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A Comparative Mechanistic Study of Cu-Catalyzed Oxidative Coupling Reactions with *N*-Phenyltetrahydroisoquinoline

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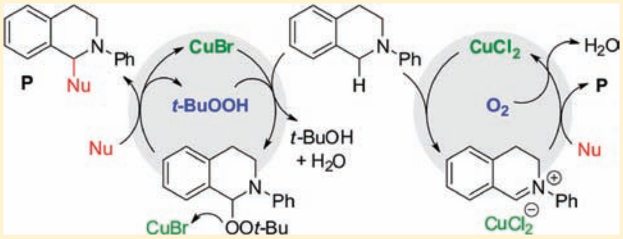
Supporting Information

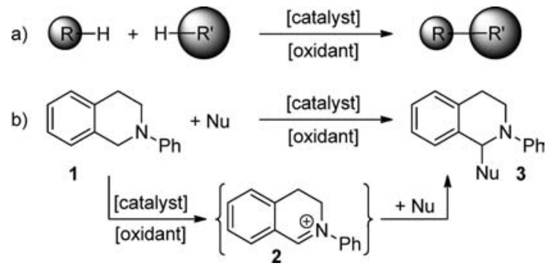


ABSTRACT: A comparative mechanistic study of Cu-catalyzed oxidative coupling reactions of *N*-phenyltetrahydroisoquinoline with different nucleophiles was conducted. Two previously reported combinations of catalyst and oxidant were studied, $CuCl_2 \cdot 2H_2O/O_2$ and CuBr/*tert*-butyl hydroperoxide (TBHP). On the basis of a synthetic study with different nucleophiles, the electrophilicity of the intermediate iminium ion was estimated and differences between the two methods were revealed. The key intermediate in the aerobic method is shown to be an iminium ion, formed through oxidation by copper(II), which can react with any nucleophile of sufficient reactivity. The role of oxygen is the reoxidation of the reduced catalyst. In the CuBr/TBHP system, an α-amino peroxide is proposed as a true intermediate within the catalytic cycle, formed from the amine and TBHP by a Cu-catalyzed radical reaction pathway and acting as a precursor to the iminium ion intermediate.

INTRODUCTION

The activation of carbon−hydrogen (C−H) bonds for coupling reactions is an important area in research on sustainable chemistry. C−H bonds are ubiquitous in organic molecules, and their functionalization enables the direct synthesis of complex products from simple starting materials, without prior introduction of activating groups. Under oxidative conditions, two C−H or heteroatom−H bonds can be coupled directly to form a new bond (Scheme 1a).[1] Oxidative coupling reactions can meet the criteria of green chemistry:[2] using a catalyst and low molecular weight oxidants such as elemental oxygen, they are atom economic and produce at best only water as the byproduct.

Scheme 1. (a) Oxidative Coupling for the Functionalization of C−H Bonds. (b) Oxidative Coupling of *N*-Phenyltetrahydroisoquinoline 1 with Nucleophiles via Proposed Iminium Ion 2



Among these reactions, the oxidative coupling of amines, in particular *N*-phenyltetrahydroisoquinoline (**1**), with nucleophiles has received alot of attention (Scheme 1b).[3] A large number of different methods has been developed since the pioneering studies of Murahashi and Li.[4] Various nucleophiles have been employed, including cyanides,[4e,5] nitroalkanes,[5k,6] activated methylene compounds,[5f,6b,d,g,7] ketones,[8] electron-rich arenes,[4g,9] alkynes,[4f,10] organometallic[11] or siloxy compounds,[12] and heteroatom nucleophiles.[4c,d,6g,13] The oxidation protocols involve predominantly metal catalysts together with oxygen or synthetic oxidants, but organocatalytic,[8c] photochemical,[5a,6f,g,13e] electrochemical,[5b,14] and noncatalytic methods[5d,e,j,9e,12d] are also known. Even a nonoxidative method that releases hydrogen has been reported.[15] Many methods reported in the literature focus on one particular type of catalyst, oxidant, or nucleophile, while there are only a few reports of a truly diverse scope of nucleophiles.[16] The most notable exception is the combination of CuBr as catalyst and *tert*-butyl hydroperoxide (TBHP) in decane as oxidant, introduced by the C.-J. Li group, which has been used for a large number of nucleophiles.[4f,g,5f,6a,9b,10a,11,12h,13a]

The generally proposed rationale for oxidative coupling reactions with tertiary amines and **1** in particular is the formation of an intermediate iminium species **2**, which reacts with nucleophiles to product **3** (Scheme 1b). Given the large number of catalysts, oxidants, and nucleophiles reported for this reaction, the question remains whether all methods are in principle interchangeable, i.e., whether each oxidation mode can be combined with each nucleophile. If so, one could choose the most suitable method based on practicability, cost, and sustainability and combine it with the desired nucleophile. In general, detailed mechanistic studies in this area are lacking. Studies which highlight the similarities and differences between

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individual methods may prove particularly useful. In some cases, potential intermediates have been investigated or radical mechanisms have been probed by the addition of inhibitors, but no comprehensive mechanistic picture has been gained.[4f,g,10e,12b,i,14] The proposed iminium ion **2** has been observed for the first time by Todd and co-workers, isolated from a catalyst-free reaction using DDQ as the oxidant.[17]

Here, we present a mechanistic study of oxidative coupling reactions according to Scheme 1b, investigating the generality of nucleophiles and the role of the oxidant. Two methods will be compared: the $CuCl_2{\cdot}2H_2O/O_2$ system developed in our own group[12c] and the CuBr/TBHP system developed by Li et al.[4f]

■ RESULTS AND DISCUSSION

We have previously reported the observation and characterization of the intermediates **2a**, **4**, and **5** in oxidative coupling reactions of **1** with silyl enolates using the $CuCl_2{\cdot}2H_2O/O_2$ system.[12g] X-ray structural analysis revealed iminium **2a** to be an ionic compound with a dichlorocuprate(I) counterion (Figure 1), in contrast to the common suggestion of a π-bound metal–iminium species.[1a,4e,g] Compounds **4** and **5** were shown to be off-cycle intermediates formed reversibly from **2a** in the presence of methanol and water, respectively. The formation of **4** was suggested to provide a stabilizing reservoir for **2a**, making methanol the solvent of choice if weak nucleophiles are used. The use of CuBr under otherwise identical conditions resulted in the formation of an iminium ion **2b** with a $(Cu_2Br_4)^{2-}$ counterion.

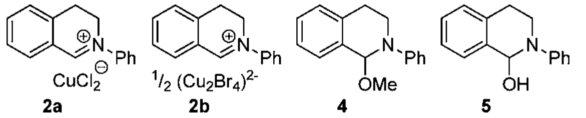


Figure 1. Characterized intermediates in the oxidative coupling with **1** using $CuCl_2{\cdot}2H_2O$ as catalyst and O_2 as oxidant.

In further mechanistic studies and to address the above questions, we screened selected nucleophiles **6** from different substrate classes to test the generality of the aerobic copper-catalyzed reaction (Table 1). In order to estimate the electrophilicity of **2a**, we used predominantly compounds with reported nucleophilicity values. We refer to the reactivity scales developed by the Mayr group for nucleophiles and electrophiles.[18,19] The products were isolated after complete conversion of amine **1** as indicated by thin layer chromatography, unless noted otherwise.

The coupling product **3a** with nitromethane (**6a**) was received in good yield if the nucleophile was used as the reaction solvent (Table 1, entry 1), as had been observed previously in reactions using other oxidation protocols.[6] Dimethyl malonate **6b** also reacted well, and the coupling product **3b** was isolated in 94% yield after 13 h (entry 2). With **3b** as a representative example, we also attempted to optimize the reaction with respect to more sustainable conditions. Air instead of pure oxygen was a nearly equally effective oxidant, resulting in 82% yield after 28 h (entry 3). Reducing the catalyst loading to 2 mol % was possible, leading to slightly prolonged reaction times but still giving a good yield of 82% (entry 4). Instead of 3.0 equiv of nucleophile, which was originally chosen to provide fast reaction rates and high yields, a reduction to 1.5 equiv is also possible, giving a nearly unchanged yield of 89% after 24 h (entry 5).

A cyanide group can be introduced in good yields by using either TMS-CN or sodium cyanide (entries 6 and 7). In the latter case, the use of acetic acid as cosolvent was beneficial, as was observed previously by Murahashi in Ru-catalyzed reactions.[4e] In the absence of acetic acid, only traces of the product **3c** were visible after a reaction time of three weeks. *N*-Methylpyrrole **6d** and indoles **6e** and **6f** gave medium to good yields of the expected products **3d–f** (entries 8–10). The relatively low yield of 41% for the coupling product **3d** is probably due to the formation of a mixture of regioisomers or double addition products, as had been observed previously using an Fe catalyst.[9d]

Isocyanides **6g–i** are good nucleophiles,[19f] yet they have not been utilized in oxidative coupling reactions with amines previously. We tested three different ones with *N* values from 5.47 to 4.90 and found that the corresponding amide products **3g–i** could be formed with 58–76% yield in DMF as solvent (entries 12–14), making this an interesting alternative to form amino acid derivatives. Methanol was not a suitable solvent, giving very low yields. In acetone as solvent, medium yields were achieved, but the desired product was accompanied by up to 20% of the coupling product with acetone. In all cases, full conversion was not achieved; the reactions were arbitrarily stopped after several days. Potentially, the isocyanides suppress catalytic activity by strong coordination to copper. Better yields could be achieved at higher catalyst loadings: with 10 mol %, only 39% of product **3g** was formed after one week, while with 20 mol %, 76% could be isolated after four days (entries 11 and 12).

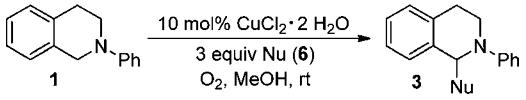
Phenylacetylene **6j** reacted fast under standard conditions, giving product **3j** in 89% yield after stirring overnight (entry 15). The low nucleophilicity value of 0.34 for **6j** cannot be used for the discussion, because the acetylene will be activated as a more reactive acetylide by the copper catalyst.[4f,10a–d]

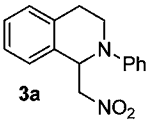
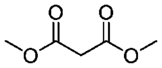
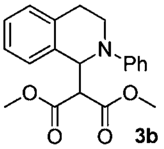
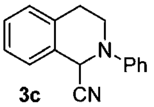
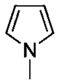
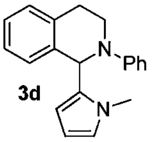
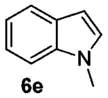
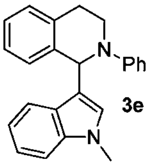
A selection of other nucleophiles that have previously been employed[12c,g] in coupling reactions with **1** under the same reaction conditions as in Table 1 are shown in Scheme 2, with an emphasis on the nucleophilicity range. Most of these nucleophiles fall within the nucleophilicity range of the substrates used in Table 1. Methylallylsilane **10** and enolate **11** are the least nucleophilic reagents we found that are still reactive enough to form the coupling products (N = 4.41 and 3.78).[19d] In order to determine the reactivity threshold, we also looked at weak nucleophiles that failed to react (Figure 2).

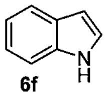
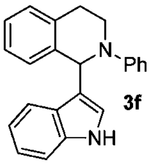
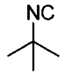
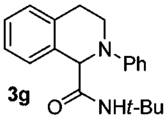
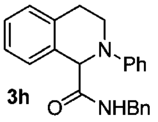
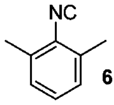
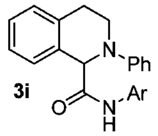
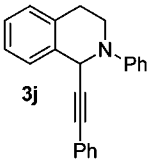
We found that no reaction took place in the presence of 1,3-dimethoxybenzene **13** (N = 2.48),[19d] allylsilane **14** (N = 1.79),[19d] *p*-cresol **15**, or 2-naphthol **16**[21] (no *N* value reported, for comparison: N(phenol) = 1.9).[20] In the reaction with 2-methylfuran **12** (N = 3.61),[19d] analysis by TLC indicated the formation of a new product over three days, which could, however, not be isolated. These results indicate that the nucleophilicity threshold necessary for a reasonable rate lies approximately at 3.8, corresponding to enolate **11**.

On the basis of Mayr's rule of thumb "that electrophiles can be expected to react with nucleophiles at room temperature when $E + N > -5$",[19g] one can estimate the electrophilicity E of **2a** to be around −8 and −9. Because the concentration of **2a** during the reaction is always low, the true value of E(**2a**) could actually be higher.[22] This correlates relatively well with the electrophilicity parameters determined by Mayr et al. for comparable iminium ions, which lie between −5 and −10.[19g,h]

Table 1. Oxidative Coupling of *N*-Phenyltetrahydroisoquinoline with Various Nucleophiles[a]

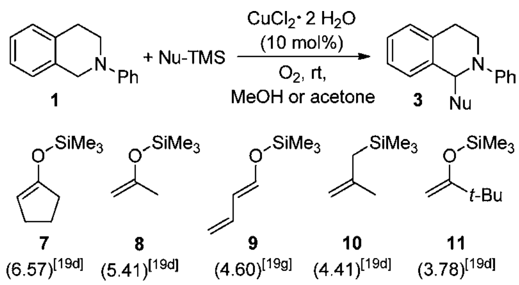


Entry	Nucleophile 6 (*N*)[b]	Product 3	Time (h)	Yield (%)[c]
1[d]	—NO_2 **6a** (20.71[e])[19a]	 **3a**	24	82
2	 **6b** (OEt: 20.22[i])[19b]	 **3b**	13	94
3[f]			28	82
4[g]			17	82
5[h]			24	89
6	TMS-CN **6c** (16.27[e])[19c]	 **3c**	21	77
7[j]	NaCN		24	69
8	 **6d** (5.85)[19d]	 **3d**	17	41
9	 **6e** (5.75)[19e]	 **3e**	24	88

Entry	Nucleophile 6 (*N*)[b]	Product 3	Time (h)	Yield (%)[c]
10	 **6f** (5.55)[19e]	 **3f**	22	86
11[k]	 **6g** (5.47)[19f]	 **3g**	168	39
12[l]			92	76
13[l]	Bn—NC **6h** (4.90)[19f]	 **3h**	168	58
14[l]	 **6i** (4.59)[19f]	 **3i** Ar = 2,6-Me_2Ph	168	68
15	Ph—≡ **6j** (0.34)[19d]	 **3j**	17	89

[a]General conditions: 0.36 mmol of **1**, 1.5 mL of MeOH, 1.08 mmol of **6**, 0.036 mmol of $CuCl_2 \cdot 2H_2O$, O_2. [b]Nucleophilicity parameter *N*. [c]Isolated yield. [d]Nitromethane as solvent. [e]Nucleophilicity parameter *N* of the corresponding anion. [f]Air as oxidant. [g]2 mol % catalyst. [h]1.5 equiv of **6b**. [i]*N* of the diethyl malonate anion. [j]1.5 mL of MeOH:AcOH 4:1 as solvent. [k]DMF as solvent. [l]DMF as solvent, 20 mol % catalyst.

Scheme 2. Literature-Reported Successful Nucleophiles in the Aerobic Cu-Catalyzed Oxidative Coupling of 1[12c,g] (in brackets: nucleophilicity parameter *N*[19d,g])



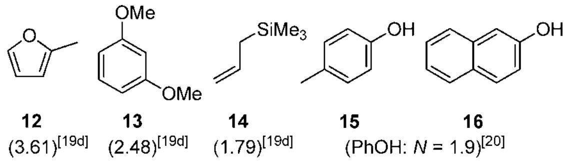


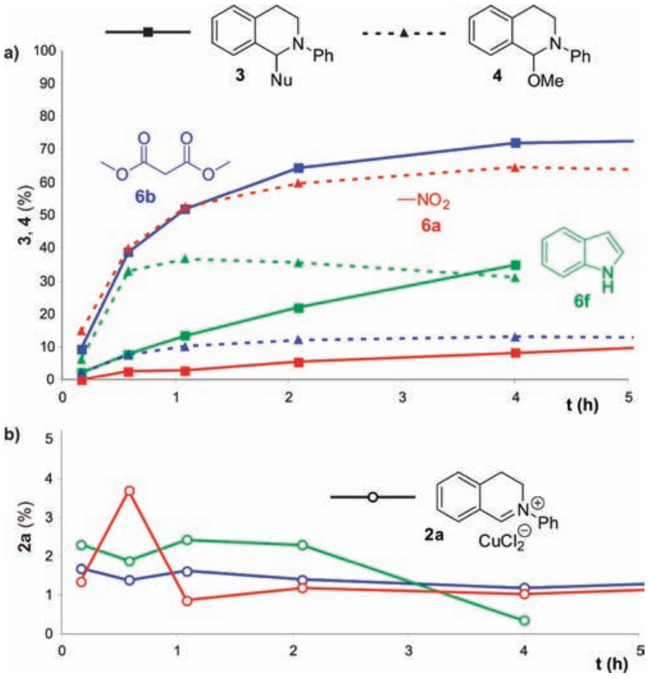
Figure 2. Nucleophiles unreactive under the conditions of Table 1; in brackets: corresponding nucleophilicity parameters *N*.[19d,20]

While this is just an estimate based on a synthetic study which does not aim to deliver a precise electrophilicity parameter, it still provides a correlation that can serve in future studies with other nucleophiles. It also supports the notion that the key step of the reaction is the oxidative formation of an iminium ion that reacts with any nucleophile of sufficient reactivity without significant involvement of the catalyst.

In order to gain further information on the occurrence of intermediates **2a**, **4**, and **5** depending on the nucleophiles used, we monitored the reaction of **1** with a diverse set of substrates over a wide range of nucleophilicity *N*. We investigated the coupling with nitromethane (**6a**, *N* = 20.71), dimethyl malonate (**6b**, *N*(diethyl malonate) = 20.22), and indole (**6f**, *N* = 5.55) by taking samples for NMR analysis over the course of the reaction (Scheme 3).

Under these conditions, hemiaminal **5** was not observed or only in very low amounts. The products **3** were formed with different rates, which do not clearly follow their nucleophilicity values. This is, however, not surprising, because the reaction conditions in the kinetic studies by Mayr et al. often involve preformed electrophile and nucleophile salts with chemically inert counterions, whereas in our study, both the formation of the iminium ion **2a** and the reaction with the nucleophile might

Scheme 3. (a) Monitoring the Formation of Products 3 (squares, solid line) and Intermediate 4 (triangles, dashed line) in the $CuCl_2{\cdot}2H_2O/O_2$ System with Nucleophiles 6a (red), 6b (blue), and 6f (green).[a] (b) Monitoring the Presence of Iminium Ion 2a (open circles) in the Same Set of Reactions[b]



[a]Reaction conditions: 0.36 mmol of **1**, 3.0 equiv of **6**, 5 mol % catalyst, 1.5 mL of MeOH, O_2.

[b]For a full display over 24 h, see the Supporting Information.

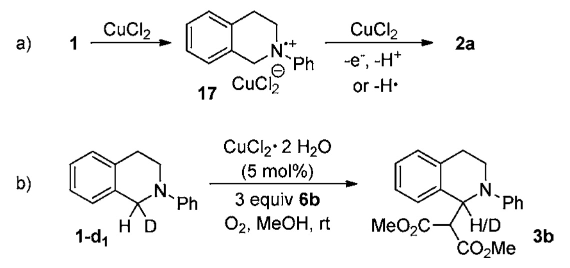
be subject to some interactions between catalyst and substrates. More importantly, the *N* values for **6a** and **6b** have been determined for the corresponding anions while the current reactions conditions (in the presence of amines **1** and **3**) are not basic enough to provide complete deprotonation of these nucleophiles.

The methoxy amine **4** was visible in all reactions during the initial stages and eventually vanished at full conversion to products **3**. It also shows a clear correlation to the rate of product formation: with **6b** as the fastest reacting nucleophile, the product **3b** is formed in a much larger amount than **4**; with a nucleophile of medium reactivity (**6f**), both **3f** and **4** are formed in comparable amounts, and in the slowest reaction using **6a**, **4** clearly dominates. The iminium ion **2a** was also visible and showed an approximately stationary concentration, especially in the reactions with **6a** and **6b** (Scheme 3b).

These trends further support a competition between methanol and the nucleophiles **6** for the iminium ion **2a**. With reactive nucleophiles, **2a** is quickly trapped to give the product **3** and only small amounts of **4** are formed. With less reactive nucleophiles, **4** builds up in larger amounts. However, because of reversible formation, it is ultimately converted to the more stable products **3**. The same trends were observed previously with enolate **8** and allyl silane **10**.[12g]

The role of the oxidant was probed by reacting amine **1** with $CuCl_2{\cdot}2H_2O$ in methanol in the absence of oxygen. Iminium ion **2a** was formed immediately, visible to the naked eye by an orange solution and the precipitation of **2a** as yellow crystals. Accordingly, copper(II) is oxidizing the amine, being reduced to copper(I) in turn, and oxygen as the terminal oxidant is only involved in the reoxidation of copper.[23] The oxidation of **1** most likely involves single-electron transfer (SET) to Cu(II), forming an ammoniumyl radical cation **17**. Hydrogen transfer or a combination of electron and proton transfer then forms the iminium salt **2a** (Scheme 4a).

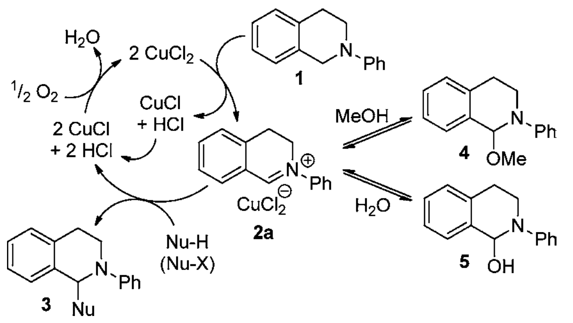
Scheme 4. (a) Potential Mechanism of Oxidation of 1 to 2a. (b) Kinetic Isotope Effect Experiment with Monodeuterated 1-d_1



Further information on this part of the reaction was gained from a kinetic isotope effect (KIE) experiment (Scheme 4b). The monodeuterated amine **1**-d_1 was employed in the oxidative coupling reaction with dimethyl malonate **6b**, forming a mixture of **3b** and 1-deuterated **3b**. After full conversion of the amine, a primary KIE value k_H/k_D of 4.5 was calculated from the ratio of the signal intensity in the 1-position relative to reference signals. This is in accordance with a fast SET preceding rate-determining C−H bond cleavage (see the Supporting Information for full details).[24]

A catalytic cycle that summarizes all our results is given in Scheme 5. Amine **1** is oxidized by two molecules of the copper(II) catalyst to give Cu^ICl and the iminium dichlorocuprate **2a**. In methanol as a solvent or in the presence of water, off-cycle equilibria form the hemiaminal ether **4** or hemiaminal **5**, providing a reservoir of **2a** that can have a stabilizing effect.[12g,25] Any sufficiently reactive nucleophile can trap the iminium ion, giving the desired products and releasing CuCl and HCl. The latter could be buffered by the amines present. Reaction of CuCl and HCl with oxygen produces water and regenerates the active catalyst $CuCl_2$.

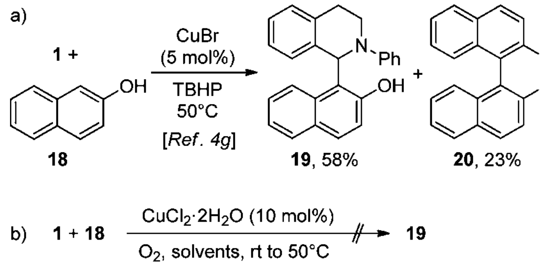
Scheme 5. Mechanism of the Cu-Catalyzed Aerobic Oxidative Coupling



It is likely that other reported aerobic methods for the oxidative coupling with **1** proceed by very similar mechanisms. For example, aerobic coupling reactions using CuBr as catalyst will proceed analogously via iminium salt **2b**. However, a comparison with the widely applied method by Li using TBHP as oxidant indicated differences that prompted us to further investigate and compare both methods using the same tools as described above.

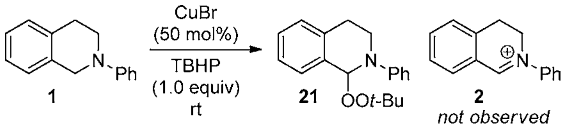
Li et al. reported the successful coupling of 2-naphthol (**18**) with **1** using their CuBr/TBHP system at 50 °C, giving the cross-coupling product **19** next to significant amounts of binaphthol **20** (Scheme 6a).[4g] In contrast, the same reaction did not occur under the conditions of the $CuCl_2{\cdot}2H_2O/O_2$ system, even if it was performed at 50 °C, in different solvents or with prolonged reaction times (Scheme 6b). As mentioned above, this was rationalized by the low nucleophilicity of 2-naphthol.[20]

Scheme 6. 2-Naphthol as a Nucleophile in the Oxidative Coupling with 1



We next investigated the occurrence of potential intermediates in the CuBr/TBHP system. Analogous to our previous studies,[12g] we reacted amine **1** with 50 mol % of catalyst in the presence of oxidant (TBHP) but in the absence of any nucleophile. NMR analysis of the resulting mixture did not show any signals corresponding to the iminium ion **2a** that was observed under aerobic conditions using either CuBr or $CuCl_2$ dihydrate. The only new species identifiable was the amino peroxide **21** (Scheme 7). A *tert*-butyl hemiaminal ether analogous to **4** was not observed.

Scheme 7. Attempted Observation of Iminium Ions Using CuBr/TBHP, Generating Only 21 as the Major Product

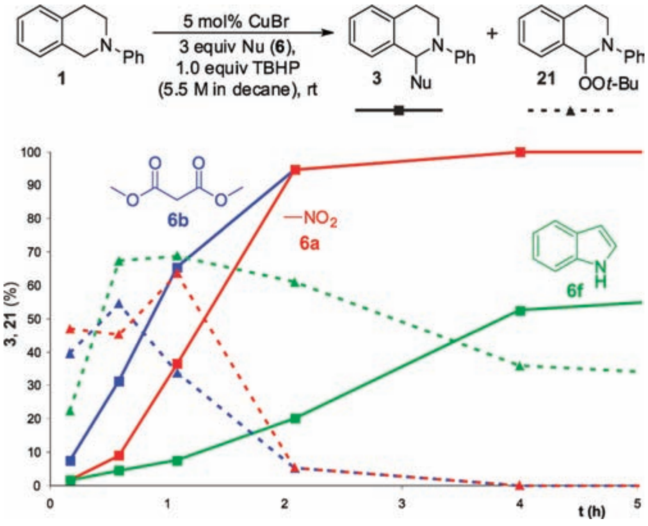


Peroxide **21** had been observed previously in oxidative coupling reactions and was discussed as a potential reaction intermediate, albeit with no definite conclusion.[4f,9b,10e] It was also intentionally prepared,[26] for example as a potential precursor to an iminium ion **2**,[4c] and a related compound had been observed in a Rh-catalyzed oxidative coupling reaction.[12b] In light of the aerobic reaction mechanism of Scheme 5, the question arises whether **21** is an off-cycle byproduct, similar to the structurally related hemiaminal ether **4**, or if **21** is a true reaction intermediate within the catalytic cycle.

To shed further light on the role of **21**, we monitored oxidative coupling reactions of **1** with various nucleophiles using the CuBr/TBHP method, looking for the occurrence of reaction intermediates by NMR (Scheme 8), analogous to the experiments shown above in Scheme 3.

In contrast to the $CuCl_2{\cdot}2H_2O/O_2$ system, isocyanide **6g** and the silyl nucleophiles **8** and **10** did not yield the desired products; amine **1** was simply converted to peroxide **19** instead. Potentially, the isocyanides deactivate the catalyst, as they were also suppressing the reaction rate in the $CuCl_2{\cdot}2H_2O/O_2$ system. We also found that the use of TMS-CN as a nucleophile resulted in the inhibition of the reaction, not even forming any **21**. This is possibly due to a reaction of TMS-CN with TBHP, silylating and deactivating the oxidant. However, the exact reasons for the failure of these nucleophiles are at present unknown. Insufficient nucleophilicity is unlikely to be the cause: the *N* values of the failing nucleophiles **6c**, **6g**, and **8** (16.27 (anion), 5.47, 5.41) are very close to the *N* value of indole **6f** (5.55), which converts to product **3f**,[9b] as reported.

Scheme 8. Monitoring the Formation of Products 3 (squares, solid line) and Intermediate 21 (triangles, dashed line) in the CuBr/TBHP System with Nucleophiles 6a (red), 6b (blue), and 6f (green)[a]



[a]See the Supporting Information for further details.

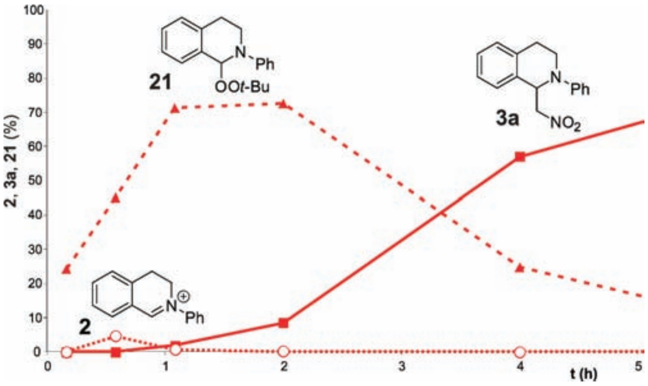
No iminium ion **2** could be observed during the reaction, and the only other amine species identifiable next to products and starting material was the peroxide **19**, which was consumed toward the end of the reaction. In contrast to the hemiaminal intermediate **4** formed in the $CuCl_2{\cdot}2H_2O/O_2$ system, the amount of peroxide **21** surpasses that of product **3** in the initial stages of the reaction, being formed in 20−70% yield during the first 30 min. Although the amount of **21** varies somewhat depending on the nucleophile used, it can be clearly correlated neither to their nucleophilicities nor to the rate of product formation, as was the case in Scheme 3. The slightly sigmoidal shape of the product curves also suggests that the rate of product formation is rising during the initial stages of all reactions. This could indicate that they are formed from a transient intermediate that is accumulated during the initial stages of the reaction and not from an intermediate with a quasistationary concentration such as the iminium ion **2a** under aerobic conditions.

For an off-cycle formation of **21** to be operative analogous to the formation of **4**, its nucleophilicity would have to surpass that of all the nucleophiles used, by approximately 1 order of magnitude. To our knowledge, a direct nucleophilicity value for TBHP has not been reported. However, the reactivity of the *tert*-butylperoxy anion has been compared with related nucleophiles in several kinetic studies: in water, its reactivity was found to be in between that of hydroxide and hydroperoxide[27] and similar to hydrazine.[27a] On the basis of the Mayr nucleophilicity values of these compounds ($N(\mathrm{OH}^-)$ = 10.47,[19i] $N(\mathrm{OOH}^-)$ = 15.44,[19i] $N(\mathrm{H_2NNH_2})$ = 13.47[19j]), the value for the *tert*-butylperoxy anion can be estimated to lie around $N = 13$, certainly not larger than 15.44, which is in any case well below the nucleophilicity of the nitromethane and malonate anions at $N > 20$.[19a,b]

However, under the conditions of the oxidative coupling reactions, the nucleophiles and TBHP will not be fully deprotonated, making an assessment of their relative nucleophilicities difficult.[28] Under such conditions, the equilibrium between protonated and deprotonated state will strongly influence the apparent nucleophilicity. The pK_a values of nitromethane and TBHP in water have been determined as 10.0−10.3[29] and 12.8,[30] respectively. Thus, nitromethane should have a kinetic advantage over TBHP in a competition for attack on the iminium ion.

To probe how such an acid−base equilibrium affects the reaction rate, we conducted the reaction between **1** and nitromethane in the presence of 5 mol % methanesulfonic acid (Scheme 9). Under these conditions, the iminium ion **2** could be observed as an intermediate. The formation of the reaction product **3a** is slowed considerably; after 2 h, ca. 10% of **3a** is formed in contrast to ca. 95% under standard conditions. This agrees well with a suppressed nucleophilicity of nitromethane by reducing the amount of its conjugate base. In contrast, the formation of **21** appears to be largely unaffected by the presence of the acid, suggesting a formation via a nonionic pathway. The transient appearance of **21** together with the clearly sigmoidal product formation profile suggests that **21** acts as a direct precursor to **3a**. The same trend was also observed when the reaction was performed in the presence of 10 mol % acid (see the Supporting Information).

Scheme 9. Reaction Progress of the Oxidative Coupling with Nitromethane Using the CuBr/TBHP Method in the Presence of 5 mol % Methanesulfonic Acid



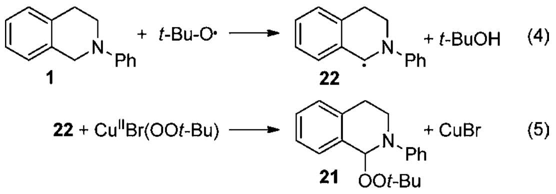
Accordingly, an off-cycle formation of **21** as is the case with **4** in Scheme 5 above appears not to be operative. Instead, **21** is most likely a species *within* the catalytic cycle that is formed by a radical pathway and acts as a direct precursor to the presumed iminium ion **2**.

Kharasch and Fono had previously suggested a radical mechanism for the synthesis of a peroxide derived from *N*,*N*-dimethylaniline and TBHP by copper catalysis.[31] Kochi and Minisci have later proposed more refined models for the mechanism of the Kharasch reaction and the related Gif reaction by Barton.[32,33] An analogous mechanism is probably operative in the present CuBr/TBHP system (eqs 1−5). Copper(I) is oxidized to copper(II) by TBHP, generating a *tert*-butyloxy radical (eq 1), which can abstract a hydrogen atom from **1**, forming the radical species **22** and *tert*-butyl alcohol (eq 4). Such hydrogen abstraction reactions from the α-carbon of tertiary amines are well established.[34] Copper(II) can react with a second molecule of TBHP to form a *tert*-butylperoxy complex (eq 2) that transfers the peroxide group to the radical **22**, producing **19** (eq 5). Alternatively, the *tert*-butyloxy radical can abstract hydrogen from TBHP, generating a *tert*-butylperoxy radical (eq 3), which could combine with **22** to form **21**. This reaction is generally fast, but disfavored under concentrated and basic conditions, making it less likely to contribute to the formation of **21** under the present conditions.[32b] The selective formation of **21** without larger amounts of a *tert*-butyl hemiaminal ether, formed by combination of **22** and a *tert*-butyloxy radical, for example, or a dimer of **22** could be explained by a persistent radical effect, as discussed for related reactions.[35]

$$\mathrm{CuBr} + t\text{-BuOOH} \longrightarrow \mathrm{Cu^{II}Br(OH)} + t\text{-Bu-O}\bullet \quad (1)$$

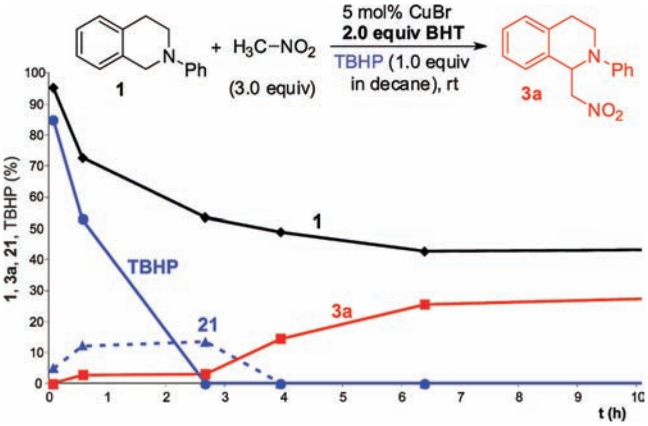
$$\mathrm{Cu^{II}Br(OH)} + t\text{-BuOOH} \longrightarrow \mathrm{Cu^{II}Br(OO}t\text{-Bu)} + \mathrm{H_2O} \quad (2)$$

$$t\text{-Bu-O}\bullet + t\text{-BuOOH} \longrightarrow t\text{-Bu-OH} + t\text{-Bu-O-O}\bullet \quad (3)$$



In contrast to what would be expected for a radical mechanism, the addition of 2.0 equiv of the radical inhibitor 2,6-di-*tert*-butyl-4-methylphenol (BHT) was reported to have no significant effect on the CuBr/TBHP method (70% versus 84% yield in the oxidative coupling reaction of **1** with nitromethane).[4g] Because the reaction time in these experiments was overnight and thus considerably longer then necessary (see Scheme 8) we decided to monitor the effect of BHT addition more closely by NMR spectroscopy (Scheme 10). Indeed, BHT was found to have a significant effect, as it slowed the conversion of **1** to the intermediate **21** and the product **3a** and eventually stopped the reaction after several hours. However, the product was still formed in ca. 34% yield.

Scheme 10. Coupling of Nitromethane with 1 in the Presence of the Radical Inhibitor BHT



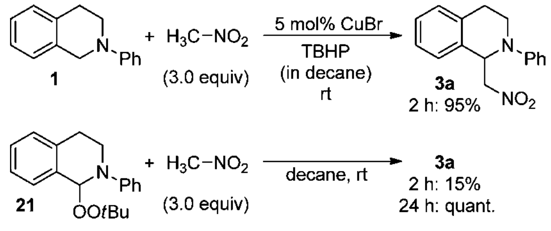
It can be seen that the oxidant TBHP is consumed after ca. 2 h, during which time ca. 45% of amine **1** was converted. Apparently, the inhibiting effect of BHT is too slow to fully suppress the reaction. Even after TBHP is fully consumed, the amount of product is still rising through conversion of **21** and possibly other mechanisms, for example by oxidation with oxygen being present in solution (the reaction was performed under one atmosphere of argon, but without degassing the solution). In conclusion, the significant suppression of the reaction by BHT provides support for a mechanism proceeding via radical intermediates. The results also show that such experiments have to be treated with caution and that a mere analysis of product yield after extended reaction time can be misleading.

A kinetic isotope study was conducted, analogous to the one shown in Scheme 4b, employing **1**-d_1 in the oxidative coupling with **6b** under the standard conditions of the CuBr/TBHP system. A primary KIE value of 3.4 was determined, consistent with C−H bond cleavage occurring in the rate-limiting step.

Another indication for the formation of **21** via a radical mechanism without involvement of iminium ions **2** comes from the above-mentioned coupling reaction with 2-naphthol (Scheme 6a). Its nucleophilicity is apparently not high enough to react with **2a**, because cross-coupling product **19** was not formed with the $CuCl_2{\cdot}2H_2O/O_2$ system. The formation of binaphthol **20** by copper catalysis has been suggested to proceed via the coupling of naphthyl radicals or rather copper-bound naphthyl radical equivalents.[36] Accordingly, the formation of both **19** and **20** under the conditions of the CuBr/TBHP system suggests a mechanism involving such naphthyl radicals and **22**, respectively, and not a free iminium ion.

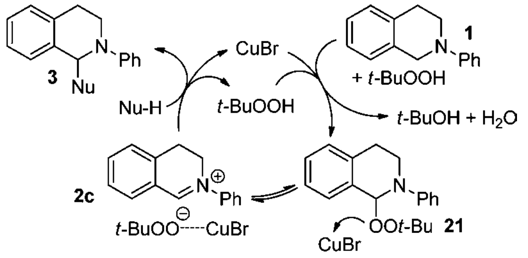
The substitution of the peroxide residue in **21** by a nucleophile to give the final reaction product most likely occurs via an iminium ion **2**, formed by reversible heterolytic bond cleavage, catalyzed by CuBr acting as a Lewis acid. However, the substitution of an α-*tert*-butylperoxy residue in an amine with methanol as a nucleophile was shown to occur even in the absence of a catalyst.[12b] To clarify whether Cu catalysis is operative in the present reaction, we studied the reaction between nitromethane and **21**. The latter was purified by filtration over magnesium silicate and essentially free of copper (<2 ppm), as revealed by trace element analysis using ICP-OES. A mixture of **21** and nitromethane in decane slowly converted to product **3a** over 24 h, clearly showing that Cu catalysis is not required, at least for this nucleophile. However, the reaction rate is considerably slower than that for the oxidative coupling reaction: after 2 h, 15% of **21** was converted to **3a**, while in the Cu-catalyzed reaction, nearly full conversion to **3a** was achieved at that time (Scheme 11).

Scheme 11. Coupling Nitromethane with 1 under Standard Reaction Conditions and with 21 in the Absence of CuBr



In conclusion, the substitution of the peroxy residue in **21** by the employed nucleophile is catalyzed by the copper catalyst, but a background reaction contributes significantly to this transformation. A catalytic cycle that summarizes the mechanistic findings discussed above is given in Scheme 12.

Scheme 12. Mechanism of the Oxidative Coupling Using the CuBr/TBHP System



Amine **1** reacts with two molecules TBHP under Cu catalysis via a radical mechanism to peroxide **21** and *tert*-butyl alcohol. An iminium salt **2c** is formed in small amounts in rapid equilibrium from **21**, aided by Lewis acid catalysis by CuBr. Trapping of **2c** with a nucleophile furnishes product **3** and regenerates one molecule of the oxidant TBHP.

It is likely that other transition-metal-catalyzed oxidative coupling reactions with peroxides as oxidant proceed in a manner similar to that shown in Scheme 12.[5i,8b,12b,e,37] A radical mechanism as indicated in eqs 1−5 has been suggested for the transformation of various organic substances into *tert*-butylperoxides in the presence of Cu, Co, Mn, and Fe catalysts, for example.[31,32b] Details such as the involvement of specific radicals (e.g., *tert*-butyloxy vs *tert*-butylperoxy), individual reaction rates (e.g., eq 3), or radical recombination vs radical oxidation can of course depend on reaction conditions and the nature of substrates.[34b,35a]

When comparing the reaction progress of the two methods under study (Schemes 5 and 12), two other major differences become apparent: the failure to observe the iminium ion **2** under the CuBr/TBHP conditions and the different rates of product formation, which is most obvious for nitromethane as nucleophile. Apart from concentration and solvent[38] effects on the rate, the mechanisms suggested provide an explanation for both differences by predicting a difference in pH. In the aerobic method using $CuCl_2$, HCl is formed, making the reaction mixture more acidic than in the CuBr/TBHP system. This will shift the equilibria between **2a**, **4**, and **5** toward the iminium ion, allowing it to be observed. At the same time, the acidic conditions will suppress the reactivity of C−H acidic nucleophiles such as nitromethane. In the CuBr/TBHP system, the more basic conditions favor deprotonation of such nucleophiles, thus enhancing their reactivities. On the other hand, these conditions will also shift the putative equilibrium between **2a** and **21** so that the iminium ion **2** cannot be observed.

Indeed, the effect of acid on the CuBr/TBHP system as seen in Scheme 9 supports this interpretation: the rate of product formation is suppressed, while an iminium species **2** can be observed. This reasoning is further corroborated by measuring the solution pH value during the reaction between **1** and nitromethane. Using the $CuCl_2{\cdot}2H_2O/O_2$ method, a slightly acidic pH range of 5.3−6.1 was measured, while with the CuBr/

TBHP method, more basic conditions with a pH of 6.3−7.2 were found.

■ SUMMARY AND CONCLUSIONS

We have conducted a comparative mechanistic study of Cu-catalyzed oxidative coupling reactions of *N*-phenyltetrahydroisoquinoline **1** with various nucleophiles, using two previously reported methods: the $CuCl_2·2H_2O/O_2$ system and CuBr/TBHP. For the $CuCl_2·2H_2O/O_2$ system, the nucleophile scope was shown to be only limited by the reactivity of the nucleophile, the threshold lying at a nucleophilicity parameter of ca. $N = 3.8$ with respect to Mayr's reactivity scales. These synthetic studies allowed a rough estimation of the electrophilicity parameter E for the observable intermediate iminium ion **2a**. On the basis of these and previous studies, a catalytic cycle is proposed, where the actual oxidant for **1** is the copper(II) catalyst and the role of the terminal oxidant O_2 is the reoxidation of copper(I).

Differences in the reaction mechanism were found when the same investigation was conducted with the CuBr/TBHP system. Despite a relatively low nucleophilicity parameter, 2-naphthol is oxidatively coupled with **1** under these conditions (as previously reported), while it does not react in the $CuCl_2·2H_2O/O_2$ system. Also, silyl nucleophiles were found to be unreactive with the CuBr/TBHP method. An iminium ion **2** could not be observed when the reaction progress was monitored by NMR spectroscopy; the amino *tert*-butylperoxide **21** was the only identifiable intermediate. Regardless of the reactivity of the nucleophiles used, **21** is always formed in large amounts at the beginning of the reaction. On the basis of these and other observations, **21** is proposed to form by a radical mechanism and to be an intermediate within the catalytic cycle, acting as a precursor to the iminium ion **2c**. The latter then reacts with nucleophiles to give the final reaction products. The differences in individual rates and in the visibility of the iminium ion in the two methods are explained by a difference in overall pH of the reaction solutions.

These findings illustrate that the oxidant can change the reaction mechanism distinctively. They also show that the nucleophile scope in oxidative coupling reactions with **1** is in principle only limited by the reactivity of iminium ion and nucleophile. Thus, it should be possible to freely choose a combination of reported catalyst/oxidant system and nucleophile with respect to practicability, cost, and sustainability in order to synthesize the desired product. While the CuBr/TBHP system appears to be incompatible with isocyanides and silyl nucleophiles, it allows the coupling with 2-naphthol, probably via a radical coupling. This could open the possibility to design coupling reactions with substrates of low nucleophilicity but reactivity toward carbon radicals. We hope the present work and future mechanistic studies will contribute to the development of new oxidative C−H functionalization reactions with highly sustainable conditions and synthetically important applications.

■ EXPERIMENTAL SECTION

General Procedure for the Aerobic Oxidative Coupling Reaction. To a solution of *N*-phenyltetrahydroisoquinoline (**1**, 75 mg, 0.36 mmol) in methanol (1.5 mL) were added nucleophile **6** (1.08 mmol, 3 equiv) and $CuCl_2·2H_2O$ (6 mg, 10 mol %) at room temperature. After being stirred for the appropriate time under 1 atm of oxygen, the solution was concentrated in vacuo. The crude residue was directly purified by flash column chromatography on silica gel (5−10% EtOAc/pentane) to afford the corresponding coupling product.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details including product characterization and NMR experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (b) Klussmann, M.; Sureshkumar, D. *Synthesis* **2011**, 353. (c) Yoo, W.-J.; Li, C.-J. *Top. Curr. Chem.* **2010**, *292*, 281. (d) Scheuermann, C. J. *Chem. Asian J.* **2010**, *5*, 436. (e) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439.

(2) Anastas, P.; Eghbali, N. *Chem. Soc. Rev.* **2010**, *39*, 301.

(3) (a) Jones, K. M.; Klussmann, M. *Synlett* **2012**, *23*, 159. (b) Campos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1069.

(4) (a) Murahashi, S.-I.; Zhang, D. *Chem. Soc. Rev.* **2008**, *37*, 1490. (b) North, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4126. (c) Murahashi, S.-I.; Naota, T.; Yonemura, K. *J. Am. Chem. Soc.* **1988**, *110*, 8256. (d) Murahashi, S.; Naota, T.; Miyaguchi, N.; Nakato, T. *Tetrahedron Lett.* **1992**, *33*, 6991. (e) Murahashi, S.-I.; Komiya, N.; Terai, H.; Nakae, T. *J. Am. Chem. Soc.* **2003**, *125*, 15312. (f) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810. (g) Li, Z.; Bohle, D. S.; Li, C.-J. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 8928.

(5) (a) Santamaria, J.; Herlem, D.; Khuong-Huu, F. *Tetrahedron* **1977**, *33*, 2389. (b) Chiba, T.; Takata, Y. *J. Org. Chem.* **1977**, *42*, 2973. (c) Murata, S.; Teramoto, K.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1297. (d) Sundberg, R. J.; Théret, M.-H.; Wright, L. *Org. Prep. Proc. Int.* **1994**, *26*, 386. (e) Zhdankin, V. V.; Kuehl, C. J.; Krasutsky, A. P.; Bolz, J. T.; Mismash, B.; Woodward, J. K.; Simonsen, A. J. *Tetrahedron Lett.* **1995**, *36*, 7975. (f) Li, Z.; Li, C.-J. *Eur. J. Org. Chem.* **2005**, 3173. (g) Murahashi, S.-I.; Nakae, T.; Terai, H.; Komiya, N. *J. Am. Chem. Soc.* **2008**, *130*, 11005. (h) Singhal, S.; Jain, S. L.; Sain, B. *Chem. Commun.* **2009**, 2371. (i) Han, W.; Ofial, A. R. *Chem. Commun.* **2009**, 5024. (j) Allen, J. M.; Lambert, T. H. *J. Am. Chem. Soc.* **2011**, *133*, 1260. (k) Alagiri, K.; Prabhu, K. R. *Org. Biomol. Chem.* **2012**, *10*, 835.

(6) (a) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 3672. (b) Baslé, O.; Li, C.-J. *Green Chem.* **2007**, *9*, 1047. (c) Tsang, A. S.-K.; Todd, M. H. *Tetrahedron Lett.* **2009**, *50*, 1199. (d) Shu, X.-Z.; Xia, X.-F.; Yang, Y.-F.; Ji, K.-G.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* **2009**, *74*, 7464. (e) Zeng, T.; Song, G.; Moores, A.; Li, C.-J. *Synlett* **2010**, 2002. (f) Condie, A. G.; González-Gómez, J. C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2010**, *132*, 1464. (g) Hari, D. P.; König, B. *Org. Lett.* **2011**, *13*, 3852.

(7) Pandey, G.; Kumaraswamy, G.; Reddy, P. Y. *Tetrahedron* **1992**, *48*, 8295.

(8) (a) Shen, Y.; Li, M.; Wang, S.; Zhan, T.; Tan, Z.; Guo, C.-C. *Chem. Commun.* **2009**, 953. (b) Sud, A.; Sureshkumar, D.; Klussmann, M. *Chem. Commun.* **2009**, 3169. (c) Pintér, Á.; Sud, A.; Sureshkumar, D.; Klussmann, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 5004. (d) Rueping,

M.; Vila, C.; Koenigs, R. M.; Poscharny, K.; Fabry, D. C. *Chem. Commun.* **2011**, 2360.

(9) (a) Murata, S.; Miura, M.; Nomura, M. *Chem. Commun.* **1989**, 116. (b) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 6968. (c) Ohta, M.; Quick, M. P.; Yamaguchi, J.; Wünsch, B.; Itami, K. *Chem. Asian J.* **2009**, *4*, 1416. (d) Liu, P.; Zhou, C.-Y.; Xiang, S.; Che, C.-M. *Chem. Commun.* **2010**, *46*, 2739. (e) Daniels, M. H.; Hubbs, J. *Tetrahedron Lett.* **2011**, *52*, 3543.

(10) (a) Li, Z.; Li, C.-J. *Org. Lett.* **2004**, *6*, 4997. (b) Niu, M.; Yin, Z.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2008**, *73*, 3961. (c) Xu, X.; Li, X. *Org. Lett.* **2009**, *11*, 1027. (d) Volla, C. M. R.; Vogel, P. *Org. Lett.* **2009**, *11*, 1701. (e) Li, Z.; MacLeod, P. D.; Li, C.-J. *Tetrahedron: Asymmetry* **2006**, *17*, 590.

(11) Baslé, O.; Li, C.-J. *Org. Lett.* **2008**, *10*, 3661.

(12) (a) Pandey, G.; Rani, K. S.; Lakshmaiah, G. *Tetrahedron Lett.* **1992**, *33*, 5107. (b) Catino, A. J.; Nichols, J. M.; Nettles, B. J.; Doyle, M. P. *J. Am. Chem. Soc.* **2006**, *128*, 5648. (c) Sureshkumar, D.; Sud, A.; Klussmann, M. *Synlett* **2009**, 1558. (d) Chu, L.; Qing, F.-L. *Chem. Commun.* **2010**, *46*, 6285. (e) Kumaraswamy, G.; Murthy, A. N.; Pitchaiah, A. *J. Org. Chem.* **2010**, *75*, 3916. (f) Mitsudera, H.; Li, C.-J. *Tetrahedron Lett.* **2011**, *52*, 1898. (g) Boess, E.; Sureshkumar, D.; Sud, A.; Wirtz, C.; Farès, C.; Klussmann, M. *J. Am. Chem. Soc.* **2011**, *133*, 8106. (h) Chu, L.; Zhang, X.; Qing, F.-L. *Org. Lett.* **2009**, *11*, 2197. (i) Shen, Y.; Tan, Z.; Chen, D.; Feng, X.; Li, M.; Guo, C.-C.; Zhu, C. *Tetrahedron* **2009**, *65*, 158.

(13) (a) Zhang, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Org. Lett.* **2007**, *9*, 3813. (b) Shono, T.; Matsumura, Y.; Inoue, K.; Ohmizu, H.; Kashimura, S. *J. Am. Chem. Soc.* **1982**, *104*, 5753. (c) Baslé, O.; Li, C.-J. *Chem. Commun.* **2009**, 4124. (d) Han, W.; Ofial, A. R. *Chem. Commun.* **2009**, 6023. (e) Rueping, M.; Zhu, S.; Koenigs, R. M. *Chem. Commun.* **2011**, *47*, 8679.

(14) Baslé, O.; Borduas, N.; Dubois, P.; Chapuzet, J. M.; Chan, T.-H.; Lessard, J.; Li, C.-J. *Chem.—Eur. J.* **2010**, *16*, 8162.

(15) Shu, X.-Z.; Yang, Y.-F.; Xia, X.-F.; Ji, K.-G.; Liu, X.-Y.; Liang, Y.-M. *Org. Biomol. Chem.* **2010**, *8*, 4077.

(16) Freeman, D. B.; Furst, L.; Condie, A. G.; Stephenson, C. R. J. *Org. Lett.* **2012**, *14*, 94.

(17) Tsang, A. S.-K.; Jensen, P.; Hook, J. M.; Hashmi, A. S. K.; Todd, M. H. *Pure Appl. Chem.* **2011**, *83*, 655.

(18) For an overview, see: Mayr, H.; Ofial, A. R. *J. Phys. Org. Chem.* **2008**, *21*, 584.

(19) (a) Bug, T.; Lemek, T.; Mayr, H. *J. Org. Chem.* **2004**, *69*, 7565. (b) Lucius, R.; Loos, R.; Mayr, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 91. (c) Tishkov, A. A.; Mayr, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 142. (d) Mayr, H.; Bug, T.; Gotta, M. F.; Hering, N.; Irrgang, B.; Janker, B.; Kempf, B.; Loos, R.; Ofial, A. R.; Remennikov, G.; Schimmel, H. *J. Am. Chem. Soc.* **2001**, *123*, 9500. (e) Lakhdar, S.; Westermaier, M.; Terrier, F.; Goumont, R.; Boubaker, T.; Ofial, A. R.; Mayr, H. *J. Org. Chem.* **2006**, *71*, 9088. (f) Tumanov, V. V.; Tishkov, A. A.; Mayr, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 3563. (g) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66. (h) Lakhdar, S.; Tokuyasu, T.; Mayr, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 8723. (i) Minegishi, S.; Mayr, H. *J. Am. Chem. Soc.* **2002**, *125*, 286. (j) Phan, T. B.; Breugst, M.; Mayr, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 3869. (k) Kaumanns, O.; Lucius, R.; Mayr, H. *Chem.—Eur. J.* **2008**, *14*, 9675.

(20) Tsuji, Y.; Toteva, M. M.; Garth, H. A.; Richard, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 15455.

(21) Phenols have been used in a V-catalyzed coupling reaction with preformed amine *N*-oxides, see: Hwang, D.-R.; Uang, B.-J. *Org. Lett.* **2002**, *4*, 463.

(22) We thank an anonymous reviewer for pointing this out.

(23) For an aerobic $CuCl_2$-catalyzed reaction with anilines, suggesting radical intermediates as reactive species, see: Nishino, M.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2011**, *76*, 6447.

(24) SET preceding rate-determining C-H bond cleavage was also found by KIE experiments in: Jung, H. H.; Floreancig, P. E. *Tetrahedron* **2009**, *65*, 10830.

(25) For additional support of this reservoir model, see: Xia, W.; Zhao, G.; Yang, C.; Guo, L.; Sun, H.; Chen, C. *Chem. Commun.* **2012**, *48*, 2337−2339.

(26) Höft, E.; Schultze, H. *Z. Chem.* **1967**, *7*, 149.

(27) (a) Behrman, E. J.; Biallas, M. J.; Brass, H. J.; Edwards, J. O.; Isaks, M. *J. Org. Chem.* **1970**, *35*, 3069. (b) McIsaac, J. E.; Subbaraman, L. R.; Subbaraman, J.; Mulhausen, H. A.; Behrman, E. J. *J. Org. Chem.* **1972**, *37*, 1037. (c) Curci, R.; di Furia, F. *Int. J. Chem. Kinet.* **1975**, *7*, 341. (d) Davies, D. M.; Deary, M. E. *J. Chem. Soc., Perkin Trans. 2* **1992**, 559.

(28) Our own attempts at comparing the nucleophilicity of TBHP and nitromethane in the presence of tertiary amine bases were also not very conclusive; see the Supporting Information.

(29) (a) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456. (b) Bernasconi, C. F.; Kliner, D. A. V.; Mullin, A. S.; Ni, J. X. *J. Org. Chem.* **1988**, *53*, 3342.

(30) Everett, A. J.; Minkoff, G. J. *Trans. Faraday Soc.* **1953**, *49*, 410.

(31) Kharasch, M. S.; Fono, A. *J. Org. Chem.* **1959**, *24*, 72.

(32) (a) Kochi, J. K. *Tetrahedron* **1962**, *18*, 483. (b) Minisci, F.; Fontana, F.; Araneo, S.; Recupero, F.; Banfi, S.; Quici, S. *J. Am. Chem. Soc.* **1995**, *117*, 226.

(33) For a Rh-catalyzed reaction, see: McLaughlin, E. C.; Choi, H.; Wang, K.; Chiou, G.; Doyle, M. P. *J. Org. Chem.* **2009**, *74*, 730.

(34) Such hydrogen abstraction reactions from the α-carbon of tertiary amines are well established; see for example: (a) Griller, D.; Howard, J. A.; Marriott, P. R.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 619. (b) Bietti, M.; Salamone, M. *Org. Lett.* **2010**, *12*, 3654. (c) Salamone, M.; Anastasi, G.; Bietti, M.; DiLabio, G. A. *Org. Lett.* **2010**, *13*, 260.

(35) (a) Bravo, A.; Bjørsvik, H.-R.; Fontana, F.; Liguori, L.; Minisci, F. *J. Org. Chem.* **1997**, *62*, 3849. (b) Studer, A. *Chem.—Eur. J.* **2001**, *7*, 1159. (c) Fischer, H. *Chem. Rev.* **2001**, *101*, 3581.

(36) See for example: (a) Armstrong, D. R.; Cameron, C.; Nonhebel, D. C.; Perkins, P. G. *J. Chem. Soc., Perkin Trans. 2* **1983**, 563. (b) Li, X.; Hewgley, J. B.; Mulrooney, C. A.; Yang, J.; Kozlowski, M. C. *J. Org. Chem.* **2003**, *68*, 5500. (c) Roithova, J.; Schroeder, D. *Chem.—Eur. J.* **2008**, *14*, 2180.

(37) For examples of oxidative coupling reactions with substrates other than **1** using TBHP as oxidant, see: (a) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2006**, *128*, 56. (b) Zhao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 7075. (c) Pan, S.; Liu, J.; Li, H.; Wang, Z.; Guo, X.; Li, Z. *Org. Lett.* **2010**, *12*, 1932. (d) Ghobrial, M.; Harhammer, K.; Mihovilovic, M. D.; Schnürch, M. *Chem. Commun.* **2010**, 8836. (e) Ghobrial, M.; Schnürch, M.; Mihovilovic, M. D. *J. Org. Chem.* **2011**, *76*, 8781. (f) Xie, J.; Huang, Z.-Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 10181. (g) Yang, F.; Li, J.; Xie, J.; Huang, Z.-Z. *Org. Lett.* **2010**, *12*, 5214.

(38) See ref 12g for a comparison of MeOH and acetone in the aerobic method.