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Direct C–H functionalisation of azoles *via* Minisci reactions

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Azoles have widespread applications in medicinal chemistry; for example, thiazoles, imidazoles, benzimidazoles, isoxazoles, tetrazoles and triazoles appear in the top 25 most frequently used N-heterocycles in FDA-approved drugs. Efficient routes for the late-stage C–H functionalisation of azole cores would therefore be highly desirable. The Minisci reaction, a nucleophilic radical addition reaction onto N-heterocyclic bases, is a direct C–H functionalisation reaction that has the potential to be a powerful method for C–H functionalisations of azole scaffolds. However, azoles have not been as widely studied as substrates for modern Minisci-type reactions as they are often more electron-rich and thus more challenging substrates compared to electron-poor 6-membered N-heterocycles such as quinolines, pyrazines and pyridines typically used in Minisci reactions. Nevertheless, with the prevalence of azole scaffolds in drug design, the Minisci reaction has the potential to be a transformative tool for late-stage C–H functionalisations to efficiently access decorated azole motifs. This review thus aims to give an overview of the C–H functionalisation of azoles *via* Minisci-type reactions, highlighting recent progress, existing limitations and potential areas for growth.

1. Introduction

Azoles are a subclass of heterocycles with modern applications in various fields, including supramolecular materials, coordination and organometallic chemistry, and the agrochemical industry.[1] One of the main applications of azoles, however, lies within the field of medicinal chemistry (see Fig. 1);[2] therefore

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David T. Mooney

David T. Mooney received his MSci (Hons) in Chemistry with Medicinal Chemistry from the University of Glasgow in 2020. He also completed a placement year in industry at AstraZeneca (Macclesfield) before returning to Glasgow to complete a Master's project in the France group, working on the development of anti-viral compounds for targeting Ebola. He is currently pursuing his doctoral studies at Heriot-Watt University under the supervision of Ai-Lan Lee and Samuel Drane (AstraZeneca), funded by an EPSRC/AstraZeneca Industrial CASE Award. His research interests focus on the development of direct C–H amidations of N-heterocycles via *decarboxylative radical formation.*

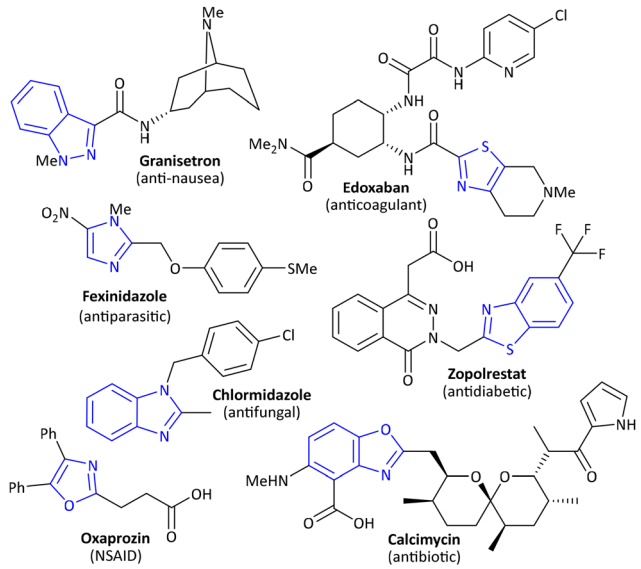
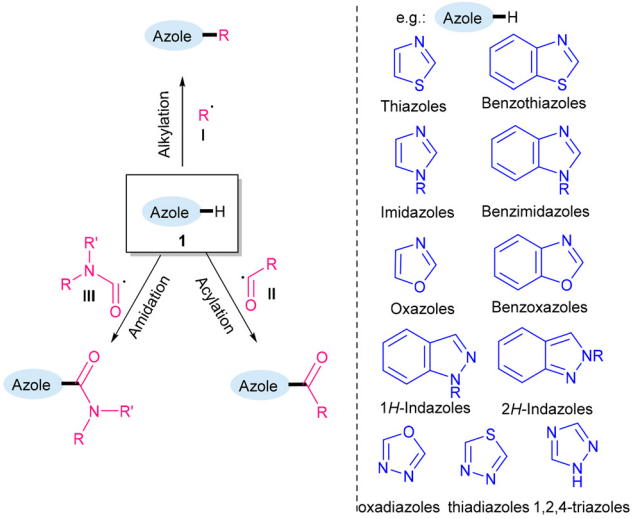


Fig. 1 Examples of pharmaceutical compounds with azole cores.



Scheme 1 Minisci-type C–H functionalisations of azoles.

establishing an efficient route to the late-stage functionalisation[3] of azoles would be highly desirable. Methods for direct C–H functionalisation of azoles would be ideal, as it allows for shorter, more efficient pathways and thus more cost-effective protocols.[4] The Minisci reaction is one such direct C–H functionalisation reaction which has sparked a resurgence of interest, given that it facilitates the nucleophilic attack of a carbon radical species (*e.g.*, **I–III**, Scheme 1) onto N-heterocyclic bases.[5]

So far, however, azoles have not been as widely studied as substrates for modern Minisci-type reactions, despite their aforementioned prevalence in medicinal chemistry. This is likely because azoles are more electron-rich and thus more challenging substrates compared to more typically studied electron-poor 6-membered N-heterocycles such as quinolines, pyrazines and pyridines.[6] Azoles are thus thought to be less reactive towards nucleophilic radical additions required in a typical Minisci-type reaction. Indeed, azole drug compounds are notably absent from a recent review summarising the list of pharmaceutical compounds that can undergo Minisci-type reactions.[5f] Nevertheless, the direct Minisci C–H functionalisation of azoles could potentially be a very powerful method for efficiently accessing decorated azole motifs. Therefore, the purpose of this review is to give an overview of Minisci-type C–H functionalisations of azoles (Scheme 1), with particular emphasis on recent advances, existing limitations and areas for further development.

Heather McKee

Heather received her MChem (Hons) in Chemistry from Heriot-Watt University in 2023, undertaking her MChem project under the supervision of Prof. Ai-Lan Lee, developing a light-mediated methodology for the direct C–H amidation of 1,3-azoles. A summer placement at the Institute of Cancer and Genetics, University of Edinburgh, fuelled her interest in medicinal chemistry further, and since graduating, Heather has entered the pharmaceutical industry and is a Development Chemist at Veranova (Macfarlan Smith).

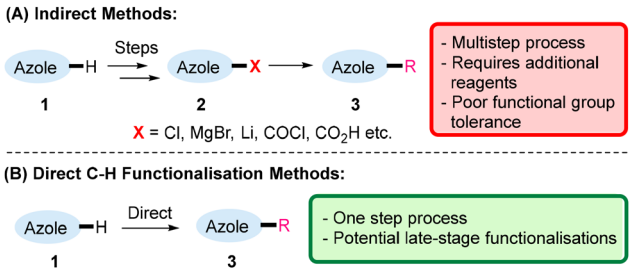
2. Azoles

2.1 Background and application

Azoles are classified as five-membered heterocyclic aromatic compounds which contain nitrogen and at least one other heteroatom and are common scaffolds in drug design.[2a] For example, imidazoles, thiazoles, tetrazoles, benzimidazoles, pyrazoles, 1,2,4-triazoles and isoxazoles are included in the top 25 most frequently used N-heterocycles in U.S. FDA-approved drugs.[2b,c,7] Thiazoles, imidazoles, tetrazoles and benzimidazoles also constitute four out of the top five most common five-membered aromatic nitrogen heterocycles in U.S. FDA approved drugs.[2b,c] In addition to the azoles listed above, 2,4,-dihydro-1,2,4-triazol-3-one, 1,3,4-thiadiazoles, indazoles, benzoindazoles, 1,2,3-triazoles and benzothiazoles also appear in the top 100 most frequently used ring systems in small-molecule drugs.[2c]

2.2 Routes to the functionalisation of azoles

Due to their importance as scaffolds in medicinal chemistry, methods for functionalising unactivated azole cores are crucial for transforming azole cores into pharmaceutically relevant compounds. Such functionalisations have classically pro-



Scheme 2 General indirect (A) and direct (B) methods for azole functionalisation.

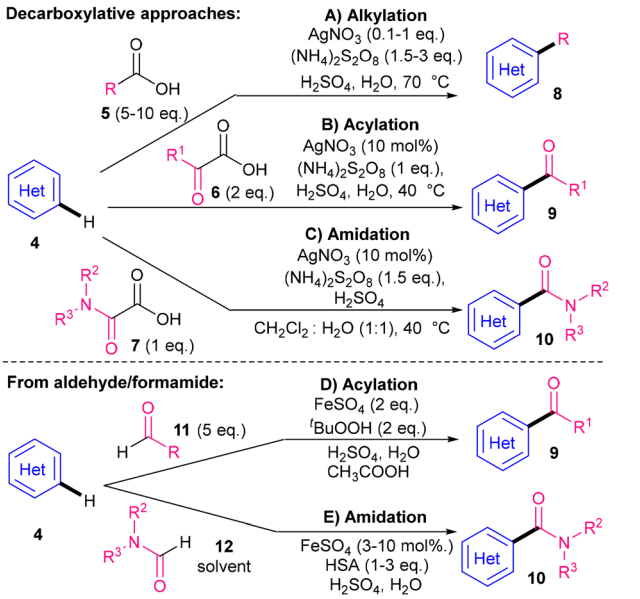
ceeded *via* indirect methods (**1** → **2** → **3**, Scheme 2A), whereby the installation of a functional group (X in **2**) is required.[8] For example, acylation of (benzo)thiazole motifs has been achieved through the use of Grignard reagents[9] and alkylations of imidazoles have been conducted *via* directed lithiations.[10] Nevertheless, there is clear inefficiency in synthetic pathways that require multiple steps and non-atom economical pre-functionalisations, and the use of strongly basic reagents such as Grignard reagents and lithiations can preclude late-stage functionalisations.

In contrast, direct C–H functionalisations (**1** → **3**, Scheme 2B) such as the Minisci-type reactions, occur in one step and can potentially be utilised for late-stage functionalisations.[5a–c,f] A brief overview of the classical Minisci reaction will be given in the next section (Section 3) before the review will focus on its main topic, the Minisci-type reactions of azoles (Section 4).

3. Classical Minisci reaction

In 1971, Minisci and co-workers demonstrated that alkyl carboxylic acids **5** can be used as cheap and readily available alkyl radical **I** precursors[11] for the C–H alkylation of N-heterocyclic bases **4**, using $AgNO_3$, $(NH_4)_2S_2O_8$ as an oxidant, and sulfuric acid to activate the N-heterocyclic base substrates (Scheme 3A).[12] C–H acylations soon followed, using α-keto acids[13] **6** as acyl radical **II** precursors (Scheme 3B),[14] although acylation can alternatively proceed *via* aldehydes **11** using iron(II) sulfate, *tert*-butylhydroperoxide, H_2SO_4 and acetic acid (Scheme 3D).[14,15] The carboxyamidation equivalent was not developed until the 1990s using oxamic acids **7**[16] as carbamoyl radical **III** precursors (Scheme 3C).[17] An earlier carboxyamidation method mediated by iron(II) sulfate and hydroxylamine *O*-sulfonic acid (HAS) in the presence of H_2SO_4 is less versatile, as it requires solvent quantities of formamide **12** as the radical precursor (Scheme 3E).[18] N-heterocycles **4** typically used in these early studies were pyridines, (iso)quinolines and pyrazines, although a study on one azole (benzothiazole) was carried out under the iron(II) sulfate-mediated conditions shown in Scheme 3D.[19]

There are, however, several apparent sustainability concerns with the classical Minisci conditions, including the reliance



Scheme 3 Minisci and co-workers' seminal results.

on substoichiometric amounts of expensive and non-sustainable silver,[20] the large excess of radical precursors (for **5**, **11** and **12**), some high temperatures and strong acid activators, which can limit the substrate scope.[21] Thus, many modern Minisci-type reactions have been developed in an attempt to overcome some of these limitations,[5a] and milder reaction conditions are also preferable for applications in late-stage C–H functionalisations.

The prevalence of azoles in pharmaceutical drugs is the reason for the focus on azoles in this review (Section 4).[7] This review will focus on publications published since 2012[22] and will cover only Minisci-type reactions of azoles (*i.e.*, nucleophilic radical additions onto azoles). Other methodologies for C–H functionalisation of azoles, such as transition metal cross-couplings,[23] as well as tri- and di-fluoromethylations are outside the scope of this review.[24]

4. Minisci reactions of azoles

Recent developments in various Minisci-type reactions initially focused on electron-poor six-membered N-heterocycles, typically incorporating only one or two azole moieties (if any) into the substrate scope.[5a] Optimisation studies were not typically carried out on azole substrates. It is only recently that more thorough investigations into Minisci reactions of azoles have been carried out, and more emphasis will be placed on these publications. This section will be divided into three major subsections: Minisci-type alkylations (Section 4.1), acylations (Section 4.2) and amidations (Section 4.3).

4.1 Minisci alkylation of azoles

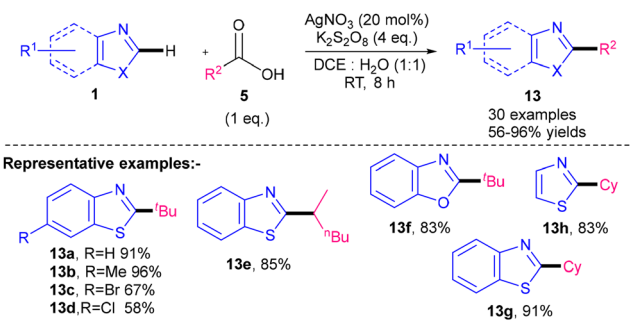
Minisci alkylations are by far the most studied of the three classes of functionalisations mentioned above, and many

groups who developed Minisci-type alkylation protocols may have included one azole (usually benzothiazole) in their substrate scope studies. This review will only cover selected seminal examples of those and will place more emphasis on Minisci alkylation studies that specifically focused on azole substrates.

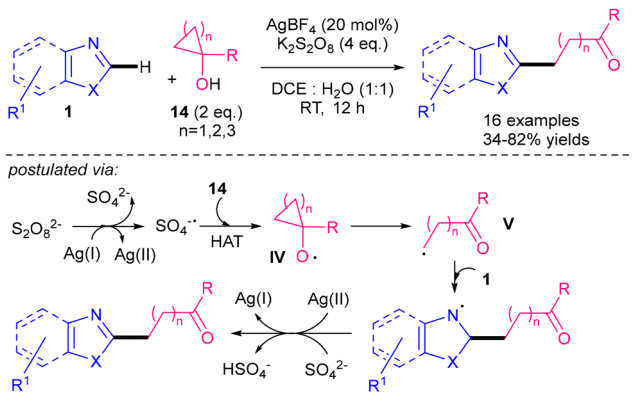
4.1.1 Metal-catalysed alkylations. With the notable success of silver- and iron-mediated protocols in Minisci's original procedures (Scheme 3), many research groups have naturally employed such protocols for the structural diversification of azoles.[5a] In 2014, Chen, Zhao and co-workers reported Minisci-type alkylations focused on azoles[25,26] *via* the silver-catalysed decarboxylation of carboxylic acids **5** using $K_2S_2O_8$, without the need for an acid activator (Scheme 4). The alkylation of benzothiazoles, thiazoles and benzoxazoles **1** occurred in generally good yields (56–96%) and showed a broad scope of secondary and tertiary alkylations. Azoles with electron-donating substituents (**13b**) tended to give better yields than those with electron-poor substituents (**13c–d**). Advantages include good yields and the use of readily available, inexpensive, stable and non-toxic carboxylic acids **5** as radical precursors. Nevertheless, limitations include high $AgNO_3$ loadings (20 mol%), the use of an environmentally hazardous solvent, dichloroethane (DCE), and unsuitability for primary alkylations.

An extension of this methodology was reported by Li's group in 2017, using cycloalkanols **14** as radical precursors (Scheme 5).[27] Their methodology was applicable to benzothiazoles, thiazoles and benzoxazole substrates. Hydrogen atom transfer (HAT) with cycloalkanol **14** followed by fragmentation of the subsequent alkoxy radical **IV** gives a primary C-centred radical nucleophile **V**, which adds to the azole substrates in the usual Minisci fashion (Scheme 5).

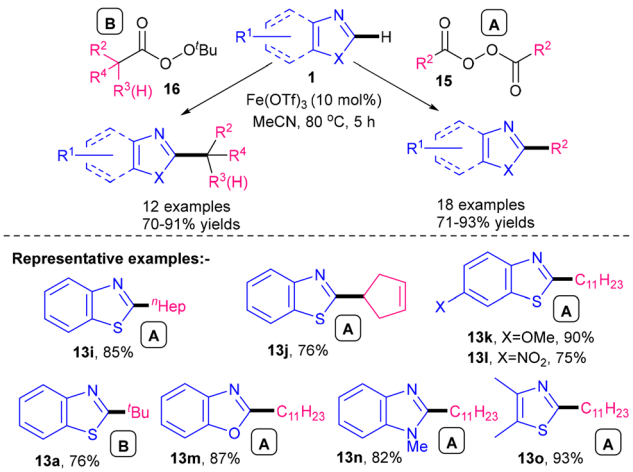
In 2017, iron catalysis was used to access primary, secondary and tertiary alkylations of azoles (Scheme 6).[28] Bao's group used diacyl peroxides **15** as acid precursors for primary and secondary alkylations whereas alkyl *tert*-butyl peresters **16** were employed for secondary and tertiary alkylations (*e.g.* **13a**, Scheme 6). The main azole investigated was benzothiazole, although two benzoxazoles (*e.g.* **13m**), one *N*-Me-benzimidazole (**13n**) and one thiazole (**13o**) also reacted well. Advantages of this protocol are the use of a cheaper and more sustainable



Scheme 4 Silver-catalysed alkylation of azoles.[25]



Scheme 5 Silver-catalysed alkylation of azoles using cycloalkanols.[27]

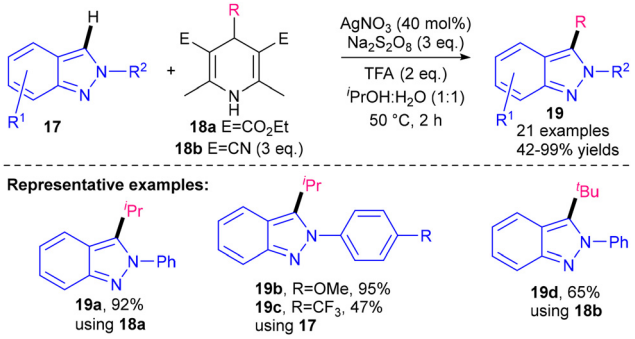


Scheme 6 Iron-catalysed alkylation of azoles.[28]

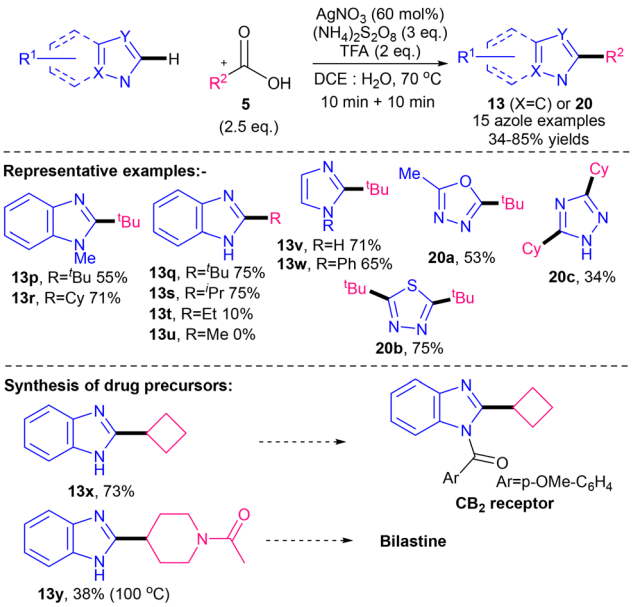
iron catalyst, good yields and a broad substrate scope. However, **15** and **16** are less accessible than their carboxylic acid counterparts **5** and the use of peroxides with heating may also pose safety concerns, especially on larger scales.

In 2020, the alkylation of 2*H*-indazoles **16** using alkyl-DHP reagents **18** as radical precursors was reported by the groups of Du and Tan (Scheme 7).[29] Their conditions were compatible with secondary alkylations (**19a–c**) and one example of a tertiary alkylation was also shown (**19d**). The short reaction times (2 h) are a highlight, although the use of alkyl-DHP **18** is less atom economical and not as readily available as using **5** directly (*e.g.* Scheme 4). The silver nitrate loading was relatively high at 40 mol%, and TFA was required to activate the indazole substrates.

Very recently, Ronchi and Bellina and co-workers disclosed a direct decarboxylative method for the alkylation of azoles using acids **5** (Scheme 8).[6] Unlike the work described in Scheme 4,[25] this work focused primarily on (benz)imidazoles, using sub-stoichiometric silver nitrate (60 mol%), ammonium persulfate as the oxidant, and crucially, various acid additives were screened to reveal TFA as optimal for activating the azole substrates.[6] While tertiary (**13p–q**) and secondary (**13r–s**) alky-



Scheme 7 Silver-catalysed acylation of 2*H*-indazoles.[29]



Scheme 8 Silver-mediated alkylation of azoles and its application to the synthesis of drug precursors.[6]

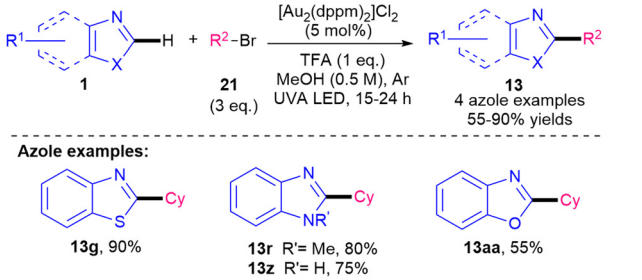
lations proceeded smoothly, primary alkylations were less successful (**13t–u**, 0–10%). The highlight of this work is that it is one of the very few examples to investigate azole substrates with three heteroatoms: oxadiazole (**20a**, 53%), thiadiazole (dialkylated, **20b**, 75%) and 1,2,4-triazole (dialkylated, **20c**, 34%). Crucially, two benzimidazole drug precursors were also successfully formed in one step from benzimidazole (**13x**, 73% and **13y**, 38%), showcasing the potential of the Minisci reaction for synthesis of azole drug molecules. Nevertheless, the conditions are still relatively demanding, using 60 mol% of the expensive and non-sustainable silver catalyst,[20] 70 °C and an acid additive.

4.1.2 Light-mediated alkylations. In recent years, many research groups have developed light-mediated methods for the alkylation of N-heteroarenes in order to render the reactions milder and reduce the reliance on sub-stoichiometric amounts of metal catalysts.

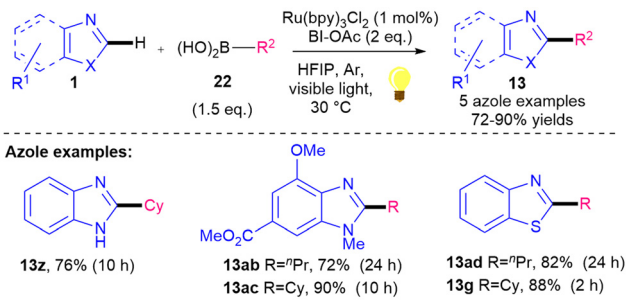
4.1.2.1 Transition metal photocatalysed alkylations. In 2016, Barriault and co-workers described a gold(I)-catalysed alkylation of N-heterocycles using alkyl bromides **21** (Scheme 9).[30,31] The study included 3 azoles: benzothiazole was the most reactive (**13g**, 90%), followed by benzimidazole (**13r**, **13z**, 75–80%) and benzoxazole (**13aa**, 55%). The methodology was pioneering; however, drawbacks include the use of an expensive gold catalyst and high energy UV irradiation.[32] Most of the subsequent light-mediated methodologies have moved towards visible light irradiation.

For example, in 2016 a Ru(II)-catalysed alkylation of N-heterocycles was reported by the groups of Liu and Chen, using primary and secondary alkyl boronic acids **22** as radical precursors (Scheme 10).[33] The key advancement here is the use of visible light irradiation, which does not require specialized setup and is more functional group tolerant compared to UVA irradiation.[32] The authors incorporated three benzimidazoles (**13z**, **13ab–ac**) and two benzothiazoles (**13ad** and **13g**) into the substrate scope, forming the desired products in good yields (72–90%). Advantages include good yields and low catalyst loading, although ruthenium has toxicity, cost and sustainability implications.[20] The use of costly 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) solvent also poses environmental and toxicity concerns.

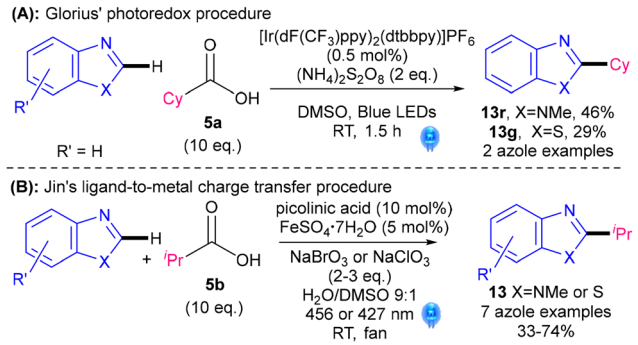
Ir-photocatalysed alkylations using carboxylic acids **5** by the group of Glorius (Scheme 11A)[34] have the advantages of wide availability, stability, non-toxicity and low cost of **5** compared to many other radical precursors.[11] The heteroaromatic scope included a benzimidazole (**13r**, 46%) and benzothiazole (**13g**, 29%). Limitations, however, include the use of a large excess



Scheme 9 Gold-photocatalysed alkylation (4 azole examples).[30]



Scheme 10 Ru-photocatalysed alkylation (5 azole examples).[33]



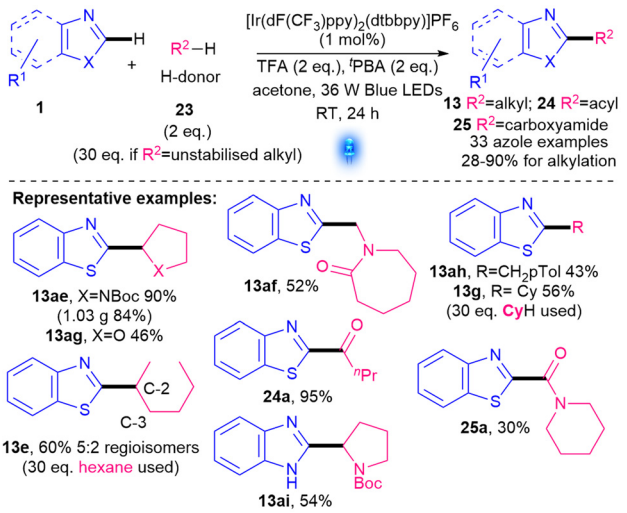
Scheme 11 (A) Ir- and (B) Fe-photocatalysed alkylation of N-heterocycles (2 and 7 azole examples).[34,36]

of radical precursor **4** (10 eq.), as well as the use of an expensive and non-sustainable[20] Ir photocatalyst (£858.50 per g).[35] In 2019, Jin and co-workers developed a cheaper iron-catalysed Minisci alkylation, utilising the ligand-to-metal charge transfer (LMCT) pathway of *in situ* formed iron carboxylate complexes (Scheme 11B).[36]

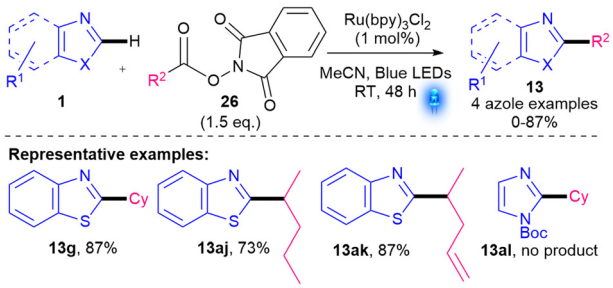
An Ir-photocatalysed methodology using radical precursors **23** and *tert*-butyl peracetate (^{t}PBA) as the oxidant was revealed by Wang's group in 2018 (Scheme 12).[37] Although the reaction was initially developed to achieve α-aminoalkylations (*e.g.* **13ae–af**), it was also found to work on other H donors **23**, such as ethers (*e.g.* **13ag**, 46%), aldehydes (to form acylation product **24a**, 95%), formamides (to form amidation product **25a**, 30%), *p*-xylene (**13ah**, 43%), and alkanes (*e.g.* **13g**, **13e** 56–60%). The main azole studied was benzothiazole (32 examples), although one benzimidazole also showed a decent yield (**13ai**, 54%). The key advantages are the atom-economical nature of **23**, the good substrate scope and mild conditions. Nevertheless, as the key radical R$^\bullet$ is formed *via* HAT, the reaction works best for stabilised R$^\bullet$ (α-to N/O, or benzylic). Unstabilised alkyls require a large excess of **23** (**13g**, **13e**) and can result in regioisomers (*e.g.* **13e**) unless symmetrical cyclic alkanes are utilised. The reaction also requires the use of expensive and non-sustainable[20] Ir photocatalysts, TFA as an acid activator and *tert*-butyl peracetate (^{t}PBA) as the oxidant.

In the same year, a Ru-photocatalysed methodology using *N*-hydroxyphthalimide esters (NHP-esters) **26** as radical precursors was developed by Opatz and co-workers (Scheme 13).[38] A highlight of their protocol is that further external oxidant is not required. Alkylation of benzothiazole proceeded smoothly (**13g**, **13aj–ak**); however, the reaction with Boc-protected imidazole yielded no desired product (**13al**). Only 1.5 eq. of NHP-ester **26** were required since **26** is more activated towards decarboxylation than acids **5**. However, NHP-esters **26** are less atom-economical and less accessible than **5** or **23**. Nevertheless, the yields with benzothiazole are good. Other potential limitations include the use of an expensive and non-sustainable Ru catalyst as well as extended reaction times (48 h).

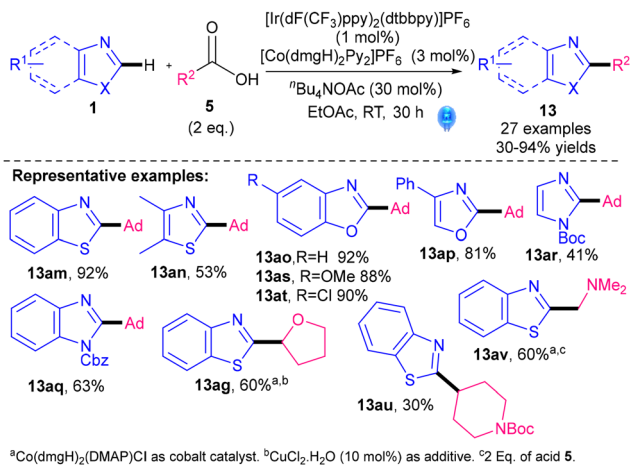
An alternative method which avoids the use of a stoichiometric oxidant was revealed by Li's group in 2019 (Scheme 14).[39] A cobalt co-catalyst $[Co(dmgH)_2Py_2]PF_6$ is used instead, and the base, $^nBu_4NOAc$, is only needed in sub-stoi-



Scheme 12 Ir-photocatalysed alkylation of azoles.[37]



Scheme 13 Ru-catalysed alkylation using NHP-esters (4 azole examples).[38]



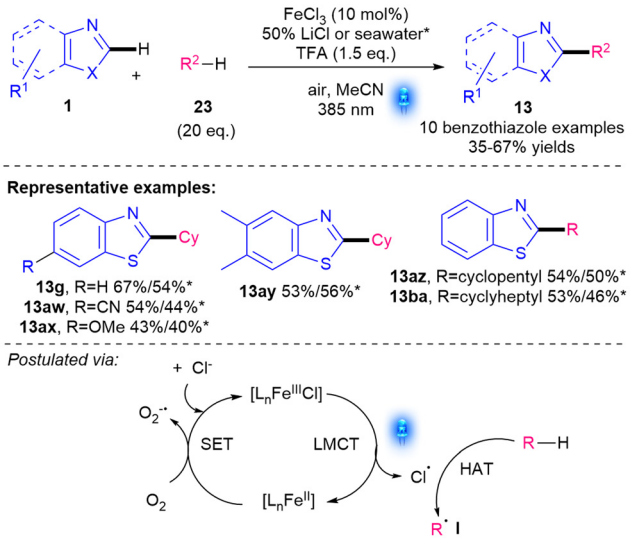
Scheme 14 Ir-photocatalysed alkylation of azoles with a Co co-catalyst.[39a]

chiometric amounts. The authors demonstrated perhaps the best 1,3-azole scope so far, with the whole range of 1,3-azoles: benzothiazole, thiazole, benzoxazole, oxazole, benzimidazole and imidazole all successfully C–H alkylated. Their procedure is best for tertiary alkylation (**13am–at**) and poor for unstabilised primary and secondary alkylations (**13au**). Primary and secondary alkylations where the radical is stabilised (α-to O/N, *e.g.* **13ag**, **13av**) worked well. Advantages of this methodology are the removal of a stoichiometric oxidant and the excellent 1,3-azole substrate scope. Nevertheless, the use of $[Co(dmgH)_2Py_2]PF_6$ introduces sustainability issues related to cobalt, along with the sustainability and cost issues already associated with Ir.[20]

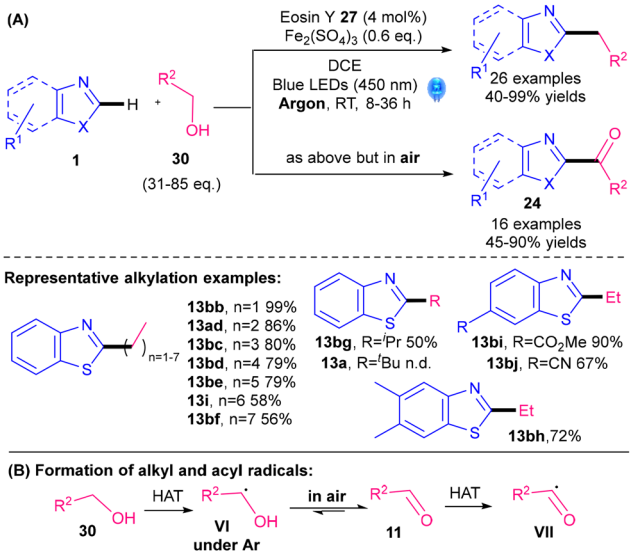
In 2023, chlorine radicals were used as an HAT reagent for alkanes **23** (Scheme 15).[40] The reaction developed by Jian, Tong and co-workers is catalysed by inexpensive $FeCl_3$, with either LiCl or seawater as an additive (and an extra Cl source in addition to $FeCl_3$), although yields are generally better with LiCl. As part of their substrate scope, eight different benzothiazoles were studied with three different alkanes **23**. While benzothiazole itself gave a decent 67% yield of **13g**, substituents on the benzothiazole core appear to cause a drop in yields (**13aw-ax**). Advantages of this method are the use of atom-economical alkanes **23** and a cheap $FeCl_3$ photocatalyst. Disadvantages, however, include the requirement of 20 eq. of radical precursor **23**, the use of symmetrical alkanes to avoid regioselectivity issues and generally moderate yields.

4.1.2.2 Organophotocatalysed alkylations. With the drive for greener chemistry, many research groups subsequently moved to organophotocatalysis instead of transition metal-based photocatalysis.

A noble-metal-free photocatalytic Minisci alkylation protocol for benzothiazoles was revealed by Jian and Tong's groups in 2022 (Scheme 16).[41] Readily available alcohols **30** are utilised as the radical precursors, with a cheap organic dye, Eosin



Scheme 15 Fe-photocatalysed alkylation of azoles.[40]



Scheme 16 Noble-metal-free photocatalytic alkylation of benzothiazoles.[41]

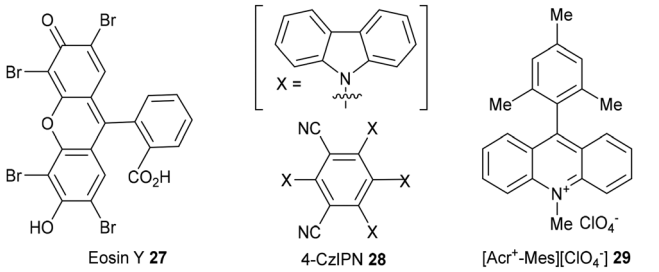
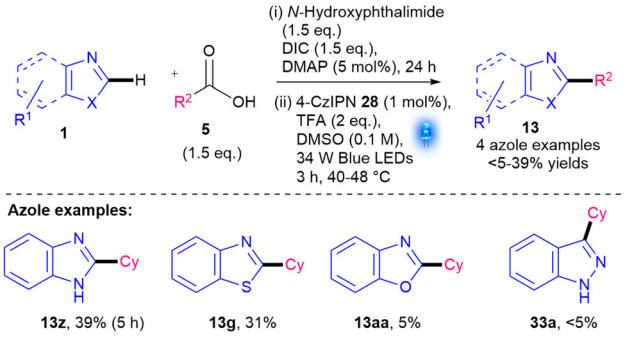


Fig. 2 Examples of organophotocatalysts.

Y **27** (Fig. 2), as the photocatalyst and $Fe_2(SO_4)_3$ as the Lewis acid. One of the interesting aspects of their protocol is that the reaction can be switched from alkylation if performed under argon to acylation if performed under air (Scheme 16A). Under argon, the reactive radical species is **VI** whereas in air, **VI** undergoes oxidation and HAT to give acyl radical **VII** (Scheme 16B). In contrast to examples using **5** as the radical precursor, their protocol works best for primary alkylations (**13bb–bf**, **13ad**, **13i**), is moderate for secondary alkylations (**13bg**) and does not work for tertiary alkylations (**13a**). The procedure is therefore very complementary to procedures using **5**. Nevertheless, one drawback is the need for a large excess of the alcohol reactant **30** (31–85 eq.).

Sherwood's group utilised 4-CzIPN **28** for alkylations, proceeding *via* the *in situ* formation of *N*-acyloxyphthalimide (NAPs) from the reaction of **5** with *N*-hydroxyphthalimide (Scheme 17).[42] Four azoles were studied as part of their substrate scope: alkylation of benzimidazole (**13z**, 39%) and benzothiazole (**13g**, 31%) were low yielding, and only trace amounts of alkylated benzoxazole (**13aa**) and 2*H*-indazoles (**33a**) were formed. Advantages include the use of an organophotocatalyst instead of a metal-catalyst and only 1.5 eq. of the

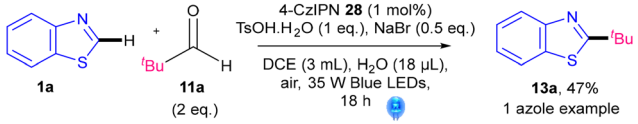


Scheme 17 4-CzIPN-Photocatalysed alkylation (4 azole examples).[42]

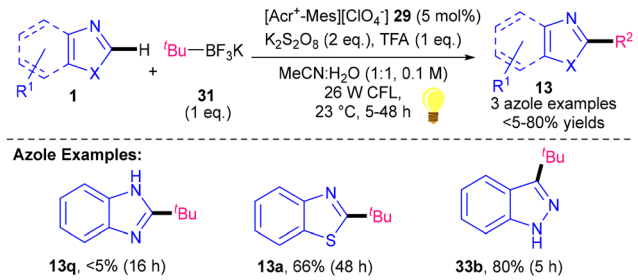
readily available acids **5**. The formation of activated NAPs *in situ*, however, reduces the atom economy and requires the use of toxic reagents including DIC and DMAP.

Ji, Zhao, Huang and co-workers later utilised 4-CzIPN **28** in the aerobic photocatalytic alkylation of N-heterocycles, *via* the decarbonylation of aldehyde precursors **11** (Scheme 18).[43] Only one azole (**1a**) was investigated, giving **13a** in a moderate 47% yield.

Despite 4-CzIPN **28** being a step in the right direction in terms of sustainability, it is currently very expensive, costing approximately £3596 per g.[35] Various research groups subsequently utilised the much cheaper (£62 per g)[35] Fukuzumi photocatalyst [Acr$^+$-Mes][ClO$_4^-$] (**29**, Fig. 2). Molander and co-workers utilised alkyltrifluoroborates **31** as radical precursors using photocatalyst **29** and $K_2S_2O_8$ as the oxidant (Scheme 19), obtaining yields ranging from <5% for benzimidazole to 80% for 1*H*-indazole (**13a**, **13q**, **33b**).[44] A very appealing feature is that the reaction relies on only one equivalent of **31**, albeit they are relatively expensive radical precursors compared to the more readily available acids **5** and aldehydes **11**.



Scheme 18 4-CzIPN-Photocatalysed alkylation (1 azole example).[43a]

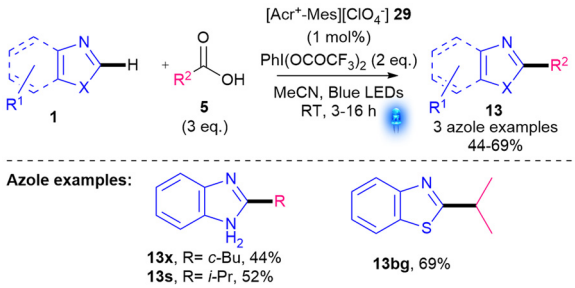


Scheme 19 Use of alkyltrifluoroborates for alkylations (3 azole examples).[44]

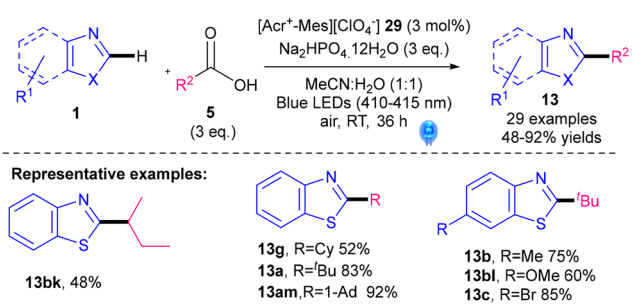
An alternative approach by Frenette's group makes use of acid precursors **5** in the [Acr$^+$-Mes][ClO$_4^-$]-catalysed alkylations with a hypervalent iodine reagent PhI(OCOCF$_3$)$_2$ as the oxidant (Scheme 20).[45] The scope included benzimidazoles and benzothiazoles, furnishing **13** in moderate yields (**13x**, **13s** and **13bg**, 44–69%). An advantage of the approach is that it uses only 1 mol% of photocatalyst. The use of acids **5** is also highly advantageous in terms of commercial availability, cost and atom economy,[11] especially since the equivalents of **5** are greatly reduced compared to previous methods.[34]

In 2019, Li, Wang and co-workers also utilised [Acr$^+$-Mes][ClO$_4^-$] **29** and acid precursors **5**, but this time the study was focused solely on benzothiazoles and the protocol used sustainable air as the oxidant (Scheme 21).[46] Alkylations proceeded in moderate to good yields (48–92%). The ambient reaction temperature and availability of reagents are highlights; however, the reaction time is relatively lengthy at 36 h. Tertiary carboxylic acids gave the respective alkylated products in excellent yields (**13a**, **13am**), secondary carboxylic acids in moderate yields (**13bk**, **13aj**, **13g**), while primary carboxylic acids did not react, reflecting the relative stabilities of the corresponding alkyl radicals.

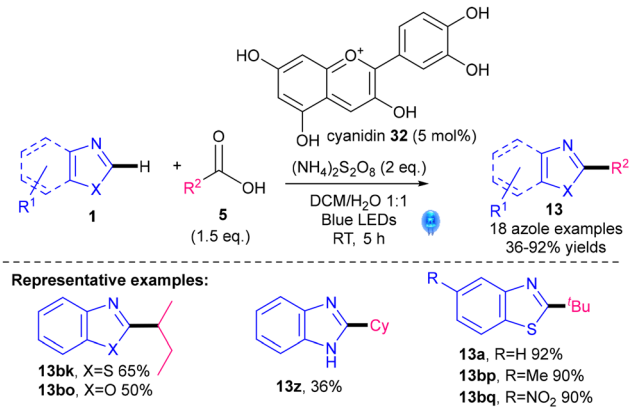
While **28** and **29** are well-known organophotocatalysts, other cheaper organophotocatalysts can also be utilised. In 2020, Chu, Sun and co-workers used the anthocyanidin pigment, cyanidin **32**, as a photocatalyst (Scheme 22).[47] Benzothiazoles seem to react better than benzoxazoles, which in turn perform better than benzimidazole (**13bk** 65% *vs.* **13bo** 50% *vs.* **13z** 36%). In terms of the alkylation scope, tertiary



Scheme 20 Organophotocatalysed alkylation (3 azole examples).[45]



Scheme 21 Alkylation of benzothiazoles using air as an oxidant.[46]

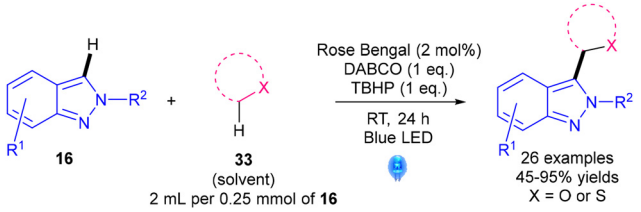


Scheme 22 Cyanidin-catalysed alkylation of (benzo)azoles.[47]

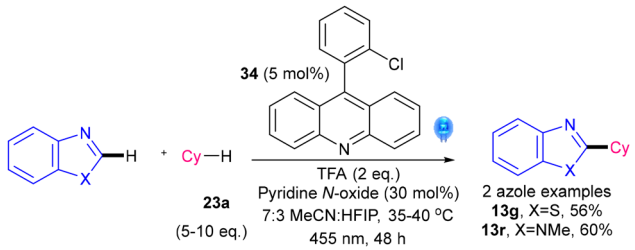
(**13a**) and secondary (**13bk**) alkylations were possible, but primary alkylation was not successful.

In 2019, Hajra's group reported on the etherification of 2*H*-indazoles **16** using a Minisci-like reaction (Scheme 23).[48] Advantages include the use of the cheap organic dye rose bengal as the catalyst; however, limitations include the large excess of ether precursor **33** required.

Very recently, a visible-light methodology that uses neutral 9-arylacridinium pre-catalyst **34** in the presence of TFA and pyridinium *N*-oxide to alkylate N-heterocycles, including 2 azoles, was revealed by Bosque and Gonzalez-Gomez's groups (Scheme 24).[49] The authors highlight that the methodology is free of chemical oxidants, metals or chlorinated solvents. Nevertheless, a perfluorinated solvent (HFIP) is required, and the reaction times are relatively long at 48 h.



Scheme 23 Rose bengal-photocatalysed etherification of 2*H*-indazoles.[48]



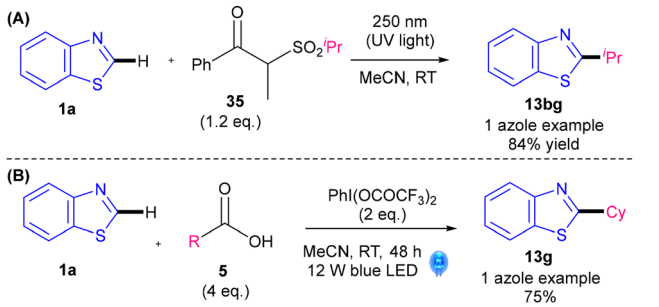
Scheme 24 Alkylations using a neutral 9-arylacridinium catalyst (2 azole examples).[49]

4.1.2.3 Photocatalyst-free light-mediated alkylations. In 2017, a UV light-mediated approach to functionalise various heteroaromatics, which included one azole alkylation, was reported by C.-J. Li's group (Scheme 25A).[50] Advantages include the discovery of an air- and water-stable sulfone compound **35** that can be cleaved under light irradiation without a photocatalyst. Disadvantages include the use of UV light and the relatively poor atom economy of **35**.

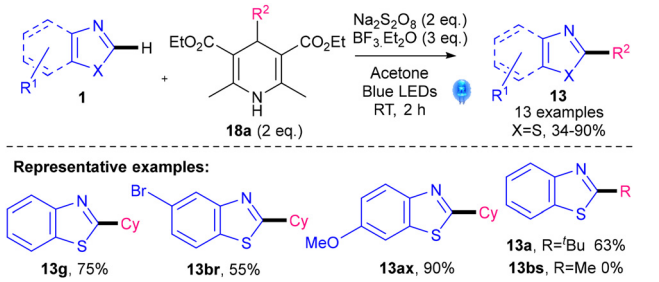
A year later, a photocatalyst-free visible light-mediated procedure was developed using 2 eq. of $PhI(OCOCF_3)_2$ (Scheme 25B).[51] Yang and Zhang's groups investigated only one azole (benzothiazole) as part of their substrate scope, and although the yield of **13g** was good (75%), the reaction time was much longer compared to other N-heterocyclic bases screened (48 h *vs.* 12 h).

In 2021, Tan and Du's groups devised a procedure focused specifically on benzothiazoles (Scheme 26).[52] The procedure requires only 2 eq. of DHP **18a** and $Na_2S_2O_8$, and it proceeds at RT in only 2 h. A Lewis acid additive was found to be essential. Tertiary (**13a**) and secondary (**13g**) alkylations were successful, but not primary alkylations (**13bs**). Although only 2 eq. of **18a** are required, a downside is that this radical precursor is neither atom-economical nor commercially available.

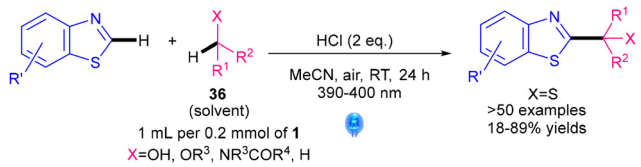
An alkylation of benzothiazoles with alcohols, ethers, lactams, amides and alkanes **36** using combined self-photoredox catalysis and HAT was reported by J. Li's group in 2022 (Scheme 27).[53] The authors consider the reaction *self-catalysed* due to the photosensitivity of benzothiazoles. As expected, benzimidazoles and benzoxazoles are not suitable substrates



Scheme 25 Photocatalyst-free (A) UV light-mediated alkylation (1 azole example)[50] and (B) $PhI(OCOCF_3)_2$-mediated alkylation (1 azole example).[51]



Scheme 26 Photocatalyst-free alkylation of benzothiazoles.[52]



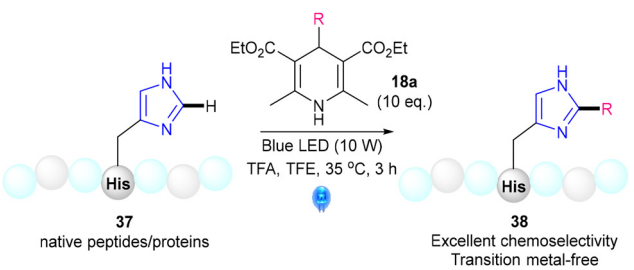
Scheme 27 "Self-catalysed" alkylation of benzothiazoles.[53]

as they are not photosensitive under visible light. Thiazole and 4,5-dimethylthiazole also failed to react. The advantages of this procedure are that it is metal- and photosensitiser-free; however, **36**, although atom economical in nature, has to be used in large excess. The self-catalysed nature of the procedure is a highlight, although it necessarily limits the procedure to azoles that are photosensitive under visible light (*i.e.* benzothiazoles).

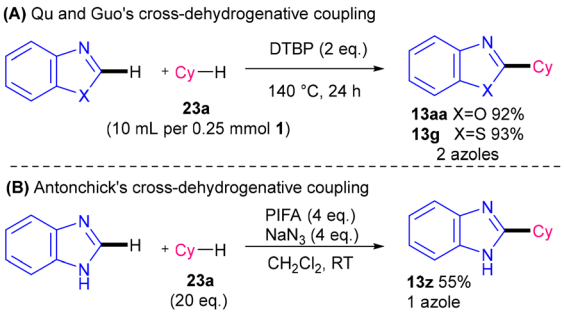
In 2019, the groups of Chen and Wang very elegantly showed the utility of visible light-mediated Minisci-type alkylation of azoles in their histidine-specific peptide modification (Scheme 28).[54] Since histidine carries an imidazole side chain, it allows for highly chemoselective alkylations onto the imidazole of histidine in native peptides/proteins **37**. This overcomes the previous limitations of histidine modifications, which relied on *N*-substitution reactions of the imidazole, thereby inherently suffering from interferences with cysteine and lysine residues. Additionally, the reaction is transition-metal-free and exhibits a broad scope for peptides **37** and DHP **18a**. DHP **18a** is thought to act as both the alkylating reagent and the oxidant. Their report very elegantly showcases the application of the Minisci reaction of azoles in chemical biology.

Despite the utility of light-mediated protocols for enabling milder reactions, one potential drawback is that batch scale-up can be problematic due to less permeating light irradiation.[55] Although continuous flow can sometimes address this issue,[55] the option of cheap and operationally simple procedures is also in demand. As such, several metal- and light-free Minisci alkylation procedures have been developed and will be the topic of the next section.

4.1.3 Metal- and light-free alkylations. Alkylation of purines was studied by Qu and Guo's groups in 2012,[56,57] and the substrate scope was extended to include two azoles under



Scheme 28 Minisci alkylation in histidine-specific peptide modification.[54]

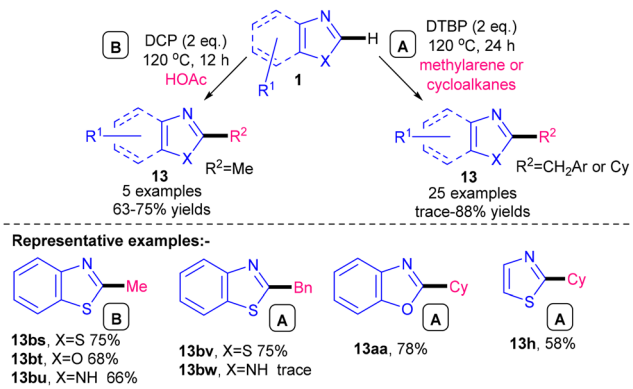


Scheme 29 (A) DTBP-[56] and (B) PIFA-mediated[58] metal-free alkylation of N-heterocycles (2 azole and 1 azole examples respectively).

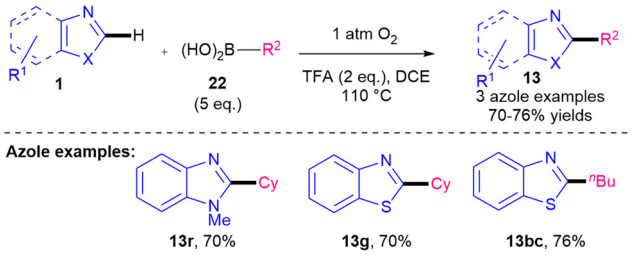
metal-free conditions (Scheme 29A). The reaction was performed using di-*tert*-butyl peroxide (DTBP) at 140 °C, which may potentially have safety concerns. Despite this, the reaction uses alkanes **23** which are atom economical, and excellent yields were obtained for the alkylation of both benzoxazole (**13aa**, 92%) and benzothiazole (**13g**, 93%). The reaction was however limited to symmetrical cycloalkanes due to selectivity reasons and **23** is used in large excess.

In 2013, hypervalent iodine PIFA was utilised in conjunction with NaN_3 for a much milder cross-dehydrogenative coupling (Scheme 29B).[58] Only one azole (benzimidazole) was included as part of Antonchick and co-workers' substrate scope (55%, **13z**). The reaction is mild, transition metal-free, and uses atom economical alkanes **23**. However, a large excess (20 eq.) of **23** is required and the reaction requires the use of toxic NaN_3.

A more azole specific study was carried out by Cai and co-workers in 2017, using oxidants DTBP or dicumyl peroxide (DCP) at 120 °C in a metal-free procedure (Scheme 30).[59] Alkylations with CH_2Ar and Cy were carried out using DTBP as the oxidant and methylarene or cyclohexyl respectively as the alkyl radical precursor, whereas methylation was carried out using DCP as the oxidant and acetic acid as the Me radical precursor (Scheme 31). The methylation was compatible with benzothiazole (**13bs**), benzoxazole (**13bt**) and benzimidazole



Scheme 30 DTBP- and DCP-mediated metal-free alkylation of azoles.[59]

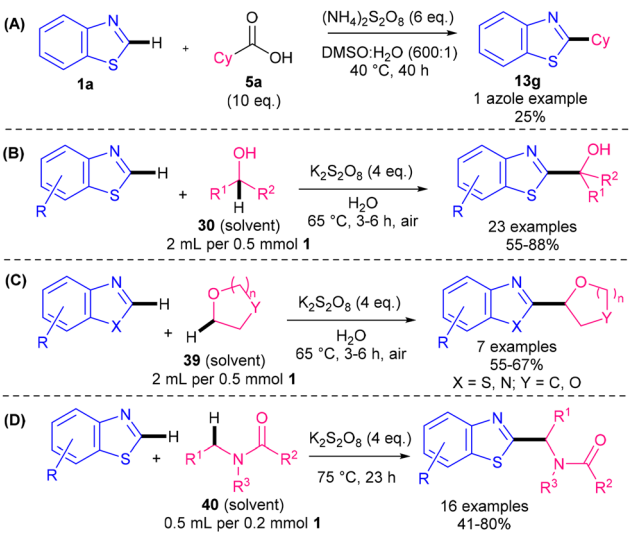


Scheme 31 Molecular oxygen-mediated alkylation (5 azole examples).[60]

(**13bu**) whereas the DTBP method was shown to be compatible with benzothiazole (**13bv**), benzoxazole (**13aa**) and thiazole (**13h**) but not with benzimidazole (**13bw**). Advantages of this method include a good azole substrate scope and the use of methylarenes and cycloalkanes as radical precursors, although they have to be used in solvent quantities. The alkylation scope is also limited to –Me, –Cy and –CH_2Ar groups and the use of peroxides at elevated temperatures may pose safety risks at larger scales.

In 2017, a molecular oxygen-mediated alkylation with boronic acids was developed by Liu and co-workers and 3 azoles were included in their substrate scope (Scheme 31).[60] The advantage of this procedure is the metal-free aspect and the use of O_2 as an oxidant; however, elevated temperatures (110 °C) are required, as well as 5 eq. of alkylboronic acids **22**, which are not as cheap or readily available as **5** or **23**.

In 2018, our research group devised a much milder (40 °C) metal- and light-free procedure for the alkylation of N-heterocycles (Scheme 32A).[61] Whilst good to excellent yields were obtained across a variety of N-heterocycles (50–91%), a much lower yield (25%) was presented for benzothiazole (**13g**). In 2019, Wang's group also revealed metal-free Minisci alkylations using $(NH_4)_2S_2O_8$ in DMSO, using α-ketoacids[62] or organosilanes[63] as radical precursors, which included 1–2 benzothiazoles in their substrate scope. Weng's group revealed a persulfate-mediated hydroxyalkylation of benzothiazoles in 2019, using alcohols **30** as radical precursors (Scheme 32B).[64] Ethers **39** were also suitable radical precursors (Scheme 32C). While alcohols and ethers are readily available, one disadvantage is that these radical precursors are used in large excess as solvents.



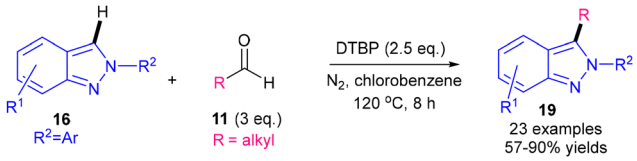
Scheme 32 Persulfate-mediated metal-free alkylations using: (A) carboxylic acids,[61] (B) alcohols,[64] (C) ethers[64] and (D) amides.[65]

It should be noted that in 2020 a similar reaction was reported using Selectfluor with light[66] and in 2024 Mantry and Gandeepan developed a related visible light-induced $PhI(OAc)_2$ mediated reaction.[67] An amidoalkylation of benzothiazoles was developed by Huang and Zhu's groups in 2016, again with the disadvantage that the radical precursor **40** is used as a solvent in large excess (Scheme 32D).[65] In 2019, Weng and co-workers used Eosin Y and visible light irradiation with $K_2S_2O_8$ to carry out a very similar reaction, but at room temperature.[68]

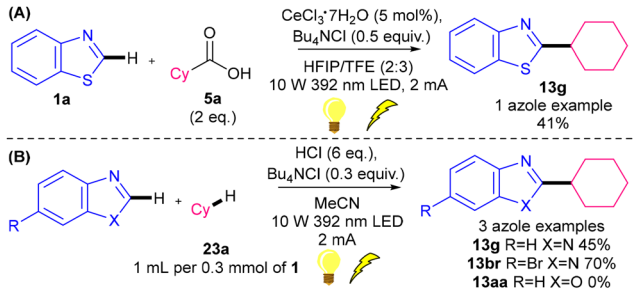
In 2022, a metal-free alkylation of 2*H*-indazoles **16** using aldehydes **11** as radical precursors and mediated by DTBP at 120 °C was revealed by Lin's group (Scheme 33).[69] Alkylation occurred when R^2 = alkyl and acylation occurred when R^2 = aryl (see Section 4.2.3), likely due to the reduced propensity for $R^2CO^{\bullet}$ to decarbonylate when R^2 = aryl. While the reaction is metal-free, heating a peroxide to 120 °C and the use of toxic chlorobenzene may pose safety issues on larger scales.

4.1.4 Electrochemical alkylations. Many of the initial developments on electrocatalytic Minisci-type alkylations utilised a combination of electrocatalysis and photocatalysis. For example, in 2019, Xu's group revealed an electrophotocatalytic alkylation using $^{i}PrBF_3K$ with a benzothiazole,[70] followed by a seminal paper on direct, decarboxylative C–H functionalisation of heteroarenes in 2020.[71] While C-radicals generated through electrochemical decarboxylations of acids **5** are notoriously prone to unwanted dimerisations[72] or overoxidation to carbocations,[72] the use of a dual electrocatalytic and photocatalytic methodology overcomes this problem. Thus, electrophotocatalysis was utilised to perform alkylations on a wide range of N-heterocycles including one azole **1a** (Scheme 34A), using a Ce catalyst. The main advantage of the electrophotocatalytic method is that it renders the reaction stoichiometric chemical oxidant-free. However, the bespoke reaction setup and expensive fluorinated solvents (HFIP/TFE) are potential limitations.

Xu's group followed up with an electrophotocatalytic methodology using atom economical alkanes **23** as radical precursors, employing chlorine radicals (generated from HCl) as a simple but effective HAT reagent for **23** (Scheme 34B).[73,74] The



Scheme 33 DTBP-mediated metal-free alkylation of 2*H*-indazoles.[69]

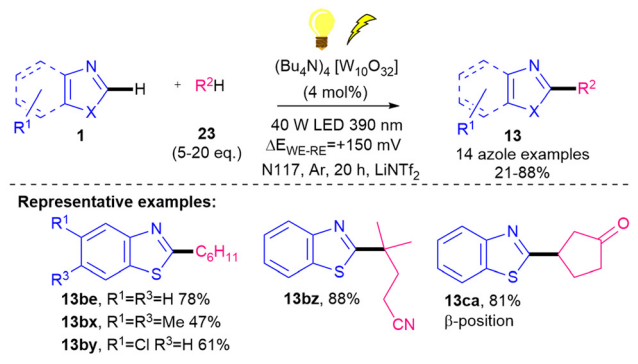


Scheme 34 Electrophotocatalytic alkylations (A) from carboxylic acids (1 azole example)[71] and (B) from alkanes (3 azole examples).[73]

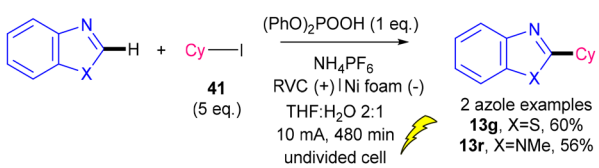
reaction worked well for benzothiazoles (**13g**, **13br**) but not for benzoxazole (**13aa**). As with many procedures using alkanes **23**, a large excess of **23** is required.

In 2021, an electrophotocatalytic Minisci alkylation of benzothiazoles using alkanes **23** as radical precursors was revealed by Ravelli's group (Scheme 35).[75] A stoichiometric oxidant is not required and TBADT was utilised in a threefold role: as the HAT photocatalyst to activate the sp^3 C–H bond of **23**, as a photoredox catalyst and as an electrocatalyst.[75] Various benzothiazole cores were successfully alkylated (**13be**, **13bx–ca**). While symmetrical alkanes **23** are usually relied on to avoid regioselectivity issues, Ravelli's results are notable for their selective functionalisation of isocapronitrile (**13bz**) and cyclopentanone (**13ca**) in good yields.

More recently in 2022, an electrochemical Minisci-type alkylation using alkyl iodides **41** was disclosed by the groups of Fernández-Salas and Alemán (Scheme 36).[76] Two azoles were investigated as part of their substrate scope studies: benzothiazole (**13g**) and benzimidazole (**13r**). Advantages include



Scheme 35 Electrophotocatalytic alkylation of benzothiazoles.[75]



Scheme 36 Electrocatalytic alkylation (2 azole examples).[76]

being free of stoichiometric chemical oxidants; however, alkyl iodides **41** are not as readily available or cheap as other commonly used radical precursors such as acids **5** or alkanes **23**.

Electrochemical and electrophotocatalytic Minisci reactions are clearly areas of recent development which allow the Minisci reaction to occur without stoichiometric chemical oxidants. The seminal reports were not necessarily developed for azole substrates, so the yields for the 1–2 azoles tested were not always good. Nevertheless, recent reports have started to focus more on azole substrates[75] and there will undoubtedly be further future developments in this area.

4.2 Minisci acylation of azoles

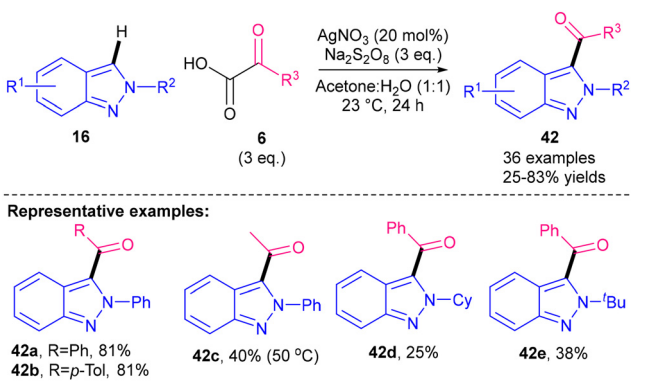
Minisci-type acylations of N-heterocycles are the second most studied reaction after alkylations. This section gives an overview of some of the methods available for Minisci acylation of azoles.

4.2.1 Metal-catalysed acylations. Unsurprisingly, the transition-metal catalysed Minisci-type acylations of azoles tend to be silver- or iron-catalysed, since these were very successful in Minisci's original methodologies (Scheme 3).

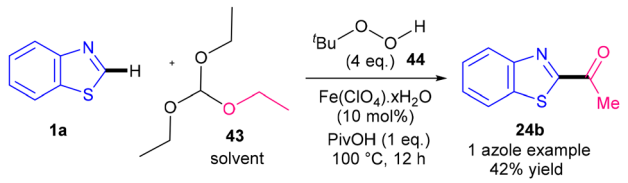
In 2018, Oh and co-workers reported a protocol for the acylation of 2-*H* indazoles **16** using α-keto acids[13,77] **6** as precursors for acyl radicals *via* silver- and persulfate-mediated decarboxylation (Scheme 37).[78] The reaction proceeded at mild RT, forming 3-acyl-2*H*-indazoles **42** in 25–83%. The use of 20 mol% $AgNO_3$, however, is a potential limitation in terms of sustainability and cost. The reaction was found to be compatible with phenyl-substituted α-keto acids **6** (R^3 = Ar, **42a–b**). Alkyl α-keto acids **6** (R^3 = alkyl), however, required higher temperatures of 50 °C, yet still achieved only 40% yield (**42c**). Moving from an *N*-2 phenyl substituent (**42a** 81%) to an *N*-2 alkyl substituent (**42d–e** 25–38%) also causes a drop in yield.

An alternative iron(II) catalysed acylation of N-heterocycles making use of triethyl orthoformate **43** and ^{t}BuOOH **44** was reported in 2019 by Reddy's group (Scheme 38).[79] Only one azole was investigated: benzothiazole **1a** to yield **24b** (42%). Triethylorthoformate **43** acts as both a substrate and solvent under their conditions.

Also in 2019, an iron-catalysed acylation of N-heterocycles using α-keto acids **6** as the acyl radical precursor was reported



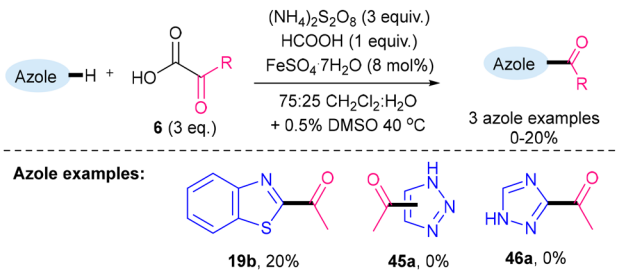
Scheme 37 Silver-catalysed acylation of 2*H*-indazoles.[78]



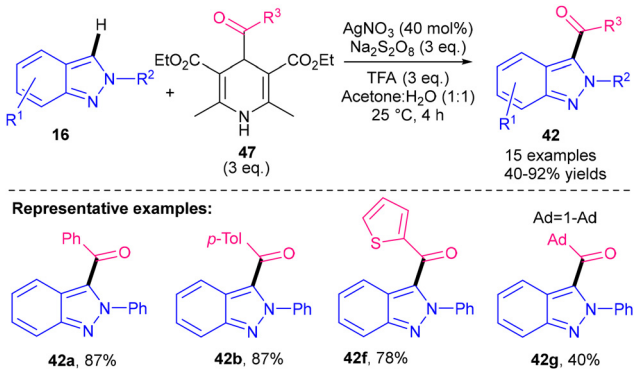
Scheme 38 Fe-catalysed acylation of N-heterocycles (1 azole example).[79]

by Zeng's group (Scheme 39).[80] The authors were able to render the classical Minisci reaction silver-free by instead utilising a much cheaper and more abundant iron catalyst. However, the methodology was not very successful with azoles. Three azoles were investigated as part of the scope: a benzothiazole (**19b**, 20%) and two triazoles which were both unsuccessful (**45a**, **46a**, Scheme 39).

In 2020, Du, Tan and co-workers reported the acylation of 2-*H* indazoles **16**, using acyl-DHP **47** as radical precursors (Scheme 40).[29] While the substrate scope was generally good, the reaction may not compare as favourably with the previously described methodology using α-keto acids **6** (Scheme 37),[78] since non-commercial and less atom-economical acyl-DHP **47**, higher $AgNO_3$ catalyst loadings (40 mol%) and the addition of TFA (3 eq.) are needed. Nevertheless, an advantage is that the reaction is more time efficient (4 h *vs.* 24 h).



Scheme 39 Fe-catalysed acylation (3 azole examples).[80]



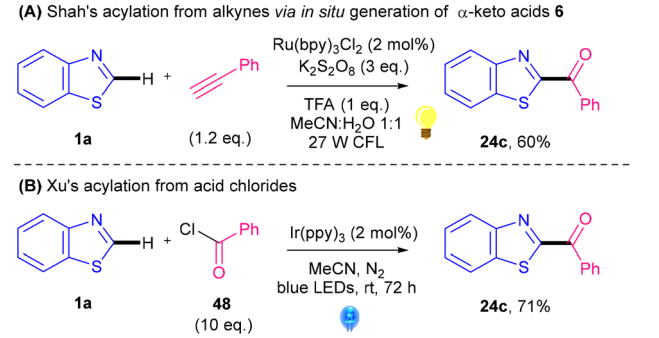
Scheme 40 Silver-catalysed acylation of 2*H*-indazoles.[29]

4.2.2 Light-mediated acylations

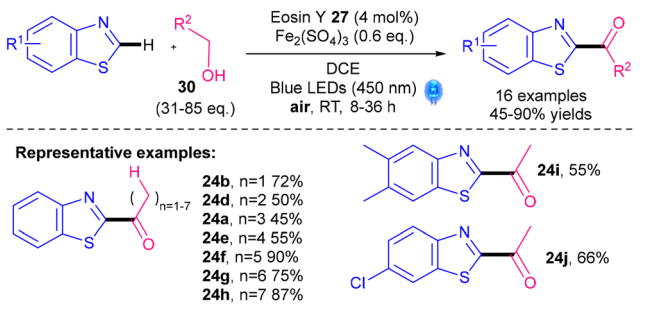
4.2.2.1 Photocatalysed acylations. In 2018, a $Ru(bpy)_3Cl_2$ photocatalysed acylation of N-heterocycles using $K_2S_2O_8$ as the oxidant and TFA as an acid activator was reported by Shah's group (Scheme 41A).[81] Interestingly, alkynes are used as the radical precursor *via in situ* generation of α-keto acid **6a**. Only one azole was studied as part of the general substrate scope (**24c**).

A year later, Xu and co-workers published a photocatalysed Minisci-type reaction of N-heteroarenes.[82] One example of an acylated benzothiazole (**24c**) was reported using acyl chloride **48** as the radical precursor (Scheme 41B). While this method is milder than the classical silver catalysed Minisci-type acylations, silver has now been replaced by a more expensive iridium catalyst.[20] Other limitations include extended reaction times and the use of 10 eq. of acid chloride **48**.

As discussed in Section 4.1.2, a noble-metal-free photocatalytic protocol was developed for benzothiazoles by Jian and Tong's groups (Scheme 16).[41] The reaction can be switched from alkylation (under Ar) to acylation (under air, Scheme 42). One big advantage is that the acylation scope is complementary to the corresponding reactions using α-keto acids **6** or activated ester derivatives; the latter tends to work best with aromatic acyls and poorly or not at all with aliphatic acyls. The method in Scheme 42, in contrast, works well with aliphatic acyls (*e.g.* **24ab,d–h**). A drawback, however, is the need for a large excess of the alcohol reactant **30** (31–85 eq.).



Scheme 41 (A) Ru-[81] and (B) Ir-catalysed[82] acylations (1 azole example).

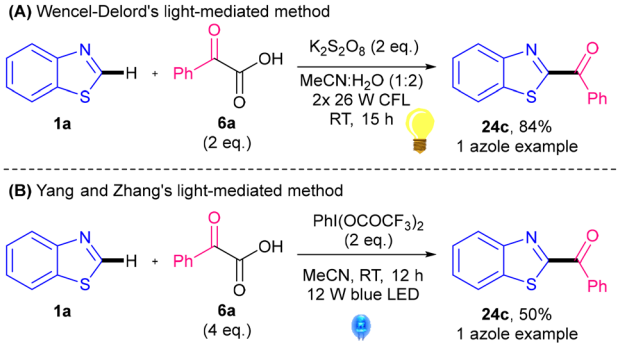


Scheme 42 Noble-metal-free photocatalytic acylation of benzothiazoles.[41]

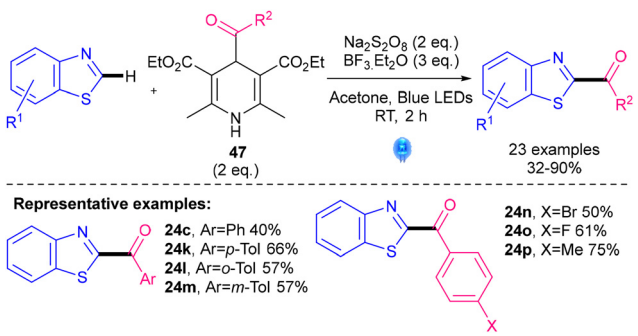
4.2.2.2 Photocatalyst-free light-mediated acylations. In 2018, a seminal persulfate- and visible light-mediated acylation of N-heterocycles was developed by Wencel-Delord's group, using α-keto acid **6** without the need for a photocatalyst (Scheme 43A).[83] The heterocyclic scope included 1 azole: benzothiazole **1a** (84% **24c**). In the same year, Zhang's group independently reported a procedure using hypervalent iodine(III) reagent $PhI(OCOCF_3)_2$ (Scheme 43B, 50% **24c**).[51] Both methodologies have the advantage of not requiring a photocatalyst; however, $PhI(OCOCF_3)_2$ is less economical than persulfate.

In 2021, an alternative light-mediated route to acylation was devised by Tan and Du's groups, focusing on benzothiazoles (Scheme 44).[52] The reaction uses DHP **47** as radical precursors, synthesised from their parent glyoxal hydrates. The optimised conditions rely on only 2 equiv. of DHP **47** and $Na_2S_2O_8$ as the oxidant and a Lewis acid additive. One downside is the non-atom-economical nature of the DHP radical precursor **47** and the fact that it is not commercially available.

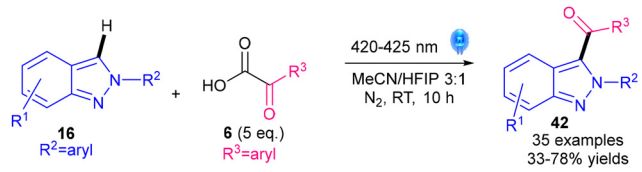
Very recently in 2024, a metal-, photocatalyst- and oxidant-free methodology for the acylation of 2*H*-indazoles **16** was reported by the groups of Cao, Li and Shen (Scheme 45).[84] They propose that **16** absorbs visible light to form its excited state **16***, which then undergoes energy transfer to α-ketoacid **6**, with the excited **6*** subsequently homolyzing to form the key acyl radical **II**. The protocol may therefore be specific to visible light-absorbing 2*H*-indazole substrates **16**. However, their UV-vis studies show that **16** does not absorb visible light, which somewhat contradicts the proposed mechanism. Nevertheless, advantages include not requiring metals, photocatalysts or oxidants, but the use of costly and toxic HFIP solvent could be a disadvantage.



Scheme 43 (A) Persulfate-[83] and (B) PIFA-mediated[51] light-mediated acylation (1 azole example).



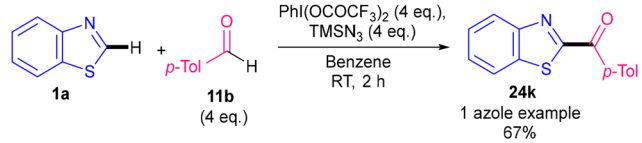
Scheme 44 Acylation of benzothiazoles using DHP.[52]



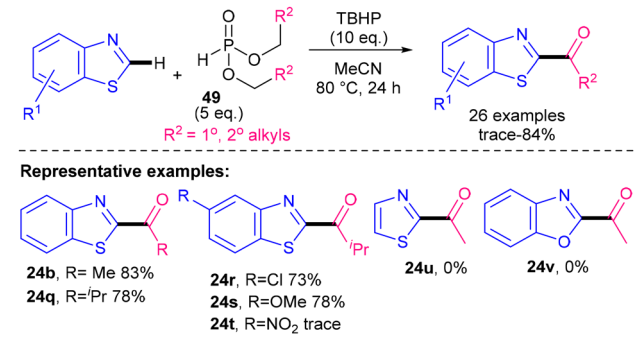
Scheme 45 Photocatalyst- and oxidant-free acylation of 2*H*-indazoles.[84]

4.2.3 Metal- and light-free acylations. In 2013, Antonchick's group proposed a facile method for the cross-dehydrogenative coupling of aldehydes and N-heterocycles (Scheme 46).[85] Only one azole was studied as part of the substrate scope: benzothiazole **1a** (67% **24k**). Advantages include the use of atom economical aldehydes **11** and mild reaction temperatures, although toxic $TMSN_3$, as well as carcinogenic benzene, is used.

In 2014, a metal-free method for acylating benzothiazoles using *H*-dialkyl phosphonates **49** was disclosed by Chen and Qu's groups (Scheme 47).[86] Benzothiazoles were successfully acylated (**24b**, **24q–s**). The authors also investigated thiazole and benzoxazole, but both failed to produce any acylated products (**24u**, **24v**). One of the key advantages of their method is that it has a good substrate scope for aliphatic acyls, particularly given that most Minisci acylation methodologies tend to focus on aroylations. Nevertheless, limit-



Scheme 46 PIFA-mediated acylation of benzothiazole.[85]



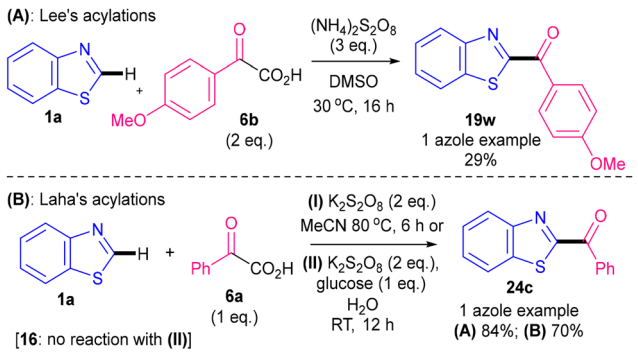
Scheme 47 Metal-free acylation using *H*-dialkyl phosphonates.[86]

ations include the acute toxicity of TBHP, the safety implications of heating TBHP to elevated temperatures (especially at larger scales) and the non-atom-economical nature of radical precursor **49**.

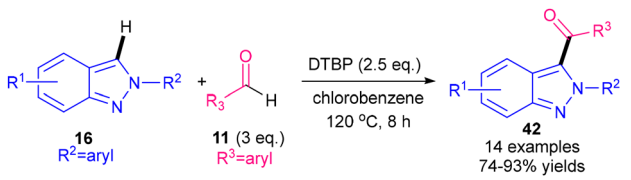
Our group developed a metal- and light-free method for direct C–H acylations of N-heterocycles in 2019,[87] optimised for (iso)quinolines, where yields were up to 98%. Only one azole was investigated: benzothiazole **1a**, which gave a poor yield of 29% for **24w** (Scheme 48A). In 2020, Laha's group developed a persulfate-mediated methodology for the acylation of electron-rich pyrroles,[88] and included one azole as part of their substrate scope study (**24c**, Scheme 48BI).

Two years later, Laha's group disclosed a procedure using glucose to activate the persulfate and break it down to the key sulfate radical anion at RT in water, thereby avoiding the need for high temperatures, UV light or metals (Scheme 48BII).[89] Two azoles were investigated: benzothiazole worked well (**24c**) but indazole **16** failed to undergo acylation. This methodology looks promising as the reaction is mild and a green solvent is used. Nevertheless, more studies are needed on azole motifs to ascertain whether the methodology is applicable to other azoles apart from benzothiazole.

In 2022, a metal-free acylation of 2*H*-indazoles **16** using aldehydes **11** as radical precursors and mediated by DTBP at 120 °C was revealed by Lin's group (Scheme 49).[69] Acylation occurred when R^2 = aryl (and alkylation occurred when R^2 = alkyl, see Section 4.1.3). Advantages include being metal-free, although the heating of a peroxide to 120 °C and the use of toxic chlorobenzene may pose safety issues on larger scales.



Scheme 48 Persulfate-mediated acylations by (A): Lee[87] and (B): Laha's groups.[88,89]



Scheme 49 Metal-free acylation of 2*H*-indazoles.[69]

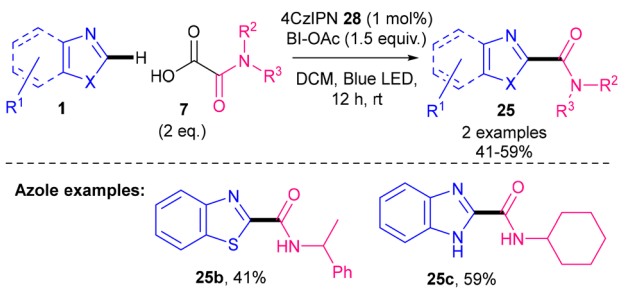
4.3 Minisci amidations of azoles

Minisci amidations of azoles are far less studied than alkylations and acylations; however, some recent studies have significantly expanded the scope of azoles that can be successfully amidated *via* Minisci-type reactions.

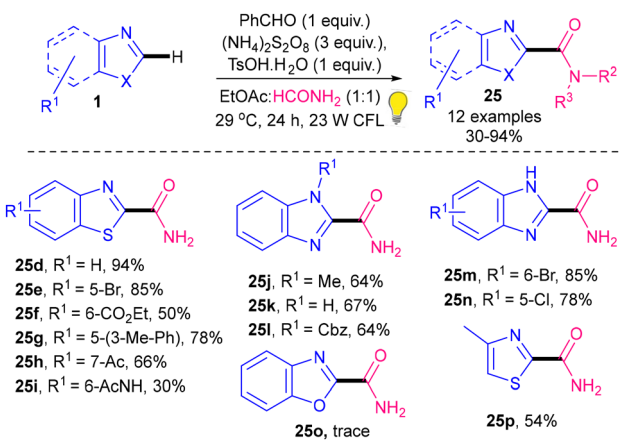
4.3.1 Light-mediated amidations

4.3.1.1 Photocatalysed amidations. In 2019, an amidation of N-heterocycles *via* a photocatalytic Minisci-type reaction using 4-CzIPN **28** as a photocatalyst was reported by Landais (Scheme 50).[90] Although a wide substrate scope was demonstrated, only two azoles were studied to give **25b** and **25c** in moderate yields of 41% and 59% respectively. The reaction is metal-free, very mild and is complete in 12 h at RT. Nevertheless, the 4-CzIPN **28** catalyst is currently very expensive commercially (£3596 per g).[35]

4.3.1.2 Photocatalyst-free light-mediated amidations. In 2016, a visible light-mediated Minisci-type amidation of azoles, using stoichiometric benzaldehyde as a photosensitiser, was published by Ji's group (Scheme 51).[91] Benzothiazoles (**25d–i**, 6 examples) and benzimidazoles (**25j–n**, 5 examples) were studied in more detail but one thiazole (**25p**) was also shown to be compatible. An attempt to functionalise benzoxazoles, though, was not successful (**25o**). The reaction has the advantage of proceeding at a mild temperature (29 °C). One limitation, however, is that only functionalisation with primary



Scheme 50 Photocatalysed azole amidation (2 azole examples).[90]

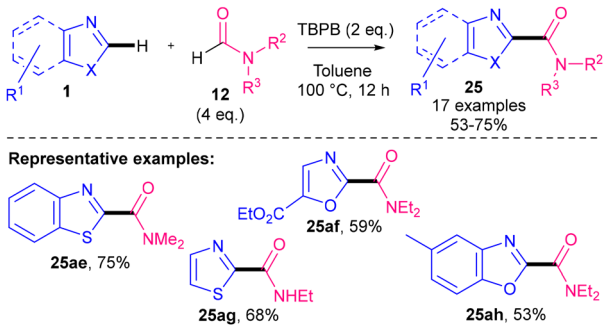


Scheme 51 Light-mediated amidation using formamide.[91]

amides was possible and formamide was used in solvent quantities.

We recently developed one thermal methodology (Conditions A) and one photosensitiser-free, light-mediated methodology (Conditions B) for direct Minisci-type C–H amidation of 1,3-azoles (Scheme 52).[92] The reaction was applicable to the four most important 1,3-azoles in medicinal chemistry: thiazoles (**25t–y**), benzothiazoles (**25s**), benzimidazoles (**25r**) and imidazoles (**25q**). Both conditions worked well, although Conditions A were more amenable to batch scale-up (**25s**, 81% g scale) and the milder and more efficient Conditions B were more functional group tolerant (**25u**). A wide variety of primary (**25w**), secondary (**25x**) and tertiary (**25y**) amides were successfully installed onto all four 1,3-azole classes investigated. It is of note that the reaction concentration had to be optimised separately for each azole class in order to achieve good yields. Late-stage C–H amidation of 1,3-azole-based drug molecules was successfully demonstrated (*e.g.* **25z–25aa**),[92] highlighting the application of this methodology.

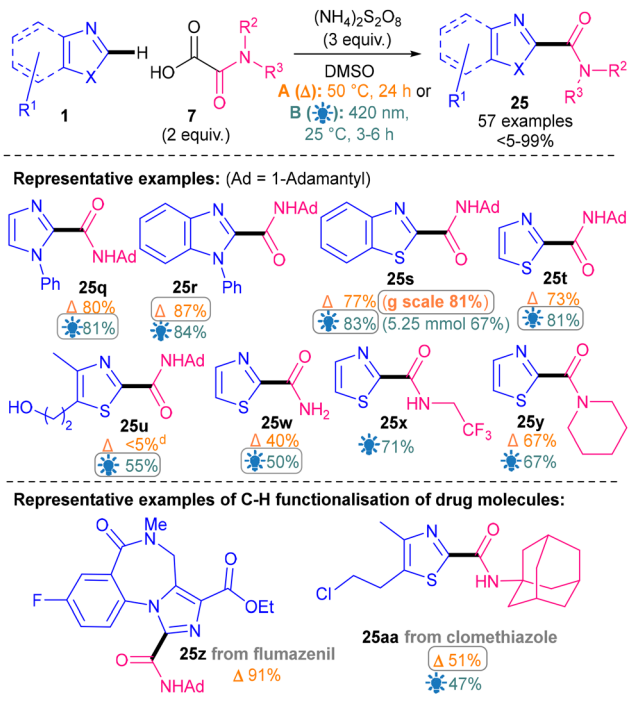
4.3.2 Metal- and light-free amidations. In 2011, Wang and co-workers demonstrated carboxyamidation of azoles using formamide **12** as a radical precursor and *tert*-butyl perbenzoate (TBPB) as an oxidant (Scheme 53).[93] The reaction was amenable to benzothiazole, thiazole, benzoxazole and oxazole moieties, achieving desirable yields of 53–75% (**25ae–ah**). A diverse selection of secondary and tertiary amidations was successful with benzoxazole. Nevertheless, high temperatures (100 °C) were required in the presence of a peroxide.



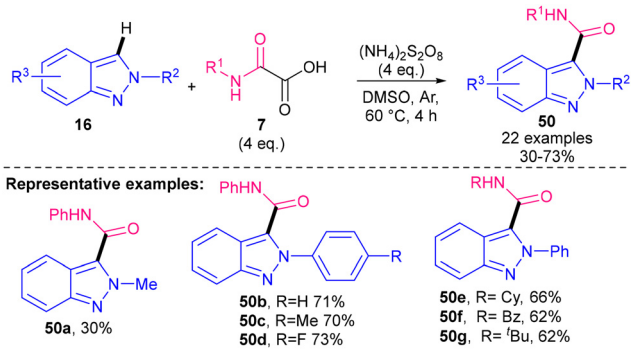
Scheme 53 Amidation of azoles using formamides.[93]

In 2021, a metal- and light-free protocol for the amidation of 2*H*-indazoles was reported by Bhat and Lee (Scheme 54).[94] The thermally mediated reaction utilises oxamic acid **7** as the carbamoyl precursor and ammonium persulfate as the oxidant at 60 °C. Advantages include a short reaction time, the absence of metals and efficient scalability to a 1 g scale. Various electron-withdrawing and -donating substituents were tolerated on the *N*2-phenyl ring (**56c–d**) but only secondary amidations were reported (*e.g.* **56e–g**). In 2022, Zhang and Jiang developed a photocatalysed version of the same transformation, using 4-CzIPN **28** as the photocatalyst.[95]

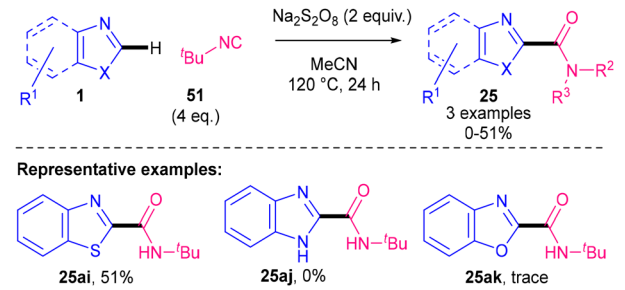
Li and co-workers published an amidation of N-heterocycles in 2021, this time *via* isocyanide (Scheme 55).[96] Benzothiazole was included in their substrate scope (**25ai**),



Scheme 52 Thermal- and light-mediated amidation of 1,3-azoles and its application to the C–H functionalisation of drug molecules.[92]



Scheme 54 Amidation of 2*H*-indazoles.[94]

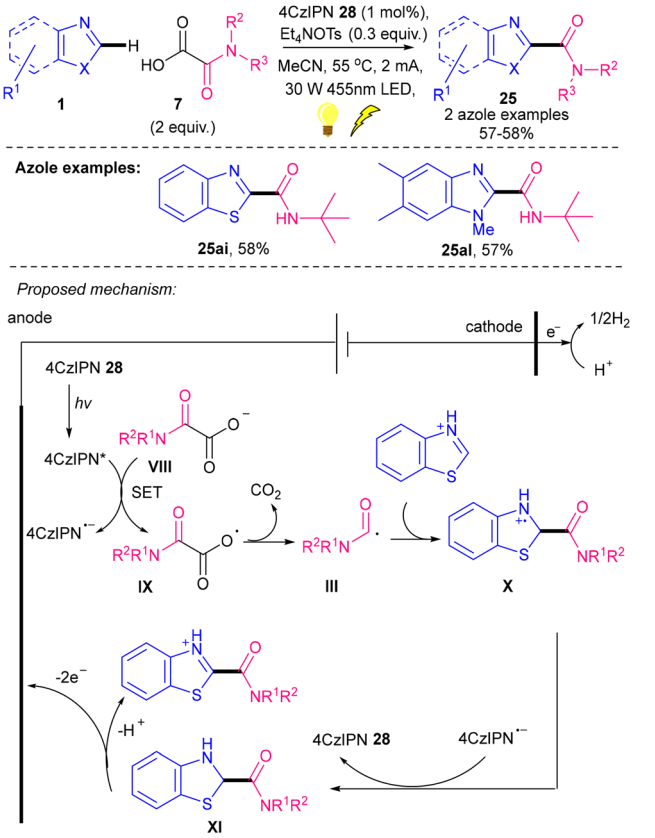


Scheme 55 Amidation using isocyanide (3 azole examples).[96]

along with benzimidazole and benzoxazole, although the latter two were not suitable substrates (**25aj–ak**). The major drawback of this chemistry is the elevated temperature (120 °C), which will likely preclude it from being applicable to late-stage functionalisations.

Our research group also developed metal- and light-free amidations of azoles which are already discussed in Scheme 52.[92]

4.3.3 Electrophotocatalytic amidations. In 2020, Xu's group revealed a dual electrocatalytic and photocatalytic methodology to perform amidations on a wide range of N-heterocycles (Scheme 56),[71] including two azoles: benzothiazole (**25ai**, 58%) and 1,5,6-trimethyl-1*H*-benzo[*d*]imidazole (**25al**, 57%). The excited 4-CzIPN photocatalyst oxidises oxamate **VIII** *via* SET to afford **IX**, which subsequently decarboxylates to give the key nucleophilic carbamoyl radical **III**. Radical **III** then attacks the protonated N-heterocycle to afford intermediate **X**. In a conventional photocatalytic Minisci-type reaction, intermediate **X** would subsequently be oxidised *via* a HAT/SET, followed by deprotonation to afford the product. However, in this case, in the absence of a chemical oxidant, intermediate **X** accepts an electron from the highly persistent 4CzIPN$^{\bullet-}$ radical anion formed in the reaction to give intermediate **XI**. Finally, intermediate **XI** is oxidised by the anode to afford the protonated product. In addition to being very mild, unlike most other Minisci methods, this protocol is free from stoichiometric chemical oxidants. However, the reaction setup is bespoke and the organophotocatalyst used (4-CzIPN **28**) is currently very expensive commercially.[35] As a way of addressing these issues, Hou and Wang's groups very recently developed an electrophotocatalytic C–H amidation of heteroarenes (15 benzothiazole examples, trace-86%) using formamides **12** instead of **7** as radical precursors and using the cheaper 9,10-phenanthrenequinone (10 mol%) as the photocatalyst.[97]



Scheme 56 Electrophotocatalytic amidation (2 azole examples).[71]

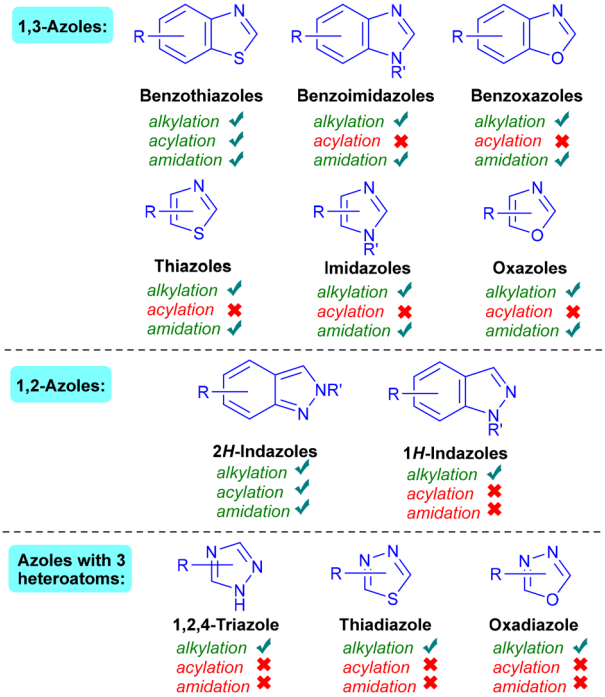


Fig. 3 List of azoles that have been successfully C–H functionalised *via* the Minisci reaction.

5. Conclusion and outlook

Whilst the pivotal work of Minisci and co-workers laid the foundations, growing sustainability concerns as well as the drive towards milder reaction conditions have resulted in multiple developments in the Minisci reaction. For example, there has been a push to replace costly and non-sustainable silver[20] with metal-free procedures. Many visible-light-mediated methodologies have also been developed to render Minisci-type reactions milder, with the initial use of expensive and non-sustainable[20] Ir and Ru photocatalysts being subsequently overtaken by a variety of organophotocatalytic and photocatalyst-free protocols. Stoichiometric oxidant-free procedures have also been revealed, such as the use of electrophotocatalytic methods, although these are in their early stages of development. Nevertheless, it is clear that there is a consistent move towards developing metal-free, milder and more sustainable protocols for Minisci-type reactions.

A review of the literature reveals 1,3-azoles (benzothiazoles, benzimidazoles, benzofurans, thiazoles, imidazoles and oxazoles) to be the most explored azole substrates for Minisci-type reactions (Fig. 3). Minisci-type C–H functionalisations of benzothiazoles, in particular, have been very well studied. Conversely, only one class of 1,2-azoles (indazoles) has been routinely investigated, leaving plenty of room for further developments with other 1,2-azole motifs. To the best of our knowledge, there are very few reports of successful Minisci-type C–H functionalisation of azoles with three heteroatoms. Promisingly, a handful of initial successful reactions with these motifs[6] hint at potential future opportunities. Since isoxazoles, triazoles and thiadiazoles are important motifs in medicinal chemistry,[2b,c,7] a future challenge would be the successful Minisci direct C–H functionalisations of these motifs under mild and sustainable conditions.

The vast majority of Minisci reactions of azoles focus on alkylations and acylations, with fewer publications focusing on amidations. Nevertheless, it is in fact acylations that currently exhibit the poorest azole substrate scope (Fig. 3), with successful reports on only benzothiazoles and indazoles. This is likely the result of acyl radicals being less nucleophilic than carbamoyl or alkyl radicals.[94] As such, there is potential for further developments, particularly with respect to the lesser-studied azole cores such as triazoles, thiadiazoles and oxadiazoles, as well as acylations of azoles other than benzothiazoles and indazoles. It is also evident that successful Minisci C–H functionalisations of azoles often require specific optimisation for different azole cores and this should be taken into consideration.[92]

Recently, applications in chemical biology,[54] synthesis of drug precursors[6] and late-stage C–H functionalisations of drug molecules[92] have emerged. Chen, Wang and co-workers' histidine-specific peptide modification[54] elegantly showcases the application of the Minisci reaction of azoles in chemical biology. Our late-stage C–H amidations on azole drug molecules also showcase the potential synthetic applications of this methodology.[92] We envisage that further future applications of Minisci C–H functionalisations of azoles will emerge as more efficient, milder and more sustainable methodologies are being developed for azoles.

Data availability

Not applicable as this is a review article with no new data generated.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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