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Bifunctional Copper-Based Photocatalyst for Reductive Pinacol-Type Couplings.

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ABSTRACT: A bifunctional copper-based photocatalyst has been prepared that employs a pyrazole-pyridine ligand incorporating a sulfonamide moiety that functions as an intramolecular hydrogen-bond donor for a photochemical PCET process. In typical reductive PCET processes, the photocatalyst and H-bond donor must have an appropriate redox potential and pKa respectively to promote the PCET. When working in concert in a bifunctional catalyst such as Cu(pypzs)(BINAP)BF_4, the pKa of the H-bond donor can have an acidity that is orders of magnitude less and still efficiently promote the PCET process. A reductive pinacol-type coupling can be performed using a base-metal derived photocatalyst to afford valuable diols (24 examples, 46-99 % yield), from readily available aldehydes and ketones.

Photocatalysis can impact sustainable chemistry through promoting unique reactivity and achieving novel transformations, under relatively mild conditions.[1] Consequently, much interest has been placed on synthesis employing visible-light and inexpensive photocatalysts at low catalyst loadings. In the last half-dozen years, copper-based photocatalysis has attracted considerable attention. Cu-based complexes are generally easily prepared, can promote photochemistry through outer- and inner-sphere mechanisms, can exhibit long excited state lifetimes and are excellent excited-state reductants.[2] As such, they are attractive photocatalysts for a variety of transformations,□ including proton-coupled electron transfers (PCETs). PCETs are non-classical redox processes in which a proton and electron are exchanged in a concerted manner,□□and can proceed via both oxidative and reductive manifolds. In the reductive homolytic activation of ketones,□ some photocatalysts (PCs) may not possess an excited state capable of promoting the PCET process. As such, the PC in its excited state abstracts an electron from an electron donor (reductive quenching), such as a tertiary amine, and it is the ground state radical anion that participates in the PCET process (Figure 1, *top left*). In some instances, it has been proposed that the radical cation of the tertiary amine can act to promote the single-electron transfer (SET) from the PC radical anion via hydrogen bonding, or 2-electron/3-center bonding.[7] If the excited state of a photocatalyst has a sufficiently high excited state potential, it will donate an electron directly via the excited state to a carbonyl (oxidative quenching) that is simultaneously activated via hydrogen-bonding, typically achieved with an added acid in the reaction mixture (Figure 1, *top right*). The PCET process generates a ketyl radical for further chemistry, and the PC is regenerated via SET with an electron-doner, again typically a tertiary amine. Considering the aforementioned mechanisms, it was proposed that connecting both the PC and the acid activator within the same catalyst structure could improve PCET processes. Through proximity, the rate of PCET could be increased, improving yields.□ Association of the ketone (or aldehyde) with the bifunctional catalyst could result in the steric environment influencing the stereoselectivity of the resulting chemistry of the ketyl radical. Preferably, designing a bifunctional catalyst would take place from PCs that have already demonstrated ease of synthesis, tunability, and application in PCET processes. Consequently, heteroleptic copper-based complexes were selected as ideal candidates; our group has previously evaluated libraries of heteroleptic copper-based complexes having one diamine and one bisphosphine ligand for photocatalysis, and reported their activity in a PCET process involving the homolytic activation of ketones, generating neutral ketyl radicals.□ Herein we report on the synthesis and evaluation of a bifunctional copper-based photocatalyst in reductive pinacol-type PCET processes.

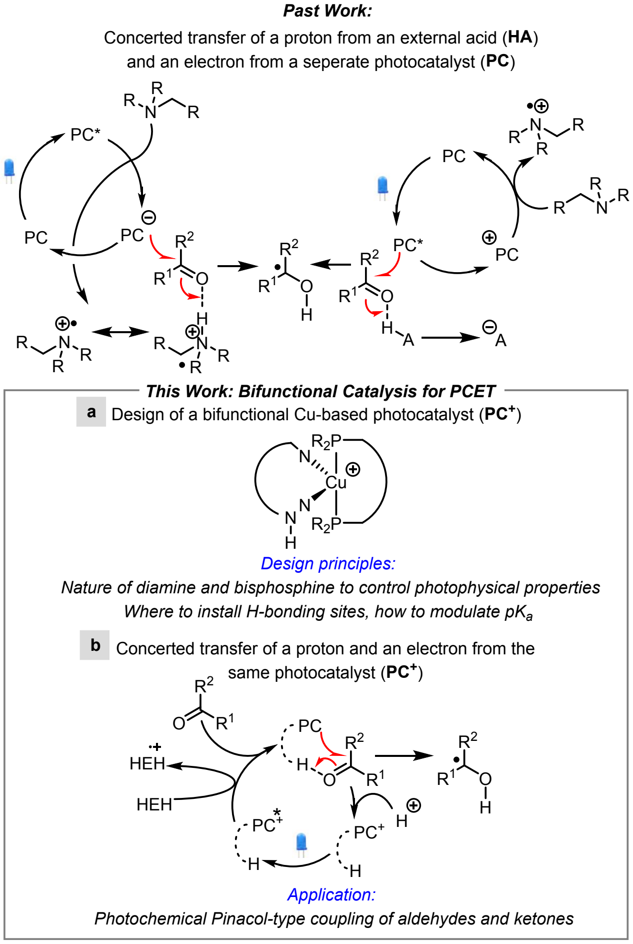
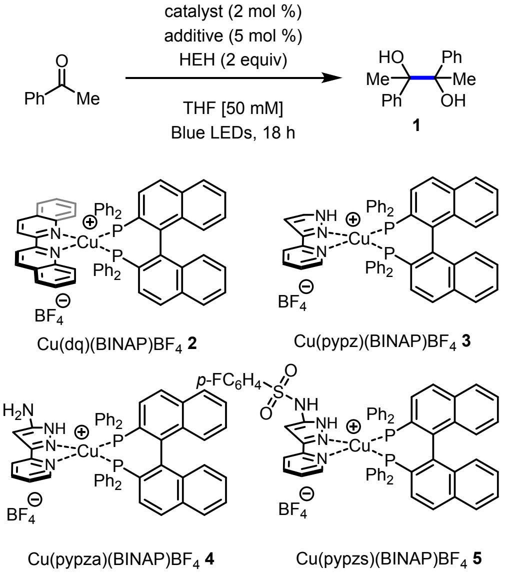


Figure 1. Bifunctional catalysis for photocatalytic PCET reactions.

To investigate the possibility of using a bifunctional catalyst for photocatalytic PCET reactions, the pinacol-type reductive coupling of ketones was selected for study.[1□] The photochemical pinacol-type coupling has been previously reported by Rueping and co-workers using an Ir-based catalyst system,[7] while some organic dyes have also been show to effective photocatalysts.[11a] The pinacol process provides access to valuable diol products and alternative synthetic routes call for excess amounts of reducing metals and trialkylsilane-based protection strategies to prevent inhibition with the metal-based reagents.[11]

Table 1. Pinacol-Type Coupling Employing Bifunctional Cu-Based Photocatalysts.



	Catalyst	Additive	Yield 1 (%)^{a}
1	Cu(dq)(BINAP)BF$_4$	dppa	90
2	Cu(dq)(BINAP)BF$_4$	-	0
3	Cu(pypz)(BINAP)BF$_4$	dppa	78
4	Cu(pypz)(BINAP)BF$_4$	-	25
5	Cu(pypza)(BINAP)BF$_4$	dppa	95
6	Cu(pypza)(BINAP)BF$_4$	-	14
7	Cu(pypzs)(BINAP)BF$_4$	dppa	86
8	Cu(pypzs)(BINAP)BF$_4$	-	76
9^{b}	Cu(pypzs)(BINAP)BF$_4$	-	0
10	Cu(dq)(BINAP)BF$_4$	ppyzs	0
11^{c}	Cu(pypzs)(BINAP)BF$_4$	-	0
12^{d}	Cu(pypzs)(BINAP)BF$_4$	-	76
13^{e}	-	-	0

^{a} Isolated yields. 1:1 ratio of diastereomers observed in all cases. ^{b} Using Et$_3$SiH instead of HEH. ^{c} No light. ^{d} Using purple LEDs (394 nm). ^{e} Using purple LEDs (394 nm) with no catalyst. BINAP: (rac)-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene. pypz: 3-(2-pyridyl)-pyrazole. pypza 5-amino-3-(2-pyridyl)-pyrazole. pypzs: 5-(4-fluorosulfonyl)amino-3-(2-pyridyl)-pyrazole.

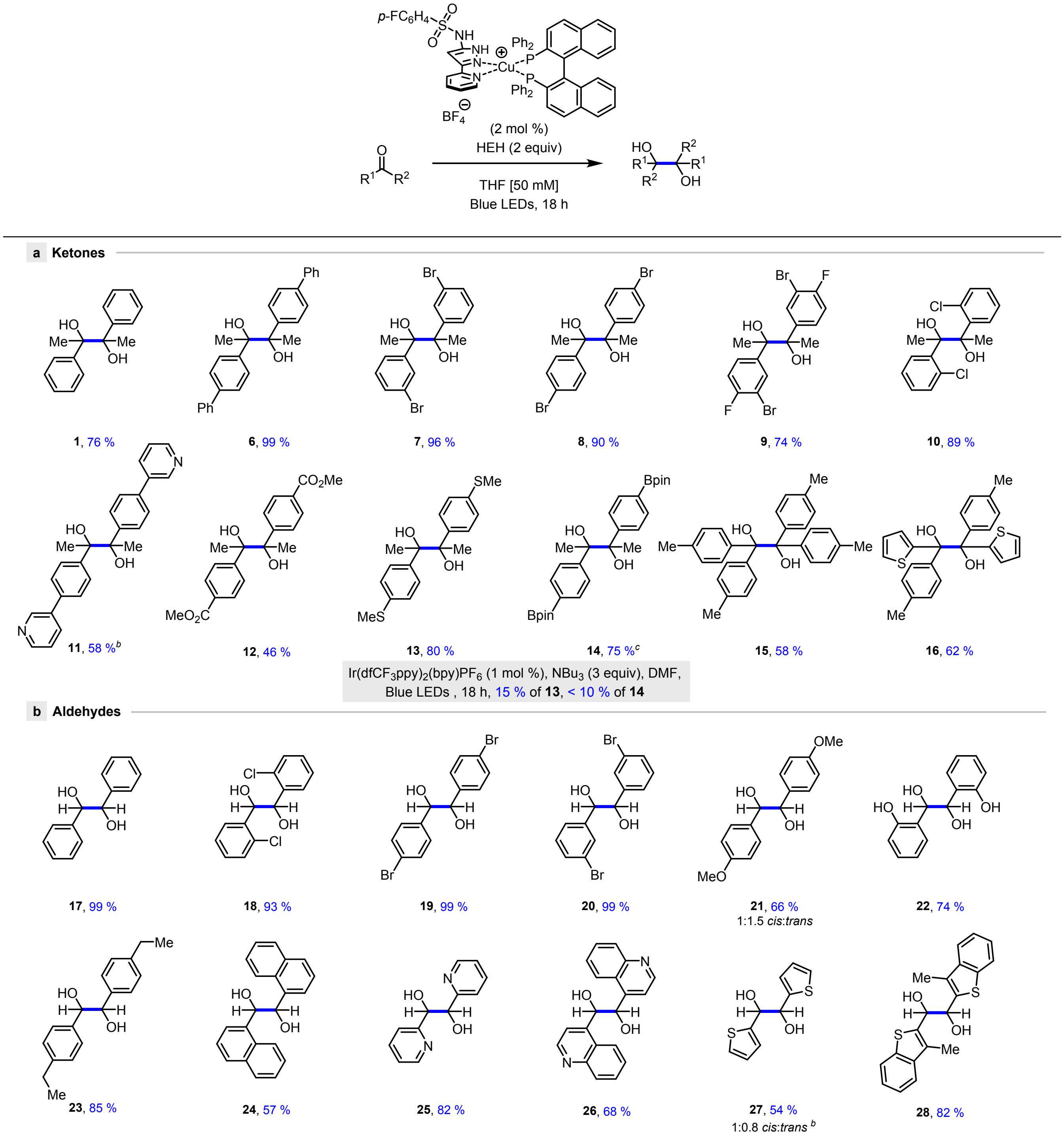
The catalyst Cu(dq)(BINAP)BF$_4$ **2** had been identified as a promising candidate for PCET processes.[9] Indeed, in the reaction of acetophenone with Cu(dq)(BINAP)BF$_4$ using diphenyl phosphoric acid (dppa) as an external acid and Hantzsch ester (HEH) as a hydrogen-atom donor, the catalyst **2** afforded the corresponding diol **1** in 90 % yield (Table 1). However, when the reaction was repeated in the absence of dppa, no trace of the desired diol was observed. As such, it was proposed to exchange the dq ligand for diamines containing hydrogen bond donors. The ligands pypz and pypza were identified as they had been previously utilized in asymmetric photocatalysis.[12] In addition to being readily available in two synthetic steps, the pypza ligand was especially attractive, as diversification of the NH$_2$ group could be envisioned for further fine-tuning. As such, the catalysts Cu(pypz)(BINAP)BF$_4$(**3**) and Cu(pypza)(BINAP)BF$_4$ (**4**) were prepared in hopes that the new ligands would participate in hydrogen bonding. Each catalyst was capable of promoting the PCET reaction of acetophenone in the presence of dppa (78 and 95 % of **1** with catalysts **3** and **4** respectively). However, only low yields (14-25 %) of the desired diol **1** were observed in the absence of dppa. As such, the pypza ligand was further modified through sulfonylation with *p*-fluorosulfonyl chloride to afford the pypzs ligand, in hopes that the sulfonamide moiety would help augment H-bonding. Gratifyingly, Cu(pypzs)(BINAP)BF$_4$(**5**) promoted the reductive pinacol coupling of acetophenone both with dppa (86 % **1**) *and without* dppa (76 % **1**). No PCET-type reactivity was observed for Cu(pypzs)(BINAP)BF$_4$ in the absence of light. Attempts at replacing HEH with an alternative H-atom dodnor like Et$_3$SiH provided no trace of diol **1**. Also, the PCET pinacol-type processes employed blue LEDs for irradiation. The reductive pinacol coupling of acetophenone was also attempted with Cu(pypzs)(BINAP)BF$_4$ under purple LEDs, but identical yields of **1** (76 %) were obtained. No background pinacol coupling of acetophenone was observed under purple LEDs in the absence of catalyst. Interestingly, attempting to promote the PCET process to form **1** using Cu(dq)(BINAP)BF$_4$ with added pypzs to replace dppa did not afford any product. In comparing the relative acidities, the pKa of dppa (□3.72, DMSO)[1□] is orders of magnitude lower than either a pyrazole N-H (□14.2)[1□] or a sulfonamide (PhSO$_2$NH$_2$ □16.1, DMSO)[1□] moiety present in the pypzs ligand. As such, the success of the bifunctional catalyst Cu(pypzs)(BINAP)BF$_4$ is likely a result of the proximity of the hydrogen-bond donor and the photoactive complex.

Next, the scope of the pinacol-type couplings were explored using both ketones and aldehydes (Table 2). Both phenylmethylketone and (4-phenyl)phenylmethylketone underwent coupling to afford the corresponding diols **1** and **6** in 76 and 99 % yields. A variety of halogen-substituted methylketones all were homocoupled in good to excellent yields. Substrates substituted with 3-bromo-, 4-bromo-, 3-bromo-4-fluoro- and 2-chloro- all afforded the corresponding diols in good to excellent yields (**7**□**10**, 74□96 %). A variety of other functional groups were compatible. Pinacol-type coupling with a phenylmethylketone having a 3-pyridyl substituent afforded the corresponding diol **11** in 58 % yield. Diol **12** was isolated in 46 % having pendant methyl esters substituents. Other substituted aryl ketones that were not compatible under previously reported conditions using Ir-based catalysts (Ir(dfCF$_3$ppy)$_2$(bpy)PF$_6$ (1 mol %), NBu$_3$ (3 equiv), DMF, Blue LEDs, 18 h), were viable coupling partners when using bifunctional catalyst **5**. The diol **13** formed via pinacol coupling of 4-SMe substituted methylketone was isolated in 80% yield, was only isolated in 15 % yield under Ir-catalysis. In addition, diol **14**, adorned with pinacolborate esters that could be used as handles for further functionalization of the diols, was formed in 75 % yield using Cu-catalyst **5**, but was isolated in less than 10% yield when using the Ir-based conditions. Diarylketones also underwent pinacol-type coupling in good yields, the *p*-tolyl substituted diol **15** was obtained in 58 % yield, while the diol **16** adorned with thiophene and *p*-tolyl groups was formed in 62 % yield.

A number of aldehydes also underwent pinacol-type coupling with the bifunctional copper-based catalyst **5** (Table 2). Diols formed from the homocoupling of benzaldehyde (**17**, 99 %), 2-chlorobenzaldehyde (**18**, 93 %), 4-bromobenzaldehyde (**19**, 99 %), 3-bromobenzaldehyde (**20**, 99 %), 4-methoxybenzaldehyde (**21**, 66 %), 2-hydroxybenzaldehyde (**22**, 74 %) and 4-ethylbenzaldehyde (**23**, 85 %)

could all be isolated. Polycyclic derivatives were also compatible as 1-naphthyl aldehyde afforded the corresponding diol **24** in 57% yield.

Table 2. Scope of the Reductive Pinacol-Type Coupling Employing a Bifunctional Cu-Based Catalyst[a]



$Ir(dfCF_3ppy)_2(bpy)PF_6$ (1 mol %), NBu_3 (3 equiv), DMF, Blue LEDs , 18 h, 15 % of **13**, < 10 % of **14**

[a] Yields following chromatography. The *cis:trans* ratios are 1:1 unless indicated otherwise. [b] Isolated as a single isomer. [c] Using 4 mol % of catalyst **.**

Heterocyclic derivatives also functioned well under the reaction conditions: diols derived from pyridine (**25**), quinolone (**26**), thiophene (**27**) and benzothiophene (**28**) were isolated in 54-82 % yield.

When considering a possible mechanism for the pinacol-type coupling employing the copper-based bifunctional catalyst, the failure of using an alternative H-atom donor such as Et_3SiH was suprising. When investigating lifetime emission quenching studies, it was shown that it was not acetophenone, but HEH that quenched the excited state of the catalyst. As such, upon excitation of copper-based catalyst **5**, electron transfer with HEH is proposed (Figure 2**a**). Evano and coworkers have similarly proposed such SET transfers to Cu-based catalysts in the presence of suitable electron donors.[1□] Note that HEH can be easily oxidized ($E_{1/2(HEH/HEH^{+\cdot})}$= 0.404 V) and if there are traces of oxygen present, HEH is also rapidly converted to HEH$^{[O]}$.[17] In addition, all of the new catalysts (PC^{+}) possess excited state potentials ($E_{1/2(PC+*/PC)}$) capable of accepting an electron from HEH; (**3** (pypz) 2.12 V; **4** (pypza) 1.87 V; **5** (pypzs) 1.86 V). Note that although all the new catalysts can theoretically accept an electron from HEH in the excited state, their potentials in the resulting ground state ($E_{1/2(PC/PC+)}$) will not be sufficient to promote electron transfer to acetphenone ($E_{½=}$ -2.48 V vs. Fc).[1□] Indeed, a sufficiently strong proton-donor is required to undergo activation through hydrogen bonding. Note that none of the photocatalysts possess a potential ($E_{1/2(PC+/PC)}$) high enough to accept an electron from HEH in the ground state (**3** (pypz) -0.18 V; **4** (pypza) -0.43 V; **5** (pypzs) -0.18 V). If a suitable electron donor is necessary in the PCET process, then it should be possible to use Et$_3$SiH as an H-atom donor if another electron donor, such as a tertiary amine, is added. Indeed, when the pinacol-type coupling was performed using acetophenone, catalyst **5** and both Et$_3$SiH and iPr$_2$NEt, the PCET process was once again productive (37 % of diol **1**, Figure 2**b**). In the proposed mechanism, intermediate **A** could then engage in hydrogen bonding with the sulfonamide proton, pyrazole hydrogen or combination thereof resulting in activation of the ketone or aldehyde for proton-coupled electron transfer. A ^{1}H NMR study (Figure 2**c**) of the catalyst Cu(pypzs)(BINAP)BF$_4$ in the presence of acetophenone in THF-d$_8$ indicated that both the pyrazole N-H and sulfonamide N-H signals (Figure 2**c**, **Ha** and **Hb** respectively)[1□] underwent desheilding (Δδ **Ha** = 0.073-0.193 ppm, Δδ **Hb** = 0.086-0.201 ppm), suggesting hydrogen bonding is occurring.

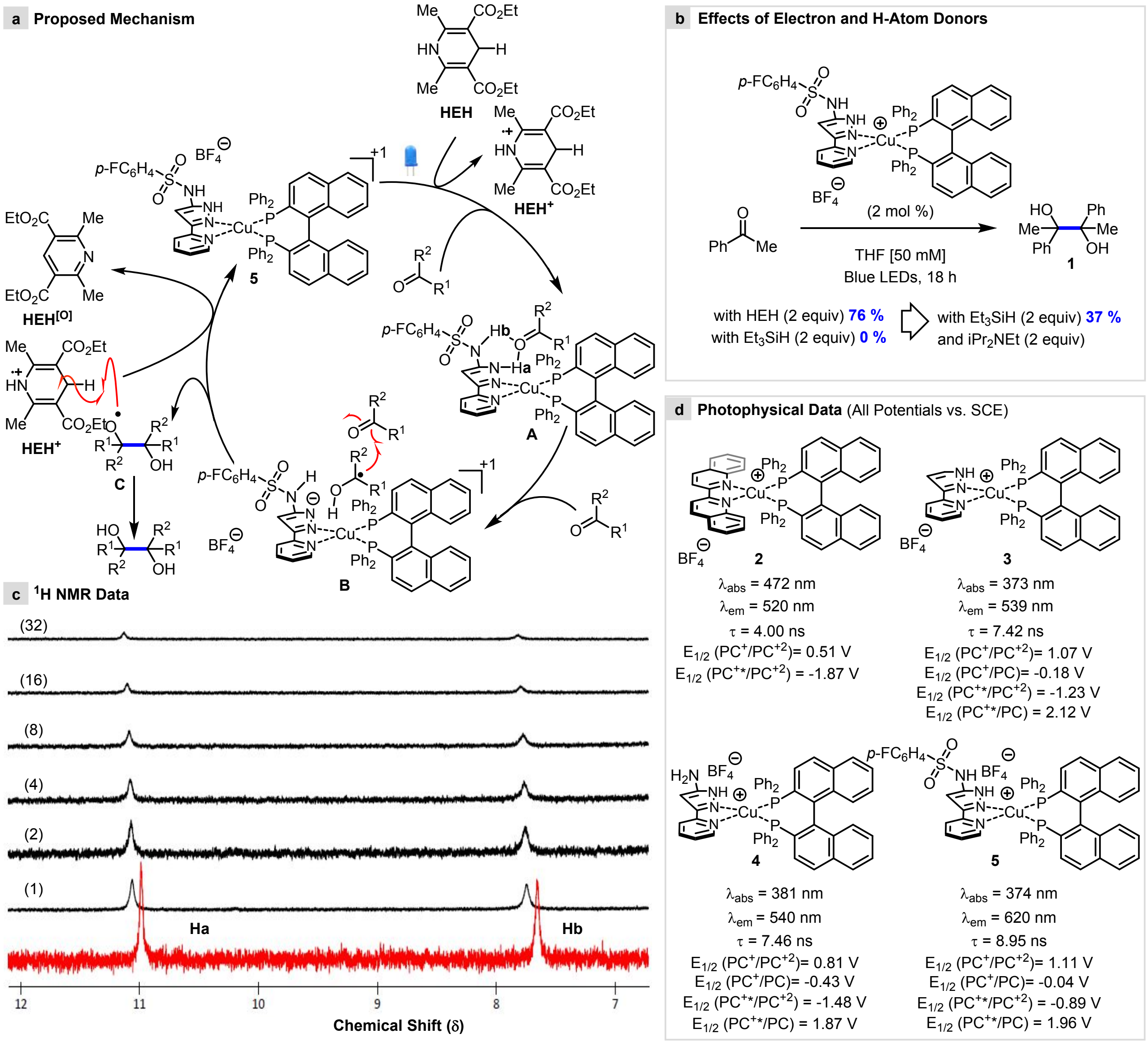


Figure 2. **a**. Proposed reaction mechanism. **b**. Effects of electron and hydrogen atom donors. **c**. Selected ^{1}H NMR data (THF-d$_4$) of catalyst **5** (in red) in the presence of increasing numbers of equivalents of acetophenone (indicated in paratheses). **d.** Comparison of photophysical properties of four copper-based photocatalysts.

Furthermore, the PCET pinacol process afforded much lower yields in protic or polar solvents which could interfere with hydrogen-bonding (acetophenone→**1**, in EtOH 11 %; in DMF 30 %).[2□] Following the PCET event, the resulting ketyl radical can react with another equivalent of the ketone or aldehyde to afford the pinacol-type intermediate **C**. The desired diols are formed via H-atom transfer (HAT) from HEH$^+$ (or HEH). The radical cation of HEH also serves to regenerate the copper-based catalyst via proton transfer. The nature of the pypzs ligand present in the bifunctional catalyst **5** impacts the photophysical properties, and results in differences with regards to other copper-based catalysts such as Cu(dq)(BINAP)BF$_4$, used in a previous PCET process (Figure 2**d**). For example the extended π-surface of the dq ligands results in excellent absorbance for Cu(dq)(BINAP)BF$_4$ at 472 nm. In contrast, Cu(pypzs)(BINAP)BF$_4$, as well as the two other bifunctional catalysts Cu(pypz)(BINAP)BF$_4$ and Cu(pypza)(BINAP)BF$_4$ exhibit maximum absorbances in a narrow range at 373-381 nm, and only weakly absorb within the blue range. In fact, it is surprising that Cu(pypzs)(BINAP)BF$_4$ is so efficient when irradiated with blue LEDs given its low absorption. All copper catalysts have similar emission spectra with λ_{max} between 520-540 nm, with the exception of Cu(pypzs)(BINAP)BF$_4$ which has a weak emission at 620 nm. Interestingly, all catalysts having a N-H bond donor have excited-state lifetimes longer than Cu(dq)(BINAP)BF$_4$ (τ = 4.00 ns), with the pypzs ligand augmenting the excited-state lifetime of its respective catalyst the furthest (τ = 8.95 ns) in comparison to the other catalysts evaluated (Cu(pypz)(BINAP)BF$_4$ τ= 7.42 ns; Cu(pypza)(BINAP)BF$_4$ τ= 7.46 ns). The data supports that bifunctional catalyst **5** acts as a photocatalyst for reductive PCET reactions through its sufficiently strong hydrogen-bond donor.

In summary, a bifunctional copper-based photocatalyst has been prepared that employs a designed pyrazole-pyridine based ligand adorned with sulfonamide moiety that functions as an intramolecular hydrogen-bond donor for a photochemical PCET process. The catalysis is the first application of base-metal photocatalysts toward pinacol-type couplings. The diols prepared herein are formed from a variety of aldehydes and ketones, and in several cases the bifunctional catalyst was capable of promoting pinacol-coupling of substrates that were low yielding when using previously Ir-based catalyst systems. In reductive PCET processes, the PC and H-bond donor must have an appropriate redox potential and pKa respectively to promote the PCET. Importantly, when working in concert in a bifunctional catalyst such as Cu(pypzs)(BINAP)BF$_4$, the pKa of the H-bond donor can have an acidity that is orders of magnitude less and still efficiently promote the PCET process. The modularity and ease of synthesis of the copper catalysts is noteworthy, and further modification of the steric environment of the diamine, alteration of the hydrogen-bond donors and substitution of the bisphosphine could all lead to new catalysts capable of further influencing the stereoselectivities of PCET processes. Given that H-bonding ligands are being used increasingly in asymmetric transition metal catalysis, there could be used for future tuning and development of asymmetric processes.

ASSOCIATED CONTENT

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REFERENCES

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(1) (a) Ciamician, G. The Photochemistry of the Future. *Science* **1912**, *36*, 385–394; (b) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. Photoredox Catalysisin Organic Chemistry. *J. Org. Chem*. **2016**, *81*, 6898–6926; (c) Margrey, K. A.; Nicewicz, D. A. A General Approach to Catalytic Alkene Anti-Markovnikov Hydrofunctionalization Reactions via Acridinium Photoredox Catalysis. *Acc. Chem. Res*. **2016**, *49*, 1997–2006; (d) Koike, T.; Akita, M. Fine Design of Photoredox Systems for Catalytic Fluoromethylation of Carbon-Carbon Multiple Bonds. *Acc. Chem.Res*. **2016**, *49*, 1937–1945; (e) Narayanam, J. M. R.; Stephenson, C. R. J. Visible Light Photoredox Catalysis. *Chem. Soc. Rev*. **2011**, *40*, 102–113. (f) Chen, J.-R.; Hu, X.-Q.; Lu, L.-Q.; Xiao, W.-J. Exploration of Visible-Light Photocatalysis in Heterocycle Synthesis and Functionalization. *Acc. Chem. Res*. **2016**, *49*, 1911–1923; (g) Hopkinson, M. N.; Tlahuext-Aca, A.; Glorius, F. Merging Visible Light Photoredox and Gold Catalysis. *Acc. Chem. Res*. **2016**, *49*, 2261–2272; (h) König, B. Photocatalysis in Organic Synthesis - Past, Present, andF uture. *Eur. J. Org. Chem*. **2017**, 1979–1981; (i) Marzo, L.; Pagire, S. K.; Reiser, O.; König, B. Visible-Light Photocatalysis: Does It Make a Difference in Organic Synthesis? *Angew. Chem.Int. Ed*. **2018**, *57*, 10034–10072.

(2) Hernandez-Perez, A. C.; Collins, S. K. Heteroleptic Cu-Based Sensitizers in Photoredox Catalysis. *Acc. Chem. Res*. **2016**, *49*, 1557–1565.

(3) (a) Hossain, A.; Vidyasagar, A.; Eichinger, C.; Lankes, C.; Phan, J.; Rehbein, J.; Reiser, O. Visible-Light-Accelerated Copper(II) Catalyzed Regio- and Chemo-selective Oxo-Azidation of Vinyl Arenes. *Angew.Chem. Int. Ed*. **2018**, *57*, 8288-8292; (b) Rawner, T.; Lutsker, E.; Kaiser, C. A.; Reiser, O. The Different Faces of Photoredox Catalysts. *ACS Catal*. **2018**, *8*, 3950–3956; (c) Pirtsch, M.; Paria, S.; Matsuno, T.; Isobe, H.; Reiser, O. Cu(dap)2Cl as an Efficient Visible-Light-Driven Photoredox Catalyst in Carbon-Carbon Bond-Forming Reactions. *Chem. Eur. J*. **2012**, *18*, 7336–7340; (d) Paria, S.; Pirtsch, M.; Kais, V.; Reiser, O. Visible-Light-Induced Intermolecular Atom-Transfer Radical Addition of Benzyl Halides to Olefins. *Synthesis* **2013**, *45*, 2689–2698. (e) Michelet, B.;Deldaele, C.; Kajouj, S.;Moucheron, C.; Evano, G. A General Copper Catalyst for Photoredox Transformations of Organic Halides. *Org. Lett*. **2017**, *19*, 3576–3579. (f) Zhao, W.; Wurz, R. P.; Peters, J. C.; Fu, G. C. Photoinduced, Copper-Catalyzed Decarboxylative C–N Coupling to Generate Protected Amines: An Alternative to the Curtius Rearrangement. *J. Am. Chem. Soc*. **2017**, *139*, 35, 12153–12156. (g) Kainz, Q. M.; Matier, C. D.; Bartoszewicz, A.; Zultanski, S. L.; Peters, J. C.; Fu, G. C. Asymmetric Copper-Catalyzed C-N Cross-Couplings Induced by Visible Light. *Science* **2016**,*351*, 681-684. (h)

Chenneberg, L.; Baralle, A.; Fensterbank, L.; Goddard, J. P.; Ollivier, C. Visible Light Photocatalytic Reduction of O-Thiocarbamates: Development of a Tin-Free Barton–McCombie Deoxygenation Reaction. *Chem. Eur. J.* **2013**, *19*, 10809–10813. (i) Wang, D. P; Shelar, D. P.; Han, X. Z.; Li, T. T.; Guan, X. G.; Lu, W.; Liu, K.;. Chen, Y.; Fu, W. F.;Che, C. M. Long-Lived Excited States of Zwitterionic Copper(I) Complexes for Photoinduced Cross-Dehydrogenative Coupling Reactions *Chem. Eur. J.* **2015**, 21, 1184– 1190.(h) Nitelet, A.;Thevenet, D.;Schiavi, B.; Hardouin, C.; Fournier, J.;Tamion, R.; Pannecoucke, X.; Jubault, P.; Poisson, T. Copper-Photocatalyzed Borylation of Organic Halides under Batchand Continuous-Flow Conditions. *Chem. Eur. J.* **2019**, 25, 3262-3266. (i) Li, Y.; Zhou, K.; Wen, Z.; Cao, S.; Shen, X.; Lei, M.; Gong, L. Copper(II)-Catalyzed Asymmetric Photoredox Reactions: Enantioselective Alkylation of Imines Driven by Visible Light. *J. Am. Chem. Soc.* **2018**, *140*, 15850–15858 (j) Fumagalli, G.; Rabet, P. T. G.; Boyd, S.; Greaney, M. F. Three-Component Azidation of Styrene-Type Double Bonds: Light-Switchable Behavior of a Copper Photoredox Catalyst. *Angew. Chem., Int. Ed.* **2015**, *54*, 11481-11484. (k) Wang, C.; Guo, M.; Qi, R.; Shang, Q.; Liu, Q.; Wang, S.; Zhao, L.; Wang, R.; Xu, Z. Visible-Light-Driven, Copper-Catalyzed Decarboxylative C(sp3)–H Alkylation of Glycine and Peptides. *Angew. Chem., Int. Ed.* **2018**, *57*, 15841-15846. (l) Guo, Q.; Wang, M.; Peng, Q.; Huo, Y.; Liu, Q.; Wang, R.; Xu, Z. Dual-Functional Chiral Cu-Catalyst-Induced Photoredox Asymmetric Cyanofluoroalkylation of Alkenes. *ACS Catal.* **2019**, *9*, 4470-4476.

(4) (a) Musacchio, A. J.; Lainhart, B. C.; Zhang, X.; Naguib, S. G.; Sherwood,T. C.; Knowles, R. R. Catalytic Intermolecular Hydroaminations Of Unactivated Olefins with Secondary Alkyl Amines. *Science* **2017**, 355,727–730. (b) Reece, S. Y.; Nocera, D. G. Proton-Coupled Electron Transfer in Biology: Results from Synergistic Studies in Natural and Model Systems. *Annu. Rev. Biochem.* **2009**, *78*, 673-699. (c) Warren, J. J.; Tronic, T. A.; Mayer, J. M. Thermochemistry of Proton-Coupled Electron Transfer Reagents and its Implications. *Chem. Rev.* **2010**, *110*, 6961-7001. (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. Proton-Coupled Electron Transfer. *Chem. Rev.* **2012**, *112*, 4016-4093. (d) Miller, D. C.; Tarantino, K. T.; Knowles, R. R. Proton-Coupled Electron Transfer in Organic Synthesis: Fundamentals, Applications, and Opportunities. *Top. Curr. Chem.* **2016**, *374*, 145-204.

(5) Hammes-Schiffer, S. Theory of Proton-Coupled Electron Transfer in Energy Conversion Processes. *Acc. Chem. Res.* **2009**, *42*, 1881–1889.

(6) Tarantino, K. T.; Liu, P.; Knowles, R. R.Catalytic Ketyl-Olefin Cyclizations Enabled by Proton-Coupled Electron Transfer. *J. Am. Chem. Soc.* **2013**, *135*, 10022–10025.

(7)Nakajima, E.; Fava, E.; Loescher, S.; Jiang, Z.; Rueping,M. Photoredox-Catalyzed Reductive Coupling of Aldehydes, Ketones, and Imines with Visible Light. *Angew. Chem. Int. Ed.* **2015**, *54*, 8828–8832.

(8)(a) Hale, L. V. A.; Szymczak, N. K. Hydrogen Transfer Catalysis beyond the Primary Coordination Sphere. *ACS Catal.* **2018**, *8*, 6446-6461. (b) Xiong, B.; Chen, L.; Shi, J. Anion-Containing Noble-Metal-Free Bifunctional Electrocatalysts for Overall Water Splitting. *ACS Catal.* **2018**, *8*, 3688-3707. (c) Chung, W.-j.; Denmark, S. E.Bifunctional and Synergistic Catalysis: Lewis Acid Catalysis and Lewis Base-Assisted Bond Polarization (n □ σ*) Lewis Base Catalysis in Organic Synthesis (Vedejs, E.; Denmark, S. E., Eds) 2016, 1213-1258. (d) Davis, T. A.; Wilt, J. C.; Johnston, J. N. Bifunctional Asymmetric Catalysis: Amplification of Brønsted Basicity Can Orthogonally Increase the Reactivity of a Chiral Brønsted Acid. *J Am Chem Soc.* **2010**, *132*, 2880–2882.(d) Schwieter, K. E.; Johnston, J. N. Enantioselective Addition of Bromonitromethane to Aliphatic N-Boc Aldimines Using a Homogeneous Bifunctional Chiral Organocatalyst. *ACS Catal.* **2015**, *5*, 6559-6562.

(□) Minozzi, C.; Caron, A.; Grenier-Petel, J.-C.; Santandrea, J.; Collins, S. K. Heteroleptic Copper(I)-Based Complexes for Photocatalysis: Combinatorial Assembly, Discovery, and Optimization. *Angew. Chem., Int. Ed.* **2018**, *57*, 5477-5481.

(10) (a) Ciamician, G.; Silber, P. *Ber. Dtsch. Chem. Ges.* **1900**, *33*, 2911-2913. (b) Seebach, D.; Daum, H. *J. Am. Chem. Soc.* **1971**, *93*, 2795-2796. (c) Suzuki, K.; Tamiya, M. Pinacol Coupling Reaction in (Knochel, P.; Molander, G. A, Eds.) Comprehensive Organic Synthesis 2nd Ed. 2014, 3, 580-620. (d) Terra, B. S.; Macedo, F., Jr. Progress in Intermolecular Pinacol Cross Coupling Methodologies. *ARKIVOC* **2012**, *1*, 134-151. (e) Chatterjee, A.; Joshi, N. N. Evolution of the Stereoselective Pinacol Coupling Reaction. *Tetrahedron* **2006**, *62*, 12137-12158.

(11) (a) Gualandi, A.; Rodeghiero, G.; Rocca, E. D.; Bertoni, F.; Marchini, M.; Perciaccante,R.; Jansen, T. P.; Ceronia, P.; Cozzi, P. G. Application of coumarin dyes for organic photoredox catalysis. *Chem. Commun.* **2018**, *54*, 10044-10047. (b) Wang, R.; Ma, M.; Gong, X.; Fan, X.; Walsh, P. J. Reductive Cross-Coupling of Aldehydes and Imines Mediated by Visible Light Photoredox Catalysis. *Org. Lett.* **2019**, *21*, 27–31. For other examples of the reductive coupling of ketones and imines see: (c) Rong, J.; Seeberger, P. H.; Gilmore, K. Chemoselective Photoredox Synthesis of Unprotected Primary Amines Using Ammonia. *Org. Lett.* **2018**, *20*, 4081-4085. (d) Foy, N. J.; Forbes, K. C.; Crooke, A. M.; Gruber, M. D.; Cannon, J. S. For more reductive coupling of ketones see: Dual Lewis Acid/Photoredox-Catalyzed Addition of Ketyl Radicals to Vinylogous Carbonates in the Synthesis of 2,6-Dioxabicyclo[3.3.0]octan-3-ones. *Org. Lett.* **2018**, *20*, 5727-5731. (e) Rossolini, T.; Leitch, J. A.; Grainger, R.; Dixon, D. Photocatalytic Three-Component Umpolung Synthesis of 1,3-Diamines. J. *Org. Lett.* **2018**, *20*, 6794-6798. (f) Cao, K.; Tan, S. M.; Lee, R.; Yang, S.; Jia, H.; Zhao, X.; Qiao, B.; Jiang, Z. Catalytic Enantioselective Addition of Prochiral Radicals to Vinylpyridines. *J. Am. Chem. Soc.* **2019**, *141*, 5437-5443.

(g) Qiu, G.; Knowles, R. R. Rate–Driving Force Relationships in the Multisite Proton-Coupled Electron Transfer Activation of Ketones. *J. Am. Chem. Soc.* **2019**, *141*, 2721-2730.

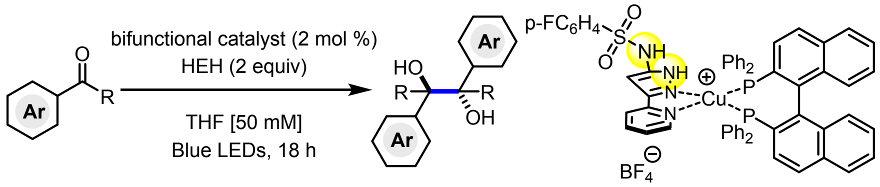
(12) (a) Skubi, K. L.; Kidd, J. B.; Jung, H.; Guzei, I. A.; Baik, M.-H.; Yoon, T. P. Enantioselective Excited-State Photoreactions Controlled by a Chiral Hydrogen-Bonding Iridium Sensitizer. *J. Am. Chem. Soc.* **2017**, *139*, 17186-17192. (b) Xu, W.; Arieno, M.; Low, H.; Huang, K.; Xie, X.; Cruchter, T.; Ma, Q.; Xi, J.; Huang, B.; Wiest, O.; Gong, L.; Meggers, E. Metal-Templated Design: Enantioselective Hydrogen-Bond-Driven Catalysis Requiring Only Parts-per-Million Catalyst Loading. *J. Am. Chem. Soc.* **2016**, *138*, 8774-8780. (c) Chen, L.-A.; Xu, W.; Huang, B.; Ma, J.; Wang, L.; Xi, J.; Harms, K.; Gong, L.; Meggers, E. Asymmetric Catalysis with an Inert Chiral-at-Metal Iridium Complex. *J. Am. Chem. Soc.* **2013**, *135*, 10598-10601.

(13) Christ, P.; Lindsay, A. G.; Vormittag, S. S.; Neudçrfl, J-M.; Berkessel, A.; ODonoghue, A. M. C. pKa Values of Chiral Brønsted Acid Catalysts: Phosphoric Acids/Amides, Sulfonyl/Sulfuryl Imides, and Perfluorinated TADDOLs (TEFDDOLs). *Chem. Eur. J.* **2011**, *17*, 8524 – 8528.

(14) Alam, J.; Alam, O.; Alam, P.; Naim, M. J. A Review on Pyrazole Chemical Entity and Biological Activity. *International Journal of Pharma Sciences and Research* **2015**, *6*, 1433-1442.

(15) Bordwell, F. G.; Fried, H. E.; Hughes, D. L.; Lynch, T. Y.; Satish, A. V.; Whang, Y. E. Acidities of Carboxamides, Hydroxamic acids, Carbohydrazides, Benzenesulfonamides, and Benzenesulfonohydrazides in DMSO Solution. *J. Org. Chem*. **1990**, 55, 3330–3336.
(16) Michelet, B.; Deldaele, C.; Kajouj, S.; Moucheron, C.; Evano, G. A General Copper Catalyst for Photoredox Tranformations or Organic Halides.*Org. Lett*. **2017**, *19*, 3576-3579.
(17) Arguello, J.; Nunez-Vergara, L. J.; Sturm, J. C.; Squella, J. A. Voltammetric oxidation of Hantzsch 1,4-dihydropyridines in protic media: substituent effect on positions 3,4,5 of the heterocyclic ring. *Electrochim. Acta* **2004**, *49*, 4849-4856.
(18) Hasegawa, E.; Seida, T.; Chiba, N.; Takahashi, T.; Ikeda, H. Contrastive Photoreduction Pathways of Benzophenones Governed by Regiospecific Deprotonation of Imidazoline Radical Cations and Additive Effects. *J. Org. Chem*. **2005**, *70*, 9632-9635.

TOC GRAPHIC



Bifunctional catalyst enables pinacol-type coupling via photochemical PCET

(1□) The pyrazole N-H signal is observed further downfield in the ^{1}H NMR spectra for both catalyst **4** (δ = 11.2 ppm, $(CD_3)_2CO$) and catalyst **5** (δ = 12.1 ppm, $(CD_3)_2CO$).
(2□) For additional detail, see Supporting Information.