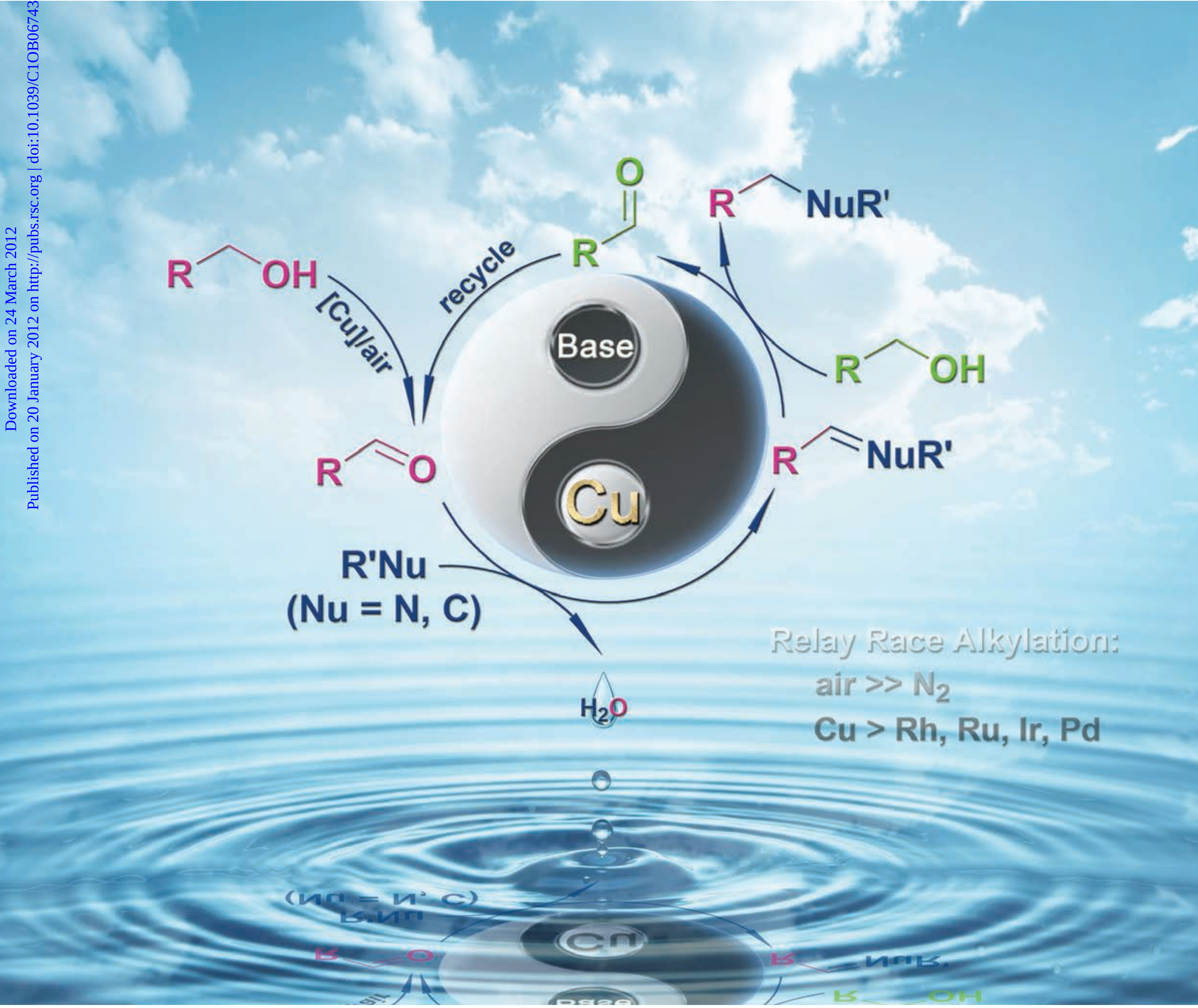
Organic & Biomolecular Chemistry

www.rsc.org/obc

Volume 10 | Number 15 | 21 April 2012 | Pages 2897–3132



ISSN 1477-0520

RSC Publishing

FULL PAPERS
Qing Xu *et al.*
Cu-catalyzed *N*- and *C*-alkylation reactions using alcohols employing the aerobic relay race methodology

1477-0520(2012)10:15;1-F

Organic &
Biomolecular
Chemistry

Dynamic Article Links
View Online

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 2966

www.rsc.org/obc

PAPER

Copper-catalyzed *N*-alkylation of amides and amines with alcohols employing the aerobic relay race methodology†

Qiang Li, Songjian Fan, Qing Sun, Haiwen Tian, Xiaochun Yu and Qing Xu*

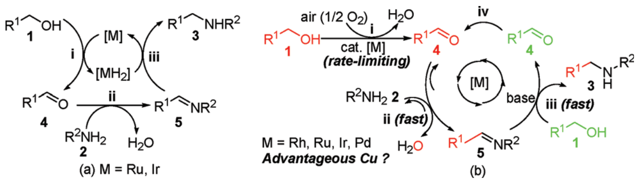
Received 17th October 2011, Accepted 21st November 2011
DOI: 10.1039/c1ob06743e

By employing aerobic oxidation to aldehydes as a more effective alcohol activation strategy, we developed a green Cu-catalyzed *N*-alkylation method for various amides and amines with alcohols. This reaction is more advantageous than the literature methods for it uses a ligand-free copper catalyst, can be readily carried out under milder aerobic conditions and generates water as the only byproduct. More importantly, based on our mechanistic studies and also supported by the literature, rather than following the previously-proposed mechanisms, we deduce that the newly-proposed relay race process should be the most possible and a more rational mechanism for the reactions, especially under aerobic conditions.

Introduction

Copper catalysts have received broad interests and utilities in both academy and industry for their many advantages such as ready availability, economy, high activity, high efficiency and low toxicity.[1–5] In addition, due to their high capacity in dioxygen activation[6] and by using oxygen or air as the green oxidant, coppers are particularly superior catalysts or co-catalysts in cross-dehydrogenative couplings (CDC),[2] C–H activations[4] and subsequent oxidative couplings with C–H and heteroatom–H compounds,[3,4] and also aerobic alcohol oxidations for aldehydes, ketones and fine chemical synthesis.[5]

Regarding the recently developed methodologies[1–3,7] for the versatile amine and amide derivatives,[8] the borrowing hydrogen or hydrogen autotransfer methodology (Scheme 1a) is a relatively environmentally-benign alternative for using alcohols as the greener alkylating reagents and high atom efficiency achievable by yielding water as the only byproduct.[9] However, due to the thermodynamically unfavourable anaerobic dehydrogenative activation of the alcohols (step i)[9c] and the sensitive nature of the active hydridometal species, expensive, not readily available noble metal complexes derived from ruthenium and iridium or addition of capricious ligands for catalyst activation were usually required under inert atmosphere protection, which greatly limits the utilities of the methods and makes 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.[10–13] Although having been widely adopted in other methodologies for amine and amide derivative synthesis,[1–3] the advantageous copper catalysts have seldom been used in *N*-alkylation reactions of alcohols and amines/amides in the past.[9f] Only a few heterogeneous[10] and homogeneous[11] methods have been reported recently.



Scheme 1 Metal-catalyzed *N*-alkylation methods.

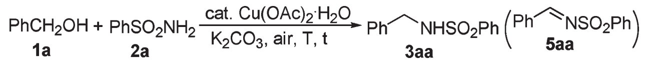
In contrast with the known borrowing hydrogen methods,[9–12] we recently discovered an air-promoted metal-catalyzed *N*-alkylation method[13a] that can effectively use the more practical ligand-free Rh, Ru and Ir catalysts.[13b] We also proposed a relay race mechanism (Scheme 1b) for these aerobic reactions, which, to our knowledge, had never been discovered and proposed in the field before.[9–12] We deduce that the initial aerobic alcohol oxidation step (step i) should be a greener and more effective aldehyde generation process that can consequently lead to more efficient reactions under aerobic conditions than under anaerobic conditions. However, contrary to the CDC[2] and anaerobic dehydrogenation[9] strategies, this has not been recognized as an alcohol activation alternative by the field so far.[9–13] We then envisioned other metals,[13c] such as the copper, may also be a promising catalyst for its potential in aerobic alcohol activations.[5] Interested in developing more practical and more preferable catalysts and extending the scope of the aerobic

---

College of Chemistry and Materials Engineering, Wenzhou University, Wenzhou, 325035, China. E-mail: qing-xu@wzu.edu.cn; Fax: (+)-86-577-88373111; Tel: (+)-86-13857745327

† Electronic supplementary information (ESI) available: Detailed experimental procedures, condition screening tables, control experiments, mechanistic studies, characterization data and ^{1}H and ^{13}C NMR spectra of all of the products. See DOI: 10.1039/c1ob06743e

Table 1 Condition screening and optimization[a,15]



Run	Cu (mol%), Cu/**1a**[b]	K_2CO_3 (mol%), K_2CO_3/**1a**[b]	*T*, *t*	**3aa** %[c]
1[d]	2, 0.0033	100, 0.167	120 °C, 12 h	70
2[e]	1, 0.0025	100, 0.25	120 °C, 12 h	97
3[e]	1, 0.0025	10, 0.025	120 °C, 12 h	31
4[f]	1, 0.0078	10, 0.077	135 °C, 24 h	89 (78)

[a] See Electronic Supplementary Information for operations†. The reactions were monitored by TLC and/or GC-MS. [b] Catalyst and base concentrations are indicated in mol/mol ratios to **1a**, since **1a** is also the solvent in the reaction. [c] GC yield (isolated yield in parenthesis) based on **2a**. High **3aa**/**5aa** ratios (>99/1) were obtained. [d] 6 mmol **1a** (6 equiv.) and 1 mmol **2a** used. [e] 4 mmol **1a** (4 equiv.) and 1 mmol **2a** used. [f] 2.6 mmol **1a** (1.3 equiv.) and 2 mmol **2a** used.

alkylation method,[13] we also examined copper's activity in the reaction and now report our independent results[11] of a greener and more advantageous Cu-catalyzed aerobic *N*-alkylation method for various amides and amines with alcohols and propose a mechanism for these reactions.

Results and discussion

Condition optimization and substrate extension

Previous Cu-catalyzed *N*-alkylation methods were mostly performed under rather harsh conditions, such as at high temperature (≥150 °C), under an inert atmosphere, using solvents and large amounts of the alcohols (4 equiv.) or the bases (1–4 equiv.), or requiring a long reaction time (up to 5 days).[10,11] Thus, in our studies, a $Cu(OAc)_2\cdot H_2O$-catalyzed[14,15] model reaction of benzyl alcohol **1a** and benzenesulfonamide **2a** was firstly optimized under solvent-free and aerobic conditions (Table 1).[15] Although the reactions were found to be very efficient at 120 °C in the presence of large excess amounts of **1a** and the base (runs 1 and 2), the product yield decreased greatly when the catalyst and base loadings were reduced (run 3), which was also the same case with a series of reactions conducted at higher temperatures or using the anhydrous $Cu(OAc)_2$ as the catalyst.[15] Realizing that the catalyst and base concentrations (as indicated in mol/mol ratios to **1a** in the table) affected the reaction efficiency greatly so that higher concentrations inevitably lead to faster reactions and higher yields of the product, by further enhancing the catalyst and base concentrations by reducing the alcohol loadings to almost 1 equiv., the reaction using only 1 mol% of Cu catalyst and 10 mol% of K_2CO_3 was still highly efficient at only 135 °C, affording a high yield of the product in 24 h (run 4).

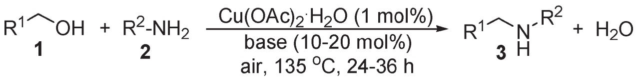
After optimization of the reaction conditions, a series of amides, amines and alcohols were then investigated to extend the scope of the method (Table 2). Almost all of the electron-rich and -deficient sulfonamides (runs 1–9) and benzylic alcohols (runs 10–16) gave good to high yields of the products under similar conditions. Like *para*- and *meta*-substituted substrates, the sterically more bulky *ortho*-substituted ones also gave good results under the same conditions (runs 2, 5, 11, 13). Heteroaromatic and aliphatic sulfonamides and a heterobenzylic alcohol could also afford the target products under air (runs 8, 9, 17). Moreover, this aerobic method is not limited to sulfonamides only,[11a] aromatic and heteroaromatic amines[11b,c] could also be effectively alkylated under air (runs 18–29). Except an *ortho*-methyl substituted amine that gave a low yield of the product possibly due to steric reasons (run 22), all of the aromatic and heteroaromatic amines react efficiently with alcohols under air to give good to high yields of the products. Like the literature reports and our previous findings,[9–13] alkali metal hydroxides were found to be better bases than K_2CO_3 for these substrates. The five-membered cyclic aminobenzothiazole **2o** was highly reactive under present aerobic conditions, giving a high yield of the product in only 6 h at 120 °C (run 25). These results revealed that inert atmosphere protection is in fact unnecessary for these substrates (runs 18–29). More importantly, operation of the reactions could be simplified and reaction rates greatly improved by simply carrying out the reactions under air. To our knowledge, the present method is much milder and more advantageous than several recent reports on the reactions of sulfonamides,[9] including the Cu-catalyzed ones,[11] such as less in alcohol and base loadings, lower in reaction temperature, higher in efficiency, and avoids the use of inert atmosphere protection, ligands and solvents.

Effects of the additives

As mentioned above, Cu-catalyzed *N*-alkylation reactions have been reported[10,11] during our previous work.[13a,b] Some of them were also carried out under air,[10c,11a] found to be more efficient than the reactions under anaerobic conditions[11] and proposed to follow the borrowing hydrogen mechanism involving CuH_2 as the active species.[11a] However, it has been reviewed that the generation of Cu–H species usually requires harsh conditions, such as using strong coordinating phosphines and strong hydride-donating silanes under inert conditions and that they are prone to be destroyed by molecular oxygen.[16] Recently, Ramón and coworkers also proposed another possible reaction path close to our proposal[13b] for the reactions with external aldehydes added, even though all of their reactions were carried out under argon.[11b] Moreover, in related *C*-alkylation methods,[9] whether the aerobic reactions[17] 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.[17a,b] Clearly, air's role and the mechanisms of the aerobic alkylation reactions are worthy of a more careful examination. All of these points prompt us to take the aerobic systems with particular concern, to examine the mechanistic aspects of the reactions more carefully and to present our independent results and findings in detail in the present Cu-catalyzed aerobic *N*-alkylation reactions.

During our studies, different to the report that an *in situ* generated ligand, *N*,*N*′-ditosylbenzimidamide, was supposed to promote the reaction as a catalyst stabilizer,[11a] we only noticed

Table 2 Cu-catalyzed aerobic *N*-alkylation of amides and amines with alcohols[a]



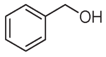
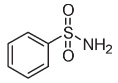
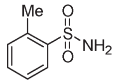
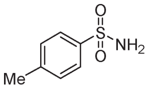
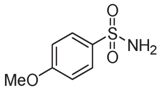
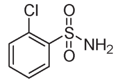
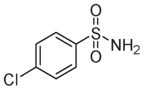
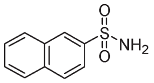
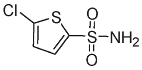
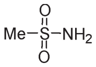
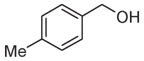
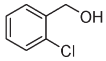
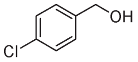
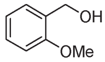
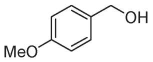
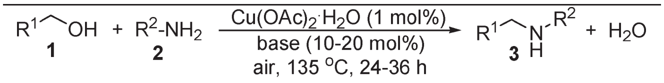
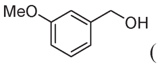
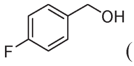
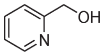
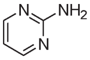
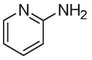
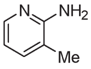
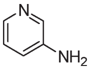
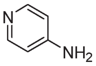
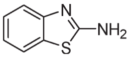
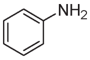
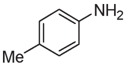
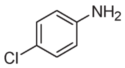
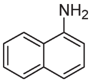
Run	1	2	3%[b]
1	 (1a)	 (2a)	89 (78)
2	1a	 (2b)	98 (86)
3	1a	 (2c)	99 (95)
4	1a	 (2d)	67 (41)
5	1a	 (2e)	61 (52)
6	1a	 (2f)	91 (79)
7	1a	 (2g)	57 (51)
8	1a	 (2h)	49 (43)
9	1a	 (2i)	92 (83)
10	 (1b)	2a	90 (78)
11	 (1c)	2a	97 (87)
12	 (1d)	2a	91 (64)
13	 (1e)	2a	91 (60)
14	 (1f)	2a	91 (74)

Table 2 *(Contd.)*

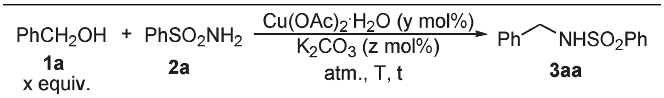


Run	1	2	3%[b]
15	 (1g)	2a	93 (79)
16[c]	 (1h)	2a	83 (80)
17[d]	 (1i)	2a	88 (53)
18[e]	1a	 (2j)	94 (90)
19[e]	1b	2j	99 (91)
20[e]	1d	2j	99 (94)
21[e]	1a	 (2k)	91 (89)
22[f]	1a	 (2l)	30 (19)
23[e]	1a	 (2m)	87 (83)
24[g]	1a	 (2n)	74 (65)
25[h]	1a	 (2o)	99 (95)
26[g]	1a	 (2p)	95 (90)
27[g]	1a	 (2q)	92 (90)
28[g]	1a	 (2r)	97 (83)
29[g]	1a	 (2s)	95 (90)

[a] 1.3–1.5 equiv. of **1** and 10–20 mol% K_2CO_3 were used. [b] GC yields (isolated yields in parenthesis) based on **2**. **3**/**5** ratios were usually high (>99/1). [c] 40 mol% K_2CO_3. [d] 2.0 equiv. of **1**. [e] 40 mol% NaOH, 150 °C. [f] 50 mol% NaOH, 150 °C, 36 h. [g] 40 mol% $CsOH \cdot H_2O$, 150 °C. [h] 20 mol% NaOH, 120 °C, 6 h.

that air, byproducts aldehyde **4** (or contaminant **4** in alcohol **1**) and imine **5** can affect the reaction rates to a great extent.[18,19] For example, as shown in Table 3, with a large excess of absolute **1a** (freshly distilled and 100% purity as confirmed by GC analysis), trace or no product was detected with either 5 or 1 mol % of Cu catalyst under nitrogen at 120 °C (runs 1 and 3, condition **A**). In contrast, when 6 mL air was carefully introduced to the reaction vessel, considerable amounts of the product was produced and detected (run 2, condition **A**). Similar reactions under air were even more efficient.[15] When degassed commercial **1a** (0.79*x*% **4a** if based on **2a**) was used, the reactions were much more efficient, giving higher yields of the product under the same conditions (runs 1 and 3, condition **B**). Similarly, the reaction of an older sample of **1a** (2.28*x*% **4a** if based on **2a**) was even more efficient than those of the former two samples, giving high yields of the product at 120 °C under nitrogen (run 3, condition **C**). More reactions using these three samples of **1a** under a series of identical conditions were all the same in the order of reaction rates (runs 4–9), with the reactions of sample **A** being the slowest and those of the sample **C** the fastest. Of course, the aerobic reactions were much more efficient (runs 6, 9) than the anaerobic ones (runs 5, 8). Similar to aldehyde, the addition of intermediate imine **5aa** to a standard reaction of **1a** and **2a** could initiate the anaerobic reactions and promote the aerobic reactions greatly.[15]

Table 3 Effects of air and alcohol purity on reaction efficiency^{a}

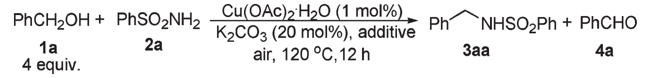


Run	*x*, *y*, *z*	Atm. *T*, *t*	**3aa**%^{a}		
			A^{b}	**B**^{c}	**C**^{d}
1	6, 5, 100	N_2, 120 °C, 12 h	trace	95	—^{e}
2^{f}	6, 5, 100	N_2, 120 °C, 24 h	68	—	—
3	6, 1, 100	N_2, 120 °C, 12 h	ND^{g}	71	86
		24 h	trace^{g}	99	99
4	4, 1, 20	N_2, 100 °C, 36 h	ND	30	67
5	4, 1, 20	N_2, 120 °C, 12 h	ND	38	59
		24 h	ND	81	99
6	4, 1, 20	air, 120 °C, 12 h	57	77	99
7	4, 1, 20	N_2, 150 °C, 12 h	57	95	99^{h}
8	1.3, 1, 10	N_2, 120 °C, 36 h	ND	trace	44
9	1.3, 1, 10	air, 135 °C, 24 h	79	89	93
		36 h	95	—	—

[a] GC yield based on **2a**. [b] Sample **A**: absolute **1a** (freshly distilled from CaH_2, degassed and stored under N_2 in a Schlenk flask, 100% purity without any contaminants as confirmed by GC analysis) was used. [c] Sample **B**: commercial **1a** (containing 0.79% PhCHO **4a** as detected by GC) was used. [d] Sample **C**: an older sample of **1a** (containing 2.28% PhCHO **4a** as detected by GC) was used. [e] The reactions were not conducted. [f] 6 mL air (cal. 5.7 mol% O_2) was carefully added under nitrogen *via* a syringe with a long needle into a 50 mL Schlenk tube. [g] ND (not detected) or trace as determined by TLC. [h] The reaction completed in only 6 h.

Above results implied that, in the case where the reactions are carried out under air, air most probably promotes the reaction *via* formation of aldehydes by Cu-catalyzed aerobic alcohol oxidation.[5,13] Indeed, this was further supported by using bipyridine and TEMPO, the well-known ligand and co-catalyst in Cu-catalyzed aerobic alcohol oxidations,[5] as additives in the reactions (Table 4, 4 equiv. of **1a**, present temperature: 120 °C) under conditions similar to the previous report (4 equiv. of **1a**, literature temperature: 150 °C).[11a] Thus, 1 mol% bipyridine alone could promote a smooth reaction (run 1) in a great deal (run 2), enhancing the yield of the product from 57% to 71%. Additional loading of 2 mol% TEMPO was even more effective. It dramatically drove the reaction to complete in 12 h at only 120 °C, with more benzaldehyde **4a** produced as the byproduct (run 3). The bipyridine/TEMPO system is so effective that the reactions of other less active Cu catalysts also afforded high yields of the product under the same conditions,[15,20] revealing that it is far more effective than the assumed "ligand",[11a] needless to mention its potentially broader utilities in substrate and catalyst scope.[21] *Vice versa*, due to the prohibition of the alcohol oxidation by the absence of air, no product could be detected when the same reactions were conducted under nitrogen (runs 4-5). However, if the same reaction (run 1) was carried out under pure dioxygen (run 6), over oxidation easily took place to produce considerable amounts of benzaldehyde **4a** (34%) and imine **5aa** (29%), but only a low yield of the target product **3aa** (30%). This result (run 6), not only agrees well with the findings in the previous report that considerable amounts of aldehydes and imines can be detected in reactions under large excess amounts of air,[11a] but clearly indicates that air does work to oxidize the alcohol to aldehydes. In fact, many groups including us, have reported that imines can be directly prepared from alcohols and amines under aerobic conditions.[22] All of these results clearly revealed that air is the most influential factor in the present Cu-catalyzed reactions than any other (ligands, *etc.*). Moreover, that the tested ligands could not facilitate the Cu-catalyzed reactions under nitrogen also implied that, unlike Ru, Rh and Ir catalysts whose reactions can be assisted by adding ligands,[9,13b] but similar to Pd catalysts,[13c] Cu is not a typical borrowing hydrogen catalyst and thus may not be able to catalyze the reactions *via* a borrowing hydrogen process.

Table 4 Additive effects in the presence of a large excess of alcohol^{a}



Run	Atm., additive (mol%)	**3aa**%^{b}	**4a**%^{b}
1	air, -	57	6
2	air, Bipy (1)	71	6
3	air, Bipy (1), TEMPO (2)	99	12
4	N_2, Bipy (1)	ND	—
5	N_2, Bipy (1), TEMPO (2)	ND	—
6	O_2 (1 atm.), -	30	34 (**5aa**: 29%)

[a] Absolute **1a** (100% GC purity) was used. [b] GC yield based on **2a**.

Mechanistic discussion

The above results and findings implied that the new mechanism we recently proposed (Scheme 1b)[13] should be more suitable for the present Cu-catalyzed aerobic *N*-alkylation reactions than the conventional borrowing hydrogen mechanism (Scheme 1a).[9–12] Thus, the individual reactions in Scheme 1b were further investigated to confirm our hypothesis and to figure out the most possible mechanism for the Cu-catalyzed aerobic reactions.

The first step is Cu-mediated alcohol oxidation (Scheme 1b, step i).[5] As shown in Table 5, no reaction was observed when absolute **1a** and Cu(II) were heated at 120 °C under nitrogen (run 1), but 2–6% yield of **4a** could be detected if the same reactions were performed under air (run 2).[15] These results are consistent with our previous observations that the reactions did not occur at 120 °C under nitrogen, but could afford a good yield of the

Table 5 Cu-mediated alcohol oxidation^{a}

$$\underset{\textbf{1a}}{PhCH_2OH} \xrightarrow[K_2CO_3,\ atm., T, t]{Cu(OAc)_2 \cdot H_2O} \underset{\textbf{4a}}{PhCHO} + \underset{\textbf{6a}}{PhCH_2OAc}$$

Run	Cu (mol%)	Atm., *T*, *t*	**4a**%^{b}	**6a**%^{b}
1	5	N_2, 120 °C, 6 h	NR^{c}	
2	5	air, 120 °C, 6 h	2.8	
3	5	N_2, 150 °C, 12 h	2.4	
4	5	N_2, 180 °C, 12 h	2.7	
5	10	N_2, 150 °C, 12 h	4 (4)	(13)
6	20	N_2, 150 °C, 12 h	5.5 (8)	(33)
7^{d}	10,^{e} or 20, or 50	N_2, 150 °C, 6 h	NR	

[a] Unless otherwise noted, $Cu(OAc)_2 \cdot H_2O$ and 4 mmol absolute **1a** (100% GC purity) were used. [b] GC yield (NMR yield in parenthesis). [c] No reaction. [d] CuI used as the catalyst. [e] 1.8% **4a** detected when heated under air in 12 h.

product under air (Tables 1 and 3). When the same reactions (run 1) were heated at higher temperatures under nitrogen (runs 3 and 4, 150–180 °C), the reaction temperature and time were surprisingly found to be irrelevant to yields of **4a**, but the amounts of Cu(II) added were relevant, *i.e.*, nearly half amounts of **4a** (in mol/mol ratio to Cu(II) added) were always generated under these conditions. This was further confirmed by adding larger amounts of Cu(II) and by both GC and NMR spectroscopic analysis (runs 5, 6). In the latter cases, *ca.* 1–2 folds of benzyl acetate **6a** (in mol/mol ratio to Cu(II) added) were also detected and confirmed (runs 5, 6).[23] Since 10–50 mol% of a Cu(I) species (CuI), although an active alcohol oxidation and *N*-alkylation catalyst,[15] were found inactive under nitrogen even at 150 °C (run 7), we deduce, Cu(I) species may be generated in the anaerobic reactions of Cu(II) and **1a** (runs 3–6) *via* eqns (1–3), giving constant yields of **4a** and **6a**. Thus, when heated under nitrogen, $Cu(OAc)_2$ first reacts with **1a**, resulting in the reduction of Cu(II) to a Cu(I) species like CuOAc and concurrent oxidation of **1a** to **4a**, giving also the acetic acid (HOAc) as a byproduct (eqn (1)).[24] Due to the presence of a large excess of **1a**, the generated HOAc may quickly undergo dehydrative esterification with **1a** at the high temperatures to give benzyl acetate **6a** (eqn (2)). As a result, half amounts of **4a** were generated during the process, with the detection of **6a** as a byproduct (eqn (3)).[23] In these cases, Cu(II) may essentially be the direct oxidant for the alcohols under anaerobic conditions, with itself reduced to Cu(I) by the alcohol.[4,24,25]

$$2\,\mathrm{Cu(OAc)_2} + \underset{1a}{\mathrm{PhCH_2OH}} \rightarrow 2\,\mathrm{CuOAc} + \underset{4a}{\mathrm{PhCHO}} + 2\,\mathrm{HOAc} \tag{1}$$

$$\mathrm{HOAc} + \underset{1a}{\mathrm{PhCH_2OH}} \rightarrow \underset{6a}{\mathrm{PhCH_2OAc}} + \mathrm{H_2O} \tag{2}$$

Overall reaction (eqn (1) + eqn (2)):

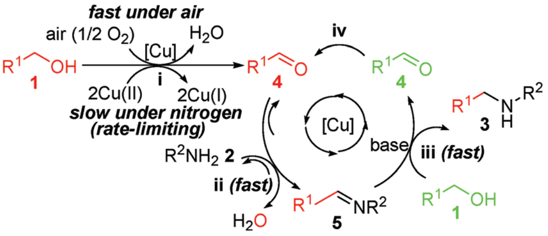
$$\begin{aligned} 2\mathrm{Cu(OAc)_2} + 3\mathrm{PhCH_2OH} &\rightarrow 2\mathrm{CuOAc} + \underset{1a}{\mathrm{PhCHO}} \\ &+ \underset{4a}{2\mathrm{PhCH_2OAc}} + \underset{6a}{\mathrm{H_2O}} \end{aligned} \tag{3}$$

Then there is the condensation step (Scheme 1b, step ii), a standard organic reaction.[26] Although metal catalysts have been held not to affect this step in the past according to the borrowing hydrogen concept,[9–12] we did observe that Cu catalysts do promote the reaction to some extent[15] as other catalysts did.[13] On the other hand, imines can be prepared from alcohols and amines in aerobic systems,[22] strongly supporting the occurrence of the first two steps in the proposed mechanism (Scheme 1b, steps i-ii).

The transfer hydrogenation step (Scheme 1b, step iii) is also a well-known reaction.[27,28] In our hands, Cu alone catalyzed the reaction to some extent, and, as Bäckvall had pointed out,[29] base indeed promoted this reaction effectively, affording high yield of the product in 8 h at only 100 °C.[15] In addition, quantitative generation of the byproduct **4a** could be detected clearly by NMR analysis (eqn (4)), confirming the transfer hydrogenation step of the proposed mechanism. Since copper may not be a borrowing hydrogen catalyst and the Cu–H species is the least likely to be generated under the reaction conditions,[16] this step should be more likely to proceed *via* a six-membered cyclic Meerwein–Pondorf–Verley-type transition state.[9b,13,28]

$$\underset{1a}{\mathrm{PhCH_2OH}} + \underset{5aa}{\mathrm{PhSO_2N{=}CHPh}} \xrightarrow[\mathrm{K_2CO_3\ (20\ mol\%),\ N_2,\ 100\ ^oC}]{\mathrm{Cu(OAc)_2{\cdot}H_2O\ (1\ mol\%)}} \underset{3aa}{\mathrm{PhSO_2NHCH_2Ph}} + \underset{4a}{\mathrm{PhCHO}} \tag{4}$$

run	t	**3aa**%^{NMR}	**4a**%^{NMR}	**4a/3aa**^{NMR}
1	4 h	69	69	1.00/1.00
2	6 h	83	70	0.84/1.00



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

Based on above findings, a new mechanism was proposed for the Cu-catalyzed *N*-alkylation reactions (Scheme 2). Thus, under air, Cu catalyst first catalyzes the aerobic alcohol oxidation efficiently to give aldehyde **4** (step i, up), and then promotes the condensation (step ii) and catalyzes the transfer hydrogenation to give product amides/amines **3** (step iii), with aldehydes **4** quantitatively regenerated during the process and recycled (step iv) for next *N*-alkylation cycles. Similarly, contaminant aldehydes in the alcohols, intermediate imines, oxidation ligands and co-catalysts under certain circumstances are all potentially more effective alcohol activation alternatives than the anaerobic conditions. Under an inert atmosphere, the reaction is also more likely to proceed *via* the new mechanism since the initiating aldehyde can also be generated by Cu(II)-oxidized way (eqns (1–3); Scheme 2, step i, down).[4,24,25] Even not to exclude the speculative Cu–H species at higher temperatures under an inert atmosphere (at temperatures ≥150 °C as observed), the reaction is also more likely to undergo the new reaction path, since, in contrast with the condensation (step ii) and transfer hydrogenation (step iii) that can take place easily even at lower temperatures (100–120 °C), the anaerobic dehydrogenative alcohol activation to Cu–H species and aldehydes, a thermodynamically unfavourable process in nature,[9c] will become the bottleneck and rate-limiting step of the whole reaction. Therefore, once the initiating aldehyde is generated *via* either route, it is no longer necessary for the reactions to undergo the demanding borrowing hydrogen pathway, since the aldehydes have already been regenerated quantitatively in the easy transfer hydrogenation reaction. Based on the above mechanistic studies and considering that all of the individual reactions in the proposed mechanism are all well-documented processes in the literature,[4–6,22–29] we can conclude not only that Scheme 2 should be the most rational and most possible mechanism for the Cu-catalyzed *N*-alkylation reactions, but also that some previous mechanistic proposals in the aerobic systems were possibly wrong.

Conclusion

In summary, by simply carrying out the reactions under air with aerobic alcohol oxidation being a more effective alcohol activation strategy, we developed a greener and more advantageous Cu-catalyzed aerobic *N*-alkylation method for various amides and amines by using alcohols as the green alkylating reagents and generating water as the only byproduct. Based on our mechanistic studies and also supported by the literature, we propose that the newly-proposed relay race mechanism rather than the previously-concluded borrowing hydrogen mechanism should be the most possible and is a more rational mechanism for the Cu-catalyzed aerobic *N*-alkylation reactions. Due to copper's many advantages, this aerobic alkylation method should be of potential utility and interest in synthesis.[30] Further extension and applications of these Cu-catalyzed aerobic reactions are also in progress in this laboratory.

Acknowledgements

We thank NNSFC (No. 20902070), SRF for ROCS of SEM, NSF (No. Y4100579) and QJTP (No. QJD0902004) of Zhejiang Province for financial support. Q. S. thanks the Science and Technology Department of Zhejiang Province (No. 2009R424048).

Notes and references

1 (*a*) S. V. Ley and A. W. Thomas, *Angew. Chem., Int. Ed.*, 2003, **42**, 5400–5449; (*b*) D. Ma and Q. Cai, *Acc. Chem. Res.*, 2008, **41**, 1450–1460; (*c*) G. Evano, N. Blanchard and M. Toumi, *Chem. Rev.*, 2008, **108**, 3054–3131; (*d*) F. Monnier and M. Taillefer, *Angew. Chem., Int. Ed.*, 2009, **48**, 6954–6971; (*e*) D. S. Surry and S. L. Buchwald, *Chem. Sci.*, 2010, **1**, 13–31; (*f*) H. Rao and H. Fu, *Synlett.*, 2011, 745–769.

2 (*a*) C.-J. Li and Z. Li, *Pure Appl. Chem.*, 2006, **78**, 935–945; (*b*) C.-J. Li, *Acc. Chem. Res.*, 2009, **42**, 335–344; (*c*) C. J. Scheuermann, *Chem.–Asian J.*, 2010, **5**, 436–451; (*d*) C. Liu, H. Zhang, W. Shi and A. Lei, *Chem. Rev.*, 2011, **111**, 1780–1824.

3 (*a*) A. E. Wendlandt, A. M. Suess and S. S. Stahl, *Angew. Chem., Int. Ed.*, 2011, **50**, 11062–11087; (*b*) M. Klussmann and D. Sureshkumar, *Synthesis*, 2011, 353–369; (*c*) H. A. Stefani, A. S. Guarezemini and R. Cella, *Tetrahedron*, 2010, **66**, 7871–7918; (*d*) Z. Zhao and F. Peng, *Angew. Chem., Int. Ed.*, 2010, **49**, 9566–9668.

4 (*a*) J. L. Bras and J. Muzart, *Chem. Rev.*, 2011, **111**, 1170–1214; (*b*) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215–1294; (*c*) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147–1169; (*d*) C.-L. Sun, B.-J. Li and Z.-J. Shi, *Chem. Commun.*, 2010, **46**, 677–685; (*e*) L. Ackermann, R. Vicente and A. R. Kapdi, *Angew. Chem., Int. Ed.*, 2009, **48**, 9792–9826; (*f*) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094–5115.

5 (*a*) M. F. Semmelhack, C. R. Schmid, D. A. Cortes and C. S. Chou, *J. Am. Chem. Soc.*, 1984, **106**, 3374–3376; (*b*) I. E. Markó, P. R. Giles, M. Tsukazaki, S. M. Brown and C. J. Urch, *Science*, 1996, **274**, 2044–2046; (*c*) I. E. Markó, A. Gautier, R. Dumeunier, K. Doda, F. Philippart, S. M. Brown and C. J. Urch, *Angew. Chem., Int. Ed.*, 2004, **43**, 1588–1591; (*d*) E. T. T. Kumoulainen and A. M. P. Koskinen, *Chem.–Eur. J.*, 2009, **15**, 10901–10911; (*e*) L. Liang, G. Rao, H.-L. Sun and J.-L. Zhang, *Adv. Synth. Catal.*, 2010, **352**, 2371–2377.

6 (*a*) C. J. Cramer and W. B. Tolman, *Acc. Chem. Res.*, 2007, **40**, 601–608; (*b*) E. A. Lewis and W. B. Tolman, *Chem. Rev.*, 2004, **104**, 1047–1076; (*c*) L. M. Mirica, X. Ottenwaelder and T. D. P. Stack, *Chem. Rev.*, 2004, **104**, 1013–1045.

7 (*a*) J. F. Hartwig, *Acc. Chem. Res.*, 2008, **41**, 1534–1544; (*b*) L. Jiang and S. L. Buchwald, in *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed. (ed.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, Germany, 2004; (*c*) R. P. Tripathi, S. S. Verma, J. Pandey and V. K. Tiwari, *Curr. Org. Chem.*, 2008, **12**, 1093–1115; (*d*) T. E. Müller, K. C. Hultzsch, M. Yus, F. Foubelo and M. Tada, *Chem. Rev.*, 2008, **108**, 3795–3892; (*e*) G. Evano, A. Coste and K. Jouvi, *Angew. Chem., Int. Ed.*, 2010, **49**, 2840–2859; (*f*) K. A. DeKorver, H. Li, A. G. Lohse, R. Hayashi, Z. Lu, Y. Zhang and R. P. Hsung, *Chem. Rev.*, 2010, **110**, 5064–5106; (*g*) R. N. Salvatore, C. H. Yoon and K. W. Jung, *Tetrahedron*, 2001, **57**, 7785–7811; (*h*) D. S. Surry and S. L. Buchwald, *Chem. Sci.*, 2011, **2**, 27–50.

8 (*a*) G. T. Brooks and T. R. Roberts, *Pesticide Chemistry and Bioscience*, Royal Society of Chemistry, Cambridge, U.K., 1999; (*b*) J. L. McGuire, *Pharmaceuticals: Classes, Therapeutic Agents, Areas of Application*, vols. 1–4, Wiley-VCH, Weinheim, Germany, 2000; (*c*) R. Hili and A. K. Yudin, *Nat. Chem. Biol.*, 2006, **2**, 284–287; (*d*) E. D. Cox and J. M. Cook, *Chem. Rev.*, 1995, **95**, 1797–1842; (*e*) J. M. Humphrey and A. R. Chamberlin, *Chem. Rev.*, 1997, **97**, 2243; (*f*) C. Hansch, P. G. Sammes and J. B. Taylor *Comprehensive Medicinal Chemistry*, Pergamon Press, Oxford, 1990, vol. 2, chapter 7.1; (*g*) E. E. Connor, Sulfonamide antibiotics, *Primary Care Update for OB/GYNS*, 1998, **5**, 32; (*h*) A. Kleemann, J. Engel, B. Kutscher and D. Reichert, *Pharmaceutical Substances, Synthesis, Patents, Applications*, Thieme, Stuggart, 1999.

9 (*a*) A. J. A. Watson and J. M. J. Williams, *Science*, 2010, **329**, 635–636; (*b*) G. E. Dobereiner and R. H. Crabtree, *Chem. Rev.*, 2010, **110**, 681–703; (*c*) R. H. Crabtree, *Organometallics*, 2011, **30**, 17–19; (*d*) T. D. Nixon, M. K. Whittlesey and J. M. J. Williams, *Dalton Trans.*, 2009, 753–762; (*e*) T. Suzuki, *Chem. Rev.*, 2011, **111**, 1825–1845; (*f*) G. Guillena, D. J. Ramónand and M. Yus, *Chem. Rev.*, 2010, **110**, 1611–1641; (*g*) K.-I. Fujita and R. Yamaguchi, *Synlett.*, 2005, 560–571.

10 (*a*) T. Yamakawa, I. Tsuchiya, D. Mitsuzuka and T. Ogawa, *Catal. Commun.*, 2004, **5**, 291–295; (*b*) J. He, K. Yamaguchi and N. Mizuno, *Chem. Lett.*, 2010, **39**, 1182–1183; (*c*) P. R. Likhar, R. Arundhathi, M. L. Kantam and P. S. Prathima, *Eur. J. Org. Chem.*, 2009, 5383–5389.

11 (*a*) F. Shi, M. K. Tse, X. Cui, D. Gördes, D. Michalik, K. Thurow, Y. Deng and M. Beller, *Angew. Chem., Int. Ed.*, 2009, **48**, 5912–5915 see also: X. Cui, F. Shi, M. K. Tse, D. Gördes, K. Thurow, M. Beller and Y. Deng, *Adv. Synth. Catal.*, 2009, **351**, 2949–2958; (*b*) A. Martínez-Asencio, D. J. Ramón and M. Yus, *Tetrahedron*, 2011, **67**, 3140–3149; (*c*) F. Li, H. Shan, Q. Kang and L. Chen, *Chem. Commun.*, 2011, **47**, 5058–5060.

12 For other *N*-alkylation reactions carried out under air: (*a*) R. Kawahara, K.-I. Fujita and R. Yamaguchi, *Adv. Synth. Catal.*, 2011, **353**, 1161–1168; (*b*) A. Martínez-Asencio, M. Yus and D. J. Ramón, *Synthesis*, 2011, 3730–3740.

13 (*a*) S. L. Feng, C. Z. Liu, Q. Li, X. C. Yu and Q. Xu, *Chin. Chem. Lett.*, 2011, **22**, 1021–1024; (*b*) C. Liu, S. Liao, Q. Li, S. Feng, Q. Sun, X. Yu and Q. Xu, *J. Org. Chem.*, 2011, **76**, 5759–5773 and references therein (*c*) L. Jiang, Q. Li, C. Liu, S. Liao, X. Yu and Q. Xu, *J. Catal.* in press (accepted).

14 Both anhydrous $Cu(OAc)_2$ and $Cu(OAc)_2\cdot H_2O$ showed the same catalytic activity under several identical conditions. Thus, $Cu(OAc)_2\cdot H_2O$ was adopted as the catalyst in our study.

15 See Electronic Supplementary Information section for details†.

16 (*a*) C. Deutsch, N. Krause and B. H. Lipshutz, *Chem. Rev.*, 2008, **108**, 2916–2927; (*b*) S. Rendler and M. Oestreich, *Angew. Chem., Int. Ed.*, 2007, **46**, 498–504; (*c*) B. H. Lipshutz, *Synlett*, 2009, 509–524.

17 For C-alkylation reactions carried out under air: (*a*) Y. M. A. Yamadav and Y. Uozumi, *Org. Lett.*, 2006, **8**, 1375–1378; (*b*) L. J. Allen and R. H. Crabtree, *Green Chem.*, 2010, **12**, 1362–1364; (*c*) G. Tang and C.-H. Cheng, *Adv. Synth. Catal.*, 2011, **353**, 1918–1922.

18 This may indicate that contamination of alcohols by corresponding aldehydes or incomplete degassing of the reaction mixture may lead to totally opposite results and conclusions.

19 According to the preparation of the assumed ligand and its easy degradation under the reaction condition as observed and reported (ref. 11*a*), it may be the ligand's degradation to aldehydes or imines that promotes the reaction.

20 On the contrary, under the optimized aerobic condition (1.3 equiv. of **1** only), addition of bipyridine/TEMPO only lead to ineffective reactions and low product yields in the reactions of either various Cu catalysts or sample **C** of **1a** (see Electronic Supplementary Information for details†). Possibly, over oxidation of the alcohol occurred and resulted in reduced amounts of the remaining alcohol **1**, leading to ineffective reduction of imine **5** to product **3** due to insufficient amounts of **1**. These results also support the transfer hydrogenation step of the proposed mechanism.

21 It was also reported that the "ligand" is suitable for only one set of the substrates because if used in the reactions of other substrates, byproduct formation from the "ligand" may contaminate the target products (see ref. 11*a*).

22 (*a*) M. S. Kwon, S. Kim, S. Park, W. Bosco, R. K. Chidrala and J. Park, *J. Org. Chem.*, 2009, **74**, 2877–2879; (*b*) S. Kegnæs, J. Mielby, U. V. Mentzel, C. H. Christensen and A. Riisager, *Green Chem.*, 2010, **12**, 1437–1441; (*c*) H. Sun, F.-Z. Su, J. Ni, Y. Cao, H.-Y. He and

K.-N. Fan, *Angew. Chem., Int. Ed.*, 2009, **48**, 4390–4393; (*d*) L. Jiang, L. Jin, H. Tian, X. Yuan, X. Yu and Q. Xu, *Chem. Commun.*, 2011, **47**, 10833–10835.

23 Since 1-2 folds of benzyl acetate **6a** (in mol/mol ratio to Cu(II) added) was produced, the equation below may also be another potential reaction that produces **6a**.

$$\mathrm{CuOAc} + \underset{1a}{\mathrm{2PhCH_2OH}} \rightarrow \mathrm{PhCH_2OCu} + \underset{6a}{\mathrm{PhCH_2OAc}} + \mathrm{H_2O}$$

24 Reduction of $\mathrm{M(OAc)_2}$ (M = Cu, Pd) to give M(I)OAc or M(0) and HOAc has been proposed. See ref. 4.

25 Oxidants were found to be initiators for metal-catalyzed *N*-alkylation reactions. See ref. 13*b*.

26 (*a*) R. W. Layer, *Chem. Rev.*, 1963, **63**, 489–510; (*b*) M. M. Sprung, *Chem. Rev.*, 1940, **26**, 297–338; (*c*) J. P. Adams, *J. Chem. Soc., Perkin Trans. 1*, 2000, 125–139.

27 Transfer hydrogenation of imines by alcohols to give amines has also been frequently employed to support the borrowing hydrogen mechanism, albeit indirectly in our opinion. See refs 9–12.

28 For selected reviews on mechanisms of transfer hydrogenation: (*a*) ref. 9*b* (*b*) S. Gladiali and E. Alberico, *Chem. Soc. Rev.*, 2006, **35**, 226–236.

29 R. L. Chowdhury and J. E. Bckvall, *J. Chem. Soc., Chem. Commun.*, 1991, 1063–1064.

30 We also report a Cu-catalyzed aerobic *C*-alkylation method and propose a new mechanism for the reaction. See: S. Liao, K. Yu, Q. Li, H. Tian, Z. Zhang, X. Yu and Q. Xu, *Org. Biomol. Chem.*, DOI: 10.1039/c1ob06739g.