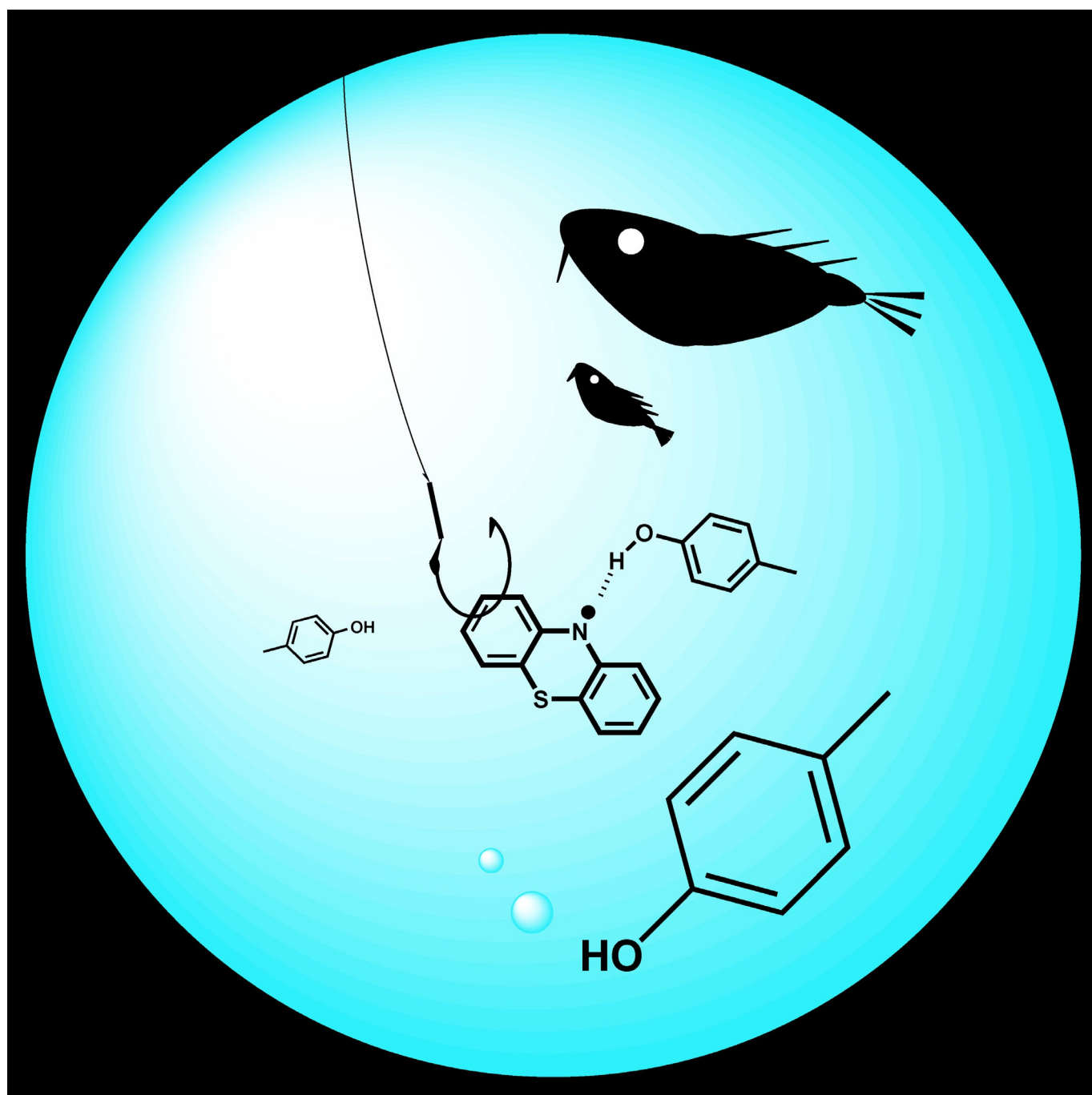


Dehydrogenative Couplings | *Hot Paper*

Mechanism of the Dehydrogenative Phenothiazination of Phenols

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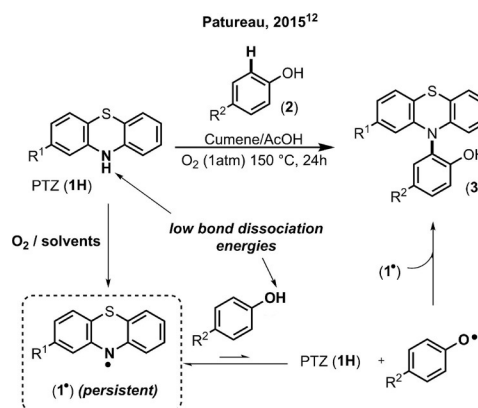
Abstract: The straightforward capture of oxidized phenothiazines with phenols under aerobic conditions represents a unique cross-dehydrogenative C–N bond-forming reaction in terms of operational simplicity. The mechanism of this cross-dehydrogenative N-arylation of phenothiazines with phenols has been the object of debate, particularly regarding the order in which the substrates are oxidized and their potentially radical or cationic nature. Understanding the selective reactivity of phenols for oxidized phenothiazines is

one of the key objectives of this study. The reaction mechanism is investigated in detail by utilizing electron paramagnetic resonance spectroscopy, cyclic voltammetry, radical trap experiments, kinetic isotope effects, and solvent effects. Finally, the key reaction steps are calculated by using density functional theory (DFT) and broken-symmetry open-shell singlet DFT methods to unravel a unique biradical mechanism for the oxidative phenothiazination of phenols.

Introduction

Phenothiazines (PTZs)^[1] are an important class of compounds in the biochemical^[2] and materials sciences.^[3] In particular, those that are N-alkylated and N-arylated are described in numerous essential applications.^[4–8] Arylated PTZs were, for example, recently utilized by Gennaro, Liu, and Matyjaszewski as polymerization photocatalysts,^[4] and they were explored as electroluminescent organic semiconductors for organic light-emitting diode (OLED) devices by Roy, Sonar, and Wadgaonkar,^[5] as blue emitters by Jou and Ghosh,^[6] and importantly as hole-transporting compounds by Grisorio and Abate for harvesting solar energy. Impressively, the latter authors reported a 17.6% energy-harvesting efficiency in a milestone 2017 paper.^[7] Some of these derivatives are also mentioned in the WHO list of essential medicines for their antipsychotic properties.^[8] Their efficient synthesis is therefore a strategic objective to make these various technologies as sustainable and as affordable as possible. Traditionally, these compounds are made by nucleophilic substitution (N-alkylated series) or by Ullmann–Goldberg condensations (N-arylated series).^[9] The latter, however, suffer from the usual requirement for large amounts of Cu salts or onerous Pd salts (Buchwald–Hartwig reaction)^[10] and, moreover, often require expensive and/or sensitive ligand architectures. In 2015, we proposed an atom- and step-efficient direct cross-dehydrogenative^[11] coupling pathway that enabled

the direct N-arylation of phenothiazines with phenols^[12,13] under an O₂ atmosphere^[14] (Scheme 1). This reaction is unusual on many accounts, notably because of its metal-free,^[15] halide-free, and preactivation-free character. Moreover, the capture of oxidized PTZs with phenols^[16] seems to be a surprisingly favorable process. In the present study, we explore the mechanism^[13b,d] of these reactions by utilizing both theoretical and experimental methods. The precise nature and intermediacy of the oxidized PTZ is investigated, as well as its reactivity with phenols. The envisaged mechanistic scenario is depicted in Scheme 1.



Scheme 1. The PTZ–phenol oxidative coupling, proposed mechanism.

Results and Discussion

To investigate why PTZs are such efficient amination substrates, particularly in comparison to diarylamines, which are typically unreactive under our reaction conditions, we first performed cyclic voltammetry measurements on three test substrates. PTZ (1aH) and PTZ-CF₃ (1bH), which often furnishes higher C–H amination yields than PTZ 1aH,^[12] were, in particular, investigated. They were compared to diarylamine 4H,^[17] which was chosen for its resemblance to PTZ-CF₃, although it is incompetent as an NH source in the present metal-free amination reaction (Figures 1 and 2). Clearly, the electrochemical oxidations of PTZ, PTZ-CF₃, and control substrate diarylamine 4H are reversible. As expected, PTZ (+0.22 V) oxidizes at a lower potential than electron-deficient PTZ-CF₃ (+0.38 V). The fact that PTZ-CF₃ often gives higher yields of coupling prod-

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Figure 1. Selection of three test substrates for CV.

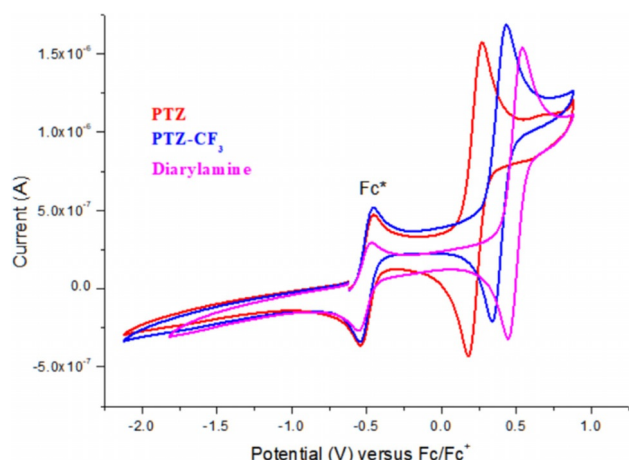


Figure 2. CV plots (room temperature) of PTZ (**1 aH**), PTZ- CF_3 (**1 bH**), and diarylamine (**4H**) in CH_2Cl_2 . $E^{\circ}_{1/2\text{ox}}$ values are reported versus ferrocene/ferrocenium (Fc^0/Fc^+) by using Fc^* as an internal standard. $E^{\circ}_{1/2\text{ox}} = +0.22$, $+0.38$, and $+0.48$ V for **1 aH**, **1 bH**, and **4H**, respectively.

ucts with phenols than PTZ may come from its intrinsically higher electrophilicity.^[12] Surprisingly, the oxidation of diarylamine **4H** is not far off from that of PTZ- CF_3 , at only $+0.48$ V. However, it does not provide the C–N coupling product with phenols under any of our reaction conditions. Instead, it produces a trace amount of a C–O coupling product, wherein the phenol is the oxygen substrate and compound **4H** is the carbon substrate. The optimization of that other coupling product with a Ru catalyst was recently reported by some of us.^[17] Under the current metal-free conditions, however, most of diarylamine **4H** either decomposes at high temperature (150°C) or, alternatively, remains unreacted at low temperature (50°C). In all cases, none of the expected C–N bond-coupling product is formed from **4H**, in contrast to PTZs. Whereas diarylamine **4H** and PTZ- CF_3 have similar CV (cyclic voltammetry) profiles, resulting radical species **4'** is presumably far less persistent as a result of poor stabilization. Indeed, free rotation of the two aryl units with respect to each other owing to the lack of the S-bridge implies poor delocalization of the formed radical, perhaps leading to an N-centered radical that is too reactive.

Next, we considered the CV profiles of some typical phenol derivatives that perform well in this reaction: 3-*tert*-butylphenol (**2aH**), 4-*tert*-butylphenol (**2bH**), and 3,5-dimethylphenol (**2cH**) (Figures 3 and 4). Clearly, the oxidation potentials of

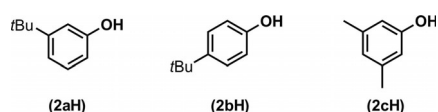


Figure 3. Selection of three test phenols for CV.

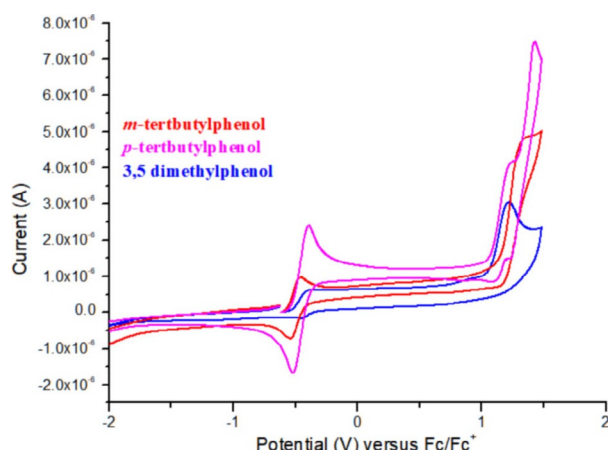


Figure 4. CV plots (room temperature) of phenols **2aH**, **2bH**, and **2cH** in CH_2Cl_2 . Peak potential for the oxidation waves are reported versus Fc^+/ Fc by using Fc^* as an internal standard. $E_{\text{ox}} = +1.31$, $+1.42$, and $+1.2$ V for **2aH**, **2bH**, and **2cH**, respectively.

these phenols are considerably higher than those of the PTZ reagents. It can, thus, be assumed that the PTZ coupling partner oxidizes first. It is important to note that these phenol oxidation potentials are, in general, higher than the reductive potential of O_2 ($+1.23$ V).^[18] For example, 4-*tert*-butylphenol (**2bH**, $+1.42$ V), one of the best phenol substrates in this reaction in terms of product yield,^[12] could not be oxidized to the binol homocoupling product with our method (Scheme 1). However, phenols,^[19] and especially PTZs,^[20] both benefit from relatively low bond-dissociation energies (BDEs), such that O–H hydrogen-atom abstraction (HAA) may be conceivable under radical reaction conditions, especially in the presence of a persistent PTZ radical species.

The radical nature of the oxidized PTZ was therefore examined by electron paramagnetic resonance (EPR) spectroscopy (Figure 5). The radical species were generated by simply bubbling air through solutions of PTZ (**1aH**) and PTZ- CF_3 (**1bH**) in $[\text{D}_6]$ benzene at room temperature. Because PTZs have relatively low N-basicities ($\text{p}K_{\text{b}} < -1$), the acetic acid co-solvent is not expected to have a major influence on the initial HAA process, expect perhaps through hydrogen bonding. We will, moreover, experimentally observe, later on, that the coupling reaction also runs without carboxylic acids, although this compromises the yields a bit. Very clean and distinct spectra were obtained, and they are characteristic for the formation of PTZ' (**1a'**) and PTZ- CF_3 ' (**1b'**) radicals. As can be expected, the line patterns are distinct owing to the presence of the CF_3 substituent in one of the substrates. The g-values and hyperfine interactions were obtained by simulation of the experimental X-band EPR spectra, and the thus-obtained experimental parameters were fully congruent with the DFT-calculated ones (see Figure 5). Thus, the radical species obtained are in good agreement with an N-centered, neutral radical structure of the PTZ moieties. According to DFT calculations, the spin density of these N-centered radical species is about 34.5% at the N atom for PTZ- CF_3 (**1b'**) and 34.3% for PTZ (**1a'**).^[21,22] Therefore, considerable de-

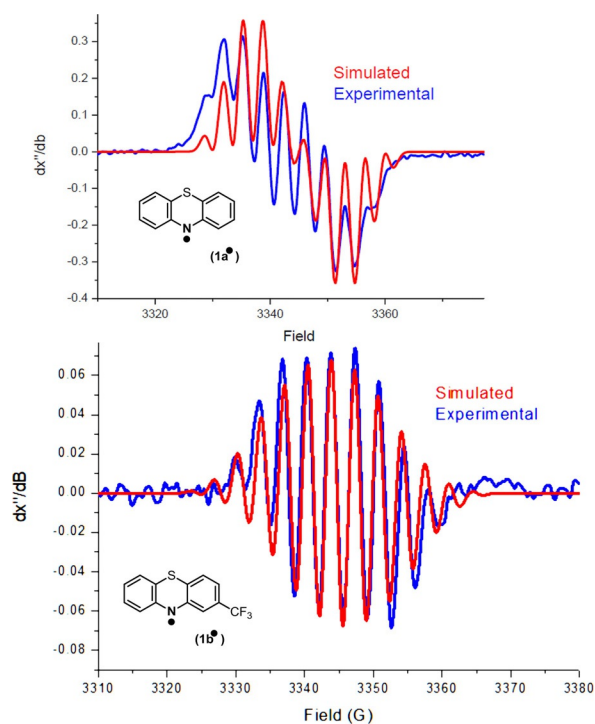
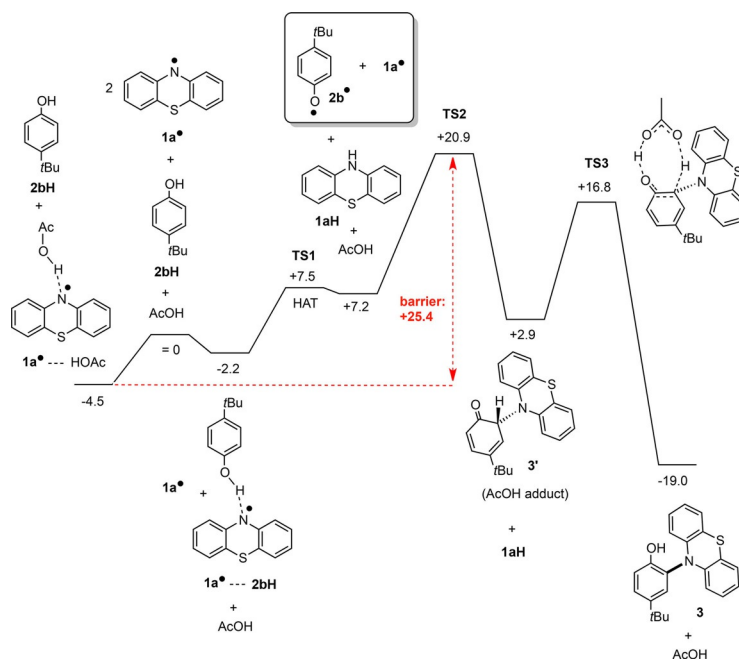


Figure 5. Top) Experimental (room temperature) and simulated EPR spectra of oxidized PTZ (**1a***). Experimental parameters: frequency = 9.384862 GHz, modulation amplitude = 1 G, power = 0.2 mW. Parameters used in the simulation: $g_{\text{iso}} = 2.0045$, $A_{\text{iso}}^{\text{N}} = 15.0$, $A_{\text{iso}}^{\text{H}^1} = -9.60$, $A_{\text{iso}}^{\text{H}^2} = -7.6$, $A_{\text{iso}}^{\text{H}^3} = -11.1$, $A_{\text{iso}}^{\text{H}^4} = 20$ (DFT computed: $A_{\text{iso}}^{\text{N}} = 14.72$, $A_{\text{iso}}^{\text{H}^1} = -10.56$, $A_{\text{iso}}^{\text{H}^2} = -8.49$, $A_{\text{iso}}^{\text{H}^3} = -8.47$, $A_{\text{iso}}^{\text{H}^4} = 10.55$ MHz). Bottom) Experimental and simulated EPR spectra of PTZ- CF_3 (**1b***). Experimental parameters: frequency = 9.384862 GHz, modulation amplitude = 1 G, power = 0.2 mW. Parameters used in the simulation: $g_{\text{iso}} = 2.0046$, $A_{\text{iso}}^{\text{N}} = 19$, $A_{\text{iso}}^{\text{H}^1} = -10.80$, $A_{\text{iso}}^{\text{H}^2} = -8.55$, $A_{\text{iso}}^{\text{H}^3} = -9.10$, $A_{\text{iso}}^{\text{H}^4} = 3.0$ MHz (DFT computed: $A_{\text{iso}}^{\text{N}} = 14.75$, $A_{\text{iso}}^{\text{H}^1} = -10.80$, $A_{\text{iso}}^{\text{H}^2} = -8.55$, $A_{\text{iso}}^{\text{H}^3} = -10.10$, $A_{\text{iso}}^{\text{H}^4} = 3.81$ MHz).

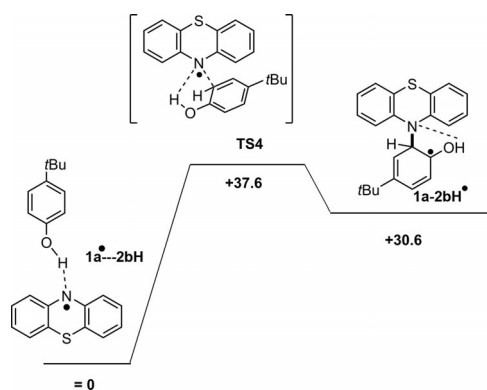
localization/stabilization of the radical species occurs in these structures, which explains their persistency. Notably, under similar conditions, no EPR signals were obtained from a solution of control diarylamine **4H** (nor from the test phenols of Figure 3). Nevertheless, the electronic structure of the corresponding N-centered radical was calculated. The noncyclic structure of diarylamine **4*** is expected to have an N-centered radical character of 42.3%. Thus, this species should be less persistent. Therefore, diarylamine **4H** is not only more difficult to oxidize than the PTZs (+1.25 V, Figure 2), but once it is oxidized, it is also expected to be much more (perhaps too) reactive, which thus provides a likely explanation for its poor performance in the C–N coupling reaction.

With these initial experimental data in hand, we decided to explore the mechanism by using DFT methods to obtain complementary information (see Scheme 2). Geometry optimizations were performed at the DFT level by using the b3-lyp functional and def2-TZVP basis of all stationary points. Grimme's D3 dispersion corrections^[23] were used in all calculations (disp3, "zero damping"). Given that we showed that

persistent N-centered PTZ radical **1a*** could be easily generated even at room temperature, we propose this species to be a key intermediate in the reaction sequence leading to the formation of product **3**. The potential N–N radical-coupled dimerized product^[24] of PTZ radical **1a*** was computed to be uphill by +4.8 kcal mol⁻¹ (gas-phase free energy), such that this compound presumably remains a pool of N-centered radicals. A plausible first elementary reaction step in the mechanism is hydrogen-atom transfer (HAT) from phenol **2bH** to **1a*** over transition state **TS1**. This is, in fact, a low-barrier (10.2 kcal mol⁻¹) and endergonic (+7.2 kcal mol⁻¹) equilibrium reaction according to DFT and produces phenoxyl radical **2b***. Subsequent radical–radical coupling of phenoxyl radical **2b*** with another persistent PTZ radical **1a*** over transition state **TS2** to produce C–N coupled intermediate **3'** is again a relatively low-barrier process (+13.7 kcal mol⁻¹). However, relative to "resting-state" hydrogen-bonded adduct **1a*–HOAc**, this is the overall highest barrier of the reaction sequence (+25.4 kcal mol⁻¹). Subsequent AcOH-mediated keto–enol tautomerization over transition state **TS3** converts intermediate **3'** into final product **3**. The latter process again has a low barrier (+13.3 kcal mol⁻¹) and is strongly exergonic (–19.0 kcal mol⁻¹). An alternative pathway, involving C–N bond formation between PTZ radical **1a*** and phenol **2bH** to form radical adduct **1a–2bH***, followed by HAT to **1a*** (or O_2)^[14b] to form product **3**, was also considered. However, although viable, this pathway has a higher barrier (+37.6 kcal mol⁻¹, Scheme 3, see the Supporting Information). Moreover, anisoles, which are electronically similar to phenols but lack an OH functional group, are not competent substrates in this reaction. This fact tends to support the former mechanistic scenario, in which HAT between **1a*** and **2bH** must occur prior to C–N bond formation (Scheme 2). The



Scheme 2. DFT calculated mechanism (Turbomole, b3-lyp, def2-TZVP, disp3). Relative energies in kcal mol⁻¹.



Scheme 3. Alternative pathway with a higher barrier (see the Supporting Information).

overall barrier of $+25.4 \text{ kcal mol}^{-1}$ obtained from the gas-phase calculations described in Scheme 2 is perhaps a bit too low for reactions requiring 150°C to proceed smoothly. Perhaps oxidation of 1aH to 1a^\bullet is the actual rate-limiting step under the applied experimental (polar) reaction conditions, for which the formation of ionic species 1aH^+ (i.e., protonation of 1a^\bullet) and/or O_2 diffusion/concentration limitations could be contributing factors, and this is aggravated by the need for 2 equivalents of 1a^\bullet in the proposed mechanism. If this hypothesis and the overall barrier of $+25.4 \text{ kcal mol}^{-1}$ are correct, nonaerobic oxidants, present in higher concentrations at the beginning of the reaction, should accommodate considerably milder reaction temperatures. This is indeed the case, as demonstrated later on in the study in a series of mechanistic experiments with various oxidants (Table 1, see below).

The potential role of H-bonding was also considered, particularly in view of literature precedent.^[25] We initially anticipated that H-bonding between the PTZ and phenol coupling partners might play an important role in the reaction. However, in the presence of a carboxylic acid co-solvent and at these relatively elevated reaction temperatures, these interactions are expected to be marginal. Another argument is the fact that phenols that are not substituted in the *para* position tend to lead to mixtures of *ortho/para*-phenothiazinated phenols.^[12a] Strong H-bonding control might have arguably led to exclusive *ortho* selectivity. The *ortho*-coupling products, nevertheless, display an interesting intramolecular $\text{OH}\cdots\text{N}$ hydrogen bond characterized by redshifted O–H IR bands (see the Supporting Information) and by X-ray crystallography of some of the congeners (Figure 6).

With EPR, CV, and DFT computational studies all pointing to the involvement of persistent PTZ radicals being responsible for the observed unusual reactivity, one could wonder whether the solvent also has an active (radical) role in the reaction at all, as some of us previously suggested.^[12a] Therefore, we took a closer look at the solvent scope of the reaction. Cumene and acetic acid, the solvent mixture in which the reaction was originally reported,^[12a] is an excellent solvent system to perform this cross-dehydrogenative coupling.^[26] However, as now expected in view of the PTZ radical persistency, the radical-susceptible benzylic position of cumene is not absolutely necessa-

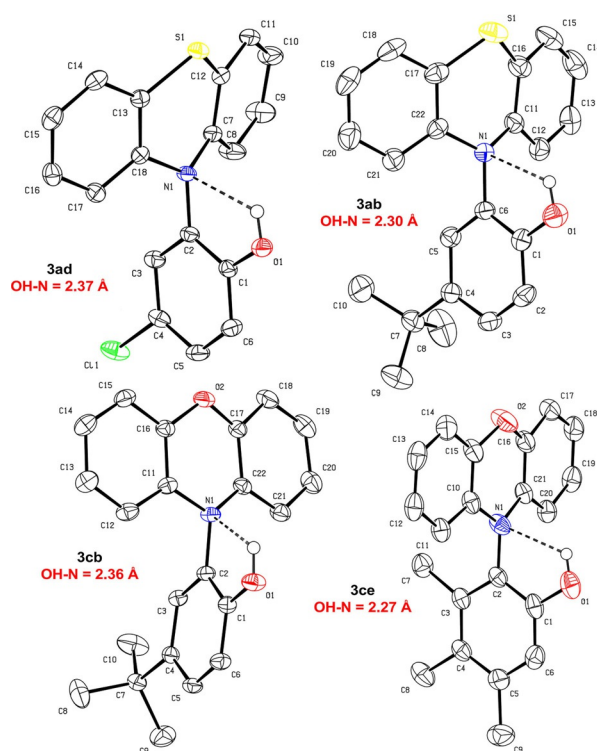
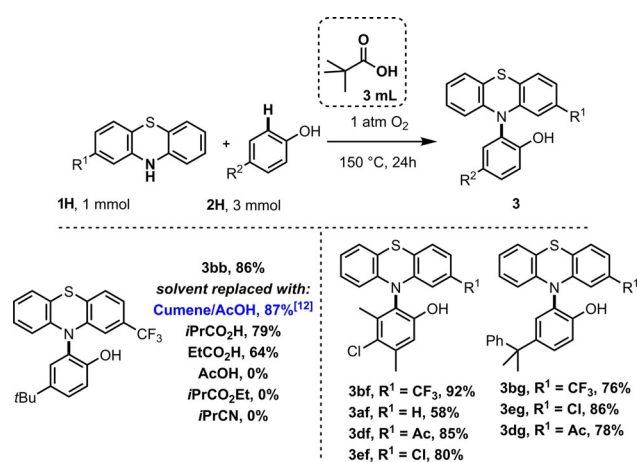


Figure 6. Intramolecular H-bonded character: selected X-ray structures of products **3ab**, **3ad**, **3cb**, and **3ce** at the 50% probability level; H-atoms are omitted for clarity.^[12,21]

ry. Indeed, isobutyric acid and especially pivalic acid (PivOH) perform just as well (selected examples in Scheme 4).^[27] Clearly, cumene and its strong radical chain propagation capacity are not required for aerobic oxidation conditions. Finally, it should be noted that utilizing an excess amount of the phenol coupling partner is not a necessity. Reducing the phenol loading to 1 equivalent instead of 3 equivalents reduced the yield of **3bb** from 86% (yield of isolated product, Scheme 4) to 80% (yield determined by NMR spectroscopy), respectively. One could thus say that the heterocoupling character of the reac-



Scheme 4. Examples with the new pivalic acid method; yields of the isolated products are given.

tion is quite persistent. Next, we considered the key role of the oxidant. The persistence of the PTZ radical, its low BDE and low oxidation potential, and its proposed role as a HAT agent suggest that the nature of the terminal oxidant of the reaction may be somewhat flexible. To verify this hypothesis, we performed a series of mechanistic experiments, in which the nature of the oxidant was varied (Table 1). The most important findings are that: 1) O₂ can only be utilized at higher temperatures (Table 1, entries 2–4); 2) the acidic conditions are not absolutely necessary; however, they do provide higher yields (Table 1, entries 6 and 8 vs 7 and 9, respectively); 3) cumyl hydroperoxide is a reasonable oxidant intermediate in the case of cumene/O₂ oxidizing systems. To those competent oxidants of Table 1, one should also add periodates (NaIO₄)^[13c] and persulfates (Na₂S₂O₈)^[13d] which have already been exemplified in the recent literature. During the reviewing period of this study, the group of Aiwen Lei reported an electrochemical oxidative variant of this reaction at room temperature.^[28] In other words, the reaction is highly specific to PTZs and phenols but not to the utilized oxidant. Concerning the carboxylic acid additive, one hypothesis could be that it lowers the energy of some transition states of the reaction mechanism through hydrogen-bonding assistance, such as, for example, in transition state **TS3** (Scheme 2). Interestingly, calculating **TS3** without acetic acid leads to an unrealistically high energy level (above 40 kcal mol⁻¹) owing to angular constraints (see the Supporting Information), which thus supports the acetic acid hydrogen-bonding hypothesis. Importantly, utilizing nonaerobic oxidants clearly allows the reaction temperature to be lowered significantly from 150 to only 50 °C.^[13c,d] This lower reaction temperature is in better accordance with the DFT (and EPR) data and may indicate that the more sustainable O₂/AcOH oxidant is associated with **1 a'** protonation and/or diffusions/concentration limitations.

We next investigated whether a typical radical scavenger such as 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) might affect the results to confirm the radical nature of these reac-

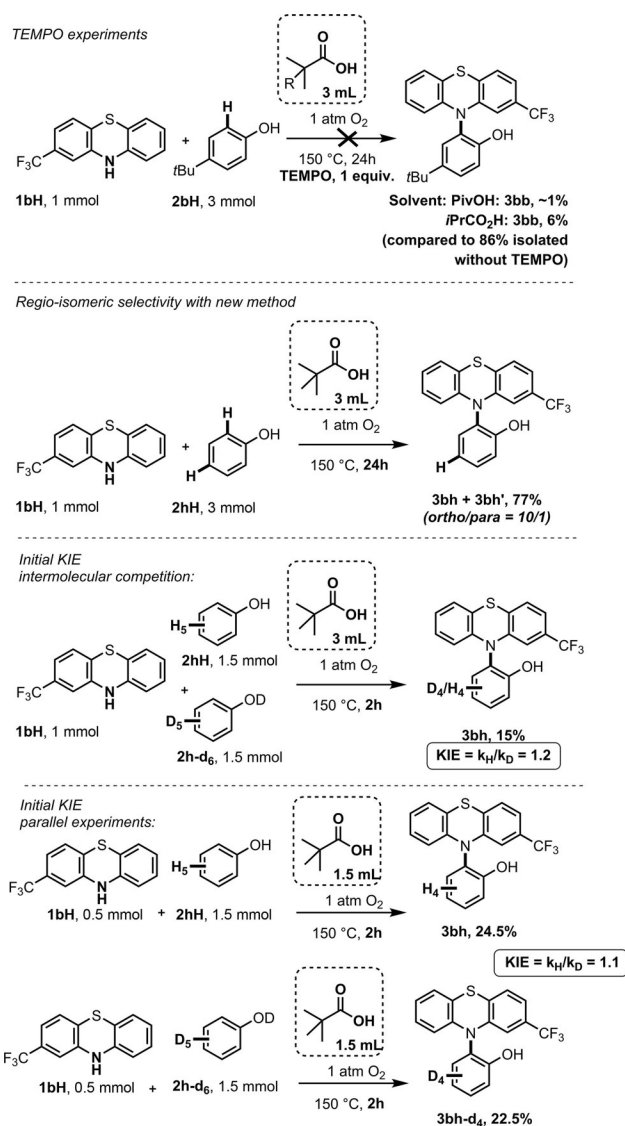
tions (Scheme 5). Indeed, it was found that in the presence of 1 equivalent of TEMPO the reaction was almost completely suppressed under the new isobutyric acid or pivalic acid conditions. Unfortunately, neither GC–MS analysis nor column chromatography allowed trapped TEMPO adducts to be detected or identified. A reason for this could be the N-basicity of TEMPO, which may lead to partial or full protonation under the acidic reaction conditions. If true, it is interesting that protonated TEMPO seems to maintain radical inhibition properties under those acidic reaction conditions. It should, moreover, be noted that TEMPO is surprisingly tolerated in the original cumene/AcOH mixture,^[12] which indicates that solvents with specific radical character such as cumene may offer alternative radical chains but are not essential for the dehydrogenative coupling reaction to proceed. Before moving to H/D kinetic investigations, we first evaluated the reactivity and regioselectivity of ordinary phenol (substrate **2 hH**, Scheme 5). Much to our surprise, not only was the yield acceptable (**3 bh** + **3 bh'**, 77 %) but so was the *ortho/para* regioisomeric selectivity (**3 bh**/**3 bh'** = 10:1). This represents a significant increase in the regioselectivity relative to that obtained with cumene (Scheme 1),^[12] in which the same substrates afforded a *ortho/para* ratio of only 1.3:1. This also supports the notion of carboxylic acid supramolecular assistance in some of the transition states of the reaction.

Finally, some H/D kinetic experiments were considered to probe the mechanistic scenario of Scheme 2. In a first experiment, an intermolecular competition between phenol (**2 hH**) and phenol-d₆ (**2 h-d₆**) was considered at an early conversion stage (*t* = 2 h, **3 bh**, 15%). Under those conditions, only a secondary kinetic isotope effect was observed (KIE = *k_H*/*k_D* = 1.2), which suggested that C–H bond cleavage was not the rate-limiting step. A similar result was obtained upon comparing the initial rates for phenol (**2 hH**) and phenol-d₆ (**2 h-d₆**) in two separate and parallel experiments. In the latter comparison, a similar KIE of 1.1 was observed. It should, moreover, be noted that phenol-d₆ (**2 h-d₆**) is fortunately robust enough to survive

Table 1. Mechanistic experiments: influence of additives.

Entry	Oxidant	Solvent	<i>T</i> [°C]	Yield ^[a] [%]
1	cumene hydroperoxide/N ₂	PivOH (3 mL)	150	71
2	O ₂	PivOH (3 mL)	50	0
3	O ₂	cumene (2.5 mL), AcOH (0.5 mL)	50	0
4	O ₂	cumene (2.5 mL) (no acid)	50	0
5	Ag ₂ O/N ₂	cumene (2.5 mL), AcOH (0.5 mL)	150	70
6	Ag ₂ O/N ₂	cumene (2.5 mL), AcOH (0.5 mL)	50	85
7	Ag ₂ O/N ₂	cumene (2.5 mL) (no acid)	50	70
8	cumene hydroperoxide/N ₂	cumene (2.5 mL), AcOH (0.5 mL)	50	25
9	cumene hydroperoxide/N ₂	cumene (2.5 mL) (no acid)	50	10

[a] The yield was determined by ¹H NMR spectroscopy by using 1,2-dichloroethane as an internal standard.



the reaction conditions (PivOH, 150 °C, 2 h) without measurable loss of deuterium on its benzene ring, which thus allowed those KIE experiments in the first place. These secondary KIE are therefore in good accordance with the proposed C–N bond-forming step as the rate-determining step.

Conclusions

In conclusion, we undertook a detailed mechanistic study of the O₂-mediated cross-dehydrogenative C–N bond-forming reaction between phenols and phenothiazines (PTZs). This was done by aid of electron paramagnetic resonance spectroscopy, cyclic voltammetry, DFT calculations, radical-trapping experiments, kinetic isotope effect measurements, and studying the effects of varying the oxidants and solvent systems. The persistent N-centered radical was suggested to be a key intermediate in this reaction. Its persistence is notably considered to be

responsible for the high heterocoupling selectivity, even upon utilizing a phenol-to-PTZ loading of only 1:1. Indeed, as soon the hydrogen-atom transfer step occurs at the phenol coupling partner, the resulting phenol radical would be captured by the excess amount of the accumulating persistent PTZ radical. In view of these considerations, the herein proposed mechanism might well be operative in some of the other variants of this reactions.^[13b–d,28] This high heterocoupling specificity may, moreover, facilitate the design of future radical cross-dehydrogenative coupling methods.

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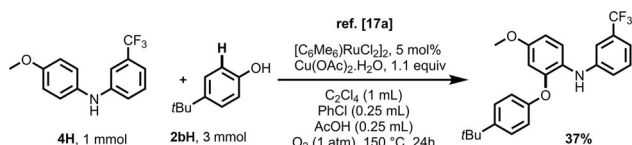
Conflict of interest

The authors declare no conflict of interest.

Keywords: cross dehydrogenative couplings · click chemistry · homolytic aromatic substitution · oxidative amination · radicals

- [1] A. Bernthsen, *Annalen* **1885**, 230, 73.
- [2] M. J. Ohlow, B. Moosmann, *Drug Discovery Today* **2011**, 16, 119.
- [3] See for example: Z. Iqbal, W.-Q. Wu, D.-B. Kuang, L. Wang, H. Meier, D. Cao, *Dyes Pigm.* **2013**, 96, 722.
- [4] a) X. Pan, M. Lamson, J. Yan, K. Matyjaszewski, *ACS Macro Lett.* **2015**, 4, 192; b) X. Pan, C. Fang, M. Fantin, N. Malhotra, W. Y. So, L. A. Peteanu, A. A. Isse, A. Gennaro, P. Liu, K. Matyjaszewski, *J. Am. Chem. Soc.* **2016**, 138, 2411; c) N. J. Treat, H. Sprafke, J. W. Kramer, P. G. Clark, B. E. Barton, J. Read de Alaniz, B. P. Fors, C. J. Hawker, *J. Am. Chem. Soc.* **2014**, 136, 16096.
- [5] J. K. Salunke, F. L. Wong, K. Feron, S. Manzhos, M. F. Lo, D. Shinde, A. Patil, C. S. Lee, V. A. L. Roy, P. Sonar, P. P. Wadgaonkar, *J. Mater. Chem. C* **2016**, 4, 1009.
- [6] S. Kumar, M. Singh, J.-H. Jou, S. Ghosh, *J. Mater. Chem. C* **2016**, 4, 6769.
- [7] a) R. Grisorio, B. Roose, S. Colella, A. Listorti, G. P. Suranna, A. Abate, *ACS Energy Lett.* **2017**, 2, 1029; b) D. B. Shinde, J. K. Salunke, N. R. Candeias, F. Tinti, M. Gazzano, P. P. Wadgaonkar, A. Priimagi, N. Camaioni, P. Vivo, *Sci. Rep.* **2017**, 7, 46268.
- [8] World Health Organisation, (2013) WHO Model Lists of Essential Medicines: <http://www.who.int/medicines/publications/essentialmedicines/en/>.
- [9] *Copper-Mediated Cross-Coupling Reactions* (Eds.: G. Evano, N. Blanchard), John Wiley & Sons, Hoboken, **2014**.
- [10] Buchwald–Hartwig amination: a) D. S. Surry, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2008**, 47, 6338; *Angew. Chem.* **2008**, 120, 6438; b) J. F. Hartwig, *Acc. Chem. Res.* **2008**, 41, 1534.
- [11] Selected references on CDC concepts: a) S. A. Girard, T. Knauber, C.-J. Li, *Angew. Chem. Int. Ed.* **2014**, 53, 74; *Angew. Chem.* **2014**, 126, 76; b) C. S.

- Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215; c) C.-J. Li, *Acc. Chem. Res.* **2009**, *42*, 335.
- [12] a) M.-L. Louillat-Habermeyer, R. Jin, F. W. Patureau, *Angew. Chem. Int. Ed.* **2015**, *54*, 4102; *Angew. Chem.* **2015**, *127*, 4175; b) PhD thesis of M.-L. Louillat-Habermeyer, TU Kaiserslautern, **2015**.
- [13] See also: a) K. V. N. Esguerra, J.-P. Lumb, *ACS Catal.* **2017**, *7*, 3477; b) Y. Zhao, B. Huang, C. Yang, B. Li, B. Gou, W. Xia, *ACS Catal.* **2017**, *7*, 2446; c) R. Jin, F. W. Patureau, *Org. Lett.* **2016**, *18*, 4491; d) Y. Zhao, B. Huang, C. Yang, W. Xia, *Org. Lett.* **2016**, *18*, 3326.
- [14] A selected review: a) N. Gulzar, B. Schweitzer-Chaput, M. Klussmann, *Catal. Sci. Technol.* **2014**, *4*, 2778, and references therein. See also: b) D. P. Curran, A. I. Keller, *J. Am. Chem. Soc.* **2006**, *128*, 13706.
- [15] Selected examples of metal-free dehydrogenative amination mediated by hypervalent iodine: a) S. Manna, K. Matcha, A. P. Antonchick, *Angew. Chem. Int. Ed.* **2014**, *53*, 8163; *Angew. Chem.* **2014**, *126*, 8302; b) R. Samanta, J. O. Bauer, C. Strohmman, A. P. Antonchick, *Org. Lett.* **2012**, *14*, 5518. See also: c) R. Samanta, K. Matcha, A. P. Antonchick, *Eur. J. Org. Chem.* **2013**, 5769, and references therein. Selected related reactions: d) M. Ochiai, Y. Takeuchi, T. Katayama, T. Sueda, K. Miyamoto, *J. Am. Chem. Soc.* **2005**, *127*, 12244; e) M. Uyanik, H. Okamoto, T. Yasui, K. Ishihara, *Science* **2010**, *328*, 1376; f) M. Uyanik, K. Ishihara, *ChemCatChem* **2012**, *4*, 177.
- [16] Reactivity of phenols with radicals, see for example: a) P. Franchi, M. Lucarini, G. F. Pedullì, L. Valgimigli, B. Lunelli, *J. Am. Chem. Soc.* **1999**, *121*, 507; b) D. W. Snelgrove, J. Lusztyk, J. T. Banks, P. Mulder, K. U. Ingold, *J. Am. Chem. Soc.* **2001**, *123*, 469; c) G. Litwinienko, K. U. Ingold, *J. Org. Chem.* **2003**, *68*, 3433; d) G. Litwinienko, K. U. Ingold, *Acc. Chem. Res.* **2007**, *40*, 222.
- [17] Applications of diarylamine **4H** in catalysis: a) C. Heitz, A. W. Jones, B. S. Oezkaya, C. L. Bub, M.-L. Louillat-Habermeyer, V. Wagner, F. W. Patureau, *Chem. Eur. J.* **2016**, *22*, 17980; b) see also ref. [13b].



- [18] a) S. G. Bratsch, *J. Phys. Chem. Ref. Data* **1989**, *18*, 1. See also: b) M. L. Pegis, J. A. S. Roberts, D. J. Wasylenko, E. A. Mader, A. M. Appel, J. M. Mayer, *Inorg. Chem.* **2015**, *54*, 11883, and references therein.
- [19] O–H BDEs of phenols, see for example: a) M. Lucarini, P. Pedrielli, G. F. Pedullì, *J. Org. Chem.* **1996**, *61*, 9259. For selected oxidative transformations with phenols, see for example: a) W. W. Kaeding, *J. Org. Chem.* **1963**, *28*, 1063; b) M. Nakajima, I. Miyoshi, K. Kanayama, S.-I. Hashimoto, *J. Org. Chem.* **1999**, *64*, 2264; c) Y. E. Lee, T. Cao, C. Torruellas, M. C. Kozlowski, *J. Am. Chem. Soc.* **2014**, *136*, 6782; d) N. Y. More, M. Jeganmo-

- han, *Org. Lett.* **2015**, *17*, 3042; e) W. Xu, B. J. Nachtsheim, *Org. Lett.* **2015**, *17*, 1585; f) A. Wetzels, G. Pratsch, R. Kolb, M. R. Heinrich, *Chem. Eur. J.* **2010**, *16*, 2547; g) K. Morimoto, K. Sakamoto, T. Ohshika, T. Dohi, Y. Kita, *Angew. Chem. Int. Ed.* **2016**, *55*, 3652; *Angew. Chem.* **2016**, *128*, 3716; h) A. Wiebe, D. Schollmeyer, K. M. Dyballa, R. Franke, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2016**, *55*, 11801; *Angew. Chem.* **2016**, *128*, 11979.
- [20] PTZs are reputed to have a very low bond dissociation energy: M. Lucarini, P. Pedrielli, G. F. Pedullì, L. Valgimigli, D. Gimes, P. Tordo, *J. Am. Chem. Soc.* **1999**, *121*, 11546.
- [21] See SI. CCDC 1822700–3 contain the supplementary crystallographic data for this paper, as well as the X-ray structures of **3ab**, **3ce**, **3ad**, and **3cb**, respectively. These data are provided free of charge by The Cambridge Crystallographic Data Centre.
- [22] See also: a) L. Hermosilla, J. M. Garcia de la Vega, C. Sieiro, P. Calle, *J. Chem. Theory Comput.* **2011**, *7*, 169; b) O. Brede, A. Maroz, R. Hermann, S. Naumov, *J. Phys. Chem. A* **2005**, *109*, 8081; c) H. D. Burrows, T. J. Kemp, M. M. Welbourn, *J. Chem. Soc. Perkin Trans. 2* **1973**, 969; d) B. C. Gilbert, P. Hanson, R. O. C. Norman, B. T. Sutcliffe, *Chem. Commun.* **1966**, 161.
- [23] S. Grimme, J. Antony, S. Ehrlich, H. Krieg, *J. Chem. Phys.* **2010**, *132*, 154104.
- [24] For a recent selected reference, see: B. R. Rosen, E. W. Werner, A. G. O'Brien, P. S. Baran, *J. Am. Chem. Soc.* **2014**, *136*, 5571.
- [25] For an interesting study on Hydrogen-bonding effects on the properties of phenoxy radicals, see: M. Lucarini, V. Mugnaini, G. F. Pedullì, M. Guerra, *J. Am. Chem. Soc.* **2003**, *125*, 8318.
- [26] The solubility of O_2 is expected to be an important parameter, see for example: T. Sato, Y. Hamada, M. Sumikawa, S. Araki, H. Yamamoto, *Ind. Eng. Chem. Res.* **2014**, *53*, 19331.
- [27] Interestingly, in several C–H bond activation coupling reactions, pivalate additives were often directly compared to and identified as superior to their acetate counterparts: a) X. Wang, B. S. Lane, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 4996; b) M. LaFrance, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 16496; c) P. Arockiam, V. Poirier, C. Fischmeister, C. Bruneau, P. H. Dixneuf, *Green Chem.* **2009**, *11*, 1871; d) B. Haffemayer, M. Gulias, M. J. Gaunt, *Chem. Sci.* **2011**, *2*, 312; e) T. Saget, S. J. Lemouzy, N. Cramer, *Angew. Chem. Int. Ed.* **2012**, *51*, 2238; *Angew. Chem.* **2012**, *124*, 2281; f) A. W. Jones, M.-L. Louillat-Habermeyer, F. W. Patureau, *Adv. Synth. Catal.* **2015**, *357*, 945; see also this recent study: g) T. Fujihara, A. Yoshida, M. Satou, Y. Tanji, J. Terao, Y. Tsuji, *Catal. Commun.* **2016**, *84*, 71.
- [28] S. Tang, S. Wang, Y. Liu, H. Cong, A. Lei, *Angew. Chem. Int. Ed.* **2018**, *57*, 4737.

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