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Continuous Flow Synthesis of Morpholines and Oxazepanes with Silicon Amine Protocol (SLAP) Reagents and Lewis Acid Facilitated Photoredox Catalysis

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ABSTRACT: Photocatalytic coupling of aldehydes and silicon amine protocol (SLAP) reagents enables the simple, scalable synthesis of substituted morpholines, oxazepanes, thiomorpholines and thiazepanes under continuous flow conditions. Key to the success of this process is the combination of an inexpensive organic photocatalyst (TPP) and a Lewis acid additive, which form an amine radical cation that is easily reduced to complete the catalytic cycle. Di- and tri-substituted SLAP reagents are formed in one step by an iron-catalyzed aminoetherification of olefins.

A continuing challenge in the renaissance of photoredox catalysis is expanding the substrate scope to the synthesis of molecules typically encountered in drug development and lead optimization studies.[1,2] To this end, we recently reported a photocatalytic synthesis of *N*-Bn piperazines from aldehydes and silicon amine protocol (SLAP) reagents using $[Ir(ppy)_2dtbbpy]PF_6$ as the catalyst (Figure 1 A).[3] These simple, convenient conditions, however, completely failed for the formation of the related thiomorpholines and morpholines from the corresponding SLAP reagents due to the mismatch between the redox potentials of the photocatalyst and the required potentials for the single-electron transfer steps in a possible catalytic cycle. To a limited extent, we could address this by a combination of Lewis acids and the $[Ir(ppy)_2dtbbpy]PF_6$ photoredox catalyst, which provided successful conditions for the formation of thiomorpholines (Figure 1 B).[4] Mechanistic studies traced the origin of this success to a switch from Ir^{III}* reductive quenching pathway to Ir^{III}* oxidative quenching, resulting in the formation of the stronger oxidant Ir^{IV} ($E_{1/2}^{IV/III}$ = +1.69 V vs SCE in CH_3CN),[4,5,6] which could successfully oxidize the $RSCH_2SiMe_3$ moiety in the SLAP reagent for the synthesis of thiomorpholines (SLAP TM).

Unfortunately, this strategy could not be directly applied to the synthesis of morpholines with SLAP M reagent **1**, as the required oxidation potential of the $ROCH_2SiMe_3$ (E_p = +1.90 V vs SCE in CH_3CN)[4,7,8,9] was still too high, even for the Ir^{IV} species. A number of organic photoredox catalysts are known to possess a sufficiently high redox potential in the photoexcited state,[10,11] but the resulting reduced forms ($PC^{\bullet}$) are not able to complete the catalytic cycle by SET to the N-centered radical ($E_{1/2}$ = –1.70 V vs SCE in CH_3CN)[12] formed after cyclization. During the course of our previous studies we observed that coordination of the N-atom with a Lewis acid forms an amine radical cation with a higher redox potential, allowing – in principle – a photoredox catalyst that is a strong oxidant but a poor reducing agent to complete the catalytic cycle.[4]

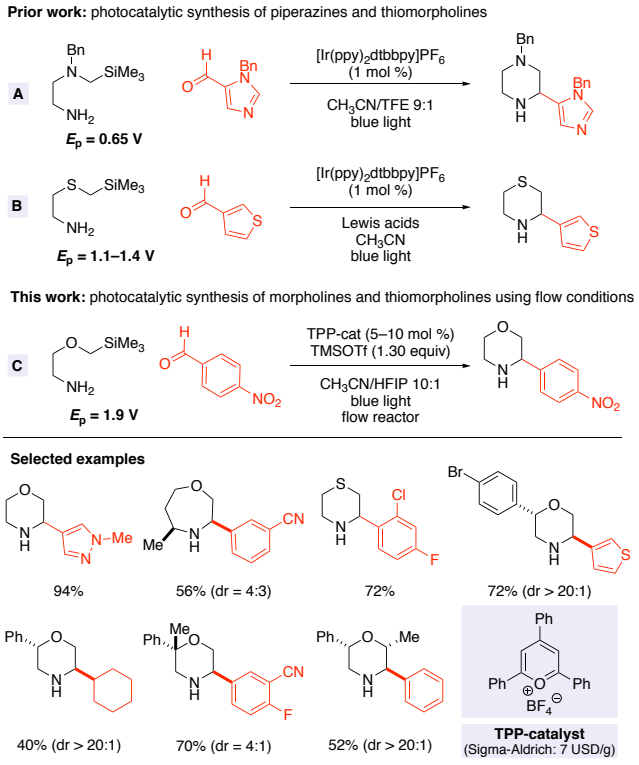


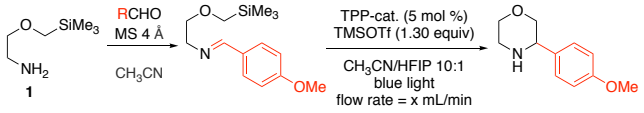
Figure 1. SLAP reagents for the synthesis of various substituted morpholines, thiomorpholines and oxazepanes; E_p = peak potential

We now report the successful implementation of these findings into a general approach to the synthesis of *C*-substituted morpholines, oxazepanes, thiomorpholines, and thiazepanes using SLAP reagents and the inexpensive organic photoredox catalyst 2,4,6-triphenylpyrylium tetrafluoroborate (TPP) (Figure 1 C). We have also developed convenient continuous flow conditions that reduce reaction times and facilitate scale up.[13] Finally, we have utilized a recently reported amino etherification of olefins[14] to prepare new classes of SLAP reagents for the synthesis of morpholines in one-step, including reagents that were inaccessible by alkylation-based approaches.

The TPP-catalyst provides an excited state redox potential $E_{1/2}(PC^{*+}/PC^{\bullet}) = +2.30$ V vs SCE in CH_3CN[11,15] that is sufficient to oxidize the $ROCH_2SiMe_3$ moiety ($E_p = +1.90$ V vs SCE in CH_3CN).[4,7,8,9] The relatively low redox potential of the reduced catalyst $E_{1/2}(PC^{+}/PC^{\bullet}) = -0.37$ V vs SCE in CH_3CN[11,16] should not be able to complete the catalytic cycle, but coordination of the N-centered radical to the Lewis acid forming a radical cation significantly raises its redox potential ($E_{1/2} = +1.10$ V vs SCE in CH_3CN for piperidine radical cation)[17,18] compared to the neutral N-centered radical ($E_{1/2} = -1.70$ V vs SCE in CH_3CN for dialkylaminyl radicals).[12] Previously, we could demonstrate that the combination of TPP and $Bi(OTf)_3$ as the Lewis acid additive were effective for the formation of a few morpholines from aldehydes and the SLAP M reagent **1** (see Supporting Information for batch experiments).[4]

These were not general conditions, however, as they did not work well for heteroaromatic aldehydes and gave low yields when performed on larger scale. We screened for alternative Lewis acid additives and reaction conditions (see Supporting Information), and identified TMSOTf as broadly effective. To improve the scalability of the reaction, we elected to establish a continuous flow procedure in a homemade photo-flow reactor that ensured convenience, reproducibility, and scalability (Table 1).

Table 1. Reaction optimization using the flow reactor[a]



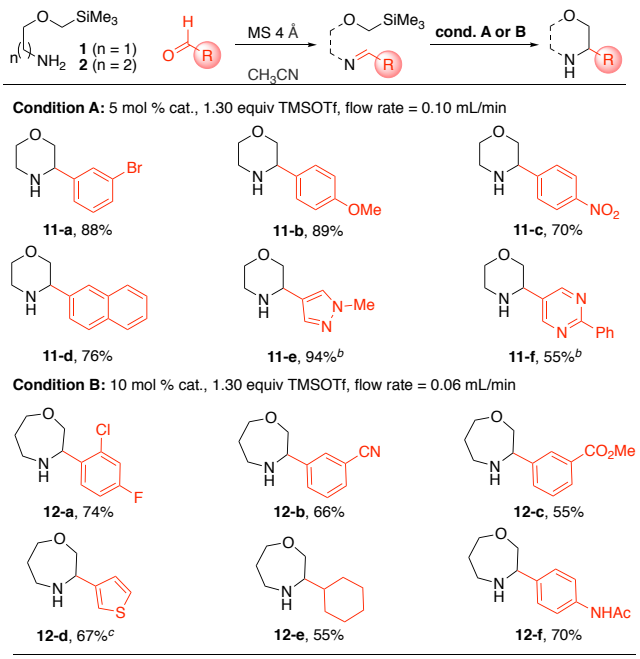
entry	deviation from above	flow rate [mL/min]	conv [%]	yield [%][b]
1	none	0.06 (t_r = 28 min)[c]	100	90
2	none	0.10 (t_r = 17 min)[c]	100	90
3	none	0.13 (t_r = 13 min)[c]	80	65
4[d]	$(MesAcr)ClO_4$	0.10 (t_r = 17 min)[c]	20	<15
5	no TMSOTf	0.10 (t_r = 17 min)[c]	0	0
6	no catalyst	0.10 (t_r = 17 min)[c]	0	0
7	no light	0.10 (t_r = 17 min)[c]	0	0

[a]Reactor volume = 1.70 mL. [b]From ^{1}H-NMR spectroscopy using 1,3.5-trimethoxybenzene as the internal standard on a 0.25 M scale. [c]Values in parentheses are residence times (t_r = reactor volume / flow rate) [d]3-Bromobenzaldehyde used as the aldehyde

Under this protocol, a 0.10 M solution of the pre-formed imine in CH_3CN/HFIP 10:1 containing 5 mol % TPP catalyst and 1.30 equiv TMSOTf were passed through a glass chip (channel size = 1.0 mm, volume = 1.7 mL) at a flow rate = 0.10 mL/min illuminated by a Luxeonstar LXML-PR02-A900 Royal blue (λ_{max} = 460 nm, I = 700 mA). On a 0.50 mmol scale, the reactions were complete within 1 hour.

These flow conditions were applicable to most aldehydes tested – only those containing groups sensitive to strong acid such as *N*-Boc amines failed (see Scheme 1). With slightly longer reaction times and higher catalyst loadings, these conditions could also be extended to SLAP OA (oxazepane) reagents **12**.

Scheme 1. Substrate scope for the cyclization of SLAP M and SLAP OA[a]



[a]Reactions were performed on a 0.50 mmol scale using the indicated SLAP reagent (1.00 equiv) and the aldehyde (1.00 equiv); yields of isolated, analytically pure compounds after chromatography are given. [b]3.30 equiv TMSOTf. [c]2.30 equiv TMSOTf

The identical conditions in terms of concentration, catalyst loading and flow-rate could be used to scale up the reaction to 30.0 mmol (Figure 2).

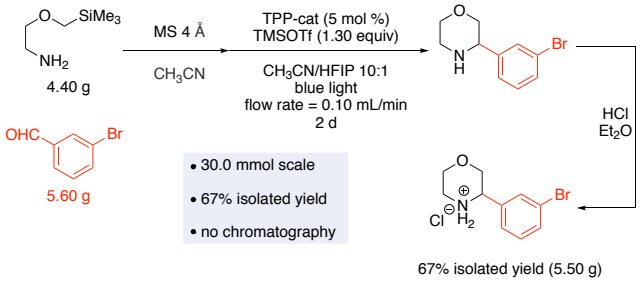
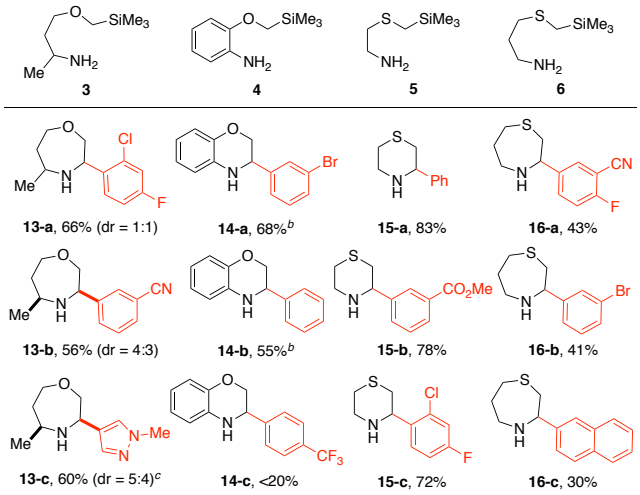


Figure 2. Gram-scale synthesis of 3-(3-bromophenyl)morpholine) hydrochloride; the SLAP reagent (1.00 equiv) was condensed with the aldehyde (1.00 equiv) and cyclized.

A number of other SLAP reagents **3**–**6** were readily prepared and applied to the synthesis of more substituted products (Scheme 2). Importantly, these conditions allowed us to expand the scope to the formation of benzomorpholines **14** using

SLAP reagent **4**, which were not accessible using the related SnAP chemistry.[2] The continuous flow conditions could also be directly applied to the formation of thiomorpholines **15** and thiazepanes **16** using SLAP reagent **5** and **6**, with results comparable to our previously reported method but with greater convenience, simplified reaction setup and better scalability (Scheme 2).[4]

Scheme 2. Synthesis of substituted oxazepanes, benzomorpholines, thiomorpholines, and thiazepanes[a]



[a]Isolated yields are given on a 0.50 M scale; diastereomeric ratio (dr) determined by ^{1}H-NMR analysis of the unpurified reaction mixtures. [b]2.00 equiv of aldehyde. [c]3.30 equiv of TMSOTf.

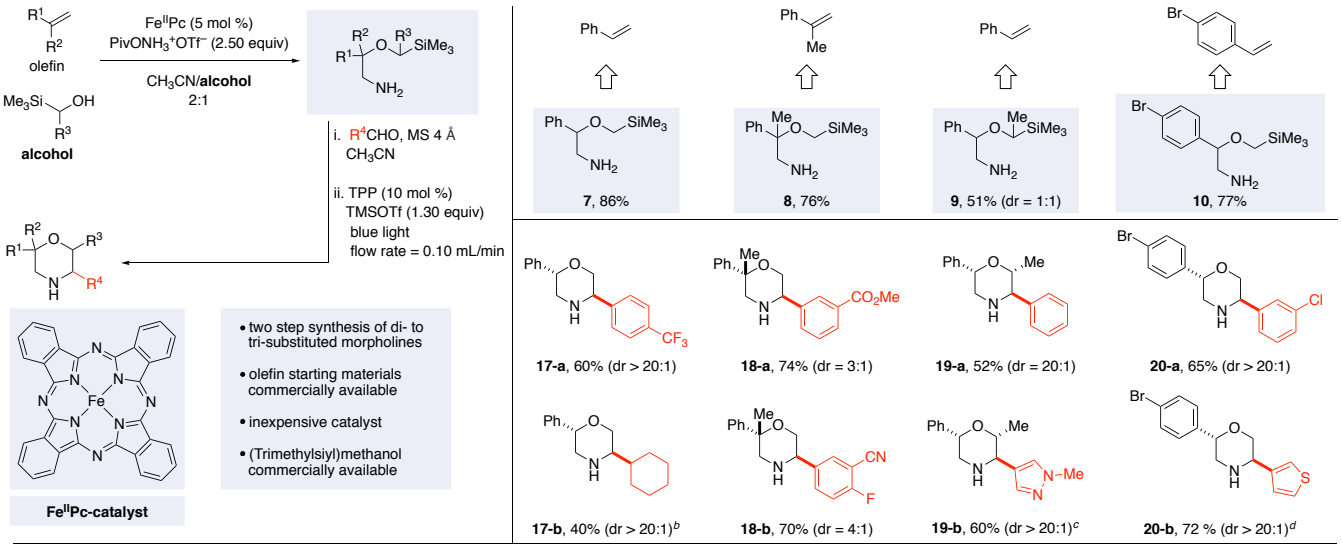
A recently reported aminoetherification of styrenes[14] offered the opportunity to construct new, substituted SLAP reagents **7–10** in a single step, provided that commercially available $TMSCH_2OH$ could be used in the process (Scheme 3).

This volatile, commercially available alcohol proved to be a good reaction partner, allowing the one-step synthesis of new SLAP reagents for the synthesis of morpholines including SLAP 2-Me-2-Ph M **8**, SLAP 2-Ar M **10** and SLAP 2-Ph-6-Me M **9**, a reagent that allows the synthesis of tri-substituted morpholines. Previously, these SLAP reagents were either inaccessible by alkylation of the sterically hindered secondary or tertiary alcohols or required lengthy syntheses.[19] All of the new reagents (**7–10)** performed well in the flow-based SLAP reaction, providing two-step access to an array of substituted morpholines **17–20** that would be difficult to access by any other method (Scheme 3).

Unlike our previous report on Lewis assisted photocatalytic SLAP reactions to form thiomorpholines,[4] in which the excited photocatalyst (PC*) was oxidatively quenched to form a stronger oxidant ($PC^{\bullet+}$), we believe that under these conditions the excited TPP catalyst acts directly as the oxidant (Figure 3). The resulting C-centered radical cyclizes with the TMS-coordinated imine **23** to give radical cation **24**, which is reduced by the TPP radical formed in the oxidation step.[20] These studies provide further evidence that Lewis acid additives can expand the range of overall redox neutral reactions performed under photocatalytic conditions.[4,21]

In summary, we have documented the synthesis of saturated *N*-heterocycles including general conditions for the photocatalytic preparation of morpholines and thiomorpholines under continuous flow conditions and Lewis acid assisted photoredox catalysis. Further increasing the attractiveness of this overall approach is the streamlined synthesis of novel SLAP reagents by aminoetherification of olefins. Further advances in both of these catalytic methods will expand access to stereodefined, substituted *N*-heterocycles for drug discovery and development.

Scheme 3: Two-step synthesis of various substituted morpholines starting from commercially available olefins[a]



[a]Cyclizations were performed on a 0.50 M scale using the indicated SLAP reagent (1.00 equiv) and the aldehyde (1.00 equiv); yields are isolated yields of analytically pure compounds; diastereomeric ratio (dr) determined by ^{1}H-NMR analysis of the unpurified reaction mixtures; relative configurations were determined by NMR-analysis (^{1}H-NMR, COSY, NOESY, HSQC); for **18-b** relative configuration was furthermore confirmed by X-ray analysis (CCDC 1546374). [b]Flow rate = 0.06 mL/min. [c]3.30 equiv of TMSOTf. [d]2.30 equiv of TMSOTf.

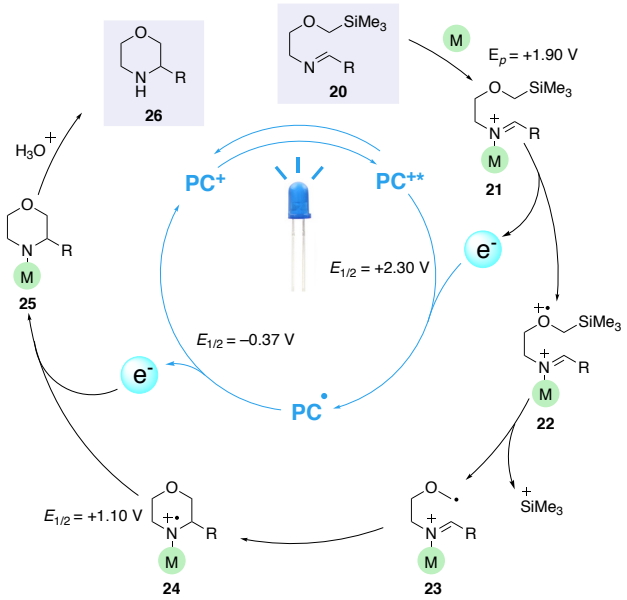


Figure 3. Proposed catalytic cycle for the cyclization of SLAP reagents[20]; M = TMS^+ or H^+

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and characterization data (PDF)
Crystallographic data for **18-b** (CIF)

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

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REFERENCES

(1) Selected literature on photoredox catalysis: a) Shaw, M. H.; Shurtleff, V. W.; Terrett, J. A.; Cuthbertson, J. D.; MacMillan, D. W. C. *Science* **2016**, *352*, 1304–1308. b) Griffin, J. D.; Zeller, M. A.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2015**, *137*, 11340–11348. c) Teegardin, K.; Day, J. I.; Chan, J.; Weaver, *J. Org. Process Res. Dev.* **2016**, *20*, 1156–1163. d) Goddard, J.; Ollivier, C.; Fensterbank, L. *Acc. Chem. Res.* **2016**, *49*, 1924–1936. e) Romero, N. A.; Nicewicz, D. A. *Chem. Rev.* **2016**, *116*, 10075–10166. f) Nicholls, T. P.; Leonori, D.; Bissember, A. C. *Nat. Prod. Rep.* **2016**, *33*, 1248–1254. g) Gutiérrez-Bonet, A.; Tellis, J. C.; Matsui, J. K.; Vara, B. A.; Molander, G. A. *ACS Catal.,* **2016**, *6*, 8004–8008. h) Nielsen, M. K.; Shields, B. J.; Liu, J.; Williams, M. J.; Zacuto, M. J.; Doyle, A. G.; *Angew. Chem. Int. Ed.* **2017**, *56*, 7191–7194.

(2) Previous non-photoredox studies by our group: a) Vo, C.-V.; Mikutis, G.; Bode, J. W. *Angew. Chem. Int. Ed.* **2013**, *52*, 1705–1708. b) Luescher, M. U.; Vo, C.-V.; Bode, J. W. *Org. Lett.* **2014**, *16*, 1236–1239. c) Vo, C.-V.; Luescher, M. U.; Bode, J. W. *Nature Chem.* **2014**, *6*, 310–314. d) Geoghegan, K.; Bode, J. W. *Org. Lett.* **2015**, *17*, 1934–1937. e) Luescher, M. U.; Bode, J. W. *Angew. Chem. Int. Ed.* **2015**, *54*, 10884–10888. f) Jackl, M. K.; Kreituss, I.; Bode, J. W. *Org. Lett.* **2016**, *18*, 1713–1715. g) Luescher, M. U.; Bode, J. W. *Org. Lett.* **2016**, *18*, 2652–2655.

(3) Hsieh, S-Y.; Bode, J. W. *Org. Lett.* **2016**, *18*, 2098–2101.

(4) Hsieh, S-Y.; Bode, J. W. *ACS Cent. Sci.* **2017**, *3*, 66–72.

(5) Slinker, J. D.; Gorodetsky, A. A.; Lowry, M. S.; Wang, J.; Parker, S.; Rohl, R.; Bernhard, S.; Malliaras, G. G. *J. Am. Chem. Soc.* **2004**, *126*, 2763–2767.

(6) Lowry, M. S.; Goldsmith, J. I.; Slinker, J. D.; Rohl, R.; Pascal, R. A.; Malliaras, G. G.; Bernhard, S. *Chem. Mater.* **2005**, *17*, 5712–5719.

(7) Yoshida, J.-i.; Maekawa, T.; Murata, T.; Matsunaga, S.; Isoe, S. *J. Am. Chem. Soc.* **1990**, *112*, 1962–1970.

(8) Yoshida, J.-i. *Top. Curr. Chem.* **1994**, *170*, 39–81.

(9) Yoshida, J.-i.; Kataoka, K.; Horcajada, R.; Nagaki, A. *Chem. Rev.* **2008**, *108*, 2265–2299.

(10) Nicewicz, D. A.; Nguyen, T. M. *ACS Catal.* **2014**, *4*, 355–360.

(11) These values are converted from +2.53 V vs NHE and –0.13 V vs NHE, see: Martiny, M.; Steckhan, E.; Esch, T. *Chem. Ber.* **1993**, *126*, 1671– 1682.

(12) This value is converted from –1.46 V vs NHE, see: Jonsson, M.; Wayner, D. D. M.; Lusztyk, J. *J. Phys. Chem.* **1996**, *100*, 17539–17543.

(13) Selected literature on flow chemistry: a) Su. Y.; Straathof, N. J. W.; Hessel, V.; Noël, T. *Chem. Eur. J.* **2014**, *20*, 10562–10589. b) Guerra, J.; Cantilloa D.; Kappe, C. O. *Catal. Sci. Technol.*, **2016**, *6*, 4695–4699. c) Lima, F.; Kabeshov, M. A.; Tran, D. N.; Battilocchio C.; Sedelmeier J.; Sedelmeier, G.; Schenkel, B.; Ley, S. V. *Angew. Chem. Int. Ed.* **2016**, *55*, 14085–14089. d) Straathof, N. J. W.; Tegelbeckers, B. J. P.; Hessel, V.; Wang, X.; Noël, T. *Chem. Sci*., **2014**, *5*, 4768–4773. e) Tucker, J. W.; Zhang, Y.; Jamison, T. F.; Stephenson, C. R. J. *Angew. Chem. Int. Ed.* **2012**, *51*, 4144–4147. f) Cambie, D.; Bottecchia, C.; Straathof, N. J. W.; Hessel, V.; Noël, T. *Chem. Rev.*, **2016**, *116*, 1027–10341.

(14) Legnani, L.; Morandi, B. *Angew. Chem. Int. Ed.* **2016**, *55*, 2248–2251.

(15) Miranda, M. A.; Garcia, H. *Chem. Rev.* **1994**, *94*, 1063–1089.

(16) Ramamurthy, P.; Morlet-Savary, J F.; Fouassier, J. P. *J. Chem. Soc. Faraday Trans.* **1993**, *89*, 465–469.

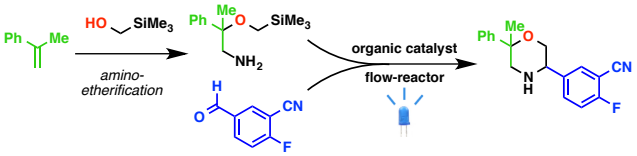
(17) This value is converted from +1.34 V vs NHE, see: Jonsson, M.; Wayner, D. D. M.; Lusztyk, J. *J. Phys. Chem*. **1996**, *100*, 17539–17543.

(18) Jonsson, M.; Lind, J.; Merenyi, G.; Eriksen, T. E. *J. Chem. Soc., Perkin Trans. 2*, **1995**, 61–65.

(19) Gubta, P.; Rouf, A.; Shah, B. A.; Mukherjee, D.; Taneja, S.C. *Synth. Commun*. **2013**, 505–519.

(20) An alternative diradical mechanism was considered, starting with the reduction of the activated imine by PC^{*+} followed by oxidation of the α-trimethylsilyl ethers by $PC^{\bullet+}$ to generate the diradical species. While possible, we consider it less likely based on both kinetic considerations and the poor reduction ability of the TPP^{*+}.

(21) a) Fukuzumi, S.; Jung, J.; Min Lee, Y.; Nam, W. *Asian J. Org. Chem.* **2017**, *6*, 397–409. b) Renaud, P.; Gerster, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 2562–2579.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organic catalyst
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