute **3a** and/or **4a**, and KOH (AR grade, >90% purity) was sealed under air or N₂ in a 20-mL Schlenk tube. The mixture was then heated and monitored by GC-MS and/or ¹H NMR analysis. As analyzed by ¹H NMR, commercial **1a** is contaminated by <1% **3a**, commercial **2a** by <2% **4a**.

^[b] Conversions of the reactions based on 2a and 5aa/7aa ratios were determined by ¹H NMR spectroscopic analysis of the reaction mixture.

^[c] 1.3 equiv. **1a**.

^[d] KOH of 99.52% purity was used.

^[e] The yield in parenthesis is isolated yield.

^[f] 30 mol% 18-crown-6 (1 equiv. to 30 mol% KOH).

^[g] Virgin glassware and stirring bar, absolute **1a**, **2a** and **3a**, and 4N grade KOH (99.99% purity) were used.^[22]

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ble by-product and also the intermediate of the reaction, α , β -unsaturated ketone **6aa**, was not detected. During condition screening, we found that both aldehyde and KOH are crucial for the reaction.^[19] Thus, more loadings of KOH could give higher yield and higher selectivity of the product (run 3), and aldehyde is a much better catalyst than 4a (run 4) or than directly running the reactions under air (run 5).^[19,20] Further condition screening showed that the product yield and selectivity could be improved by running the reaction under nitrogen (run 6) even at lower temperatures (runs 7-10), albeit requiring longer reaction times. The reaction at 110°C (run 9) was chosen as the best condition for it was completed to afford target **5aa** in a high isoalted yield (92%) and the highest selectivity (>99%).

Since both aldehyde and base are crucial and they have a synergistic effect on catalyzing the reaction, this C-alkylation reaction is most possibly a transition metal-free process.^[14] Firstly, 18-crown-6, well-known in having strong complexation ability with potassium cations,^[21] was added to the reaction. The results showed that it greatly retarded the reaction to give only a moderate yield of the product (Table 1, run 11), confirming that potassium cation plays a dominant role in the reaction other than the unclear transition metal contaminants.^[14] Moreover, the facts that the reaction with only 1 equivalent of AR-KOH was not effective $(run 5)^{[19]}$ and the reaction of 2N KOH gave the same good result as with AR-KOH under the same conditions (runs 7 and 8) also indicated that the amounts of the metal contaminants in the bases (associated with the base purity) do not affect the reaction at all. This point is further supported by other proofs. For example, the results of base effect screening^[19] not only revealed that different bases vary greatly in activities and that KOH is the best base for the reaction, but also implied that the possible metal contaminants in the AR grade bases do not work in the reaction and that KOH played a much more significant role than those metal contaminants. In addition, to exclude the possibilities of transition metal contaminants-catalyzed processes, a control reaction using virgin glassware and stirring bar, absolute 1a, 2a and 3a, and 4N grade KOH (99.991% purity) was also examined under the optimized conditions (run 12) and it gave a rather good result.^[22] Therefore, the possibilities of transition metal-catalyzed processes due to metal contamination in the bases, catalysts, and substrates can be excluded.

The reactions of a series of benzylic and aliphatic, primary alcohols and methyl carbinols were then examined to extend the scope of the aldehyde-catalyzed C-alkylation method (Table 2). Firstly, under conditions similar to the optimized ones, both electron-rich and electron-deficient benzylic alcohols 1 and 1-arylethanols 2, including the sterically more bulky ones (runs 9, 12, 17) and those with reactive substituents (runs 4, 10–15), reacted to give usually good to high yields of the target alcohols in good to high selectivities (runs 1–17). In some cases, since the reactions under the optimized conditions were not satisfactory enough, they were conducted under conditions using slightly higher amounts of **3** and/or KOH (runs 3–5), or at higher temperatures in longer times (runs 5, 13– 17) to improve the product yields and selectivities. As to heterobenzylic alcohols, the reactions were generally slower than those of the benzylic alcohols and thus were conducted at higher temperatures to obtain satisfactory results (runs 18–21).

The same method is also suitable for primary and secondary aliphatic alcohols; although these reactions had to be carried out at a higher temperature of 160 °C in longer time by using 30 mol% of 3 (runs 22-30), possibly due to the lower reactivity of the aliphatic alcohols. Thus, both electron-rich and electron-deficient benzylic alcohols reacted with secondary aliphatic alcohols to afford moderate to good yields of the products in high selectivities (runs 22-26). The reactions of primary aliphatic alcohols with electronrich and electron-deficient 1-arylethanols are similar (runs 27-30). In similar circumstances, it was found that the catalyst aldehydes were better to be added in three portions (runs 21, 25, 28), for better results could be obtained in this way (see runs 27 and 28 for comparison). The reaction of a cyclic secondary alcohol was not that satisfactory at present, giving only a lower yield and a lower selectivity of the products at present (run 31). Moreover, secondary benzylic alcohols could also be used as the alkylating reagent. Thus, under similar conditions in the presence of catalyst 4a, 2a alone afforded good yield of the target product in good selectivity (run 32).

As to the mechanism of the reaction, based on our own work^[11,12,14] and the literature,^[16,23] and as demonstrated below, the transition metal-free relay race mechanism (Scheme 1)^[14] rather than other types of mechanisms should be the most probable one for this aldehyde-catalyzed *C*-alkylation reaction.

Firstly, in the presence of KOH, the added aldehyde **3** should undergo the Meerwein–Pondorf– Verley–Oppenauer (MPV-O) redox reaction with the methyl carbinols **2** to give the corresponding reduced alcohol **1** and oxidized ketone **4** [Scheme 1, step (i)], or the added **4** react with **1** to give **2** and **3** (see Table 1, runs 9, 10). This transition metal-free MPV-O transfer hydrogenation step has not only been documented in the literature,^[23] but can also be easily confirmed by cross-interconversion reactions of aldehydes and methyl carbinols and of primary alcohols and ketones.^[19] Thus, as shown in Eq. (4), the reaction of aldehyde **3a** and secondary alcohol **2j** readily occurred to give **1a** and **4j** in the presence of KOH and *vice versa*.^[19,24,25] Table 2. Extension of the substrates.^[a]



Run	Alcohols 1		Alcohols 2		5+7 [%] (5%); 5/7 ^[b]
1	ОН	1a	ОН	2a	>99 (92);>99/1
2		1 a	Me	2b	>99 (81); 94/6
3 ^[c]		1 a	MeO	2c	>99 (87);>99/1
4 ^[c]		1 a	СІ—	2d	>99 (80); 94/6
5 ^[c,d]		1 a	F ₃ C	2e	>99 (68); 91/9
6	Me	1b		2a	>99 (83); 94/6
7	MeO	1c		2a	>99 (81); 94/6
8	меО	1d		2a	>99 (78);>99/1
9	OMe	1e		2a	>99 (74); 94/6
10	CI	1f		2a	>99 (83);>99/1
11	СІ	1g		2a	98 (74); 96/4
12	CI	1h		2a	78 (51); 97/3
13 ^[e]	F-	1i		2a	60 (44); 87/13
14 ^[e]	Br	1j		2a	93 (69); 95/5
15 ^[e]	Br	1k		2a	89 (63); 91/9
16 ^[e]	ОН	11		2a	>99 (79); 94/6
17 ^[e]	ОН	1m		2a	>99 (75); 86/14
18 ^[d,f]	€ OH	1n		2a	92 (61); 87/13
19 ^[d,f] 20 ^[d,f]		1n 1n		2b 2d	97 (69); 84/16 44 (32); 94/6

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Table 2. (Continued)

Run	Alcohols 1		Alcohols 2		5+7 [%] (5 %); 5 / 7 ^[b]
21 ^[e-h]	€ OH	10		2a	>99 (66); 78/22
22 ^[d,f]		1 a	ОН	2f	87 (59);>99/1
$\begin{array}{c} 23^{[d,f]} \\ 24^{[d,f]} \end{array}$		1b 1f		2f 2f	57 (34);>99/1 72 (45);>99/1
$25^{[d,f,h]}$		1 a	OH	2g	72 (52);>99/1
$26^{\left[d,f ight]}$		1a	ОН	2h	53 (37);>99/1
$27^{[d,f]}$ $28^{[d,f,h]}$ $29^{[d,f]}$ $30^{[d,f]}$	ОН	1р 1р 1р 1р		2a 2a 2b 2d	72 (43); > 99/1 83 (69); > 99/1 54 (41); > 99/1 56 (39); > 99/1
31 ^[d,f,i]		1 a	OH	2i	75 (35); 59/41
32 ^[d,i,j]		1 a	~ ~	2a	92 (64); 85/15

[a] Unless otherwise noted, commercial alcohols 1 (3.9 mol, 1.3 equiv.) and 2 (3 mmol), corresponding aldehyde 3 (20 mol%), and KOH (30 mol%) were degassed and then sealed under nitrogen in a 20-mL Schlenk tube. The mixture was then heated at 110°C for 32 h and monitored by GC-MS and/or ¹H NMR analysis.

^[b] Unless otherwise noted, conversions of the reactions based on 2 and 5/7 ratios were determined by ¹H NMR spectroscopic analysis of the reaction mixture. Isolated yields of 5 based on 2 are shown in parenthesis.

^[c] 1.5 equiv. **1**, 30 mol% **3**, 50 mol% KOH.

^[d] 160 °C, 72 h.

^[e] 130°C, 48 h.

^[f] 30 mol% **3**.

^[g] 3 mmol **1** and 6 mmol **2** (2 equiv.).

^[h] The aldehyde was added in 3 portions (10 mol% per portion).

^[1] Conversion and ratio of the reaction were determined by GC-MS analysis due to unidentifiable complex NMR spectra.

^[j] 6 mmol **2a** and 30 mol% **4a**.

Secondly, once the the more reactive aldehyde **3** and ketone **4** are both present in the reaction, they should undergo the facile dehydrative aldol condensation to give α , β -unsatutated ketones **6** [Scheme 1, step (ii).] Since this step is a classic organic reaction, well-



Scheme 1. Proposed mechanism for the aldehyde-catalyzed *C*-alkylation reaction of methyl carbinols with alcohols.

proven in previous studies,^[3-7,10,12] and can readily occur at room temperature in the presence of KOH [Eq. (5)],^[19] it should be a fast step in the catalytic cycle. As a result, it can drive the interconversion reactions [step (i)] forward by producing intermediate **6** as **6** will be further reduced to **7** and **5**.

Finally, the transfer hydrogenative reduction of **6** by primary alcohols **1** and/or methyl carbinols **2** to give product **5** and by-product **7** [Scheme 1, steps (iii) and (iv)] could also be easily confirmed. As shown in Eq. (6) (a similar condition to the reactions in Table 1), by using **1a** or **2a** as the hydrogen source and KOH as the base, **6aa** could be easily reduced to **5aa** and **7aa** in moderate to good yields and good to high selectivities in the absence of metal catalysts.^[19] More importantly, as shown in Eq. (7), by using 1 equivalent of phenyl(*p*-tolyl)methanol **2k** as the reducing alcohol, the ratio of the hydrogen atoms per molecule) and **7aa** (2 hydrogen atoms per molecule) to those donated by **2k** to give **4k** (2 hydrogen atoms per



molecule) can be clearly analyzed by ¹H NMR spectroscopy to be almost 1/1 [Eq. (7), run 1].^[19] Similarly, another reaction using 3 equivalents of 2k also reflected well the same transformation [Eq. (7), run 2]. These results clearly indicate that the hydrogen atoms of alcohols 1 and/or 2 were quantitatively transferred to intermediate 6 to give intermediate 7 and finally the product 5 in the transfer hydrogenation steps [Scheme 1, steps (iii) and (iv)], regenerating meanwhile quantitative amounts of **3** and **4** as the by-products, which should soon be recovered [step (v)] in the next condensation step [step (ii)] to finish the catalytic cycle. Besides, the first transfer hydrogenation step [step (iii)] should be a fast reaction and the second one [step (iv)] a slower reaction in the catalytic cycle, since 6 was not observed and 7 was detected as the by-product in the reaction media. On the other hand, since no metal catalysts were used and the possibilities of transition metal-catalyzed pathways have been excluded, these transfer hydrogenation steps should also proceed via similar MPV-O type processes.[14,16,23]

In summary, we have developed an efficient and green aldehyde-catalyzed transition metal-free dehydrative *C*-alkylation method for preparation of the useful long chain alcohols that can directly use various benzylic and aliphatic, primary alcohols and methyl carbinols as the substrates. This work demonstrates again that addition of aldehydes is indeed an effective protocol of alcohol activation, extending the scope of aldehyde-catalyzed alkylation method and the transition metal-free relay race mechanism.^[14] Although the aldehyde of the corresponding alcohol was used as the catalyst, this method is still preferable from a synthetic point of view because it requires no expensive metal catalysts and activating ligands, but merely the cheap and readily available aldehydes and base, which may in turn solve the catalyst recovery, reuse, deactivation, and metal leaching and residue problems accompanied with the metal-catalyzed methods. Due to the many obvious advantages, this alcohol-based aldehyde-catalyzed dehydrative alkylation method should potentially be of wide interest in many fields. Further extension and deeper mechanistic studies of the reaction are underway.

Experimental Section

Typical Procedure for Aldehyde-Catalyzed Dehydrative *C*-Alkylation of Methyl Carbinols with Alcohols

The mixture of benzyl alcohol **1a** (0.40 mL, 3.9 mmol, 1.3 equiv.), 1-phenylethanol **2a** (0.36 mL, 3.0 mmol), KOH (50.5 mg, 0.9 mmol, 30 mol%), and absolute benzaldehyde **3a** (61 μ L, 0.06 mmol, 20 mol%) in a 20-mL Schlenk tube was sealed under nitrogen, and then heated at 110 °C. After completion of the reaction as was monitored by GC-MS and/or ¹H NMR (>99% yield and >99/1 selectivity by ¹H NMR), the mixture was quenched with ethyl acetate, washed successively with dilute hydrochloric acid, brine, and water, and extracted with ethyl acetate. The combined organic layer was then dried over MgSO₄ and concentrated under vacuum. Column chromatography of the crude product using ethyl acetate and petroleum ether (60–90 °C) (v/v 1/30) gave **5aa**; isolated yield: 0.586 g (92%).

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- [16] A base-mediated reaction carried out under air without using transition metal catalysts has been reported by Crabtree and co-workers (ref.^[10c]). The mechanistic proposal of the reaction, although not confirmed by direct experimental proofs and remained a hypothesis at the time, supports the conclusions in our previous studies (refs.^[11,12,14]) and the present work.
- [17] A ferrocenecarboxaldehyde-catalyzed *C*-alkylation reaction recently reported by Sun and co-workers (ref.^[6d]) should also be mentioned. Differently, it was proposed to proceed *via* an Fe–H species participating in the mechanism.
- [18] Commercial alcohols 1 and 2 are usually contaminated by trace amounts of the corresponding carbonyl compounds 3 and 4. This may account for the formation of trace products in the reactions.
- [19] See the Supporting Information for details.
- [20] Possibly because the conditions adopted in our work are different to those reported by Crabtree (ref.^[10c]), different results were obtained in the aerobic reactions. As shown in our work, the product selectivities in aerobic reactions are lower than those under nitrogen.

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- [24] The reactions of 1-arylethanols or ketones were also tested, but complex reaction mixtures were obtained.
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