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Mechanistic Investigation of Oxidative Mannich Reaction with *tert*-Butyl Hydroperoxide. The Role of Transition Metal Salt

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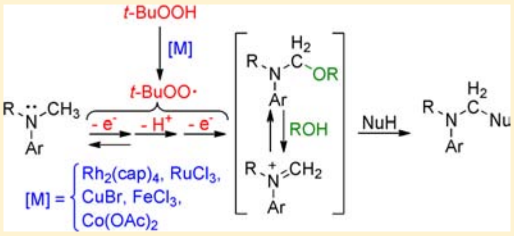
Ⓢ *Supporting Information*

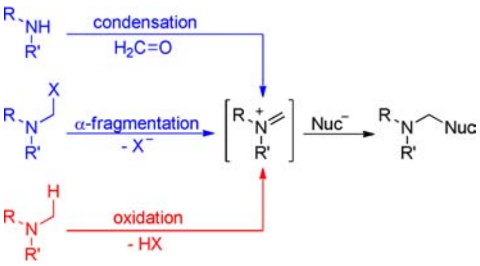
ABSTRACT: A general mechanism is proposed for transition metal-catalyzed oxidative Mannich reactions of *N*,*N*-dialkylanilines with *tert*-butyl hydroperoxide (TBHP) as the oxidant. The mechanism consists of a rate-determining single electron transfer (SET) that is uniform from 4-methoxy- to 4-cyano-*N*,*N*-dimethylanilines. The *tert*-butylperoxy radical is the major oxidant in the rate-determining SET step that is followed by competing backward SET and irreversible heterolytic cleavage of the carbon−hydrogen bond at the α-position to nitrogen. A second SET completes the conversion of *N*,*N*-dimethylaniline to an iminium ion that is subsequently trapped by the nucleophilic solvent or the oxidant prior to formation of the Mannich adduct. The general role of $Rh_2(cap)_4$, $RuCl_2(PPh_3)_3$, CuBr, $FeCl_3$, and $Co(OAc)_2$ in *N*,*N*-dialkylaniline oxidations by T-HYDRO is to initiate the conversion of TBHP to *tert*-butylperoxy radicals. A second pathway, involving O_2 as the oxidant, exists for copper, iron, and cobalt salts. Results from linear free-energy relationship (LFER) analyses, kinetic and product isotope effects (KIE and PIE), and radical trap experiments of *N*,*N*-dimethylaniline oxidation by T-HYDRO in the presence of transition metal catalysts are discussed. Kinetic studies of the oxidative Mannich reaction in methanol and toluene are also reported.



■ INTRODUCTION

The Mannich reaction is a powerful transformation for the syntheses of nitrogen-containing natural products and active pharmaceutical ingredients.[1] Iminium ions, key intermediates in the Mannich reaction, react with a large variety of nucleophiles.[2] Despite the synthetic value of iminium ions, only simple *N*,*N*-dimethylmethylidene-ammonium halides (Eschenmoser's salts) are commercially available. Hence, iminium ions are commonly prepared in situ by methods that limit the scope of the nucleophiles with which they are compatible. Strategies allowing access to Mannich reaction intermediates include condensation of secondary amines with aldehydes,[1a] α-fragmentation of iminium ion precursors,[1b] and the oxidation of tertiary amines (Scheme 1).[2a−c,3,4] The latter method directly and under mild conditions functionalizes otherwise inert C−H bonds that are adjacent to nitrogen.

Scheme 1. Strategies for Preparation the Key Intermediate of the Mannich Reaction



In the past decade several catalytic systems were developed for the conversion of *N*,*N*-dialkylanilines to their corresponding iminium ions. The scope of catalysts for this transformation include Ru,[4a,5] Rh,[3] Cu,[2b,c,6] Fe,[7] Mo,[8] and V[9] complexes. Recent advances in the oxidative Mannich reaction of *N*,*N*-dialkylanilines enabled the use of dioxygen[4a,6a,b] or di-*tert*-butylperoxide (DTBP) as oxidants.[10] However, mild conditions[3] and often higher yields[2b,6a,f] are achieved with *tert*-butyl hydroperoxide (TBHP) that prevails as the oxidant of choice.

The mild conditions of transition metal-catalyzed oxidation of *N*,*N*-dialkylanilines to iminium ions with TBHP enable utilization of selected nucleophiles such as siloxyfurans,[3] enol silanes,[6b,11] allyl silanes,[7b] indoles,[5b,6c,7c,12] cyanides,[4a,5c,7a,8,9b,13] alkynes,[2b,c] ketones,[5a,6c,e,9a,14] nitroalkanes,[5d,8,15] 1,3-dicarbonyl compounds,[15b,16] electron-rich arenes,[17] heterarenes,[6a,7c,17] boronic acids,[18] and heteroatom nucleophiles[19] in the oxidative Mannich reaction. The majority of these nucleophiles were employed in the copper(I)-catalyzed oxidative reactions of *N*-aryl-tetrahydroisoquinolines.[2b,c,6a] The use of Rh[3] and Ru[5b,19a] complexes, on the other hand, provides a broader substrate scope that includes *N*,*N*-dilakylanilines, but this substrate class has a limited scope of nucleophiles that can be employed. The question remains open whether the scope of *N*,*N*-dialkylanilines and reactive nucleophiles in the oxidative Mannich reactions is catalyst-specific or could be generalized among different catalysts and conditions. An understanding of the role of the transition metal in the *N*,*N*-dialkylaniline oxidation step

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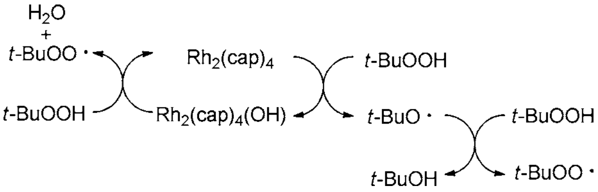
and in the subsequent Mannich reaction would provide an answer to this question. The detailed mechanism of each step could also lead to a reduction in the excess of *N*,*N*-dialkylanilines required to achieve high yields[3,5b] and facilitate the development of new catalytic systems that utilize inexpensive catalysts and more atom economical oxidants, such as O_2.

Oxidative Mannich reactions consist of two independent steps – oxidation of *N*,*N*-dialkylaniline to the iminium ion and reaction of the iminium ion or the associated intermediate with a nucleophile (Scheme 2). Investigations of possible intermediates leading to the Mannich adduct have received considerable attention[3,5b,6a] while only a few mechanistic studies have been reported on the transition metal-catalyzed *N*,*N*-dialkylaniline oxidations by TBHP (discussed below).[5b,19a]

Scheme 2. General Scheme of Oxidative Mannich Reaction with TBHP

Dirhodium caprolactamate $[Rh_2(cap)_4]$ is a useful catalytic platform for mechanistic comparison of oxidations by TBHP that proceed via transition metal–oxo complexes or *tert*-butylperoxy radicals.[20] Prior publications have shown unequivocally that the sole role of $Rh_2(cap)_4$ in reactions with TBHP is to generate a flux of *tert*-butylperoxy radicals in both allylic oxidation and the peroxidation of phenols (Scheme 3).[20] Comparison of the characteristics of $Rh_2(cap)_4$-catalyzed TBHP oxidations with those of with other catalysts can overcome uncertainty in their mechanistic descriptions.

Scheme 3. Mechanism of $Rh_2(cap)_4$-Catalyzed Conversion of *tert*-Butyl Hydroperoxide to the *tert*-Butylperoxy Radicals



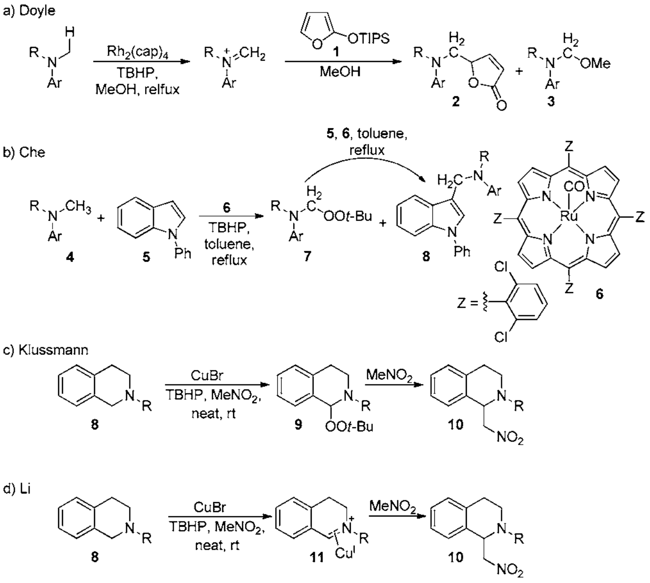
In this article we present a comprehensive mechanistic investigations of the $Rh_2(cap)_4$-catalyzed oxidative Mannich reaction with TBHP. The role of the transition metal–oxo complexes in *N*,*N*-dialkylaniline oxidation and formation of possible intermediates in nucleophilic and non-nucleophilic media is assessed. The generality of the proposed mechanism is evaluated in a comparative study of Rh, Ru, Cu, Fe, and Co complexes.

■ RESULTS AND DISCUSSION

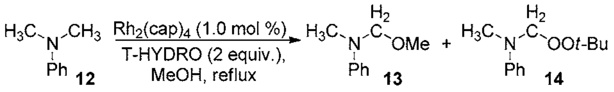
N,*N*-Dimethylanilines have higher oxidation potentials[21] than similar tetrahydroisoquinolines.[22] The selection of *N*,*N*-dimethylanilines[5b,19a,23] for mechanistic investigations of the $Rh_2(cap)_4$-catalyzed oxidative Mannich reaction with 70% aqueous solution of *tert*-butyl hydroperoxide (T-HYDRO) not only allows comparison with other mechanistic models that have been proposed for other metal-catalyzed oxidations[2c,5b,6a,19a] but the results obtained can be extrapolated to the more reactive tetra-isoquinolines.

Iminium Ions in the Mannich Reaction. From investigations of possible intermediates leading to the Mannich adduct (Scheme 2)[3,5b,6a] relating to the mechanism of catalytic *N*,*N*-dialkylaniline oxidations by TBHP,[5b,19a] Doyle postulated a competitive capture of an iminium ion by the solvent methanol and siloxyfuran **1** in the oxidative Mannich reaction (Scheme 4a).[3] Che found that peroxy hemiaminal **7** formed in the Ru-catalyzed oxidative Mannich reaction performed in toluene is converted to **8** under the reaction conditions (Scheme 4b).[5b] However, no kinetic data were provided to answer whether **7** is an intermediate or a side-product of a competing pathway that can be converted to **8** under the reaction conditions. Klussmann showed that the rate of formation of **10** in the oxidative Mannich reaction has a sigmoidal shape which indicates that peroxy hemiaminal **9** is a direct precursor of **10** (Scheme 4c).[6a] Klussmann coined the term "iminium ion reservoir" to describe the role of peroxy hemiaminal **10**. Li, on the other hand, postulated[2c] the intermediacy of copper-bound iminium ion **11** (Scheme 4d) although no experimental evidence for formation of **11** was provided. The latter proposal was subsequently adopted by several groups for the iron(III)[7b] and copper(I)[6f]-catalyzed oxidative Mannich reaction.

Scheme 4. Proposed Intermediates of in the Oxidative Mannich Reaction with TBHP



We began investigations of the oxidative Mannich reaction by focusing on understanding the role of intermediates in the Mannich reaction (Scheme 2). The conditions previously developed in our lab[3] were adopted for the oxidative Mannich reaction. We have reported the exclusive formation of **13** in the *N*,*N*-dimethylaniline oxidation by T-HYDRO in methanol in the absence of nucleophile and that **13** exists in an equilibrium between **14** (eq 1),[3] and we have selected the same conditions to obtain data on the rate of exchange between **13** and **14**.



(1)

Oxidation of *N*,*N*-dimethylaniline by T-HYDRO in methanol catalyzed by $Rh_2(cap)_4$ furnishes **13** and **14**.[3] As previously reported,[3] **13** is formed as a major product after 5 min, and the ratio of **13** to **14** is *12.0* (Figure 1). It is of note that the ratio of methanol and TBHP in this reaction mixture is *12.4*. Thus, nearly identical ratios of **13**-to-**14** and methanol-to-TBHP suggest that iminium ion **15** preferentially reacts with the nucleophilic solvent, methanol (eq 2). Additionally, the larger amount of **13** at the initial stages of **12** oxidation by TBHP is not consistent with reaction between the α-amino radical and the *tert*-butylperoxy radical leading to **14** in the last step of the $Rh_2(cap)_4$-catalyzed *N*,*N*-dialkylaniline oxidation by T-HYDRO.

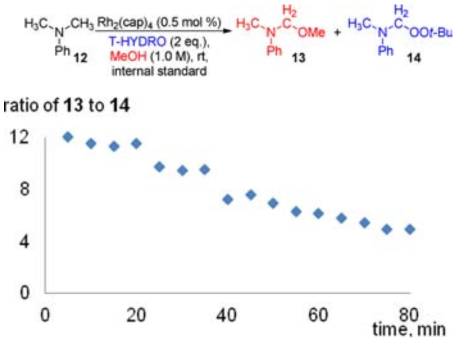
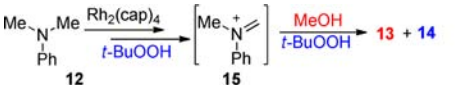


Figure 1. Change in the ratio of **13**-to-**14** with time in the oxidation of *N*,*N*-dimethylaniline by 2 equiv of T-HYDRO catalyzed by 0.5 mol % of $Rh_2(cap)_4$.



(2)

The ratio of **13**-to-**14** decreased from 12.0 to 4.9 over 80 min (Figure 1), suggesting that an equilibrium between **13** and **14** favoring **14**[3] could play a role in a variable ratio. To evaluate this hypothesis, peroxy hemiaminal **14** was prepared,[3] and its conversion to **13** in methanol at 0.14 M concentration occurred on the time scale of the $Rh_2(cap)_4$-catalyzed *N*,*N*-dimethylaniline oxidation by T-HYDRO (Figure 2). Identical ratios of **13** and **14** measured after 8 and 24 h gave the equilibrium constant of 11.7 that favors **14** (eq 3). Thus, the data confirm the proposal[3] that the thermodynamically less stable methoxy hemiaminal **13** is formed under kinetic control at the initial stage and serves as a resting state for the iminium ion **15** that is an immediate result of oxidation of **12**.

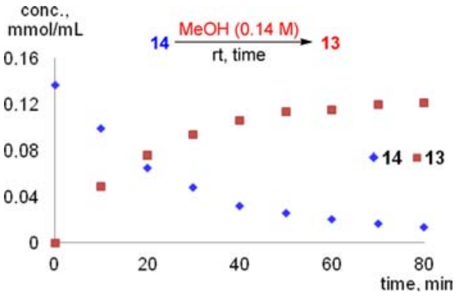
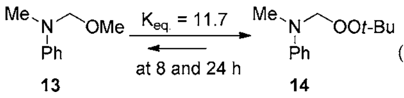
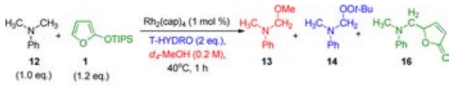


Figure 2. Kinetics of equilibration of **14** to **13** in 0.14 M solution of methanol at room temperature.

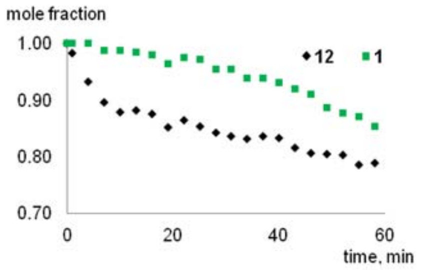


(3)

Determination of the reactive intermediates for the $Rh_2(cap)_4$-catalyzed *N*,*N*-dimethylaniline oxidation by T-HYDRO raised the question of whether **13** and **14** are side products[2b,c,3,4] or iminium ion reservoirs.[6a] To distinguish the two roles of **13** and **14**, kinetic data were obtained for the $Rh_2(cap)_4$-catalyzed oxidative Mannich reaction in methanol by T-HYDRO of **12** and siloxyfuran **1** at 40 °C. The mechanistic model of Li[2c] suggested that under these conditions **1** should outcompete the less nucleophilic methanol and TBHP to yield **16** without the formation of peroxy or methoxy hemiaminals. However, this hypothesis was not consistent with our experimental data. The initial rate of consumption of **12** was greater than the initial rate of siloxyfuran **1** consumption (Figure 3a). Furthermore, methoxy hemiaminal **13** was the major product at low conversion (Figure 3b). The accumulation of **13** in the reaction mixture at low conversion was followed by a decrease in its concentration. A noticeable rate of formation of **16** is evident only after the concentration of **13** reaches its maximum (Figure 3b). Interestingly, the concentration of **14** remained lower than the concentration of **16**, indicating the preferential trapping of the iminium ion formed from **13** by siloxyfuran **1** and not by TBHP.



a) Rate of consumption of 12 and 1.



b) Rate of formation of 13, 14, and 16.

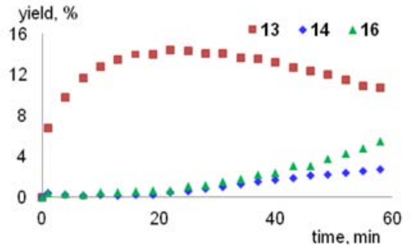
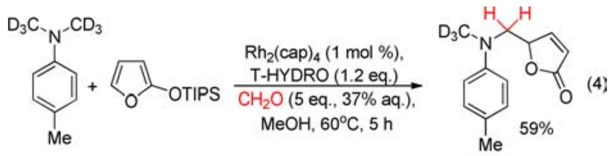


Figure 3. Kinetics of the $Rh_2(cap)_4$-catalyzed oxidative Mannich reaction of *N*,*N*-dimethylaniline and siloxyfuran **1** by T-HYDRO in methanol at 40 °C.

The role of **13** and **14** as intermediates was evaluated with an isotope-scrambling experiment. The $Rh_2(cap)_4$-catalyzed oxidative Mannich reaction of d_6-**17** and **1** was conducted in the presence of an excess of 37% aqueous solution of formaldehyde (eq 4). The isolated product lacked any deuterium labeling in

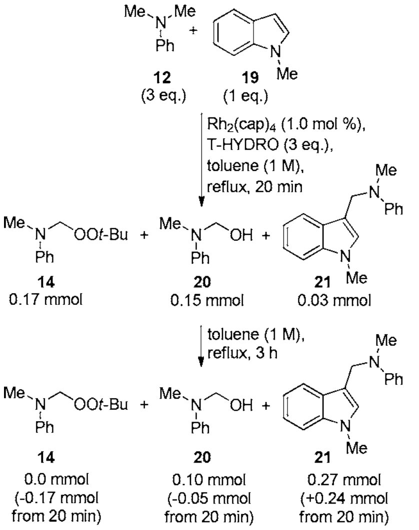


d$_6$-**17** **1** *d*$_3$-**18**

its methylene group, and this result unequivocally showed that hemiaminal equilibria are faster than iminium ion trapping by **1**. In other words, formation of the Mannich adduct of iminium ion and **1** is a thermodynamic sink for the oxidative Mannich reaction.

Having proposed a mechanistic model of the oxidative Mannich reaction with T-HYDRO in a nucleophilic solvent, the oxidative Mannich reaction by T-HYDRO in non-nucleophilic toluene was investigated. Che showed the viability of these conditions for the Ru-catalyzed oxidative Mannich reaction of *N,N*-dialkylanilines with indoles.[5b] However, according to the Che proposal, non-nucleophilic media should facilitate the capture of an iminium ion by indoles in the oxidation of *N,N*-dialkylanilines. When the oxidative Mannich reaction of **12** and *N*-methylindole (**19**) using $Rh_2(cap)_4$ as a catalyst was performed in toluene intermediates **14** and **20** were preferentially formed initially (Scheme 5), but continuation of this reaction for 3 h quantitatively converted **14** and **20** into the final adduct **21** (Scheme 5). Thus, hemiaminals are the precursors to the Mannich adducts even in non-nucleophilic media.

Scheme 5. $Rh_2(cap)_4$-Catalyzed Oxidative Mannich Reaction of 12 and 19 in Toluene

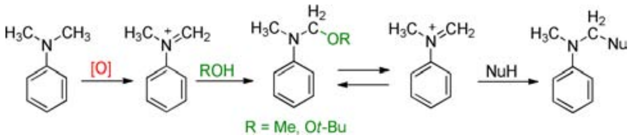


In summary, the transition metal-catalyzed oxidation of *N,N*-dimethylanilines by T-HYDRO forms an iminium ion that is initially trapped by either nucleophilic solvent or TBHP. The resulting methoxy and peroxy hemiaminals exist in the thermal equilibrium with iminium ions that irreversibly form Mannich adducts with a carbon nucleophile present in the reaction (Scheme 6). It is unlikely that $Rh_2(cap)_4$, a weak Lewis acid,[24] can catalyze the formation of iminium ions from oxidation intermediates in the presence of large amounts of water.

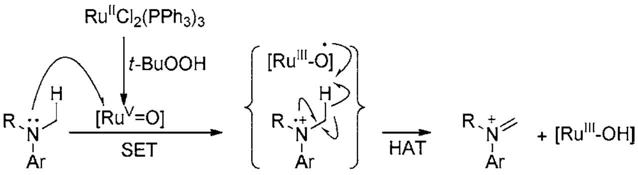
Oxidative Mechanism of the Transition Metal-Catalyzed Oxidation of *N,N*-Dialkylanilines by T-HYDRO.

Systematic mechanistic studies of catalyzed *N,N*-dialkylaniline oxidations by TBHP have been reported.[5b,19a] Murahashi[19a] used primary isotope effects values of 1.64 and 3.53 and the -0.84 ρ value in the Hammett linear free-energy relationship (LFER) obtained for demethylation of *N,N*-dimethylanilines by TBHP catalyzed by $RuCl_2(PPh_3)_3$ to adopt a mechanism postulated[25] for cytochrome P450-catalyzed demethylation of *N,N*-dimethylanilines by O_2. According to this proposal the ruthenium−oxo complex formed upon reaction of $RuCl_2(PPh_3)_3$ and TBHP abstracts two electrons and a proton in a series of single electron transfers (SET) and hydrogen atom transfer (HAT) steps (Scheme 7).[19a] Recently, Che obtained a Hammett ρ value of -1.09 and primary isotope effect values of 1.2−3.8 in the oxidative Mannich reaction of *N,N*-dimethylanilines and indoles catalyzed by **6**.[5b] Furthermore, the ruthenium porphyrin oxo complex of **6** was found to be a competent stoichiometric oxidant, and **6** catalyzed the oxidation of *N,N*-dimethylaniline by TBHP and by 2,6-dichloropyridine *N*-oxide. Li proposed two possible nonradical mechanisms of copper(I)-catalyzed *N,N*-dialkylaniline oxidations by TBHP involving copper−oxo complexes (Scheme 8a and 8b). A decrease in the isolated yield of **23** from 84% to 70%

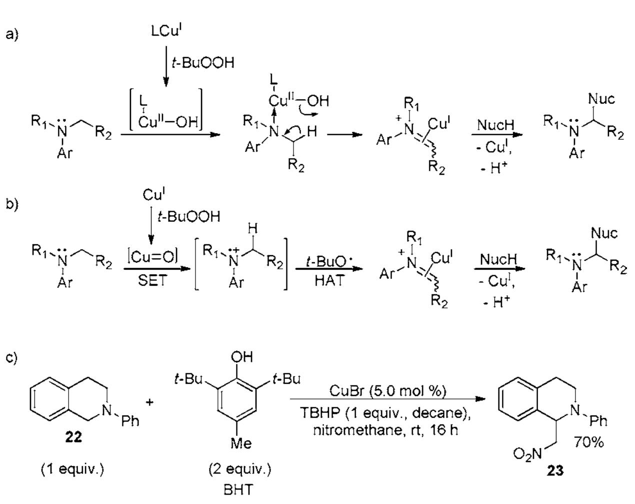
Scheme 6. Summary of Conversion of an Iminium Ion Formed in the Oxidation of *N,N*-Dialkylanilines to the Mannich Adduct



Scheme 7. Proposed Mechanism of $RuCl_2(PPh_3)_3$-Catalyzed *N,N*-Dialkylaniline Oxidation by TBHP

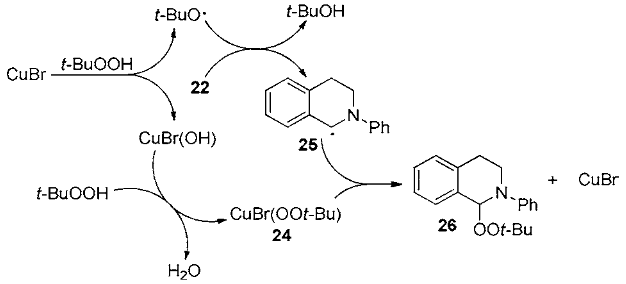


Scheme 8. Experiment with Radical Scavenger and Two Mechanisms Proposed by Li for the CuBr-Catalyzed Oxidative Mannich Reaction with TBHP As the Oxidant



in the copper(I)-catalyzed oxidative Mannich reaction performed in the presence of the radical trap BHT (Scheme 8c) was used by Li to support nonradical pathways. However, Huang[6c] and Klussmann[6a] stated that, although BHT has a detrimental effect on the oxidative Mannich reaction, the copper(I)-catalyzed oxidation of **22** has radical character. Referencing the work of Minisci[26] and Doyle,[20b] Klussmann proposed hydrogen atom abstraction from the benzylic position of **22** by the *tert*-butoxy radical followed by *tert*-butylperoxy group transfer from **24** to α-amino radical **25** (Scheme 9) to account for the primary isotope effect value of 3.4 and deceleration of the Mannich reaction of **22** and nitromethane in the presence of BHT.[6a]

Scheme 9. Mechanism proposed by Klussmann for CuBr-catalyzed oxidation of tetrahydroisoquinoline by TBHP



Previous studies of oxidative Mannich reactions catalyzed by transition metal compounds have led to divergent mechanistic proposals: (1) rate-limiting steps SET from *N,N*-dialkylaniline to a ruthenium–oxo complex in ruthenium-catalyzed reactions (Scheme 7),[5b,19a] (2) hydrogen atom transfer (HAT) from the 1-position of 4-aryl-tetrahydroisoquinoline by the *tert*-butoxy radical in copper(I)-catalyzed reactions (Scheme 9),[6a] and (3) oxidation of copper followed by elimination of water in copper(I)-catalyzed reactions (a and b of Scheme 8).[2c,6f] Hence, the initial focus of our mechanistic investigation was to discern the electron demand of the rate-determining step. The ρ value of the Hammett analysis close to zero would suggest HAT or oxidation of a metal center by TBHP as the rate-determining step; a positive ρ value would indicate elimination of water as the rate-determining step; finally, a negative ρ would be consistent with a SET step.[23]

The Hammett LFER analysis was conducted for a series of competition experiments of the $Rh_2(cap)_4$-catalyzed oxidations by T-HYDRO of 4-methoxy- (**27**), 4-methyl- (**17**), 4-fluoro- (**28**), 4-bromo- (**29**), 4-ethylcarboxylato- (**30**), 4-trifluoromethyl- (**31**), and 4-cyano-*N,N*-dimethylanilines (**32**) against **12**. The initial competition experiments were performed under the conditions used for monitoring of oxidation of **12** by T-HYDRO in methanol (0.5 mol % of $Rh_2(cap)_4$, 2 equiv of T-HYDRO, 40 °C, methanol as a solvent).

The correlation of natural logarithms of the relative initial rates was higher with σ^+ Hammett parameters (R^2 = 0.975) than with σ_{para} Hammett parameters (R^2 = 0.909). The linear correlation from 4-methoxy- to 4-cyano- groups was observed, indicating that there was no change in the nature of the rate-determining step for the studied range of 4-substituents (Figure 4). Additionally, the measured ρ value of −2.638 was consistent with SET in the rate-determining step.[19a,22,23]

The Hammett analysis was consistent with the SET mechanism but did not provide information regarding the nature of the single electron acceptor. The higher oxidation potential of the *tert*-butylperoxy radical (0.52 V vs SCE)[27] relative to the *tert*-butoxy radical (−0.30 V vs SCE)[28] and $[Rh_2(cap)_4]^+$ (11 mV vs SCE)[29] defines the peroxy radical as the thermodynamically preferred oxidant.

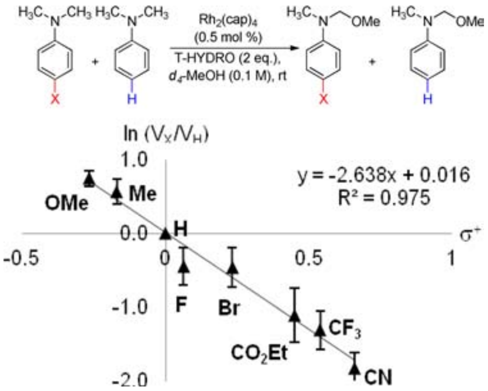
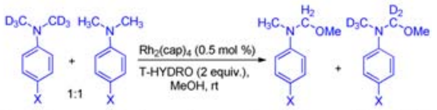


Figure 4. Hammett LFER analysis of the $Rh_2(cap)_4$-catalyzed oxidations by T-HYDRO of 4-substituted *N,N*-dimethylanilines at room temperature in methanol. Each reaction rate was measured at least three times, and the error margins were calculated as a standard deviation of the reaction rates.

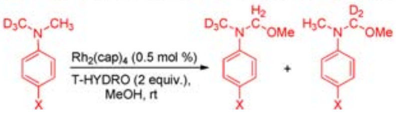
The nature of the C–H cleavage step was investigated by kinetic and product isotope effects (KIE and PIE, respectively). Kinetic isotope effects for $Rh_2(cap)_4$-catalyzed oxidation by T-HYDRO were determined from the deuteration level of the methylene and methyl groups of the corresponding methoxy hemiaminals in oxidation of 1:1 mixtures of *N,N*-dimethylanilines and *N,N*-bis(trideuteromethyl)anilines (Scheme 10a).

Scheme 10. KIE and PIE of the $Rh_2(cap)_4$-Catalyzed Oxidations of 4-Substituted *N,N*-Dimethylanilines by T-HYDRO

a) Reaction used to determine kinetic isotope effect (KIE).



b) Reaction used to determine product isotope effect (PIE).



Product isotope effects were determined from the ratio of integrated absorptions in ^{1}H NMR spectra that corresponded to methylene and methyl groups of methoxy hemiaminals in oxidation of *N*-methyl-*N*-(trideuteromethyl)anilines (Scheme 10b). Each measurement of KIE and PIE was repeated at least three times, and the average value along with error margins are reported. The measured values of KIE and PIE values remained on the level of 1.61 ± 0.08 and 2.39 ± 0.24, respectively, from **17** to **29** (Figure 5). The KIE values start to increase for the **30** and approach PIE values for **32**.

The characteristic gap between KIE and PIE values, previously reported by Watanabe[23] for the enzymatic demethylations of *N,N*-dimethylanilines catalyzed by cytochrome P450, was also observed for $Rh_2(cap)_4$-catalyzed oxidations of 4-substituted *N,N*-dimethylanilines by T-HYDRO. According to the steady-state kinetic model of

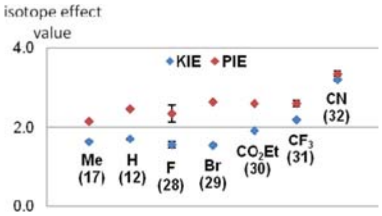
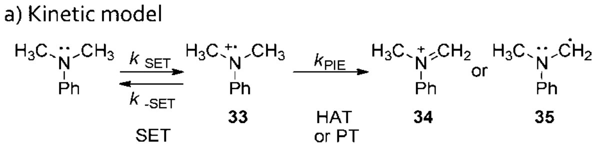


Figure 5. KIE and PIE measured for the $Rh_2(cap)_4$-catalyzed oxidative Mannich reaction by T-HYDRO. Each measurement was repeated at least three times, and the error margins were calculated as a standard deviation of the measured isotope effects.

Watanabe,[23] a rate-determining forward SET forms a constant concentration of cation radicals that are consumed either by a competing backward SET or by an irreversible C−H bond cleavage (Scheme 11a). The relationship between KIE and PIE was derived by Watanabe[23] from this kinetic model and is presented in Scheme 11b. The PIE value depends only on the C−H bond cleavage step and is determined by its late transition state. On the other hand, KIE values additionally depend on the backward SET (k_{-SET}). Thus, KIE values approach 1.0 if the rate of backward SET is slower than the rate of the irreversible C−H cleavage ($k_{PIE} > k_{-SET}$). Alternatively, a higher KIE value is a result of a higher rate of backward SET relative to the rate of the irreversible step ($k_{PIE} < k_{-SET}$). In the data from Figure 5, oxidation of **32** is the limiting case of $k_{-SET} \gg k_{PIE}$ where the KIE value (3.20) approached PIE value (3.26).

Scheme 11. Kinetic Model of the $Rh_2(cap)_4$-Catalyzed Oxidations of 4-Substituted *N,N*-Dimethylanilines by T-HYDRO



b) Equation for kinetic and product isotope effects

$$\frac{k^H_{KIE}}{k^D_{KIE}} = \frac{k^H_{PIE}}{k^D_{PIE}} \times \frac{(k_{-SET} + k^D_{PIE})}{(k_{-SET} + k^H_{PIE})}$$

KIE and PIE values measured for the $Rh_2(cap)_4$-catalyzed oxidation of 4-substituted *N,N*-dimethylanilines by T-HYDRO are two independent experimental measurements that offer an answer to the question of whether $RuCl_2(PPh_3)_3$, CuBr, $FeCl_3$, and $Co(OAc)_2$ form oxo complexes that act as sole oxidants under the same conditions. *N,N*-Dimethylanilines **17** (σ^+ = −0.311), **12** (σ^+ = 0.00), and **29** (σ^+ = 0.150) were chosen to represent substrates of different electronic properties. The KIE and PIE values were determined in the same fashion as KIE and PIE of the $Rh_2(cap)_4$-catalyzed oxidations (Scheme 10). Thus, the measurements of KIE and PIE values for three different substrates totals up to six independent measurements of transition metal salt-catalyzed oxidation of *N,N*-dimethylanilines by T-HYDRO.

The comparison of KIE (Table 1) and PIE (Table 2) values shows identical trends as a function of *N,N*-dimethylaniline substituent. The identical isotope effects in each table are above the dotted line (Tables 1 and 2). The KIE and PIE numbers determined for oxidations of three *N,N*-dimethylanilines by T-HYDRO catalyzed by $Rh_2(cap)_4$ and $RuCl_3$ show identical values within experimental error that suggests the same operating mechanism for $RuCl_3$ as for $Rh_2(cap)_4$. Thus, the role of $Rh_2(cap)_4$ and $RuCl_3$ is to convert TBHP into *tert*-butylperoxy radicals according to the mechanism described in Scheme 3. The copper(I) bromide-catalyzed oxidation shows values identical to those determined for $Rh_2(cap)_4$-catalyzed oxidation of **12** and **17** but not that of **29**, which shows slightly higher values. Iron(III) and cobalt(II) salts-catalyzed oxidations have consistently higher KIE and PIE values than those measured for the $Rh_2(cap)_4$-catalyzed oxidation.

The storage of methanol solutions opened to air of **12** and d_6-**12** in the presence of $Co(OAc)_2$ and **17** and d_6-**17** in the presence of $RuCl_3$ (Table 3, entries 6–7) offered a clue to the explanation of the observed deviations of KIE and PIE for CuBr, $FeCl_3$, and $Co(OAc)_2$. In these reactions *N,N*-dimethylanilines underwent partial oxidation by dioxygen in air; in the presence of $RuCl_3$ and $Co(OAc)_2$, KIE values were 2.09 ± 0.11 and 3.36 ± 0.33, respectively, from reactions performed overnight at room temperature. Noteworthy, the value measured for the $Co(OAc)_2$-catalyzed *N,N*-dimethylaniline oxidation by T-HYDRO was between the KIE values of *tert*-butylperoxy radical oxidative pathway (entry 1) and the dioxygen oxidative pathway (entry 6). This fact indicated that the values measured for CuBr, $FeCl_3$, and $Co(OAc)_2$-catalyzed oxidations of 4-substituted *N,N*-dimethyl-anilines could be a combination of the competing *tert*-butylperoxy radical oxidative pathway and a dioxygen oxidative pathway. If this is the case, bubbling N_2 through the reaction mixture would decrease the contribution from the of dioxygen oxidative pathway by removal of most of the dioxygen originating from air and from dimerization of the *tert*-butylperoxy radicals (eq 5). Indeed, N_2 flow decreased KIE values for Co-catalyzed oxidation of **12** to 2.17 ± 0.05 and CuBr-catalyzed oxidation of **29** to 1.58 ± 0.06. Consequently, dioxygen interference was confirmed for the Cu(I), Fe(III), and Co(II) salts-catalyzed oxidations of 4-substituted *N,N*-dimethylanilines by T-

Table 1. Kinetic Isotope Effects of the Transition Metal Salt-Catalyzed Oxidations of 4-Substituted *N,N*-Dimethylanilines by T-HYDRO

			KIE		
entry	catalyst	catalyst loading, %	4-Me (**17**)	4-H (**12**)	4-Br (**29**)
1	$Rh_2(cap)_4$	1.0	1.63 ± 0.03[a]	1.71 ± 0.08	1.54 ± 0.02
2	$RuCl_3$	1.0	1.69 ± 0.16	1.66 ± 0.18	1.55 ± 0.06
3	CuBr	5.0	1.58 ± 0.07	1.79 ± 0.01	1.71 ± 0.15
4	$FeCl_3$	2.0	1.91 ± 0.01	1.95 ± 0.02	1.67 ± 0.02
5	$Co(OAc)_2$	10.0	1.94 ± 0.03	2.42 ± 0.16	1.69 ± 0.02

[a] Error margins are calculated as a standard deviation of measured kinetic isotope effects.

Table 2. Product Isotope Effects of the Transition Metal Salt-Catalyzed Oxidations of 4-Substituted *N*,*N*-Dimethylanilines by T-HYDRO

			PIE		
entry	catalyst	catalyst loading, %	4-Me (**17**)	4-H (**12**)	4-Br (**29**)
1	$Rh_2(cap)_4$	1.0	2.15 ± 0.02[a]	2.46 ± 0.22	2.63 ± 0.01
2	$RuCl_3$	1.0	2.20 ± 0.06	2.37 ± 0.06	2.55 ± 0.08
3	CuBr	5.0	2.21 ± 0.10	2.36 ± 0.04	3.04 ± 0.14
4	$FeCl_3$	2.0	2.46 ± 0.07	3.16 ± 0.20	2.62 ± 0.07
5	$Co(OAc)_2$	10.0	4.84 ± 0.16	4.42 ± 0.23	2.93 ± 0.12

[a] Error margins are calculated as a standard deviation of measured kinetic isotope effects.

Table 3. Kinetic Isotope Effects of the Transition Metal Salt-Catalyzed Oxidations of 4-Substituted *N*,*N*-Dimethylanilines by T-HYDRO with and without N_2 Flow and by O_2

					KIE		
entry	catalyst	catalyst loading, %	oxidant	N_2 flow	4-Me (**17**)	4-H (**12**)	4-Br (**29**)
1	$RuCl_3$	1.0	T-HYDRO	no	1.69 ± 0.16[a]	1.66 ± 0.18	1.55 ± 0.06
2	CuBr	5.0	T-HYDRO	no	1.58 ± 0.07	1.79 ± 0.01	1.71 ± 0.15
3	$Co(OAc)_2$	10.0	T-HYDRO	no	1.94 ± 0.03	2.42 ± 0.16	1.69 ± 0.02
4	CuBr	5.0	T-HYDRO	yes	nd[b]	nd	**1.58 ± 0.06**
5	$Co(OAc)_2$	10.0	T-HYDRO	yes	nd	**2.17 ± 0.05**	nd
6	$RuCl_3$	1.0	O_2	no	nd	2.09 ± 0.11	nd
7	$Co(OAc)_2$	10.0	O_2	no	3.36 ± 0.33	nd	nd

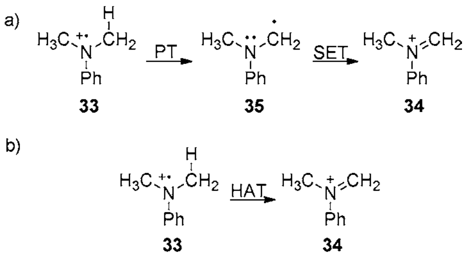
[a] Error margins are calculated as a standard deviation of measured kinetic isotope effects. [b] nd - not determined.

HYDRO. Furthermore, the KIE value of 1.58 ± 0.06 is identical within experimental error to the KIE values obtained for $Rh_2(cap)_4$, $RuCl_3$, and CuBr, thus indicating *the same operating mechanism for these transition metal catalysts.*

$$t\text{-BuOO}\cdot + \cdot\text{OO}t\text{-Bu} \rightarrow t\text{-BuOO}t\text{-Bu} + O_2 \qquad (5)$$

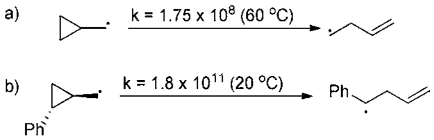
The two possible pathways for the irreversible C−H cleavage step include proton transfer (PT) forming an α-amino radical **35** (Scheme 12a) and hydrogen atom transfer (HAT) leading directly to the iminium ion **34** (Scheme 12b). Radical trap substituents were employed to test the possible formation of a transient α-amino radical. These substituents do not undergo ring-opening in the presence of adjacent onium cations,[30] but they show high rates of intramolecular ring-opening when they are adjacent to a carbon radical center (Scheme 13).[31]

Scheme 12. Possible Mechanisms of the Irreversible C−H Cleavage in Transition Metal Salt-Catalyzed Oxidation of *N*,*N*-Dimethylanilines

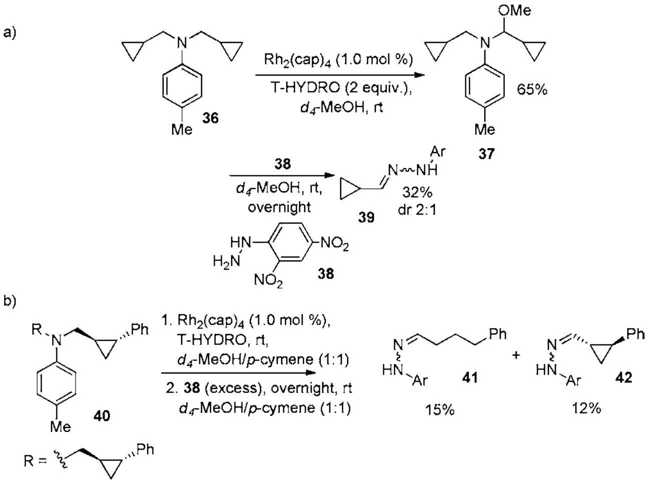


Conditions developed in our lab[3] for the oxidative Mannich reaction were chosen for the radical trap experiments (Scheme 14). The $Rh_2(cap)_4$-catalyzed oxidation by T-HYDRO of **36** formed its methoxy hemiaminal in 65% yield without cyclopropane ring-opening (Scheme 14a) that was seemingly consistent with either the HAT step (Scheme 12b) or with a SET that was much faster than cyclopropane ring-opening. The oxidation of **40** that had a more sensitive radical trap substituent (Scheme 14b) led to decomposition of *N*,*N*-dialkylaniline with the formation of unknown products with high-molecular weight. *p*-Cymene was added as a hydrogen atom donor to minimize possible radical side reactions of the resulting benzyl radical (Scheme 13b). Indeed, the oxidation of **40** in 1:1 mixture of methanol and *p*-cymene furnished a number of absorptions corresponding to aldehydes according

Scheme 13. Rate of Cyclopropane-Opening Rates of Radical Trap Substituents

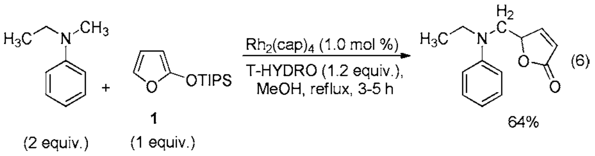


Scheme 14. $Rh_2(cap)_4$-Catalyzed Oxidations by T-HYDRO of *N*,*N*-Dialkylanilines Bearing Radical Trap Substituents



to the ^{1}H NMR spectroscopy of the reaction mixture. Free 4-phenylbutanal was trapped with 2,4-dinitrophenylhydrazine (**38**) and was isolated in 15% yield as **41** along 12% of hydrazone **42**, suggesting that the pathway described in Scheme 12a is operative with a very fast SET that follows the PT step which occurs in competition with cyclopropane ring-opening of the cyclopropylcarbinyl radical generated from **40**. However, an alternate interpretation that the two pathways that were outlined in a and b of Scheme 12 are competitive cannot be excluded.

Opening of the cyclopropane ring is consistent with the formation of a transient α-amino radical (Scheme 12a) in the transition metal salt-catalyzed *N*,*N*-dialkylaniline oxidation by T-HYDRO. Proton transfer should occur at the most acidic carbon of unsymmetrical *N*,*N*-dialkylaniline cation radicals. According to the report of Albini, Falvey, and Mariano,[32] the acidity of carbon adjacent to nitrogen decreases in order Me,Me > Me,H > H,H > H,CHCH$_2$ > H,Ph > H, CCH. Thus, *irreversible PT offers the first explanation of the observed regioselectivity of the oxidation of unsymmetrical N,N-dialkylanilines by T-HYDRO.*[3] Steric factors may also play a role in regioselectivity because the oxidative Mannich reaction of *N*-methyl-*N*-ethylaniline and siloxyfuran **1** occurs only at the *N*-methyl group (eq 6) although the acidity ratio suggests 3:1 regioselectivity.

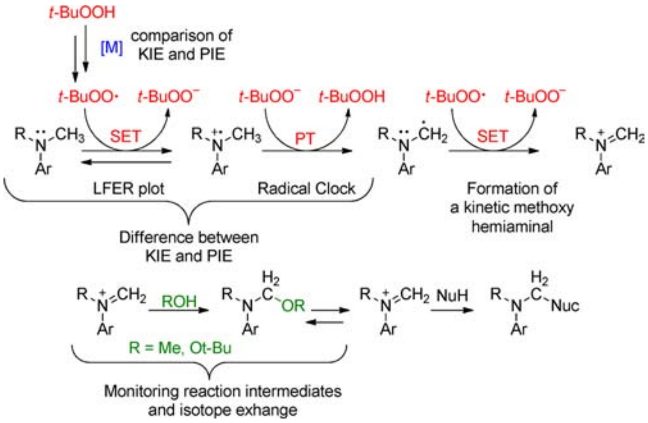


CONCLUSION

In conclusion, the mechanistic models of Murahashi,[19a] Che,[5b] Li,[2c] and Klussmann[6a] of the transition metal salt-catalyzed oxidative Mannich reaction of *N*,*N*-dialkylaniline with TBHP were evaluated, and a new mechanistic scheme is proposed (Scheme 15).

A combination of LFER analysis and the oxidation potentials of [Rh$_2$(cap)$_4$] and the *tert*-butylperoxy radical suggests that, unlike the Li[2c] and Klussmann[6a] proposals, *N*,*N*-dialkylanilines undergo SET to *tert*-butylperoxy radicals, the thermodynamically preferred oxidant, in the rate-determining step that is uniform between 4-methoxy- and 4-cyano-substituted *N*,*N*-dimethylanilines. The difference between KIE and PIE of *N*,*N*-dimethylaniline oxidations by THBP is explained by the competition between backward SET and irreversible proton transfer after the rate-determining SET. The formation of a transient α-amino radical is consistent with the cyclopropane ring-opening in the radical trap experiments. No experimental evidence of kinetic competence of ruthenium−oxo complex was found in the RuCl$_3$-catalyzed *N*,*N*-dialkylaniline oxidation by TBHP. Unlike earlier models involving ruthenium−[5b,19a] and copper−oxo complexes[2c], the general role of Rh$_2$(cap)$_4$, RuCl$_3$, CuBr, FeCl$_3$, and Co(OAc)$_2$ in converting TBHP to the *tert*-butylperoxy radical is consistent with their identical KIE and PIE values for oxidations of **12**, **17**, and **29** by T-HYDRO in methanol and the decrease of KIE and PIE values of CuBr and Co(OAc)$_2$-catalyzed oxidations with N$_2$ flow. The role of hemiaminals as precursors to Mannich adducts and not side products[3] was determined by monitoring the initial stage of the Rh$_2$(cap)$_4$-catalyzed oxidative Mannich reaction of **12** and **1** in methanol and **12** and *N*-methylindole in toluene.

Scheme 15. Summary of Mechanistic Investigations of Transition Metal-Catalyzed Oxidative Mannich Reaction with TBHP as an Oxidant



ASSOCIATED CONTENT

Supporting Information

Experimental procedures and product characterization are included in Supporting Information. 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) Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. *Chem. Rev.* **2011**, *111*, 3076. (b) Toure, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439.

(2) (a) Murahashi, S.-i.; Komiya, N. Ruthenium-catalyzed oxidation for organic synthesis. In *Modern Oxidation Methods*, 2nd ed.; Baeckvall, J.-E., Ed. Wiley-VCH: Weinheim, Germany, 2010; pp 241; (b) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (c) Li, Z.; Bohle, D. S.; Li, C.-J. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 8928. (d) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1045.

(3) Catino, A. J.; Nichols, J. M.; Nettles, B. J.; Doyle, M. P. *J. Am. Chem. Soc.* **2006**, *128*, 5648.

(4) (a) Murahashi, S.-I.; Nakae, T.; Terai, H.; Komiya, N. *J. Am. Chem. Soc.* **2008**, *130*, 11005. (b) Jones, K. M.; Klussmann, M. *Synlett* **2012**, *23*, 159.

(5) (a) Rueping, M.; Vila, C.; Koenigs, R. M.; Poscharny, K.; Fabry, D. C. *Chem. Commun.* **2011**, *47*, 2360. (b) Wang, M.-Z.; Zhou, C.-Y.; Wong, M.-K.; Che, C.-M. *Chem.—Eur. J.* **2010**, *16*, 5723. (c) Murahashi, S.; Komiya, N.; Terai, H.; Nakae, T. *J. Am. Chem. Soc.* **2003**, *125*, 15312. (d) Condie, A. G.; Gonzalez-Gomez, J. C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2010**, *132*, 1464.

(6) (a) Boess, E.; Schmitz, C.; Klussmann, M. *J. Am. Chem. Soc.* **2012**, *134*, 5317. (b) Boess, E.; Sureshkumar, D.; Sud, A.; Wirtz, C.; Fares,

C.; Klussmann, M. *J. Am. Chem. Soc.* **2011**, *133*, 8106. (c) Yang, F.; Li, J.; Xie, J.; Huang, Z.-Z. *Org. Lett.* **2010**, *12*, 5214. (d) Zhao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 7075. (e) Xie, J.; Huang, Z.-Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 10181. (f) Ghobrial, M.; Schnuerch, M.; Mihovilovic, M. D. *J. Org. Chem.* **2011**, *76*, 8781.

(7) (a) Han, W.; Ofial, A. R. *Chem. Commun.* **2009**, 5024. (b) Kumaraswamy, G.; Murthy, A. N.; Pitchaiah, A. *J. Org. Chem.* **2010**, *75*, 3916. (c) Liu, P.; Zhou, C.-Y.; Xiang, S.; Che, C.-M. *Chem. Commun.* **2010**, *46*, 2739.

(8) Alagiri, K.; Prabhu, K. R. *Org. Biomol. Chem.* **2012**, *10*, 835.

(9) (a) Sud, A.; Sureshkumar, D.; Klussmann, M. *Chem. Commun.* **2009**, 3169. (b) Singhal, S.; Jain, S. L.; Sain, B. *Chem. Commun.* **2009**, 2371.

(10) Volla, C. M. R.; Vogel, P. *Org. Lett.* **2009**, *11*, 1701.

(11) (a) Sureshkumar, D.; Sud, A.; Klussmann, M. *Synlett* **2009**, 1558. (b) Chu, L.; Zhang, X.; Qing, F.-L. *Org. Lett.* **2009**, *11*, 2197.

(12) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 6968.

(13) Murata, S.; Teramoto, K.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1297.

(14) Shen, Y.; Li, M.; Wang, S.; Zhan, T.; Tan, Z.; Guo, C.-C. *Chem. Commun.* **2009**, 953.

(15) (a) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 3672. (b) Basle, O.; Li, C.-J. *Green Chem.* **2007**, *9*, 1047. (c) Zeng, T.; Song, G.; Moores, A.; Li, C.-J. *Synlett* **2010**, 2002.

(16) Li, Z.; Li, C.-J. *Eur. J. Org. Chem.* **2005**, 3173.

(17) Ohta, M.; Quick, M. P.; Yamaguchi, J.; Wuensch, B.; Itami, K. *Chem.—Asian J.* **2009**, *4*, 1416.

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

(19) (a) Murahashi, S.; Naota, T.; Yonemura, K. *J. Am. Chem. Soc.* **1988**, *110*, 8256. (b) Zhang, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Org. Lett.* **2007**, *9*, 3813. (c) Basle, O.; Li, C.-J. *Chem. Commun.* **2009**, 4124. (d) Han, W.; Ofial, A. R. *Chem. Commun.* **2009**, 6023.

(20) (a) Ratnikov, M. O.; Farkas, L. E.; McLaughlin, E. C.; Chiou, G.; Choi, H.; El-Khalafy, S. H.; Doyle, M. P. *J. Org. Chem.* **2011**, *76*, 2585. (b) McLaughlin, E. C.; Choi, H.; Wang, K.; Chiou, G.; Doyle, M. P. *J. Org. Chem.* **2009**, *74*, 730.

(21) Dombrowski, G. W.; Dinnocenzo, J. P.; Zielinski, P. A.; Farid, S.; Wosinska, Z. M.; Gould, I. R. *J. Org. Chem.* **2005**, *70*, 3791.

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

(23) Goto, Y.; Watanabe, Y.; Fukuzumi, S.; Jones, J. P.; Dinnocenzo, J. P. *J. Am. Chem. Soc.* **1998**, *120*, 10762.

(24) Xu, X.; Doyle, M. P. *Inorg. Chem.* **2011**, *50*, 7610.

(25) (a) Heimbrook, D. C.; Murray, R. I.; Egeberg, K. D.; Sligar, S. G.; Nee, M. W.; Bruice, T. C. *J. Am. Chem. Soc.* **1984**, *106*, 1514. (b) Burka, L. T.; Guengerich, F. P.; Willard, R. J.; Macdonald, T. L. *J. Am. Chem. Soc.* **1985**, *107*, 2549.

(26) Minisci, F.; Fontana, F.; Araneo, S.; Recupero, F.; Banfi, S.; Quici, S. *J. Am. Chem. Soc.* **1995**, *117*, 226.

(27) Das, T. N.; Dhanasekaran, T.; Alfassi, Z. B.; Neta, P. *J. Phys. Chem. A* **1998**, *102*, 280.

(28) Bietti, M.; Di Labio, G. A.; Lanzalunga, O.; Salamone, M. *J. Org. Chem.* **2010**, *75*, 5875.

(29) Das, K.; Kadish, K. M.; Bear, J. L. *Inorg. Chem.* **1978**, *17*, 930.

(30) Barrett, A. G. M.; Doubleday, W. W.; Tustin, G. J.; White, A. J.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1994**, 1783.

(31) (a) Beckwith, A. L. J.; Bowry, V. W. *J. Org. Chem.* **1989**, *54*, 2681. (b) Newcomb, M.; Manek, M. B. *J. Am. Chem. Soc.* **1990**, *112*, 9662.

(32) Zhang, X.; Yeh, S.-R.; Hong, S.; Freccero, M.; Albini, A.; Falvey, D. E.; Mariano, P. S. *J. Am. Chem. Soc.* **1994**, *116*, 4211.