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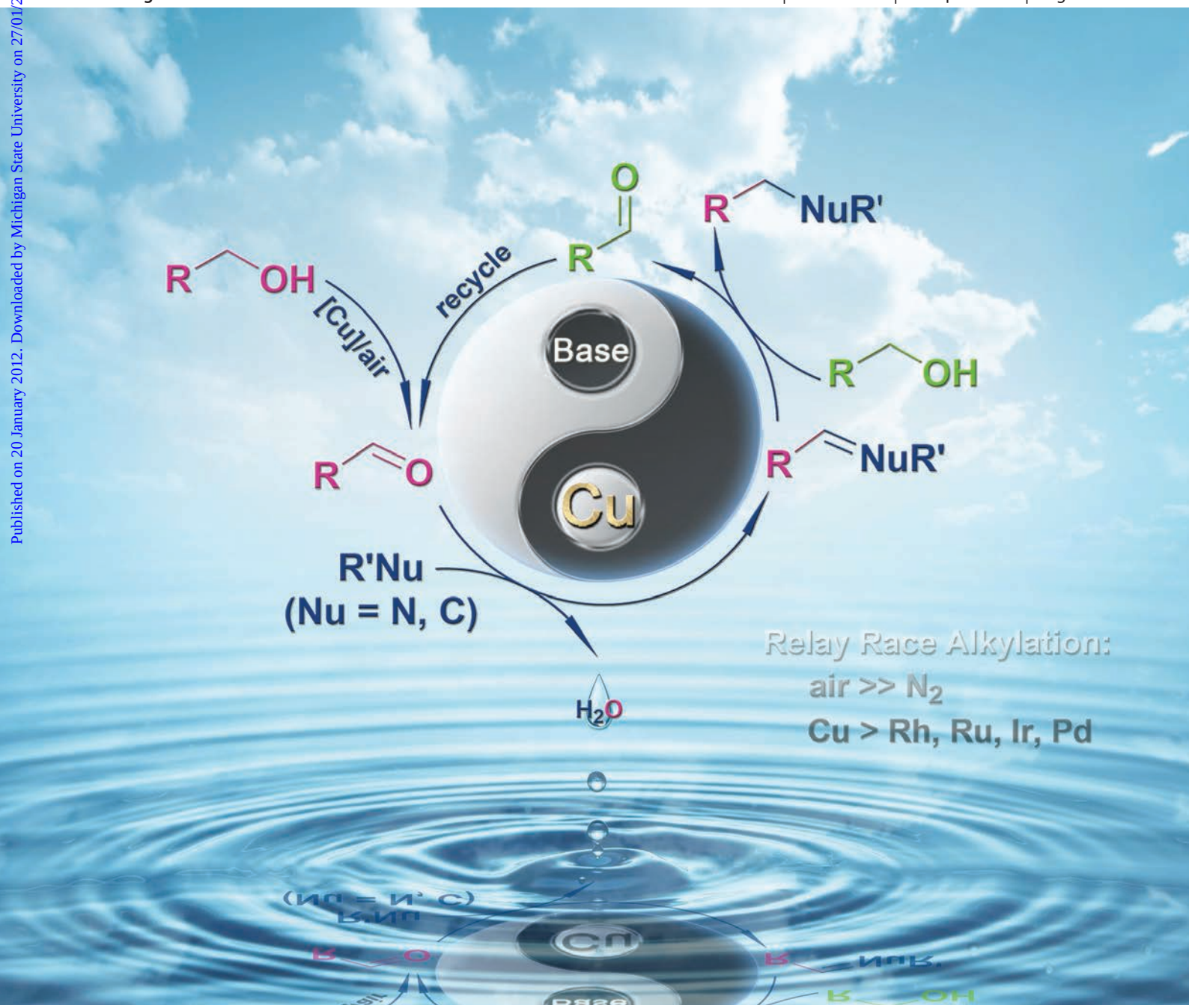

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FULL PAPERS

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PAPER

Copper-catalyzed *C*-alkylation of secondary alcohols and methyl ketones with alcohols employing the aerobic relay race methodology†

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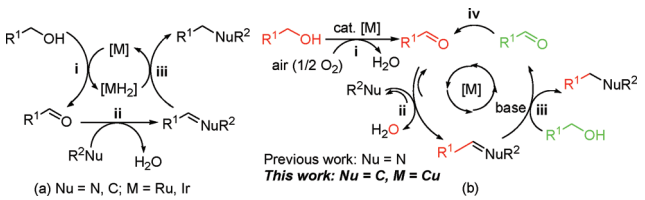
By employing aerobic oxidation to aldehydes as a more effective alcohol activation strategy, ligand-free copper catalysts were found to be superior catalysts than other metals in aerobic dehydrative *β*-alkylation of secondary alcohols and *α*-alkylation of methyl ketones using alcohols as the green alkylating reagents. Based on our mechanistic studies and also supported by the literature, we deduce that the newly-proposed relay race process rather than the conventional borrowing hydrogen-type mechanisms should be the most possible and a more rational mechanism for the aerobic *C*-alkylation reactions.

Introduction

Because stoichiometric preoxidation of reactants and the production of wastes can be avoided and a wider scope of substrates can be tolerated in the more economic, more environmentally-benign and milder one-pot tandem reactions, in recent years, transition metal-catalyzed dehydrogenation reactions have become a widely accepted substrate-activation strategy and powerful tool for greener synthesis of versatile carbon–carbon and carbon–heteroatom compounds.[1–3] For example, in cross-dehydrogenative couplings (CDC),[1] C–H functionalization can be achieved by initial oxidization of the amine and ether derivatives to the more reactive imine, iminium or oxocarbenium intermediates using oxidants, such as dioxygen or even air.[1]

On the other hand, by employing the borrowing hydrogen or hydrogen autotransfer methodology (Scheme 1a) *via* anaerobic dehydrogenative activation to the more reactive aldehydes (step i),[3] alcohols can be used as greener alkylating reagents[3–9] instead of the preactivated organohalides or carbonyl compounds as in conventional multi-step reactions. However, since the anaerobic dehydrogenation step (step i) is a thermodynamically unfavorable process,[3c] and due to the sensitive nature of the generated catalytic hydridometal species, expensive, not readily available noble metal complexes derived from ruthenium and iridium or the addition of capricious ligands for catalyst activation were usually required under inert atmosphere protection. Some reactions even suffer from the use of large amounts of hydrogen acceptors or bases, or low selectivities of the products.[3–10] All of these issues greatly limit the utilities of the methods and make them not as green and practical as were originally expected. Therefore, greener reactions that can be performed under milder conditions using cheaper and more available catalysts are highly desirable.[10–12]



Scheme 1 Metal-catalyzed alkylation methods.

In contrast with the above anaerobic borrowing hydrogen methods,[3] we recently developed a general and advantageous air-promoted metal-catalyzed aerobic *N*-alkylation method (Scheme 1b: Nu = N; M = Rh, Ru, Ir, Pd, Cu)[12] and proposed a relay race mechanism for these aerobic reactions. We also propose the aerobic alcohol oxidation (step i) to be a greener and more effective aldehyde generation alternative that can lead to more efficient reactions under aerobic conditions than under anaerobic conditions. However, despite our efforts[12] and contrary to the CDC[1] and anaerobic dehydrogenation[3] strategies, this has not been recognized as an alcohol activation alternative by the field so far.[3–12] We also envisioned that this aerobic method should be applicable to *C*-alkylation reactions (Nu = C),[3] typically the *β*-alkylation of alcohols and *α*-alkylation of ketones that used to be achieved by using ruthenium,[4,5] iridium,[6,7] or other noble metal catalysts[8,9] under inert conditions. Along with the copper-catalyzed *N*-alkylation method,[12d] herein, we report a ligand-free copper-catalyzed aerobic β-alkylation of secondary alcohols and α-alkylation of

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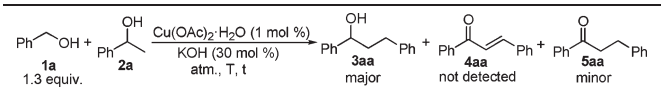
† Electronic supplementary information (ESI) available: Detailed experimental procedures, condition screening tables, mechanistic studies, characterization data, and NMR spectra of the products. See DOI: 10.1039/c1ob06739g

Table 1 Condition screening[a,13]



Run	Atm., *T*, *t*	**3aa** + **5aa**%[b]	**3aa**/**5aa**[b]
1[c]	N_2, 110 °C, 36 h	trace	—
2	N_2, 110 °C, 36 h	54	95/5
3	air, 110 °C, 24 h	98	97/3
4[d]	air, 110 °C, 24 h	78	>99/1
5	**air, 120 °C, 24 h**	**99 (87)**	**>99/1**

[a] See Electronic Supplementary Information for operations†. The reactions were monitored by GC-MS and/or ^{1}H NMR. [b] NMR yields (isolated yields in parenthesis) based on **2a**. **3aa**/**5aa** ratios measured by ^{1}H NMR. [c] No metal catalysts added. [d] 2,2′-Bipyridine (1 mol%) added.

methyl ketones using alcohols as the alkylating reagents, and propose a new mechanism for the aerobic *C*-alkylation reactions.

Results and discussion

Condition optimization and substrate extension

In our studies, conditions similar to our previous *N*-alkylation methods[12] were adopted to optimize the model reaction of benzyl alcohol **1a** and 1-phenylethanol **2a** (Table 1)[13] using only catalytic amounts of KOH, the most often used base in related *C*-alkylation reactions.[4,6,8,10] Initially, no reaction was observed in a blank reaction carried out under nitrogen without adding any metal catalyst (run 1). Then, the ligand-free metal catalysts derived from Rh, Ru and Ir that used to be active catalysts in aerobic *N*-alkylation reactions[12b] were investigated. However, these catalysts were not efficient, giving only low to moderate yields of the target product **3aa** in 36 h at 110 °C under either aerobic or anaerobic conditions.[13] $Pd(OAc)_2$ and $Cu(OAc)_2{\cdot}H_2O$ were found to be comparatively more effective,[13] with the Cu-catalyzed aerobic reaction being the most efficient one, giving an almost quantitative yield and high selectivity of the product (run 3). Ligands were found ineffective to promote the reaction under the same conditions and thus may be unnecessary for the reaction (run 4). Unlike the literature methods that usually require large amounts of base (1–5 equiv.),[4,6,8,10] in the present method, 30 mol% of KOH was found to be efficient enough to give high yields and selectivities of the product. As screened, heating the same reaction (run 3) at a slightly higher temperature (120 °C) could afford the product in the highest yield (99% by GC) and highest selectivity (>99/1 by NMR) (run 5). Generally, no or only trace amounts of byproduct **5aa** were detected in the reaction, leading to the easy isolation of pure **3aa** in high yield (87%). In contrast, another possible byproduct **4aa** was not detected at all. Similar to $Cu(OAc)_2{\cdot}H_2O$, various Cu catalysts were also investigated in the reaction and found to be highly active catalysts under the condition.[13]

After optimization of the reaction conditions, a series of benzylic and aliphatic, primary and secondary alcohols were then investigated to extend the scope of the method (Table 2). All of the electron-rich and -deficient 1-arylethanols (runs 1–4) and benzylic alcohols (runs 5–10), including a sterically more bulky *ortho*-substituted **1g** (run 10), reacted efficiently to give high yields of the products in high selectivities under the aerobic conditions. Unlike the benzylic alcohols, the reactions of heterobenzylic alcohols were generally slower, but could still afford moderate to high yields of the products in high selectivities at higher temperatures (runs 11–14).

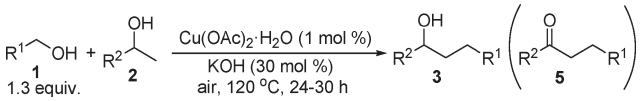
A similar method is also applicable to either primary or secondary aliphatic alcohols. The reactions of benzylic alcohols with secondary aliphatic alcohols afforded moderate to good yields of the products in high selectivity at a higher temperature (runs 15–19), as did the reactions of primary aliphatic alcohols with the 1-arylethanols (runs 20–23). The reaction of a cyclic secondary alcohol was not successful at present, giving only a low yield and low selectivity of the products (run 24). In contrast, secondary benzylic alcohols could also be used as the alkylating reagent, *e.g.*, heating **2a** alone afforded a good yield of the target product in high selectivity (run 25).

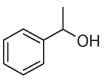
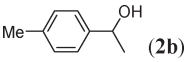
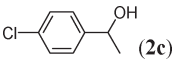
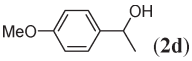
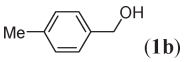
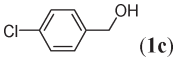
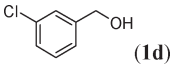
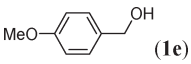
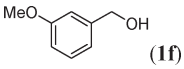
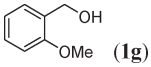
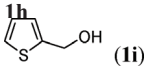
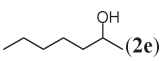
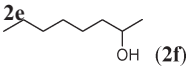
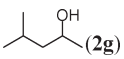
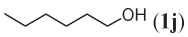
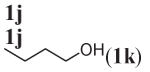
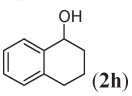
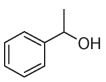
The above method could also be extended to aerobic α-alkylation of methyl ketones. With excess alcohols **1**, the alkylated alcohols **3** could also be easily obtained from methyl ketones **6** (Table 3). In this reaction, KOH was found to be not a suitable base because considerable unidentified byproducts were generated, nor was CsOH.[13] In contrast, NaOH was found to be the best base, giving a much higher yield and selectivity of the product under the same conditions (85%, 78/22). Further condition screening showed that all of the Cu catalysts were similarly active and the reaction was best carried out using 3 equiv. of **1**, 1 mol% of Cu catalyst, and 90 mol% of NaOH, affording 99% (85% isolated) yield of the product **3aa** with 95/5 selectivity (run 1).[13] This condition is applicable to a series of benzylic and aliphatic alcohols and methyl ketones. Thus, the electron-rich and -deficient methyl ketones and benzylic alcohols, including a sterically more bulky *ortho*-substituted **1g**, also reacted effectively to give high yields of the products with high selectivities (runs 1–8). An aliphatic alcohol also reacted smoothly to give the target product in good yield and good selectivity at a higher temperature (run 9).

Mechanistic discussion

As an ongoing study of our aerobic method[12] extended to the *C*-alkylation reactions, the mechanistic aspects of the present aerobic reactions are therefore our next concern. To our knowledge, before and after the report of our previous work,[12a,b] some *N*- and *C*-alkylation reactions were also carried out under air and found to be more efficient than the anaerobic reactions.[10,11] In some cases, whether the aerobic *C*-alkylation reactions proceeded *via* the borrowing hydrogen-type mechanisms (with M–H species involved as the key and active catalyst) has been seriously questioned by some researchers.[10a,b] However, since air's role in those reactions had not been well-studied and the mechanisms not properly understood and proposed, those reactions were mostly reverted to the borrowing hydrogen-type systems.[10,11] In the present Cu-catalyzed *C*-alkylation reactions, as in our previous reports,[12] the aerobic reactions were also found to be more efficient than the parallel anaerobic ones (Table 1).[13] We thus infer that, rather than following any other

Table 2 Cu-catalyzed aerobic β-alkylation of secondary alcohols with alcohols[a]

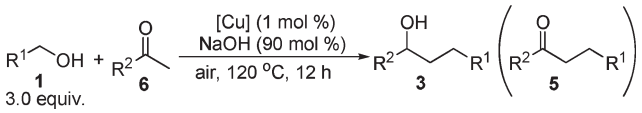


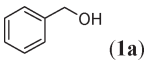
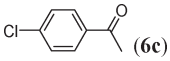
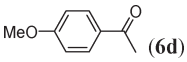
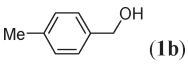
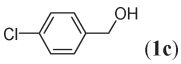
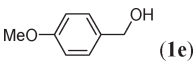
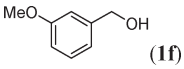
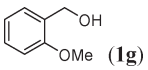
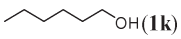
Run	1	2	3 + 5%[b]	3/5[b]
1	 (**1a**)	 (**2a**)	99	>99/1
2	**1a**	 (**2b**)	99	96/4
3	**1a**	 (**2c**)	88	95/5
4	**1a**	 (**2d**)	99	95/5
5	 (**1b**)	**2a**	98	92/8
6	 (**1c**)	**2a**	96	93/7
7	 (**1d**)	**2a**	97	>99/1
8	 (**1e**)	**2a**	99	92/8
9	 (**1f**)	**2a**	94	97/3
10	 (**1g**)	**2a**	98	97/3
11[c]	 (**1h**)	**2a**	90	94/6
12[c]	**1h**	**2b**	93	84/16
13[c]	**1h**	**2c**	63	93/7
14[d]	 (**1i**)	**2a**	54	>99/1
15[c]	**1a**	 (**2e**)	57	>99/1
16[c]	**1b**	**2e**	45	>99/1
17[c]	**1c**	**2e**	71	>99/1
18[c]	**1a**	 (**2f**)	69	>99/1
19[c]	**1a**	 (**2g**)	68	>99/1
20[c]	 (**1j**)	**2a**	67	>99/1
21[c]	**1j**	**2b**	38	>99/1
22[c]	**1j**	**2c**	53	>99/1
23[c]	 (**1k**)	**2a**	39	>99/1
24[c]	**1a**	 (**2h**)	(26)	(50/40)
25[c]	 (**2a**)	**2a**	(84)	(99/1)

[a] Reactions monitored by GC-MS and/or ^{1}H NMR. [b] Yields and **3**/**5** ratios were determined by ^{1}H NMR. Results in parenthesis were determined by GC-MS analysis due to unidentifiable complex NMR spectra of the reactions. [c] 160 °C, 48 h. [d] 135 °C, 48 h.

kind of mechanism,[3–11] these reactions most probably proceed *via* a process similar to the relay race mechanism we recently proposed (Scheme 1b).[12] Thus, as depicted in Scheme 2, the individual reactions in the path, *i.e.*, the aerobic alcohol

Table 3 Cu-catalyzed aerobic α-alkylation of methyl ketones with alcohols[a]



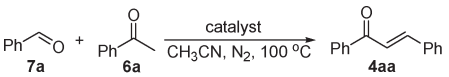
Run	1	6	3 + 5%[b]	3/5[b]
1	 (**1a**)	 (**6a**)	99	95/5
2	**1a**	 (**6c**)	99	93/7
3	**1a**	 (**6d**)	99	95/5
4	 (**1b**)	**6a**	99	96/4
5	 (**1c**)	**6a**	99	96/4
6	 (**1e**)	**6a**	99	91/9
7	 (**1f**)	**6a**	99	>99/1
8	 (**1g**)	**6a**	99	93/7
9[c]	 (**1k**)	**6a**	74	88/12

[a] Reactions monitored by GC-MS and/or ^{1}H NMR. [b] Yields and **3**/**5** ratios determined by ^{1}H NMR. [c] 160 °C, 48 h.

oxidation, aldol condensation and transfer hydrogenation reactions, were investigated to achieve more mechanistic insight into the aerobic *C*-alkylation reactions and to probe their possibilities to undergo the relay race type mechanism.

The first step, Cu-catalyzed aerobic alcohol oxidation (Scheme 2, step i), has been well-studied in the literature.[14] In present cases, we have proved that the oxidation of primary alcohols should proceed *via* either Cu-catalyzed aerobic oxidation under air or the Cu(II)-oxidized way under nitrogen,[12d,13] which is also similar to the case found with secondary alcohols.[13] These results, not only agree well with the contrasting reaction efficiencies of the aerobic and anaerobic reactions[10–12] (Table 1), but clearly reveal that the aerobic conditions give a more effective alcohol activation process and thus may account for the reason why the aerobic reactions are always more efficient than the anaerobic ones.

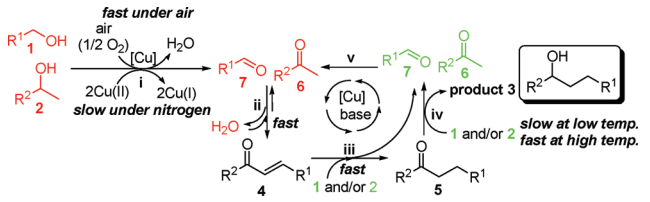
The second step, dehydrative aldol condensation of aldehydes and ketones to give α,β-unsaturated ketones (Scheme 2, step ii),[15] also a classic organic reaction that has long appeared in the text books, is known to take place easily under basic conditions at room temperature. Although metal catalysts were held not to affect this step according to the borrowing hydrogen concept,[3–10] we did observe Cu's promoting effect on the reaction (eqn (1)) as in the aldehyde and amine condensations.[12] Thus, when heated at 100 °C, the Cu catalyst facilitated effectively a blank reaction of **7a** and **6a** that barely occurred (run 1) to give 75–87% yields of the product under the same conditions (run 2). Other Cu catalysts were also found to promote the reaction similarly.[13] In fact, metal-catalyzed aerobic oxidative reactions of alcohols and ketones giving α,β-unsaturated ketones were reported years ago,[16] which strongly supports the occurrence of the first two steps in the proposed mechanism (Scheme 2, step i + ii).



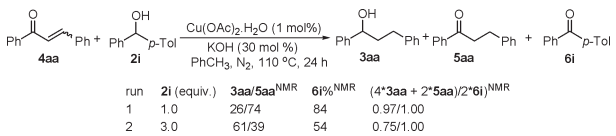
run	cat. [Cu] (mol%)	**4aa**% (GC yield based on **6a**)	
1	none	6 h: 0.9%;	12 h: 1.4%
2	$Cu(OAc)_2 \cdot H_2O$ (5)	6 h: 75%;	12 h: 87%

(1)

As to the transfer hydrogenation steps (Scheme 2, steps iii and iv),[17] our several initial attempts using **1a** as the hydrogen source to confirm these reactions failed because the occurrence of complex reactions only resulted in unidentifiable spectra unsuitable for analysis. Fortunately, the reactions using **2i** as the reducing reagent succeeded, giving clear NMR spectra, in which the transfer hydrogenated product **3aa**, byproduct **5aa**, and corresponding ketone **6i** generated by the oxidation of **2i**, could all be clearly clarified (eqn (2)).[13,18] Thus, in the presence of 1 equiv. of **2i**, the ratio of the hydrogen atoms received by **4aa** to give **3aa** (4 hydrogen atoms per molecule) and **5aa** (2 hydrogen atoms per molecule) to those donated by **2i** to give **6i** (2 hydrogen atoms per molecule) is 0.97/1.00 (run 1). Another reaction using 3 equiv. of **2i** was less precise due to the inevitable integration errors (run 2),[13] but still reflects the same transformation.



Scheme 2 The proposed mechanism for Cu-catalyzed aerobic *C*-alkylation reactions.



run	**2i** (equiv.)	**3aa**/**5aa**^{NMR}	**6i**%^{NMR}	(4*3aa + 2*5aa)/2*6i)^{NMR}
1	1.0	26/74	84	0.97/1.00
2	3.0	61/39	54	0.75/1.00

(2)

The above results clearly indicated that, during the transfer hydrogenation step (Scheme 2, steps iii and iv), the hydrogen atoms of alcohols **1** and/or **2** were transferred to intermediate **4** to give another intermediate **5** and then the product **3**, meanwhile regenerating quantitative amounts of **6** and **7** as the byproducts. Since copper may not be a typical borrowing hydrogen catalyst[12*d*] and Cu–H species is the least possible to be generated under the reaction conditions,[19] the transfer hydrogenation is more likely to proceed *via* a six-membered cyclic Meerwein–Pondorf–Verley type transition state.[12,20] Therefore, once kenones **6** and aldehydes **7** are regenerated, they will be recycled (step v) and condense quickly with each other to give **4** again, hence furnishing the catalytic cycle. On the other hand, as can be deduced, catalytic amounts of air should be adequate for the whole reaction to be initiated effectively. Indeed, as calculated, there is *ca.* 6.3 mol% oxygen (21% *v*/*v* in 20 mL air) contained in a standard 3 mmol reaction in a 20 mL tube.

Moreover, since intermediate **4** was not detected at all in the reaction media (Tables 1–3), we deduce that transfer hydrogenation of **4** to **5** by **1** and/or **2** (step iii) should be a fast reaction under the reaction conditions, as shown in Scheme 2. In contrast, as byproduct **5** could be detected in small amounts in the reaction media (Tables 1–3) and less than 1% at 120 °C in the model reaction (Table 1, run 5; in contrast to 3–5% at 110 °C), and that **5aa** was detected in considerable amounts in the transfer hydrogenation of **4aa** by **2i** at 110 °C (eqn (2)),[18] we also deduce that the further reduction of **5** to **3** by **1** and/or **2** (step iv) may be a faster reaction at higher temperatures and a slower reaction at lower temperatures, as indicated in Scheme 2.

Conclusion

In summary, simply by carrying out the reactions under air with aerobic alcohol oxidation being a more effective alcohol activation strategy, we successfully developed a practical and advantageous ligand-free Cu-catalyzed aerobic *C*-alkylation method for secondary alcohols and methyl ketones to achieve long chain alcohols using simple alcohols as the green alkylating reagents and generating water as the only byproduct. Based on our mechanistic studies and also supported by the literature, the relay race mechanism that has not been noticed in previous aerobic *C*-alkylation reactions was proposed for the present Cu-catalyzed reactions. Due to copper's many advantages, this method should be of potential utility and interest in synthesis. Further applications of these Cu-catalyzed aerobic reactions are also in progress in this laboratory.

Acknowledgements

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17 Transfer hydrogenation of α,β-unsaturated ketones by alcohols to give product ketones or alcohols has also been frequently employed to support the borrowing hydrogen mechanism, albeit indirectly in our opinion. See refs 3–10.

18 Possibly because **2i** is a sterically more bulky alcohol than other primary and secondary alcohols, it is a less reactive reducing alcohol in the reaction, leading to relatively higher selectivities of the byproduct **5aa**.

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