LETTER

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Alcohols as alkylating agents in heteroarene C–H functionalization

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Redox processes and radical intermediates are found in many biochemical processes, including deoxyribonucleotide synthesis and oxidative DNA damage[1]. One of the core principles underlying DNA biosynthesis is the radical-mediated elimination of H_2O to deoxygenate ribonucleotides, an example of 'spin-centre shift'[2], during which an alcohol C–O bond is cleaved, resulting in a carbon-centred radical intermediate. Although spin-centre shift is a well-understood biochemical process, it is underused by the synthetic organic chemistry community. We wondered whether it would be possible to take advantage of this naturally occurring process to accomplish mild, non-traditional alkylation reactions using alcohols as radical precursors. Because conventional radical-based alkylation methods require the use of stoichiometric oxidants, increased temperatures or peroxides[3–7], a mild protocol using simple and abundant alkylating agents would have considerable use in the synthesis of diversely functionalized pharmacophores. Here we describe the development of a dual catalytic alkylation of heteroarenes, using alcohols as mild alkylating reagents. This method represents the first, to our knowledge, broadly applicable use of unactivated alcohols as latent alkylating reagents, achieved via the successful merger of photoredox and hydrogen atom transfer catalysis. The value of this multi-catalytic protocol has been demonstrated through the late-stage functionalization of the medicinal agents, fasudil and milrinone.

During DNA biosynthesis, ribonucleoside diphosphates are converted into their deoxyribonucleoside equivalents via the enzymatic activity of ribonucleotide reductase (class I–III)[8]. Crucially, a (3′,2′)-spin-centre shift occurs, resulting in β-C–O scission and elimination of water (Fig. 1a). Considering the efficiency of this mild enzymatic process to cleave C–O bonds to generate transient radicals, we postulated whether an analogous chemical process could occur with simple alcohols, such as methanol, to access radical intermediates for use in challenging bond constructions (Fig. 1b). In the medicinal chemistry community, there is growing demand for the direct introduction of alkyl groups, especially methyl groups, to heteroarenes, given their influence on drug metabolism and pharmacokinetic profiles[9]. The open-shell addition of alkyl radical intermediates to heteroarenes, known as the Minisci reaction[10], has become a mainstay transformation with broad application within modern drug discovery[11]. Unfortunately, many current methods are limited in their application to late-stage functionalization of complex molecules owing to their dependence on the use of strong stoichiometric oxidants or increased temperatures to generate the requisite alkyl radicals[3–6]. A photoredox-catalysed alkylation protocol using peroxides as the alkyl radical precursors was recently demonstrated[7]. Given the state of the art, we questioned whether a general alkylation protocol could be devised in which a broad range of substituents could be installed from simple commercial alcohols under mild conditions.

Visible light-mediated photoredox catalysis has emerged in recent years as a powerful technique in organic synthesis that facilitates single-electron transfer events with organic substrates[12–14]. This general strategy allows for the development of bond constructions that are often elusive or currently impossible via classical two-electron pathways. Recently, our laboratory introduced a new dual photoredox-organocatalytic platform to enable the functionalization of unactivated sp^3 C−H bonds[15–17]. This catalytic manifold provides access to radical intermediates via C−H abstraction, resulting in the construction of challenging C−C bonds via a radical–radical coupling mechanism. With the insight gained from this dual catalytic system and our recent work on the development of a photoredox-catalysed Minisci reaction[18], we questioned whether it would be possible to generate alkyl radicals from alcohols and use them as alkylating agents in a heteroaromatic C–H functionalization reaction (Fig. 1c). While there are a few early reports of alcohols as alkyl radical precursors formed via high-energy irradiation (ultraviolet light and gamma rays)[19–21], a general and robust strategy for using alcohols as latent alkylating agents has been elusive. This transformation would represent a direct C−H alkylation of heteroaromatics with alcohols via a spin-centre shift pathway, eliminating H_2O as the only by-product. We recognized that this mild alkylating procedure would serve as a powerful and general method in late-stage functionalization, using commercially available and abundant alcohols as latent alkylating agents.

A detailed description of our proposed dual catalytic mechanism for the alkylation of heteroarenes with alcohols is outlined in Fig. 2. Irradiation of $Ir(ppy)_2(dtbbpy)^+$ (**1**) (in which ppy = 2-phenylpyridine, dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine) will generate the long-

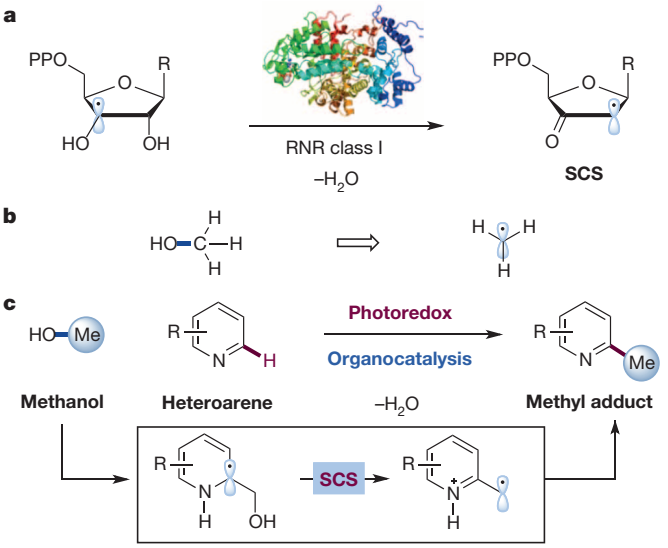

Figure 1 | Bio-inspired alkylation process using alcohols as spin-centre shift equivalents via a dual catalytic platform. a, DNA biosynthesis occurs via a spin-centre shift (SCS) process, catalysed by ribonucleotide reductase (RNR) class I to generate a carbon-centred radical, after elimination of H_2O as a by-product. **b**, Alcohols (for example, methanol) as radical intermediates when spin-centre shift allowed. **c**, Proposed direct installation of alkyl groups using alcohols under mild photoredox organocatalytic conditions.

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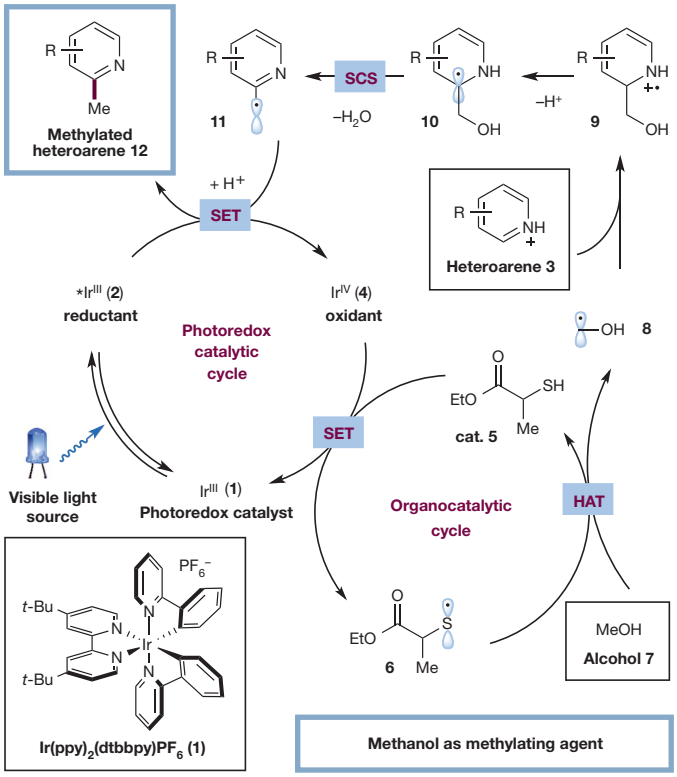


Figure 2 | Proposed mechanism for the direct alkylation of heteroaromatic C–H bonds via photoredox organocatalysis. The catalytic cycle is initiated via excitation of photocatalyst **1** to give the excited state **2**. A sacrificial amount of heteroarene **3** oxidizes $*Ir^{III}$ **2** to Ir^{IV} **4**, which then oxidizes thiol catalyst **5** to generate thiyl radical **6** and regenerate catalyst **1**. Thiyl radical **6** then abstracts a hydrogen atom from alcohol **7** to form α-oxy radical **8**. Radical **8** adds to heteroarene **3**, producing radical cation **9**, which after deprotonation forms α-amino radical **10**. Spin-centre shift elimination of H_2O forms radical intermediate **11**. Protonation and reduction by $*Ir^{III}$ **2** delivers alkylated product **12**. HAT, hydrogen atom transfer; MeOH, methanol; SET, single-electron transfer.

lived $*Ir(ppy)_2(dtbbpy)^+$ (**2**) excited state ($\tau = 557$ ns)[22]. As $*Ir(ppy)_2(dtbbpy)^+$ (**2**) can function as either a reductant or an oxidant, we postulated that **2** would undergo a single-electron transfer event with a sacrificial quantity of protonated heteroarene **3** to initiate the first catalytic cycle and provide the oxidizing $Ir(ppy)_2(dtbbpy)^{2+}$ (**4**). Given the established oxidation potential of $Ir(ppy)_2(dtbbpy)^{2+}$ (**4**) ($E_{1/2}^{red} = +1.21$ V versus saturated calomel electrode in CH_3CN)[22], we anticipated that single-electron transfer from the thiol catalyst **5** ($E_{1/2}^{red} = +0.85$ V versus saturated calomel electrode for cysteine)[23] to $Ir(ppy)_2(dtbbpy)^{2+}$ (**4**) would occur and, after deprotonation, furnish the thiyl radical **6** while returning $Ir(ppy)_2(dtbbpy)^+$ (**1**) to the catalytic cycle. At this stage, we presumed that the thiyl radical **6** would undergo hydrogen atom transfer with the alcohol **7** (a comparable thiol, methyl 2-mercaptoacetate S–H bond dissociation energy = 87 kcal mol^{-1} (ref. 24), methanol α-C–H bond dissociation energy = 96 kcal mol^{-1} (ref. 25)) to provide the α-oxy radical **8** and regenerate the thiol catalyst **5**, driven by the polar effect in the transition state[26]. The polar effect is a remarkable property that enables considerably endergonic C–H abstractions that would not be possible otherwise[27]. The nucleophilic α-oxy radical **8** would then add to the protonated electron-deficient heteroarene **3** in a Minisci-type pathway to afford the aminyl radical cation **9**. The resulting α-C–H bond of **9** is sufficiently acidic to undergo deprotonation to form the α-amino radical **10** (ref. 28). At this juncture, intermediate **10** is primed to undergo a spin-centre shift to eliminate H_2O and generate benzylic radical **11**. The resulting open-shell species would then undergo protonation followed by a second single-electron transfer event with the excited photocatalyst **2** to regenerate the active oxidant $Ir(ppy)_2(dtbbpy)^{2+}$ (**4**), while providing the desired alkylation product **12**.

We first examined this new alkylation protocol using isoquinoline and methanol as the coupling partners, and evaluated a range of photocatalysts and thiol catalysts. Using $Ir(ppy)_2(dtbbpy)PF_6$ (**1**) and ethyl 2-mercaptopropionate (**5**), along with *p*-toluenesulfonic acid and blue light-emitting diodes as the light source, we were able to achieve the desired C–C coupling to provide 1-methylisoquinoline (**15**) with a 92% yield (see Supplementary Information). Notably, we observed none of the desired product in the absence of photocatalyst, thiol catalyst, acid or light, demonstrating the requirement of all components in this dual catalytic protocol. In addition, this method requires only weak visible light and ambient temperature to install methyl substituents using methanol as the alkylating agent.

With the optimal conditions in hand, we sought to evaluate the generality of this dual catalytic alkylation transformation. As highlighted in Fig. 3a, a wide range of heteroaromatics are methylated under the reaction conditions. Isoquinolines with electron-donating or -withdrawing substituents (such as methyl substituents, esters and halides) are functionalized in excellent efficiencies (**15**–**18**, 85–98% yield). Quinolines perform effectively, including those that contain non-participating functionality (**19**–**23**, 65–95% yield), in addition to phthalazine and phenanthridine coupling partners (**24** and **25**, 70% and 93% yield). Moreover, a wide range of pyridine derivatives containing diverse functionality (such as esters, amides, arenes, nitriles and trifluoromethyl groups) can be converted into the desired methylation products in high yield (**26**–**32**, 65–91% yield).

Next, we sought to investigate the nature of the alcohol coupling partner, as demonstrated in Fig. 3b. A broad array of primary alcohols can effectively serve as alkylating agents in this new alkylation reaction. In contrast to the methylation conditions highlighted above, alcohols in Fig. 3b typically use methyl thioglycolate **13** as the C–H abstraction catalyst. Notably, simple aliphatic alcohols such as ethanol and propanol deliver the alkylated isoquinoline product in high yields (**33** and **34**, 95% and 96% yield). Steric bulk proximal to the alcohol functionality is tolerated, as exemplified by the presence of isopropyl, β-tetrahydropyran, β-aryl and β-adamantyl substituents (**35**–**38**, 87–92% yield). The presence of an electron-withdrawing trifluoromethyl (CF_3) group distal to the alcohol decreases the rate of the reaction; however, using the more electrophilic thiol catalyst, 2,2,2-trifluoroethanethiol (**14**), can promote the transformation more efficiently, possibly owing to the polar effect on the hydrogen atom transfer transition state (**39**, 93% yield)[26]. We found that diols also participate readily in this alkylation protocol (**40** and **41**, 88% and 81% yield). It should be noted that 1,3-butanediol demonstrates exceptional chemoselectivity and undergoes alkylation exclusively at the primary alcohol site. We speculate that the corresponding α-oxy radical at the secondary alcohol position does not attack the protonated heteroarene owing to its increased steric hindrance. For these alkylating agents with several reactive sites (**41**, **43** and **44**), thiol catalyst **5** is the most effective hydrogen atom transfer catalyst—mechanistic studies are continuing to determine the origin of these differences in catalyst reactivity. Ethers, in the form of differentially substituted tetrahydrofurans, are also competent alkylating agents in this dual catalytic platform (**42**–**44**, 72–90% yield). In the elimination step, the tetrahydrofuran ring opens to reveal a pendent hydroxyl group. Interestingly, 3-hydroxytetrahydrofuran and tetrahydrofurfuryl alcohol react regioselectively at the ether α-oxy site distal to the alcohol to afford alkylation products with terminal pinacol motifs. We attribute this exclusive regioselectivity to a subtle influence on C–H bond dissociation energy owing to the inductive influence of the oxygen atoms. The application of these substrates represents an effective method to install vicinal diol motifs that would be inaccessible using traditional oxidative alkylation methods. Finally, the utility of this mild alkylation protocol has been demonstrated by the late-stage

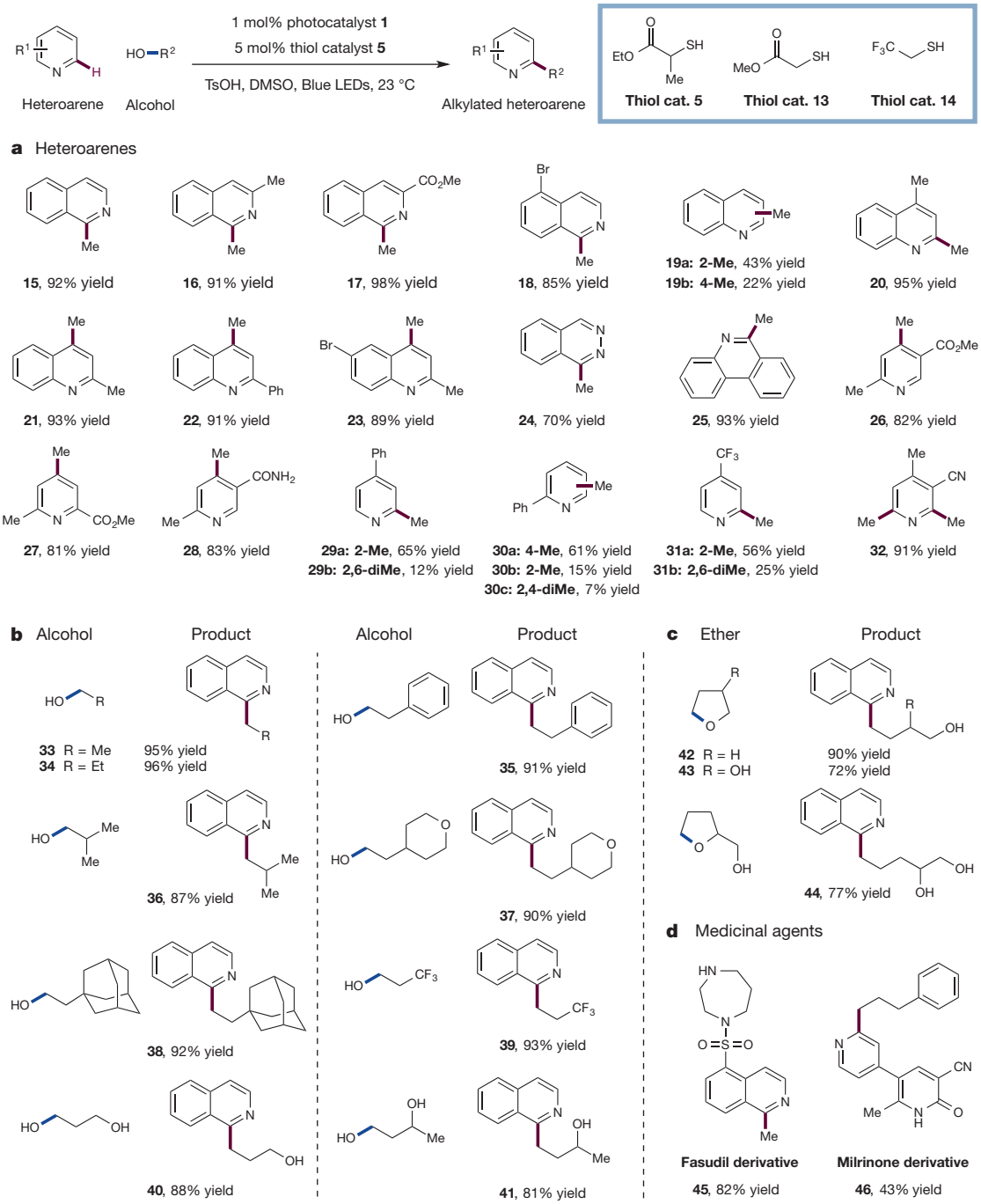
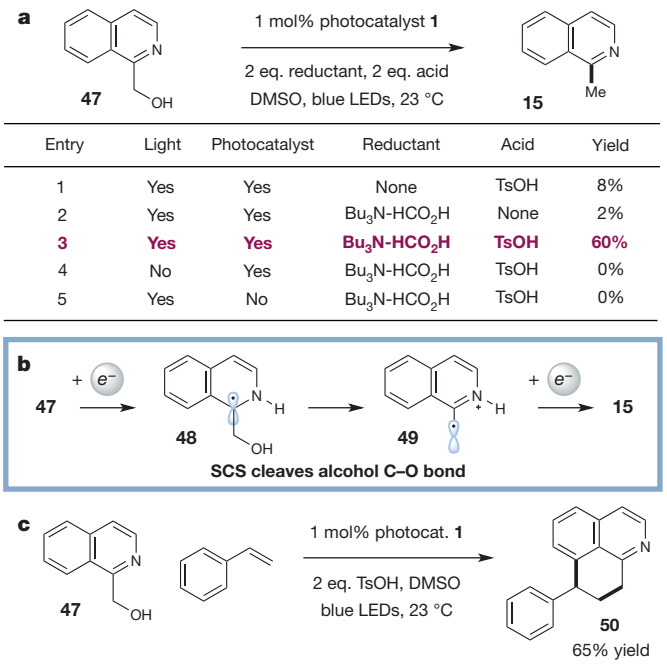


Figure 3 | Substrate scope for the alkylation of heteroaromatic C–H bonds with alcohols via the dual photoredox organocatalytic platform. A broad range of heteroaromatics and alcohols are efficiently coupled to produce alkylated heterocycles under the standard reaction conditions (top, generalized reaction). **a**, A variety of isoquinolines, quinolines, phthalazines, phenanthridines and pyridines are efficiently methylated using methanol as the alkylating reagent. **b**, A diverse selection of alcohols serve as effective alkylating agents in this dual catalytic protocol. **c**, Ethers are also amenable to the transformation; the products are the corresponding ring-opened alcohols. **d**, Two pharmaceuticals, fasudil and milrinone, can be alkylated using this protocol, demonstrating its utility in late-stage functionalization. Isolated yields are indicated below each entry. See Supplementary Information for experimental details.

functionalization of several pharmaceutical compounds. Using methanol as a simple methylating agent, fasudil, a potent Rho-associated protein kinase inhibitor and vasodilator, can be methylated in 82% yield (product **45**). Additionally, milrinone, a phosphodiesterase 3 inhibitor and vasodilator, can be alkylated with 3-phenylpropanol in 43% yield (product **46**).

Mechanistic studies have been conducted to support the proposed pathway outlined in Fig. 2. Stern–Volmer fluorescence quenching experiments have demonstrated that the $^*Ir^{III}$ excited state **2** is quenched in the presence of protonated heteroarene **3**, but not in the presence of the unprotonated heteroarene or thiol catalyst **5**, indicating an oxidative quenching pathway (see Supplementary Information). Furthermore, a series of experiments were conducted to investigate the proposed spin-centre shift elimination. After exposing hydroxylated intermediate **47** to the reaction conditions, only a modest amount of the methylated isoquinoline **15** is observed (8% yield, entry 1, Fig. 4a). In the absence of an acid additive, only trace yields of the desired product are formed (2% yield, entry 2, Fig. 4a). However, in



Entry	Light	Photocatalyst	Reductant	Acid	Yield
1	Yes	Yes	None	TsOH	8%
2	Yes	Yes	Bu_3N-HCO_2H	None	2%
3	**Yes**	**Yes**	**Bu_3N-HCO_2H**	**TsOH**	**60%**
4	No	Yes	Bu_3N-HCO_2H	TsOH	0%
5	Yes	No	Bu_3N-HCO_2H	TsOH	0%

Figure 4 | Mechanistic studies support spin-centre shift elimination pathway. **a**, Hydroxymethyl intermediate **47** can be converted to methylated **15** under net reductive conditions after addition of formic acid-tributylamine and *p*-toluenesulfonic acid (TsOH). **b**, Deoxygenation of **47** probably proceeds via a spin-centre shift pathway to cleave the alcohol C–O bond. **c**, In the presence of styrene, **47** is converted to **50**, presumably by trapping of radical **49**. DMSO, dimethylsulfoxide; LEDs, light-emitting diodes.

the presence of a stoichiometric reductant and *p*-toluenesulfonic acid, the elimination of oxygen can be achieved in good efficiency (60% yield, entry 3, Fig. 4a). Crucially, this elimination pathway is shut down in the absence of either light or photocatalyst (entry 4 or 5, respectively, Fig. 4a). Therefore, this net reductive process supports the proposed generation of α-amino radical **48**, which could readily form deoxygenated product **15** via a spin-centre shift pathway to β-amino radical **49** (Fig. 4b). This elimination pathway is further corroborated by a series of radical trapping experiments (Fig. 4c and Supplementary Information). In the presence of styrene, hydroxymethyl arene **47** is transformed to adduct **50** (65% yield, Fig. 4c), presumably via the intermediacy of β-amino radical **49**. Finally, while we support the mechanism outlined in Fig. 2, we cannot rule out the possibility of a radical chain pathway in which radical **11** abstracts an H-atom from alcohol **7** or thiol catalyst **5**.

In summary, this alkylation strategy represents the first, to our knowledge, general use of alcohols as simple alkylating agents and enables rapid late-stage derivatization of medicinally relevant molecules. Given the influence on drug pharmacokinetics and absorption, distribution, metabolism and excretion (ADME) properties, this method of installing inert alkyl groups will probably find wide application in the medicinal chemistry community. We have developed a mild and operationally simple alkylation reaction via the synergistic merger of photoredox and thiol hydrogen atom transfer organocatalysis to forge challenging heteroaryl C–C bonds using alcohols as latent nucleophiles. This bio-inspired strategy mimics the key step in enzyme-catalysed DNA biosynthesis via a new spin-centre shift elimination of H_2O to generate radical intermediates from simple alcohols.

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