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Short Communication

Efficient and eco-compatible transition metal-free Oppenauer-type oxidation of alcohols

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ABSTRACT

Catalytic amounts of cheap, non-toxic, easy-to-handle and non-sensitive sodium tert-butoxide are able to promote the dehydrogenative oxidation of a wide array of secondary alcohols using inexpensive benzophenone as the H-acceptor. The corresponding ketones, highly important intermediates and targets throughout life and material sciences, are very selectively obtained under mild conditions.

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1. Introduction

The oxidation of alcohols to their corresponding carbonyl compounds constitutes a very important reaction in organic synthesis [1]. Classical methods involve stoichiometric amounts of chromium [2] or manganese oxides [3], and activated DMSO [4] or hypervalent iodine derivatives [5]. Most of these oxidants are difficult-to-handle, hazardous and the high amounts of wastes produced are of environmental concern [2–5]. The search for catalytic, cheap and eco-compatible methods is thus crucial for laboratory- and large-scale processes. Along these lines, transition metal-based systems are able to catalytically promote oxidations of alcohols in the presence of oxygen or peroxides [6–9]. However, these catalysts are generally sophisticated and often expensive. Additionally, oxidations consisting in the hydrogen transfer (H-transfer) from the alcohol to an H-acceptor (e.g. ketone) also constitute attractive methodologies [10–12]. Discovered by Oppenauer in the 1930s, such oxidations initially involved stoichiometric amounts of aluminum or alkali alkoxides [10–14]. Afterwards, lanthanides [11] and transition metals (ruthenium [15–17], iridium [18–20], iron [21–24]) were found to achieve Oppenauer-type oxidations catalytically. Besides, we and others recently reported that catalytic amounts of alkali hydroxides and alkoxides were able

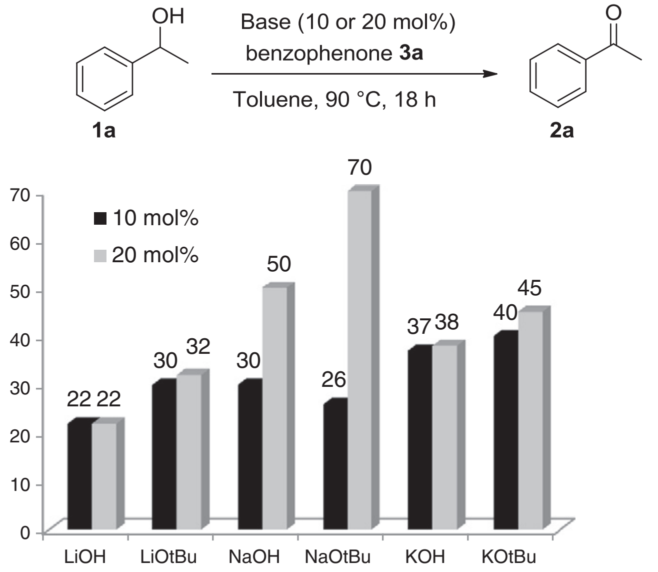

Fig. 1. Oxidation of **1a** into **2a** catalyzed by various alkali bases: yields of **2a** (%)[a,b] ([a]base (0.1 or 0.2 mmol), **1** (1 mmol), **3a** (2 mmol), toluene (2 mL); [b]conversions of **1a** determined by ^{1}H NMR with 1,3-dimethoxybenzene as standard (selectivities >98%)).

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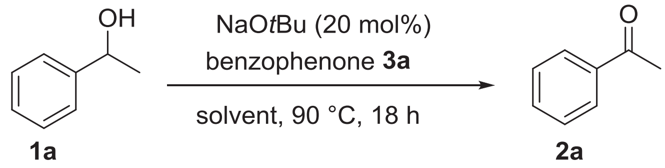
Table 1
Oxidation of **1a** into **2a** via H-transfer in the presence of NaO*t*Bu in various solvents.[a,b]



	Solvent	Conversions of **1a** (%)[b]
1	DMSO[c]	37
2	Acetonitrile[c]	40
3	Dioxane	43
4	Dichloromethane	47
5	THF	50
6	Toluene	70

[a] **1a** (1 mmol), NaO*t*Bu (0.2 mmol), **3a** (2 mmol), solvent (2 mL).
[b] Determined by ^{1}H NMR with 1,3-dimethoxybenzene as standard (selectivities >99%).
[c] Side aldol condensation and crotonization. Selectivities: in DMSO: 50%; and in acetonitrile: 70%.

to promote the reverse Meerwein–Ponndorf–Verley reduction of ketones using alcohols as H-donors [25–29]. Hence this paper reports the route to cheap and non-toxic alkali-based catalytic systems for the complementary Oppenauer-type oxidation of alcohols [10–12,30,31]. These results have been patented [26].

2. Experimental

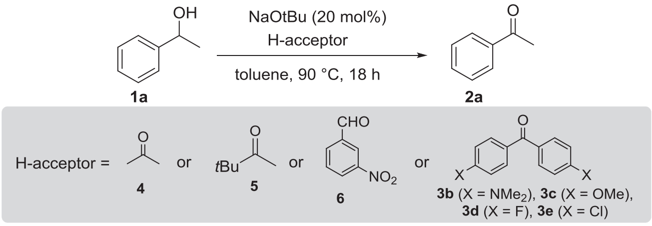
2.1. Materials and instruments

Reactants were purchased from commercial sources and used without purification. NaO*t*Bu (99.9%, Aldrich and 97%, Alfa Aesar), KO*t*Bu (99.99%, Aldrich), LiO*t*Bu (99.9%, Alfa Aesar), NaOH (99.99%, Aldrich), KOH (99.99%, Aldrich), and LiOH (99.9%, Alfa Aesar), were carefully ground to a fine powder before use. Column chromatography was performed with SDS 60 Å C.C. silica gel and thin layer chromatography using Merck silica gel 60 F_{254} plates. NMR spectra were recorded on a Bruker 400 spectrometer and GC/MS on an Agilent 6890N instrument.

2.2. General procedures for the oxidation of alcohols with NaOtBu

A Radley tube (Carousel RR98030) with a magnetic stirring bar was charged with NaO*t*Bu (Aldrich (99.9%) and Alfa Aesar (97%), 0.2 mmol), benzophenone (2 mmol), alcohol (1 mmol) and toluene (2 mL). The tube was closed, stirred and heated. After cooling, dichloromethane

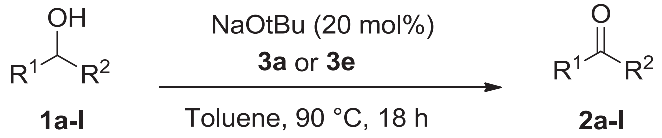
Table 2
Oxidation of **1a** into **2a** via H-transfer in the presence of different H-acceptors.[a]

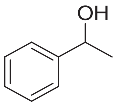
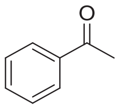
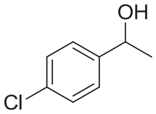
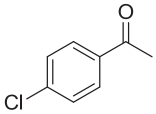
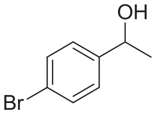
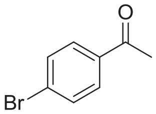
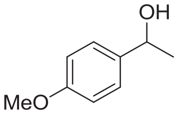
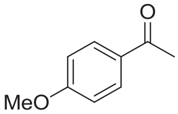
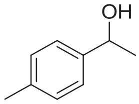
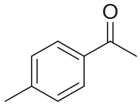
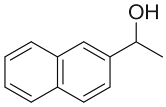
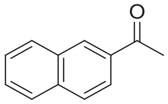
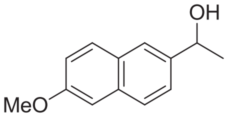
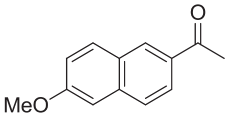
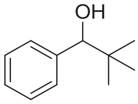
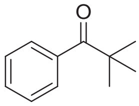
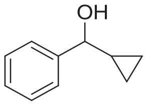
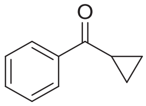
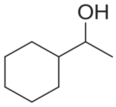
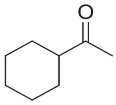
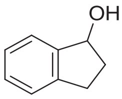
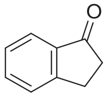
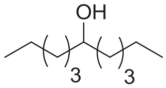
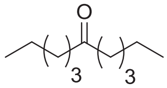


	H-acceptor	Conversions of **1a** (%)[b]
1	**4**	2
2	**4**[c]	10
3	**5**	35
4	**6**	20[d]
5	**3b**	26
6	**3c**	55
7	**3d**	70
8	**3e**	85

[a] **1a** (1 mmol), NaO*t*Bu (0.2 mmol), H-acceptor (2 mmol), toluene (2 mL).
[b] Determined by ^{1}H NMR with 1,3-dimethoxybenzene as standard (selectivities >99%).
[c] **4** used as the solvent.
[d] Aldol condensation between **2a** and **6** (selectivity: 60%).

Table 3
Oppenauer-type oxidation of alcohols.[a]



	Alcohol	Compound		Conversions of **1a–l** (%)[b]
1			**2a**	70 85[c]
2			**2b**	60 64[c]
3			**2c**	54 59[c] 93[d]
4			**2d**	75
5			**2e**	72 85[d]
6			**2f**	76
7			**2g**	80
8			**2h**	60
9			**2i**	100
10			**2j**	34
11			**2k**	45
12			**2l**	50 100[e]

[a] NaO*t*Bu (0.2 mmol), alcohol (1 mmol), **3a** (2 mmol), toluene (2 mL).
[b] Conversions of **1a–l** determined by ^{1}H NMR with 1,3-dimethoxybenzene as standard (selectivities >99%).
[c] **3e** instead of **3a**.
[d] 48 h.
[e] 110 °C.

(10 mL) and 1,3-dimethoxybenzene (130 μL) were added. The mixture was filtrated, the filtrate washed twice with water, further dried over Na_2SO_4 and analyzed by GC–MS and ^{1}H NMR (after concentration) for the determination of yields or directly concentrated under vacuum to yield the crude product. Ketones can be purified by distillation of the crude and subsequent column chromatography (when necessary). All products (previously described and commercial) were analyzed by ^{1}H NMR and GC–MS; coadditions of authentic samples were performed.

3. Results and discussion

3.1. Bases screening

Oxidation of 1-phenylethanol **1a** into acetophenone **2a** via H-transfer was first performed with benzophenone **3a** as the H-acceptor in toluene at 90 °C and with alkali alkoxides and hydroxides as catalysts (10 or 20 mol%). At 10 mol% (Fig. 1, dark), yields of acetophenone were low (22 to 40%) whatever the base. The effect of increasing catalyst loading to 20 mol% (Fig. 1, light) was highly cation-dependent. Indeed, no or little improvement was observed for lithium and potassium bases. By contrast, oxidation performances were greatly improved for sodium bases, the yield of **2a** increasing from 30 to 50% for NaOH and from 26 to 70% for NaO*t*Bu. Such alkali cation influence and superiority of sodium were previously highlighted in the reverse MPV reduction [25]. Noteworthy, with these sodium bases, the equilibrium (Oppenauer oxidation, mirror process of MPV reduction, is an equilibrium reaction) is almost reached after 9 h at 20 but also at 10 mol% (with 20 mol% of NaOH, **2a** was obtained in 30% yield after 2 h and 46% after 9 h while with 20 mol% of NaO*t*Bu, **2a** was formed in 50% yield after 2 h and 68% after 9 h, see Supplementary data for more values). For Li and K bases, the low yields reported after 18 h (Fig. 1) also correspond to maximum yields that can be obtained at the equilibrium. Besides, so far, alkali alkoxides were reported to be efficient only when used in stoichiometric amounts [11]. The ability of NaO*t*Bu at 20 mol% to efficiently promote Oppenauer oxidation catalytically is thus unexpected. Additionally, **2a** could be selectively obtained and side aldol condensation usually encountered in Oppenauer oxidations involving stoichiometric amounts of alkali alkoxides occurred to very few extent (<2%) [11].

3.2. Solvents screening

Oxidation of 1-phenylethanol **1a** was next performed with NaO*t*Bu (20 mol%) and benzophenone in various solvents (Table 1). Polar solvents like DMSO or acetonitrile allowed to obtain **2a** in 37 and 40% yields respectively but the side aldol condensation and subsequent crotonization were favored in these media (entries 1 and 2). The selectivities were significantly improved in less polar solvents such as dioxane, dichloromethane and THF, with **2a** being selectively obtained however in moderate yields (43, 47, 50% respectively, entries 3–5). From this study, toluene appeared as the most suitable solvent for H-transfer oxidation (70%, entry 6).

3.3. H-acceptor screening

The nature of the H-acceptor was next modified (Table 2) [32]. Acetone **4** did not efficiently promote oxidation of **1a**, neither when used stoichiometrically, nor as solvent (entries 1 and 2). The ability of pinacolone **5** to act as an H-acceptor was also explored and **2a** was obtained in 35% yield in that case (entry 3). With 3-nitrobenzaldehyde **6** as the H-acceptor, **2a** was obtained in low yields (20%) and side aldol condensation between **2a** and **6** significantly decreased the selectivity (Table 2, entry 4). Benzophenone still thus appeared as the best candidate and different commercially available 4,4′-disubstituted benzophenones (entries 5–8) were next tested. The substituents are expected to modify the H-acceptor capabilities of the benzophenone by modulating the electron-density onto the carbonyl function. As expected, electron-rich H-acceptor **3b** or **3c** revealed to be less efficient than **3a**, with **2a** being obtained in 26 and 55% (entries 5 and 6) yields respectively instead of 70%. Despite the presence of electron-withdrawing fluoro substituents, **3d** did not behave as a better H-acceptor than **3a** (entry 7). Interestingly, **3e** involving electron-withdrawing chloride substituents significantly improved the performances, with **2a** being obtained in 85% yield (entry 8).

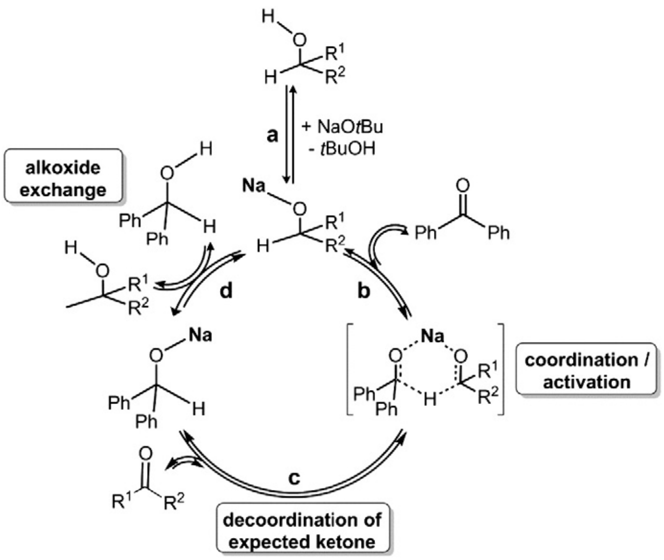


Fig. 2. Mechanism proposal.

3.4. Substrate scope

Oxidation of various 1-arylethanols was tested with NaO*t*Bu (20 mol%) and H-acceptor **3a** in toluene (Table 3, entries 1–5). Electron-poor substrates were converted into ketones **2b** and **2c** in moderate yields (60 and 54% respectively) and H-acceptor **3e** did not allow to significantly improve the performances (64 and 59%, entries 2^{c}, 3^{c}). However, the yield of **2c** was increased to 93% by increasing the reaction time to 48 h using a cheaper H-acceptor **3a** (entry 3^{d}). For electron-rich substrates (entries 4 and 5), **2d** and **2e** were obtained in 75 and 72% yields respectively and increasing the reaction time allowed to get **2e** with 85% yield (entry 5). Good performances were also observed for naphthalene-derived alcohols, with **2f** and **2g** being formed in 76 and 80% yields respectively (entries 6 and 7). The catalytic system could also be applied to non-enolizable benzyl alcohols, with **2h** being obtained in 60% yield and **2i** quantitatively prepared (entries 8 and 9). The performances of aliphatic alcohols oxidations depended on the substrate structures. Aliphatic alcohols involving cyclic substituents were transformed in fair yields (34 and 45% for **2j** and **2k**, entries 10 and 11) and neither an increase of the temperature or reaction time, nor the use of H-acceptor **3e** allowed to improve yields. By contrast, linear 6-undecanol, converted in 50% yield at 90 °C, was quantitatively oxidized at 110 °C (entry 12).

3.5. Mechanism proposal

To account for the base-catalyzed Oppenauer-oxidation of alcohols, we propose a reversible catalytic cycle (Fig. 2) consistent with the mechanism of the reverse reduction of ketones [25,33]. Therefore, deprotonation of the alcohol (step **a**, [34]) would give the corresponding sodium alcoholate. The latter could next activate acetophenone (step **b**) via coordination to the cation to give a cyclic intermediate encountered in stoichiometric Meerwein-Ponndorf-Verley reductions promoted by aluminum alkoxides [30]. The H-transfer and release of expected ketone (step **c**) could give sodium benzhydrolate which could next react with another molecule of substrate in step **d** (alkoxide exchange). Steps **b** to **d** can be described as coordination-activation and decoordination between the sodium (Lewis acid) and the ketone or alkoxide (Lewis base). The global order of reactivity (Na > K > Li) observed for *t*BuOM (M = Li, Na, K) and MOH probably indicates that Na represents the right balance in terms of Lewis acidity versus K and Li.

4. Conclusion

In summary, catalytic amounts of NaO*t*Bu are able to efficiently promote the dehydrogenative oxidation of various alcohols into the corresponding ketones. The method is versatile for benzyl and linear aliphatic alcohols with some limitations for aliphatic cyclic alcohols. This catalytic transition metal-free system is cheap, easy-to-handle and inexpensive benzophenone is used as the H-acceptor. The method is thus competitive compared to most of existing transition metal-catalyzed oxidations involving an oxidant [6–9] or an H-acceptor [15–24]. Extension of the application field and mechanistic studies are now ongoing in our laboratories.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.catcom.2013.12.030.

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