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Cu-Catalyzed Sequential Dehydrogenation–Conjugate Addition for β-Functionalization of Saturated Ketones: Scope and Mechanism

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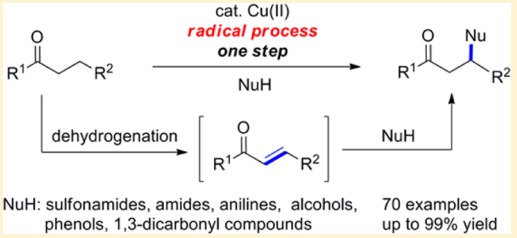
Supporting Information

ABSTRACT: The first copper-catalyzed direct β-functionalization of saturated ketones is reported. This protocol enables diverse ketones to couple with a wide range of nitrogen, oxygen and carbon nucleophiles in generally good yields under operationally simple conditions. The detailed mechanistic studies including kinetic studies, KIE measurements, identification of reaction intermediates, EPR and UV–visible experiments were conducted, which reveal that this reaction proceeds via a novel radical-based dehydrogenation to enone and subsequent conjugate addition sequence.



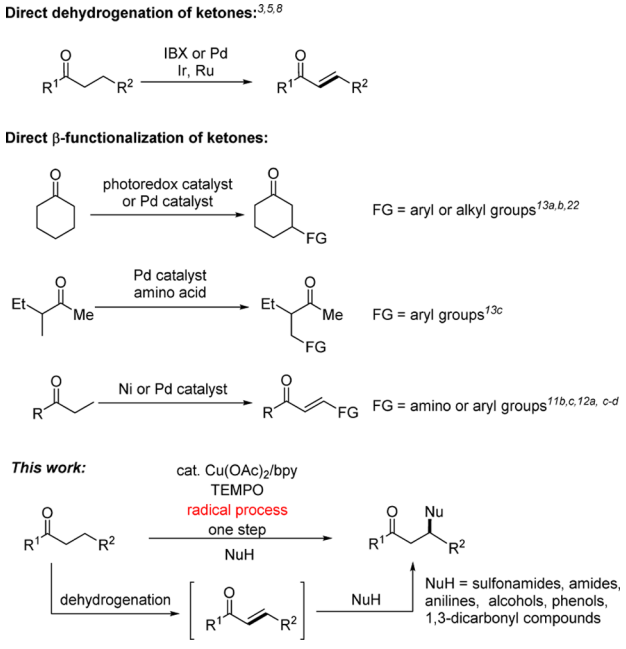
INTRODUCTION

α,β-Unsaturated ketones are ubiquitous in bioactive compounds and generally regarded as versatile synthetic intermediates in the syntheses of fine chemicals, pharmaceuticals and materials.[1] Traditionally, approaches to access enone architecture involve α,β-dehydrogenation of the parent saturated ketones, which require multistep preparation routes[2] or use of stoichiometric reagents such as 2-iodoxybenzoic acid (IBX)[3] and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ),[4] and often suffer from limited functional group compatibility and poor regioselectivity. Recently, transition-metal-catalyzed C–H functionalization reactions have shown their powerful ability to convert carbonyl compounds to the corresponding unsaturated derivatives. For example, Pd(II)-catalyzed aerobic dehydrogenation methods[5] provide a facile access to α,β-unsaturated ketones (Scheme 1). Efforts have further been made to develop Pd-based catalyst for the dehydrogenation of more challenging aliphatic esters, nitriles and amides.[6] Besides the widely used palladium catalyst, the iridium and ruthenium catalysts have shown their powerful ability to promote alkane dehydrogenation.[7] However, reports of applying these catalysts to ketone dehydrogenation are rare.[8] These Pd, Ir and Ru catalysts generally capitalize on their inherent catalytic attributes to form metal-enolate intermediate and subsequent β-hydride elimination to generate desired enones. Although this type of catalytic manners have appeared frequently in the literature, examples of first-row metal catalysts capable of effecting ketone desaturation via radical type mechanism are much less common, and their reaction mechanisms have been less studied in depth.

As a matter of fact, first-row metals such as Cu, Ni and Mn are not only earth-abundant and inexpensive, but also insensitive to catalyst poisoning caused by strong coordinating heteroatom functionalities. Catalytic systems employing such metals are expected to exhibit higher cost economy as well as more diverse substrate scope. Actually, of the few approaches reported, the majority requires stoichiometric first-row metals that serve as oxidants and the conversions are only applicable to specific substrates.[9] Consequently, the invention of first-row-metal-catalyzed protocol to achieve regio- and chemoselective desaturation of unactivated ketones in a broadly applicable manner would be highly desirable.

As our ongoing interest in the development of C–H functionalization reactions[10] to promote efficient ketone

Scheme 1. Overview of Ketone Dehydrogenation and Saturated Ketone β-Functionalization



Received: February 5, 2016
Published: April 11, 2016

DOI: 10.1021/jacs.6b01337
J. Am. Chem. Soc. 2016, 138, 5623–5633

couplings, we have recently reported several methods for Pd-catalyzed dehydrogenative olefination of (hetero)arenes via olefin intermediates generated in situ from saturated ketones and nitroalkanes.[11] In the Pd-catalyzed decarboxylative olefination of carboxylic acid with saturated ketones,[11b] $Cu(OAc)_2$ was much more efficient than other oxidants such as Ag salts, implying that $Cu(OAc)_2$ might play dual roles. Here, we report a 2,2′-bipyridine (bpy)-supported Cu catalyst system that enables direct, selective and controlled desaturation of ketones to enones and subsequent conjugate addition with sulfonamides, amides, amines and anilines to generate Mannich-type products, as well as alcohols, phenols and 1,3-dicarbonyl compounds to form β-oxygenated or β-alkylated ketones (Scheme 1). To the best of our knowledge, our findings represent the first example of intermolecular reaction for directly installing heteroatom functionalities to the β-C−H (sp^3) bonds of unactivated ketones.

The strategy to combine initial substrate dehydrogenation to olefin intermediate with secondary olefin transformations represents a new avenue to the direct C−H functionalization reactions, and has a tremendous potential to rapidly construct diverse complex molecular frameworks from simple starting materials owing to versatile reactivity of olefins.[12−17] Since 1,4-conjugate addition of nucleophiles to α,β-unsaturated ketones is the most commonly used approach to β-functionalized ketones,[18] we envisioned that a novel ketone dehydrogenation process in combination with subsequent conjugate addition would provide an appealing, atom-economical alternative to traditional methods by elimination of the need for troublesome prepreparation and isolation of α,β-unsaturated ketones. The potential of this strategy in the synthesis of β-functionalized carbonyls has been illustrated by the recent pioneering studies, such as the transition metal-catalyzed ketone β-amination,[12a] ketone β-arylation,[12c−e,13] β-arylation of β-keto esters,[14] α-substituted esters[15] and aldehydes,[19] and multidehydrogenation of ketone to benzenes.[12g] The directing group-assisted C−H activation methods has also been established to functionalize β-C−H (sp^3) bonds of carboxylic acid derivatives (e.g., amides and esters).[20] Meanwhile, the organocatalysts (e.g., N-heterocyclic carbenes and amines) have been successfully used to effect β-functionalization of saturated esters and aldehydes.[21] The photoredox catalysis, in combination with organocatalysis, also proves to be a promising approach to the β-C−H (sp^3) functionalization of aldehydes and cyclic ketones.[22] These prominent advances provided useful starting points for our investigation of other innovative β-functionalization protocols.

To achieve the desired general β-functionalization of saturated ketones via tandem ketone dehydrogenation-conjugate addition sequence, the catalyst system must meet the following requirements: (1) the catalyst system is capable of facilitating both ketone desaturation and conjugate addition; (2) the catalyst system selectively dehydrogenates ketone starting material over β-functionalized ketone products to avoid overoxidation of products; (3) the oxidative dehydrogenation conditions are compatible with conjugate addition donor (a nucleophilic coupling partner).

RESULTS AND DISCUSSION

Considering β-Amino ketones are well accepted as key synthetic intermediates of pharmaceutical interest,[23] we decided to initiate our studies with exploring reaction conditions suitable for the direct β-amination of saturated ketones.[24] Conventional methods for accessing β-Amino ketones include aza-Michael addition and Mannich reaction.[25] For conjugate addition reactions, preparation and isolation steps of activated enones were required. Particularly, if the enones were vinyl ketones, they would be unstable and prone to polymerization. On the other hand, electron-deficient amides were deactivated substrates in Mannich reaction and the employment of unsymmetrical ketones usually gave rise to regioisometric mixtures. In this context, propiophenone (**1a**) was chosen as model substrate to surrogate its corresponding unstable vinyl ketone. Additionally, *N*-methyl-*p*-toluene sulfonamide (**2a**) was selected as the amide source for the reason that benzenesulfonamide scaffolds are prevalent in medicinal molecules. Copper salts were chosen as our catalyst candidates because copper complexes were widely used in conjugate addition of enones.[26] Also, copper catalysts have shown their ability to effect alkane dehydrogenation to alkene[27] and oxidative condensation of cyclic enones with alcohol to aryl ethers.[28] However, these precedents often require nonselective peroxides as stoichiometric oxidants and are not applicable to dehydrogenation of linear ketone. These limitations prompted us to investigate a mild and broadly applicable copper-catalyzed protocol that could not only facilitate ketone dehydrogenations to enone but also benefit subsequent conjugate addition of enone intermediate.

To examine the feasibility of our proposed protocol, a variety of copper precursors, ligands, solvents and additives were evaluated (Table 1). After extensive screening, we found that the use of copper acetate as the catalyst, bpy (2,2′-bipyridine) as the ligand and TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl) as the oxidant in 1,2-dichlorobenzene was optimal to form the desired carbon−nitrogen bond at the β-position of **1a**. The afforded β-amidation product **3a** could be isolated in 95% yield without significant overoxidation (<5%) (entry 1). Notably, although 3.0 equiv of ketone was used, nearly half of the starting **1a** remained intact after the reaction was finished (see Table S1 in the Supporting Information). Reducing the amount of **1a** to 1.5 equiv led to a decrease in reaction efficiency but still afforded a synthetically useful yield (72%) (entry 2). Control experiments revealed that no product was obtained in the absence of either $Cu(OAc)_2$ or TEMPO, implying the indispensable roles of these two reaction components (entries 3 and 4). The reaction conducted without bpy ligand could still generate **3a** in 62% yield (entry 5). Of the ligands tested, 1,10-phenanthroline showed similar yield to bpy, and monodentate pyridine could also enhance the efficiency of Cu catalyst when its loading was increased to 0.5 equiv (entries 6−8). Attempts to utilize catalytic amount of TEMPO lead to inferior results (entry 9). Other TEMPO derivatives with diverse electronic characters also exhibited low efficiency (see Table S1 in the Supporting Information). Increasing the amount of TEMPO led to a decrease in yield due to overoxidation of the desired product (entry 10). Although Cu/TEMPO catalyzed aerobic oxidations are well established by Stahl et al.,[29] the oxygen atmosphere completely shut down this transformation (entry 11). Moreover, the yield dropped dramatically when the model reaction was carried out under air atmosphere (entry 12). Thus, these experimental data suggest that our reaction proceeds through a mechanism different from the systems of Stahl et al. The choice of additives also proved to be pivotal for the formation of **3a** since other previously reported oxidants in copper-catalyzed dehydrogenation reactions such as NHPI (*N*-hydroxyphthalimide) and peroxides did

DOI: 10.1021/jacs.6b01337
J. Am. Chem. Soc. 2016, 138, 5623−5633

Table 1. Selected Reaction Development

entry	variations from standard conditions	isolated yield (%) 3a	3a′
1	none	95	<5
2	1a (1.5 equiv)	72	<5
3	w/o $Cu(OAc)_2$	0	0
4	w/o TEMPO	0	0
5	w/o bpy	62	<5
6	1,10-phenanthroline instead of bpy	94	<5
7	0.2 equiv of pyridine instead of bpy	76	<5
8	0.5 equiv of pyridine instead of bpy	87	<5
9	0.2 equiv of TEMPO	54	0
10	2.0 equiv of TEMPO	79	16
11	0.2 equiv of TEMPO, O_2 (1 atm) atmosphere	0	0
12	air atmosphere	50	<5
13	1.0 equiv of NHPI instead of TEMPO	0	0
14	2.0 equiv of *t*BuOOH (5.0−6.0 M in decane) instead of TEMPO	0	0
15	2.0 equiv of *t*BuOO*t*Bu instead of TEMPO	0	0
16	$CuSO_4$ instead of $Cu(OAc)_2$	0	0
17	$Cu(OTf)_2$ instead of $Cu(OAc)_2$	15	0
18	$CuCl_2$ instead of $Cu(OAc)_2$	0	0
19	PhCl instead of 1,2-dichlorobenzene	90	0
20	DME instead of 1,2-dichlorobenzene	49	0
21	DMF instead of 1,2-dichlorobenzene	45	0
22	DMSO instead of 1,2-dichlorobenzene	<5	0
23	1,4-dioxane instead of 1,2-dichlorobenzene	49	0
24	toluene instead of 1,2-dichlorobenzene	73	<5

not work for this reaction (entries 13−15). Changing the acetate counterion of the copper catalyst resulted in decreased yields (entries 16−18). Finally, we surveyed the effects of solvent and observed that chlorobenzene was slightly less efficient than 1,2-dichlorobenzene and other screened solvents led to sluggish conversion to **3a** (entries 19−24).

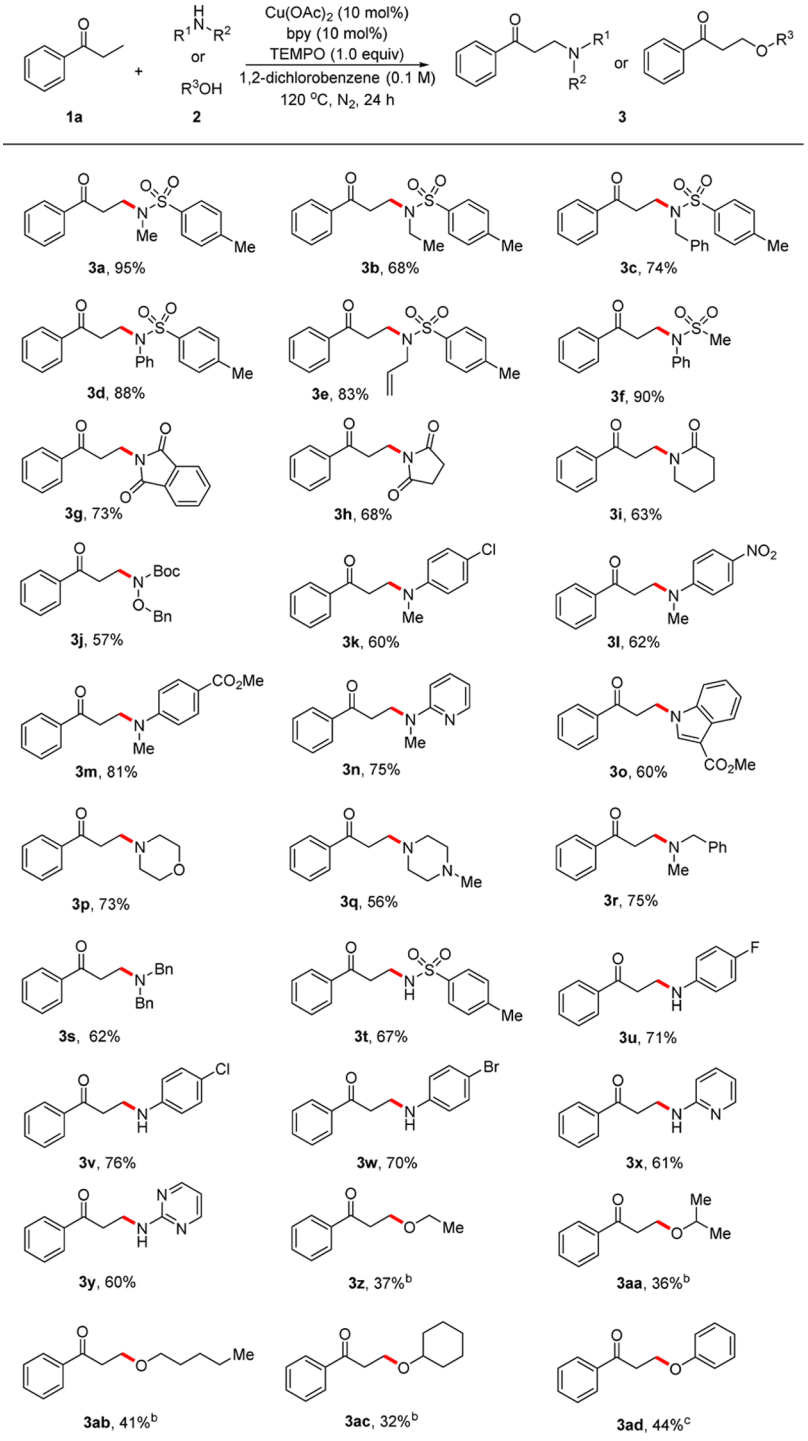
With this catalytic system in hand, we initially investigated the substrate scope with respect to a wide range of nitrogen-containing nucleophiles (Scheme 2). As illustrated, secondary sulfonamides with various substituted groups at the nitrogen atom participated in this transformation (**3a**−**3f**). Particularly, a terminal alkene substituent of sulfonamides could be tolerated to give **3e** in 83% yield, highlighting the excellent functional group compatibility of the reaction conditions. In addition to sulfonamides, amides and *Boc*-protected alkoxylamine also proved to be suitable substrates (**3g**−**3j**). Secondary anilines bearing chloro, nitro or ester functionalities smoothly underwent the reaction to produce the desired β-amination products (**3k**−**3m**). Heterocyclic nitrogen nucleophiles like *N*-methyl 2-aminopyridine and a 3-substituted indole were also effective coupling partners (entries **3n** and **3o**), indicative of the robustness of the Cu catalytic system against the poisoning caused by Lewis basic heterocycles. Although the nitrogen-vicinal and benzylic positions of aliphatic amines are prone to be oxidized, the established oxidative conditions enabled both cyclic and acyclic aliphatic amines to participate in the reaction in good yields with no side-product from oxidation of these amines observed (**3p**−**3s**). To our delight, primary sulfonamides, anilines and heteroanilines all served well under the current conditions to give high yields of N,N-disubstituted products (**3t**−**3y**). Primary alkyl amine such as butylamine did not give the target product due to the decomposition of substrate under current conditions. Both primary and secondary alcohols could serve as nucleophiles to give β-alkoxylation products (**3z**−**3ac**) in moderate yields. The low yields in the reaction of alcohols probably stemmed from their weak nucleophilicity and competitive alcohol oxidation. Finally, phenol served as a substrate to furnish the desired product in 44% yield (**3ad**).

Subsequently, we evaluated the substrate scope with respect to various ketones (Scheme 3). A variety of electronically diverse functionalities on the phenyl ring of propiophenones were well tolerated to give desired β-amination products in excellent yields (**4a**−**4g**). Additionally, heteroaromatic ketones such as 3-propionylpyridine, 2-propionylfuran and 2-propionylthiophene smoothly underwent the reaction without side-reactions at their reactive C-2 or C-3 positions of heteroaromatic rings, demonstrating high chemo- and regioselectivity of this transformation (**4h**−**4j**). Moreover, the generality of this protocol can be further demonstrated by its compatibility with aliphatic ketones and its ability to effect β-amination of challenging β-substituted ketones (**4k**−**4p**). As demonstrated, aliphatic ketones served as suitable substrates in this transformation (**4k**−**4n**) in the presence of higher loadings of $Cu(OAc)_2$ and bpy, which circumvented the formidable synthesis of aliphatic vinyl ketones used in traditional conjugate addition reactions and exhibited high selectivity comparing with Mannich reaction. For β-substituted ketones (**4o** and **4p**), the relatively low conversion was attributed to retardation of the conjugate addition step due to steric hindrance, rather than a less effective dehydrogenation (see p. S60 in the Supporting Information). To further test the practicability and scalability of this reaction, a large scale reaction was conducted to synthesize commercial drug dyclonine (an oral anesthetic medicine), which furnished 0.94 g of product in 65% yield (**4q**). Unfortunately, cyclic ketones such as cyclohexanone gave rise to none of the desired β-amination products (**4r**). Finally, attempts to apply this strategy to esters and amides were unsuccessful, probably due to their higher pK_a value of the α−C-H bonds (**4s** and **4t**).

To show the generality of this transformation, we next explored the possibility of extending this Cu(II)-catalyzed dehydrogenation-conjugate addition approach to the synthesis of β-alkylated ketones using 1,3-dicarbonyl compounds as carbon nucleophiles (Scheme 4). Initial attempts with our standard conditions only provided low conversions. Considering that 1,3-dicarbonyl compounds had the tendency to chelate copper salt and therefore deactivate the Cu catalyst, we raised the Cu(II)/bpy loadings to prevent catalyst from poisoning. Gratifyingly, when 20 mol % $Cu(OAc)_2$/bpy was used, the reactions displayed a broad substrate scope for both ketones and 1,3-dicarbonyl compounds, similarly to that observed with nitrogen nucleophiles. As revealed in Scheme 4, aryl-containing β-diketones and β-ketoesters served well to afford the corresponding products in good to excellent yields (**6a**−**6e**). Dimethyl malonate, a relatively weak nucleophile, also delivered the product **6f** in moderate yield. Once again, heteroaryl ketones, halogen-containing ketones and aliphatic ketones all participated in the reaction, exhibiting high functional-group tolerance (**6g**−**6q**). Sterically encumbered substrates such as tertiary 1,3-dicarbonyl compounds and β-substituted ketones

DOI: 10.1021/jacs.6b01337
J. Am. Chem. Soc. 2016, 138, 5623−5633

Scheme 2. Substrate Scope of Nitrogen and Oxygen Nucleophiles[a]



[a]Reaction conditions: **1a** (0.6 mmol), **2** (0.2 mmol), $Cu(OAc)_2$ (0.02 mmol), bpy (0.02 mmol), TEMPO (0.2 mmol), 1,2-dichlorobenzene (2 mL), 120 °C, N_2 atmosphere, 24 h. All isolated yields. [b]**1a** (0.5 mmol), **2** (5 mmol), $Cu(OAc)_2$ (0.1 mmol), bpy (0.1 mmol), Li_2CO_3 (0.5 mmol) TEMPO (0.5 mmol), 1,2-dichlorobenzene (2 mL), 120 °C, N_2 atmosphere, 24 h. [c]**1a** (0.2 mmol), **2** (1.0 mmol) were used.

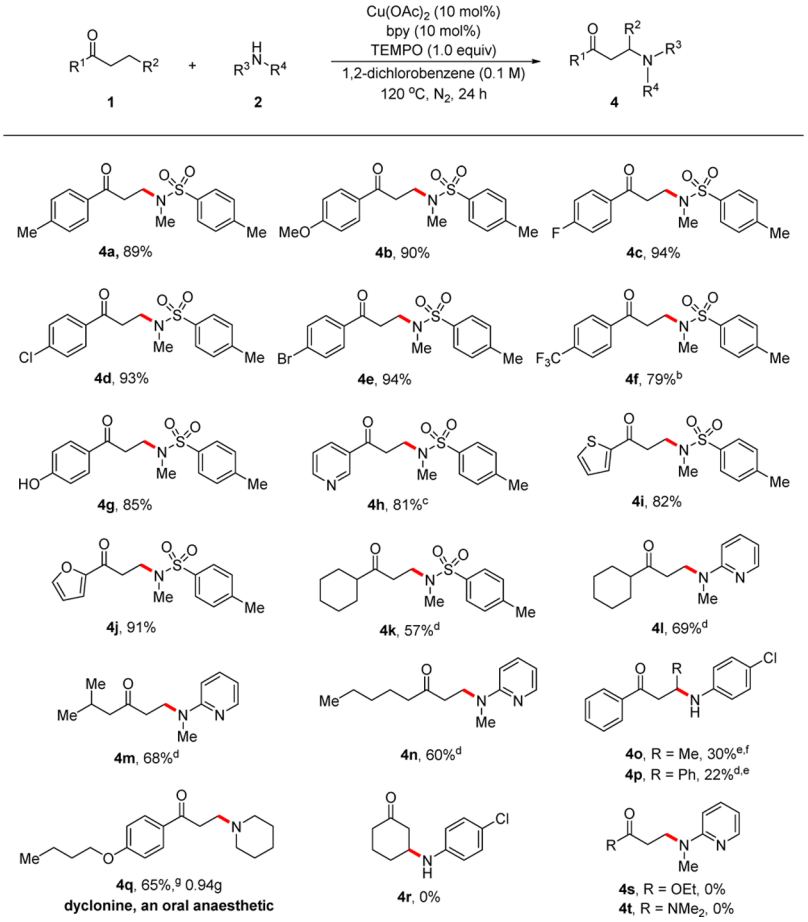
were difficult to undergo efficient couplings in the presence of catalytic amount of $Cu(OAc)_2$, however, stoichiometric $Cu(OAc)_2$ enabled efficient conversions of these challenging substrates (**6r**–**6w**). It should be mentioned that the syntheses of **6r** and **6s** offered a facile avenue to construction of quaternary carbon centers at the γ-position of saturated ketones. Moreover, β-substituted ketones including γ-keto ester and 1,4-diketone were also alkylated at the positions β to keto-group using dimethyl malonate as a coupling partner (**6v** and **6w**).

EXPERIMENTAL MECHANISTIC STUDIES

To gain in-depth insights into the reaction mechanism, we carried out a series of experimental investigations. At first, we checked the behavior of propiophenone **1a** under our standard conditions without adding any nucleophiles, and observed that phenyl vinyl ketone could

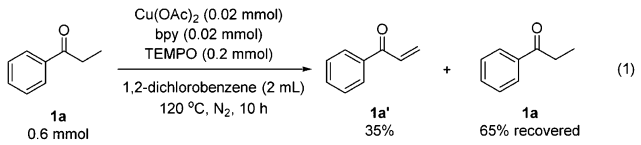
DOI: 10.1021/jacs.6b01337
J. Am. Chem. Soc. 2016, 138, 5623–5633

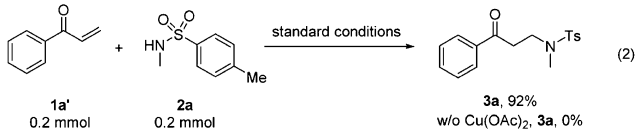
Scheme 3. Substrate Scope of Ketones[a]



[a]Reaction conditions: **1** (0.6 mmol), **2** (0.2 mmol), $Cu(OAc)_2$ (0.02 mmol), bpy (0.02 mmol), TEMPO (0.2 mmol), 1,2-dichlorobenzene (2 mL), 120 °C, N_2 atmosphere, 24 h. All isolated yields. [b]Conducted at 100 °C. [c]No bpy added. [d]$Cu(OAc)_2$ (30 mol %) and bpy (30 mol %) were used. [e]**1** (0.2 mmol) and **2** (0.6 mmol) were used. [f]$Cu(OAc)_2$ (10 mol %), bpy (20 mol %) and Na_2CO_3 (0.5 equiv) were used. [g]5 mmol scale.

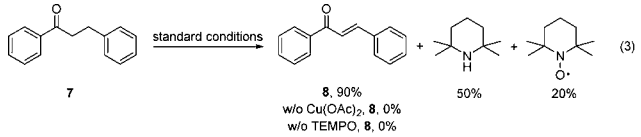
be generated in 35% yield after 10 h with 65% of **1a** recovered (eq 1). Then, we observed that the conjugate addition reaction of prepreparedphenyl vinyl ketone **1a**′ with sulfonamide **2a** gave **3a** in 92% yield under the standard conditions (eq 2). Further control experiment





revealed that copper salt as a Lewis acid catalyst was indispensable to the conjugate addition step. The observed ketone dehydrogenation to generate **1a**′ and the conjugate addition of Michael donor to **1a**′ support our original hypothesis that ketone β-functionalization may proceed via a tandem dehydrogenation-conjugate addition sequence.

Since the Lewis acid-promoted conjugate addition is a well-known process, we focused our attention on the detailed mechanism of ketone dehydrogenation process. This mechanistic investigation would be of interest because the copper-catalyzed ketone dehydrogenation to enones remained an unknown transformation. We chose 3-phenylpropiophenone (**7**) as a mechanistic probe for ketone dehydrogenation process because chalcone (**8**), the expected dehydrogenation product, was of low reactivity toward Michael addition (see p.S60 in the Supporting Information), nonvolatile and easy to handle. The reaction of 3-phenylpropiophenone (**7**) under the standard conditions produced chalcone (**8**) in 90% isolated yield. Further analysis of this reaction residue showed that 2,2,6,6-tetramethylpiperidine were generated in 50% yield (eq 3). Additionally, neither chlorobenzene

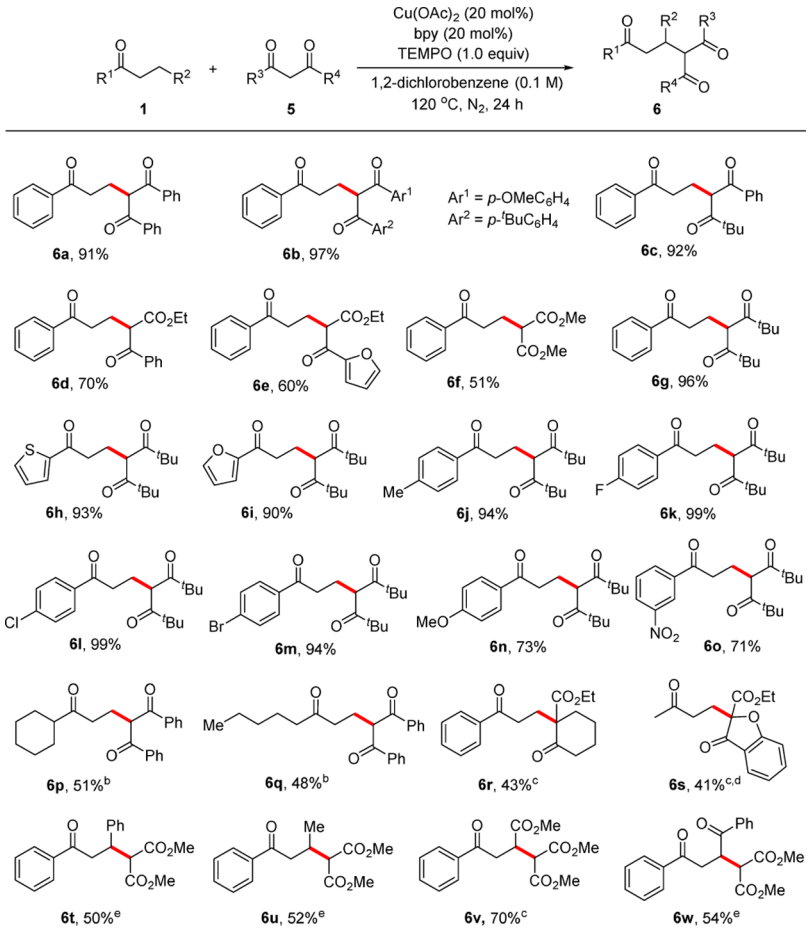


nor benzene was detected. These observations revealed that TEMPO was the sole oxidant during the reaction.[30] And because the ultimate reduced form of TEMPO, 2,2,6,6-tetramethylpiperidine, was detected, it could explain the observation that 1.0 equiv of TEMPO was enough to effect the dehydrogenation. Control experiments revealed that both $Cu(OAc)_2$ and TEMPO are indispensable for the dehydrogenation. Therefore, these results, in combination with the above observations, disclosed that $Cu(OAc)_2$ simultaneously catalyzed both dehydrogenation and conjugate addition, and TEMPO as oxidant functioned only in the dehydrogenation process.

In view of the fact that our reaction did not occur under aerobic conditions, we began to wonder if a radical process was involved in this transformation. As a matter of fact, precedent IBX-mediated dehydrogenation of ketones was reported to form an intermediate with a carbon radical at the α-position of carbonyl groups.[3d] To probe

DOI: 10.1021/jacs.6b01337
J. Am. Chem. Soc. 2016, 138, 5623−5633

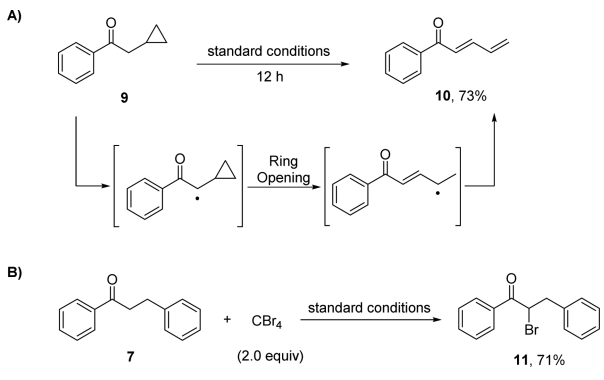
Scheme 4. Substrate Scope of Ketones and 1,3-Dicarbonyl Compounds[a]



[a]Reaction conditions: **1** (0.6 mmol), **5** (0.2 mmol), $Cu(OAc)_2$ (0.04 mmol), bpy (0.04 mmol), TEMPO (0.2 mmol), 1,2-dichlorobenzene (2 mL), 120 °C, N_2 atmosphere, 24 h. [b]$Cu(OAc)_2$ (30 mol %) and bpy (30 mol %) were used. [c]**1** (0.6 mmol), **5** (0.2 mmol), $Cu(OAc)_2$ (0.2 mmol), TEMPO (0.4 mmol), Li_2CO_3 (0.2 mmol), and DME (2 mL) were used. [d]Cs_2CO_3 (0.2 mmol) was used instead of Li_2CO_3. [e]**1** (0.2 mmol), **5** (0.6 mmol), $Cu(OAc)_2$ (0.2 mmol), TEMPO (0.5 mmol), Cs_2CO_3 (0.2 mmol), and DME (2 mL) were used.

this possibility, we synthesized **9**, a radical-clock probe and observed that **9** was converted, in 73% yield, to conjugated diene **10** under the standard conditions (Scheme 5A).[31] Additionally, to further assess the potential intermediacy of α-radical carbonyl, 3-phenylpropiophenone (**7**) was exposed to the standard conditions in the presence of CBr_4, which formed α-bromosubstituted product **11** in 71% yield (Scheme 5B). Collectively, the observed ring-opening product **10** and α-bromosubstituted product **11** provided strong evidence to support that this copper-catalyzed ketone dehydrogenation to enone involved α-radical intermediate formation. Notably, these results also help make a distinction between our catalytic conditions and Stahl's system since it has been proved that no radical intermediates is involved in Stahl's Cu/nitroxyl-catalyzed aerobic alcohol oxidation.[32]

Scheme 5. Experiments to Probe the Proposed Radical Intermediate



Kinetic Studies. To provide further information about the reaction mechanism, kinetic experiments were performed to establish the rate laws of the dehydrogenation process by monitoring the concentration of chalcone (**8**) generated from 3-phenylpropiophenone (**7**) dehydrogenation (Figure 1). All the kinetic data were taken at the time points in the early stage of reaction (the early period of 6–24 min). The measurement of initial rate of dehydrogenation of 3-phenylpropiophenone (**7**) as a function of concentration of **7** displayed a first-order kinetic dependence with respect to **7** (Figure 1A). Furthermore, the initial reaction rate exhibited a first-order kinetic dependence with respect to Cu(II)/bpy (Figure 1B, the ratio of Cu(II) to bpy is 1:1). The effect of TEMPO concentration on the reaction rate showed a zero-order dependence with TEMPO (Figure 1C).

Kinetic Isotope Effects. After the kinetic data of each reaction components in the dehydrogenation process were obtained, we turned our attention to the identification of turnover-limiting step in this conversion. For this purpose, both α- and β-deuterated **7** were synthesized. Then, **7**, α- and β-deuterated **7** were subjected to identical standard conditions in separate reaction vessels, and the initial reaction rates of their dehydrogenation to chalcone (**8**) were measured from parallel experiments, as shown in Figure 2. Comparison of the initial reaction rates between **7** and α-deuterated **7** revealed a significant

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J. Am. Chem. Soc. 2016, 138, 5623–5633

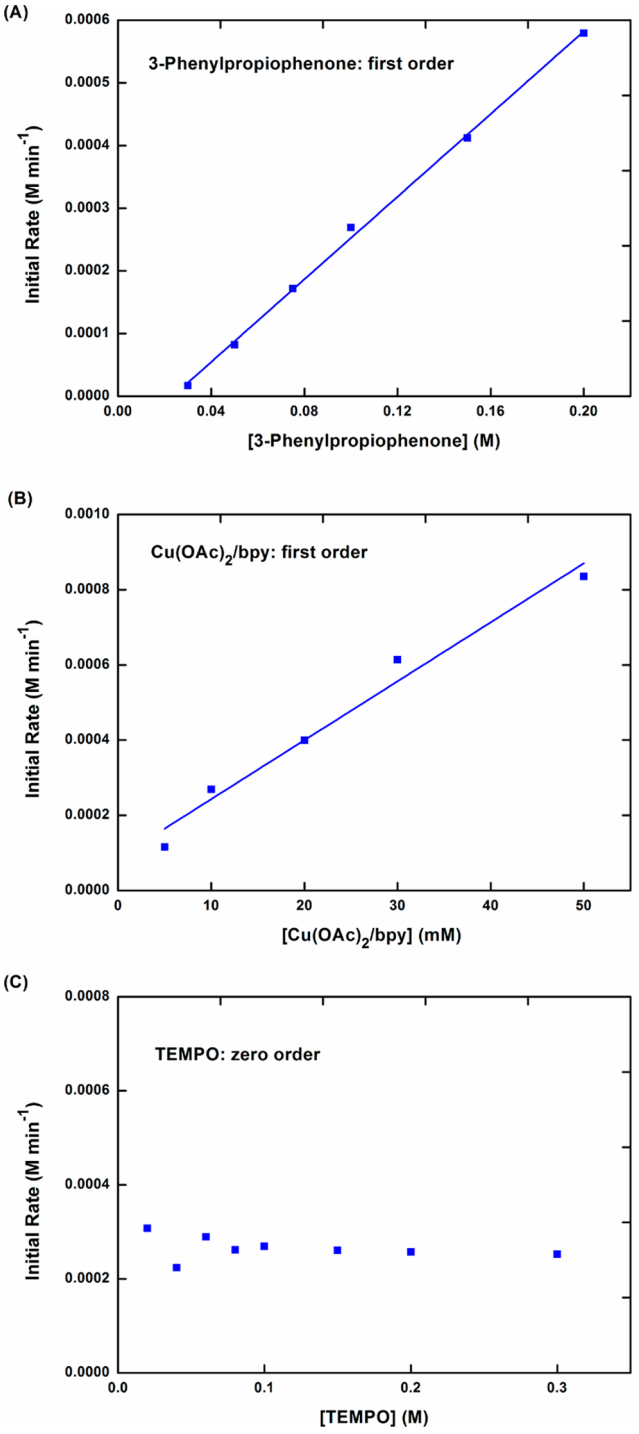


Figure 1. Dependence of $Cu(OAc)_2$/bpy-catalyzed ketone dehydrogenation on initial (A) 3-phenylpropiophenone concentration, (B) Cu/bpy concentration and (C) TEMPO concentration. Standard reaction conditions: 0.1 M 3-phenylpropiophenone, 10 mM $Cu(OAc)_2$, 10 mM bpy, 0.1 M TEMPO, 2.0 mL 1,2-dichlorobenzene, N_2, 120 °C.

primary kinetic isotope effect of 5.32, while the dehydrogenation of β-deuterated **7** exhibited no significant kinetic isotope effect (k_H/k_D = 1.02). These observations mean that C−H bond cleavage at the α-position of carbonyl group is involved in the turnover-limiting step of the dehydrogenation process. This conclusion is consistent with the zero-order dependence of initial rate on TEMPO that was observed in the aforementioned kinetic investigations.

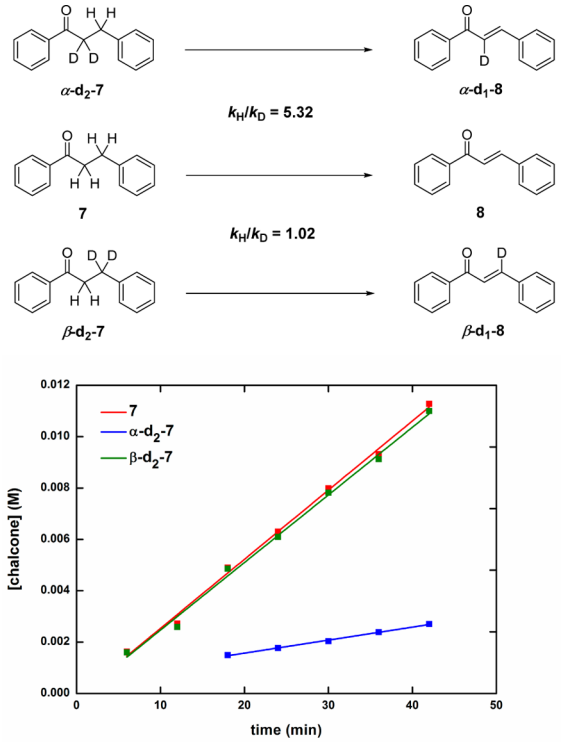
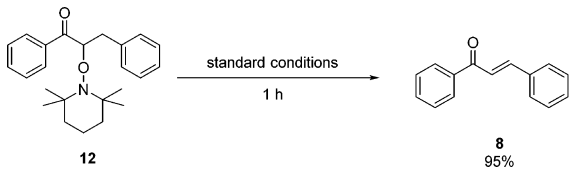


Figure 2. Kinetic profiles for the dehydrogenation of **7** (red), α-d_2-**7** (blue), β-d_2-**7** (green) by (bpy)$Cu(OAc)_2$/TEMPO. Yields were obtained by GC analysis. Standard reaction conditions: 10 mM $Cu(OAc)_2$, 10 mM bpy, 0.1 M TEMPO, 2.0 mL of 1,2-dichlorobenzene, N_2, 120 °C.

Detection of Reaction Intermediate. Although the α-radical intermediate and the rate-determining step of this copper-catalyzed dehydrogenation have been identified, more efforts are still needed to clarify the more detailed dehydrogenation pathway after the α-radical intermediate is formed. In literature reports, the IBX-mediated ketone dehydrogenation, the alkane dehydrogenation promoted by copper-peroxide systems and other radical initiated dehydrogenation processes[33] were proposed to proceed via hydrogen atom abstraction to form alkyl radical, then oxidation of the alkyl radical to alkyl cation, and final deprotonation of alkyl cation to form alkene. Such a dehydrogenation pathway, however, is unlikely operative in our current dehydrogenation process because the ketone radical cation located at α-position is hard to generate due to its high instability. Since TEMPO is well-known as a radical scavenger capable of capturing the active radical species, we reasoned that the formed ketone α-radical intermediate could be intercepted by TEMPO to deliver α-TEMPO-substituted ketone.[34] To verify this, the α-TEMPO-substituted ketone **12** was prepared and its reactivity was investigated. As a result, we observed that **12** underwent rapid TEMPOH (hydroxylamine) elimination to generate **8** in 95% yield under standard conditions within 1 h (eq 4). Accordingly, we speculated that



(4)

12 was likely formed as an intermediate prior to final enone formation. However, the fast TEMPOH-elimination makes it difficult to directly observe this possible transient intermediate. Moreover, the similar polarity of **7** and **12** impedes the separation of these compounds via conventional column chromatography. Being aware of the fact that the

DOI: 10.1021/jacs.6b01337
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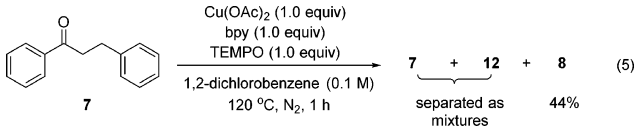
ketone dehydrogenation is first-order in Cu(II)/bpy, we envisioned that increasing the amount of Cu(II)/bpy could lead to a more rapid formation of **12** for convenient monitoring. Actually, with an increased Cu(II)/bpy loadings, we indeed observed the formation of **12** by ^{1}H NMR analysis (eq 5 and Figure 3). This observation thus provides



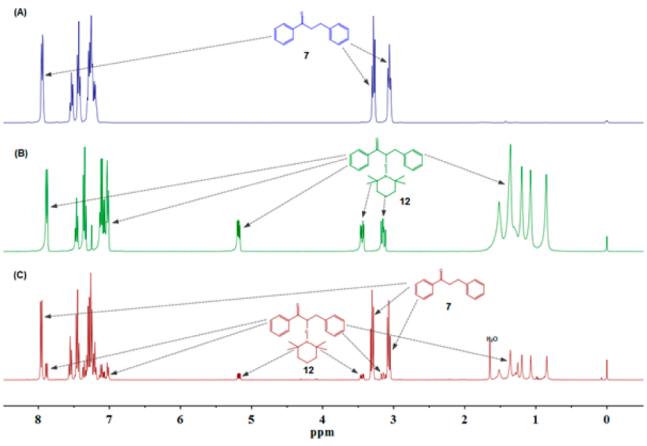


Figure 3. ^{1}H NMR spectra of (A) pure 3-phenylpropiophenone **7**, (B) pure α-TEMPO-adducted 3-phenylpropiophenone **12** and (C) mixtures of **7** and **12** isolated from the reaction described in eq 5.

solid evidence to support that α-TEMPO-substituted ketone **12** is the reaction intermediate in ketone dehydrogenation to enone. It is worth to mention that the direct formations of α-TEMPO-substituted ketones under catalytic conditions were rare and the TEMPOH-elimination to generate alkene was sporadically observed as side reactions with low efficiencies in precedent literatures.[35] Consequently, our copper-catalyzed dehydrogenation process represents a unique and unprecedented transformation that is different from the previously reported metal-catalyzed β-hydride elimination to enone pathway.

EPR and UV−Visible Experiments. EPR and UV−visible spectroscopic studies were conducted to gain more information about the nature of the copper catalyst (Figure 4 and 5). To mimic the catalysis process, we used 10 mol % of $Cu(OAc)_2$, 10 mol % bpy and 50 mol % TEMPO in the EPR studies of the dehydrogenation of **7**. As shown in Figure 4, a decrease of both Cu(II) and TEMPO signals could be observed as the reaction proceeded. This trend was also observed via UV−visible experiments, in which Cu(II) signal dropped along with Cu(I) signal rose.

Proposed Mechanism. On the basis of the above-mentioned mechanistic studies, a plausible mechanism was proposed (Scheme 6). At first, $Cu(OAc)_2$ as Lewis acid reacts with ketone to form metal-enolate complex **13**. Then, homolysis of the Cu(II)-enolate bond generates Cu(I) species and ketone intermediate 15 is captured by TEMPO to form α-TEMPO-substituted ketone **16** that undergoes fast TEMPOH-elimination to form enones. Since only *trans*-enone is formed, the TEMPOH-elimination likely occurs via β-H abstraction assisted by another molecule of TEMPO (**17**). Then, enone reacts with various nucleophiles under copper catalyst to achieve the overall direct β-functionalization of ketones. Finally, oxidation of Cu(I) species by TEMPO or TEMPOH regenerates Cu(II) species with 2,2,6,6-tetramethylpiperidine and water released. To clarify the regeneration of Cu(II) species from oxidation of Cu(I), reactions of CuOAc/bpy complex with TEMPO or TEMPOH have been performed, which demonstrated that both TEMPO[36] and TEMPOH[37] could oxidize Cu(I) to Cu(II) (see Figure S26−S29 in the Supporting Information). Additionally, control experiments using Cu(I) salt as

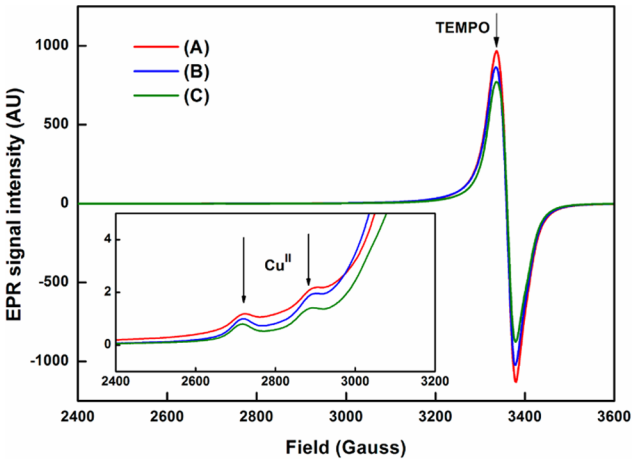


Figure 4. EPR spectra acquired from the dehydrogenation of 3-phenylpropiophenone at (A) 0.5 h, (B) 1.0 h and (C) 2.0 h. Reaction conditions: 0.1 M 3-phenylpropiophenone, 10 mM $Cu(OAc)_2$, 10 mM bpy, 50 mM TEMPO, 2.0 mL 1,2-dichlorobenzene, N_2, 120 °C.

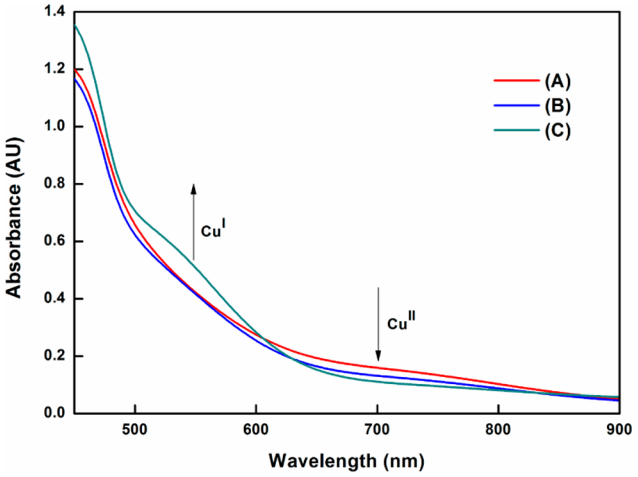
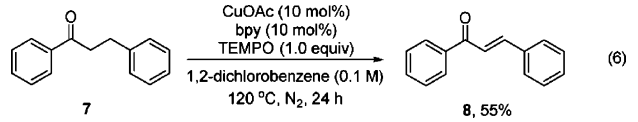
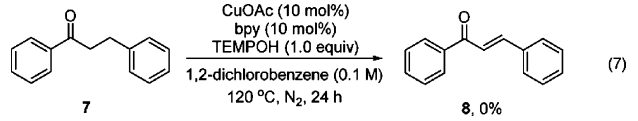


Figure 5. UV−visible spectra acquired from the dehydrogenation of 3-phenylpropiophenone at (A) 0.5 h, (B) 1.0 h and (C) 2.0 h. Reaction conditions: 0.1 M 3-phenylpropiophenone, 10 mM $Cu(OAc)_2$, 10 mM bpy, 0.1 M TEMPO, 2.0 mL 1,2-dichlorobenzene, N_2, 120 °C.

catalyst precursor have also been done to verify that the CuOAc/bpy as a catalyst system effects the dehydrogenation of 3-phenylpropiophenone in the presence of TEMPO (eq 6). In contrast, in



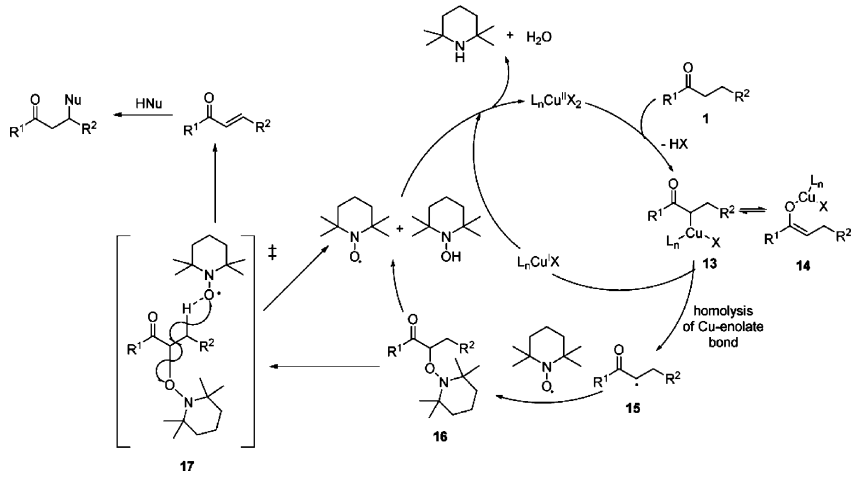
the presence of TEMPOH as an oxidant, CuOAc/bpy did not promote the dehydrogenation of 3-phenylpropiophenone (eq 7),



although oxidization of the CuOAc/bpy system to Cu(II) species by TEMPOH has been established. No dehydrogenation to occur in the experiment described in eq 7 may stem from the lack of TEMPO component in the reaction system, which probably provides a clue for the oxidation of Cu(I) by TEMPOH. There are two possible ways for

DOI: 10.1021/jacs.6b01337
J. Am. Chem. Soc. 2016, 138, 5623−5633

Scheme 6. Proposed Mechanism



oxidation of Cu(I) by TEMPOH: (1) oxidative addition of N−O bond to Cu(I) species to generate Cu(III) species, followed by the reaction of Cu(III) species with another Cu(I) species to regenerate Cu(II) species; (2) oxidation of Cu(I) species by the oxoammonium from disproportionation of TEMPOH.[36] The latter way would involve formation of TEMPO. Consequently, no dehydrogenation in the reaction of eq 7 suggested that the oxidation of Cu(I) by TEMPOH did not involve generation of TEMPO and therefore rose the possibility that the oxidation of Cu(I) by TEMPOH proceeded via Cu(III) intermediate.

CONCLUSIONS

In summary, we have developed a copper-catalyzed method for direct β-functionalization of unactivated ketones with a wide range of nitrogen, oxygen and carbon nucleophiles, which proceeds through a tandem ketone dehydrogenation-conjugate addition sequence. This protocol obviates the need for additional preparation steps and careful handing of α,β-unsaturated ketones, and therefore opens up a new door to construction of β-functionalized ketones in a highly efficient fashion. This coupling also shows excellent functional group tolerance as well as high chemo- and regioselectivity due to its mild oxidative conditions. Mechanistic studies were carried out to provide in-depth insight into this transformation using control experiments, kinetic studies, identification of reaction intermediates and KIE measurements. As disclosed by mechanistic studies, our Cu-catalyzed dehydrogenation of ketones represents an unprecedented radical-based process. We expect that our mechanistic findings will be useful for the development of new methodologies as well as the catalysts of the first-row transition-metals.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b01337.

Detailed experimental procedures, ^{1}H, ^{13}C and ^{19}F NMR spectra data for compounds, kinetic data, and additional experiment data. (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank Prof. Armido Studer for the fruitful discussion of mechanism and Prof. Zhongning Chen for the helpful discussion of UV−visible spectra. We also thank two referees for helpful suggestions for mechanistic studies. Financial support from NSFC (21431008, 21332001, 21402196 and 21401197), and the CAS/SAFEA International Partnership Program for Creative Research Teams is greatly appreciated.

REFERENCES

(1) Patai, S.; Rappoport, Z. *The Chemistry of Enones*; John Wiley & Sons: New York, 1989.

(2) For reviews of α,β-dehydrogenation, see: (a) Reich, H. J.; Wollowitz, S. *Org. React.* **1993**, *44*, 1. (b) Muzart, J. *Eur. J. Org. Chem.* **2010**, *2010*, 3779. (c) Stahl, S. S.; Diao, T. *Comp. Org. Synth.* **2014**, *7*, 178. (d) Turlik, A.; Chen, Y.; Newhouse, T. R. *Synlett* **2016**, *27*, 331.

(3) (a) Nicolaou, K. C.; Zhong, Y. L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596. (b) Nicolaou, K. C.; Gray, D. L. F.; Montagnon, T.; Harrison, S. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 996. (c) Nicolaou, K. C.; Montagnon, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 993. (d) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y. L. *J. Am. Chem. Soc.* **2002**, *124*, 2245. (e) Uyanik, M.; Akakura, M.; Ishihara, K. *J. Am. Chem. Soc.* **2009**, *131*, 251.

(4) (a) Walker, D.; Hiebert, J. D. *Chem. Rev.* **1967**, *67*, 153. (b) Bhattacharya, A.; DiMichele, L. M.; Dolling, U. H.; Douglas, A. W.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, *110*, 3318.

(5) (a) Diao, T.; Stahl, S. S. *J. Am. Chem. Soc.* **2011**, *133*, 14566. (b) Diao, T.; Wadzinski, T. J.; Stahl, S. S. *Chem. Sci.* **2012**, *3*, 887. (c) Gao, W.; He, Z.; Qian, Y.; Zhao, J.; Huang, Y. *Chem. Sci.* **2012**, *3*, 883. (d) Diao, T.; Pun, D.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 8205. For a Pd-catalyzed Wacker oxidation−dehydrogenation to α,β-unsaturated ketones, see: (e) Bigi, M. A.; White, M. C. *J. Am. Chem. Soc.* **2013**, *135*, 7831.

(6) (a) Chen, Y.; Romaire, J. P.; Newhouse, T. R. *J. Am. Chem. Soc.* **2015**, *137*, 5875. (b) Chen, Y.; Turlik, A.; Newhouse, T. R. *J. Am. Chem. Soc.* **2016**, *138*, 1166.

(7) (a) Burk, M. J.; Crabtree, R. H. *J. Am. Chem. Soc.* **1987**, *109*, 8025. (b) Liu, F.; Pak, E. B.; Singh, B.; Jensen, C. M.; Goldman, A. S. *J. Am. Chem. Soc.* **1999**, *121*, 4086. For a recent review, see: (c) Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681.

(8) (a) Yi, C. S.; Lee, D. W. *Organometallics* **2009**, *28*, 947. (b) Zhang, X.; Wang, D. Y.; Emge, T. J.; Goldman, A. S. *Inorg. Chim. Acta* **2011**, *369*, 253. (c) Kusumoto, S.; Akiyama, M.; Nozaki, K. *J. Am. Chem. Soc.* **2013**, *135*, 18726.

DOI: 10.1021/jacs.6b01337
J. Am. Chem. Soc. 2016, 138, 5623−5633

(9) (a) Evans, D. L.; Minster, D. K.; Jordis, U.; Hecht, S. M.; Mazzu, A. L.; Meyers, A. I. *J. Org. Chem.* **1979**, *44*, 497. (b) Barrish, J. C.; Singh, J.; Spergel, S. H.; Han, W. C.; Kissick, T. P.; Kronenthal, D. R.; Mueller, R. H. *J. Org. Chem.* **1993**, *58*, 4494. (c) Meyers, A. I.; Tavares, F. X. *J. Org. Chem.* **1996**, *61*, 8207. (d) Ramirez, T. A.; Zhao, B.; Shi, Y. *Tetrahedron Lett.* **2010**, *51*, 1822. (e) Wang, Y.; Li, Z.; Huang, Y.; Tang, C.; Wu, X.; Xu, J.; Yao, H. *Tetrahedron* **2011**, *67*, 7406. (f) Dawsey, A. C.; Li, V.; Hamilton, K. C.; Wang, J.; Williams, T. J. *Dalton Trans.* **2012**, *41*, 7994.

(10) (a) Segawa, Y.; Maekawa, T.; Itami, K. *Angew. Chem., Int. Ed.* **2015**, *54*, 66. (b) Wencel-Delord, J.; Patureau, F.; Glorius, F. *Top. Organomet. Chem.* **2015**, *55*, 1. (c) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788. (d) Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res.* **2012**, *45*, 936. (e) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281. (f) Shin, K.; Kim, H.; Chang, S. *Acc. Chem. Res.* **2015**, *48*, 1040. (g) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (h) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (i) Guo, X.-X.; Gu, D.-W.; Wu, Z.; Zhang, W. *Chem. Rev.* **2015**, *115*, 1622. (j) Cheng, C.; Hartwig, J. F. *Chem. Rev.* **2015**, *115*, 8946. (k) Liu, C.; Yuan, J.; Gao, M.; Tang, S.; Li, W.; Shi, R.; Lei, A. *Chem. Rev.* **2015**, *115*, 12138.

(11) (a) Zhang, M.; Zhou, J.; Kan, J.; Wang, M.; Su, W.; Hong, M. *Chem. Commun.* **2010**, *46*, 5455. (b) Zhou, J.; Wu, G.; Zhang, M.; Jie, X.; Su, W. *Chem. - Eur. J.* **2012**, *18*, 8032. (c) Shang, Y.; Jie, X.; Zhou, J.; Hu, P.; Huang, S.; Su, W. *Angew. Chem., Int. Ed.* **2013**, *52*, 1299. (d) Zhang, M.; Hu, P.; Zhou, J.; Wu, G.; Huang, S.; Su, W. *Org. Lett.* **2013**, *15*, 1718.

(12) (a) Ueno, S.; Shimizu, R.; Kuwano, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 4543. (b) Ueno, S.; Maeda, R.; Yasuoka, S.; Kuwano, R. *Chem. Lett.* **2013**, *42*, 40. (c) Terao, Y.; Kametani, Y.; Wakui, H.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron* **2001**, *57*, 5967. (d) Moon, Y.; Kwon, D.; Hong, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 11333. (e) Gandeepan, P.; Rajamalli, P.; Cheng, C.-H. *ACS Catal.* **2014**, *4*, 4485. (f) Izawa, Y.; Zheng, C.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2013**, *52*, 3672. (g) Izawa, Y.; Pun, D.; Stahl, S. S. *Science* **2011**, *333*, 209.

(13) (a) Huang, Z.; Sam, Q. P.; Dong, G. *Chem. Sci.* **2015**, *6*, 5491. (b) Huang, Z.; Dong, G. *J. Am. Chem. Soc.* **2013**, *135*, 17747. (c) Zhang, F.-L.; Hong, K.; Li, T.-J.; Park, H.; Yu, J.-Q. *Science* **2016**, *351*, 252.

(14) (a) Leskinen, M. V.; Yip, K.-T.; Valkonen, A.; Pihko, P. M. *J. Am. Chem. Soc.* **2012**, *134*, 5750. (b) Leskinen, M. V.; Madarász, Á.; Yip, K.-T.; Vuorinen, A.; Pápai, I.; Neuvonen, A. J.; Pihko, P. M. *J. Am. Chem. Soc.* **2014**, *136*, 6453. (c) Nimje, R. Y.; Leskinen, M. V.; Pihko, P. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 4818.

(15) (a) Renaudat, A.; Jean-Gérard, L.; Jazzar, R.; Kefalidis, C. E.; Clot, E.; Baudoin, O. *Angew. Chem., Int. Ed.* **2010**, *49*, 7261. (b) Larini, P.; Kefalidis, C. E.; Jazzar, R.; Renaudat, A.; Clot, E.; Baudoin, O. *Chem. - Eur. J.* **2012**, *18*, 1932. (c) Aspin, S.; Goutierre, A.-S.; Larini, P.; Jazzar, R.; Baudoin, O. *Angew. Chem., Int. Ed.* **2012**, *51*, 10808.

(16) (a) Stang, E. M.; White, M. C. *J. Am. Chem. Soc.* **2011**, *133*, 14892. (b) Goldman, A. S.; Roy, A. H.; Huang, Z.; Ahuja, R.; Schinski, W.; Brookhart, M. *Science* **2006**, *312*, 257. (c) Jia, X.; Huang, Z. *Nat. Chem.* **2016**, *8*, 157.

(17) For reviews of β-functionalization of ketones, see: (a) Huang, Z.; Lim, H. N.; Mo, F.; Young, M. C.; Dong, G. *Chem. Soc. Rev.* **2015**, *44*, 7764. (b) Huang, Z.; Dong, G. *Tetrahedron Lett.* **2014**, *55*, 5869.

(18) For selected reviews of conjugate addition, see: (a) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187. (b) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829.

(19) (a) Zhang, C.; Santiago, C. B.; Crawford, J. M.; Sigman, M. S. *J. Am. Chem. Soc.* **2015**, *137*, 15668. (b) Werner, E. W.; Mei, T.-S.; Burckle, A. J.; Sigman, M. S. *Science* **2012**, *338*, 1455. (c) Mei, T.-S.; Patel, H. H.; Sigman, M. S. *Nature* **2014**, *508*, 340.

(20) (a) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965. (b) Shang, R.; Ilies, L.; Matsumoto, A.; Nakamura, E. *J. Am. Chem. Soc.* **2013**, *135*, 6030. (c) Zhang, S.-Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 12135. (d) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2014**, *136*, 898. (e) Wu, X.; Zhao, Y.; Ge, H. *J. Am. Chem. Soc.* **2014**, *136*, 1789. (f) Chen, G.; Shigenari, T.; Jain, P.; Zhang, Z.; Jin, Z.; He, J.; Li, S.; Mapelli, C.; Miller, M. M.; Poss, M. A.; Scola, P. M.; Yeung, K.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *137*, 3338. (g) Zhang, Q.; Yin, X.-S.; Chen, K.; Zhang, S.-Q.; Shi, B.-F. *J. Am. Chem. Soc.* **2015**, *137*, 8219. (h) Zhang, J.; Chen, H.; Lin, C.; Liu, Z.; Wang, C.; Zhang, Y. *J. Am. Chem. Soc.* **2015**, *137*, 12990. For reviews, see: (i) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726. (j) Qiu, G.; Wu, J. *Org. Chem. Front.* **2015**, *2*, 169.

(21) (a) Mo, J.; Shen, L.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2013**, *52*, 8588. (b) Jin, Z.; Chen, S.; Wang, Y.; Zheng, P.; Yang, S.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2014**, *53*, 13506. (c) Fu, Z.; Xu, J.; Zhu, T.; Leong, W. W. Y.; Chi, Y. R. *Nat. Chem.* **2013**, *5*, 835. (d) Hayashi, Y.; Itoh, T.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 3920. (e) Zhang, S.-L.; Xie, H.-X.; Zhu, J.; Li, H.; Zhang, X.-S.; Li, J.; Wang, W. *Nat. Commun.* **2011**, *2*, 211.

(22) (a) Petronijević, F. R.; Nappi, M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 18323. (b) Terrett, J. A.; Clift, M. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 6858. (c) Jeffrey, J. L.; Petronijević, F. R.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2015**, *137*, 8404. (d) Pirnot, M. T.; Rankic, D. A.; Martin, D. B. C.; MacMillan, D. W. C. *Science* **2013**, *339*, 1593. (e) Okada, M.; Fukuyama, T.; Yamada, K.; Ryu, I.; Ravelli, D.; Fagnoni, M. *Chem. Sci.* **2014**, *5*, 2893.

(23) (a) Stanovnik, B.; Svete, J. *Chem. Rev.* **2004**, *104*, 2433. (b) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044.

(24) For related examples of α-amination of ketones, see: (a) Evans, R. W.; Zbieg, J. R.; Zhu, S.; Li, W.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 16074. (b) Lamani, M.; Prabhu, K. R. *Chem. - Eur. J.* **2012**, *18*, 14638. (c) Jiang, Q.; Xu, B.; Zhao, A.; Jia, J.; Liu, T.; Guo, C. *J. Org. Chem.* **2014**, *79*, 8750. (d) Lv, Y.; Li, Y.; Xiong, T.; Lu, Y.; Liu, Q.; Zhang, Q. *Chem. Commun.* **2014**, *50*, 2367. (e) Fisher, D. J.; Burnett, G. L.; Velasco, R.; Read de Alaniz, J. *J. Am. Chem. Soc.* **2015**, *137*, 11614. (f) Tokumasu, K.; Yazaki, R.; Ohshima, T. *J. Am. Chem. Soc.* **2016**, *138*, 2664. (g) Kainz, Q. M.; Matier, C. D.; Bartoszewicz, A.; Zultanski, S. L.; Peters, J. C.; Fu, G. C. *Science* **2016**, *351*, 681.

(25) (a) Verkade, J. M. M.; Hemert, L. J. C. v.; Quaedflieg, P. J. L. M.; Rutjes, F. P. J. T. *Chem. Soc. Rev.* **2008**, *37*, 29. (b) Enders, D.; Wang, C.; Liebich, J. X. *Chem. - Eur. J.* **2009**, *15*, 11058. (c) Krishna, P. R.; Sreeshailam, A.; Srinivas, R. *Tetrahedron* **2009**, *65*, 9657. (d) Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. *Chem. Rev.* **2011**, *111*, 2626.

(26) (a) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796. (b) Jerphagnon, T.; Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *Chem. Soc. Rev.* **2009**, *38*, 1039.

(27) (a) Conde, A.; Vilella, L.; Balcells, D.; Díaz-Requejo, M. M.; Lledós, A.; Pérez, P. J. *J. Am. Chem. Soc.* **2013**, *135*, 3887. (b) Rout, S. K.; Guin, S.; Ali, W.; Gogoi, A.; Patel, B. K. *Org. Lett.* **2014**, *16*, 3086. (c) Tran, B. L.; Driess, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 17292. (d) Zhao, J.; Fang, H.; Han, J.; Pan, Y. *Org. Lett.* **2014**, *16*, 2530. (e) Wang, C.-Y.; Song, R.-J.; Wei, W.-T.; Fan, J.-H.; Li, J.-H. *Chem. Commun.* **2015**, *51*, 2361.

(28) Simon, M.-O.; Girard, S. A.; Li, C.-J. *Angew. Chem., Int. Ed.* **2012**, *51*, 7537.

(29) (a) Semmelhack, M. F.; Schmid, C. R.; Cortes, D. A.; Chou, C. S. *J. Am. Chem. Soc.* **1984**, *106*, 3374. (b) Gamez, P.; Arends, I. W. C. E.; Reedijk, J.; Sheldon, R. A. *Chem. Commun.* **2003**, *19*, 2414. (c) Hoover, J. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2011**, *133*, 16901. (d) Hoover, J. M.; Ryland, B. L.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 2357. (e) Steves, J. E.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 15742. (f) Ryland, B. L.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2014**, *53*, 8824. (g) Sonobe, T.; Oisaki, K.; Kanai, M. *Chem. Sci.* **2012**, *3*, 3249. (h) Han, B.; Yang, X.-L.; Wang, C.; Bai, Y.-W.; Pan, T.-C.; Chen, X.; Yu, W. *J. Org. Chem.* **2012**, *77*, 1136. (i) Flanagan, J. C. A.; Dornan, L. M.; McLaughlin, M. G.; McCreanor, N. G.; Cook, M. J.; Muldoon, M. J. *Green Chem.* **2012**, *14*, 1281.

DOI: 10.1021/jacs.6b01337
J. Am. Chem. Soc. 2016, 138, 5623−5633

(30) For reviews of TEMPO, see: (a) Wertz, S.; Studer, A. *Green Chem.* **2013**, *15*, 3116. (b) Tebben, L.; Studer, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 5034.
(31) (a) Maillard, B.; Forrest, D.; Ingold, K. U. *J. Am. Chem. Soc.* **1976**, *98*, 7024. (b) Mathew, L.; Warkentin, J. *J. Am. Chem. Soc.* **1986**, *108*, 7981.
(32) Ryland, B. L.; McCann, S. D.; Brunold, T. C.; Stahl, S. S. *J. Am. Chem. Soc.* **2014**, *136*, 12166.
(33) (a) Kochi, J. K.; Bemis, A.; Jenkins, C. L. *J. Am. Chem. Soc.* **1968**, *90*, 4616. (b) Hull, J. F.; Balcells, D.; Sauer, E. L. O.; Raynaud, C.; Brudvig, G. W.; Crabtree, R. H.; Eisenstein, O. *J. Am. Chem. Soc.* **2010**, *132*, 7605. (c) Bigi, M. A.; Reed, S. A.; White, M. C. *Nat. Chem.* **2011**, *3*, 216. (d) Voica, A.-F.; Mendoza, A.; Gutekunst, W. R.; Fraga, J. O.; Baran, P. S. *Nat. Chem.* **2012**, *4*, 629.
(34) (a) Pouliot, M.; Renaud, P.; Schenk, K.; Studer, A.; Vogler, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 6037. (b) Li, Y.; Pouliot, M.; Vogler, T.; Renaud, P.; Studer, A. *Org. Lett.* **2012**, *14*, 4474. (c) Mabe, P. J.; Zakarian, A. *Org. Lett.* **2014**, *16*, 516. (d) Li, L.; Yu, Z.; Shen, Z. *Adv. Synth. Catal.* **2015**, *357*, 3495. For related examples of α-oxyamination of aldehydes, see: (e) Sibi, M. P.; Hasegawa, M. *J. Am. Chem. Soc.* **2007**, *129*, 4124. (f) Van Humbeck, J. F.; Simonovich, S. P.; Knowles, R. R.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 10012. (g) Akagawa, K.; Fujiwara, T.; Sakamoto, S.; Kudo, K. *Org. Lett.* **2010**, *12*, 1804. (h) Kano, T.; Mii, H.; Maruoka, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 6638.
(35) (a) Wetter, C.; Jantos, K.; Woithe, K.; Studer, A. *Org. Lett.* **2003**, *5*, 2899. (b) Molawi, K.; Schulte, T.; Siegenthaler, K. O.; Wetter, C.; Studer, A. *Chem. - Eur. J.* **2005**, *11*, 2335. (c) Birch, P.; Parsons, A. F.; Cross, P. *Tetrahedron Lett.* **2012**, *53*, 822. (d) Dinca, E.; Hartmann, P.; Smrček, J.; Dix, I.; Jones, P. G.; Jahn, U. *Eur. J. Org. Chem.* **2012**, *2012*, 4461.
(36) Dijksman, A.; Arends, I. W. C. E.; Sheldon, R. A. *Org. Biomol. Chem.* **2003**, *1*, 3232.
(37) (a) Carloni, P.; Damiani, E.; Iacussi, M.; Greci, L.; Stipa, P.; Cauzi, D.; Rizzoli, C.; Sgarabotto, P. *Tetrahedron* **1995**, *51*, 12445. (b) Wu, X.-F.; Bheeter, C. B.; Neumann, H.; Dixneuf, P. H.; Beller, M. *Chem. Commun.* **2012**, *48*, 12237. (c) Lucarini, M.; Marchesi, E.; Pedulli, G. F.; Chatgilialoglu, C. *J. Org. Chem.* **1998**, *63*, 1687.

DOI: 10.1021/jacs.6b01337
J. Am. Chem. Soc. 2016, 138, 5623−5633