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Redox-Neutral TEMPO Catalysis Toward Direct Radical (Hetero)Aryl C–H Di- and Trifluoromethoxylation

Johnny W. Lee,[1‡] Sanghyun Lim,[1‡] Daniel N. Maienshein,[2] Peng Liu,[2*] and Ming-Yu Ngai[1*]

Dedicated to Professor Barry M. Trost on the occasion of his 80th birthday.

Abstract: Applications of TEMPO• catalysis for the development of redox-neutral transformations are rare. Herein, we report the *first* TEMPO•-catalyzed, redox-neutral C–H di- and trifluoromethoxylation of (hetero)arenes. The reaction exhibits a broad substrate scope, has high functional group tolerance, and can be employed for the late-stage functionalization of complex drug-like molecules. Kinetic measurements, isolation and resubjection of catalytic intermediates, UV-Vis studies, and DFT calculations support the proposed oxidative TEMPO•/TEMPO$^+$ redox catalytic cycle. Mechanistic studies also suggest that Li_2CO_3 plays an important role in preventing catalyst deactivation. These findings will provide new insight into the design and development of novel reactions through redox-neutral TEMPO• catalysis.

TEMPO• (2,2,6,6-tetramethylpiperidine 1-oxyl radical) and its derivatives have a rich history in the fields of biochemistry, materials science, and organic chemistry.[1] These open-shell species have diverse reactivity and can undergo reactions such as a single-electron transfer (SET) process to access three discrete oxidation states (i.e., TEMPO$^-$/TEMPO•/TEMPO$^+$) or abstract hydrogen atoms from C–H/X–H bonds.[2] Their unique redox properties and chemical reactivity render TEMPO• and related aminoxyl radicals a versatile class of radical reagents to achieve one/two-electron oxidation,[3] hydrogen atom transfer (HAT),[4] proton-coupled electron transfer (PCET),[5] or radical trapping reactions.[6] The majority of these transformations, however, require either a stoichiometric amount of aminoxyl radicals or the addition of external oxidants such as hypochlorite, silver, or molecular oxygen (O_2) to recycle aminoxyl radicals.[7] In lieu of common external oxidants, elegant aminoxyl radical-catalyzed reactions driven by electrooxidation have been recently reported by Lei,[8] Lin,[9] Minteer,[10] Stahl,[11] and others.[12]

Despite recent advances, applications of aminoxyl radical catalysis for the development of redox-neutral transformations[13] without the aid of an external oxidant or electrooxidation are rare. Baran et al. reported a seminal TEMPO•-mediated intramolecular, redox-neutral, radical alkane desaturation reaction.[14] Although they tested the catalytic activity of TEMPO•, they pointed out that its low turnover number (TON ≤ 3) renders the catalytic reaction inefficient. To date, efficient redox-neutral TEMPO• catalysis that proceeds through a TEMPO•/TEMPO$^+$ redox cycle remains elusive. The successful development of such a catalytic platform could expand the reactivity profile of the aminoxyl radical's redox chemistry and advance fundamental knowledge in radical chemistry.

In our quest for the establishment of redox-neutral TEMPO• catalysis, we focused our attention on the development of unprecedented TEMPO•-catalyzed intermolecular, redox-neutral (hetero)aryl C–H functionalization. Herein, we report the first success in this area, describe the experimental and computational studies that support the TEMPO•/TEMPO$^+$ redox cycle, and outline a new approach for the preparation of di- and trifluoromethoxylated (hetero)arenes (Figure 1). We looked to highly sought-after di- and trifluoromethoxylated (hetero)arenes[15] as synthetic targets because of the unique structural[16] and electronic properties[17] that make them an important group of ethers in the pharmaceutical, agrochemical, and materials sciences.[15a-c] Recently, we and others reported the synthesis of di- and/or trifluoromethoxylated (hetero)arenes by employing visible-light photoredox catalysts,[18] transition metals,[18f] and/or stoichiometric oxidants/activators.[19] However, utilizing TEMPO• as a catalyst for synthesis offers an attractive alternative due to its low cost,[20] environmental friendliness,[21] and thermodynamic[22] and kinetic stability.[23] Also, our findings could provide new insight into the design and development of new reactions through redox-neutral TEMPO• catalysis.

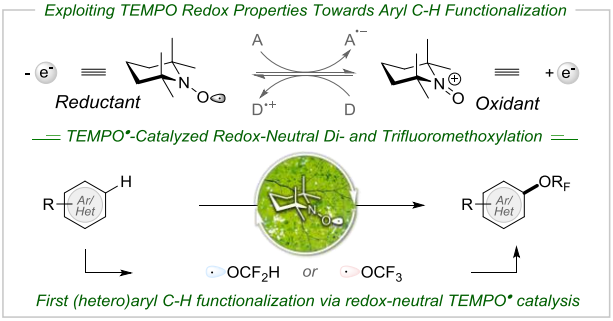

Figure 1. TEMPO•-Catalyzed redox-neutral aryl C-H functionalization.

The mechanistic hypothesis of the proposed transformation is outlined in Scheme 1. We envisioned that the reaction proceeds through an oxidative redox cycle beginning SET between di- or trifluoromethoxylating reagent **1a** (E_p = +0.11 V vs SCE)[18g] or **1b** (E_p = +0.14 V vs SCE)[18e] and TEMPO• ($E_{1/2}$ = +0.62 V vs SCE),[12b] generating 2,2,6,6-tetramethyl-1-oxo-1λ^4-piperidine (TEMPO$^+$) and the di- or trifluoromethoxy radical (•OR$_F$). Although the SET operates against a moderate potential gradient of

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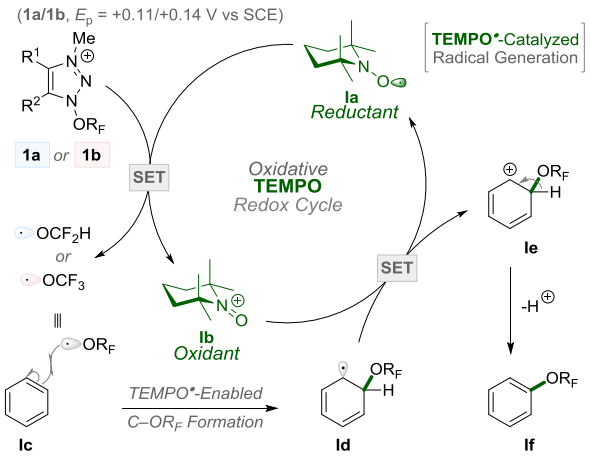
approximately +0.5 V, such a redox process is possible if the onward reaction following the electron transfer is irreversible.[24] Addition of $^{\bullet}OR_F$ to an arene forms cyclohexadienyl radical **Id** ($E_{1/2}$ = −0.10 V vs. SCE),[25] which is then oxidized by TEMPO$^+$, regenerating the TEMPO$^{\bullet}$ catalyst and delivering cyclohexadienyl cation **Ie**. Rearomatization of **Ie** via deprotonation should be highly favored, affording the desired product **If**.

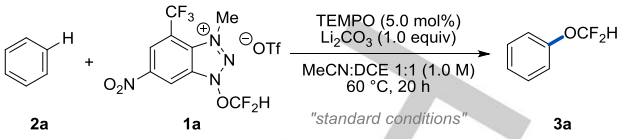


Scheme 1. Proposed mechanism for the TEMPO$^{\bullet}$-catalyzed di- and trifluoromethoxylation of (hetero)arenes.

We tested our hypothesis and obtained the desired difluoromethoxylated product (**3a**) in 83% yield when a mixture of benzene (**2a**), difluoromethoxylating reagent (**1a**), Li_2CO_3, and TEMPO$^{\bullet}$ (5 mol%) was heated at 60 °C for 20 hours (Table 1, entry 1). Control experiments indicated that both TEMPO$^{\bullet}$ and Li_2CO_3 are critical. The absence of either one of these components led to either no desired reaction or low yield (entries 2 and 3). Mechanistic studies suggested that Li_2CO_3 prevents catalyst deactivation (*vide infra*). Replacement of Li_2CO_3 with more soluble bases such as Cs_2CO_3 or 2,6-di-^{t}Bu-4-me-pyridine resulted in reagent decomposition, decreasing the yields to 29% and 39%, respectively (entries 4 and 5). When we conducted the reaction at room temperature or under diluted conditions (0.10 M), we obtained lower yields of 50% and 49%, respectively (entries 6 and 7). The use of a MeCN/DCE solvent mixture (1:1) is essential as the absence of either solvent led to poor yields (entries 8 and 9). Presumably, the partial solubility of reagent **1a** in the solvent mixture allows the slow introduction of **1a** and so maintains its integrity. While using 1 equivalent of benzene afforded the product in a lower yield, the reaction proceeded with similar efficiency in the presence of water or air (entries 10-12).

Having identified the optimal reaction conditions, we explored the scope of TEMPO$^{\bullet}$-catalyzed redox-neutral (hetero)aryl C–H difluoromethoxylation (Table 2a). We found that this protocol has a broad substrate scope and high functional group compatibility. For example, the reaction tolerated halide substituents (**3b**, **3c**, **3g**, **3r**), which provide useful handles for further structural elaborations through metal-catalyzed coupling reactions. Notably, substrates containing benzylic C–H bonds (**3d**, **3e**, **3f**, **3g**), which are often sites for undesired reactivity in radical processes, were

Table 1. Deviation from the Optimized Conditions[a]



2a 1a 3a

Entry	Deviation from the "*standard conditions*"	Yield (%)[b]	*RSM (%)*[b]
1	–	83	*0*
2	No TEMPO	0	*>99*
3	No Li_2CO_3	3	*97*
4	Cs_2CO_3 instead of Li_2CO_3	29	*31*
5	2,6-di-^{t}Bu-4-Me Pyridine instead of Li_2CO_3	39	*37*
6	23 °C instead of 60 °C	50	*47*
7	0.1 M instead of 1.0 M	49	*39*
8	Only MeCN (1.0 M)	34	*39*
9	Only DCE (1.0 M)	4	*94*
10	Benzene (1.0 equiv)	25	*40*
11	With H_2O (1.0 equiv)	73	*0*
12	Under Air	81	*0*

[a]Reactions were performed using 1 equivalent of reagent and 10 equivalents of benzene. [b]Yields were determined by ^{19}F NMR spectroscopy using trifluorotoluene as an internal standard. RSM = remaining starting material (**1a**).

compatible and afforded the desired products in good yields.[26] Arenes with other functional groups, including unprotected phenol (**3i**, **3j**, **3k**), alkene (**3j**), cyano (**3i**), nitro (**3j**), aldehyde (**3k**), ketone (**3l, 3m**), ester (**3o**), sulfone (**3p**), and carbonate (**3p**), were viable substrates as well. Importantly, our protocol is amenable for late-stage difluoromethoxylation reactions of medicinally relevant molecules using one equivalent of substrates such as Leflunomide® (antirheumatic drug, **3s**), Efavirenz® (antiretroviral drug for treating HIV, **3t**), and derivatives of Diacetonefructose (**3u**), Benzocaine® (pain killer, **3v**), and *trans*-Androsterone (**3w**).

To further demonstrate the synthetic utility of redox-neutral TEMPO$^{\bullet}$ catalysis, we successfully achieved radical trifluoromethoxylation of a broad range of (hetero)arenes using trifluoromethoxylating reagent **1b** (Table 2b). Again, the reaction tolerated a wide array of functionalities such as benzylic C–H bond (**4c**), carbonyl and cyano (**4c-4g**, **4l**), phosphine oxide (**4h**), sulfone (**4i**), carbonate (**4j**) and imide (**4k**) groups. The selectivity of the TEMPO$^{\bullet}$-catalyzed (hetero)aryl C–H di- and trifluoromethoxylation reactions is governed by the radical nature of the process, which provides rapid access to multiple regioisomeric products without labor-intensive, parallel multistep analog synthesis,[27] conveniently generating promising new candidates that might have never been evaluated otherwise.

Our mechanistic hypothesis for the TEMPO$^{\bullet}$-catalyzed redox-neutral reaction depicted in Scheme 1 is supported by kinetic measurements, catalytic intermediate isolation and resubjection, UV-Vis studies, EPR measurements, and DFT calculations. The intermolecular kinetic isotope effect (KIE) of the difluoromethoxylation reaction using equimolar amounts of benzene and benzene-d_6 was found to be 1, implying that the cleavage of the aryl C–H takes place after the rate-determining step (Figure 2a). Kinetic studies using Burés' method[28] suggested a first-order dependence on TEMPO$^{\bullet}$ (Figure S3). To understand the role of the TEMPO$^{\bullet}$ catalyst, we synthesized

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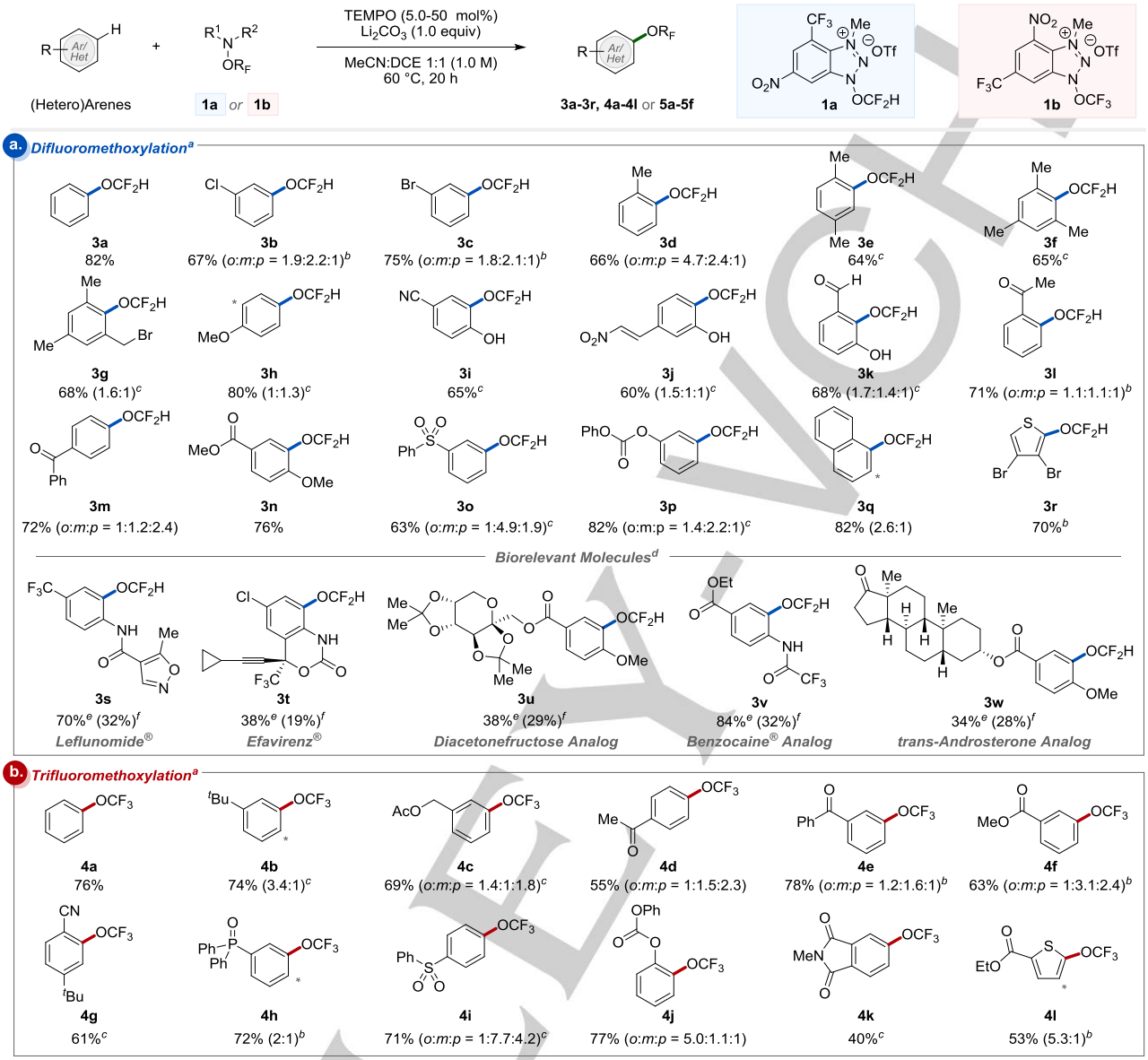
Table 2. Selected Examples of Di- and Trifluoromethoxylation of (Hetero)Arenes.



[a]Reactions were performed using 1 equivalent of reagent **1a** or **1b** and 10 equivalents of (hetero)arene. The asterisk (*) denotes the functionalization of minor regioisomeric products. Due to the high volatility of the products, overall yields and the ratio of the constitutional isomers were determined by ^{19}F NMR spectroscopy using trifluorotoluene as an internal standard. [b]Reactions were performed with 10.0 mol% of TEMPO. [c]Reactions were performed with 20 mol% of TEMPO. [d]Reactions were performed using 2.00 equivalents of reagent **1a**, 1.0 equivalent of (hetero)arene and 50 mol% TEMPO• in MeCN:DCE 1:1 (0.200 M). [e]Overall yields were determined based on the recovered starting material. [f]Isolated yield.

and compared the catalytic activity of $TEMPO^+$ and $TEMPO^-$ with TEMPO• under standard reaction conditions (Figure 2b).[29] In the presence of Li_2CO_3, while $TEMPO^-$ failed to promote the reaction, TEMPO• and $TEMPO^+$ afforded the desired product in 83% and 51% yield, respectively. In the absence of Li_2CO_3, the reactivity dropped dramatically in all cases, and only 3% of product **3a** was obtained using TEMPO•. These data showed that (i) Li_2CO_3 is critical for catalytic activity, (ii) $TEMPO^-$ is catalytically inactive, and (iii) TEMPO• and $TEMPO^+$ are catalytically active only in the presence of Li_2CO_3. Given that our di- and trifluoromethoxylation reactions generate one equivalent of acid and that acid can promote disproportionation of TEMPO• (K = 3.3 x 10^4 M^{-2}) to produce catalytically inactive $TEMPO^+$ and $TEMPOH_2^+$ species,[30] it may explain the lack of catalytic turnover of TEMPO• in the absence of base. UV-Vis measurements of $TEMPO^+$ (λ_{abs} = 290 nm)[31] showed a new peak with λ_{abs} = 245 nm after the addition of Li_2CO_3 (Figure 2c). Since carbonate can serve as a reductant and engage in SET with both inorganic complexes and organic molecules,[32] the UV-Vis data indicate that carbonate reduces $TEMPO^+$ to the putative TEMPO• (λ_{abs} = 245 nm).[31] This unprecedented

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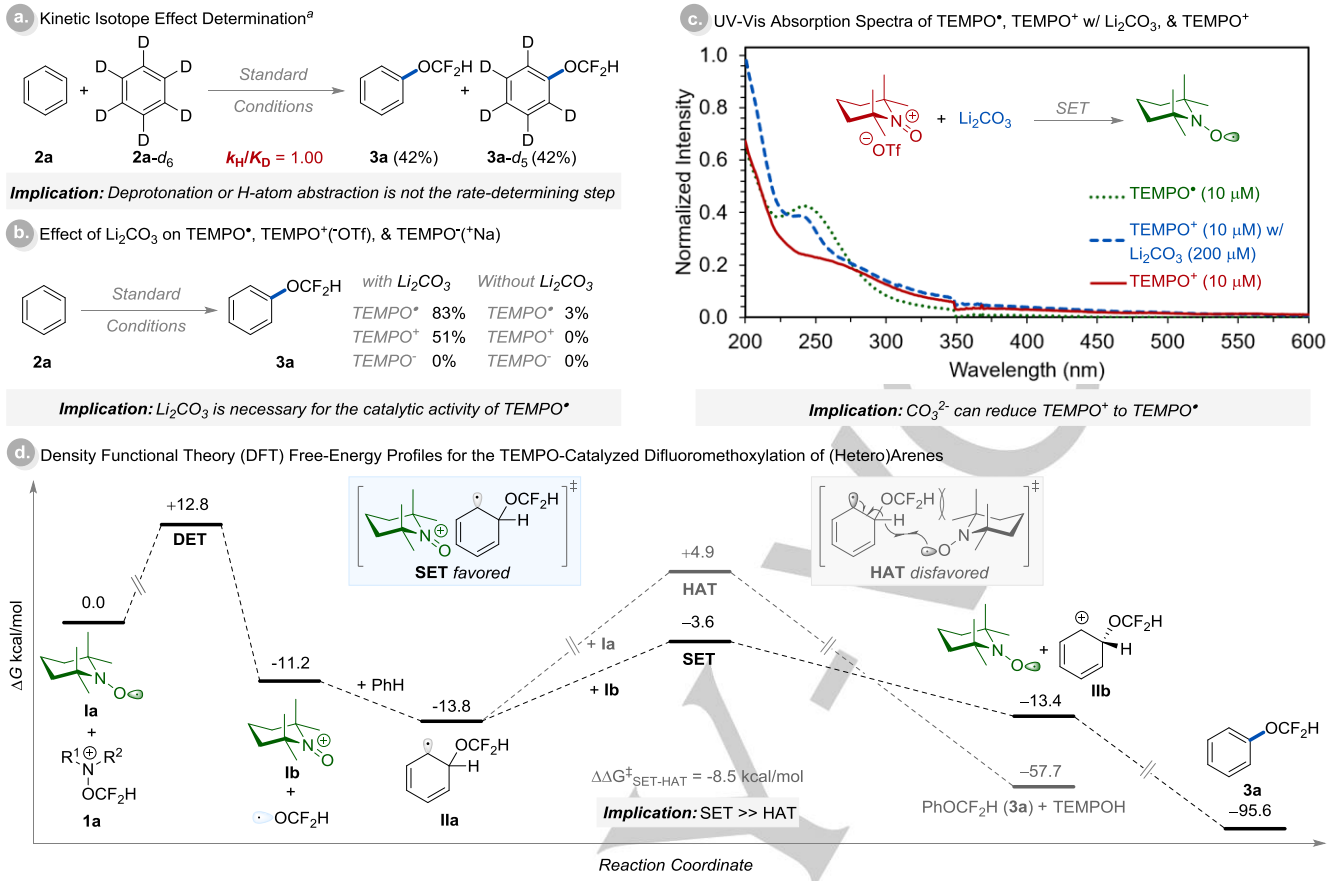

Figure 2. Mechanism Studies: [a] The reaction was performed using 5.0 equivalents of **2a**/**2a**-d_6, respectively. DFT and Marcus theory calculations were performed at the M06-2X/6-311++G(d,p)/SMD(MeCN)//M06-2X/6-31+G(d) level of theory using benzene as the substrate. All energies are in kcal/mol and are with respect to **Ia** and **1a**. See SI for details. DET = dissociative electron transfer; SET = single electron transfer; and HAT = hydrogen atom transfer.

observation is further supported by EPR studies.[33] Taken together, these results suggested that Li_2CO_3 plays a dual role as a base and a sacrificial reductant to prevent catalyst deactivation.

We performed computational studies to evaluate the energy profiles of the proposed SET reaction mechanism and another plausible catalytic cycle involving HAT by TEMPO• (Figure 2d). DFT and Marcus theory calculations suggested that the formation of the difluoromethoxyl radical (•OCF_2H) and $TEMPO^+$ via the dissociative electron transfer (DET)[34] is feasible with an activation free energy of +12.8 kcal/mol and is exergonic by –11.2 kcal/mol. The addition of the •OCF_2H to an arene to give cyclohexadienyl radical **IIa** is slightly exergonic with a ΔG° of –2.6 kcal/mol. Single-electron oxidation of **IIa** by $TEMPO^+$ to form cyclohexadienyl cation **IIb** and regenerate TEMPO• catalyst is kinetically favored by –8.5 kcal/mol as compared to the sterically challenging HAT ($\Delta G^\ddagger$ = 18.7 kcal/mol with respect to **IIa**).[35],[36] Deprotonation of **IIb** to form the desired product **3a** is highly favorable with a ΔG° of –82.2 kcal/mol. Collectively, the experimental and computational studies support the proposed catalytic cycle shown in Scheme 1.

In summary, we have developed the first application of redox-neutral TEMPO• catalysis to achieve intermolecular di- and trifluoromethoxylation of (hetero)arenes. Our strategy uses the readily available and inexpensive TEMPO• catalyst, exhibits high functional group tolerance, and offers flexible late-stage functionalization of drug-like molecules. Detailed experimental and computational studies suggest that (i) the reaction proceeds through an oxidative TEMPO•/$TEMPO^+$ redox cycle, and (ii) Li_2CO_3 prevents catalyst deactivation. We anticipate that these new findings and mechanistic insights will aid in the development of a new class of reactions in the area of nitroxyl radical chemistry.

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Keywords: TEMPO catalysis • difluoromethoxylation • trifluoromethoxylation • radical • arenes

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[36] Another possible reaction mechanism involves trapping of **IIa** with TEMPO to form a 1-OCF_2H-2-TEMPO-cyclohexadienyl intermediate, which then undergoes $TEMPO^-/H^+$ elimination to form the desired Ph-OCF_2H product and TEMPOH. However, this mechanism is unlikely because DFT calculations suggested that such a reaction mechanism is less favorable than OCF_2H^-/H^+ elimination to form side product of TEMPOPh, see SI for details. For TEMPO trapping of cyclohexadienyl radicals, see: A. Teichert, K. Jantos, K. Harms, A. Studer, *Org. Lett.* **2004**, *6*, 3477.

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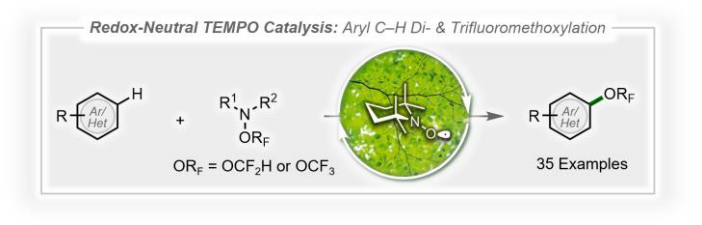

TEMPO-catalyzed redox-neutral di- and trifluoromethoxylation of arenes and heteroarenes. The strategy exhibits high functional group tolerance and offers flexible late-stage functionalization of drug-like molecules. Mechanistic studies suggest an oxidative $TEMPO^{\bullet}/TEMPO^{+}$ redox catalytic cycle and that Li_2CO_3 plays an important role in preventing catalyst deactivation.

Johnny W. Lee,[†] Sanghyun Lim,[†] Daniel N. Maienshein, Peng Liu, and Ming-Yu Ngai**

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Title: Redox-Neutral TEMPO Catalysis Toward Direct Radical (Hetero)Aryl C–H Di- and Trifluoromethoxylation