OL | Organic Letters

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

Letter

pubs.acs.org/OrgLett

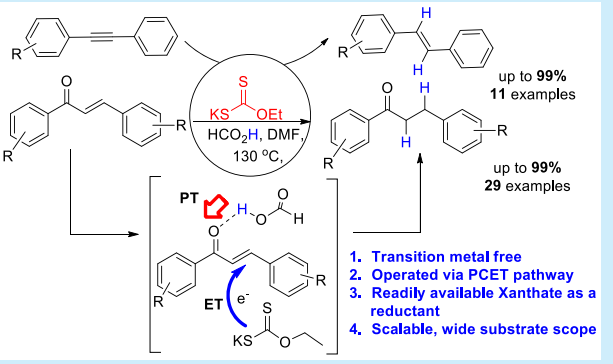
Proton-Coupled Electron Transfer: Transition-Metal-Free Selective Reduction of Chalcones and Alkynes Using Xanthate/Formic Acid

Ramanathan Prasanna, Somraj Guha, and Govindasamy Sekar*

Department of Chemistry, Indian Institute of Technology Madras, Chennai 600036, Tamil Nadu, India

Supporting Information

ABSTRACT: Highly chemoselective reduction of α,β-unsaturated ketones to saturated ketones and stereoselective reduction of alkynes to (*E*)-alkenes has been developed under a transition-metal-free condition using a xanthate/formic acid mixture through proton-coupled electron transfer (PCET). Mechanistic experiments and DFT calculations support the possibility of a concerted proton electron-transfer (CPET) pathway. This Birch-type reduction demonstrates that a small nucleophilic organic molecule can be used as a single electron-transfer (SET) reducing agent with a proper proton source.



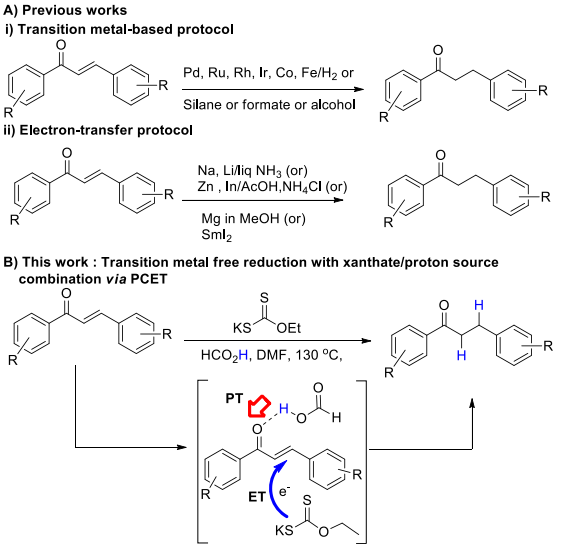
Chemoselective reduction plays a significant role in synthetic chemistry.[1] The selective reduction of a C=C bond in an α,β-unsaturated carbonyl compound is among one of the highly potent and challenging functional group transformations in organic chemistry. Although there are several ways to reduce the C=C bond of an α,β-unsaturated ketone selectively, all of them have their own merits and demerits. Transition-metal-catalyzed transfer hydrogenation[2] has proven to be an effective method for such transformations and has emerged as an alternative method for the traditional hydrogenation with hydrogen gas (H_2, Pd/C) (Scheme 1A (i)). However, the use of a relatively expensive metal complex, long reaction time, and metal contaminations are the general limitations of this elegant method.[3]

Dissolving metal reductions are also known for the selective reduction of the C=C bond of α,β-unsaturated ketones. The frequently used reagents are low-valent metals, which can easily donate one or two electrons to the molecules with an accessible LUMO in protic solvents. For examples, Li in liquid NH_3 (Birch-type reduction),[4] Mg in MeOH,[5] SmI_2 in H_2O,[6] and Zn in protic medium[7] have been used for the selective reduction of α,β-unsaturated ketones (Scheme 1A (ii)). But, metal leaching, a long reaction time, and cost of the metal constitute a persistent problem.

Therefore, the investigation of a simple, efficient, and transition-metal-free new reductive system for the chemoselective reduction of an α,β-unsaturated ketone is highly desirable

Recently, a number of neutral organic molecules known as "super electron donors" (SEDs) have been developed.[8] These SEDs undergo spontaneous loss of one or two electrons and can operate under milder reaction conditions than the reaction conditions required for dissolving metal reductions. Interestingly, the reduction potentials of these SEDs can be tuned by the appropriate modification of their structure.

Scheme 1. Selective Reduction of C=C Bond of α,β-Unsaturated Carbonyl Compound



Proton-coupled electron transfer (PCET) is another efficient process where the rate and energetics of the electron transfer (ET) can be modulated with appropriate proton sources.[9] According to Mayer et al. the term PCET encompasses the redox process where the proton transfer (PT) and ET among one or more reagents by a concerted or stepwise mechanism.[9a]

Received: February 20, 2019

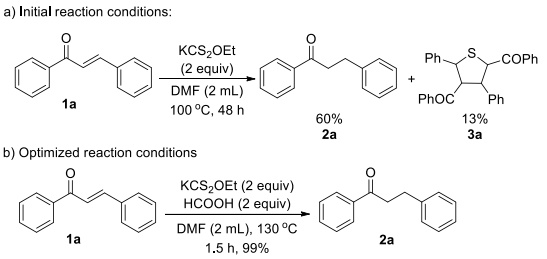
DOI: 10.1021/acs.orglett.9b00635
Org. Lett. XXXX, XXX, XXX−XXX

During PCET, the protons can modulate the electron-transfer process even if the protons do not transfer.[9a,10] Clearly, the addition of proper proton sources may offer a new general approach to enable an otherwise elusive ET process or to accelerate a slow ET process.

Recently, the reductive PCET has been employed for the reduction of the functional groups such as alkenes and ketones.[11] However, their application in selective reduction of functional groups in organic synthesis is not known. Considering the redox properties of potassium ethyl xanthate and their utility in the redox process,[12] herein, we describe how the easily available xanthate salt can act as a single electron donor and can reduce the C=C bond selectively in *α,β*-unsaturated carbonyl compounds in the presence of appropriate proton sources by following a PCET pathway (Scheme 1B). Importantly, this methodology shows that an easily available nucleophile can be used as an SET reducing agent in the presence of a proper proton source.

We started our investigation by examining the reaction between the chalcone **1a** (1 equiv) and potassium ethyl xanthate (2 equiv) in DMF at 100 °C (Scheme 2). After 48 h,

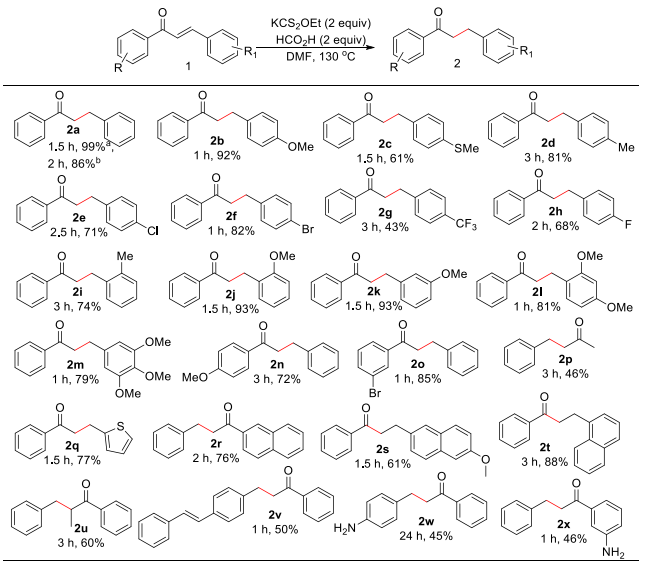
Scheme 2. Chemoselective Reduction of Chalcone by KCS_2OEt/HCO_2H



the reduced product 1,3-diphenylpropan-1-one **2a** was formed in 60% yield along with the Michael addition product **3a** in 13% yield (Scheme 2a).[13] This result indicated that the xanthate can act as an electron donor instead of a nucleophile. As DMF is a hygroscopic solvent and normal DMF contains some amount of water, we anticipated that the extent of electron-transfer process may be dependent on the concentration of the proton present in the reaction mixture. We observed that the formation of **2a** varied with different external proton sources and was completely suppressed when the reaction was carried out in dry solvent under nitrogen atmosphere (Table S1). Finally, a quick optimization of the reaction conditions showed that a 99% yield of **2a** can be obtained selectively with 2 equiv of xanthate and 2 equiv of formic acid in 2 mL of DMF at 130 °C in 1.5 h (Scheme 2b).

With this trustworthy protocol in hand, we then switched our attention in examining the scope of substrates, and the results are summarized in Scheme 3. The presence of electron-rich substituents such as methyl and methoxy at the *para*-position of the phenyl ring (*β*- to carbonyl) offered the desired products in good yields (**2b**–**2d**). Substrates with electron-withdrawing groups attached at the *para*-position of the phenyl rings were also compatible under the reaction conditions (**2e**–**2h**). When the phenyl ring (*β*- to carbonyl) contains the electron-releasing group at the *ortho*- and *meta*-positions, the yield of the products was moderate to good (**2i**–**2k**). Substrates with sterically crowded phenyl rings (*β*- to

Scheme 3. Substrate Scope with Various Enones



[a]Reaction conditions: **1** (0.5 mmol), xanthate (2 equiv), HCO_2H (2 equiv), DMF (2 mL) at 130 °C. [b]Reaction conditions: 1,3-diphenylprop-2-yn-1-one (0.5 mmol), xanthate (2 equiv), HCO_2H (2 equiv), DMF (2 mL) at 130 °C.

carbonyl) also reacted smoothly and furnished the desired products in high yields (**2l, 2m**).

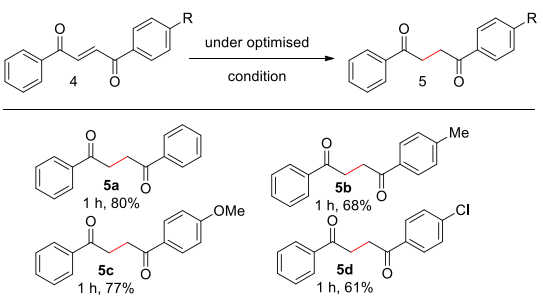
Substrates with the electron-rich and electron-deficient benzoyl rings provided a good yield of the products (**2n**–**2o**). Aliphatic ketone **2p** is well-tolerated under the reaction conditions, although low yield of the product was observed.

Substrates with aromatic rings such as thiophenyl and naphthyls were also suitable under the optimized conditions, resulting in moderate to good yields (**2q**–**2t**). The yield of the product was slightly reduced when the methyl group was present at the *α*-position of the ketone (**2u**).

The high selectivity of the present protocol was established when the electron-deficient alkene group was reduced selectively in the presence of another alkene group (**2v**). The free amine group was also observed to be well-tolerated under the optimized conditions, although a low yield of the reduced product was obtained for such substrates (**2w**, **2x**). Finally, the reduction was examined for (*E*)-1,4-arylbut-2-ene-1,4-dione. In all the cases, the corresponding saturated 1,4-ketones were obtained in high yields (Schemes 4 and 5a–d).

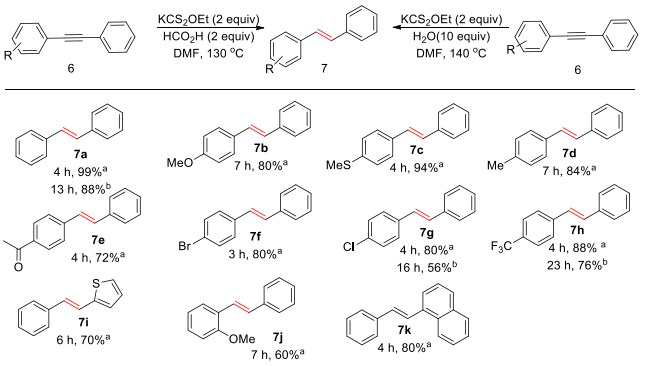
Our attention then turned to examine the efficiency of our PCET protocol for the hydrogenation of alkynes. Controlled hydrogenation of alkynes was achieved with excellent stereo-

Scheme 4. Substrate Scope with Various Diketones



DOI: 10.1021/acs.orglett.9b00635
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 5. Substrate Scope with Various Diaryl Alkynes



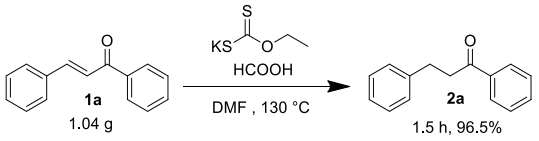
[a]Reaction conditions: **6** (0.5 mmol), xanthate (2 equiv), HCO_2H (2 equiv), DMF (2 mL) at 130 °C. [b]Reaction conditions: **6** (0.5 mmol), xanthate (2 equiv), H_2O (10 equiv), DMF (2 mL) at 140 °C.

selectivity to provide *E*-alkenes in good to excellent yield (Scheme 5).[14]

As shown in Scheme 5, the reaction was efficient with a broad spectrum of diphenyl alkynes bearing electron-rich, electron-poor, neutral, and heterocyclic aromatic rings (**7a**−**7i**)

Finally, to check the competence of this reduction in large scale, a gram scale (1.04 g) reaction was conducted under the optimized conditions, and the expected 1,3-diphenylpropan-1-one was obtained in 96.5% yield (Scheme 6).

Scheme 6. Gram Scale Reaction



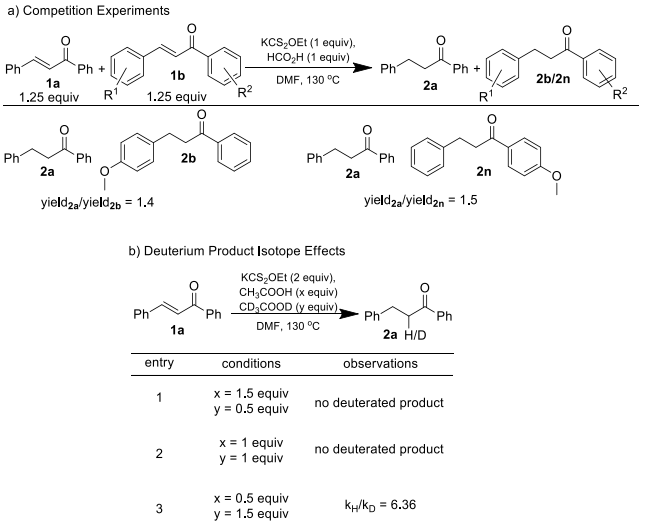
Three possible pathways can be proposed for this xanthate mediated selective reduction of chalcones in the presence of formic acid: (i) consecutive PT and ET; (ii) consecutive ET and PT; (iii) concerted transfer of electron and proton in a single kinetic step, which is known as concerted proton electron transfer or CPET.[15] All three of these pathways are considered as subsets of the PCET pathway.[9a,16]

The possibility of the pathway (i) (i.e., the initial PT followed by the ET) was probed with a competition experiment between **1a** and **1b** (Scheme 7a) following Mayer's work.[17] The reduction of a 1:1 ratio of **1a** and **1b** with a limited xanthate and formic acid mixture, yielded **2a** and **2b** in the ratio of 1.4:1.[18] This result is inconsistent with the initial rate-limiting proton transfer, because the methoxy-group-containing chalcone **1b** would form a more stable benzylic carbocation intermediate after the proton transfer, and consequently, the generation of the product **2b** would be faster than that of **2a**.

The possibility of the pathway (ii) (i.e., the initial ET followed by the PT) was checked by recording the redox potential of **1a** and potassium ethyl xanthate using a cyclic voltameter.[18] The results indicated that electron transfer from potassium ethyl xanthate ($E_{1/2}$ (oxidation) = −0.03 V vs Ag/Ag^+ in DMF) to **1a** ($E_{1/2}$ (oxidation) = 0.29 V vs Ag/Ag^+ in DMF) is unfavorable.

A competition experiment between **1a** and **1n** (1:1 mixture) was also carried out with a limited xanthate and formic acid

Scheme 7. Mechanistic Investigation for PCET Pathway



entry	conditions	observations
1	x = 1.5 equiv y = 0.5 equiv	no deuterated product
2	x = 1 equiv y = 1 equiv	no deuterated product
3	x = 0.5 equiv y = 1.5 equiv	k_H/k_D = 6.36

mixture (Scheme 7a). The ratio of the products **1a** and **1n** was observed to be 1.5:1 at the end of the reaction.[18] This result is also inconsistent with the initial rate-limiting electron-transfer pathway, because the methoxy-group-containing chalcone **1n** would form a more unstable anion radical intermediate after electron transfer, and consequently, a greater difference in the rate of generation of the product **2a** and **2n** would be observed.

As the reaction is viable in the presence of 2 equiv of acetic acid (Table S2, entry 16), product isotope effect (PIE) experiments were carried out (Scheme 7b) with the substrate **1a** in the presence of different mixtures of acetic acid and acetic acid-d_4.[18] No deuterium-labeled product was observed with 3:1 and 1:1 mixtures of acetic acid and acetic acid-d_4. However, with 1:3 mixture of acetic acid and acetic acid-d_4, a high product isotope effect (k_H/k_D = 6.36) was observed at the α-carbon to the keto group.[18] This observation is consistent with the concerted proton electron transfer or CPET pathway.[17]

The possibility of proton exchange between the starting material and acetic acid-d_4 as well as between the product and acetic acid-d_4 during the course of the reaction was examined, and no α-H exchange with deuterium was observed.[18]

Finally, the thermochemistry of this PCET pathway was studied[18] using quantum chemical calculations.[9a,19] Again, the CPET pathway was observed to be favorable.

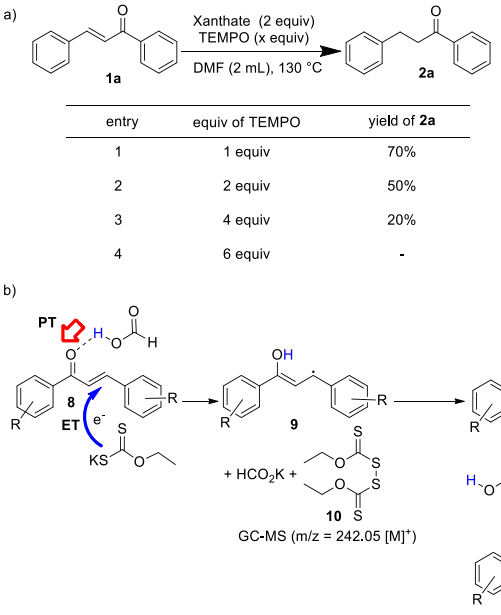
To understand more about the reaction, the reduction of **1a** was carried out in the presence of different amounts of TEMPO (Scheme 8a). This observation suggested that the reaction might follow a radical pathway.

A plausible mechanism for this reaction was proposed (Scheme 8b). After PCET, the reaction proceeds through the radical intermediate **9** and generates the byproduct dixanthogen **10**, which was detected in GC−MS. The intermediate **9** can be tautomerized to generate radical intermediate **11.** The radical **11** can be transformed to product **12** via an additional proton and electron transfer from the HCOOH/xanthate mixture. This proton and electron transfer can be concerted or stepwise. However, a detailed investigation of the mechanism of this reaction is presently underway.

In conclusion, we have developed a PCET protocol for selective reduction of a C=C functionality of α,β-unsaturated carbonyl compounds with a mixture of xanthate and formic

DOI: 10.1021/acs.orglett.9b00635
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 8. Plausible Mechanism for the Selective Reduction of C=C of α,β-Unsaturated Carbonyl Compound



entry	equiv of TEMPO	yield of **2a**
1	1 equiv	70%
2	2 equiv	50%
3	4 equiv	20%
4	6 equiv	-

acid for the first time. The reaction is an easy and user-friendly alternative to the dissolving metal reductions. The mechanistic investigation suggested that the reaction follows a concerted proton and electron transfer or CPET pathway. Importantly, this new reaction methodology indicates that a small nucleophilic organic molecule can be used as a SET reducing agent in the presence of a proper proton source such as HCO_2H.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00635.

Detailed experimental procedures, characterization data, and copies of NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: gsekar@iitm.ac.in.

ORCID

Govindasamy Sekar: 0000-0003-2294-0485

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

G.S and S.G thank IIT Madras for the IRDA project. We thank DST-FIST (for instrumentation facilities and HPCE) and IIT Madras (for computational facilities). R.P. thanks DST-SERB for NPDF.

■ REFERENCES

(1) (a) Wang, D.; Astruc, D. *Chem. Rev.* **2015**, *115*, 6621−6686. (b) Leutenegger, U.; Madin, A.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 60−61. (c) Odendaal, A. Y.; Trader, D. J.; Carlson, E. E. *Chem. Sci.* **2011**, *2*, 760−764. (d) Perez, I.; Avila-Zarraga, J. G. *Tetrahedron Lett.* **2018**, *59*, 3077−3079. (e) Frontier, A. J.; Raghavan, S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2000**, *122*, 6151−6159.

(2) (a) Ding, Z.; Zhang, Y.; Liu, M.; Sugiya, M.; Imamoto, I.; Zhang, W. *Org. Lett.* **2013**, *15*, 3690−3693. (b) Gomez-Lopez, J. L.; Chavez, D.; Parra-Hake, M.; Royappa, A. T.; Rheingold, A. L.; Grotjahn, D. B.; Miranda-Soto, V. *Organometallics* **2016**, *35*, 3148−3153. (c) Baan, Z.; Finta, Z.; Keglevich, G.; Hermecz, I. *Green Chem.* **2009**, *11*, 1937−1940. (d) Jagtap, S.; Kaji, Y.; Fukuoka, A.; Hara, K. *Chem. Commun.* **2014**, *50*, 5046−5048. (e) Broggi, J.; Jurcik, V.; Songis, O.; Poater, A.; Cavallo, L.; Slawin, A. M. Z.; Cazin, C. S. J. *J. Am. Chem. Soc.* **2013**, *135*, 4588−4591. (f) Lator, A.; Gaillard, S.; Poater, A.; Renaud, J.-L. *Chem. - Eur. J.* **2018**, *24*, 5770−5774.

(3) (a) Sun, C. L.; Shi, Z. J. *Chem. Rev.* **2014**, *114*, 9219−9280. (b) Garrett, C.; Prasad, K. *Adv. Synth. Catal.* **2004**, *346*, 889.

(4) (a) Taschner, M. J.; Shahripour, A. *J. Am. Chem. Soc.* **1985**, *107*, 5570−5572. (b) Ling, T.; Chowdhury, C.; Kramer, B. A.; Vong, B. G.; Palladino, M. A.; Theodorakis, E. A. *J. Org. Chem.* **2001**, *66*, 8843−8853.

(5) Hudlicky, T.; Sinai-Zingde, G.; Natchus, M. G. *Tetrahedron Lett.* **1987**, *28*, 5287−5290.

(6) (a) Davies, S. G.; Rodriguez-Solla, H.; Tamayo, J. A.; Garner, A. C.; Smith, A. D. *Chem. Commun.* **2004**, 2502−2503. (b) Dahlen, A.; Hilmersson, G. *Chem. - Eur. J.* **2003**, *9*, 1123−1128. (c) Davies, S. G.; Rodrıguez-Solla, H.; Tamayo, J. A.; Cowley, A. R.; Concellon, C.; Garner, A. C.; Parkes, A. L.; Smith, A. D. *Org. Biomol. Chem.* **2005**, *3*, 1435−1447. (d) Keck, G. E.; McLaws, M. D. *Tetrahedron Lett.* **2005**, *46*, 4911−4914.

(7) Li, J.; Zhang, Y.-X.; Ji, Y. J. *J. Chin. Chem. Soc.* **2008**, *55*, 390−393.

(8) (a) Broggi, J.; Terme, T.; Vanelle, P. *Angew. Chem., Int. Ed.* **2014**, *53*, 384−413. (b) Murphy, J. A. *J. Org. Chem.* **2014**, *79*, 3731−3746.

(9) (a) Warren, J. J.; Tronic, T. A.; Mayer, J. M. *Chem. Rev.* **2010**, *110*, 6961−7001. (b) Gentry, E. C.; Knowles, R. R. *Acc. Chem. Res.* **2016**, *49*, 1546−1556. (c) Hoffmann, N. *Eur. J. Org. Chem.* **2017**, *2017*, 1982−1992.

(10) Young, E. R.; Rosenthal, J.; Hodgkiss, J. M.; Nocera, D. G. *J. Am. Chem. Soc.* **2009**, *131*, 7678−7684.

(11) (a) Markle, T. F.; Darcy, J. W.; Mayer, J. M. *Sci. Adv.* **2018**, *4*, eaat5776. (b) Kolmar, S. S.; Mayer, J. M. *J. Am. Chem. Soc.* **2017**, *139*, 10687−10692. (c) Chciuk, T.; Anderson, W. R.; Flowers, R. A. *J. Am. Chem. Soc.* **2016**, *138*, 8738−8741. (d) Tarantino, K. T.; Liu, P.; Knowles, R. R. *J. Am. Chem. Soc.* **2013**, *135*, 10022−10025.

(12) (a) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102−113. (b) Teply, F. Czech, Collect. *Collect. Czech. Chem. Commun.* **2011**, *76*, 859−917. (c) Chmielewski, T.; Lekki, J. *Miner. Eng.* **1989**, *2*, 387−391. (d) Zohir, N.; Mustapha, B.; Elbaki, D. A. *J. Miner. Mater. Charact. Eng.* **2009**, *8*, 469−477.

(13) LaLonde, R. T.; Codacovi, L.; He, C. H.; Xu, C. F.; Clardy, J.; Krishnan, B. S. *J. Org. Chem.* **1986**, *51*, 4899−4905.

(14) *E*-Selectivity is confirmed by melting point of commercially available *E*-stilbin and also by crude NMR of (*E*)-1-methyl-4-styrylbenzene.

(15) Costentin, C.; Evans, D. H.; Robert, M.; Savéant, J. M.; Singh, P. S. *J. Am. Chem. Soc.* **2005**, *127*, 12490.

(16) (a) Cukier, R. I.; Nocera, D. G. *Annu. Rev. Phys. Chem.* **1998**, *49*, 337. (b) Weinberg, D. R.; Gagliardi, C. J.; Hull, J. F.; Murphy, C. F.; Kent, C. A.; Westlake, B. C.; Paul, A.; Ess, D. H.; McCafferty, D. G.; Meyer, T. J. *Chem. Rev.* **2012**, *112*, 4016.

(17) Kolmar, S. S.; Mayer, J. M. J. *J. Am. Chem. Soc.* **2017**, *139*, 10687−10692.

(18) See Supporting Information for details.

(19) (a) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215−241. (b) Ljubic, I.; Sabljic, A.; Bonifačić, M. *J. Phys. Chem. B* **2016**, *120*, 11810−11820. (c) Jacob, G. V.; Sutradhar, S.; Patnaik, A. *New J. Chem.* **2016**, *40*, 7431−7436. (d) Meyer, T. J.; Huynh, M. H. V.; Thorp, H. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 5284−5304.

DOI: 10.1021/acs.orglett.9b00635
Org. Lett. XXXX, XXX, XXX−XXX