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COMMUNICATION

Heterocyclization involving Benzylic C(sp^3)–H Functionalization Enabled by Visible Light Photoredox Catalysis

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A general and efficient method of heterocyclization involving benzylic C(sp^3)-H functionalization enabled by visible light photoredox catalysis to access a wide range of structurally diverse oxygen as well as nitrogen heterocycles up to gram scale is reported. Potential application of this new methodology is demonstrated by the total synthesis of (–)-codonopsinine and (+)-centrolobine. Herein it is proposed that selectfluor, unlike fluorination, acts an oxidative quencher and hydrogen radical acceptor.

Nitrogen and oxygen-containing heterocyclic scaffolds are dominant structural motifs present in many biologically active natural products and pharmaceuticals.[1,2] Therefore, their synthesis has been an attractive target of considerable interest among synthetic organic chemists. Although, significant progress has been made towards the advancement of this area, majority of these reactions require multistep sequence or pre-functionalized starting materials.[3] For example, classically these heterocyclizations were achieved via intra-molecular 1, 5-hydrogen transfer followed by cyclization involving highly reactive nitrogen or oxygen centered radical species to construct pyrrolidine or tetrahydrofuran moieties respectively (Figure 1a).[4] On the other hand, transition metal catalyzed (Rh, Ru, Co and Fe) intramolecular amination via nitrene insertion to the C(sp3)–H bond has been extensively used as one of the most powerful and efficient strategy for N–heterocyclization (Figure 1b).[5] However, finding a suitable nitrene source, use of an external oxidant and selectivity still remains a major issue associated with this strategy. Intramolecular allylic amination and etherification involving a π–allyl palladium complex is also reported (Figure 1c).[6] Directing group assisted transition metal catalyzed C(sp3)–H functionalization is well documented, where amine protecting group itself acts as a directing group (Figure 1d) for N-heterocyclization[7a-e] and in the case of cycloetherification a separate directing group is required (Figure 1e).[7f-g] Although, these strategies certainly address the regioselectivity issue, installation of appropriate directing group and their removal require multistep sequences. Another unique approach for N–heterocyclization involves oxidative coupling of C, N–dianions in presence of a strong base and an oxidant (Figure 1f).[3a,8] Nevertheless, the excess use of strong base precludes the functional group tolerability.

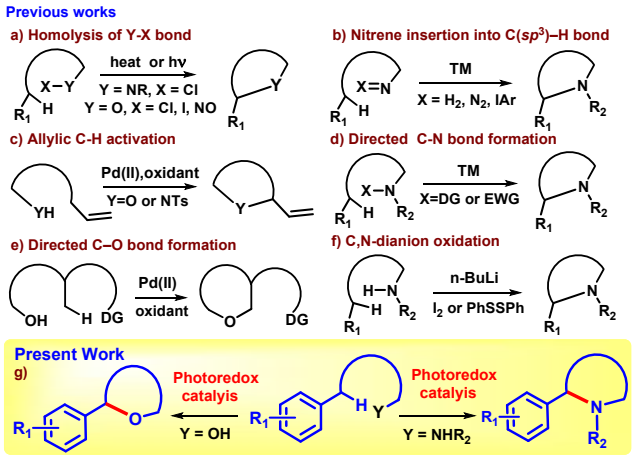

Fig. 1 Intramolecular C(sp3–H) functionalization strategies

Despite the aforementioned elegant works, still there is a compelling demand to develop a general and selective heterocyclization strategy through C(sp^3)–H functionalization to synthesize various heterocycles, which must be devoid of directing group, an oxidant, pre-oxidized substrate and harsh reaction condition. To meet such a demanding goal, though highly desirable, is a very challenging task (Figure 1g).

In the past decade, visible-light photoredox reaction involving arene radical cation has led to the development of a number of unprecedented C–X (X = N, O) bonds forming methodologies through C(sp^2)–H functionalization,[9,10a] while very few

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advancements have been made through C(sp^3)–H functionalization.[10] Our own research interest in this area has resulted in the benzylic C(sp^3)–H functionalization for both inter- and intramolecular C–O bond formation as well as intermolecular C–N bond formation using cyanoaromatic as an organophotoredox catalyst.[11a,b] However, these strategies

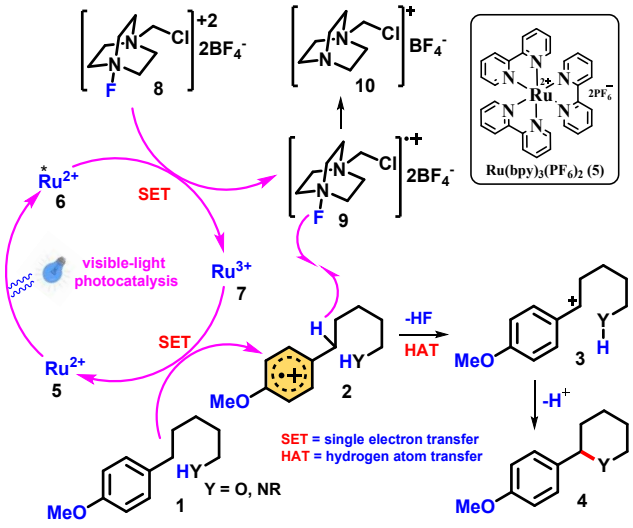
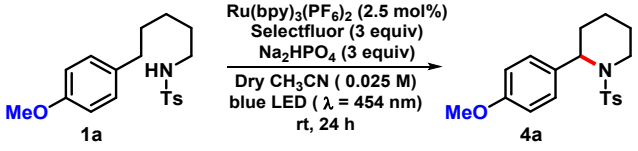


Fig. 2 Plausible catalytic cycle for heterocyclization

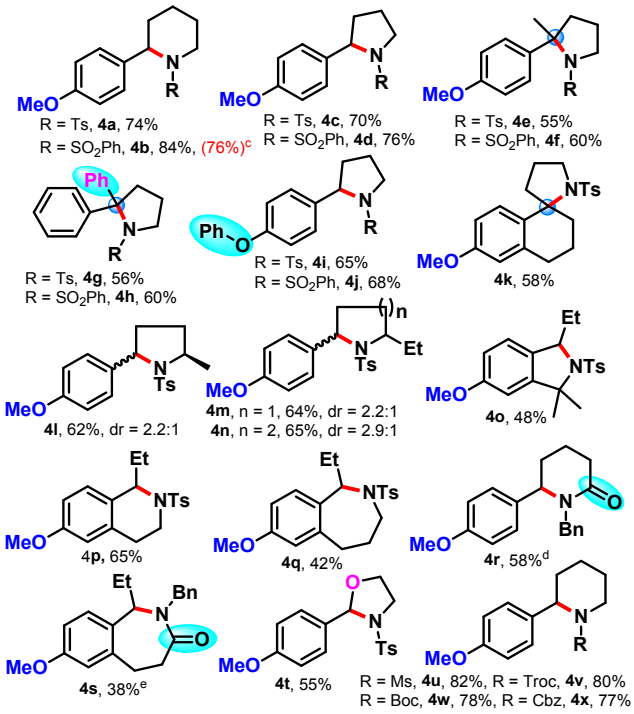
were unsuccessful for the *N*-heterocyclization reaction, albeit, we have recently reported an intermolecular C(sp^3)–H amination using Ir(III) photocatalyst.[11c,d] Considering the importance of heterocycles and impending general methodology, we sought to evaluate a new strategy based on C(sp^3)–H functionalization using photoredox catalysis as shown in Figure 2. Herein, wereport a general heterocyclizationstrategy which has also been successfully applied in the natural product synthesis.



Entry	Deviation from standard condition	Yield(%)[b]
1	none	74
2	$Ru(bpy)_3Cl_2.6H_2O$ instead of **5**	69
3	$(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ instead of **5**	74
4	K_2CO_3 instead of Na_2HPO_4	trace
5	$BrCCl_3$ instead of **8**	55
6	DMSO instead of CH_3CN	0
7	reaction mixture was degassed	74
8	in absence of light or catalyst or **8**	0
9	in absence of Na_2HPO_4	10
10	1b instead of **1a**	84

Table 1: Optimization of Reaction Conditions: (a) Reaction conditions: 1a (0.2 mmol, 1 equiv), 5 (2.5 mol %), 8 (0.6 mmol, 3.0 equiv), base (0.6 mmol, 3.0 equiv), solvent 8 mL, rt, blue LED, 24 h. (b) Isolated yield of 4a.

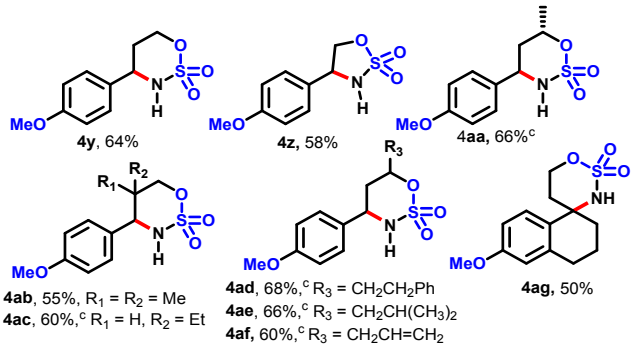
To validate our proposed hypothesis, *N*-tosyl amine (**1a**) was first irradiated with visible light (λ = 454 nm, 3 W, blue LED) over a range of photocatalysts, oxidative quenchers and bases at room temperature in different solvents (for details, see Supporting Information). To our gratification, when **1a** (1.0 equiv) was irridiated in dry CH_3CN for 24 h in the presence of 2.5 mol % of $Ru(bpy)_3(PF_6)_2$ (**5**), 3.0 equiv of selectfluor (**8**) and 3.0 equiv of Na_2HPO_4, the desired cyclised product (**4a**) was obtained in 74% isolated yield (Table 1, entry 1). Deviation from standared conditions using different catalysts (entries 2 and 3), base (entry 4), oxidative quencher (entry 5), solvent (entry 6) and degassed condtion (entry 7) failed to deliver better results. Controlled experiments justified the requirement of the light source, photocatalyst and an oxidative quencher for this cyclization reaction (entry 8). However, absence of a base led to the formation of a complex reaction mixture and diminished the yield of **4a** significantly (entry 9).



Scheme 1. Synthesis of N-Heterocycles: (a) Reaction conditions: 1 (0.20 mmol), 5 (2.5 mol %), 8 (0.6 mmol) and base (0.6 mmol) in dry CH3CN (8 mL) were irradiated at rt for 24 h using blue LED. (b) Isolated yield of the product 4. (c) Reaction was performed in 2.1 g scale. (d) Reaction time 2 h. (e) Reaction time 0.25 h.

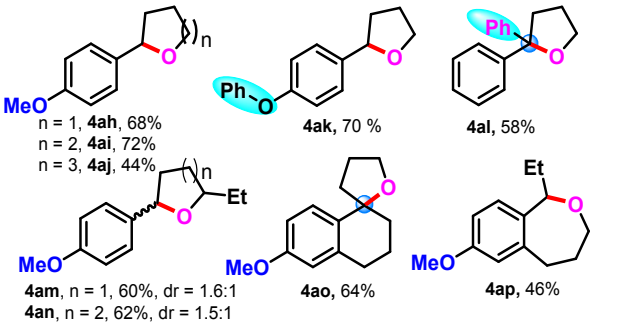
With this optimized reaction condition in hand, we then examined the substrate scope over a wide range of N-protected linear amines (**1a-x**) and found that desired cyclization proceeded smoothly to give corresponding products (**4a-ax**) withdifferent ring size and substitution pattern in 38-84% isolated yields (Scheme 1). We also observed that the cyclization proceeded more efficiently for the substrate with no substitution at benzylic position (**4a-d**, **4i-j**, and **4l-n**) compared to the substrate having an alkyl or aromatic substitution at the same position (**4e-h** and **4k**). p–OPh group instead of p–OMe group on substrate was found to have no detrimental effect on cyclization process and produced targeted products (**4i** and **4j**) in good yield. We have also synthesized more challenging spirocyclic derivative (**4k**).However, modest

diastreoselectivtitywas observed in case of α-substituted amine derivatives (**4l-n**, drupto 2.9:1). In addition, isoindoline (**4o**), tetrahydroisoquinoline (**4p**), azepane (**4q**) and oxazolidine (**4t**) derivatives were synthesized in satisfactory yield under identical condition.To our delight, the utility of this reaction was further illustrated to prepare lactams (**4r** and **4s**), which are challenging targets and profound structural motifs in bioactive molecules, via direct C–H amidation within a very short period of time.[12] Effect of various *N*-protecting groups was examined. We found amines with electron withdrawing group such as -SO2Ph, -Ms, -Cbz, -Boc and -Troc reacted efficiently to produce corresponding products (**4b** and **4u-x**). Notably, this cyclization proceeded smoothly in gram scale to deliver **4b** in good yield.



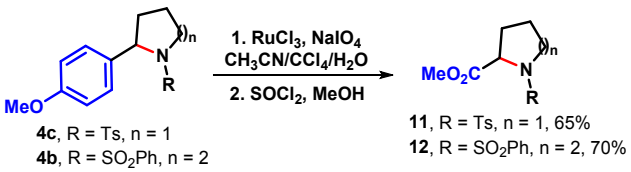
Scheme 2. Synthesis of cyclic sulfamidates: (a) Reaction conditions: 1 (0.2 mmol), 5 (2.5 mol %), 8 (0.6 mmol) and base (0.6 mmol) in CH3CN (8 mL) were irradiated at rt for 18 h using blue LED. (b) Isolated yield of the product 4. (c)dr> 20:1.

This protocol was also amenable for the cyclization of various sulfamate esters (Scheme 2, **4y-4ag**, 50-68%, dr> 20:1), a source of 1, 3-amino alcohols and related β-amino alcohols, generally obtained *via* transition metal catalyzed nitrene insertion or analogous reactions.[5b,13] Interestingly, we observed both 1, 3-*cis* isomer (**4aa** and**4ad-af**) and 1, 2-*trans* isomer (**4ac**) as a single diastereomer. We were impressed withthe excellent regioselectivity observed for **4ad-4af** which otherwise is difficult to achieve by other methods.[13] Furthermore, an optically pure product (**4aa**)was obtained in good yield and excellent diastereoselectivity (dr> 20:1) from optically pure **1aa**.



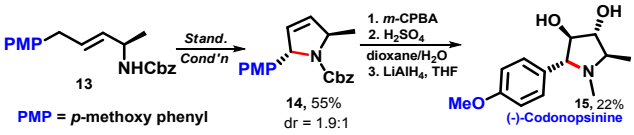
Scheme 3. Synthesis of Cyclic Ethers:(a) Reaction conditions: 1 (0.20 mmol), 5 (2.5 mol %), 8 (0.6 mmol) and base (0.6 mmol) in dry CH3CN (8 mL) were irradiated at rt for 18 h using blue LED. (b) Isolated yield of product 4.

After successful *N*-heterocyclization, we prepared a wide range of cyclic ethers from corresponding linear alcohols.[2a] A number of five-, six- and seven-membered cyclic ethers (**4ah-ap**) were prepared in moderate to good yields (44-72%, Scheme 3). To explore the potential application of this methodology, racemic unnatural amino acid derivatives (**11** and **12**) were prepared in good yield by post modification of **4b** and **4c** by oxidative cleavage of the electron-rich aromatic ring using catalytic amount$RuCl_3$ (Scheme 4).[14]



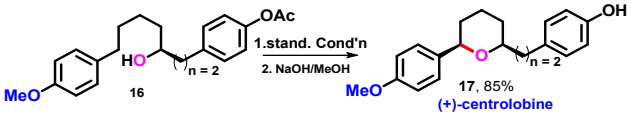
Scheme 4. Synthesis of (±) Amino Acid Derivatives

Subsequently, we undertook the synthesis of highly functionalized (-)-codonopsinine (**15**), isolated from Codonopsis clematidea, which displays significant antibiotic and hypotensive activities without affecting the central nervous system.[15a] To this end, we synthesized pivotal intermediate **14** from enantiopure **13** in modest yield and diastereoselectivity (dr = 1.9:1). Epoxidation of **14** using *m*-CPBA, followed by acid mediated ring opening and finally $LiAlH_4$ reduction gave (-)-Codonopsinine (**15**) in 22% yield over 3 steps (Scheme 5).[15b]



Scheme 5. Total synthesis of (-)-Codonopsinine (**15**)

We also targeted the synthesis of antibacterial (2R, 6S)-(+)-centrolobine (**17**),[16] an oxygen containing heterocycle which was isolated from *centrolobiumrobustum*,by direct photoredox cyclization of **16** in excellent yield (93%, dr> 1.6:1).Isolation of the major diastereomer followed by *O*-acetate deprotection resulted (+)-centrolobine (**17**)in 85% yield (Scheme 6).[16a]



Scheme 6. Total Synthesis of (+)-Centrolobine (**17**)

To evaluate the possible mechanism of heterocyclization, we performed some controlled experiments (Please see the supporting information). Since substrate **1aq** (without OMe) has very high oxidation petential ($E_{p/2}$ = + 2.28 V SCE), electron transfer(ET) to Ru(III)($E_{1/2}^{III/II}$= + 1.32 V vs SCE) is difficult and in case of substrate **1ar**(m-OMe, $E_{p/2}$ = + 1.68 V vs SCE), thoguh ET is feasible, the generated benylic carbocation intermediate (**3**) is not stabilized due to lack of +R effect of -OMe group. Based on the observations from the controlled experiment, we propose that the reaction plausibly proceeds via single electron

transfer (SET) from the excited Ru (II)* complex **6** ($E_{1/2}^{III/II*}$= –0.85 V vs SCE) to selectfluor **8** ($E_{p/2}$ =+ 0.46 V vs SCE)[17a,c] generating reduced selectfluorspecies **9** and Ru (III) ($E_{1/2}^{III/II}$= + 1.32 V vs SCE) which gets reduced to Ru (II) by oxidizing the electron rich arene moiety **1** (**1a**, $E_{p/2}$ = + 1.59 V vs SCE) to correspondingarene radical cation intermediate **2**(for details see Supporting Information). At this point, we believed that H-abstraction by **9** from benzylic position of **2** led to the formation of stable carbocation **3**, which on cyclization with a tethered nucleophile (–NHR or –OH) produced desired cyclized product **4** (Figure 2). It is worthy to mention that, selectfluor, unlike a potential fluorinating[17b-d]reagent, acts as an efficient oxidative quencher as well as hydrogen radical acceptor in this reaction.[17e]

In conclusion, we have presented an unprecedented method for both intramolecular benzylic C(sp^3)–N and C(sp^3)–O bond forming reactions *via* visible light photoredox catalysis. This mild and operationally simple protocol works well over a wide range of structurally diverse five, six and seven membered nitrogen as well as oxygen containing heterocycles in good to excellent yields. Synthetic potential of this method has been demonstrated by diastereoselective total synthesis of (–)-codonopsinine (**15**) and(+)-centrolobine (**17**). Efforts are under way to address further mechanistic details and extrapolation of this work.

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Conflicts of interest

The authors declare no competing financial interest.

References

1 (a) R. Hili, A. K. Yudin, Nat. Chem. Biol. 2006, 2, 284; (b) A. H. Lipkus, Q. Yuan, K. A. Lucas, S. A. Funk, W. F. Bartelt, R. J. Schenck, A. J. Trippe, J. Org. Chem. 2008, 73, 4443.
2 (a) A. Lorente, J. Lamariano-Merketegi, F. Albericio, M. Álvarez, Chem. Rev. 2013, 113, 4567.
3 (a) J. L. Jeffrey, R. Sarpong, Chem. Sci. 2013, 4, 4092; (b) T. A. Ramirez, B. Zhao, Y. Shi, Chem. Soc. Rev. 2012, 41, 931; (c) F. Collet, C. Lescot, P. Dauban, Chem. Soc. Rev. 2011, 40, 1926; (d) J. W. W. Chang, T. M. U. Ton, P. W. H. Chan, Chem. Rec. 2011, 11, 331–357; (e) T. G. Driver, Nat. Chem. 2013, 5, 736; (f) O. V. Zatolochnaya, V. Gevorgyan, Nat. Chem. 2014, 6, 661; (g) B. Liu, B. F. Shi, Tetrahedron Lett. 2015, 56, 15; (h) Y. Park, Y. Kim, S. Chang, Chem. Rev. 2017, 117, 9247.
4 (a) A. W. Hofmann, Ber. Dtsch. Chem. Ges. 1883, 16, 558; (b) A. W. Hofmann, Ber. Dtsch. Chem. Ges. 1885, 18, 5; (c) G. Majetich, K. Wheless, Tetrahedron 1995, 51, 7095; d) Ž. J. Čeković, Serb. Chem. Soc. 2005, 70, 287.
5 a) C. G. Espino, J. Du Bois, Angew. Chem., Int. Ed. 2001, 40, 598–600; (b) C. G. Espino, P. M. When, J. Chow, J. Du Bois, J. Am. Chem. Soc. 2001, 123, 6935; (c) J. L. Liang, S. X. Yuan, J. S. Huang, W. Y. Yu, C. M. Che, Angew. Chem., Int. Ed. 2002, 41, 3465; (d) H. Lebel, K. Huard, S. Lectard, J. Am. Chem. Soc. 2005, 127, 14198; (e) J. V. Ruppel, R. M. Kamble, X. P. Zhang, Org. Lett. 2007, 9, 4889; (f) Q. Nguyen, K. Sun, T. G. Driver, J. Am. Chem. Soc. 2012, 134, 7262; (g) J. L. Roizen, M. E. Harvey, J. Du Bois, Acc. Chem. Res. 2012, 45, 911; (h) B. Bagh, D. L. J. Broere, V. Sinha, P. F. Kuijpers, N. P. van Leest, B. de Bruin, S. Demeshko, M. A. Siegler, J. I. van der Vlugt, J. Am. Chem. Soc, 2017, 139, 5117.
6 (a) S. E. Ammann, G. T. Rice, M. C. White, J. Am. Chem. Soc. 2014, 136, 10834; (b) J. K. Fraunhoffer, M. C. White, J. Am. Chem. Soc. 2007, 129, 7274.
7 (a) J. J. Neumann, S. Rakshit, T. Droge, F. Glorius, Angew. Chem., Int. Ed. 2009, 48, 6892; (b) E. T. Nadres, O. Daugulis, J. Am. Chem. Soc. 2012, 134, 7; (c) M. Yang, B. Su, Y. Wang, K. Chen, X. Jiang, Y. F. Zhang, X. S. Zhang, G. Chen, Y. Cheng, Z. Cao, Q. Y. Guo, L. Wang, Z. J. Shi, Nat. Commun. 2014, 5, 4707; (d) X. Wu, K. Yang, Y. Zhao, H. Sun, G. Li, H. Ge, Nat. Commun. 2015, 6, 6462; (e) C. Yamamoto, K. Takamatsu, K. Hirano, M. Miura, J. Org. Chem. 2016, 81, 7675; (f) S. J. Thompson, D. Q. Thach, G. Dong, J. Am. Chem. Soc. 2015, 137, 11586; (g) H. Wang, Y. Niu, G. Zhang, X. S. Ye, Tettahedron Lett. 2016, 57, 4544.
8 (a) A. Bisai, S. P. West, R. Sarpong, J. Am. Chem. Soc. 2008, 130, 7222.
9 (a) N. A. Romero, K. A. Margrey, N. E. Tay, D. A. Nicewicz, Science. 2015, 349, 1326; (b) Y. W. Zheng, B. Chen, P. Ye, K. Feng, W. Wang, Q. Y. Meng, L. Z. Wu, C. H. Tung, J. Am. Chem. Soc. 2016, 138, 10080; (c) S. Das, P. Natarajan, B. Konig, Chem. Eur. J. 2017, 23, 18161.
10 (a) H. Zhang, A. Lei, Asian J. Org. Chem. 2018, 7, 1164; (b) L. C. Finney, L. J. Mitchell, C. J. Moody, Green Chem., 2018, 20, 2242.
11 (a) G. Pandey, S. Pal, R. Laha, Angew. Chem. Int. Ed. 2013, 52, 5146. (b) G. Pandey, R. Laha, Angew. Chem., Int. Ed. 2015, 54, 14875; (c) G. Pandey, R. Laha, D. Singh, J. Org. Chem. 2016, 81, 7161; (d) G. Pandey, D. Singh, R. Laha, Asian J. Org. Chem. 2017, 6, 469.
12 (a) S. Y. Hong, Y. Park, Y. Hwang, Y. B. Kim, M. H. Baik, S. Chang, Science, 2018, 359, 1016. (b) C. Zhu, Y. Liang, X. Hong, H. Sun, W. Y. Sun, K. N. Houk, Z. Shi, J. Am. Chem. Soc. 2015, 137, 7564.
13 (a) S. M. Paradine, J. R. Griffin, J. Zhao, A. L. Petronico, S. M. Miller, M. C. White, Nat. Chem. 2015, 7, 1. (b) M. Huang, T. Yang, J. D. Paretsky, J. F. Berry, J. M. Schomaker, J. Am. Chem. Soc. 2017, 139, 17376.
14 P. H. J. Carlsen, T. Katsuki, V. S. Martin, K. B. Sharpless, J. Org. Chem. 1981, 46, 3936.
15 (a) M. Lingamurthy, Y. Jagadeesh, K. Ramakrishna, B. V. Rao, J. Org. Chem. 2016, 81, 1367. (b) M. Yamaguchi, D. Itagaki, H. Ueda, H. Tokuyama, J. Antibiot. (Tokyo). 2016, 69, 253.
16 (a) F. Rogano, P. Rüedl, Helv. Chim. Acta 2010, 93, 1281. (b) J. R. Vyvyan, H. E. Longworth, S. K. Nguyen, Synlett 2016, 27, 2221.
17 (a) M. Rueda-Becerril, O. Mahé, M. Drouin, M. B. Majewski, J. G. West, M. O. Wolf, G. M. Sammis, J. F. Paquin, J. Am. Chem. Soc. 2014, 136, 2637. (b) A. R. Mazzotti, M. G. Campbell, P. Tang, M. J. Murphy, T. Ritter, J. Am. Chem. Soc. 2013, 135, 14012. (c) S. Ventre, F. R. Petronijevic, D. W. C. MacMillan, J. Am. Chem. Soc. 2015, 137, 5654. (d) J. B. Xia, C. Zhu, C. Chen, J. Am. Chem. Soc. 2013, 135, 17494. (e) S. Wang, J. Liu, L. Niu, H. Yi, C. W. Chiang, and A. J. Lei, Photochem. Photobiol. A: Chem. 2018, 355, 120.