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Catalyst-free photoinduced selective oxidative C(sp^3)–C(sp^3) bond cleavage in arylamines†

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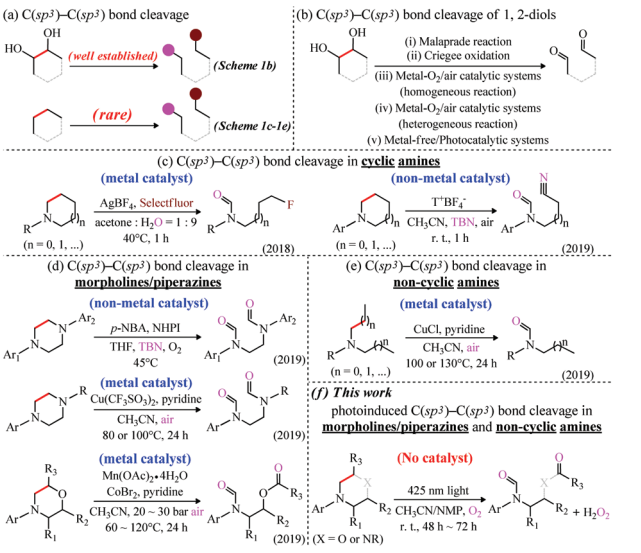
Due to the directional nature of sp^3-hybridized orbitals and the absence of π-orbitals, the oxidative cleavage of the kinetically and thermodynamically stable C(sp^3)–C(sp^3) bond is extremely difficult and remains scarcely explored. In this work, under the double argument of quantum mechanics (QM) computations and meticulous experiments on our well-designed C–C single bond cleavage mechanism, we discovered a means of photoinduced selective oxidative C(sp^3)–C(sp^3) bond cleavage in arylamines, easily achieved by simple visible light irradiation using O_2 as a benign oxidant under very mild conditions. The utility of our methodology was demonstrated by the C(sp^3)–C(sp^3) bond cleavage in morpholine/piperazine arylamines with excellent functional group tolerance. Importantly, our methodology is noteworthy, not only in that it does not require any catalysts, but also in that it provides valuable possibilities for the scalable functionalization of clinical drugs and natural products.

Site-selective cleavage of the saturated C(sp^3)–C(sp^3) bond represents a powerful and essential class of chemical transformation in chemistry and biology because of its wide applications in complex natural product constructions, and ubiquity in late-stage clinical drug modifications.[1] Hence, the development of an effective and versatile C–C single bond cleavage method is of great methodological, chemosynthetic and pharmaceutical interest.[2] However, due to the high bond dissociation energy (~90 kcal mol^{-1}) and low reactivity of the inert C–C σ-bond, efficient accomplishment of its cleavage is one of the most challenging transformations and is less accessible.[3] Fortunately, various cleavage systems have been successfully investigated, including the traditional Malaprade reaction and the Criegee oxidation which employed excess amounts of hazardous oxidants such as O_3, $NaIO_4$, HIO_4, $Pb(OAc)_4$ and $KMnO_4$ to achieve the oxidative cleavage,[4] homogeneous[5] and heterogeneous[6] metal–O_2/air catalytic systems developed in the past decades which employed metal catalysts and the ideal O_2/air oxidant to achieve the oxidative cleavage, and recently developed metal-free/photocatalytic systems[7] which employed non-metallic catalysts or photocatalysts and the ideal O_2/air oxidant to achieve the oxidative cleavage. Regrettably, these well-established systems almost all exclusively oxidize and break the C–C bond in 1,2-diols or their derivatives (*e.g.*, lignin). As for the single bond breakage in other structure types, it has never been reported and remained scarcely explored until the last three years (Scheme 1a and b).



Scheme 1 (a) Development status of the C(sp^3)–C(sp^3) bond cleavage. (b) Well-established C(sp^3)–C(sp^3) bond cleavage in 1,2-diols. (c–e) Previously established C(sp^3)–C(sp^3) bond cleavage in various amines. $T^+BF_4^-$ = 2,2,6,6-tetramethyl-1-oxopiperidin-1-ium tetrafluoroborate, TBN = *tert*-butyl nitrite, *p*-NBA = *p*-nitrobenzoic acid, NHPI = *N*-hydroxyphthalimide. (f) Proposed photoinduced C(sp^3)–C(sp^3) bond cleavage in arylamines under mild conditions without any catalysts.

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In 2018, Sarpong's group firstly realized the oxidative cleavage of the C–C single bond in cyclic amines by employing $AgBF_4$ as the metal catalyst and Selectfluor as the final oxidant (Scheme 1c).[8] Then in 2019, by using TBN as the oxidant, Fan's group also achieved the oxidative cleavage in cyclic amines using the non-metal catalyst $T^+BF_4^-$ (Scheme 1c),[9] and Jia's group further realized the oxidative cleavage in piperazines using the non-metal catalyst system *p*-NBA/NHPI (Scheme 1d).[10] Almost at the same time, Beller's group chose ideal air/O_2 as the oxidant, and achieved groundbreaking oxidative cleavage in piperazines, morpholines and non-cyclic amines with the help of the metal catalysts $Cu(CF_3SO_3)_2$, $CoBr_2$/$Mn(OAc)_2$ and CuCl, respectively (Scheme 1d and e).[11] Although the structure type extension is gratifying, from a green and practical perspective there is still a substantial need for more alternative methodologies, which not only use benign oxidants, but also avoid the high cost and pollution of metal and non-metal catalysts. In this respect, air/O_2 and non-requirement of a catalyst are the most ideal oxidant and reaction condition, respectively.[12]

From a mechanistic aspect, the oxidation of tertiary amines currently known mainly including *N*-oxidation, *N*-dealkylation, carbonylation (*i.e.*, C–H oxidation) and $C(sp^3)$–$C(sp^3)$ bond cleavage plays a vital role in nature.[11a,13] Thus, the mechanism exploration of these oxidation reactions is very important and necessary.[13] So far, the most detailed is *N*-oxidation which uses different oxidants to prepare various amine oxide products. *N*-dealkylation and carbonylation have also been explored to some extent,[14] such as the *N*-dealkylation and carbonylation in *N*,*N*-dimethyl arylamines[15] as shown in Fig. 1a and b. For *N*-dealkylation, under the action of a metal complex (Rh^{III} or Fe^{III}), the α-position of *N*,*N*-dimethyl arylamines firstly loses a hydride ion, and then the formed iminium ion **5** is hydrolyzed to the ammonium ion **6** which subsequently loses a proton to form the final *N*-dealkylation product **d**. While for carbonylation, the excited *N*,*N*-dimethyl arylamines under light firstly act as a photosensitizer to undergo an energy-transfer pathway with the triplet $^3O_2$ to afford a singlet $^1O_2$, which reacts with the ground-state *N*,*N*-dimethyl arylamines *via* a single electron transfer (SET) process to generate the radical cation **1** and $O_2^{\bullet-}$; then, a proton transfer between **1** and $O_2^{\bullet-}$ proceeds to afford the aminomethyl radical **2** and the superoxide radical $HOO^{\bullet}$, which subsequently directly drives a radical–radical coupling to form the 1-hydroperoxy methanamine intermediate **3**; finally, an intermolecular dehydration of **3** yields the carbonylation product **c** (*i.e.*, C–H oxidation product). Much less explored is the $C(sp^3)$–$C(sp^3)$ bond cleavage due to the complexity of its mechanism. For example, the only known thing about the reaction process of the $CoBr_2$/$Mn(OAc)_2$-catalyzed $C(sp^3)$–$C(sp^3)$ bond cleavage in morpholines[11b] is that its mechanism involves the intermediate **1** which is also formed in the carbonylation process of *N*,*N*-dimethyl arylamines, and an enamine intermediate **4** (Fig. 1c). Complementary to the oxidation mechanism of tertiary amines, especially to the cleavage mechanism of the $C(sp^3)$–$C(sp^3)$ bond, we herein report a photoinduced selective oxidative $C(sp^3)$–$C(sp^3)$ bond cleavage in arylamines using ideal O_2 under catalyst-free conditions (Scheme 1f) and its detailed mechanism. It is worth noting that this methodology can be easily performed in morpholine/piperazine arylamines and some non-cyclic arylamines, and even in their clinical drugs and natural products.

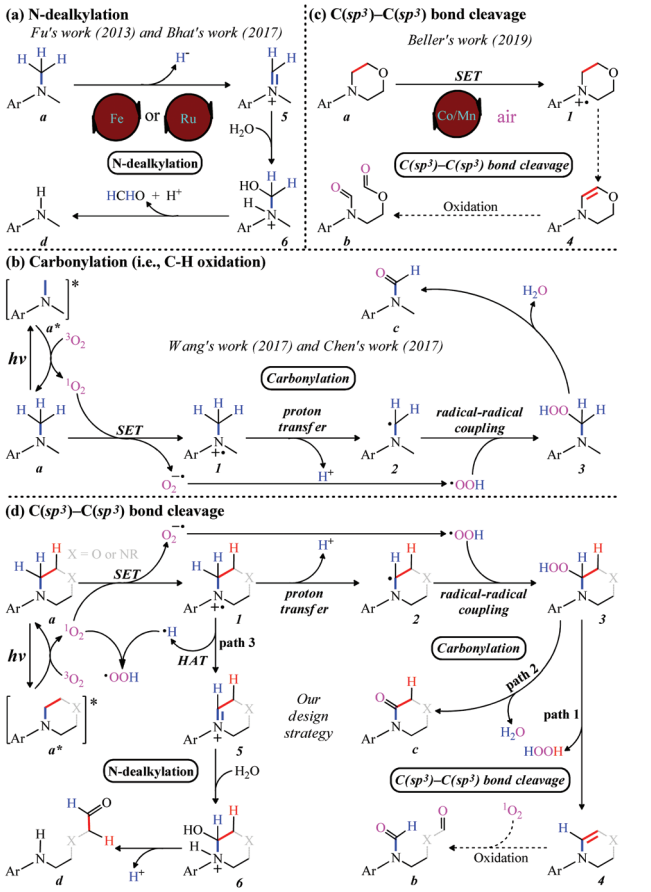


Fig. 1 Design for the photoinduced selective oxidative $C(sp^3)$–$C(sp^3)$ bond cleavage in arylamines under catalyst-free conditions.

Our design for the photoinduced oxidative cleavage was motivated by the characterized mechanism of *N*-dealkylation and carbonylation in *N*,*N*-dimethyl arylamines, and two key hypotheses. Based on the carbonylation mechanism of *N*,*N*-dimethyl arylamines, we consider that if we extend the methyl on *N*,*N*-dimethyl arylamines to a longer alkyl, such as ethyl, propyl, *etc.*, it will also be able to undergo the SET, proton transfer and radical–radical coupling to successively afford **1**, **2** and **3** under O_2 and light conditions, analogous to *N*,*N*-dimethyl arylamines. As shown in Fig. 1d, the difference is that due to the extension of the carbon chain, we guess that **3** is more likely to be converted into the enamine intermediate **4** by losing H_2O_2 than into the carbonylation product **c** by losing H_2O (hypothesis 1). The intermediate **4** was also reported by the $CoBr_2$/$Mn(OAc)_2$-catalyzed $C(sp^3)$–$C(sp^3)$ bond cleavage,[11b] and it can just react with the singlet $^1O_2$ in a 1,2-addition reaction to form the expected oxidative cleavage product **b** (Fig. 1d). Meanwhile, we also consider that in addition to

being converted into **2** by proton transfer, **1** could also be converted into **5** by hydrogen atom transfer (HAT), which then could continue to undergo hydrolysis to form the *N*-dealkylation product **d**, in the same manner as the *N*-dealkylation mechanism of *N*,*N*-dimethyl arylamines (Fig. 1d). On the basis of the carbon chain extension as shown in Fig. 1d, we guess that if we further introduce a polar atom (O, N, *etc.*) at the γ-position of amines, due to the electron-withdrawing effect of this polar atom, **1** will prefer proton transfer to form **2**, rather than HAT to form **5** (hypothesis 2). In short, based on the above two hypotheses on the mechanism, we believe that once we extend the carbon chain which may block the carbonylation pathway and introduce the polar atom at the γ-position which may block the *N*-dealkylation pathway, the photoinduced selective oxidative $C(sp^3)$–$C(sp^3)$ bond cleavage will occur in the obtained arylamine types under O_2 and catalyst-free conditions.

Some well-designed symmetric arylamine substrates were prepared to verify our two proposed hypotheses as shown in Fig. 2. By using the optimized reaction conditions shown in Tables S1 and S2 and Fig. S1† (0.3 mmol substrate under 425 nm LED and 1 bar O_2 at room temperature in 2 mL CH_3CN for 48 h), we firstly examined *N*,*N*-dimethylaniline (**1a**) which as expected furnished the carbonylation product (**1c**) and *N*-dealkylation product (**1d**) in yields of 26% and 49%, respectively. Then, we extended the methyl on **1a** to ethyl (**2a**), propyl (**3a**) and butyl (**4a**), and the reaction afforded the oxidative cleavage products (**2b–4b** in yields of 15%, 18% and 43%, respectively) and *N*-dealkylation products (**2d–4d** in yields of 50%, 43% and 21%, respectively). To our delight, none of the three substrates produced the carbonylation products, which confirmed our first hypothesis that the carbon chain extension is not conducive to the dehydration reaction but conducive to the oxidative cleavage reaction by losing H_2O_2, and thereby can block the carbonylation pathway. Finally, at the γ-position of **2a**, we further introduced the hydroxyl (**5a**) and ester (**6a**) which contain the polar oxygen atoms. Expectedly, no *N*-dealkylation product was detected and we only obtained the oxidative cleavage products **5b** and **6b** in good yields of 62% and 71%, respectively. Obviously, our second hypothesis that the polar atom at the γ-position is not conducive to the HAT between intermediates **1** and **5**, and thereby can block the *N*-dealkylation pathway, was also confirmed.

We also designed some asymmetric arylamine substrates whose two substituent chains on nitrogen are different to further confirm our proposed mechanism in Fig. 1d. As shown in Fig. 3, we firstly examined a series of *N*-(2-methoxyethyl)-*N*-methyl arylamines (**7a–10a**) by using the optimized reaction conditions (Table S1†). For *N*-methyl chains, they afforded the *N*-dealkylation products in moderate yields (**7d–10d** in yields of 45%, 52%, 50% and 45%, respectively), the

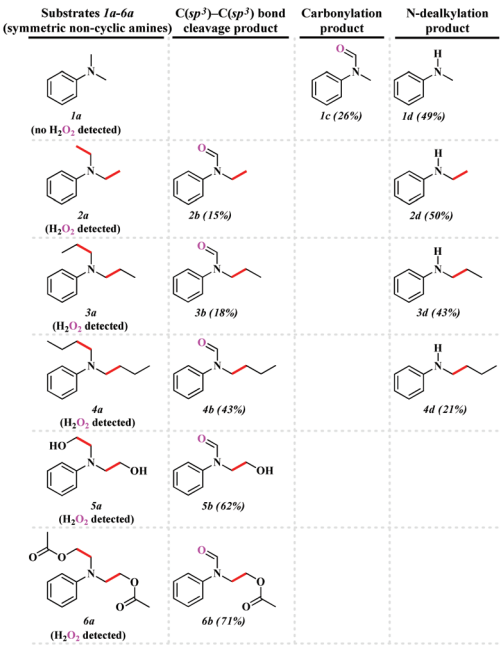


Fig. 2 Mechanism validation for our proposed photoinduced selective oxidative $C(sp^3)$–$C(sp^3)$ bond cleavage. Reaction conditions: 0.3 mmol substrate, 425 nm LED, 1 bar O_2, room temperature, 2 mL CH_3CN and 48 h (Table S1†). H_2O_2 was detected by the starch KI test solution. Isolated yield.

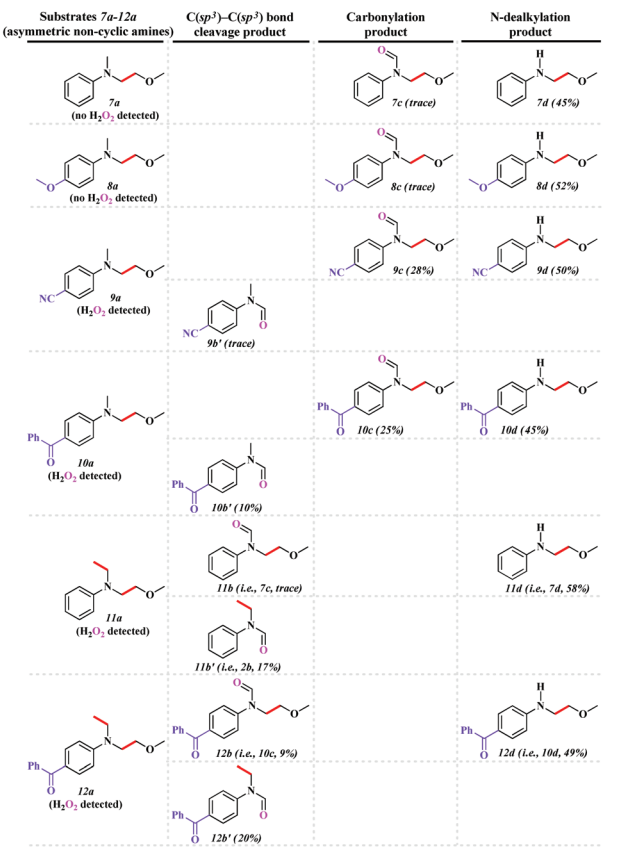


Fig. 3 Further mechanism validation for our proposed photoinduced selective oxidative $C(sp^3)$–$C(sp^3)$ bond cleavage. Reaction conditions: 0.3 mmol substrate, 425 nm LED, 1 bar O_2, room temperature, 2 mL CH_3CN and 48 h (Table S1†). H_2O_2 was detected by the starch KI test solution. Isolated yield.

carbonylation products in low yields (**9c** and **10c** in yields of 28% and 25%, respectively), and even trace yields of **7c** and **8c**. While for *N*-methoxyethyl chains, they either provided nothing or only provided the oxidative cleavage products (**9b′** and **10b′** in trace and 10% yields, respectively). We then extended the methyls on **7a** and **10a** to ethyl and obtained two *N*-(2-methoxyethyl)-*N*-ethyl arylamines (**11a** and **12a**). It showed that besides the main *N*-dealkylation products **11d** (*i.e.*, **7d**) in 58% yield and **12d** (*i.e.*, **10d**) in 49% yield, *N*-ethyl chains also provided small amounts of oxidative cleavage products **11b** (*i.e.*, **7c**, trace) and **12b** (*i.e.*, **10c**, 9%). Remarkably, no carbonylation product was detected. As for *N*-methoxyethyl chains, they still only furnished the oxidative cleavage products **11b′** (*i.e.*, **2b**) and **12b′** in yields of 17% and 20%, respectively. Overall, the carbon chain extension indeed can trigger the oxidative cleavage reaction along with the silence of carbonylation and more importantly, although the reactivity of an alkyl chain containing a polar atom at the γ-position is lower than that of a pure alkyl chain, it can be specifically selective for the oxidative cleavage reaction. Obviously, this is almost the same as our expected results based on our proposed mechanism. In addition, H_2O_2 was detected only in reactions that produced the oxidative cleavage products (Fig. 2 and 3), which also further shows the reliability of our proposed mechanism.

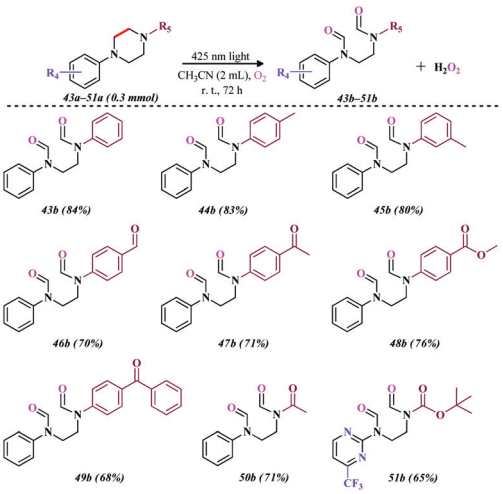
Reaction profile computations[16] were further employed to verify the proposed mechanism by rationalizing the above experimental results (Table 1). In general, **1** can undergo both proton transfer and HAT due to very low energy barriers (2.31 *vs.* 1.23, 3.30 *vs.* 1.63, 2.39 *vs.* 1.50 and 3.43 *vs.* 2.51 kcal mol^{-1} in **1a**, **2a**, methyl chain of **7a** and ethyl chain of **11a**, respectively). **3** formed by the proton transfer prefers the dehydroperoxide reaction with a lower energy barrier (29.13 and 32.18 kcal mol^{-1} in **2a** and ethyl chain of **11a**, respectively) rather than the dehydration with a higher energy barrier (42.30, 40.65, 39.83 and 41.15 kcal mol^{-1} in **1a**, **2a**, methyl chain of **7a** and ethyl chain of **11a**, respectively). **5** formed by the HAT can undergo hydrolysis with an energy barrier that can compete with the dehydroperoxide reaction (29.64, 31.34, 31.39 and 30.40 kcal mol^{-1} in **1a**, **2a**, methyl chain of **7a** and ethyl chain of **11a**, respectively). However, once the polar atom is introduced at the γ-position, there will be a huge increase of the energy barrier of HAT but a very small increase of that of proton transfer (13.00 *vs.* 4.87, 14.53 *vs.* 5.64 and 17.28 *vs.* 5.39 kcal mol^{-1} in **5a** and methoxyethyl chains of **7a** and **11a**, respectively). Moreover, the energy barrier of hydrolysis will also be increased which will cause the loss of its competitiveness to the dehydroperoxide reaction since that of the dehydroperoxide reaction will be almost unaffected (46.09 *vs.* 27.08, 47.23 *vs.* 31.73 and 46.82 *vs.* 29.07 kcal mol^{-1} in **5a** and meth-

Table 1 Reaction profiles (key data) based on the mechanism in Fig. 1d. The complete reaction profiles are shown in Fig. S2–S8.† **1_TS_2**, **1_TS_5**, **3_TS_4**, **3_TS_c** and **5_TS_6** are the transition states of proton transfer, HAT, dehydroperoxide, dehydration and hydrolysis reactions, respectively. The free energy values of **1_TS_2/2/3/1_TS_5/5**, **3_TS_4/4/b/3_TS_c/c** and **5_TS_6/6/d** are the relative values of **1**, **3** and **5**, respectively

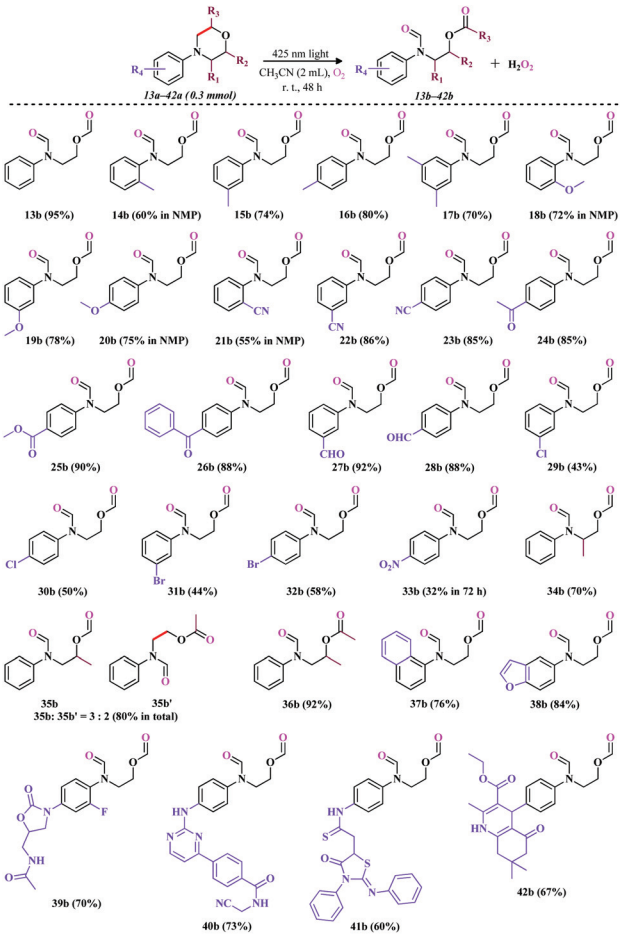
	Relative free energies (kcal mol^{-1})					
				3_TS_4	**4**	**b**
	1_TS_2	**2**	**3**	**3_TS_c**	**c**	
Substrate	**1_TS_5**	**5**		**5_TS_6**	**6**	**d**
1a	2.31	−13.42	−54.33	—	—	—
				42.30	−86.50	
	1.23	−37.47		29.64	8.56	−27.29
2a	3.30	−11.91	−52.89	29.13	−2.48	−126.37
				40.65	−91.09	
	1.63	−47.48		31.34	19.00	−28.88
5a	4.87	−17.11	−56.14	27.08	−3.87	−154.35
				45.36	−91.68	
	13.00	−42.10		46.09	15.95	−34.64
7a (methyl)	2.39	−14.16	−55.47	—	—	—
				39.83	−86.75	
	1.50	−36.34		31.39	7.86	−31.54
7a (methoxyethyl)	5.64	−17.25	−55.33	31.73	−3.56	−155.20
				46.39	−87.43	
	14.53	−43.84		47.23	11.18	−31.31
11a (ethyl)	3.43	−15.62	−56.59	32.18	−1.95	−125.47
				41.15	−90.48	
	2.51	−48.34		30.40	18.43	−30.85
11a (methoxyethyl)	5.39	−17.27	−54.17	29.07	−4.98	−156.38
				46.12	−89.63	
	17.28	−43.42		46.82	12.66	−33.45
13a	4.85	−16.26	−51.79	32.02	−10.98	−150.28
				44.86	−94.52	
	15.61	−45.31		49.51	19.44	−19.73
43a	5.51	−11.73	−47.63	35.60	−14.96	−146.21
				45.38	−94.52	

oxyethyl chains of **7a** and **11a**, respectively). Also, the polar atom will not affect the selectivity of **3** to the dehydroperoxide reaction (27.08 *vs.* 45.36, 31.73 *vs.* 46.39 and 29.07 *vs.* 46.12 kcal mol^{-1} in **5a** and methoxyethyl chains of **7a** and **11a**, respectively). Clearly, our computed reaction profiles based on the proposed mechanism can well rationalize our experimental results.

So far, we have determined the detailed mechanism and substrate structure requirement for the oxidative $C(sp^3)$–$C(sp^3)$ bond cleavage under O_2 and catalyst-free conditions. Namely, once a polar atom is introduced at the γ-position of a tertiary arylamine, it will exclusively produce the cleavage product by undergoing SET, proton transfer, radical–radical coupling, dehydroperoxide and 1,2-addition reactions. As privileged scaffolds, morpholine and piperazine arylamines, which cover several out of the top 50 pharmaceuticals and many potentially medicinal natural products,[17] also have a polar atom at the γ-position. Thus, considering the importance of drug construction and its late-stage modification, our next work was to explore the substrate scope with respect to morpholines and piperazines (Schemes 2 and 3). Before this, we confirmed their extendibility by mechanism calculations for 4-phenylmorpholine (**13a**) and 1,4-diphenylpiperazine (**43a**) as shown in the complete reaction profiles in Fig. S7 and S8 and the key data in Table 1. Moreover, we also employed **13a** to perform the electron–spin resonance (ESR) experiments to further explore the mechanism proposed in Fig. 1d. The resulting ESR spectra as shown in Fig. S9† not only proved the existence of the superoxide radical $O_2^{\bullet-}$ and singlet $^1O_2$ proposed in our mechanism (Fig. 1d), but also demonstrated that the singlet $^1O_2$ was very likely to be converted from triplet $^3O_2$ by the photosensitizer effect of the substrate, which agreed perfectly with our proposed mechanism in Fig. 1d. Meanwhile, the verification experiments of **43a** also confirmed the photosensitizer effect of the substrate (Fig. S10†).



Scheme 3 Substrate scope with respect to piperazines. Isolated yield.



Scheme 2 Substrate scope with respect to morpholines. Isolated yield.

As shown in Scheme 2, 26 different morpholine arylamines provided the desired exclusive oxidative cleavage products and H_2O_2 under the optimized reaction conditions (Table S1†). For the phenylamine containing morpholine ring, besides the fact that unsubstituted **13a** provided the desired oxidative product **13b** in a very excellent yield (95%), the substituents on the benzene ring including electron-donating groups, such as methyl (**14a–17a**) and methoxyl (**18a–20a**), and electron-withdrawing groups, such as cyano (**21a–23a**), acetyl (**24a**), methoxycarbonyl (**25a**) and benzoyl (**26a**), also exhibited excellent reactivity, furnishing oxidative cleavage products **14b–26b** in 60–90% yields. Most remarkably, the oxidative cleavage in the presence of an aldehyde (**27a** and **28a**) was rarely reported, but in our work its yield was up to 92% (**27b**) and 88% (**28b**). The substituents chlorine (**29a** and **30a**), bromine (**31a** and**32a**) and nitro (**33a**) on the benzene ring also exhibited moderate reactivity with 31–58% yields (**29b–33b**). Meanwhile, the methyl substituent on the morpholine ring (**34a–36a**) that may cause asymmetric oxidative cleavage preferred the activation of the nonsubstituted $C(sp^3)$–$C(sp^3)$ bond in 70% (**34b**), 80% (**35b** and **35b′**) and 92% (**36b**) yields. In addition to phenylamine derivatives, other arylamines, such as naphthylamine (**37a**) and benzofuramine (**38a**), also gave the preferred oxidative cleavage products in 76% (**37b**) and 84% (**38b**) yields.

To showcase late-stage drug modifications and to research the putative biosynthetic approach of natural products, linezolid (**39a**) which is an antimicrobial, momelotinib (**40a**) which is an antineoplastic, and two natural products (**41a** and **42a**) were employed to perform our reaction. To our delight, the desired exclusive oxidative cleavage products of morpholine rings were formed in good yields with excellent selectivities (60–73% yields for **39b–42b**). Notably, in the case of **42a**, although there were two C=C double bonds that were more sensitive to O_2, our oxidative cleavage still selected the C–C single bond of the morpholine ring. As shown in Scheme 3, 9 different piperazine arylamines also provided the desired exclusive oxidative cleavage products and H_2O_2. For the phenylamine containing piperazine ring, *N*-substituents, such as phenyl (**43a**), tolyl (**44a** and **45a**), 4-formyl phenyl (**46a**), 4-acetyl phenyl (**47a**), 4-methoxycarbonyl phenyl (**48a**), 4-benzoyl phenyl (**49a**) and acetyl (**50a**), gave the expected oxidative cleavage products **43b–50b** in excellent yields of 68–84%. Meanwhile, other arylamines, such as pyrilamine **51a**, also provided the oxidative cleavage product **51b** in a good yield of 65%.

Conclusions

In conclusion, complementary to the oxidation mechanism of arylamines, especially to the detailed oxidative cleavage mechanism of the C(sp^3)–C(sp^3) bond, we extended a photo-induced oxidative cleavage mechanism of the C–C single bond based on the previous state-of-the-art oxidation mechanism of arylamines. Both well-designed experiments and QM computations to some extent confirmed this extended mechanism that once a polar atom is introduced at the γ-position of a tertiary arylamine, it will avoid other oxidation reactions (carbonylation and *N*-dealkylation) and exclusively undergo the selective oxidative $C_\alpha(sp^3)$–$C_\beta(sp^3)$ bond cleavage through SET, proton transfer, radical–radical coupling, dehydroperoxide and 1,2-addition reactions under simple O_2 and catalyst-free conditions. Notably, our protocol is not only effective for the tolerance of a diverse array of functional groups, but also practical for the late-stage modification of clinical drugs and scalable functionalization of natural products. Meanwhile, studies on the C(sp^3)–C(sp^3) bond cleavage in arylamines without polar atom substitution at the γ-position are ongoing in our labs.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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