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Trifluoromethylation of Allylsilanes under Photoredox Catalysis

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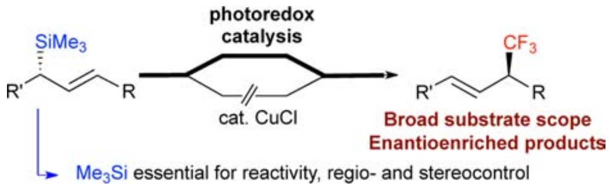
ABSTRACT



A new catalytic method to access allylic secondary CF_3 products is described. These reactions use the visible light excited $Ru(bpy)_3Cl_2\cdot 6H_2O$ catalyst and the Togni or Umemoto reagent as the CF_3 source. The photoredox catalytic manifold delivers enantioenriched allylic trifluoromethylated products not accessible under Cu(I) catalysis.

Modern drug discovery campaigns have created an increasing demand for new methods of trifluoromethylation.[1] To date, catalytic reactions to access CF_3 products with $C_{sp}{}^3{-}CF_3$ stereogenicity from substrates not activated by a carbonyl functionality are extremely limited.[2] This synthetic gap prompted us to address this challenge with a research program focused on allylic trifluoromethylation. The groups of Buchwald, Liu, Wang, and Qing reported that Cu-catalyzed trifluoromethylation of terminal alkenes leads to linear allylic CF_3 products, exclusively.[3] Our own contribution,[4] along with a similar study reported by Sodeoka and co-workers,[5] established that alkenes activated with a trimethylsilyl group on the allylic position undergo trifluoromethylation with 1-(trifluoromethyl)-1,2-benziodoxol-3(1*H*)-one (Togni reagent **I**) under Cu(I) catalysis. This method relies on the regiodirecting trimethylsilyl group to program access to allyl products with $C_{sp}{}^3{-}CF_3$ stereogenicity. However, the substrate scope is restricted to the formation of *gem*-disubstituted allyl CF_3 products, a limitation that hampers its overall utility. Herein, we report that allylsilanes are amenable to trifluoromethylation through photoredox catalysis.[6] This high-performing catalytic system for generating $CF_3{}^\bullet$ species allows access to enantioenriched allylic CF_3 products inaccessible under Cu(I) catalysis.

Initial investigations focused on the trifluoromethylation of ethyl 3-(trimethylsilyl)hex-4-enoate (*E*)-**1a** to form ethyl 6,6,6-trifluoro-5-methylhex-3-enoate **2a** (Table 1). The model allylsilane **1a** was selected on the basis that it offers a structural platform for studying the stereochemical

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(1) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev*. **2008**, *37*, 320–330.

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(3) (a) Parsons, A. T.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 9120–9123. (b) Xu, J.; Fu, Y.; Luo, D.-F.; Jiang, Y.-Y.; Xiao, B.; Liu, Z.-J.; Gong, T.-J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 15300–15303. (c) Wang, X.; Ye, Y.; Zhang, S.; Feng, J.; Xu, Y.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 16410–16413. (d) Chu, L.; Qing, F.-L. *Org. Lett.* **2012**, *14*, 2106–2109.

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(5) Shimizu, R.; Egami, H.; Hamashima, Y.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 4577–4580.

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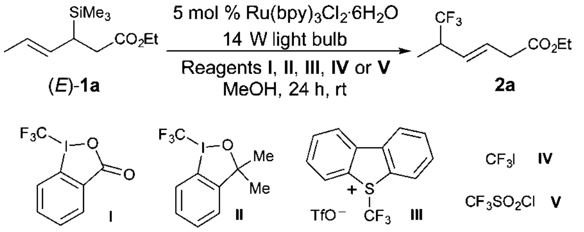
aspects of the reaction. Copper catalysis led to disappointing results; under our previously reported conditions using Togni reagent **I**,[4] the starting material was largely consumed (> 90%), but less than 5% of **2a** was formed (entry 1). Gratifyingly, the visible light–excited $Ru(bpy)_3Cl_2 \cdot 6H_2O$ catalyst provided **2a** under various conditions. Control experiments established the authenticity of the photoredox concept (entries 2 and 3) and the importance of the silyl group.[7] Togni reagent **I** and Umemoto reagent **III** outperformed Togni reagent **II**, CF_3I, and CF_3SO_2Cl in terms of conversion and/or selectivity. For **III**, we noted little influence of the counteranion and observed transesterification of both **1a** and **2a** when the reaction solvent was methanol (entries 13–17). CF_3I led to trifluoromethylation (*E*/*Z* ratio ~1) but only in the presence of *i*-Pr_2NEt (entries 18–19).[8] This observation contrasts with the detrimental effect of *i*-Pr_2NEt when using Togni reagent **I** (entry 5). The optimum solvent for this reaction is MeOH (EtOH for **III**). These initial studies led to the identification of the best reaction conditions: 1 equiv of allylsilane **1a**, 1.8 equiv of reagent **I** (or **III**), 5 mol % of $Ru(bpy)_3Cl_2 \cdot 6H_2O$, MeOH (EtOH for **III**) at rt with exposure of the reaction vessel to one household 14 W light bulb over 48 h (entry 6). Notably, the stereoselectivity of the trifluoromethylation was found to be dependent on the CF_3 source with Umemoto reagent **III** affording **2a** with the most favorable *E*/*Z* ratio.

Table 1. Trifluoromethylation of Allylsilane **1a**



entry	CF_3[a]	cond[b]	conv[c,d] (%)	yield[c,d] (%)	*E*/*Z* ratio[d]
1	**I**	CuCl[e]	91	<5	1.4
2	**I**	no Ru	<5	[f]	
3	**I**	no light	<5	[f]	
4	**I**		45	27	2.5
5	**I**	*i*Pr_2NEt[g]	30	[f]	
6	**I**[h]	48 h	90	55	1.7
7	**I**	MeCN	18	17	2.2
8	**I**	CH_2Cl_2	42	22	1.7
9	**I**	DMF	89	37	1.8
10	**II**		<5	[f]	
11	**II**	MeCN	<5	[f]	
12	**II**	DMF	<5	[f]	
13	**III**		82[i]	30[j]	5.3
14	**III**	EtOH, 48 h	74	38[j]	3.4
15	**III**[k]		75[i]	34[j]	4
16	**III**	MeCN	>99	7	8
17	**III**	DMF	76	33	5.4
18	**IV**		<5		
19	**IV**	*i*Pr_2NEt[g]	48	44	1
20	**V**		48	17	4.2
21	**V**	DMF	66	10	3
22	**V**	MeCN	<5		

[a] 1.2 equiv for **I**–**III** and **V**; 10 equiv for CF_3I (**IV**). [b] Variation from the standard conditions detailed in the scheme. [c] Conv refers to consumption of **1a** and yield refers to the formation of **2a**. [d] Analysis by ^{19}F NMR with C_6H_5F as internal standard. [e] Conditions for the reaction: 20 mol % of CuCl, MeOH, 70 °C, 2 h. [f] No product. [g] 2.0 equiv of *i*Pr_2NEt. [h] 1.8 equiv of **I**. [i] Transesterification of **1a** and **2a**. [j] Yield of isolated **2a**. [k] BF_4^- as counteranion.

The next experiments were designed to probe the reaction's tolerance to various degrees of substitution and to study its stereochemical course. Conditions **B** (Togni **I**) and/or **C** (Umemoto **III**) were considered for comparative purposes (Table 2).

The desired allyl CF_3 product was predominant with traces of unidentified but separable byproducts. Typically, higher yields were observed with reagent **I**, but **III** was superior in terms of *E*-selectivity. Careful analysis of the crude reaction mixture for the trifluoromethylation of *anti* α-substituted *β*-silyl-(*E*)-crotylsilanes **1e**–**h**[7] revealed that, out of the four possible isomers that could be obtained, the *syn*-(*E*) branched CF_3 allylic products were predominantly formed. In this series, the *E*/*Z* ratio is typically high, but significant quantities of the *anti*-isomers were formed. The stereochemical outcome of the reaction was found to be sensitive to the substitution pattern of the substrates and the CF_3 source. For the assignment of the relative stereochemistry, **2f** (major isomer) was subjected to sequential alkene then ester reduction, followed by esterification. The resulting saturated ester, 2-benzyl-6,6,6-trifluoro-5-methylhexyl 3,5-dinitrobenzoate **3**, was characterized by single-crystal X-ray diffraction.[7] The assignment of the relative stereochemistry of *syn*-**2f** indicates that the silyl group is regio- and stereodirecting, with the sense of stereocontrol being consistent with the well-established *anti*-S_E2' mode of addition observed for electrophiles other than the putative $CF_3^\bullet$ species formed under the reaction conditions.[9] The trifluoromethylation of **1h** gave the CF_3-substituted amino ester **2h** following selective Boc deprotection (entry 7). The *syn* *β*-silyl-(*E*)-crotylsilane **1i** also responded to trifluoromethylation and led preferentially to *anti*-(*E*)-**2i** in > 70% yield (entry 8). The trifluoromethylation was applied to allylsilanes that are structurally different from **1a**–**i**. The terminal linear allylsilane (*E*)-**1j** reacted under the reaction conditions **B** to give the desired terminal branched allylic CF_3 product **2j** in 44% yield along with an additional separable silylated product identified as **4** (33%) (entry 9). This side reaction indicates that the addition of the CF_3 group is not regioselective for this substrate; the allylsilanes **1a**–**i** therefore benefit from the steric constraint imposed by the proximal stereogenic silylated carbon for optimum regiocontrol during C–CF_3 bond formation. For **1k**, both the trimethylsilyl and the phenyl

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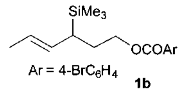
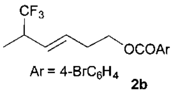
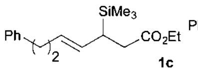
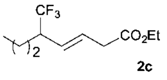
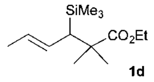
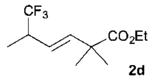
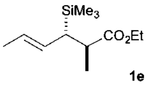
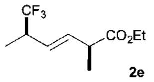
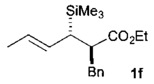
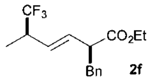
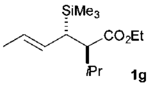
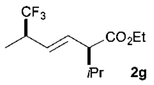
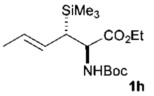
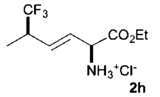
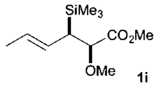
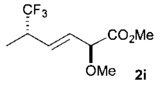
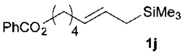
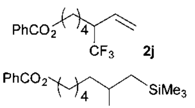
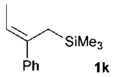
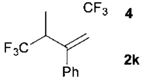
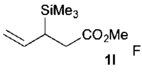
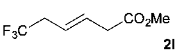
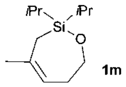
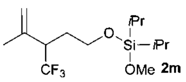
(7) For details (e.g., the synthesis of the starting materials), see the Supporting Information.

(8) The tertiary amine could serve as a sacrificial reductant and/or quench deleterious HI byproduct.

(9) (a) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293–1316. (b) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063–2192. (c) Chabaud, L.; James, P.; Landais, Y. *Eur. J. Org. Chem.* **2004**, 3173–3199.

Table 2. Trifluoromethylation of Allylsilanes **1b**−**m**

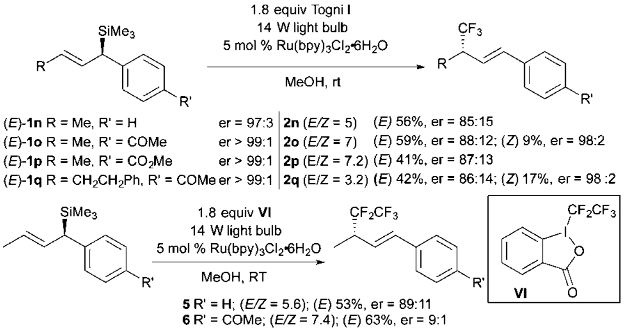
entry	allylsilane	product	cond[a]	E/Z[b] *syn*/*anti*(E)[c]	yield [%][e]
1	 Ar = 4-BrC$_6$H$_4$ **1b**	 Ar = 4-BrC$_6$H$_4$ **2b**	B C	5.8 (7)[d] (12)[d]	46 22
2	 **1c**	 **2c**	B C	1.4 (1.5)[d] 3.3 (2.5)[d]	63[f] 43
3	 **1d**	 **2d**	B	14 (> 20)[d]	69
4	 **1e**	 **2e**	B C	15 7 > 20 6.1	65 33
5	 **1f**	 **2f**	B C	15 10 > 20 8.6	83 24
6	 **1g**	 **2g**	B	> 20 3.5	55
7	 **1h**	 **2h**	B[g]	> 20 4.5	52
8	 **1i**	 **2i**	B C	4.6[h] 9.6[h]	73 76
9	 **1j**	 **2j** **4**	B	-	**2j** 44 **4** 33
10	 **1k**	 **2k**	B	-	55
11	 **1l**	 **2l**	C	3.3	33
12	 **1m**	 **2m**	B	-	41

[a] **B**: 5 mol % Ru(bpy)$_3$Cl$_2$·6H$_2$O, 14 W light bulb, 1.8 equiv of reagent **I**, MeOH, rt, 24 h. **C**: 5 mol % of Ru(bpy)$_3$Cl$_2$·6H$_2$O, 14 W light bulb, 1.8 equiv of reagent **III**, EtOH, rt, 24 h. [b] E/Z ratio determined by ^{19}F NMR. [c] *Syn*/*anti* ratio determined by ^{19}F NMR. [d] Values in parentheses refer to the measured ratio following purification. [e] Yield of isolated product. [f] For **I**, 2 × 1.5 equiv was used. [g] *N*-Boc deprotection with HCl/EtOH. [h] Ratio refers to E/Z or *anti*/*syn*; relative stereochemistry assigned assuming *anti* mode of addition with respect to the silyl group by analogy with **2f**.

substituents contribute to direct the regiochemistry of the trifluoromethylation (entry 10). The terminal branched allylsilane **1l** gave the linear allyl CF$_3$ product **2l** but only under conditions **C** (Umemoto reagent **III**). No reaction was observed with Togni reagent **I** (entry 11). This observation highlights the impact of the CF$_3$ source on reactivity. Finally, the formation of **2m** from **1m** demonstrates that the silyl group is captured with methanol (entry 12).

These results encouraged us to study the efficiency of chirality transfer upon trifluoromethylation of enantioenriched allylsilanes (R,E)-**1n**−**q** (er > 97:3) (Scheme 1).[10] Applying the standard reaction conditions **B** (Togni reagent **I**), the major products (S,E)-**2n**−**q** were isolated with some erosion of the er (> 85:15). The minor isomers (S,Z)-**2o** and (S,Z)-**2q** were formed in higher enantiomeric ratio (98:2). The installation of a CF$_2$CF$_3$ group at the allylic position was also successful with reagent **VI**[11] giving **5** and **6** with good er (9:1). The absolute configuration of the E isomers is assigned assuming an *anti*-SE′ mode of addition with respect to the silyl group in analogy with the trifluoromethylation of **1f**.

Scheme 1. Trifluoromethylation of Enantioenriched **1n**−**q**



(E)-**1n** R = Me, R′ = H er = 97:3 | **2n** (E/Z = 5) (E) 56%, er = 85:15
(E)-**1o** R = Me, R′ = COMe er > 99:1 | **2o** (E/Z = 7) (E) 59%, er = 88:12; (Z) 9%, er = 98:2
(E)-**1p** R = Me, R′ = CO$_2$Me er > 99:1 | **2p** (E/Z = 7.2) (E) 41%, er = 87:13
(E)-**1q** R = CH$_2$CH$_2$Ph, R′ = COMe er > 99:1 | **2q** (E/Z = 3.2) (E) 42%, er = 86:14; (Z) 17%, er = 98 :2

5 R′ = H; (E/Z = 5.6); (E) 53%, er = 89:11
6 R′ = COMe; (E/Z = 7.4); (E) 63%, er = 9:1

To study the mechanism of this reaction, we focused on the reaction conditions using the Togni reagent **I** (Scheme 2). Cyclic voltammetry measurements are consistent with a catalytic oxidative quenching cycle. The reduction potential of Togni reagent **I** (−0.68 V vs SCE in CH$_3$CN)[12] can be compatible with the reduction step using excited state Ru(bpy)$_3$$^{2+*}$; this implies that single electron transfer (SET) reduction of **I** would be concurrent with the oxidation of Ru(bpy)$_3$$^{2+*}$ to Ru(bpy)$_3$$^{3+}$ (−0.81 V vs SCE in CH$_3$CN).[6,13] The ensuing Togni **I** radical anion could collapse to generate the electrophilic CF$_3$$^•$, which is well suited to add regio- and stereoselectively to allylsilane **1a**. The resultant radical species **7**[14] could then undergo a second SET with the strong oxidant Ru(bpy)$_3$$^{3+}$ (+1.29 V vs SCE in CH$_3$CN),[6,13] an event regenerating the ground state photocatalyst Ru(bpy)$_3$$^{2+}$ and forming the stabilized β-silyl cation **8**.[15] Desilylation of **8** with methanol provides **2a**. A possible mechanistic scenario for the alternative reductive quenching cycle could feature the allylsilane **1a**

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(10) For the synthesis of enantioenriched allylsilanes, see: Li, D.; Tanaka, T.; Ohmiya, H.; Sawamura, M. *Org. Lett.* **2010**, *12*, 3344–3347.

(11) Li, Y.; Studer, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 8221–8224.

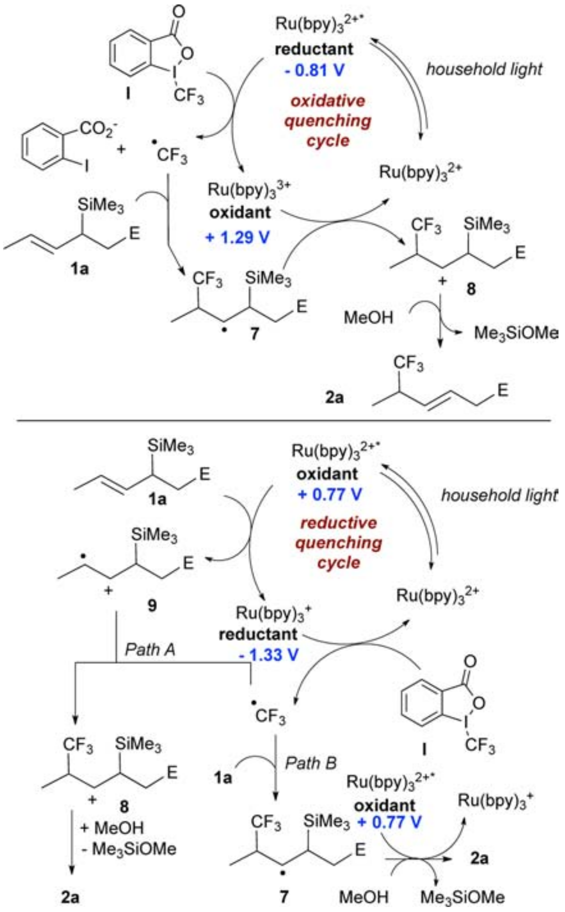
(12) Reduction potential refers to peak potential (irreversible reduction). See the Supporting Information.

(13) Haga, M.-A.; Dodsworth, E. S.; Eryavec, G.; Seymour, P.; Lever, A. B. P. *Inorg. Chem.* **1985**, *24*, 1901–1906.

(14) Fragmentation of the β-silyl radical is documented and cannot be ruled out; see: Mereau, R.; d'Antuono, P.; Castet, F.; Rouquet, G.; Robert, F.; Landais, Y. *Organometallics* **2010**, *29*, 2406–2412.

(15) Silicon has the ability to stabilize β-carbocations (29−30 kcal/mol^{-1}) through $\sigma_{\text{Si-C}}\rightarrow$p hyperconjugation and to a lesser degree β- carboradicals (2.6−4.5 kcal/mol^{-1}): Lambert, J. B.; Zhao, Y.; Emblidge, R. W.; Salvador, L. A.; Liu, X.; So, J.-H.; Chelius, E. C. *Acc. Chem. Res.* **1999**, *32*, 183–190.

Scheme 2. Mechanistic Considerations



as a reductive quencher to $Ru(bpy)_3^{2+*}$ leading to a radical cation species **9**.[16] This reactive intermediate could combine with $CF_3^\bullet$ (radical−radical coupling, path A) emerging from Togni reagent **I** via SET, an event concurrent with the oxidation of $Ru(bpy)_3^+$, which is a strong reducing agent.[6,14] This pathway was dismissed based on the high oxidation potential of allylsilane **1a** ($> +1.8$ V vs SCE in CH_3CN)[17] making the formation of the radical cation thermodynamically quite challenging. If an alternative reductive quencher to $Ru(bpy)_3^{2+*}$ is present, $CF_3^\bullet$ would add to **1a** to give the radical species **7**. Oxidation with the mild oxidant $Ru(bpy)_3^{2+*}$ (+0.77 V vs SCE in CH_3CN)[6,14] and desilylation with MeOH would afford **2a** (Path B). No product **2a** was obtained when the reaction was conducted in MeOH with the reductive quencher *i*-Pr_2NEt (Table 1, entry 5). Moreover, the reaction was successfully performed in CH_3CN, DMF and CH_2Cl_2 in the absence of MeOH (entries 7−9, Table 1). None of these solvents can act as a reductive quencher to $Ru(bpy)_3^{2+*}$. The mechanism depicted in Scheme 2 does not account for the different *E*/*Z* and *syn*/*anti* ratios observed for the products depending on the CF_3 source. The mechanistic details remain unclear, but we verified that **1a** and **2a** do not undergo *E*/*Z* isomerization in the presence of 5 mol % of $Ru(bpy)_3Cl_2 \cdot 6H_2O$ under visible light activation. Monitoring of product distribution over time also confirmed that all isomers are stable under the reaction conditions. Control "light/dark" experiments verified the necessity of light and are not supportive of a radical chain propagation mechanism.[18] In addition, a silylated product resulting from addition of Togni reagent **I** (or **II**) across the alkene functionality could never be detected.

This work discloses a photoredox-based catalytic method for the synthesis of enantioenriched branched allylic CF_3 products. The silyl group in the starting material is an important entity to control the regioselectivity of the trifluoromethylation. It also programs the stereochemical outcome of the reaction in synergy with the CF_3 reagent. On a more fundamental level, this work highlights the influence of the CF_3 source on photoredox catalyzed processes in terms of both reactivity and stereoselectivity. We are continuing work to gain further insight into the reaction mechanism as this information should enable future applications and facilitate the design of new CF_3 reagents.

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Supporting Information Available. Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Desilylation of **9** with MeOH may lead to an allyl radical, which can combine with $CF_3^\bullet$. In a control experiment, no TEMPO−allyl adduct was observed.

(17) Oxidation potential refers to peak potential (irreversible oxidation).

(18) This process could have potentially accounted for the differences in *E*/*Z* selectivity, with oxidation of **7** into **8** triggered by the trifluoromethylation reagent instead of $Ru(bpy)_3^{3+}$.

The authors declare no competing financial interest.