

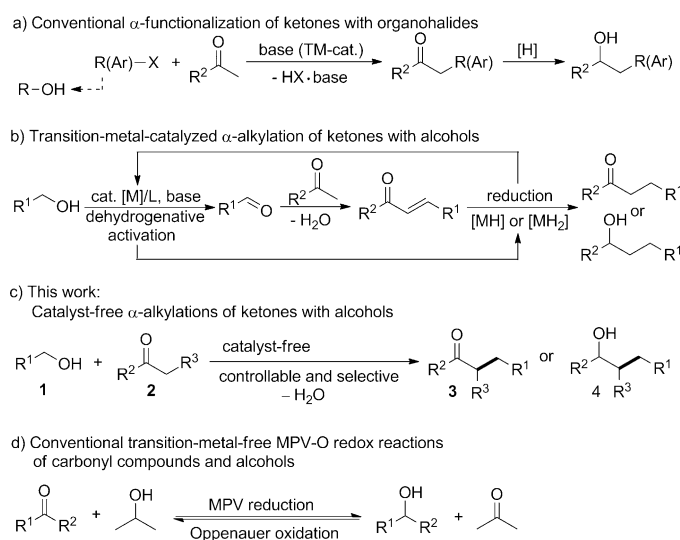
# Synthetic Methods

## Catalyst-Free Dehydrative $\alpha$ -Alkylation of Ketones with Alcohols: Green and Selective Autocatalyzed Synthesis of Alcohols and Ketones\*\*

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**Abstract:** Direct dehydrative  $\alpha$ -alkylation reactions of ketones with alcohols are now realized under simple, practical, and green conditions without using external catalysts. These catalyst-free autocatalyzed alkylation methods can efficiently afford useful alkylated ketone or alcohol products in a one-pot manner and on a large scale by C=C bond formation of the *in situ* generated intermediates with subsequent controllable and selective Meerwein–Ponndorf–Verley–Oppenauer-type redox processes.

Among C–C bond construction methods,  $\alpha$ -functionalization of carbonyl compounds is one of the most fundamental strategies to synthesize heterocycle-, pharmaceutical-, and natural-product-directed molecules.<sup>[1,2]</sup> Conventionally,  $\alpha$ -functionalization of carbonyl compounds was achieved by reactions of carbonyl compounds and organohalides (Scheme 1a).<sup>[1,2]</sup> However, these methods require reactive and toxic organohalides and large amounts of bases, and the concurrent formation of undesired waste salts is inevitable. Since alcohols are comparatively greener chemicals, and organohalides are mostly obtained from alcohols by halogenation, alcohols have recently been directly used as greener alkylating reagents.<sup>[3,4]</sup> Regarding the  $\alpha$ -alkylation of ketones to generate alkylated ketone or alcohol products,<sup>[2]</sup> several transition-metal (TM)-catalyzed methods have been achieved by anaerobic dehydrogenative alcohol activation (Scheme 1b).<sup>[5–7]</sup> Despite their advantages, these TM-catalyzed reactions still have obvious drawbacks, such as the use of expensive and toxic rare metal complexes (Ru,<sup>[5]</sup> Ir,<sup>[6]</sup> Pd,<sup>[7]</sup> etc.<sup>[7]</sup>) or capricious ligands, large amounts of hydrogen acceptors or bases, and metal contamination in products. Herein we report the catalyst-free autocatalyzed dehydrative  $\alpha$ -alkylation reactions of ketones with alcohols (Scheme 1c), which selectively afforded useful alkylated ketone or alcohol products under simple and practical one-pot conditions. As to known TM-free reactions of carbonyl compounds and alcohols, they were limited to simple Meerwein–Ponndorf–Verley–Oppenauer (MPV–O)



**Scheme 1.** Background of the research.

redox reactions (Scheme 1d)<sup>[8]</sup> without the formation of new C–C bonds.

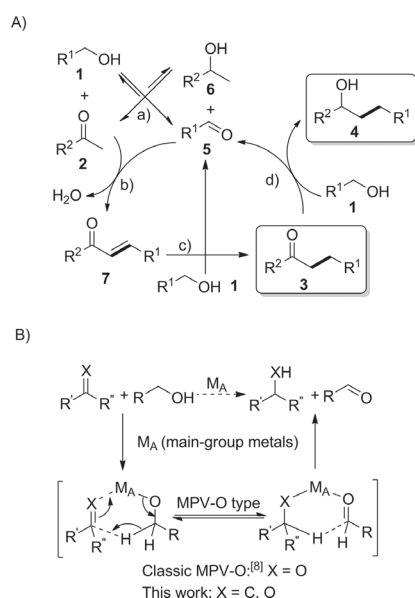
In our studies on alcohol-based TM-catalyzed aerobic reactions,<sup>[4a,9,10]</sup> we accidentally observed that aldehydes efficiently catalyzed dehydrative alkylation reactions of amides, amines, and secondary alcohols with alcohols by a TM-free mechanism involving MPV–O-type redox processes.<sup>[11,12]</sup> We thus deduced that ketones may similarly be good catalysts<sup>[13,14]</sup> and can lead to new TM-free alkylation methods. As shown in Scheme 2A, we hypothesized that  $\alpha$ -alkylation of ketones with alcohols may proceed successively by an MPV–O-type aldehyde formation (step a; Scheme 2B, X = O),<sup>[8]</sup> dehydrative aldol condensation (step b), and MPV–O-type reduction of chalcone intermediates by alcohols to give alkylated ketones or alcohol products (steps c and d; Scheme 2B, X = C, O), thus regenerating aldehydes for the catalytic cycle.<sup>[11b]</sup> If this process can be realized, it may lead to advantageous and green catalyst-free autocatalyzed  $\alpha$ -alkylation reactions because no additional ketones are required. Consequently, the use of external catalysts can be avoided.

We began our study by investigating the reaction of benzyl alcohol (**1a**) and acetophenone (**2a**) without adding any external catalysts (Table 1).<sup>[15]</sup> Thus, directly heating solvent-free mixtures of **1a** and **2a** with different bases<sup>[16]</sup> at 110 °C under air led to the formation of the alkylated ketone **3a** and alcohol **4a** in varied yields and ratios. The results showed that

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**Scheme 2.** A) Postulated route for catalyst-free autocatalyzed  $\alpha$ -alkylation of ketones with alcohols. B) TM-free MPV-O-type redox processes.

**Table 1:** Optimization of reaction conditions for the synthesis of alkylated alcohols.<sup>[a]</sup>

| $\text{Ph-CH}_2\text{-OH (1a)} + \text{Ph-C(=O)-Ph (2a)} \xrightarrow[\text{-H}_2\text{O}]{\text{NaOH, neat, atm., T, 24 h}} \text{Ph-CH(OH)-CH}_2\text{-Ph (4a)} + \text{Ph-C(=O)-CH}_2\text{-Ph (3a)}$ |            |              |                |        |                   |                      |
|--|------------|--------------|----------------|--------|-------------------|----------------------|
| Entry  | 1a (equiv) | NaOH (mol %) | Atm.           | T [°C] | 4a + 3a Yield [%] | 4a/3a <sup>[b]</sup> |
| 1  | 1.5        | 30           | air            | 110    | 95                | 70:30                |
| 2  | 1.5        | 30           | N <sub>2</sub> | 110    | 96                | 75:25                |
| 3  | 2.0        | 30           | N <sub>2</sub> | 120    | 98                | 87:13                |
| 4  | 2.0        | 60           | N <sub>2</sub> | 120    | 97                | 90:10                |
| 5  | 3.0        | 60           | N <sub>2</sub> | 120    | 98                | 93:7                 |
| 6  | 3.0        | 100          | N <sub>2</sub> | 130    | 98 (76)           | 97:3                 |

[a] Solvent-free mixture of **1a**, **2a** (2 mmol), and NaOH sealed in a 10 mL Schlenk tube in air or N<sub>2</sub> was heated for 24 h and then monitored by <sup>1</sup>H NMR spectroscopy or GC-MS. [b] Conversions of **2a** and **4a/3a** ratios were determined by <sup>1</sup>H NMR analysis. Yields of isolated **4a** are shown in parenthesis.

NaOH is a better base.<sup>[16,17]</sup> Thus, with 1.5 equivalents of **1a**, the reaction gave **4a** as the major product in a good yield and selectivity (entry 1). In contrast, other bases (LiOH, KOH, CsOH) either gave lower yields or lower selectivities of **4a**, or led to the formation of unknown by-products.<sup>[15]</sup> In contrast to using a solvent, which led to decreased selectivity of **4a**,<sup>[15]</sup> a nitrogen atmosphere, higher loadings of **1a** and NaOH, and higher temperatures were all capable of enhancing the selectivity of **4a**. Thus, by using 3 equivalents of **1a** and 100 mol % of NaOH, the reaction at 130 °C could afford a good yield of **4a** in high selectivity (entry 6).

The optimized reaction conditions were then applied to various primary alcohols and ketones (Table 2). Thus, both electron-rich (**4b–e**, **4k**, and **4l**) and electron-deficient benzylic alcohols (**4f–j**), including an *ortho*-substituted one (**4e**), those bearing bulky groups (**4k** and **4l**), and those with the reactive F, Cl, and Br groups, all afforded the target

**Table 2:** Synthesis of alkylated alcohols.<sup>[a]</sup>

| $\text{R}^1\text{-CH}_2\text{-OH (1)} + \text{R}^2\text{-C(=O)-R}^3 \xrightarrow[\text{-H}_2\text{O}]{\text{NaOH (100 mol %), N}_2, \text{ neat, 130 }^\circ\text{C, 24 h}} \text{R}^2\text{-CH(OH)-CH}_2\text{-R}^1 \text{ (4)} + \text{R}^2\text{-C(=O)-CH}_2\text{-R}^1 \text{ (3)}$ |                                       |                                       |  |
|---|---------------------------------------|---------------------------------------|--|
| <b>4a</b> : 76%, 97:3   | <b>4b</b> : 74%, 95:5                 | <b>4c</b> : 72%, 92:8                 |  |
| <b>4d</b> : 68%, 91:9   | <b>4e</b> : 72%, 98:2                 | <b>4f</b> : 56%, 83:17                |  |
| <b>4g</b> : 75%, 98:2   | <b>4h</b> : 74%, 98:2                 | <b>4i</b> : 67%, 96:4                 |  |
| <b>4j</b> : 53%, 97:3   | <b>4k</b> : 61%, 92:8                 | <b>4l</b> : 68%, 92:8                 |  |
| <b>4m</b> : 67%, >99:1  | <b>4n</b> : 68%, 78:22                | <b>4o</b> : 75%, 97:3                 |  |
| <b>4p</b> : 58%, 90:10  | <b>4q</b> : 61%, 89:11                | <b>4r</b> : 58%, 92:8                 |  |
| <b>4s</b> : <sup>[b]</sup> 40%, 85:15   | <b>4t</b> : <sup>[b]</sup> 38%, 88:12 | <b>4u</b> : <sup>[c]</sup> 31%, 60:40 |  |

[a] Unless otherwise noted, see entry 6 of Table 1 for reaction conditions. Yields of isolated **4** were based on **2**. The **4/3** ratios were determined by <sup>1</sup>H NMR spectroscopy. [b] 100 mol % KOH, 160 °C, 3 days. [c] 100 mol % KOH, 160 °C, 24 h. **4/3** ratio determined by GC-MS.

alcohols **4** in moderate to good yields and high selectivities. By bearing the versatile halide groups, **4f–j** are potentially useful substrates in synthesis. Similarly, 2-thienylmethanol could also be used as the alkylating reagent, thus giving a moderate yield of **4m** in high selectivity (> 99:1). Moreover, electron-rich (**4n** and **4q**) and electron-deficient acetophenones (**4o** and **4p**), as well as a heteroaryl methyl ketone (**4r**), also reacted smoothly with **1a** to afford the target alcohols **4** in moderate to good yields and good to high selectivities. In addition, aliphatic alcohols and ketones such as *n*-hexanol and 2-octanone were also employed, but they require harsher reaction conditions with KOH as the base. The reactions afforded low yields of the products (**4s** and **4t**), and is most possibly due to the much lower reactivities of the aliphatic substrates. As for the substituted ketone 3,4-dihydronaphthalen-1(2*H*)-one, selectivity of the reaction was not high and only a low yield of **4u** was obtained. This result may be attributed to the steric hindrance of the substituents in the reduction step, and further implies that it may be more suitable for ketone-product preparation. In comparison with our previous TM-free dehydrative  $\beta$ -alkylation of secondary alcohols,<sup>[11b]</sup> the present method requires no external catalysts at all, thus greatly simplifying the reaction conditions.

We then considered the  $\alpha$ -alkylation reaction leading to the alkylated ketones **3**. Since solvent-free conditions, inert atmosphere, higher loadings of **1**, and higher temperatures favor the production of **4**, we deduced that solvent, aerobic conditions, lower loadings of **1**, and lower temperatures should favor the formation of **3**. However, initial attempts with **1a** and **2a**, employing the above-mentioned protocols, were not successful.<sup>[15]</sup> In contrast, the reaction of the substituted **1b** and **2b** gave a rather good yield and selectivity for **3b** and **4b** when they were directly heated with NaOH under air in toluene at 110 °C (Table 3, entry 1). Consistent with preceding observations, more air enhanced the selectivity for **3b** (entry 2). The same was observed when KOH was used (entries 3 and 4), thus implying that air can oxidize **4** into **3** under basic conditions. As a result, KOH exhibited higher yield and selectivity to give a good isolated yield of **3b**. Addition of the substrates in reverse order was also tested to improve the yield and selectivity of **3b**, however, only a lower yield of **3b** was obtained because of the formation of by-products (entry 5). Additional screening of the reaction conditions using higher or lower amounts of KOH and solvent<sup>[15]</sup> showed that by using double the loading of both KOH and toluene, yet still maintaining the same base concentration, the reaction afforded a higher yield of **3b** in the highest (> 99 %) selectivity (entry 6).

The optimized reaction conditions were then applied to other benzylic alcohols and ketones (Table 4). Thus, various electron-rich (**3b–e** and **3m**) and electron-deficient (**3g–l**) benzylic alcohols and the unsubstituted **1a** (**3f**), all reacted efficiently with **2b** to give a greater than 99 % selectivity of alkylated ketones **3** in moderate to good yields. Similarly, by using substituted benzylic alcohols, **2a** and substituted acetophenones reacted efficiently to give **3** in good yields and greater than 99 % selectivity (**3r–t**). Additionally, heteroaryl methanols such as pyridyl methanols and 2-thienylmethanol, were used as the alkylating reagents to afford **3p** and **3q**, respectively, in greater than 99 % selectivity, albeit in lower yields resulting from formation of unknown by-products. In addition to the above methyl ketones, this method could also be applied to substituted 3,4-dihydronaphthalen-1(*2H*)-ones to give good yields and greater than 99 % selectivity of the target **3u** and **3v**. In contrast, it seemed **1a/2a** is the only unsuitable substrate combination in the present method, for under similar reaction conditions only a low yield of **3a** was obtained in a low selectivity.<sup>[15]</sup> NaOH was a better base, but the yield and selectivity of **3a** were not high either. Thus, the best result was obtained by using NaOH as the base in the presence of more air by adapting the reaction tube with an air balloon. The low selectivity of **3a** may be attributed to easy reduction of the unsubstituted **3a** into **4a** by **1a** (e.g., Table 1, entry 1).

The synthetic potential of the above  $\alpha$ -alkylation reactions was also tested by running the model reactions on a larger scale. For example, 20 mmol

**Table 3:** Optimization of the reaction conditions for synthesis of alkylated ketones.<sup>[a]</sup>

| $\text{R}^1\text{CH}_2\text{OH} + \text{R}^2\text{C(=O)CH}_3 \xrightarrow[\text{-H}_2\text{O}]{\text{base, air, toluene, 110 }^\circ\text{C, 24 h}} \text{R}^2\text{C(=O)CH}_2\text{CH(R}^1\text{)CH}_3 \quad \left( \text{R}^2\text{C(=O)CH}_2\text{CH(R}^1\text{)CH}_2\text{OH} \right)$ <p>1.2 equiv <b>1b</b> + <b>2b</b> → <b>3b</b> (major) + <b>4b</b> (minor)<br/>R<sup>1</sup> = R<sup>2</sup> = <i>p</i>-MeOC<sub>6</sub>H<sub>4</sub></p> |              |           |                         |                                 |                             |
|--|--------------|-----------|-------------------------|---------------------------------|-----------------------------|
| Entry  | Base (mol %) | Sol. (mL) | Air (mL) <sup>[b]</sup> | <b>3b</b> + <b>4b</b> Yield [%] | <b>3b/4b</b> <sup>[c]</sup> |
| 1  | NaOH (50)    | 2         | 10                      | 93                              | 82:18                       |
| 2  | NaOH (50)    | 2         | 100                     | 80                              | 93:7                        |
| 3  | KOH (50)     | 2         | 10                      | 99                              | 89:11                       |
| 4  | KOH (50)     | 2         | 100                     | 95 (68)                         | 95:5                        |
| 5 <sup>[d]</sup>   | KOH (50)     | 2         | 100                     | (43)                            | 94:6                        |
| 6  | KOH (100)    | 4         | 100                     | 97 (71)                         | > 99:1                      |

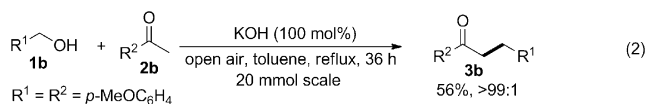
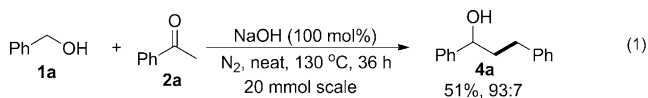
[a] Unless otherwise noted, **1b** (1.2 equiv), **2b** (2 mmol), and base in toluene were sealed under air in a Schlenk tube. The mixture was then heated at 110 °C for 24 h and monitored by GC-MS. [b] 10 or 100 mL Schlenk tubes were used. [c] Conversions of **2b** and **3b/4b** ratios were determined by GC-MS. Yields of isolated **3b** are shown within parentheses. [d] 1.2 equiv of **2b**.

**Table 4:** Synthesis of alkylated ketones.<sup>[a]</sup>

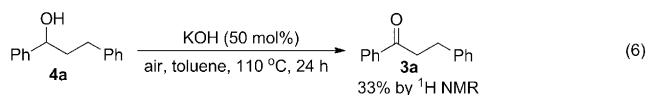
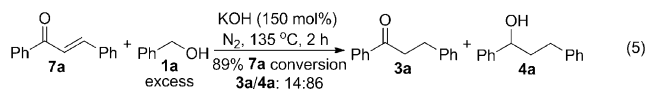
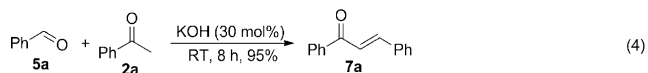
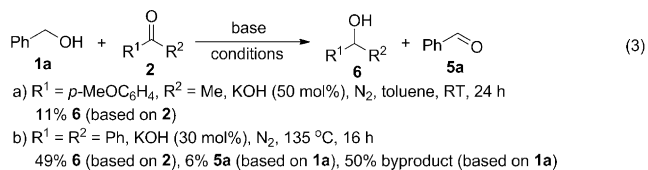
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|--|---|---------------------------------------|---------------------------------------|---------------------------------------|------------------------|
| $\text{R}^1\text{CH}_2\text{OH} + \text{R}^2\text{C(=O)CH}_3 \xrightarrow[\text{-H}_2\text{O}]{\text{KOH (100 mol %), air, toluene, 110 }^\circ\text{C, 24 h}} \text{R}^2\text{C(=O)CH}_2\text{CH(R}^1\text{)CH}_3 \quad \left( \text{R}^2\text{C(=O)CH}_2\text{CH(R}^1\text{)CH}_2\text{OH} \right)$ <p>1.2 equiv <b>1</b> + <b>2</b> → <b>3</b> + <b>4</b></p> |   |                                       |                                       |                                       |                        |
| <b>3b</b> : 71%, >99:1   | <b>3c</b> : 69%, >99:1                  | <b>3d</b> : 67%, >99:1                | <b>3e</b> : 71%, >99:1                | <b>3f</b> : 66%, >99:1                | <b>3g</b> : 54%, >99:1 |
| <b>3h</b> : 72%, >99:1   | <b>3i</b> : 65%, >99:1                  | <b>3j</b> : 63%, >99:1                | <b>3k</b> : 65%, >99:1                | <b>3l</b> : 57%, >99:1                | <b>3m</b> : 60%, >99:1 |
| <b>3n</b> : 45%, >99:1   | <b>3o</b> : 50%, >99:1                  | <b>3p</b> : 52%, >99:1                | <b>3q</b> : 37%, >99:1                | <b>3r</b> : 73%, >99:1                | <b>3s</b> : 70%, >99:1 |
| <b>3t</b> : 65%, >99:1   | <b>3u</b> : <sup>[b,c]</sup> 66%, >99:1 | <b>3v</b> : <sup>[b]</sup> 71%, >99:1 | <b>3a</b> : <sup>[d]</sup> 23%, 40:60 | <b>3a</b> : <sup>[e]</sup> 42%, 67:33 |                        |

[a] Unless otherwise noted, see entry 6 of Table 3 for reaction conditions. Yields of the isolated **3** were based on **2**. The **3/4** ratios were determined by GC-MS. [b] 120 °C. [c] 2 equiv of **1a**. [d] 50 mol % KOH, 2 mL toluene. [e] 50 mol % NaOH, 4 mL toluene, air balloon.

scale reactions of **1a** with **2a** and **1b** with **2b** could effectively afford the target alcohol **4a** and ketone **3b**, respectively, in acceptable yields and high selectivities [Eqs. (1) and (2)].<sup>[15]</sup> These results imply that the present autocatalyzed alkylation methods should be more suitable for preparative purposes than other methods since no external catalysts are required.



Clearly, the above satisfactory results (Tables 1–4) suggest that the proposed autocatalyzed route in Scheme 2A has been realized, and was further investigated as follows. Firstly, for MPV-O reduction of **2** by **1** under basic conditions to give the aldehydes **5** and secondary alcohols **6** (step a), the key step for initiating the reaction, is known in the literature<sup>[8]</sup> and can be easily confirmed. Thus, the ketones **2** could be reduced by **1a** to give the corresponding alcohols **6** and benzaldehyde (**5a**) in the presence of KOH [Eq. (3)].<sup>[11b,15]</sup> Then, base-mediated aldol condensation of **2** and **5**, which is well documented, gave the intermediate chalcones **7** [Eq. (4)].<sup>[11b]</sup> As shown in Scheme 2A, **7** underwent a TM-free MPV-O-type reduction by **1** to give **3** and **4** [Eq. (5); Scheme 2B, X = C, O] with regeneration of **5** to continue the catalytic cycle.<sup>[11b]</sup> As to the reason for the higher selectivity of **4** under a nitrogen atmosphere and higher selectivity of **3** under air, it is most likely that air can oxidize alcohols into ketones under basic conditions. Indeed, we observed that heating **4a** under an atmosphere of air in the presence of KOH afforded a considerable yield of **3a** [Eq. (6)]. This result is consistent with previous reports,<sup>[11b,12,18]</sup> and can satisfactorily explain the higher selectivity for **3** under air, and for **4** under a nitrogen atmosphere.



In conclusion, we have developed catalyst-free autocatalyzed dehydrative α-alkylation reactions of ketones with alcohols to selectively afford ketone or alcohol products by

C=C bond formation and controllable and selective MPV-O-type redox processes under simple, practical, green, and one-pot conditions. These results not only represent a technical and conceptual advance in the field, but also reveal that these potentially useful methods may provide new possibilities in synthesis. Extension of the autocatalyzed alkylation methods, synthetic applications, and additional mechanistic studies are underway.

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