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Iron porphyrin catalysed light driven C–H bond amination and alkene aziridination with organic azides†

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Visible light driven nitrene transfer and insertion reactions of organic azides are an attractive strategy for the design of C–N bond formation reactions under mild reaction conditions, the challenge being lack of selectivity as a free nitrene reactive intermediate is usually involved. Herein is described an iron(III) porphyrin catalysed sp³ C–H amination and alkene aziridination with selectivity by using organic azides as the nitrogen source under blue LED light (469 nm) irradiation. The photochemical reactions display chemo- and regio-selectivity and are effective for the late-stage functionalization of natural and bioactive compounds with complexity. Mechanistic studies revealed that iron porphyrin plays a dual role as a photosensitizer and as a catalyst giving rise to a reactive iron–nitrene intermediate for subsequent C–N bond formation.

Introduction

The development of efficient methods for selective C–N bond formation under mild reaction conditions is important in organic synthesis owing to the ubiquity of amino groups in bioactive natural products and pharmaceuticals. Nitrene C–H insertion and alkene aziridination are powerful methods for installing amino groups into organic molecules.[1] In this regard, there is burgeoning interest in using organic azides as the nitrene source as only nitrogen gas is produced as a by-product and an external oxidant is not required. However, nitrene transfer reactions of organic azides, especially for intermolecular reactions, often require elevated temperature, which may limit the substrate scope and product selectivity, as well as increase the chance for competitive side reactions. Photochemical activation of organic azides offers a potential solution to this issue. As an example, Yoon and co-workers found that irradiation of azidoformates and alkenes with visible light in the presence of [Ir(ppy)₂(dttbpy)]PF₆ led to aziridination products at room temperature.[2a] König and co-workers employed [Ru(bpy)₃](Cl)₂ as a photosensitizer to achieve sp² C–H

amidation of electron-rich heteroaromatics with benzoyl azides under visible light irradiation.[2c] These reactions proceeded *via* a free nitrene intermediate generated through energy transfer from triplet excited states of transition metal sensitizers to organic azides. While free nitrenes react efficiently with organics, their high reactivity and short lifetime present significant hurdles for the reactions with relatively unreactive sp³ C–H bonds or multi C–H bonds in a selective manner. As metal–nitrenes are envisioned to display higher selectivity than free nitrenes, photochemical generation of reactive metal–nitrene species from organic azides would be appealing. We are interested in the studies of Newcomb and co-workers on the generation of reactive iron–oxo species for C–H hydroxylation through light irradiation of iron porphyrins in the presence of ClO_4^-.[3] A collaborative study by Martin-Diaconescu, Neese, Roithova, Bill, Lloret-Fillol, Costas and their co-workers reported the generation of iron–nitrido species by photolysis of an iron–azide complex bearing a pentadentate aminopyridine ligand.[4] Abu-Omar and co-workers revealed the first examples of mononuclear imido complexes of manganese(V) and chromium(V) corroles under photolytic or thermal conditions.[5] We conceive that metalloporphyrins with labile axial coordination sites are potential appealing catalysts for visible-light driven nitrene C–H insertion and aziridination with organic azides,[6] in which metalloporphyrin acts as the photosensitizer and at the same time captures free nitrene to give a reactive metal–nitrene/imido intermediate. Herein is described a light induced intermolecular sp³ C–H bond amination and alkene aziridination with organic azides and intramolecular sp³ C–H bond amination of alkyl azides catalysed by iron porphyrin (Scheme 1). Robert and co-workers reported an iron(III) porphyrin that

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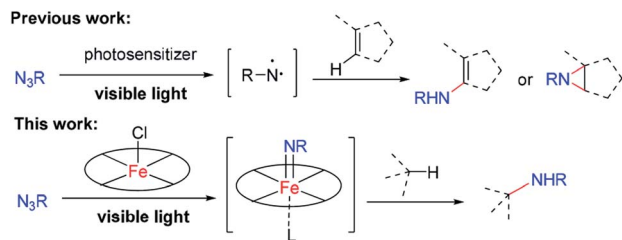
Scheme 1 C–H amination with organic azides by iron porphyrin photocatalysis.

catalyses light-induced CO_2 reduction to CO.[7a] Draksharapu, Gruden, Browne and co-workers reported a non-heme iron photocatalyst for light driven aerobic oxidation of methanol.[7b]

Results and discussion

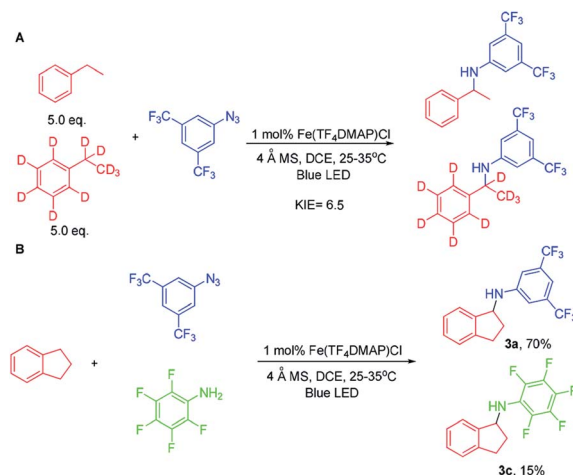### Reaction conditions and mechanism of iron-porphyrin photocatalysis

At the outset, we examined a panel of iron porphyrins for light driven C–H amination of indane **1a** with 3,5-bis(tri-fluoromethyl)phenyl azide **2a** (Scheme 2). The reaction was conducted at 25–35 °C with blue LED (469 nm) irradiation. Fe(TTP)Cl, Fe(p-Cl-TPP)Cl, Fe(TMP)Cl, Fe(p-F-TPP)Cl, Fe(TDCPP)Cl, Fe(TDCDMAP)Cl, Fe(F$_{20}$TPP)Cl and Fe(TF$_4$-DMAP)Cl gave C–H amination product **3a** in 12–99% yields with Fe(TF$_4$DMAP)Cl[8] being the most effective one (99% yield in 24 h; 93% yield in 15 h; Table S1 in the ESI†). No reaction was observed in the absence of the iron porphyrin catalyst or blue LED irradiation revealing that both the iron porphyrin catalyst and light are indispensable in the photochemical C–H amina-tion reaction. The photo-stability of Fe(TF$_4$DMAP)Cl and Fe(F$_{20}$TPP)Cl in deaerated DCE was examined. As portrayed in Fig. S1 and S2,† respectively, the UV-visible absorption spectra of these two complexes remained unchanged upon blue LED (469 nm) irradiation for at least 18 hours. An iron(II) porphyrin mono(dialkylcarbene) complex, Fe(F$_{20}$TPP)(Ad) (Ad = 2-ada-mantylidene),[9] also catalysed the reaction to give **3a** in 98% yield. [Fe(F$_{20}$TPP)]$_2$(μ-O), which was slowly converted to Fe(F$_{20}$-TPP)Cl upon light irradiation (Fig. S3†), is another effective catalyst affording **3a** in 96% yield. Other Ru, Mn, Co and Ir

porphyrins were less effective, giving **3a** in 15% to 82% yields along with by-product 3,5-bis(trifluoromethyl)aniline **4a** in 8–50% yields. Other iron complexes supported by non-porphyrin N$_4$/N$_5$ ligands failed to give the desired C–H amination product under the same reaction conditions. In the absence of molecular sieves, the product yield dropped to 30%. The use of free porphyrin H$_2$TF$_4$DMAP or [Ru(bpy)$_3$](Cl)$_2$·6H$_2$O as the photosensitizer furnished **3a** in 10% and 15% yields, respec-tively. When Rh$_2$(OAc)$_4$ was used as the catalyst, no reaction was observed under the same conditions. The photochemical reac-tion could also take place to give **3a** in 93% yield under thermal conditions with Fe(TF$_4$DMAP)Cl as the catalyst but at a reaction temperature of 120 °C. When the reaction was performed under irradiation of a green LED (530 nm) for 36 h, **3a** was obtained in 25% yield.

To investigate whether the metal–nitrene intermediate was involved in this light driven C–H amination, several experi-ments were conducted. [1] The kinetic isotope effect (KIE) was examined by the reaction of ethylbenzene, d$_{10}$-ethylbenzene and arylazide **2a** under the photocatalytic conditions (Scheme 3A). A KIE value of 6.5 was obtained. This KIE value in the range of 5–11 observed in transition metal porphyrin catalysed sp^3 C–H amination is supportive of a metal–nitrene intermediate that reacts with the C–H bond via a H-atom abstraction mech-anism.[10] Bettinger and co-workers found that a free nitrene (R$_2$BN) generated from the photolysis of azidoboranes can undergo intermolecular insertion into a C–H bond of cyclo-hexane. The KIE value was measured to be 1.35.[10d] [2] To examine if the reaction involves a radical chain mechanism, the quantum yields (QY) of these photo-chemical reactions have been estimated by using potassium ferrioxalate as a chemical actinometer. It was found that the QY for the reaction of styrene and **2a** was 12% while that of indane and **2a** was 5.5%. A lower QY of 3.5% was found with Fe(3,5-Di^{t}Bu-Chenphyrin)Cl[11] instead of Fe(TF$_4$DMAP)Cl as the photocatalyst. Since the QY values of these reactions were less than 100%, the photo-chemical reaction is less likely to involve a radical chain mechanism.[12] [3] The cross-over reaction of indane with **2a** and
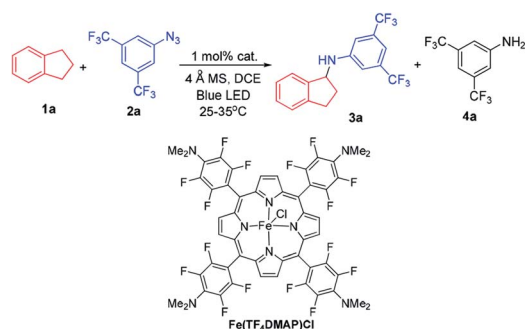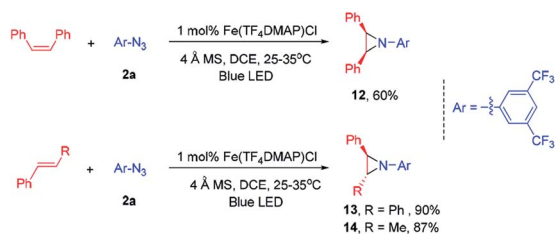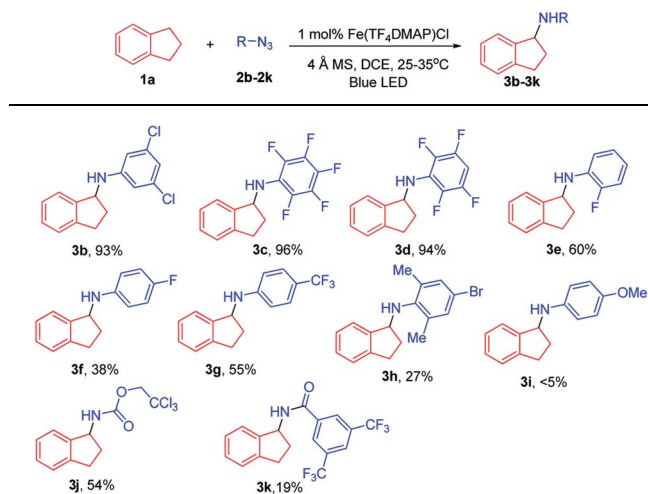

Scheme 2 C–H amination of indane **1a** with azide **2a** and the structure of Fe(TF$_4$DMAP)Cl.

Scheme 3 Mechanistic study.

Scheme 4 Asymmetric C–H amination and aziridination catalysed by chiral iron porphyrin. ^{a} 5 mol% catalyst was used.

2,3,4,5,6-pentafluoroaniline gave C–H amination products **3a** and **3c** in 70% and 15% yield, respectively, suggesting a step-wise mechanism (Scheme 3B). [4] When the photochemical C–H amination of indane with arylazide **2a** was performed with the chiral Fe(D$_4$-por*)Cl (H$_2$(D$_4$-por*) = *meso*-tetrakis-{(1R,4S,5S,8R)-1,2,3,4,5,6,7,8-octahydro-1,4:5,8-dimethano-anthracen-9-yl}-porphyrin) catalyst, the C–H aminated product **3a** was obtained in 82% yield and with 20% ee (Scheme 4). With Fe(D$_4$-por*)Cl as the catalyst, the reaction of styrene with TsN$_3$ led to aziridine **11d** in 49% yield and with 34% ee. This result is comparable to that in our previous work in which the stoichiometric reaction of styrene with Ru(D$_4$-por*)(NTs)$_2$ gave **11d** with 27% ee.[13] [5] MALDI-MS analysis of the stoichiometric reaction of Fe(TF$_4$DMAP)Cl and azide **2a** showed a *m/z* signal at 1355.1475, corresponding to the iron–nitrene/imido formulation (Fig. S4†). [6] The aziridination of alkenes and **2a** under photocatalytic conditions displayed good stereospecificity, giving *cis*-aziridines from *cis*-alkenes and *trans*-aziridines from *trans*-alkenes in up to 90% yield (Scheme 5), which favours the involvement of a metal–nitrene intermediate rather than a free triplet nitrene. [7] We attempted to detect if any short-lived species would be generated from the iron(III) porphyrin chloride complexes (Fe(TF$_4$DMAP)Cl and Fe(F$_{20}$TPP)Cl) upon photo-excitation in the presence of azide **2a** by nanosecond time-resolved absorption spectroscopy. A transient signal of spectral change at 350–420 nm was observed 1 μs after laser flash and decayed back to the initial base line after 25 μs; such a signal was not observed for photoexcitation of the iron porphyrin complex in the absence of azide **2a** under the same conditions. But as the signal was close to the laser excitation wavelength of 355 nm and relatively weak, it would be difficult to make any conclusive statement. These results altogether

Scheme 5 Stereospecific aziridination of alkenes and arylazide **2a** catalysed by Fe(TF$_4$DMAP)Cl.

Table 1 Scope of organic azides under photocatalytic conditions^a

^{a} Reactions were run under argon with 0.5 mmol of the azide, 5.0 mmol of indane, 5×10^{-3} mmol of the catalyst (1 mol% with respect to the azide) and 120 mg 4 Å MS in 2.0 mL of anhydrous DCE in a 10.0 mL sealed tube. The tube was irradiated with a blue LED at 25–35 °C.

suggest that in the iron porphyrin catalysed light driven C–H amination, a reactive metal–nitrene/imido species was generated in the course of photolysis.

With the optimal conditions, the scope of organic azides for the iron porphyrin-catalysed light driven sp^3 C–H amination was examined by using indane as the substrate. As shown in Table 1, electron-withdrawing substituents (CF$_3$, F and Cl) of aryl azides facilitated the intermolecular C–H amination leading to a high yield of products (93–96%, **3b–3d**). For aryl azides having only one electron-withdrawing substituent, C–H amination products were obtained in moderate yields (27–60%, **3e–3h**). The electron-donating substituent OMe was found to disfavour the reaction resulting in poor product yield (<5%, **3i**). It is worth noting that azidoformate Troc-N$_3$ was also reactive in the photocatalytic C–H amination giving **3j** in 54% yield. The use of 3,5-bis(tri-fluoromethyl)benzoyl azide under photocatalytic conditions led to poor yield of the C–H amination product **3k**. No reaction was observed when tosyl azide, diphenyl phosphorylazide or benzy-lazide was used as the nitrene source.

With azide **2a** as the nitrene source, the scope of hydrocarbons was examined. As shown in Table 2, azide **2a** underwent nitrene insertion into the benzylic C–H bonds of a range of substrates including ethylbenzene, tetralin, diphenylmethane, fluorene, xanthene, and isochroman to give the amination products in good to high yields (**5a–5l**). For substituted ethyl-benzenes, both electron-donating and -withdrawing groups (4-methoxy, 4-methyl, and 4-chloride) led to high product yields (**5g–5j**). When isopentylbenzene which bears both benzylic and tertiary C–H bonds was used as the substrate, the reaction took place regio-selectively at the benzylic C–H bond over the tertiary C–H bond (**5k**).

In the case of methyl (S)-2-(4-isobutylphenyl)propanoate which has two electronically different benzylic C–H bonds, the

Table 2 Fe(TF₄DMAP)Cl-catalysed intermolecular C–H amination with organic azide **2a** under photocatalytic conditions[a]
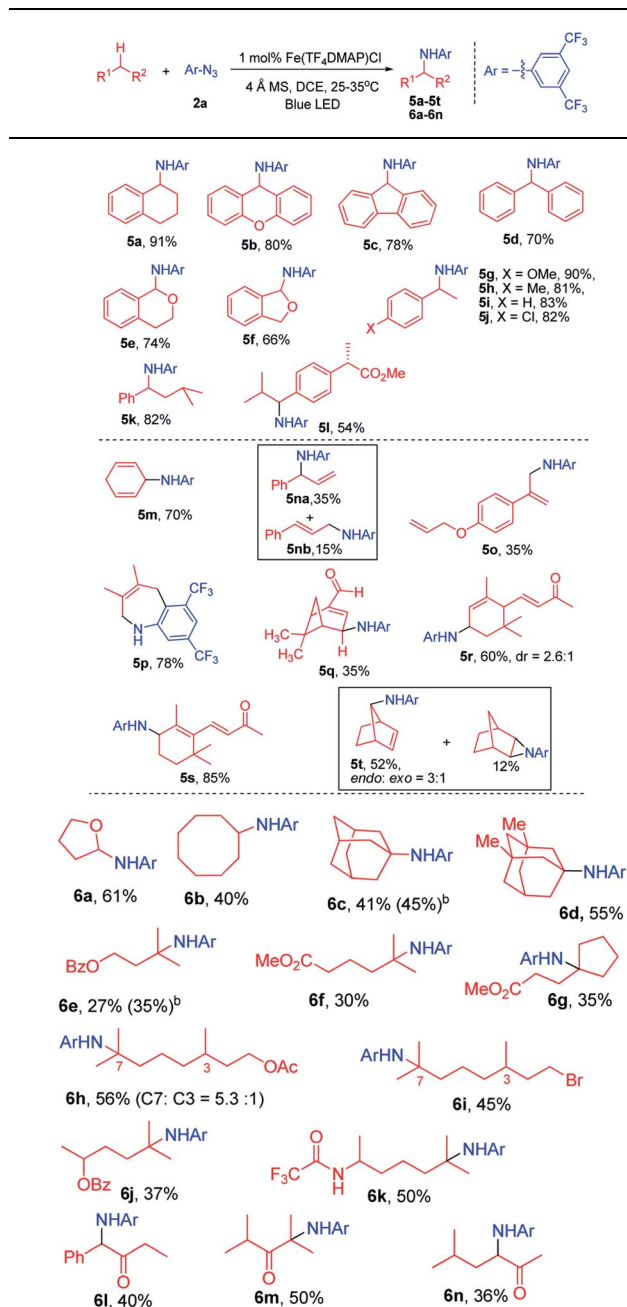
[a] Reactions were run under argon with 0.5 mmol of the azide, 5.0 mmol of the substrates, 5×10^{-3} mmol of the catalyst (1 mol% with respect to the azide) and 120 mg 4 Å MS in 2.0 mL of anhydrous DCE in a 10.0 mL sealed tube. The tube was irradiated with a blue LED at 25–35 °C. [b] 5 mol% catalyst was used.

C–H amination took place at the more electron-rich C–H bond (**5l**).

This photochemical C–H amination is also applicable to allylic C–H bonds. The reaction of cyclohexa-1,4-diene with **2a** gave the allylic C–H amination product **5m** in 70% yield. Allylbenzene gave a mixture of C–H aminated isomeric products

(**5na** and **5nb**). The reaction of 1-(allyloxy)-4-(prop-1-en-2-yl)benzene proceeded with high chemo- and regio-selectivity to give **5o** in 35% yield. When 2,3-dimethylbuta-1,3-diene was subjected to photocatalysis, a 7-membered heterocyclic product **5p** was isolated in 78% yield. The reaction also took place at the allylic C–H bond of α,β-unsaturated aldehydes and α,β-unsaturated ketones in good product yields (**5q–5s**). When cyclic 2-norbornene was used, bridged secondary C–H amination product **5t** was obtained in 52% yield with an *endo* : *exo* ratio of 3 : 1 along with the aziridination product in 12% yield. No allylic C–H amination product was observed.

We next examined the photocatalytic C–H amination of tetrahydrofuran and unactivated C–H bonds, the functionalization of which is a challenge. Tetrahydrofuran was reactive under photocatalytic conditions giving the amination product **6a** in 61% yield (Table 2). The reaction of cyclooctane with **2a** proceeded smoothly to give **6b** in 40% yield. When the substrate contains tertiary, secondary and primary C–H bonds, the photocatalytic amination preferentially occurred at the tertiary C–H bond over the secondary and primary C–H bonds (**6c–6g**). We also investigated the regioselectivity of the photochemical C–H amination of substrates bearing multiple tertiary C–H centers. When dihydrocitronellyl acetate or dihydrocitronellyl bromide was subjected to the photochemical C–H amination, the reaction occurred preferentially at the tertiary C–H bond remote from the electron-withdrawing group (acetate or bromo, **6h** or **6i**). This regioselectivity could be attributed to the deactivation of the C(3)–H bond by the electron-withdrawing group.

To our surprise, the α-C–H bond of ketone, which is generally thought to be deactivated by a carbonyl moiety, could also be aminated. Treatment of 1-phenylbutan-2-one with **2a** and a catalytic amount of iron porphyrin at room temperature under blue LED irradiation afforded α-C–H amination product **6l** in 40% yield. Likewise, 2,4-dimethylpentan-3-one and 5-methylhexan-2-one gave α-C–H aminated products **6m** and **6n** in 50% and 36% yields, respectively. No reaction was found when methyl 2-phenylacetate was used. These results suggest that **2a** might react with the enol form of ketone to afford an aziridine which underwent ring-opening to give the final α-C–H amination product.[14]

Intramolecular C–H amination of alkyl azides

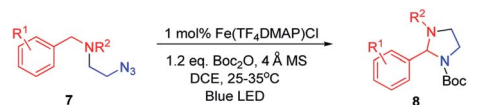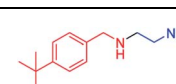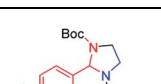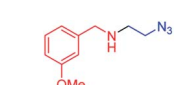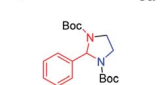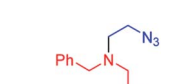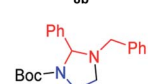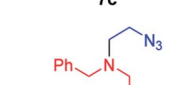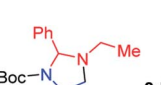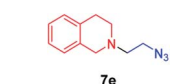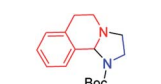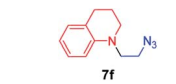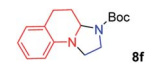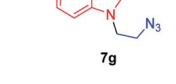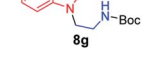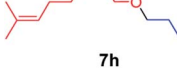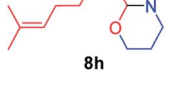We next used photocatalysis of intramolecular C–H amination of alkyl azides[15,16] to form imidazolidines,[17] a versatile class of intermediates in organic synthesis. As shown in Table 3, a variety of N-containing alkyl azides underwent C–H amination to give the corresponding imidazolidines in 45–98% yield. It is noteworthy that when 1-(2-azidoethyl)indoline was subjected to photolysis, an indole product was obtained in 95% yield presumably derived from ring-opening of the imidazolidine product (entry 7). For the reaction of O-containing alkyl azide **7h**, a 1,3-oxazinane derivative **8h** was obtained in 55% yield (entry 8).

Intramolecular C–H amination of α-azidoketones

A nitrogen bridged bicyclic moiety is prevalent in naturally occurring alkaloids.[18] This valuable scaffold can be constructed

Chemical Science

Table 3 Fe(TF$_4$DMAP)Cl-catalysed intramolecular C–H amination of N-containing alkyl azides under photocatalytic conditions^a

Entry	Substrate	Product	Yield (%)
1	**7a**	**8a**	75
2	**7b**	**8b**	70
3	**7c**	**8c**	78
4	**7d**	**8d**	61; 30^b
5	**7e**	**8e**	45
6	**7f**	**8f**	98
7	**7g**	**8g**	95
8	**7h**	**8h**	55
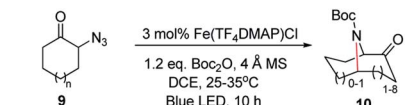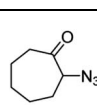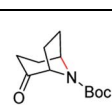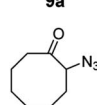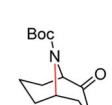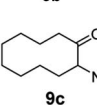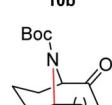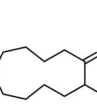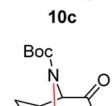
^{a} Reactions were run under argon with 0.3 mmol of the azide, Boc$_2$O (0.36 mmol), 3×10^{-3} mmol of the catalyst (1 mol% with respect to the azide) and 120 mg 4 Å MS in 2.0 mL of anhydrous DCE in a 10.0 mL sealed tube. The tube was irradiated with a blue LED at 25–35 °C. Isolated yields are shown. ^{b} [Fe(F$_{20}$TPP)Cl] was used as the catalyst. Yields were determined by ^{1}H NMR spectroscopy.

Table 4 Fe(TF$_4$DMAP)Cl-catalysed intramolecular C–H amination of α-azidoketones under photocatalytic conditions^a

Entry	Substrate	Product	Conv. (%)	Yield (%)
1	**9a**	**10a**	70	46 (42)
2	**9b**	**10b**	100	90 (80)
3	**9c**	**10c**	100	92 (85)
4	**9d**	**10d**	100	82 (77)
5	**9e**	**10e**	100	84 (77)
6	**9f**	**10f**	100	90 (82)

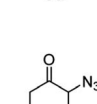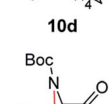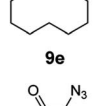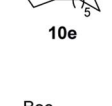^{a} Reactions were run under argon with 0.3 mmol of the azide, Boc$_2$O (0.36 mmol), 9×10^{-3} mmol of the catalyst (3 mol% with respect to the azide) and 120 mg 4 Å MS in 2.0 mL of anhydrous DCE in a 10.0 mL sealed tube. The tube was irradiated with a blue LED at 25–35 °C. Isolated yields are shown in the brackets.

by our iron-catalysed light driven C–H amination of α-azidoketones. As shown in Table 4, various medium-sized cyclic α-azidoketones underwent intramolecular C–H amination to give the corresponding nitrogen bridged bicyclic compounds in 42–85% yields (entry 1–6). It is noteworthy that 2-azidocyclohexan-1-one failed to give the intramolecular C–H amination product, suggesting that the ring strain affected the reactivity.

Derivatization of natural products

As photocatalysis can be performed under mild conditions and with high regio- and chemo-selectivity, we conceive that

this methodology has the potential to selectively aminate the C–H bond of other complex natural products which possess various C–H bonds and functional groups. We first examined the C–H amination of Ac-cholesterol that contains a total of 48 C–H bonds, 22 of which are secondary, 7 tertiary and 4 allylic (Scheme 6A). Under the photochemical conditions, Ac-Cholesterol underwent amination exclusively at the allylic C–H bond remote from the electron-withdrawing group -OAc in 77% isolated yield with a dr ratio of 4.5 : 1. Fe(F$_{20}$TPP)Cl also catalysed the light-driven amination of Ac-cholesterol with 52% product yield. Similar to cholesterol, the reaction of Bz-diosgenin gave allylic C–H bond aminated product **16** in 60% isolated yield with a dr ratio of 3 : 1 when **2b** was used as the nitrene source (Scheme 6B). Amination of the C–H
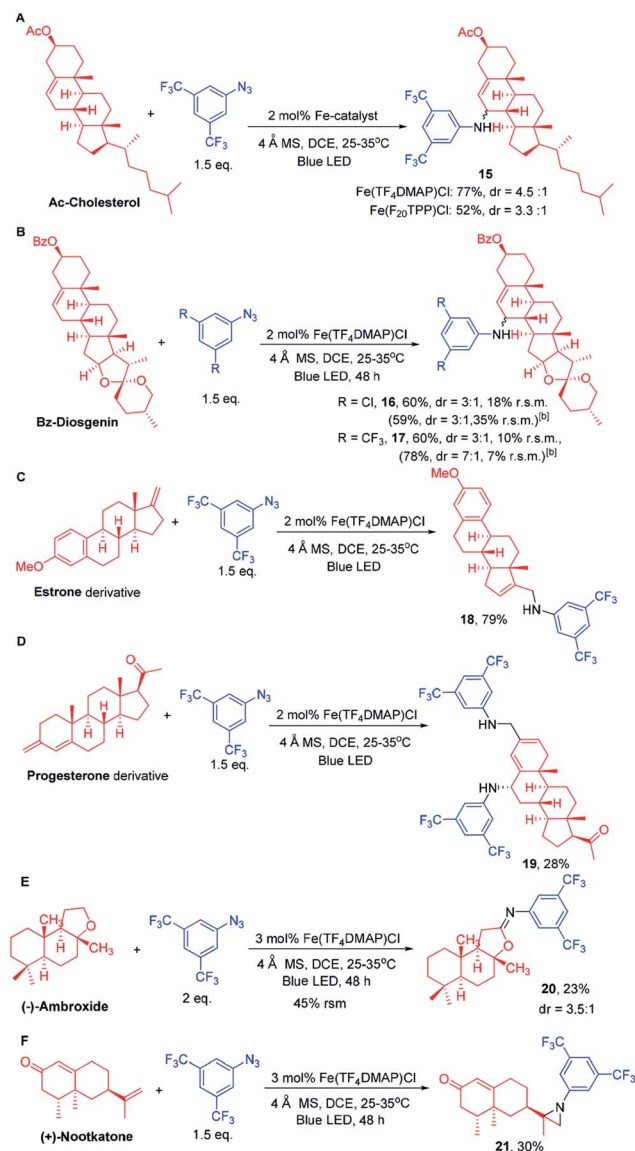
Scheme 6 Late-stage diversification of complex molecules *via* [Fe(TF$_4$DMAP)Cl]-catalysed C–H amination. [a] The reaction was conducted with 2 mol% catalyst and irradiated for 48 h. [b] The reaction was conducted with 5 mol% catalyst and irradiated for 24 h. r.s.m. = recovery of starting material.

bond adjacent to the oxygen atom was not observed. When **2a** was used as the nitrene source, the corresponding amination product was obtained in 78% yield with a dr ratio of 7 : 1. Treatment of an estrone derivative (Scheme 6C) with **2a** and Fe(TF$_4$DMAP)Cl under photocatalytic conditions gave an allylic amination product **18** in 79% yield. Likewise, a double allylic amination of a progesterone derivative (Scheme 6D) was observed with 28% yield. When (−)-ambroxide was subjected to photolysis, the C–H amination occurred at the C–H bond adjacent to the O atom giving imine product **20** in 23% yield with a recovery of 45% starting material (Scheme 6E). Treatment of (+)-nootkatone with **2a** under photochemical conditions gave an aziridination product in 30% yield.

Conclusions

In summary, we have demonstrated that the iron porphyrin Fe(TF$_4$DMAP)Cl is an efficient catalyst for selective intermolecular C–H amination and alkene aziridination of organic azides and intramolecular sp^3 C–H bond amination of alkyl azides under blue LED light irradiation. Mechanistic study revealed that Fe(TF$_4$DMAP)Cl played a dual role in the reactions acting as a photosensitizer and as a catalyst to form a metal–nitrene intermediate for subsequent C–N bond formation. A variety of sp^3 C–H bonds can be aminated in good to high yields and with excellent regioselectivity. The reactivity trend of C–H bonds for the photocatalytic amination was found to be benzylic ≈ allylic > tertiary > secondary > primary C–H bond. The method is also effective for selective late stage C–H amination of complex natural products. The photochemical reaction herein developed has several eco-friendly advantages including: (1) using organic azides as aminating agents, (2) using catalysts of biocompatible and earth abundant iron, and (3) using blue LED light as the energy source. Nonetheless the use of DCE as the solvent is not a desirable feature and studies on using an environmentally benign solvent system to replace DCE are needed to further improve this iron porphyrin catalysed photochemical amination reaction. The chiral Fe(D$_4$-por*)Cl can catalyse the light driven C–H amination and alkene aziridination with moderate enantioselectivity. To our knowledge, this work represents the first examples of visible light driven sp^3 C–H amination and alkene aziridination with organic azides by iron porphyrin photocatalysis.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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