Cu^I/H$_2$/NaOH-Catalyzed Cross-Coupling of Two Different Alcohols for Carbon–Carbon Bond Formation: "Borrowing Hydrogen"?

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To minimize salt waste byproducts and to save energy and resources during the manufacture of longer-chain (higher) alcohols, transition-metal-catalyzed direct coupling between alcohols has recently been reinvestigated.[1] Homocoupling of the carbon atoms of primary alcohols was first demonstrated as a Guerbet reaction[2] using excess alkaline metal alkoxides at a high pressure/temperature ($\approx 220\,°C$).[2a] Recent Guerbet reactions using transition-metal catalysts were proposed to involve a "borrowing hydrogen"[1b] process consisting of 1) transition metal-catalyzed oxidation (transfer dehydrogenation) of both alcohols to form the corresponding carbonyl compounds; 2) base-catalyzed aldol condensation of them to form α,β-unsaturated carbonyl compounds, and 3) transition metal-catalyzed concomitant reduction (transfer hydrogenation) of the C=C and C=O bonds using the borrowed hydrogen atoms from both alcohols. Thus far, precious metals Ir[3,4] and Ru,[4,5] respectively, have been the most widely used for this purpose and such catalyst precursors have shown reasonable reactivity by subtle modification of the original conditions. However, reaction conditions used to date for Guerbet variants are so diverse that the critical factors for promoting the reactions have been veiled: in many cases, the reaction utilizes significant amounts of base (1–3 equiv with respect to one of two substrates),[3a,c,e,4a,b,5a,c–g,6b–d,h,7] and/or sacrificial hydrogen (H$_2$) acceptors,[3b,5a,f] with a few exceptions.[4c,5b,h,6a] In some cases, the molar amount of one of the two different alcohols used exceeded[3a,6b,7a] that of the other (e.g., **1/2**=1:2[5a] or 2:1[6a] equiv). A H$_2$ atmosphere was detrimental to the pro-

ductivity of higher alcohols using a hetereogeneous catalyst.[7a] We report herein a notable advancement in this field, based on our demonstration that simple Cu$^{I[7]}$/H$_2$/NaOH catalysts are able to catalyze the cross-coupling between a range of two different alcohols; the coupling showed a wider substrate scope with the best practicality for the selective synthesis of higher alcohols (Scheme 1). Most impor-
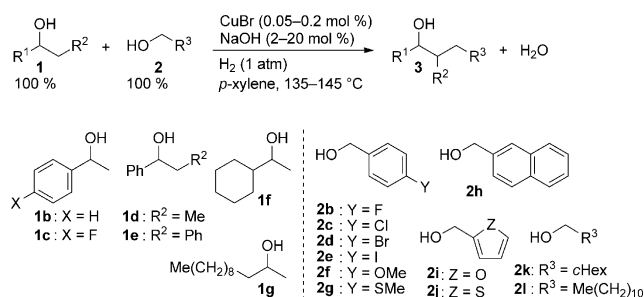
Scheme 1. General Scheme for coupling of two different alcohols.

tantly, the catalytic cycle that we found here was redox-free and was different from those involving "borrowing hydrogen" that have been reported thus far for the modified Guerbet reaction.

We first chose alcohol **1a** as a model substrate (Table 1), since a considerable amount of ketone **4aa** is generated as a side product when using a Ir[3a] or Ru[5a] catalyst system.[8] Treatment of a secondary (2°) alcohol **1a** with a primary (1°) alcohol **2a** in the presence of CuBr and NaOH (0.2/ 4 mol%: [CuBr]$_0$=1.6×10^{-3} M) in p-xylene at 135 °C under H$_2$ (1 atm) afforded, after the mixture was purified by column chromatography on silica gel, the coupling product alcohol **3aa** in an yield of 92% (Table 1, entry 5).

No reaction was observed when the base NaOH was lacking.[9] In the presence of dppe or dppp, the productivity decreased significantly, whereas moderate product alcohol/ ketone selectivity was retained (Table 1, entries 2 and 3). In comparison, H$_2$ (1 atm) was purged into the reaction solute with an expectation that this treatment would eliminate the formation of ketone **4aa**.[10] In fact, conversion and product alcohol selectivity were enhanced (Table 1, entries 4 and 5), compared with the results obtained without H$_2$ gas (entries 1–3). By taking advantage of the H$_2$ effects, the use of CuBr (0.05 mol%) and NaOH (4 mol%) gave a turnover number (TON) of >1300 at 145 °C (Table 1, entry 6). The

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☐ Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201101752.

Table 1. Effects of different factors on the coupling of **1a** with **2a**.[a]

Entry	Ligand	H$_2$ [atm]	Total yield [%][b] (**3aa/4aa**)	TON[c]
1	None	–	74 (62:38)	370
2	dppp	–	50 (74:26)	250
3	dppe	–	30 (70:30)	150
4	dppp	1	88 (93:7)	440
5	None	1	>99 (92:8)	500
6[d]	None	1	69 (97:3)	1380

[a] CuBr/ligand/base/**1a**/**2a**=1:1(or 0):20:500:500. Unless otherwise specified, the reaction was performed in *p*-xylene at 135°C for 48 h under H$_2$ or Ar. Diastereoselectivity of **3aa**=≈1:1.2. [b] Total yield of **3aa** and **4aa**. [c] Turnover number, calculated as (yield(%) of **3aa**+**4aa**)/(CuBr mol%). [d] CuBr/dppp/NaOH/**1a**/**2a**=1:0:80:2000:2000 at 145°C for 96 h.

solvent screening with CuBr (0.2 mol%)/NaOH (4 mol%) ([CuBr]$_0$=1.6×10^{-3} M) suggested that polar solvents, including DMSO, DMF and 1,4-dioxane were not promising (**3aa**: <3%).

Given the optimal conditions (**1** (100 mol%), **2** (100 mol%), CuBr (0.2 mol%), H$_2$ (1 atm), NaOH (4 mol%), and *p*-xylene at 135°C), various substrates were investigated and the results are presented in Table 2. Some characteristic features of the CuBr/H$_2$/NaOH catalyst system are as follows. 1) The reaction showed substrate generality with respect to both 1° and 2° alcohol components. Under the optimal conditions, benzylic-type (hetero)aromatic 1° and 2° alcohols were the most promising substrates, both of which were joined into the respective products **3** in high to quantitative yields. 2) The ratio **3/4** (the corresponding ketone) obtained using aliphatic alcohols was uniformly excellent (>12:1≈>99:1) under H$_2$ (Table 2, entries 15–17 and 21–24).[11] The capability of a catalytic amount of base as co-catalyst, thus far underestimated in the cross-coupling of aliphatic alcohols, was enhanced significantly. These results are in contrast to preceding Guerbet variants utilizing sacrificial H$_2$ acceptors.[3b,5a,f] 3) The procedure using H$_2$ was also beneficial for obtaining β-branched 2° alcohols **3da** and **3ea** (Table 2, entries 19 and 20). The reactivity of acyclic 2° alcohols such as **1d** and **1e** having an elongated carbon chain (R^2≠H) was overlooked in preceding attempts to modify the Guerbet conditions.[12] 4) In some cases, the addition of dppp without purging H$_2$ was enough to ensure the smoothest conversion (Table 2, entries 4, 9, and 12).

A molar concentration of the aliphatic aldehydes, generated upon oxidation of the corresponding alcohols **2k** and **2l**, would be kept at a minimum, so that neither the aldehydes nor their self-condensation was detected at least by TLC analysis. The cross-aldol condensation between aldehydes and ketones should proceed more rapidly. These points are consistent with the unique facets of Guerbet conditions including the present system.

To elucidate the reaction mechanism of this efficient catalyst system, several key experimental results should be noted. 1) Those aryl substrates having a halogen, which reacted with Pd catalysts[6a] (e.g., **3bd**:≈0%), also underwent cross-coupling under the present conditions. Even the aryl iodide remained intact upon the reaction of **2e** (Table 2, entry 7). Hence, Cu^0 is unlikely to play an essential role as the active species.[13] 2) Neither O$_2$ nor air was needed for reoxidation of such low-valent Cu species, if in fact any were present, even though apparent oxidation of alcohol was involved throughout the overall process. 3) Na/air[14a] and NaOH (or KOH)/O$_2$[14b] were recently reported to promote the oxidation and the Guerbet reaction of benzylic-type alcohols, respectively, without any transition metals. In our case, catalytic Na or NaH, in place of NaOH under otherwise identical reaction conditions (Table 2, entry 1), showed a similar reactivity (e.g., **3ba**: ≈95%) with rigorous exclusion of air from the reaction mixture.

Given these experimental findings, several control experiments were carried out using **1b** or **2a** (Table 3). The role of CuBr/NaOH/(H$_2$ or dppp) was to start the oxidation of **1b**, but also more slowly, that of **2a** (Table 3, entries 1–3).[15] No more than 5% of **1b** underwent oxidation even after 24 h. CuBr$_2$ showed a similar ineffectiveness (Table 3, entry 4). These results are in contrast to Cu^I- or Cu^{II}-initiated oxidation of alcohols in the presence of O$_2$.[13c] Without CuBr, H$_2$, and air, NaOH alone barely promoted the oxidation of both **1b** and **2a** (Table 3, entry 5). Hence, a major pathway for the oxidation of **2a** finally started presumably through a Meerwein/Ponndorf/Verley/Oppenauer (MPVO)-type hydrogen transfer from **2a** to **5b**.

Next, we intended to doubly check such a primary role of CuBr, and to clarify the mechanism of the reaction steps following the induction period of the catalysis. The cross-coupling between 1° and 2° alcohols **1b** and **2a** was conducted using different reaction conditions, which were monitored in the absence of CuBr and H$_2$, and instead by adding likely carbonyl compound(s) that might be generated in situ (**5b**, **6a**, **5b**+**6a**, or **7ba**) (Table 4). We observed a similarity and significant difference in the influence of each additive on the yield of **3ba**. Among the four different additives (Table 4, entries 1–5), **5b**+**6a** (0.5 or 1 mol% each) led to an excellent yield of **3ba** (≈90%) with a marginal amount of **4ba** (≈3%; Table 4, entries 3 and 4). It was speculated that under basic conditions with a reaction temperature of 135°C, **5b**+**6a** underwent rapid cross-aldol condensation leading to enone **7ba**. However, when **7ba** (1 mol%) was used separately as an additive, the reaction rate was slightly inferior to that obtained using **5b**+**6a** (Table 4, entry 4 vs. 5). In any event, we were able to avoid using CuBr and H$_2$ by taking advantage of the notable influence of **5b**+**6a** as an initiator of the reaction.

Additional control reactions in the absence of CuBr were carried out to probe a reducing agent for the prospective intermediate **7ba** (Table 5). The 2° alcohol **1b** showed reducing capability superior to the 1° alcohol **2a** for the transfer hydrogenation (TH) of a carbonyl group (Table 5, entry 1

Table 2. Coupling between two different alcohols: substrate scope.[a]

Entry	2° Alcohol 1	1° Alcohol 2	CuBr/dppp/NaOH/ 1/2	Product alcohol 3	Yield [%][b]
1	1b	2a	1:0:20:500:500	3ba: Y=H	95
2	1b	2a	1:0:40:2000:2000	3ba	98[c]
3	1b	2b	1:0:20:500:500	3bb: Y=F	83
4	1b	2b	1:1:20:500:500	3bb	97[d]
5	1b	2c	1:0:20:500:500	3bc: Y=Cl	97
6	1b	2d	1:0:100:500:500	3bd: Y=Br	98
7	1b	2e	1:0:100:500:500	3be: Y=I	98
8	1b	2f	1:0:20:500:500	3bf: Y=OMe	91
9	1b	2f	1:1:20:500:500	3bf	96[d]
10	1b	2g	1:0:20:500:500	3bg: Y=SMe	98
11	1b	2h	1:0:20:500:500	3bh	71
12	1b	2h	1:1:20:500:500	3bh	87[d]
13	1b	2i	1:0:20:500:500	3bi: Z=O	87
14	1b	2j	1:0:20:500:500	3bj: Z=S	99
15	1b	2k	1:0:100:500:500	3bk: R3=cHex	50[e]
16	1b	2k	1:1:100:500:500	3bk	80[e]
17	1b	2l	1:0:100:500:500	3bl: R3=Me(CH2)10	99[e]
18	1c	2a	1:0:100:500:500	3ca	99[e]
19	1d	2a	1:0:100:500:500	3da: R2=Me	85[e,f]
20	1e	2a	1:0:100:500:500	3ea: R2=Ph	82[e,f]
21	1f	2a	1:0:100:500:500	3fa: R3=Ph	98[e]
22	1f	2l	1:0:100:500:500	3fl: R3=Me(CH2)10	55[e]
23	1f	2l	1:1:100:500:500	3fl	86[e]
24	1g	2a	1:0:100:500:500	3ga	68[e]

[a] Unless otherwise specified, CuBr/(dppp)/NaOH/1/2 = 0.02:(0.02):0.4:10:10 mmol scale was used and the ratios 3/4 (4 is the corresponding ketone, e.g., 4bl (ketone instead of alcohol; R3=Me(CH2)10)) were consistently >93:<7. The reaction was performed in p-xylene at 135°C for 48 h under H2 (1 atm). [b] Of those isolated purified product alcohols 3 was determined by 1H NMR spectroscopy based on the internal standard (1,1,2,2-tetrachloroethane). [c] At 145°C for 6 days. [d] Under Ar (1 atm). [e] At 145°C for 48–144 h. [f] Diastereoselectivity was approximately 1:1–1.5.

vs. 2). In contrast, the TH of the α,β-olefin of 7ba can take place using either 1b or 2a (Table 5, entries 1 and 2). The latter TH (1,4-reduction) showed an apparent reaction rate faster than the former, judging from the product distribution in favor of olefin reduction (Table 5; TH of carbonyl/TH of olefin = 1:1.8 (entry 1) and <1:12 (entry 2)). Apparent TH

of the olefin of allylic alcohol 8 also produced desirable 3ba (Table 5, entry 3); however, this process may involve the transfer dehydrogenation (TDH: Oppenauer oxidation) of 8, followed by 1,4-reduction of the resulting 7ba and subsequent TH of the carbonyl group of 4ba (MPV reduction). In fact, an equilibrium that shifts from 8 to the respective ketone 7ba is possible through a self-induced TDH/TH (MPVO) cycle, which indeed afforded 3ba and 4ba (entry 4). Here again, the apparent 1,4-reduction of 7ba prevails over 1,2-reduction (Table 5, entries 3 and 4). Overall, in the reaction of 1b with 2a (Table 2, entry 1), formation of 7ba should be followed by a reaction sequence involving TH of the α,β-olefin of 7ba (apparent 1,4-reduction)[16] and subsequent TH of the carbonyl group of 4ba (1,2-reduction), in which 1b and 2a can promote 1,4- and 1,2-reduction.[17] Although a possibility of the inverse sequence (first step: TH of the carbonyl group of 7ba; second step: TH of the olefin) cannot be fully excluded, recovery of 8 was undetectable by 1H NMR analysis in a crude mixture of each reaction (Table 5, entries 1–4).

According to these control experiments, a likely catalytic cycle viable for promoting a major pathway can be depicted (Scheme 2). One of the most important roles of CuBr/NaOH/(H2 or dppp) is to initiate the oxidation of 2° alcohol 1 (and a very small amount of 1° alcohol 2), giving a mixture of ketone 5 and aldehyde 6.[18] Both reaction partners readily form enolate IA through deprotonation of 5 with catalytically active species M-OR. Subsequent cross-aldol condensation with 6 in IA leads to the respective enone 7. Sequential hydrogen transfer from 2 (or 1) to 7 and from 1 (or 2) to IB gives desirable 3. Concomitant formation of IC, followed by a rapid process involving intramolecular proton transfer (deprotonation of 5) regenerates IA. The sequence of multistep reactions corresponds to the basic unit of overall catalytic cycles and can circulate iteratively even without a transition metal. Thus a prospective species that catalyzes this self-induced cycle (M-OR, Scheme 2) in a hydrocarbon solvent may be a molecular cluster[19] consisting of (NaOR)m(CuOR)n (RO = alkoxide or enolate[20] derivatives; m = an integer but not 0; n = 0[21] or an integer), which is thought to have the potential to promote different sets of MPVO-type hydrogen transfer.[6a,22]

In summary, we have developed a highly efficient and practical procedure for producing longer-chain alcohols using a catalytic amount of base under anaerobic conditions. The carbon–carbon cross-coupling of two different alcohols, which were mixed in a 1:1 molar ratio, took place with high product alcohol selectivity using H2. The substrate scope was broadened using inexpensive metal sources CuBr and NaOH. We eventually found a tran-

Table 3. Control experiments: oxidation of **1b** or **2a** under different reaction conditions.[a]

Entry	Catalyst system [mol%]	Reaction **1b**→**5b** PhCOMe (**5b**) [%][b]	Reaction **2a**→**6a** PhCHO (**6a**) [%][b]
1	CuBr (0.2) NaOH (4); Ar	5	≈1
2	CuBr (0.2) NaOH (4); H$_2$	5	≈1
3	CuBr (0.2) NaOH (4) dppp (0.2); Ar	4	≈1
4	CuBr$_2$ (0.2) NaOH (4); Ar	2	2
5	NaOH (4); Ar	≈1	≈1

[a] Unless otherwise specified, the reaction was carried out using **1b** or **2a** in p-xylene at 135 °C for 24 h using each catalyst system. [b] Yields determined by NMR spectroscopy.

Table 4. Effects of additive(s) on reaction of **1b** with **2a**.[a]

1b + **2a** → (NaOH (4 mol%) / additive(s) (1–2 mol%) / p-xylene, Ar / 135 °C, 48 h) → Ph–CH(OH)–CH$_2$–CH$_2$–Ph (**3ba**) + Ph–CO–CH$_2$–CH$_2$–Ph (**4ba**)

| Entry	Additive(s) [mol%]	**3ba** [%][b]
1	**5b** (1)	39
2	**6a** (1)	39
3	**5b** (1) + **6a** (1)	93 (3)[c]
4	**5b** (0.5) + **6a** (0.5)	82 (2)[c]
5	**7ba** (1) [Ph–CO–CH=CH–Ph]	72 (3)[c]

[a] Unless otherwise specified, the reaction was carried out using **1b** (10 mmol) and **2a** (10 mmol) using NaOH (4 mol%) and additive(s) in p-xylene at 135 °C for 48 h under Ar; [NaOH]$_0$ = ≈0.04 M. [b] ^{1}H NMR yields. [c] NMR yields of **4ba**.

Table 5. Control reactions using **7ba** or **8**.[a]

7ba or Ph–CH(OH)–CH=CH–Ph (**8**) → (NaOH (4 mol%) / additive / p-xylene, Ar / 135 °C, 24 h) → **3ba, 4ba, 8, 7ba**

Entry	Starting material	Additive [mol%]	Yield [%][b] (**3ba/4ba/8/7ba**)[c]
1	**7ba**	**1b** (500)	90 (49:41:<1:<1)
2	**7ba**	**2a** (500)	86 (<4:44:<1:38)
3	**8**	**2a** (100)	95 (32:63:<1:<1)
4	**8**	–	94 (13:81:<1:<1)

[a] Unless otherwise specified, the reaction was carried out using **7ba** or **8** and additive with NaOH (4 mol%) in p-xylene at 135 °C for 24 h under Ar; [NaOH]$_0$ = 0.04 M. [b] ^{1}H NMR yields (**3ba**+**4ba**+**8**+**7ba**). [c] Determined by ^{1}H NMR spectroscopy.

sition-metal-free[14b,23] version of this process in the presence of not more than 1 mol% of carbonyl compound(s) under conditions much milder than the original Guerbet conditions. Thus this self-induced catalytic cycle, initiated by the CuBr/H$_2$(or dppp)/NaOH, clearly demonstrated a mechanistically distinct alternative to the "redox" or "borrowing hydrogen" mechanism in the previous Guerbet reaction that has been believed over some decades to be facilitated by a transition-metal catalyst.[24] A further elucidation of the role
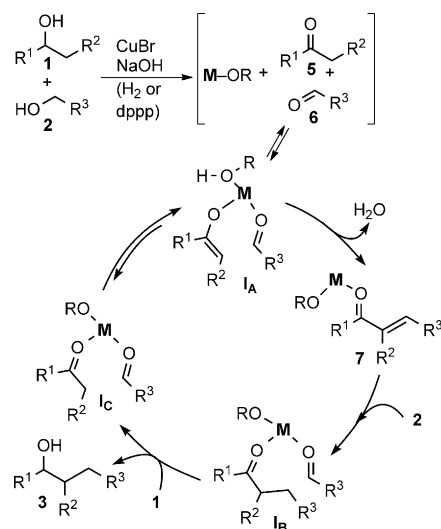
Scheme 2. Plausible major catalytic cycle.

of H$_2$[10] and the catalytically most important species participating in this CuBr/H$_2$/NaOH/alcohol/carbonyl compound(s) system is now underway in our laboratory.

Experimental Section

General procedure: A degassed and subsequently argon-filled balloon (1 L) was equipped with a Schlenk tube (100 mL). p-Xylene (10 mL), **1a** (10 mmol, 1482 mg), **2a** (10 mmol, 1081 mg), CuBr (0.02 mmol, 2.87 mg), and NaOH (0.4 mmol, 16.0 mg) was added to this vessel at 25 °C. A suspension inside the Schlenk tube was subjected to the freeze (0.5–1 mmHg, at −196 °C)–thaw (filled with Ar, at 25 °C) cycles (× 3), filled with H$_2$ (1 atm, in the 1 L balloon) and was stirred at 135 °C for 48 h, during which time droplets of water were sticking around the neck and the upper rim of the Schlenk tube. The mixture was cooled down to 25 °C and directly purified by column chromatography on silica gel (EtOAc/n-hexane = from 1:100 to 1:30) to give a mixture of **3aa** and **4aa** (2381 mg, >99% yield) in a ratio of 92:8 determined by internal standard (1,1,2,2-tetrachloroethane) method using ^{1}H NMR spectroscopy.

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[7] Heterogeneous Cu/Cr/Mn and Cu Raney catalysts with excess NaOR: a) C. Carlini, M. D. Dirolamo, M. Marchionna, M. Noviello, A. M. R. Galletti, G. Sbrana, *J. Mol. Catal. A: Chem.* **2002**, *184*, 273–280; b) C. Carlini, A. Macinai, A. M. R. Galletti, G. Sbrana, *J. Mol. Catal. A: Chem.* **2004**, *212*, 65–70.

[8] For example, with Ir (Ref. [3a]) and Ru catalyst (Ref. [5a]) in the presence of a stoichiometric or an excess amount of base (KOH or Na(OtBu)), **3aa**/**4aa** = 65:34 and 49:43, respectively.

[9] In the absence of NaOH (4 mol%), Cu(OtBu) (0.2 mol%) was also unable to promote the coupling reaction. See also the Appendix of Supporting Information (page S13–S14) for more detailed analysis of reaction conditions.

[10] The mechanism on how H$_2$ improved the reaction rate and product alcohol selectivity is still under scrutiny and needs profound investigation. When D$_2$ was used in place of H$_2$ in the reaction of **1b** with **2a** (Table 2, entry 1), no appreciable incorporation of deuterium into **3ba** was observed using ^{1}H NMR analysis.

[11] 2° alcohols of R$^2 \neq$ H are generally less reactive than 2° alcohols of R^2 = H. When we carried out separately the reaction of **3ba** with **2a** at 135–145°C under otherwise identical reaction conditions, 95% of **3ba** was recovered with ≈4% of **4ba**, checked by ^{1}H NMR spectroscopy. In fact, in situ benzylation of **3ba** did not take place (Table 2, entry 1) with prolonged heating at 135°C, as checked by GC-MS.

[12] In the initial attempts, a higher loading of CuBr (2 mol%)/NaOH (20–30 mol%) was assumed to ensure a smooth oxidation of aliphatic 1° and 2° alcohols, since these substrates should be rather reluctant to undergo oxidation, compared with benzylic alcohols. However, the product alcohol selectivity was marginal: the reaction between **1b** and **2l** at 135°C and 145°C (CuBr/dppp/NaOH = 2:2:30 mol%) for 48 h under Ar gave alcohol **3bl** and ketone **4bl** in ratios of 69:31 and 28:72 with total yields of 68 and 85%, respectively.

[13] Dehydrogenation of 1° and 2° alcohols using Cu or CuO requires a higher temperature (250–300°C): a) M. Hudlicky, *Oxidations in Organic Chemistry*, American Chemical Society, Washington DC, **1990**, pp. 114–149; Cu^I- or Cu^{II}-initiated oxidation of alcohols in the presence of O$_2$ and/or TEMPO: b) R. A. Sheldon, I. W. C. E. Arends, *Adv. Synth. Catal.* **2004**, *346*, 1051–1071; c) I. W. C. E. Arends, P. Gamez, R. A. Sheldon, *Adv. Inorg. Chem.* **2006**, *58*, 235–279; d) M. J. Schultz, M. S. Sigman, *Tetrahedron* **2006**, *62*, 8227–8241; e) C. S. Cho, W. X. Ren, S. C. Shim, *Tetrahedron Lett.* **2006**, *47*, 6781–6785; f) C. S. Cho, W. X. Ren, N. S. Yoon, *J. Mol. Catal. A: Chem.* **2009**, *299*, 117–120.

[14] a) L.-H. Zhou, X.-Q. Yu, L. Pu, *Tetrahedron Lett.* **2010**, *51*, 475–477; aliphatic alcohols showed scant reactivity using O$_2$: b) L. J. Allen, R. H. Crabtree, *Green Chem.* **2010**, *12*, 1362–1364.

[15] Hence, a molar concentration of aldehyde should be consistently much lower than that of ketone. This may be one of the reasons why aliphatic aldehydes barely underwent their self-condensation.

[16] MPV-type 1,2-reduction of α,β-enone **7ba**, followed by stepwise 1,3-hydrogen shift (hydrogen transfer from the α- to the γ-carbon of **8**) giving **4ba** also could not be fully ruled out.

[17] Deuterium experiments also revealed that deuterium as D$^-$ shifted from [D$_1$]**1b** (PhCDOH(Me)) or from [D$_2$]**2a** (PhCD$_2$OH) to the γ-carbon (with respect to the OH group of **3ba**: the β-carbon of α,β-enone **7ba**) and the α-carbon of **3ba** (the carbonyl carbon of **7ba**) under otherwise identical conditions (Table 2, entry 1). In these reactions, the deuterium ratio (D%: thus hydrogen ratio (H%) is 100–D%) at the α- and γ-carbon of **3ba** was 40 and 20% using [D$_1$]**1b** and **2a**, and 44% and 66% using **1b** and [D$_2$]**2a**. ^{1}H NMR indicated that the β-carbon of **3ba** (originally, the α-carbon of **7ba**) was not labeled by deuterium in both cases, suggesting that the α-carbon of **7ba** is protonated by H$^+$ from the OH group of alcohols. This shows a typical nature of (apparent) MPV-type 1,4-reduction of α,β-enones.

[18] The production of a metal hydride from a metal alkoxide indeed confirms a proposed unique characteristic of copper: G. V. Goeden, K. G. Caulton, *J. Am. Chem. Soc.* **1981**, *103*, 7354–7355.

[19] a) M. G. Stanton, M. R. Gagné, *J. Am. Chem. Soc.* **1997**, *119*, 5075–5076; b) M. G. Stanton, C. B. Allen, R. M. Kissling, A. L. Lincoln, M. R. Gagné, *J. Am. Chem. Soc.* **1998**, *120*, 5981–5989 and references cited therein; c) R. M. Kissling, M. R. Gagné, *J. Org. Chem.* **2001**, *66*, 9005–9010.

[20] a) P. J. Pospisil, S. R. Wilson, E. N. Jacobsen, *J. Am. Chem. Soc.* **1992**, *114*, 7585–7587; b) J. M. Gruver, L. R. L. Liou, A. J. McNeil, A. Ramirez, D. B. Collum, *J. Org. Chem.* **2008**, *73*, 7743–7747; c) T. S. De Vries, A. Goswami, L. R. Liou, J. M. Gruver, E. Jayne, D. B. Collum, *J. Am. Chem. Soc.* **2009**, *131*, 13142–13154 and references cited therein.

[21] We always observed that black solids of Cu^0, the amount of which was yet unclear, precipitated out from the reaction mixture, sticking on the wall of a Pyrex reaction vessel. The Inductively Coupled Plasma Emission (ICPE) analysis of the solution phase of the reaction as in entry 1, Table 2 indicated that the Cu content was less than about 1/500 of the Cu mass initially used (the Cu mass changed

from 116 to <0.62 ppm). However, we could not fully rule out a possibility of the participation of some Cu(OR) species in catalysis.

[22] a) R. Martínez, D. J. Ramón, M. Yus, *J. Org. Chem.* **2008**, *73*, 9778–9780; b) H. V. Mierde, P. V. D. Voort, F. Verpoort, *Tetrahedron Lett.* **2008**, *49*, 6893–6895; c) H. V. Mierde, P. V. D. Voort, F. Verpoort, *Tetrahedron Lett.* **2009**, *50*, 201–203.

[23] The ICPE analysis of NaOH pellet commercially available from Aldrich (99.999% purity) and Kanto (99.98% purity) we used indicat-

ed that the rate of content of each heavy metal (Ag, Cr, Fe, Mo, Ni, Zn) representative of any metal impurities was less than 1 ppm.

[24] We had already submitted our primary results related to the Cu/(H$_2$)NaOH system as a JP patent, dated on December 29th, 2009 (R. Noyori, S. Saito, H. Naka, O. Kose, T. Miuta (Nagoya University) 2009-299231, **2009**) before submitting this paper.