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Pursuing high efficiency in photocatalytic oxidative couplings of heteroarenes and aliphatic C–H bonds†

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5- and 6-membered heteroarenes, both azoles and azines, were directly alkylated by alkanes, ethers and carbamates using *t*-butyl peroxybenzoate under LED irradiation. As a serendipitous finding, an organic photosensitizer, 9,10-dichloroanthracene, significantly increased overall efficiency of radical couplings *via* energy transfer of exciplexes and allowed many examples of oxidative couplings to proceed in good yields, even when 1.5 equivalents of alkanes were used.

Alkylated heteroarenes are common motifs in drugs, for example, Lipitor and Veliparib in Fig. 1. The classic Minisci reaction used aliphatic carboxylic acids as alkyl radical source, and the reactivity of azaarenes (*e.g.*, pyridines, quinolines and pyrimidines) was enhanced by protonation or Lewis acids.[1] Besides carboxylic acids,[2] other sources of alkyl radicals in Minisci-type reactions of heteroarenes, have been extensively examined, such as alkyl halides,[3] alkenes,[4] aliphatic peresters,[5] alkyl trifluoroborates and alkylboronic acids,[6] alkyl silanes and silicates,[7] sulfinates,[8] *etc*. These functionalized compounds need to be prepared beforehand.

In oxidative couplings of heteroarenes,[9] alkanes and common oxygenated and nitrogenated alkanes are considered to be the cheapest source of alkyl radicals. Alkyl ethers, alcohols and alkylamine derivatives (*e.g.*, α-hydrogens of carbamates and amides) contain activated C–H bonds for the generation of alkyl radicals. After rapid extraction of α-hydrogens, the resulting α-alkyl radicals are highly nucleophilic and can add rapidly to electron-deficient heteroarenes. Unactivated alkanes are more challenging due to the high bond dissociation energies (BDE) of C–H bonds and the regiochemical issue of selective activation among multiple C–H bonds in alkanes. It should be noted that most reported procedures required a large excess of alkanes to obtain good yields (mostly 15–50 equiv.).

Often hydrogen abstraction was performed with the aid of heteroatom radicals, such as alkoxy radicals, sulfate radicals from persulfates or halogen atomsradicals.[10] Persulfate-derived sulfate radical anion proved very efficient in hydrogen abstraction from alkanes, alkyl ethers and alkylamine derivatives.[11] For example, iridium photocatalyst Ir[dF(CF$_3$)ppy]$_2$(dtbpy)PF$_6$ can accelerate persulfate-promoted couplings of protonated azines with ethers and Boc-amines, using 1.5 equiv. under optimized flow conditions (see Fig. 2a and b).[12] In another example, oxidative couplings of heteroarenes (*e.g.*, azines, benzoxazole and benzothiazole) were reported with alkanes and ethers (see Fig. 2c), in which an organic photocatalyst, 4-CzIPN, acted *via* electron transfer to activate heteroarenes.[13] Recently, other reagents have also been explored for efficient activation of unreactive C–H bonds of alkanes, for example, selectfluor,[14] organoiodine(III) reagents[15] and diacetyl as a sacrificial photosensitizer.[16] In many of the methods

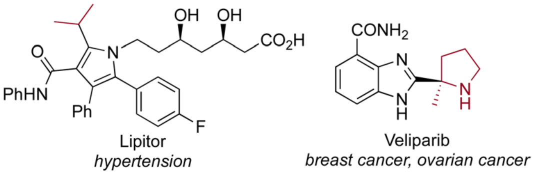

Fig. 1 Examples of drugs containing alkylated heteroarenes.

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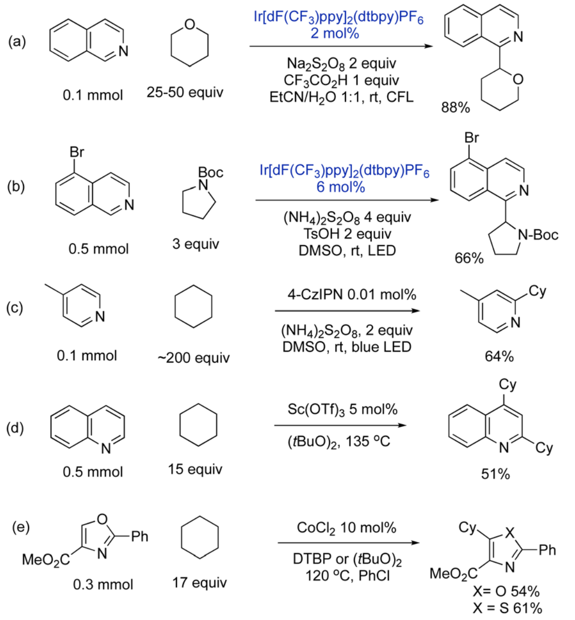


Fig. 2 Examples of oxidative couplings of heteroarenes with C–H bonds of alkanes and ethers.

above, visible light or blue LED was applied to provide the necessary energy to overcome the endergonic reactions.[17]

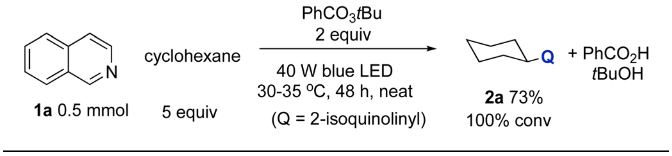
Organic peroxides and peresters constitute another major class of oxidants, and they contain weak O–O single bonds (BDE <50 kcal mol^{-1}).[18] For example, the half-life of TBPB is ~10 h at 100 °C and 1 h at 120 °C.[19] Often, thermolysis of these organic oxidants at high temperatures (100–140 °C) was employed to produce alkoxy or benzoyl radical from di-*t*-butyl peroxide or benzoyl peroxide for oxidative couplings.[20] One of these conditions employed $Sc(OTf)_3$ for *in situ* activation of azacycles, for instance (see Fig. 2d).[21] Often, redox-active transition metal salts (Co, Cu, Fe, Pd and Ru, *etc.*) were used to promote heterolytic cleavage of organic peroxides. Recently, $CoCl_2$ catalyzed oxidative coupling of oxazoles and thiazoles with ethers and cycloalkanes at 100–120 °C, using *t*-butyl peroxybenzoate (TBPB) or di-*t*-butyl peroxide (Fig. 2e).[22] $CoCl_2$ presumably activated TBPB *via* electron transfer to produce cobalt^{III} benzoate and *t*-butoxy radical. In a rare example, $Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$ was utilized to promote oxidative couplings of protonated azines (*e.g.*, benzothiazole) with 2 equiv. of reactive *N*-Boc-pyrrolidine and alkanes using *t*-butyl peracetate at rt.[23]

Herein, we report a photocatalytic dehydrogenative coupling of alkanes, ethers and carbamates with a diverse set of heteroarenes, by using TBPB under blue LED irradiation. The scope of heteroarenes includes not only five-membered azoles (*e.g.*, oxazole, thiazole, imidazole, their benzofused derivatives, pyrrole and indole), but also six-membered azines (pyridine, quinoline, pyrimidine, *etc.*). We initially found that alkylated oligomers of isoquinoline can function as an autocatalyst. Building on this insight, we eventually discovered that a cheap organic photosensitizer, 9,10-dichloroanthracene can allow 1.5 equiv. of alkanes to give good yields of products of oxidative couplings in many cases (see Fig. 6).

In a model reaction between isoquinoline and 5 equiv. of cyclohexane, we discovered that TBPB itself could afford oxidative adduct **2a** in good yield (73%) under blue LED irradiation (see Table 1, entry 1). Addition of 1 equiv. of TEMPO completely inhibited the model radical alkylation of isoquinoline, along with 4% TEMPO-cyclohexyl. The LED condition was superior to conventional heating at 100 °C and 130 °C, producing very complex mixtures containing 30–50% yields of **2a** (entries 2 and 3). Other peroxides and peresters such as *t*BuOOH, $(tBuO)_2$ and $(BzO)_2$ were much less effective by giving **2a** in 0–21% yields (entries 4–9). When the model reaction was conducted in solutions of toluene and 1,1,1-trifluorotoluene, ~50% yield was detected (entries 10 and 11). Reducing the stoichiometry of cyclohexane to 2 equiv. led to 53% yield of **2a** (entry 13). Different from previous reports, our radical alkylation was impeded or inhibited by iridium photocatalysts or transition metal salts, contrary to common perception (see the ESI†). Notably, addition of stoichiometric amounts of trifluoroacetic acid or triflic acid did not increase the efficiency of our model reaction of isoquinoline.

The optimized conditions in Table 1 were applicable to other cycloalkanes in reactions with isoquinoline (Fig. 3a). Simple cycloalkanes of 5–8 membered rings reacted efficiently (**2b–d**). Strained norbornane was heteroarylated to give **2e** as a 5 : 1 mixture of *exo*- and *endo*-isomers (determined by NMR spectroscopy and confirmed by GCMS). In the reactions of *t*-butyl cyclohexane and phenylcyclohexane, heteroarylation occurred exclusively at the equatorial sites of both C3 and C4 positions (**2f–g**) (C3/C4 selectivity 2.6 or 2.8). No heteroarylation at the C1 position was detected, because of the low reactivity of the tertiary benzylic radical toward **1f** and a congested radical center at **1g**. Similarly, heteroarylation of *trans*-decaline

Table 1 Condition optimization for oxidative coupling of isoquinoline and cyclohexane (conversion of isoquinoline and yields determined by GC)



Entry	Changes of conditions	Conversion (%)	GC yield (%)
1	None	100	73
2	Heating at 100 °C	100	33
3	Heating at 130 °C	100	50
4	$(t\text{-BuO})_2$	33	21
5	$(BzO)_2$	80	0
6	*m*CPBA	64	4
7	*t*-BuOOH	0	0
8	BocOO*t*-Bu	68	0
9	In toluene (~0.7 M)	77	50
10	In $PhCF_3$ (~0.7 M)	100	58
11	Cyclohexane 2 equiv.	72	53

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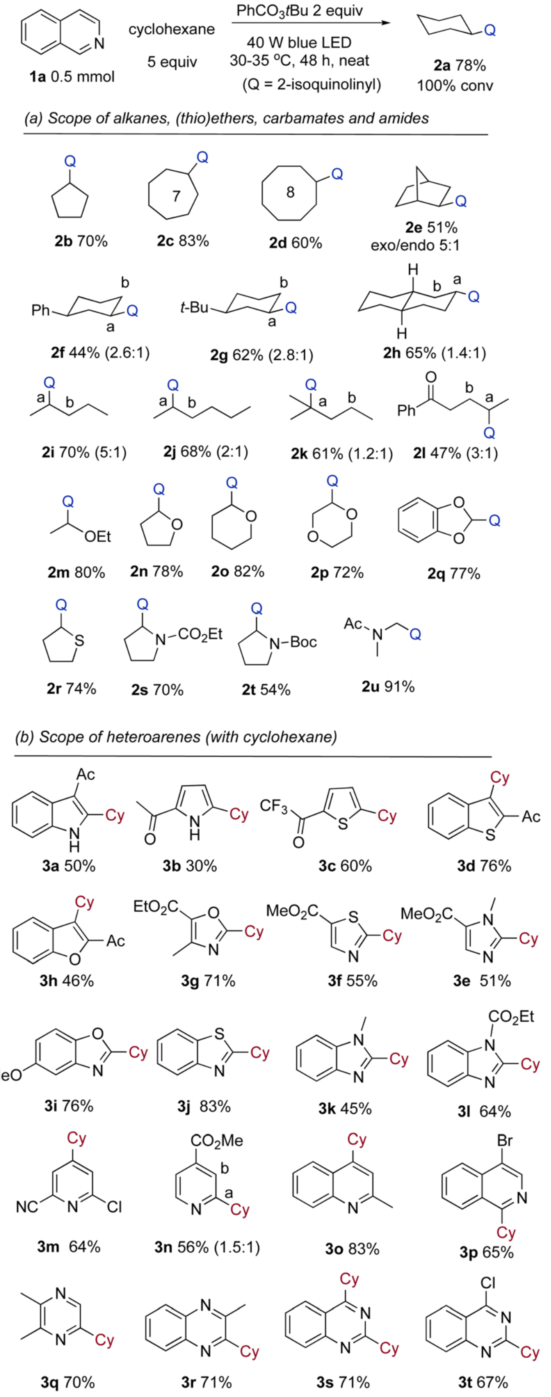

Fig. 3 (a) Oxidative heteroarylation of alkanes, cycloalkanes, (thio) ethers, carbamates and amides with isoquinoline. (b) Oxidative alkylation of azoles, benzofused azoles, azines and benzofused azines with 5 equiv. of cyclohexane (isolated yields of reactions using 0.5 mmol of heteroarenes, 2.5 mmol of alkanes and 1.0 mmol of TBPB in neat under blue LED irradiation). The regioselectivity a/b is indicated in brackets.

(**2h**) proceeded selectively at the equatorial positions with a C3/C2 ratio of 1.4 : 1.

In the reactions of linear alkanes, pentane (**2i**) formed new C–C bonds with selectivity for the C2 position (C2/C3 5 : 1) at the expense of methyl groups. Heteroarylation of isohexane (**2k**) occurred mainly at both tertiary C2 and secondary C4 positions (ratio 1.2), without coupling at the C3 and terminal methyl positions. In the coupling of valerophenone (**2l**), heteroarylation proceeded selectively at the C4 position (C4/C3 3 : 1) to give 47% yield, owing to a deactivating inductive effect of the electron-withdrawing ketone through bonds. Alkoxy radicals did not abstract α-hydrogen of carbonyl compounds due to the polarity effect. Notably, ethylbenzene led to dimerization of benzylic radicals in high yields, without any product of heteroarylation.

The oxidative procedure could also be applied to α-heteroarylation of diethyl ether, cyclic ethers (**2m–p**), an acetal (**2q**) and a thioether (**2r**) (Fig. 3a). α-Heteroarylation of *N*-ethylcarbonylpyrrolidine and *N*-Boc-pyrrolidine (**2s–t**) gave 70% and 54% yields. Heteroarylation of *N*,*N*-dimethylacetamide (**2u**) occurred selectively at one *N*-methyl group.[24] The reaction using *N*,*N*-dimethylformamide resulted in C1-formylation of isoquinoline.

Many classes of azoles proved to be good acceptors of alkyl radicals under the optimized conditions described in Table 1 (Fig. 3b). Electron-withdrawing groups on pyrrole and thiophene (**3b–c**) could improve the efficiency of radical alkylation. For instance, alkylation of 2-trifluoroacetylthiophene proceeded to give **3c** in 60% yield and good regioselectivity (10 : 1). Similar alkylation also occurred with activated indole (**3a**), benzothiophene and benzofuran (**3d–e**). In the reactions of azoles (**3f–h**), electron-withdrawing groups also proved instrumental in accelerating radical alkylation. The electronic activation was not needed with benzoxazole and benzothiazole (**3i–j**), but its effect was noticeable with benzimidazoles (**3k–l**). For example, replacing the *N*-methyl group on benzimidazole with an *N*-carbamate group increased the yield of products from 45% to 64% (**3k–l**). Six-membered azaarenes (pyridines, quinoline, isoquinoline, quinoxaline and benzopyrimidine) showed good reactivity towards alkyl radicals and gave adducts **3m–t** in moderate to good yields. To form dialkylated product **3s**, 10 equiv. of cyclohexane was used.

Mechanistically, photolysis of TBPB under blue LED irradiation may be initiated by oligomer **5** or 9,10-dichloroanthracene (see Fig. 6 below), which gave rise to *t*-butoxy radical and benzoyl radical (Fig. 4a).[19] It is distinct from the thermolysis of peresters and peroxides catalyzed by redox-active metal salts such as $Cu(OAc)_2$, $CoCl_2$ and $Fe(OTf)_2$ or iridium photocatalysts that often gave *t*BuO radical and a benzoate anion.[25] *t*-Butoxy radical allows efficient hydrogen abstraction from alkanes and alkyl ethers to produce alkyl radicals, a desired process. *t*BuO radical preferentially abstracts hydrogen from CH bonds of alkanes and α-CH bonds next to oxygen and nitrogen atoms.[26] β scission of *t*-butoxy radical to produce acetone and methyl radical is a minor process.[27] On a productive pathway (Fig. 4b), cyclohexyl radical added to the C2 position of isoquinoline, and the resulting radical adduct underwent hydrogen abstraction by *t*-butoxy radical or benzoyl radical to release final product **2a**.

When we conducted a control reaction between TBPB and cyclohexane, only 32% conversion of TBPB was detected after

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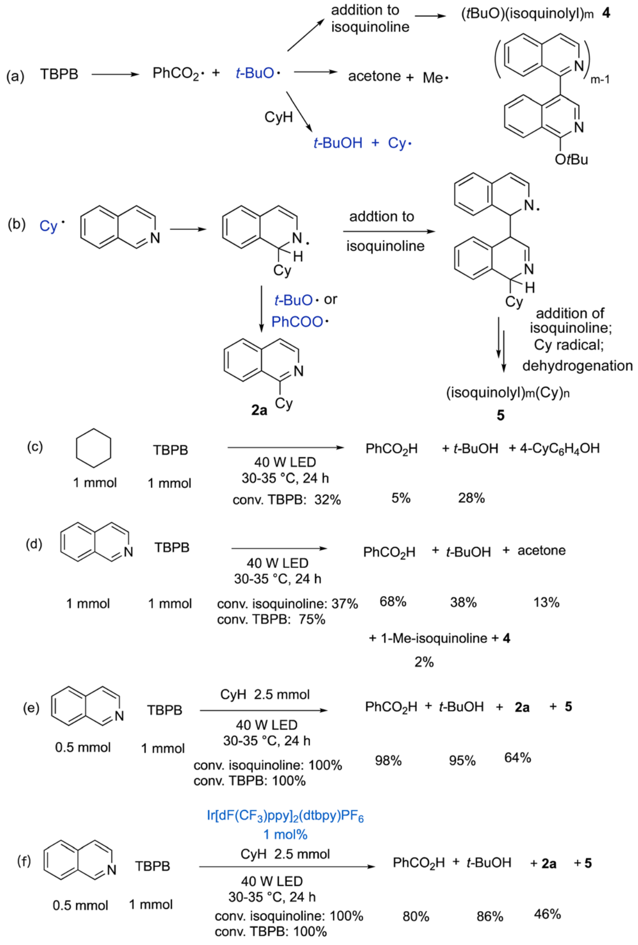

Fig. 4 Reaction mechanism and mechanistic studies.

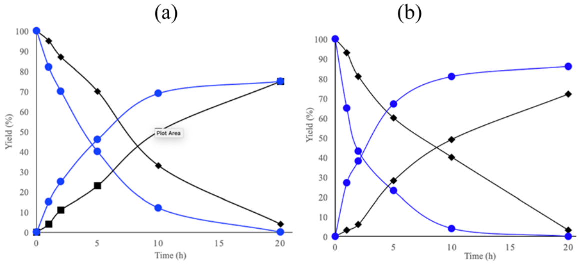

Fig. 5 Kinetics of oxidative coupling of isoquinoline (0.5 mmol), cyclohexanes (2.5 mmol) with TBPB (1.0 mmol) to produce **2a** (conversions and yields) in the absence of a photosensitizer (black), in the presence of (a) 10 mg of **5** (blue) conducted at 30–35 °C and (b) 2 mol% 9,10-dichloroanthracene (blue) conducted at 40 °C.

24 h, along with 28% yield of *t*-butanol and 0.5% acetone from β scission (Fig. 4c). It confirmed that TBPB itself poorly absorbed visible light. In another control reaction of TBPB with isoquinoline (Fig. 4d), the conversion of TBPB increased to 75% after 24 h, along with 38% *t*-butanol, 13% acetone (from β scission) and 2% 1-methylisoquinoline.[28] Furthermore, a complex mixture of oligomers of isoquinoline (*t*BuO)(isoquinolyl)$_m$ (m = 1–3) **4** were detected as highly polar fractions during silica purification (as judged by ESI-MS).

The reaction of isoquinoline and 5 equiv. of cyclohexane gave product **2a** in 70% yield after 24 h, along with 95% yield of *t*-butanol and a complex mixture of cyclohexylated oligomers of isoquinoline (isoquinolyl)$_m$(Cy)$_n$ **5**, which was isolated as polar fractions on silica gel (m = 1, 2, 3 and higher; n = 2, 3, 4 and higher as detected by ESI-MS). The immediate adduct of cyclohexyl radical to isoquinoline could add to more molecules of isoquinoline before it was quenched. Subsequent dehydrogenative rearomatization of isoquinoline rings and addition of more cyclohexyl radicals gave a complex mixture of **5** (see Fig. 4b and the ESI†).

Next, we attempted to add an isolated sample **5** (10 mg) to isoquinoline in a model reaction (Fig. 5a). The initial reaction rate increased almost two-fold, giving product **2a** in 25% and 46% yields after 2 h and 5 h (*versus* 11% and 23% without it), respectively. After 24 h, both reactions gave full conversion and a 70% yield of **2a**. Therefore, **5** can act as a photosensitizer to promote the homolysis of TBPB at ambient temperature. However, **5** was a complex mixture of cyclohexylated oligomers of isoquinoline and precluded proper characterizations (see the ESI†). Moreover, it did not serve as an efficient photosensitizer when applied to reactions of other heteroarenes.

We then attempted to use iridium photocatalyst Ir[dF(CF$_3$)ppy]$_2$(dtbpy)PF$_6$ in the model reaction of isoquinoline, but it led to only a 46% yield of **2a** and a significant amount of a mixture of **5** (Fig. 4f). It was probably caused by a mismatch in reaction rates between fast alkyl generation, fast radical addition and slow hydrogen abstraction from the immediate alkyl radical adduct of isoquinoline, which was then sidetracked to oligomerization of isoquinoline.

In search for an efficient photosensitizer, we accidentally came across 9,10-dichloroanthracene (DCA) in the literature, which possesses very promising photochemical properties. (a) It has good chemical stability under photoirradiation. (b) It has two strong absorbances at 380 and 400 nm of almost equal intensity (a molar absorption coefficient of 14 300 M^{-1} cm^{-1}) and a smaller absorbance at 360 nm, owing to the halogen substitution effect. (c) It has fluorescence emissions centering centered at 440 nm with a fluorescence quantum yield of 0.64.[29] (d) Upon photoexcitation, DCA can undergo efficient intersystem crossing (ISC) to a triplet excited state (T$_1$), due to internal heavy atom effect.[30] The latter has sufficient energy to activate TBPB *via* energy transfer.

When 2 mol% DCA was added in the model reaction of isoquinoline and 5 equiv. of cyclohexane, we found that the initial reaction rate increased almost three-fold (Fig. 5b). **2a** was formed in 38% and 67% yields after 2 h and 5 h (isolated yield 78% after 24 h). More importantly, we found that DCA allowed 1.5 equiv. of cyclohexane to produce **2a** in 75% yield in 24 h. This is a significant improvement on known dehydrogenative couplings of heteroarenes that often required a large excess unactivated alkanes. We also tested 9,10-dibromoanthracene and 9,10-diphenylanthracene, but they were much

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less effective (~30% yield). The former may be unstable upon photoexcitation and the latter lacks heavy atoms for efficient ISC.

Previously, it was suggested that fluorescence quenching of anthracene by peroxides or TBPB may proceed *via* singlet exciplexes with a charge transfer character.[31] To confirm this hypothesis, we conducted time-resolved photoluminescence (TRPL) experiments to measure fluorescence quenching of DCA upon excitation at 360 nm (Fig. 6). Three sets of TRPL data were fitted with Gaussian convoluted exponential functions (three curves on the left of Fig. 6 are the respective response functions). In a solution of toluene, however, the half-life of DCA fluorescence was slightly decreased from 4.06 ns to 3.86 ns when 100 equiv. of TBPB was added to toluene, which was expected for energy transfer *via* exciplexes. The exciplex formation is commonly observed in solid states, but it is much more difficult in dilute solutions. In neat TBPB, the half-life of DCA fluorescence was dramatically reduced to 1.75 ns.

We then successfully applied the new protocol using a catalytic amount of DCA to oxidative couplings of isoquinolines and 1.5 equiv. of alkanes, ethers, carbamates and amides (Fig. 7a). Most of the cyclic alkanes were fully consumed to give products in good yields at ~40 °C after 24 h. The reactions of acyclic alkanes were much slower and reached around 50–60% conversion after 24 h. We observed that most of α-selective heteroarylations of reactive ethers, acetals, carbamates and amides reached >90% conversions. Next, we used 1.5 equiv. of cyclohexane to couple with azoles and azines and examined their scope (Fig. 7b). Most of them reacted efficiently, including activated benzothiophene, activated thiazole, benzothiazole, *N*-methylbenzoimidazole, activated pyridines, quinoline, isoquinoline, substituted pyrazine, benzopyrazine and benzopyrimidine. We also detected 2,4-dialkylation of benzopyrimidine proceeded in high yields using 3 equiv. of cyclohexane; a poor C2/C4 regioselectivity was observed with a limiting amount of cyclohexane.

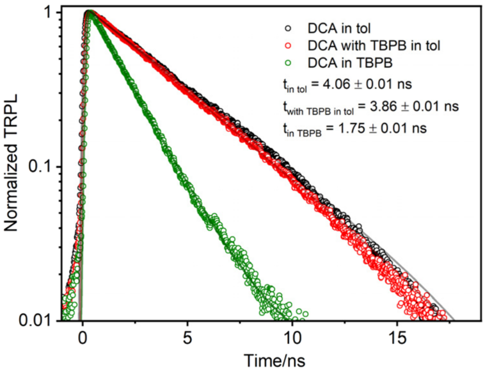

Fig. 6 Time-resolved photoluminescence (TRPL) spectra of 9,10-dichloroanthracene (DCA, 0.5 mM) in toluene (black) recorded at excitation wavelength of 360 nm at room temperature, DCA (0.5 mM) and TBPB (50 mM) in toluene (red), and DCA (1 mM) in neat TBPB (green).

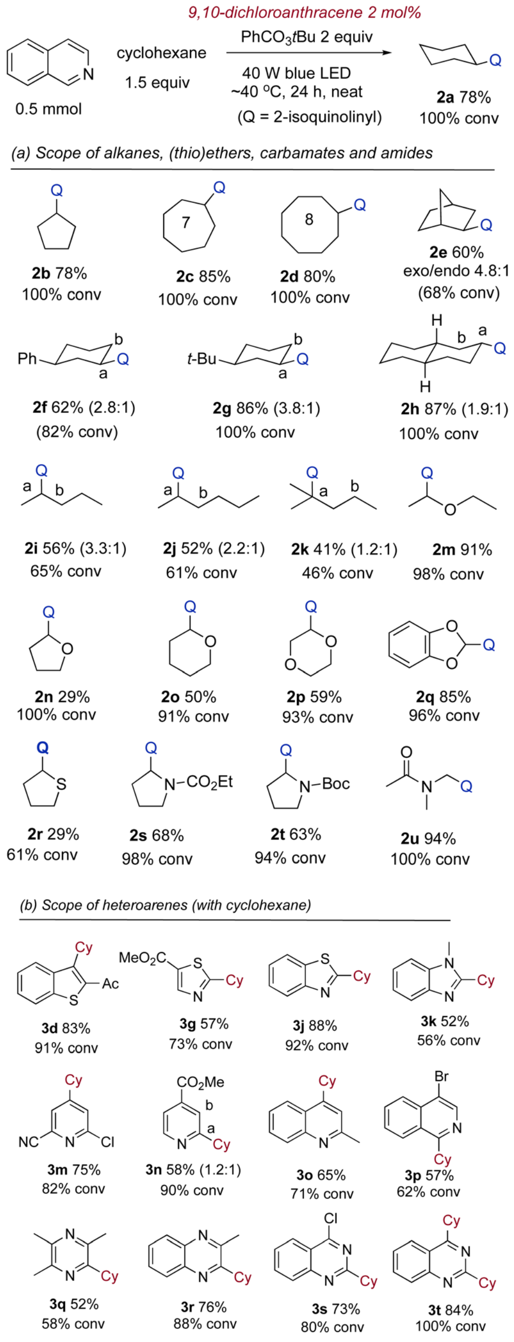

Fig. 7 Photocatalytic oxidative coupling of alkanes [with the scope in (a)] and heteroarenes [with scope in (b)] promoted by DCA (yields of reactions using 2 mol% DCA, 0.5 mmol of heteroarene, 0.75 of mmol alkanes and 1.0 mmol of TBPB in neat under blue LED irradiation). The regioselectivity a/b is indicated in brackets.

To understand the origin of C3-regioselective and equatorial-selective heteroarylation of *t*-butylcyclohexane, we performed DFT calculations (at the UB3LYP/6-31+G* level) on transition states for the addition of 3- and 4-*t*-butylcyclohexyl radicals to the C1 position of isoquinoline (see Table 2). The electronic energies for equatorial radical addition were lower than for axial addition by 1.1 and 0.7 kcal mol^{-1} at the C3 and

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Table 2 Relative energies of transition states for addition of 3- and 4-*t*-butylcyclohexyl radicals to the C1 position of isoquinoline

C–C bond formation	Relative energy (kcal mol^{-1})	Relative free energy (kcal mol^{-1})
C3-axial	1.11	1.58
C3-equatorial	**0.00**	**0.00**
C4-axial	1.09	1.37
C4-equatorial	0.41	0.52

C4 positions, respectively. Additionally, the TS energy for equatorial alkylation at the C3 positions was 0.4 kcal mol^{-1} lower than at the C4 position, which agreed reasonably well with a statistic bias of C3/C4 1.4–1.9 : 1 experimentally.

In conclusion, we reported photocatalytic oxidative couplings of alkanes, ethers, amides and carbamates with a wide range of heteroarenes, using *t*-butyl peroxybenzoate (TBPB) under blue LED irradiation. The scope of heteroarenes included many families of azoles and azines with low-lying LUMOs. We identified a chemically stable photosensitizer, 9,10-dichloroanthracene, which can greatly increase the efficiency of radical couplings and allowed only 1.5 equiv. of alkanes to give good yields in many cases. The high efficiency of this oxidative coupling reaction benefits from a few key factors: (a) homolytic cleavage of *tert*-butyl peroxybenzoate at ambient temperature was enhanced by 9,10-dichloroanthracene, which occurred *via* energy transfer *via* a singlet exciplex; (b) under neat conditions, concentrations of the substrates and perester were kept high (~1.5 M) to ensure high efficiency in exciplex energy transfer and subsequent radical processes; (c) there was a match in reaction rates of elementary steps, alkyl radical generation from *t*-butoxy radical, addition to heteroarenes and hydrogen abstraction from the initial radical adduct to release final products. A slow last step will side track the reaction such that the intermediate undergoes multiple additions of isoquinoline to eventually form side products **5**.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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