Letter

pubs.acs.org/OrgLett

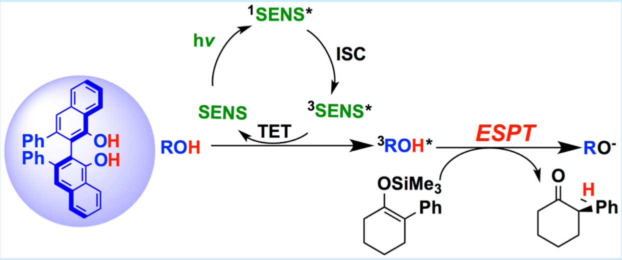
Enantioselective Protonation of Silyl Enol Ether Using Excited State Proton Transfer Dyes

Anjan Das, Suliman Ayad, and Kenneth Hanson*

Department of Chemistry & Biochemistry, Florida State University, Tallahassee, Florida 32306, United States

Supporting Information

ABSTRACT: Enantiopure excited state proton transfer (ESPT) dyes were used for the asymmetric protonation of silyl enol ether. Under 365 nm irradiation, with 3,3′-dibromo-VANOL as the ESPT dye, up to 49% enantioselectivity with a 68% yield of product was observed at room temperature. The reaction is effective with a range of silyl enol ethers and can also be achieved with visible light upon the addition of triplet sensitizer. The relatively low ee of the protonated product is due to the racemization/decomposition of the ESPT dye in the excited state as indicated by circular dichroism, HPLC, and UV–vis spectroscopy.



Enantioselective synthesis is the cornerstone of modern synthetic chemistry and a crucial step in the production of fine chemicals such as food additives, fragrances, natural products, and pharmaceuticals.[1] Historically these reactions are thermally driven, but over the past decade there has been an increased interest in enantioselective photocatalysis because the reactions can proceed at room temperature and they use light as a nontoxic reagent.[2] Most of these asymmetric, photocatalytic reactions rely on either (1) triplet energy transfer to generate a reactive organic substrate[3] or (2) photoredox reagents such as ruthenium(II) tris(2,2′-bipyridine),[4] acridinium,[5] iridium complexes,[6] and eosin[7] which, upon excitation, can initiate a wide range of chemical transformations by facile, one-electron oxidation or reduction events.

Recently our research group introduced excited state proton transfer (ESPT), in the presence of a sacrificial proton source, as an alternative photocatalytic strategy which relies on the electron density shift associated with light absorption to increase the acidity of the catalyst significantly.[8] Greater than 95% efficient photocatalytic protonation of a silyl enol ether was achieved with 1 mol % 7-bromo-2-naphthol as an ESPT catalyst and phenol as the sacrificial proton source.[8] Although there is a stereocenter, the achiral reaction conditions generate a racemic mixture of (*R*)- and (*S*)-2-phenylcyclohexanone as the product.

Enantioselective protonation of prochiral enol ether is a simple and attractive route for the generation of optically active carbonyl compounds.[9] This protonation reaction has been performed using chiral phosphoric acids (top of the Figure 1),[10] chiral BINOL Sn complexes,[11] and organocatalysts.[12] In this report we demonstrate that chiral naphthol compounds can facilitate enantioselective ESPT to a prochiral silyl enol ether substrate at room temperature (bottom of Figure 1). Enantioselective ESPT has been used for the chiral recognition of enantiopure amino acids,[13] amino alcohols,[14] amines,[15] or alcohols,[16] but to the best of our best knowledge, this is the first example of applying ESPT to a prochiral substrate for the generation of chiral products.

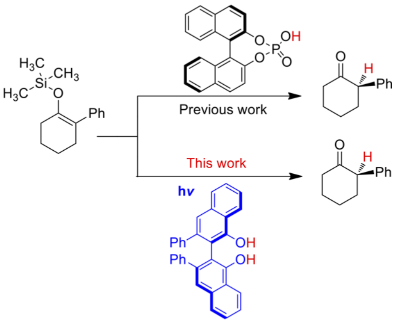


Figure 1. Enantioselective protonation of 1-phenyl-2-(trimethylsiloxy)cyclohexene to generate (*R*)-2-phenylcyclohexanone.

BINOL and VANOL compounds (Scheme 1) were selected for this work because (1) they contain naphthol chromophoric units which are known to exhibit ESPT[17] and (2) they are relatively common molecules for use in enantioselective reactions because of their axial chirality.[18]

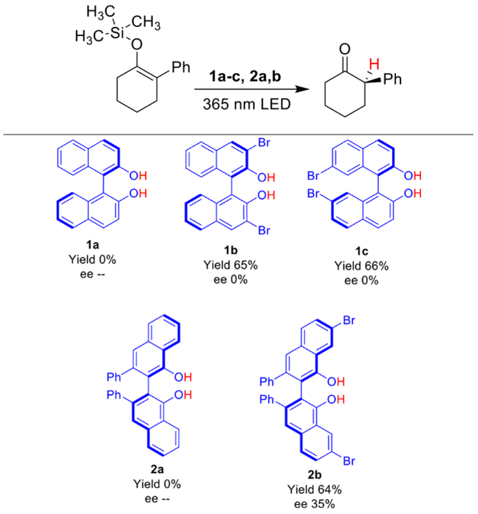
Photochemical reactions were performed with a stoichiometric mixture of 1-phenyl-2-(trimethylsiloxy)cyclohexene and enantiopure ESPT dye (**1a**–**c** and **2a**–**b**) in toluene under 365 nm irradiation (8 mW/cm^2) for 2 h. The reaction yields and ee of 2-phenylcyclohexanone were determined by NMR and HPLC, respectively.

There are several notable observations from the yield and ee shown in Scheme 1. The first is that the unsubstituted BINOL (**1a**) and VANOL (**2a**) compounds yielded no product. In

Received: September 19, 2016

DOI: 10.1021/acs.orglett.6b02820

Scheme 1. Excited State Proton Transfer Dyes, Reaction Yield, and Enantiomeric Excess of (*R*)-2-Phenylcyclohexanone[a]



[a]Reaction conditions: 1 mM of 1-phenyl-2-(trimethylsiloxy)cyclohexene and 1 mM of (*R*)-ESPT dye in 0.5 mL of toluene with 365 nm irradiation (8 mW/cm^2); yields were calculated by ^{1}H NMR using triphenylmethane as the internal reference; ee's were determined by HPLC (OD chiral column, flow rate 1 mL/min, hexane/isopropanol = 99:1).

contrast, bromine substituted compounds **1b**, **1c**, and **2b**, gave product in >60% yield. This result is in agreement with our previous report where the generation of a triplet excited state was necessary for diffusion limited contact and ESPT to occur.[8] The addition of bromine heavy atoms (**1b**, **1c**, and **2b**) effectively facilitates intersystem crossing into the long-lived triplet excited state which can undergo chemical reactions.[19]

Of the ESPT dyes in Scheme 1 only **2b** exhibited any enantioselectivity (35% ee) for the protonation of 1-phenyl-2-(trimethylsiloxy)cyclohexene. Despite the high yield, no ee was observed for **1b** and **1c**. As previously reported by Tolbert,[20] Wan,[21] and others,[21] BINOL planarizes in the excited state and can subsequently racemize. Presumably either (1) the lack of asymmetric induction from the planarized excited state or (2) racemization prior to proton transfer is responsible for the lack of enantioselectivity during the ESPT reaction with **1b** and **1c**. Our initial attempts to hinder planarization/racemization by substituting BINOL with more sterically hindered bromine atoms in the 7,7′ position did not increase the ee of reactions with **1c**. However, with (*R*)-3,3′-dibromoVANOL (**2b**) a 64% yield (61% isolated yield) with 35% enantioselectivity of (*R*)-2-phenylcyclohexanone was obtained. The significant increase in steric hindrance provided by the phenyl substituents likely impedes rotation/planarization of VANOL in the excited state.

Various conditions for the protonation of 1-phenyl-2-(trimethylsiloxy)cyclohexene by **2b** were examined, and the results are summarized in Table 1. In the absence of light, **2b** is not sufficiently acidic to protonate the substrate and generate any observable 2-phenylcyclohexanone even at elevated temperatures (entries 1−2 in Table 1). Under irradiation, increasing (60 °C) or decreasing (−5 °C) the reaction temperature had minimal effect on the reaction yield or the enantioselectivity (entries 4−6). The nature of the solvent had minimal influence on the reaction yield with only a small decrease in CHCl$_3$ (80%) relative to toluene (64%). However, in both MeCN and CHCl$_3$ no enantioselectivity is observed. Although we do not have a definitive explanation for the loss in enantioselectivity, it may be due to the increase polarity of MeCN and CHCl$_3$ effectively solvating the acidic proton and decreasing substrate−dye contact during the proton transfer event.

Table 1. Reaction Conditions for the Protonation of 1-Phenyl-2-(trimethylsiloxy)cyclohexene by 2b[a]

entry	solvent	*hν* (nm)	temp (°C)	yield (%)[b]	ee (%)[c]
1	toluene	–	60	0	nd
2	toluene	–	rt	0	nd
3	toluene	365	rt	64	35
4	toluene	365	0	72	35
5	toluene	365	−5	70	36
6	toluene	365	60	76	32
7	MeCN	365	rt	64	0
8	CHCl$_3$	365	rt	80	0

[a]All of the reactions were carried out with 1 mM of the substrates and 1 mM of **2b** with 365 nm irradiation (8 mW/cm^2) for 2 h. [b]Yield of the product was calculated by ^{1}H NMR using triphenylmethane as the internal reference. [c]Determined by HPLC (OD chiral column, flow rate 1 mL/min, hexane/isopropanol = 99:1).

To gain insights into the progress of the reaction we have monitored both ee and yield with respect to time, and the results can be seen in Figure 2. As expected, the reaction yield continues to increase over the course of the reaction. In contrast, for the first 10 min of the reaction the ee is >40% and then decreases to ∼35% over the subsequent 20 min.

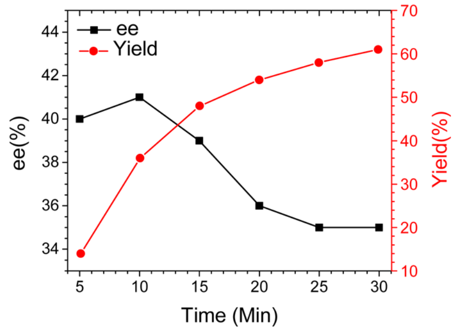
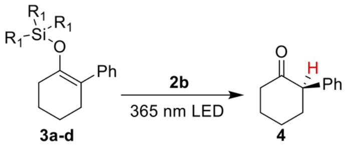


Figure 2. Reaction yield and ee of 2-phenylcyclohexanone with respect to time for a reaction mixture containing 1 mM of 1-phenyl-2-(trimethylsiloxy)cyclohexene and 1 mM of (*R*)-**2b** in 0.5 mL of toluene under 365 nm irradiation (8 mW/cm^2).

The decrease in ee as the reaction progresses can be attributed to a decrease in enantiopurity and/or decomposition of **2b** over the course of the experiment. Changes in the circular dichroism spectra with respect to time indicate that more than 50% of the initial CD intensity is lost within the first 10 min (Figure S2) and continues to decrease for at least the first 30 min. HPLC measurements after 10 min of irradiation show the generation of ∼5% (*S*)-VANOL (Figure S3). Conversely, changes in the UV−vis spectra over time show the disappearance of VANOL absorption features over the course of the reaction. These results suggest that, while slower than with BINOL, both isomerization and decomposition of VANOL contribute to the decreased ee over time.

Enantioselective ESPT was effective with a range of silyl enol ethers as summarized in Table 2. In accord with our previous report, the R$_1$ substituent had minimal influence on the reaction

Table 2. Reaction Yield and Enantiomeric Excess for Various Silyl Enol Ethers[a]



entry	R_1	yield (%)[b]	ee (%)[c]
1	$-CH_3$ (**3a**)	64 (**4**)	35
2	$-C_2H_5$ (**3b**)	64 (**4**)	20
3	$-CH(CH_3)_2$ (**3c**)	78 (**4**)	25
4	$-C_6H_5$ (**3d**)	68 (**4**)	49
5	(trimethylsiloxy)indene (**3e**)	80 (**5**[d])	13

[a] All of the reactions were carried out with 1 mM of the substrates and 1 mM of **2b** for 2 h. [b] Yield of the product was calculated by ^{1}H NMR using triphenylmethane as the internal reference. [c] Determined by HPLC (OD chiral column, Flow rate 1 mL/min, hexane/isopropanol = 99:1). [d] 2-Methyl-1-indanone.

yield. However, we observe a >30% decrease in ee as the steric bulk is increased from methyl to ethyl and isopropyl groups. The highest ee we report here, 49%, was achieved with a triphenylsilyl group. Interestingly, with 2-methyl-3-(trimethylsiloxy)indene we observe the highest reaction yield (80%; 74% isolated yield) but the lowest ee (13%).

In accord with our previous work, enantioselective ESPT can also be achieved under visible light by using the appropriate triplet sensitizer molecule and the unsubstituted ESPT dye by triplet energy transfer (TET) (Figure 3). Irradiating a mixture of substrate (1 mM), VANOL (**2a**, 1 mM), and bis(4,6-difluorophenyl-pyridine)(picolinate)iridium(III) (**SENS**, 0.05 mM) in 0.5 mL of toluene with 445 nm light gave (*R*)-2-phenylcyclohexanone in 68% yield and 25% ee. The same reaction with (*S*)-VANOL yielded (*S*)-2-phenylcyclohexanone in similar yield and ee. It is worth emphasizing that the sensitized reactions are achieved using the nonbrominated ESPT dye since the triplet state is generated on the sensitizer and then transferred to the dye.

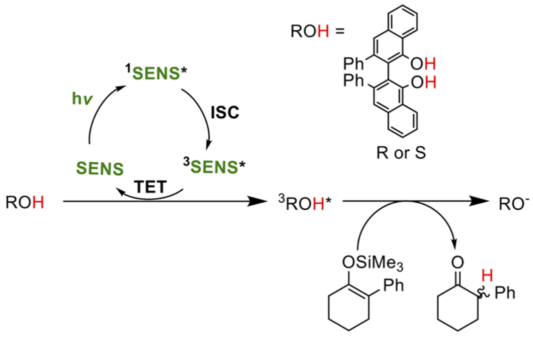


Figure 3. Sensitized enantioselective proton transfer under visible light (445 nm). **SENS** = Bis(4,6-difluorophenylpyridine) (picolinate)-iridium(III).

Initial attempts to realize enantioselective ESPT catalysis have been unsuccessful. In our previous report ESPT catalysis was demonstrated with phenol as the sacrificial proton source to regenerate 7-bromo-2-naphthol (1 mol % relative to substrate) after the proton transfer event.[8] Similar catalytic protonation of substrate by **2b** in the presence of phenol was observed, but the reaction was not enantioselective. Our working hypothesis is that hydrogen bonding between **2b** and phenol in the ground state is responsible for the loss of ee. That is, upon excitation, ESPT from **2b** to phenol can generate $PhOH_2^+$ which is still sufficiently acidic to protonate substrate, but all chiral induction is lost.[23] Attempts to limit hydrogen bonding by using thiol proton sources (ethanethiol, thiophenol, etc.) or the sterically hindered 2,6-di-*tert*-butyl-methylphenol yielded no product and no enantioselective product, respectively. In the former case, insoluble brown precipitation was quickly generated, likely due to the formation of sulfide adduct by photoinitiated radical reaction of thiols.[24] Presumably with an achiral sacrificial proton donor that lacks hydrogen bonding and has the appropriate pK_a to regenerate the ESPT dye but not protonate substrate, enantioselective ESPT catalysis could be realized.

In summary we have introduced a new strategy to enantioselectively protonate prochiral substrates using excited state proton transfer from a chiral dye. The reaction is effective with a range of silyl enol ethers and can also be achieved with visible light upon the addition of triplet sensitizer. The low ee of the protonated product is due to the racemization of the ESPT dye in the excited state as indicated by circular dichroism. The development of new enantiopure ESPT dyes that cannot photoisomerize will likely improve the ee and increase the utility of enantioselective ESPT in organic synthesis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02820.

^{1}H NMR and HPLC profiles of all enantiopure products, UV spectra of all ESPT dyes, CD spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: hanson@chem.fsu.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Authors are grateful to the American Chemical Society Petroleum Research Fund (54435-DNI4) for financial support.

■ REFERENCES

(1) Halpern, J.; Trost, B. M. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5347.

(2) Schultz, D. M.; Yoon, T. P. *Science* **2014**, *343*, 1239176.

(3) Brimioulle, R.; Lenhart, D.; Maturi, M. M.; Bach, T. *Angew. Chem., Int. Ed.* **2015**, *54*, 3872−3890.

(4) (a) Neumann, M.; Füldner, S.; König, B.; Zeitler, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 951−954. (b) Zou, Y.-Q.; Chen, J.-R.; Liu, X.-P.; Lu, L.-Q.; Davis, R. L.; Jørgensen, K. A.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2012**, *51*, 784−788. (c) Tucker, J. W.; Zhang, Y.; Jamison, T. F.; Stephenson, C. R. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 4144−4147. (d) Du, J.; Skubi, K. L.; Schultz, D. M.; Yoon, T. P. *Science* **2014**, *344*, 392−396. (e) Cismesia, M. A.; Yoon, T. P. *Chem. Sci.* **2015**, *6*, 5426−5434. (f) Hurtley, A. E.; Lu, Z.; Yoon, T. P. *Angew. Chem., Int. Ed.* **2014**, *53*, 8991−8994. (g) Zhang, P.; Le, C. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2016**, *138*, 8084−8087. (h) Shaw, M. H.; Shurtleff, V. W.; Terrett, J. A.; Cuthbertson, J. D.; MacMillan, D. W. C. *Science* **2016**, *352*, 1304.

(5) Romero, N. A.; Margrey, K. A.; Tay, N. E.; Nicewicz, D. A. *Science* **2015**, *349*, 1326−1330.

(6) Huo, H.; Shen, X.; Wang, C.; Zhang, L.; RÖse, P.; Chen, L. − A.; Harms, K.; Marsch, M.; Hilt, G.; Meggers, E. *Nature* **2014**, *515*, 100−103.

(7) Hari, D. P.; Schroll, P.; König, B. *J. Am. Chem. Soc.* **2012**, *134*, 2958−2961.

(8) Das, A.; Banerjee, T.; Hanson, K. *Chem. Commun.* **2016**, *52*, 1350−1353.

(9) Eames, J.; Weerasooriya, N. *Tetrahedron: Asymmetry* **2001**, *12*, 1−24.

(10) Cheon, C. H.; Yamamoto, H. *J. Am. Chem. Soc.* **2008**, *130*, 9246−9247.

(11) Nakamura, S.; Kaneeda, M.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 8120−8130.

(12) Poisson, T.; Gembus, V.; Dalla, V.; Oudeyer, S.; Levacher, V. *J. Org. Chem.* **2010**, *75*, 7704−7716.

(13) (a) Liu, H. − L.; Zhu, H.-P.; Hou, X. − L.; Pu, L. *Org. Lett.* **2010**, *12*, 4172−4175. (b) Wang, F.; Nandhakumar, R.; Hu, Y.; Kim, D.; Kim, K. M.; Yoon, J. *J. Org. Chem.* **2013**, *78*, 11571−11576.

(14) (a) Wang, C.; Wu, E.; Wu, X.; Xu, X.; Zhang, G.; Pu, L. *J. Am. Chem. Soc.* **2015**, *137*, 3747−3750. (b) Wang, Q.; Chen, X.; Tao, L.; Wang, L.; Xiao, D.; Yu, X. − Q.; Pu, L. *J. Org. Chem.* **2007**, *72*, 97−101.

(15) Upadhyay, S. P.; Pissurlenkar, R. R. S.; Coutinho, E. C.; Karnik, A. V. *J. Org. Chem.* **2007**, *72*, 5709−5714.

(16) Solntsev, K. M.; Tolbert, L. M.; Cohen, B.; Huppert, D.; Hayashi, Y.; Feldman, Y. *J. Am. Chem. Soc.* **2002**, *124*, 9046−9047.

(17) (a) Tolbert, L. M.; Solntsev, K. M. *Acc. Chem. Res.* **2002**, *35*, 19−27. (b) Solntsev, K. M.; Huppert, D.; Agmon, N.; Tolbert, L. M. *J. Phys. Chem. A* **2000**, *104*, 4658−4669. (c) Clower, C.; Solntsev, K. M.; Kowalik, J.; Tolbert, L. M.; Huppert, D. *J. Phys. Chem. A* **2002**, *106*, 3114−3122. (d) Agmon, N. *J. Phys. Chem. A* **2005**, *109*, 13−15.

(18) (a) Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003**, *103*, 3155−3211. (b) Shibasaki, M.; Matsunaga, S. *Chem. Soc. Rev.* **2006**, *35*, 269−279. (c) Vogl, E. M.; Matsunaga, S.; Kanai, M.; Iida, T.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 7917−7920. (d) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047−9153.

(19) (a) Mcclure, D. S.; Blake, N. W.; Hanst, P. L. *Chem. Phys.* **1954**, *22*, 255−258. (b) Mcclure, D. S. *J. Chem. Phys.* **1949**, *17*, 665.

(20) SolntSev, K. M.; Bartolo, E. − A.; Pan, G.; Muller, G.; Bommireddy, S.; HuPPert, d.; Tolbert, L. M. *Isr. J. Chem.* **2009**, *49*, 227−233.

(21) Flegel, M.; Lukeman, M.; Wan, P. *Can. J. Chem.* **2008**, *86*, 161−169.

(22) Cavazza, M.; Zandomeneghi, M. *J. Am. Chem. Soc.* **1996**, *118*, 9990.

(23) Cheon, C. H.; Yamamoto, H. *J. Am. Chem. Soc.* **2008**, *130*, 9246−9247.

(24) Tyson, E. L.; Ament, M. S.; Yoon, T. P. *J. Org. Chem.* **2013**, *78*, 2046−2050.

DOI: 10.1021/acs.orglett.6b02820
Org. Lett. XXXX, XXX, XXX−XXX