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Catalytic Olefin Hydroamidation Enabled by Proton-Coupled Electron Transfer

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Supporting Information

ABSTRACT: Here we report a ternary catalyst system for the intramolecular hydroamidation of unactivated olefins using simple *N*-aryl amide derivatives. Amide activation in these reactions occurs via concerted proton-coupled electron transfer (PCET) mediated by an excited state iridium complex and weak phosphate base to furnish a reactive amidyl radical that readily adds to pendant alkenes. A series of H-atom, electron, and proton transfer events with a thiophenol cocatalyst furnish the product and regenerate the active forms of the photocatalyst and base. Mechanistic studies indicate that the amide substrate can be selectively homolyzed via PCET in the presence of the thiophenol, despite a large difference in bond dissociation free energies between these functional groups.

Olefin hydroamidation is a powerful approach to C−N bond construction, and one that continues to motivate the development of new synthetic methods.[1−3] Among the most versatile hydroamidation technologies reported to date are those that make use of amidyl radicals. Pioneering contributions from Newcomb, Zard, Studer, Nicolaou and others have demonstrated that amidyl-based methods benefit from broad scope, predictable *anti*-Markovnikov regioselectivity, and low kinetic barriers to C−N bond formation.[4] While enabling, these methods typically require either prefunctionalization of the amide nitrogen or the use of strong stoichiometric oxidants to facilitate efficient amidyl generation (Figure 1). As such, catalytic schemes for radical hydroamidation that utilize native amide substrates and occur under redox-neutral conditions have the potential to significantly increase the value and atom economy of these methods.

To this end, we recently disclosed a catalytic protocol for olefin carboamination enabled by proton-coupled electron transfer (PCET) activation of *N*-aryl amides.[5,6] In this process, a weak phosphate base and an excited state Ir photocatalyst jointly mediate the homolysis of a strong anilide N−H bond, furnishing a reactive amidyl radical that can undergo addition to a pendant olefin.[7] Here we demonstrate that this manner of PCET activation can be further leveraged to enable efficient intramolecular hydroamidation reactions of unactivated olefin partners when carried out in the presence of a thiol H-atom donor cocatalyst (Figure 1). The development, scope, and mechanistic evaluation of this process are described herein.

Reaction Design and Optimization. Building on our carboamination protocol, we elected to retain the Ir(dF(CF$_3$)-ppy)$_2$(bpy)PF$_6$ photocatalyst and dibutyl phosphate base

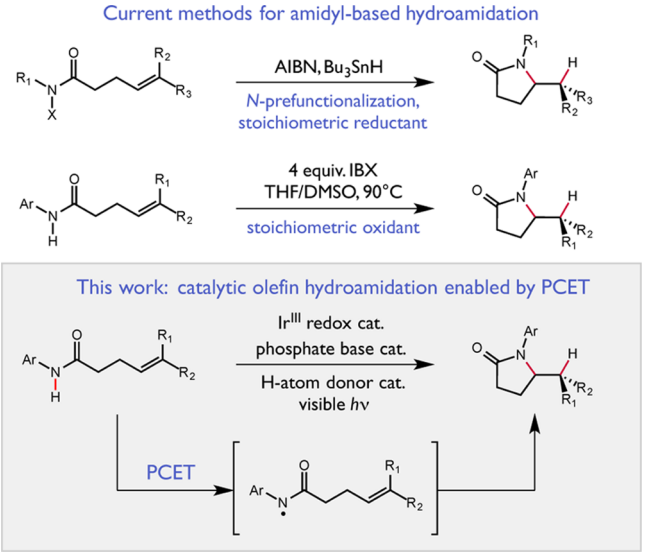

Figure 1. Catalytic olefin hydroamidation enabled by PCET activation of amide N−H bonds.

combination found to be most effective for amidyl generation. Subsequent olefin addition would result in C−N bond formation and creation of a nascent carbon-centered radical that would be reduced by an appropriate H-atom donor catalyst (Scheme 1). Next, the oxidized form of the HAT catalyst could accept an electron from the reduced form of the photocatalyst to form an anion. In turn this anion would be protonated by the phosphoric acid produced in the PCET event to regenerate the active forms of all three catalytic components. The feasibility of this proposal finds support in similar schemes reported recently for photocatalytic olefin hydrofunctionalization, most notably in the work of Nicewicz.[3a,8]

A principal concern in the development of such a process was identifying conditions wherein the amide N−H bond can be selectively homolyzed in the presence of the H-atom donor. In homolytic bond activations, selectivities are often correlated with a bond strength differential, with weaker bonds being activated preferentially.[9] As the substrate anilide N−H bonds are significantly stronger (BDFEs ≈ 100 kcal/mol) than those of any commonly used H-atom donors, it was not clear at the outset that chemoselective amide homolysis would be feasible. With these considerations in mind, we evaluated a number of potential HAT catalysts in the hydroamidation of amide **1** (Table 1). First,

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Scheme 1. Proposed Catalytic Cycle

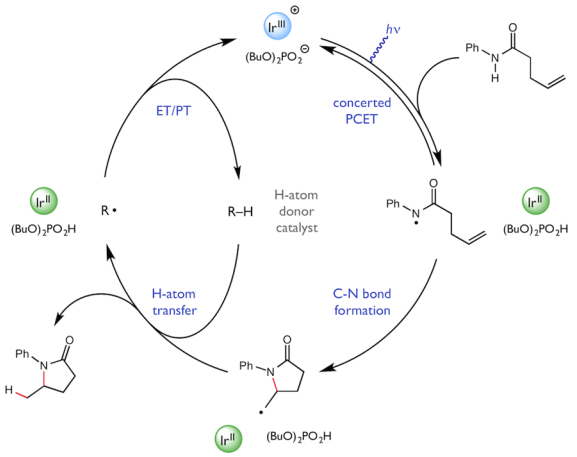
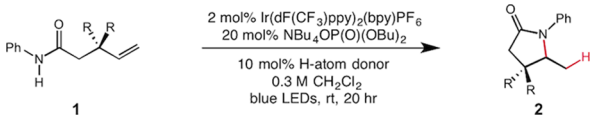


Table 1. Optimization Studies[a]



entry	R	H-atom donor	yield (%)
1	H	none	24
2	Me	none	0
3	H	phenol	18
4	H	2,4,6-tBu-phenol	19
5	H	4-aminopyridine	21
6	H	diphenyl acetonitrile	28
7	H	Ph_3SiH	16
8	H	thiophenol	95
9	H	2-naphthalenethiol	45
10	H	4-trifluoromethyl thiophenol	86
11	H	2,4,6-iPr-thiophenol	83
entry	R	change from best conditions (entry 8)	yield (%)
12	H	no light	0
13	H	no photocatalyst	0
14	H	no $NBu_4OP(O)(OBu)_2$	0
15	Me	none	89

[a]Optimization reactions run on 0.1 mmol scale. Yields determined by ^{1}H NMR analysis of the crude reaction mixture relative to an internal standard. Irradiation supplied by 4 W blue LED strips.

we observed that when amide **1** was subjected to irradiation with blue LEDs in the presence of 2 mol % $Ir(dF(CF_3)ppy)_2(bpy)PF_6$ and 20 mol % dibutyl phosphate a small amount of lactam **2** was produced together with additional nonproductive substrate conversion (Table 1, entry 1). This finding was attributed to the ability of the carbon-centered radical formed in the amidyl cyclization to abstract a H-atom from the weak allylic C–H bonds present in the starting material.[10] Consistent with this hypothesis, when these allylic protons are replaced with methyl groups, no product was observed (entry 2). Addition of catalytic quantities of many common H-atom donor classes, including phenols, triphenylsilane, arylamines, and diphenyl acetonitrile, did not provide a meaningful improvement over background (entries 3–7). Yet, we were pleased to find that inclusion of 10 mol % of thiophenol produced the desired hydroamidation product **2** in 95% yield (entry 8). Further evaluation of electronically and structurally varied thiophenols demonstrated that none were better than the parent catalyst (entries 9–11). Control experiments run in the absence of light, photocatalyst, or phosphate base furnished none of the desired product (entries 12–14). The success of thiophenol was somewhat surprising in that thiols are known to be substrates for multisite PCET activation[11] and the thiophenol S–H bond is more than 20 kcal/mol weaker (S–H BDFE ≈ 79 kcal/mol)[12] than the N–H bond of the amide substrate (N–H BDFE ≈ 99 kcal/mol).[13] The observation of efficient amide activation in the presence of such a large thermodynamic bias raises intriguing questions about the origins of selectivity in radical generation (*vide infra*).

Substrate Scope. With these optimized reaction conditions, we set out to examine the scope of this new hydroamidation process. On preparative scale, model amide **1** underwent hydroamidation to provide lactam **2** in 85% isolated yield (Table 2). With respect to the olefin component, a variety of di-, tri-, and tetrasubstituted olefins with differing substitution patterns were successfully accommodated (**3**–**6**). Styrenyl acceptors could also be utilized, though an increased loading of the thiophenol (30 mol %) was required to achieve optimal yields (**7**). Steric hindrance adjacent to the site of C–N bond formation was also tolerated (**8**). In addition to amide substrates, the hydroamidations of carbamates and ureas proceed smoothly under the standard conditions (**6**, **7**, **9**, **10**). As such the reported method provides a simple means of converting common allylic alcohol and allylic amine starting materials to vicinal amino alcohols and 1,2-diamines, respectively. Thiolcarbamates could also be cyclized to furnish thiazolidinone products (**11**). Acyclic carbamates derived from stereogenic allylic alcohols could also be amidated with synthetically useful levels of diastereoselectivity (**12**, **13**). Moreover, these reactions are largely insensitive to the olefin geometry of the substrate as carbamates derived from the isomeric polyolefins nerol and geraniol both cyclized to afford **14** in high yield. Interestingly, when hydroamidation reactions of either of these isomeric starting materials were run to partial conversion, no olefin isomerization was observed in the recovered starting material, suggesting C–N bond formation in these reactions is irreversible.

In addition to these acyclic examples, a number of bicyclic products (**15**–**19**) could be synthesized in excellent yield and high diastereoselectivity, including oxazolidinones derived from both diastereomers of carveol. Notably, these substrates demonstrate distal olefin functionality and unprotected hydroxyl groups are well tolerated. In addition, spirocyclic products bearing tertiary carbinamine centers were also accessible under standard conditions (**20**). Moreover, hydroamidation of canonical Diels–Alder products could also be accomplished to afford more complex polycyclic structures (**21**, **22**). The reaction is also successful with differentially protected glucal substrates (**23**, **24**) to furnish deoxygenated amino sugars. A number of natural product derivatives were also investigated as substrates. An amide derived from *cis*-chrysanthemic acid was successfully cyclized to deliver a fused 3,5-ring system in good yield and excellent diastereoselectivity (**25**). Similarly, a progesterone-derived carbamate was hydroamidated to furnish a vicinal amino alcohol on a steroid framework as a single detectable diastereomer (**26**). Lastly, a carbamate derived from the bridgehead alcohol of gibberellic acid provided complex polycyclic oxazolidinone **27** in 68% isolated yield.

With respect to the arene component, a variety of substituted phenyl derivatives were investigated (**28**–**38**). Of note, both electron-deficient and -rich anilides cyclized smoothly, including an oxidatively cleavable PMP derivative (**28**).[4f] Aryl bromide

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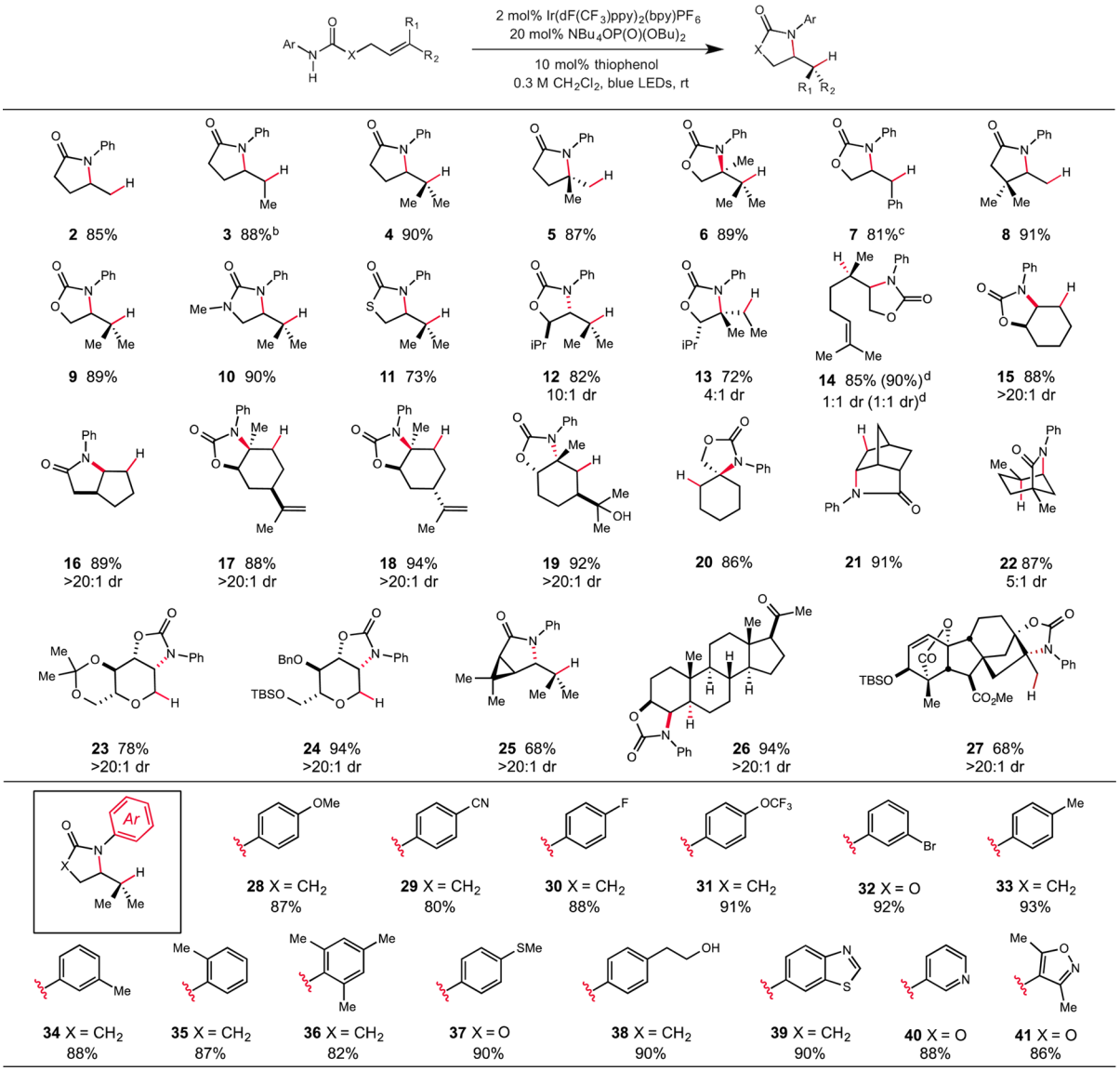
Table 2. Substrate Scope



[a]Reactions run on 1.0 mmol scale. Reported yields are for isolated and purified material and are the average of two experiments. Irradiation supplied by a 34 W Kessil LED lamp. Diastereomeric ratios determined by ^{1}H NMR analysis of the crude reaction mixtures. [b]Starting material was a *trans* olefin. [c]30 mol % thiophenol. [d]Yield and dr in parentheses are for a geraniol-derived substrate.

partners could be tolerated without any observable dehalogenation (**32**). Moreover, the reaction also proved insensitive to *ortho*-substitution (**35**) and even a sterically hindered mesityl-derived lactam **36** could be produced with high efficiency. In addition, functional groups that are typically incompatible with the current state-of-the-art hydroamidation methods employing strong iodonium oxidants, such as thioethers and unprotected primary alcohols, are readily accommodated by this catalytic protocol (**37**, **38**).[14] Numerous *N*-heteroaryl amides proved to be competent starting materials as well, undergoing hydroamidation in good to excellent yields (**39**–**41**). With respect to limitations, this method currently does not accommodate intermolecular couplings or the formation of larger rings with high efficiency. In both cases we believe that favorable back electron transfer between the amidyl and the reduced form of the photocatalyst is kinetically favored over productive C–N bond formation. Efforts to address these limitations and expand the scope of this process to include *N*-alkyl amides are ongoing.

Mechanistic Studies. The synthetic results reported above suggest that amidyl generation is possible in the presence of the thiophenol, despite the fact that both functionalities are known substrates for multisite PCET and a significant thermodynamic driving force ($\Delta\Delta G^\circ \approx 20$ kcal/mol) for thiol activation.[5,11] To shed light on these issues, we designed a series of competitive luminescence quenching experiments. First, we observed that neither acetanilide nor thiophenol affect the emission intensity of the Ir photocatalyst in CH_2Cl_2. However, solutions containing either amide or thiol as well as a phosphate base lead to efficient and concentration-dependent luminescence quenching (acetanilide $K_{sv} = 2860$ M^{-1} and thiophenol $K_{sv} = 470$ M^{-1}), consistent with PCET activation. Tellingly, solutions containing fixed concentrations of thiol and phosphate and varying concentrations of amide exhibited quenching that retained a first-order dependence on the amide concentration, albeit with slightly reduced efficiency ($K_{sv} = 1250$ M^{-1}). However, analogous experiments wherein solutions containing fixed concentrations

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of both amide and phosphate and varying concentrations of thiol exhibited no additional quenching above background. Taken together, these results indicate that amide PCET in the presence of a thiophenol is not only feasible but is likely the kinetically dominant reaction pathway for radical generation.

While the physical origins of this surprising selectivity are not certain, one potential explanation relates to the differential hydrogen bond donor abilities of the amide and thiol functionalities. Multisite PCET oxidations require the formation of a hydrogen bond between the transferring proton and the Brønsted base prior to the electron transfer event.[15] Density functional calculations (ωB97XD 6-31G++(2d,2p) CPCM=CH_2Cl_2) indicate that formation of the amide-phosphate H-bond complex is more favorable than the thiophenol−phosphate H-bond complex by 5.2 kcal/mol.[16,17] As such, there is a significantly higher concentration of amide−phosphate complex relative to the thiol−phosphate complex in solution which may contribute to this unusual but synthetically advantageous selectivity.

In conclusion, we have developed a novel method for olefin hydroamidation jointly mediated by three distinct catalysts−an iridium photocatalyst, a phosphate base, and a thiol H-atom donor. This protocol enables catalytic amidyl generation directly from simple amide starting materials and accommodates a wide variety of olefinic reaction partners. More fundamentally, this work demonstrates that multisite PCET enables the selective homolysis of strong anilide N−H bonds in the presence of a thiol with a much weaker S−H bond. Efforts to understand and generalize the basis of this surprising selectivity are currently ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b09671.

Experimental procedures and characterization data (PDF)
Crystallographic data for Structure **14** in Table 2 (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Gooßen, L. J.; Rauhaus, J. E.; Deng, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4042. (b) Wang, X.; Widenhoefer, R. A. *Organometallics* **2004**, *23*, 1649. (c) LaLonde, R. L.; William, E.; Brenzovich, W. E., Jr.; Benitez, D.; Tkatchouk, E.; Kelley, K.; Goddard, W. A., III; Toste, F. D. *Chem. Sci.* **2010**, *1*, 226. (d) Komeyama, K.; Morimoto, T.; Takaki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2938.

(2) For selected advances in catalytic hydroamination, see: (a) Utsunomiya, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 2702. (b) Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673. (c) Waser, J.; Gaspar, B.; Nambu, H.; Carreira, E. M. *J. Am. Chem. Soc.* **2006**, *128*, 11693. (d) Cochran, B. M.; Michael, F. E. *J. Am. Chem. Soc.* **2008**, *130*, 2786. (e) Shen, X.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 564. (f) Brown, A. R.; Uyeda, C.; Brotherton, C. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2013**, *135*, 6747. (g) Sevov, C. S.; Zhou, J. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 3200. (h) Yang, Y.; Shi, S. − L.; Liu, P.; Buchwald, S. L. *Science* **2015**, *349*, 62.

(3) For examples of photoredox-mediated olefin amination, see: (a) Nguyen, T. M.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2013**, *135*, 9588. (b) Nguyen, T. M.; Manohar, N.; Nicewicz, D. A. *Angew. Chem., Int. Ed.* **2014**, *53*, 6198. (c) Gesmundo, N. J.; Grandjean, J. M.; Nicewicz, D. A. *Org. Lett.* **2015**, *17*, 1316. (d) Musacchio, A. J.; Nguyen, L. Q.; Beard, G. H.; Knowles, R. R. *J. Am. Chem. Soc.* **2014**, *136*, 12217. (e) Hu, Q.-X.; Chen, J.-R.; Wei, Q.; Liu, F.-L.; Deng, Q.-H.; Beauchemin, A. M.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 12163. (f) Maity, S.; Zheng, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 9562.

(4) (a) Newcomb, M.; Esker, J. L. *Tetrahedron Lett.* **1991**, *32*, 1035. (b) Boivin, J.; Callier-Dublanchet, A.-C.; Quiclet-Sire, B.; Schiano, A.-M.; Zard, S. Z. *Tetrahedron* **1995**, *51*, 6517. (c) Kemper, J.; Studer, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 4914. (d) Guin, J.; Frohlich, R.; Studer, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 779. (e) Chou, C. M.; Guin, J.; Muck-Lichtenfeld, C.; Grimme, A.; Studer, A. *Chem. - Asian J.* **2011**, *6*, 1197. (f) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Barluenga, S.; Hunt, K. W.; Kranich, R.; Vega, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 2233. (g) Tang, Y.; Li, C. *Org. Lett.* **2004**, *6*, 3229.

(5) Choi, G. C.; Knowles, R. R. *J. Am. Chem. Soc.* **2015**, *137*, 9226.

(6) (a) Reece, S. Y.; Nocera, D. G. *Annu. Rev. Biochem.* **2009**, *78*, 673. (b) Mayer, J. M. *Annu. Rev. Phys. Chem.* **2004**, *55*, 363. (c) Hammes-Schiffer, S.; Stuchebrukhov, A. A. *Chem. Rev.* **2010**, *110*, 6939. (d) 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.

(7) For examples of excited-state PCET, see: (a) Wenger, O. S. *Acc. Chem. Res.* **2013**, *46*, 1517. (b) Gagliardi, C. J.; Westlake, B. C.; Kent, C. A.; Paul, J. J.; Papanikolas, J. M.; Meyer, T. J. *Coord. Chem. Rev.* **2010**, *254*, 2459. (c) Tarantino, K. T.; Liu, P.; Knowles, R. R. *J. Am. Chem. Soc.* **2013**, *135*, 10022.

(8) (a) Hamilton, D. S.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2012**, *134*, 18577. (b) Wilger, D. J.; Grandjean, J.-M.; Lammert, T. R.; Nicewicz, D. A. *Nat. Chem.* **2014**, *6*, 720.

(9) Warren, J. J.; Mayer, J. M. *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107*, 5282.

(10) (a) Roberts, B. P.; Steel, A. J. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2155. (b) Pais, A. A. C. C.; Arnaut, L. G.; Formosinho, S. J. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2577.

(11) (a) Gagliardi, C. J.; Murphy, C. F.; Binstead, R. A.; Thorp, H. H.; Meyer, T. J. *J. Phys. Chem. C* **2015**, *119*, 7028. (b) Medina-Ramos, J.; Oyesanya, O.; Alvarez, J. C. *J. Phys. Chem. C* **2013**, *117*, 902. (c) Kuss-Petermann, M.; Wenger, O. S. *J. Phys. Chem. Lett.* **2013**, *4*, 2535.

(12) Bordwell, F. G.; Cheng, J.-P.; Ji, G.-Z.; Satish, A. V.; Zhang, X. *J. Am. Chem. Soc.* **1991**, *113*, 9790.

(13) Cheng, J. P.; Zhao, Y. Y. *Tetrahedron* **1993**, *49*, 5267.

(14) (a) Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272. (b) Shukla, V. G.; Salgaonkar, P. D.; Akamanchi, K. G. *J. Org. Chem.* **2003**, *68*, 5422.

(15) (a) Turro, C.; Chang, C. K.; Leroi, G. E.; Cukier, R. I.; Nocera, D. G. *J. Am. Chem. Soc.* **1992**, *114*, 4013. (b) Kirby, J.; Roberts, J.; Nocera, D. G. *J. Am. Chem. Soc.* **1997**, *119*, 9230. (c) Young, E. R.; Rosenthal, J.; Hodgkiss, J. M.; Nocera, D. G. *J. Am. Chem. Soc.* **2009**, *131*, 7678. (d) Sjodin, M.; Irebo, T.; Utas, J. E.; Lind, J.; Merenyi, G.; Akermark, B.; Hammarstrom, L. *J. Am. Chem. Soc.* **2006**, *128*, 13076. (e) Markle, T. F.; Mayer, J. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 738.

(16) Chai, J. D.; Head-Gordon, M. *Phys. Chem. Chem. Phys.* **2008**, *10*, 6615.

(17) For the performance of this functional to describe hydrogen bonding: DiLabio, G. A.; Johnson, E. R.; Otero-de-la-Roza, A. *Phys. Chem. Chem. Phys.* **2013**, *15*, 12821.

DOI: 10.1021/jacs.5b09671
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