Silicon Amine Reagents for the Photocatalytic Synthesis of Piperazines from Aldehydes and Ketones

Silicon amine reagents for the photocatalytic synthesis of piperazines from aldehydes and ketones

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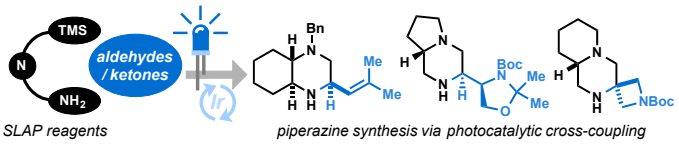
Supporting Information Placeholder

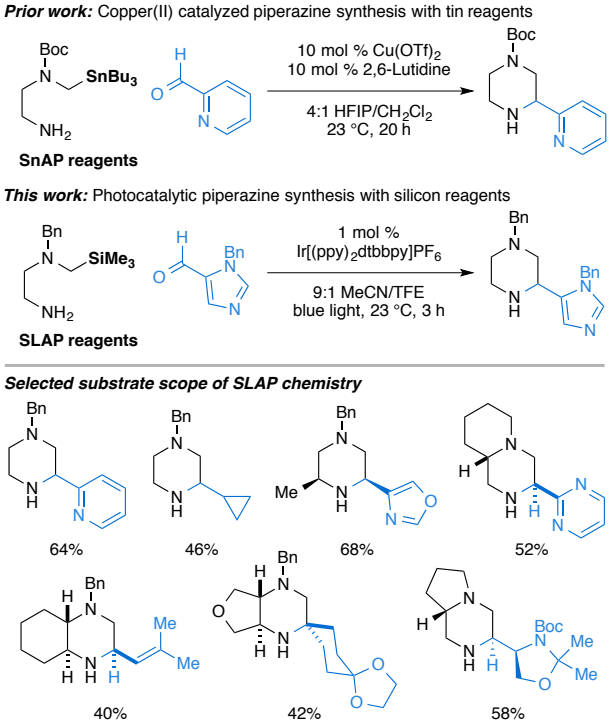


ABSTRACT: Silicon amine protocol (SLAP) reagents for the photocatalytic cross coupling with aldehydes and ketones to form *N*-unprotected piperazines have been developed. This blue light promoted process tolerates a wide range of heteroaromatic, aromatic, and aliphatic aldehydes and structurally and stereochemically complex SLAP reagents. It provides a tin-free alternative to SnAP (tin amine protocol) reagents for the synthesis of substituted piperazines.

Substituted saturated N-heterocycles are among the most valuable scaffolds for the development of new pharmaceuticals[1] and a great deal of contemporary synthetic methodology is currently devoted to improved methods for their construction.[2] Progress in lithiation chemistry,[3] C–H functionalization,[3b,c] intramolecular hydroamination,[4] and photocatalytic cross-coupling[5] offer promising new entries, but these methods are often limited in substrate scope or require difficult-to-remove groups on the nitrogen atom. As a powerful alternative, we have recently developed SnAP (stannyl amine protocol) reagents that cross-couple with aldehydes and ketones to provide one-step access to a wide variety of saturated N-heterocycles,[6] including thiomorpholines,[6a] morpholines,[6b] piperazines,[6b] and diazepanes,[6c] as well as more elaborate bicyclic and spirocyclic compounds.[6d,e] The SnAP chemistry is characterized by broad substrate scope and versatility under a standard set of reaction conditions, making it ideally suited for the preparation of libraries of saturated N-heterocycles. Its main drawback is a reliance on potentially toxic tin reagents,[7] currently being phased out of pharmaceutical research and production. To address this issue, we now report SiLicon Amine Protocol (SLAP) reagents that provide access to piperazines from aromatic, heteroaromatic, and aliphatic aldehydes and ketones using an iridium photoredox catalyst without additional reagents or the generation of toxic byproducts.

Silicon moieties are known surrogates for tin in many radical-based processes.[8] Although Kagoshima reported an example of Cu-promoted additions of α-trimethylsilyl alcohols to imines,[9] we were unable to translate this finding to our own work. Inspired by the pioneering studies of the Yoon and Mariano groups[10] and the Pandey group[11] on the photochemical generation α-amino radicals via desilylation, as well as recent photocatalytic variants reported by Nishibayashi[12] and Yoon,[13] we considered the application of photochemistry to piperazine formation. We therefore selected the inexpensive and easily prepared trimethylsilyl (TMS) reagents **1**–**3**

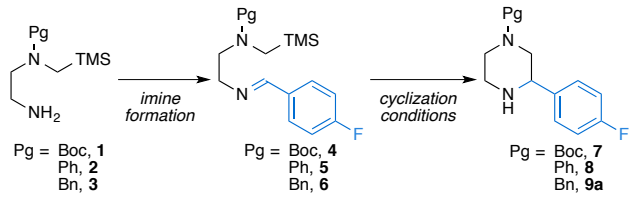
Scheme 1. Comparison of SnAP and SLAP chemistry for the piperazine synthesis



for more detailed studies, including screening of conditions for cyclization.

The TMS reagent **1** readily condensed with *para*-fluorobenzaldehyde to give a corresponding imine **4**, but this did not react under the standard conditions used for cyclization of the tin reagents (Table 1, entry 1). Nishibayahi's conditions for the

Table 1. Screening of imines and optimization of cyclization[a]

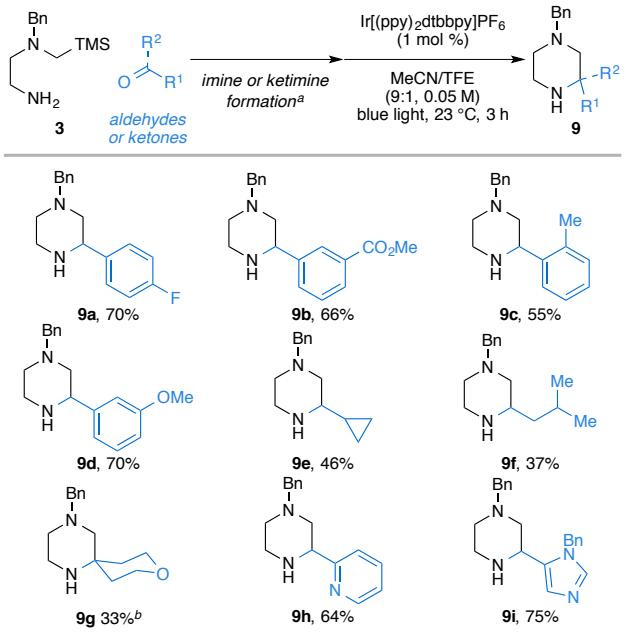


entry	imine[b]	condition	result
1	4	$Cu(OTf)_2$ (1.0 equiv), 2,6-lutidine (1.0 equiv), DCE/HFIP (1:1, 0.10 M), 16 h	imine recovered
2	4	$Ir[(ppy)_2dtbbpy]PF_6$ (1 mol %), MeCN (0.05 M), BL, 16 h	imine recovered
3	5	$Ir[(ppy)_2dtbbpy]PF_6$ (1 mol %), MeCN (0.05 M), BL, 3 h	**8**, 73%[c]
4	6	$Ir[(ppy)_2dtbbpy]PF_6$ (1 mol %), MeCN (0.05 M), BL, 3 h	**9a**, 59%[d]
5	6	$Ir[(ppy)_2dtbbpy]PF_6$ (1 mol %), MeCN/MeOH (9:1, 0.05 M), BL, 3 h	**9a**, 62%[c] (67%[d])
6	6	$Ir[(ppy)_2dtbbpy]PF_6$ (1 mol %), MeCN/HFIP (9:1, 0.05 M), BL, 3 h	**9a**, 67%[c] (71%[d])
7	6	$Ir[(ppy)_2dtbbpy]PF_6$ (1 mol %), MeCN/TFE (9:1, 0.05 M), BL, 3 h	**9a**, 70%[c]
8	6	MeCN (0.05 M), BL, 3 h	imine recovered
9	6	$Ir[(ppy)_2dtbbpy]PF_6$ (1 mol %), MeCN (0.05 M), dark, 3 h	imine recovered
10	6	$Ir(ppy)_3$ (1 mol %), MeCN (0.05 M), BL, 3 h	imine recovered[e]
11	6	$Ru(bpy)_3Cl_2 \cdot 6H_2O$ (1 mol %), MeCN (0.05 M), BL, 3 h	messy result[f]

[a]All reactions were conducted at room temperature. [b]Imine formation was performed with *p*-fluorobenzaldehyde and MS 4A in MeCN. [c]Isolated yield under 0.5 mmol scale. [d]Calculated yield from ^{1}H NMR measurement of unpurified reaction mixture under 0.1 mmol scale with 1,3,5-trimethoxybenzene as an additional internal standard. [e]Along with unidentified products in small amount. [f]The unidentified products were desilylated. BL = blue light; DCE = 1,2-dichloroethane; dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine; HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol; Pg = protecting group; ppy = 2-phenylpyridine; TFE = 2,2,2-trifluoroethanol.

photocatalytic addition of α-silyl-*N*-Ph amines to enones utilized $Ir[(ppy)_2dtbbpy]PF_6$ and blue light irradiation. We applied these conditions to the cyclization of **4** (entry 2). Although no product was observed with the imine formed from the *N*-Boc reagent, full conversion of the *N*-Ph imine **5** was observed within a few hours (entry 3). These conditions were fortunately also applicable to the more synthetically attractive *N*-Bn piperazine reagent **3** (entry 4).[14] Further optimization of the reaction conditions (entries 5–7) and control reactions (entries 8 and 9) to establish the necessity of both the blue light and the iridium photocatalyst lead to the optimized

Scheme 2. Substrate scope via basic SLAP reagent 3



[a]See the Supporting Information for the conditions of imine/ketimine formation. [b]The reaction was carried out in MeCN/MeOH (9:1, 0.05 M).

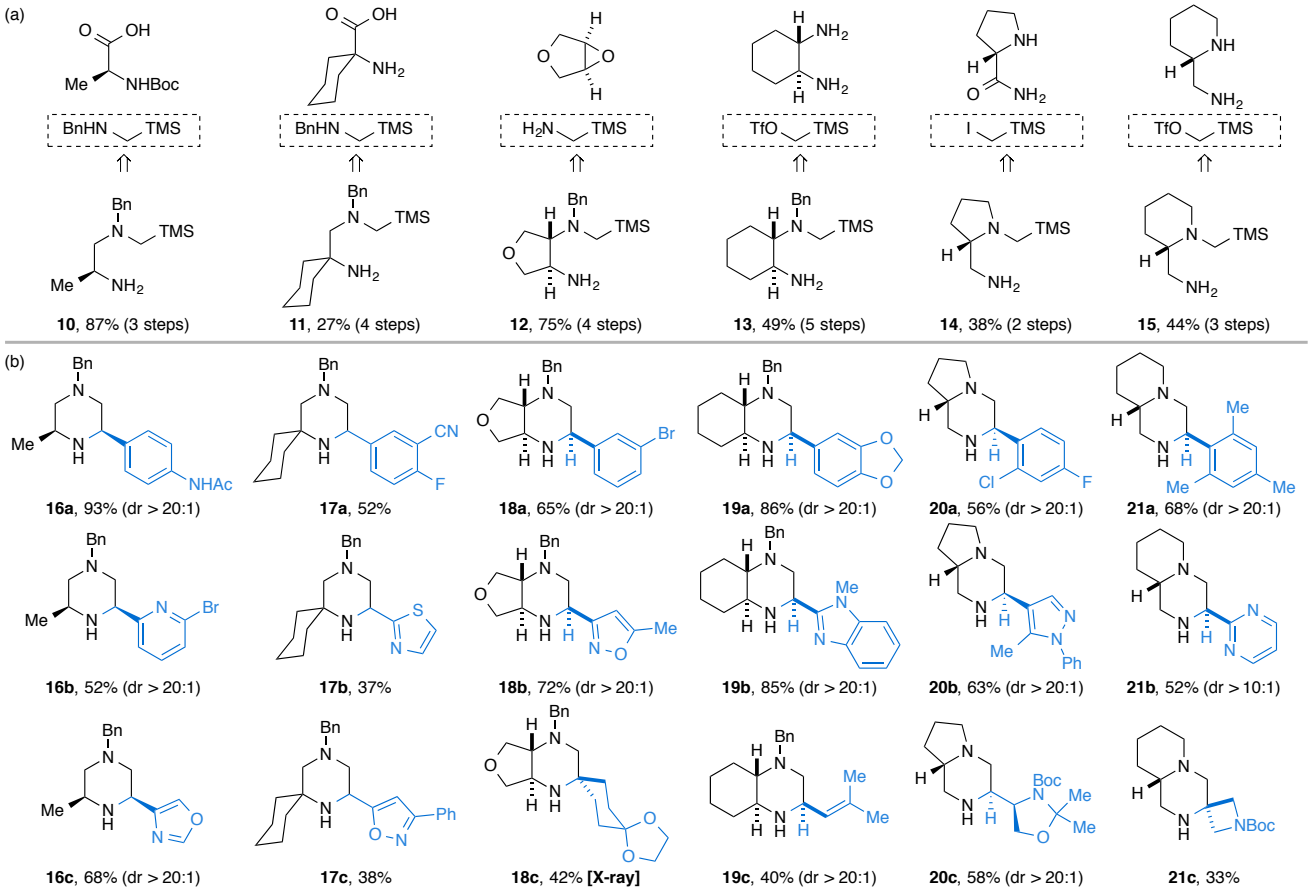
conditions. In general, MeCN was the optimal solvent, but slightly better results were obtained with alcohols as co-solvents (10% v/v).

Condensation of **3** with a variety of aromatic and aliphatic aldehydes occurred smoothly and the additional *N*-Bn piperazine products **9b**–**9i** were obtained in good yields within 3 hours (Scheme 2). A salient feature of SnAP chemistry is its remarkably high tolerance for unprotected functional groups. Any alternative must match the substrate scope of the SnAP chemistry, particularly with regard to compatibility with basic aromatic N-heterocycles. The piperazine forming SLAP reagents fulfill these criteria; heteroaromatic substrates pose no difficulty and gave excellent conversion. Aliphatic aldehydes also gave the desired products, albeit with somewhat reduced yields. In preliminary experiments, the combination of ketones with SLAP reagents provided access to spirocyclic piperazines.

The high chemical stability of the TMS group allows the construction of bespoke SLAP reagents by assembly of various commercially available trimethylsilylmethylene building blocks (Scheme 3A). This enables the preparation of SLAP reagents **10**–**15** by amidation/reduction, epoxide opening, or amine alkylation. All of these reagents proved to be suitable partners in the photocatalytic piperazine formation, regardless of the sterics or stereochemistry of the SLAP reagents. In all cases, the piperazine products were formed with excellent diastereoselectivity, in favor of the more thermodynamically stable isomers (Scheme 3B).

The postulated mechanism features the generation of an aminoalkyl radical via oxidation by the photoexcited $*Ir^{III}[(ppy)_2dtbbpy]PF_6$ (represented as Ir(III)* in Figure 1).[8c,12] This excited Ir(III)* species ($E_{1/2}^{*III/II}$ = +0.66 V vs SCE in MeCN)[15] effects single electron oxidation of the tertiary amine of **22** to generate the α-nitrogen radical **23** (E_p = +0.65 V vs SCE for

Scheme 3. (a) Custom SLAP reagents 10–15 and the TMS building blocks (shown in blue shadow) used in their synthesis.[a] (b) Representative piperazine products formed by photocatalytic coupling of SLAP reagents with aldehydes or ketones.[a,b,c]



[a]Yields are of isolated, analytically pure products. SLAP reagents **10** and **14** and piperazines **16** and **20** are enantiopure forms. [b]See Scheme 2 for photocatalytic cyclization conditions. [c]The diastereomeric ratios were determined by ^{1}H NMR measurement of unpurified reaction mixtures. The relative configurations were analyzed by 2D NOESY spectra. See the Supporting Information for details.

1-((trimethylsilyl)methyl)piperidine)[16] via desilylation and generates the Ir(II) species. Although the reduction of cyclized N-centered radical **24** ($E_{1/2}^{red}$ = –1.70 V vs SCE for dialkylaminyl radicals)[17] by the Ir(II) species ($E_{1/2}^{III/II}$ = –1.51 V vs SCE)[15] seems to be unfavorable, the substituents (R^1 and R^2) may stabilize the N-centered radical, allowing it to be reduced to give – after protonation by TFE – the piperazine product and the starting Ir(III) catalyst. It is worth noting that other photoredox catalysts, such as $Ru^I(bpy)_3^+$ ($E_{1/2}^{II/I}$ = –1.33 V vs SCE)[18], were probably not able to reduce N-centered radical **24**, despite having sufficient oxidizing ability ($E_{1/2}^{*II/I}$ = +0.77 V vs SCE for $*Ru^{II}(bpy)_3^{2+}$)[18] to perform the desilylation[13] (Table 1, entry 11). It is remarkable that the combination of SLAP reagents and the unique nature of $Ir^{III}[(ppy)_2dtbbpy]PF_6$ catalyst allows this sequence of single electron oxidation and reduction with low catalyst loadings and without forming toxic byproducts. This highlights the impact of photocatalytic methods for improving both the scope and sustainability of organic reactions, such as our SnAP chemistry.

At present, the silicon-based reagents are limited to the formation of piperazines; the corresponding reagents for morpholines, diazepanes, and thiomorpholines did not give acceptable yields of the desired products under these conditions. We attribute this to the lower oxidation potential of α-TMS substituted amines than of corresponding sulfides and ethers.[10a,19] We anticipate that the continued development of more active photoredox catalysts or other strategies to lower the oxidation potential of the SLAP reagents will address this limitation in the near future.

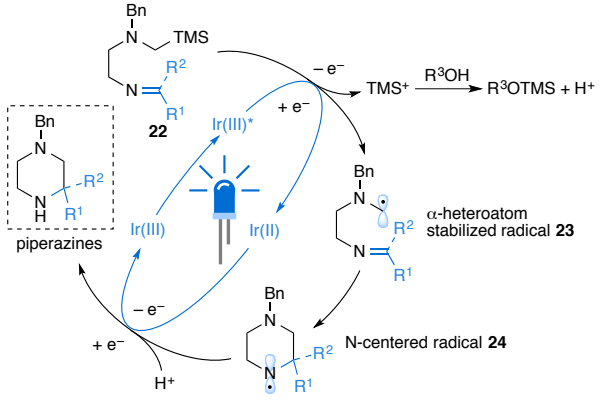


Figure 1. Postulated mechanism for photocatalytic piperizine formation. Ir(III) = $Ir^{III}[(ppy)_2dtbbpy]PF_6$.

In summary, we have applied the principles of photoredox catalysis to the development of silicon-based SLAP reagents for the one-step conversion of aldehydes and ketones into substituted piperazines. This chemistry is distinguished by the mild and attractive reaction conditions, high tolerance of unprotected functional groups and steric hindrance, direct formation of *N*-unprotected products, and ready availability of customized SLAP reagents. Although it is not yet applicable to the extremely broad range of saturated N-heterocycles suitable for tin-based SnAP chemistry, it provides an attractive alternative to piperazine synthesis and a basis for extending these findings to photocatalytic cross-coupling approaches to other saturated N-heterocycles.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data are available free of charge on the ACS Publications website.

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REFERENCES

(1) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257–10274.

(2) Recent chapters or reviews on the synthesis of saturated N-heterocycles, see: (a) Royer, J., Ed. *Asymmetric Synthesis of Nitrogen Heterocycles*. Wiley-VCH Verlag: Weinheim, 2009; (b) Schnurch, M.; Dastbaravardeh, N.; Ghobrial, M.; Mrozek, B.; D. Mihovilovic, M. *Curr. Org. Chem.* **2011**, *15*, 2694–2730; (c) Eicher, T.; Hauptmann, S.; Speicher, A. *The Chemistry of Heterocycles: Structure, Reactions, Synthesis, and Applications*. 3rd, Compl. Revised and Enlarged ed. Weinheim: Wiley-VCH, 2012; (d) Vo, C.-V. T.; Bode, J. W. *J. Org. Chem.* **2014**, *79*, 2809–2815.

(3) Selected recent reviews, see: (a) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552–560; (b) Campos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1069–1084; (c) Mitchell, E. A.; Peschiulli, A.; Lefevre, N.; Meerpoel, L.; Maes, B. U. W. *Chem. Eur. J.* **2012**, *18*, 10092–10142; (d) a recent synthesis of enantioselective piperazines by α-lithiation: Firth, J. D.; O'Brien, P.; Ferris, L. *J. Am. Chem. Soc.* **2016**, *138*, 651–659.

(4) (a) Zhai, H.; Borzenko, A.; Lau, Y. Y.; Ahn, S. H.; Schafer, L. L. *Angew. Chem. Int. Ed.* **2012**, *51*, 12219–12223; (b) Payne, P. R.; Garcia, P.; Eisenberger, P.; Yim, J. C. H.; Schafer, L. L. *Org. Lett.* **2013**, *15*, 2182–2185.

(5) Selected reviews on visible-light photoredox catalysis: (a) Yoon, T. P.; Ischay, M. A.; Du, J. *Nature Chem.* **2010**, *2*, 527–532; (b) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102–113; (c) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322–5363; (d) Reckenthäler, M.; Griesbeck, A. G. *Adv. Synth. Catal.* **2013**, *355*, 2727–2744; (e) Xi, Y.; Yi, H.; Lei, A. *Org. Biomol. Chem.* **2013**, *11*, 2387–2403; (f) Koike, T.; Akita, M. *Synlett* **2013**, *24*, 2492–2505; (g) Schultz, D. M.; Yoon, T. P. *Science* **2014**, *343*, 1239146 (1–8); (h) Angnes, R. A.; Li, Z.; Correia, C. R. D.; Hammond, G. B. *Org. Biomol. Chem.* **2015**, *13*, 9152–9167.

(6) (a) Vo, C.-V. T.; Mikutis, G.; Bode, J. W. *Angew. Chem. Int. Ed.* **2013**, *52*, 1705–1708; (b) Luescher, M. U.; Vo, C.-V. T.; Bode, J. W. *Org. Lett.* **2014**, *16*, 1236–1239; (c) Vo, C.-V. T.; Luescher, M. U.; Bode, J. W. *Nature Chem.* **2014**, *6*, 310–314; (d) Siau, W.-Y.; Bode, J. W. *J. Am. Chem. Soc.* **2014**, *136*, 17726–17729; (e) Geoghegan, K.; Bode, J. W. *Org. Lett.* **2015**, *17*, 1934–1937; (f) Luescher, M. U.; Bode, J. W. *Angew. Chem. Int. Ed.* **2015**, *54*, 10884–10888; (g) Luescher, M. U.; Geoghegan, K.; Nichols, P. L.; Bode, J. W. *Aldrichim. Acta* **2015**, *48*, 43–48.

(7) Le Grognec, E.; Chrétien, J.-M.; Zammattio, F.; Quintard, J.-P. *Chem. Rev.* **2015**, *115*, 10207–10260.

(8) (a) Steinmetz, M. G. *Chem. Rev.* **1995**, *95*, 1527–1588; (b) Chatgilialoglu, C.; Timokhin, V. I. *Adv. Organomet. Chem.* **2008**, *57*, 117–181; (c) Cho, D. W.; Yoon, U. C.; Mariano, P. S. *Acc. Chem. Res.* **2011**, *44*, 204–215.

(9) Kagoshima, H.; Yonezawa, K. *Synth. Commun.* **2006**, *36*, 2427–2432.

(10) (a) Wu, X.-D.; Khim, S.-K.; Zhang, X.; Cederstrom, E. M.; Mariano, P. S. *J. Org. Chem.* **1998**, *63*, 841–859; (b) Yoon, U. C.; Mariano, P. S. *Acc. Chem. Res.* **1992**, *25*, 233–240; (c) Yoon, U. C.; Kim, J. W.; Ryu, J. Y.; Cho, S. J.; Oh, S. W.; Mariano, P. S. *J. Photochem. Photobiol. A: Chem.* **1997**, *106*, 145–154; (d) Yoon, U. C.; Kwon, H. C.; Hyung, T. G.; Choi, K. H.; Oh, S. W.; Yang, S.; Zhao, Z.; Mariano, P. S. *J. Am. Chem. Soc.* **2004**, *126*, 1110–1124.

(11) Related work by Pandey and co-workers on single electron oxidation cyclization for pyrolidine or piperidine synthesis: Pandey, G.; Kumaraswamy, G.; Bhalerao, U. T. *Tetrahedron Lett.* **1989**, *30*, 6059–6062.

(12) (a) Miyake, Y.; Ashida, Y.; Nakajima, K.; Nishibayashi, Y. *Chem. Commun.* **2012**, *48*, 6966–6968; (b) Nakajima, K.; Kitagawa, M.; Ashida, Y.; Miyake, Y.; Nishibayashi, Y. *Chem. Commun.* **2014**, *50*, 8900–8903; (c) Miyake, Y.; Ashida, Y.; Nakajima, K.; Nishibayashi, Y. *Chem. Eur. J.* **2014**, *20*, 6120–6125; (d) Nakajima, K.; Ashida, Y.; Nojima, S.; Nishibayashi, Y. *Chem. Lett.* **2015**, *44*, 545–547.

(13) Related recent, enantioselective photoredox catalysis on α-amino radicals from TMS surrogates was recently published by Yoon, see Ruiz Espelt, L.; McPherson, I. S.; Wiensch, E. M.; Yoon, T. P. *J. Am. Chem. Soc.* **2015**, *137*, 2452–2455.

(14) For facile deprotection of *N*-Bn piperazines, see: (a) Olofson, R. A.; Martz, J. T.; Senet, J. P.; Piteau, M.; Malfroot, T. *J. Org. Chem.* **1984**, *49*, 2081–2082; (b) Yokoshima, S.; Watanabe, K.; Uehara, F.; Usui, Y.; Tanaka, H. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 5749–5751; (c) ref. 3d; (d) See the Supporting Information for the deprotection procedure of **9a**.

(15) (a) 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; (b) 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.

(16) Broka, K.; Stridins, J. P.; Sleiksa, I.; Lukevics, E. *Latv. Khim. Z.* **1992**, *5*, 575–579.

(17) (a) This value is converted from –1.46 V vs NHE. See the reference: Jonsson, M.; Wayner, D. D. M.; Lusztyk, J. *J. Phys. Chem.* **1996**, *100*, 17539–17543; (b) The value is consistent to calculated reduction potentials of N-centered radicals at the B3LYP/6-31+G* level, see Wille, U.; Heuger, G.; Jargstorff, C. *J. Org. Chem.* **2008**, *73*, 1413–1421.

(18) Juris, A.; Balzani, V.; Belser, P.; von Zelewsky, A. *Helv. Chim. Acta* **1981**, *64*, 2175–2182.

(19) (a) Yoshida, J.; Maekawa, T.; Murata, T.; Matsunaga, S.; Isoe, S. *J. Am. Chem. Soc.* **1990**, *112*, 1962–1970; (b) Yoshida, J.-i. *Top. Curr. Chem.* **1994**, *170*, 39–81; (c) Jouikov, V. V. *Russ. Chem. Rev.* **1997**, *66*, 509–540.

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