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Heteroarylation of unactivated C–H bonds suitable for late-stage functionalization†

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The late-stage introduction of diverse heterocycles onto complex small molecules enables efficient access to new medicinally relevant compounds. An attractive approach to such a transformation would utilize the ubiquitous aliphatic C–H bonds of a complex substrate. Herein, we report a system that enables direct C–H heteroarylation using a stable, commercially available *O*-alkenylhydroxamate with heterocyclic sulfone partners. The C–H heteroarylation proceeds efficiently with a range of aliphatic substrates and common heterocycles, and is a rare example of heteroarylation of strong C–H bonds. Importantly, the present approach is amenable to late-stage functionalization as the substrate is the limiting reagent in all cases.

Introduction

The site-selective, intermolecular functionalization of aliphatic C–H bonds affords unique approaches to the modification of small molecules.¹ There are several general platforms which unlock a range of valuable unactivated C–H transformations, including high-valent metal-oxo,² rhodium carbenoid,³ or polyoxometalate catalysis.⁴ Alternatively, we have demonstrated the utility of *N*-functionalized amides to facilitate a range of site-selective C–H functionalizations *via* hydrogen atom transfer (HAT) involving amidyl radical intermediates.⁵ Collectively, these approaches encompass an impressive array of C–H transformations.

Despite these achievements, there are important C–H transformations which remain inaccessible. A clear example is the direct, site-selective C(sp³)–H heteroarylation of unactivated, aliphatic C–H bonds. Such a process would enable the concise introduction of synthetically and medicinally relevant heterocycles onto small molecule substrates, while obviating the preparation of functionalized aliphatic coupling partners used in metal-catalyzed C(sp³)–C(sp²) cross-couplings, which are typically used to access such products.⁶ While there are many useful heteroarylations of weaker C–H bonds,⁷ reactions involving strong aliphatic C–H bonds have been a challenge (Fig. 1). MacMillan and co-workers reported the first examples of such a transformation *via* nickel-polyoxometalate dual catalysis and aryl halide coupling partners.⁸ While it is impressively broad in scope, excess C–H substrate was required in all cases, which is suboptimal in late-stage contexts where the starting material is precious. Several other approaches to

aliphatic C–H heteroarylation have been reported, including cross-dehydrogenative couplings,⁹ Minisci-type additions,¹⁰ and homolytic aromatic substitutions.¹¹ These transformations also require the use of substrate in large excess and feature poorly selective HAT reagents which are undesirable in applications involving complex substrates with multiple reactive sites.¹² Additionally, C–H heteroarylations involving Minisci-type additions can suffer from poor regio- and chemoselectivity in the radical addition, leading to mixtures of products and, in certain cases, overalkylation.¹³

We have recently demonstrated the ability of a simple, commercially available *O*-alkenylhydroxamate reagent to enable the broad diversification of C–H bonds using substrate as limiting reagent.^{5a} In this prior work, group transfer reagents capable of generating a sulfonyl radical to facilitate chain transfer were well suited to C–H diversification. We hypothesized that the use of readily accessed heteroaromatic sulfones in this manifold could unlock a direct heteroarylation of aliphatic C–H bonds. Herein, we report the successful development of such a process, enabling the direct C(sp³)–H heteroarylation of

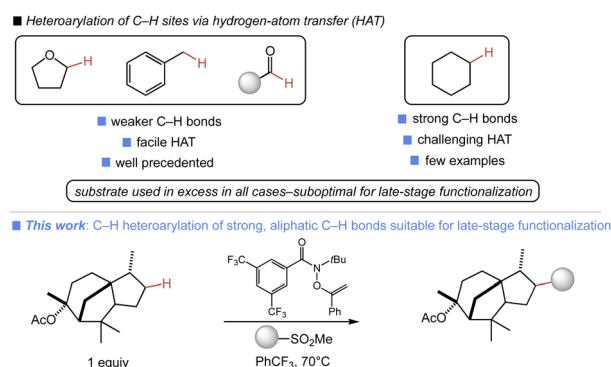


Fig. 1 Heteroarylation of C–H bonds for late-stage functionalization.

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diverse aliphatic substrates. This approach uses the substrate as limiting reagent in all cases and is thus ideally suited for the late-stage functionalization (LSF) of complex molecules.

Results and discussion

We began our studies with the C–H benzothiazoloylation of a range of simple substrates using *O*-alkenylhydroxamate **1** and 2-(methylsulfonyl)benzothiazole as coupling partner in PhCF₃ at 70 °C (Fig. 2). The reactions of common cyclic and bridged hydrocarbons provided the C–H heteroarylation products **2–6** in good yield (34–75%). Notably, the functionalization of norbornane **4** proceeded with excellent *exo* stereoselectivity (>20 : 1 dr), and that of adamantane provided **5** as a single regioisomer resulting from functionalization at the less hindered tertiary C–H site. The reaction of 2-adamantanone to afford **6** occurred selectively at the more electron-rich tertiary C–H site distal from the ketone functionality; previous heteroarylation of this substrate using decatungstate as catalyst proceeded with only modest regioselectivity.⁸ Common saturated heterocycles also reacted efficiently, delivering products **7–9** with excellent regioselectivity and good yield (47–91%). Notably, the functionalization of *N*-Boc morpholine proceeded with excellent regioselectivity to deliver **9** as a single regioisomer, in contrast

to the mixture of regioisomers produced by decatungstate-catalyzed functionalization of this substrate.⁸ Heteroarylation of [2.2.1] oxabicycloheptane produced product **10** in moderate yield (39%), but with the high levels of diastereoselectivity (>20 : 1 dr) typical of this system. Linear substrates also participate in the reaction, as demonstrated by the functionalization of the pinacol acetal of 2-pentanone, delivering **11** albeit with modest regioselectivity.

A distinct advantage of our approach is the success of the heteroarylation using substrate as limiting reagent, which is crucial to applications in LSF. As shown in Fig. 2, we next explored the site-selective C–H heteroarylation of several complex molecules. Heteroarylation of a differin precursor afforded product **12** in 54% yield. As with adamantane and 2-adamantanone, the reaction was highly selective for the less sterically encumbered tertiary C–H site. LSF of the terpenoid natural product (+)-longifolene proceeded exclusively at the least hindered methylene site to deliver **13** with high diastereoselectivity, demonstrating successful C–H heteroarylation in the presence of alkenes. The benzothiazoloylation of (–)-ambroxide produced **14** in 45% isolated yield as a single diastereomer, highlighting the excellent stereoselectivity of the reaction system; alternative LSFs of this substrate by us^{5a,5d} and

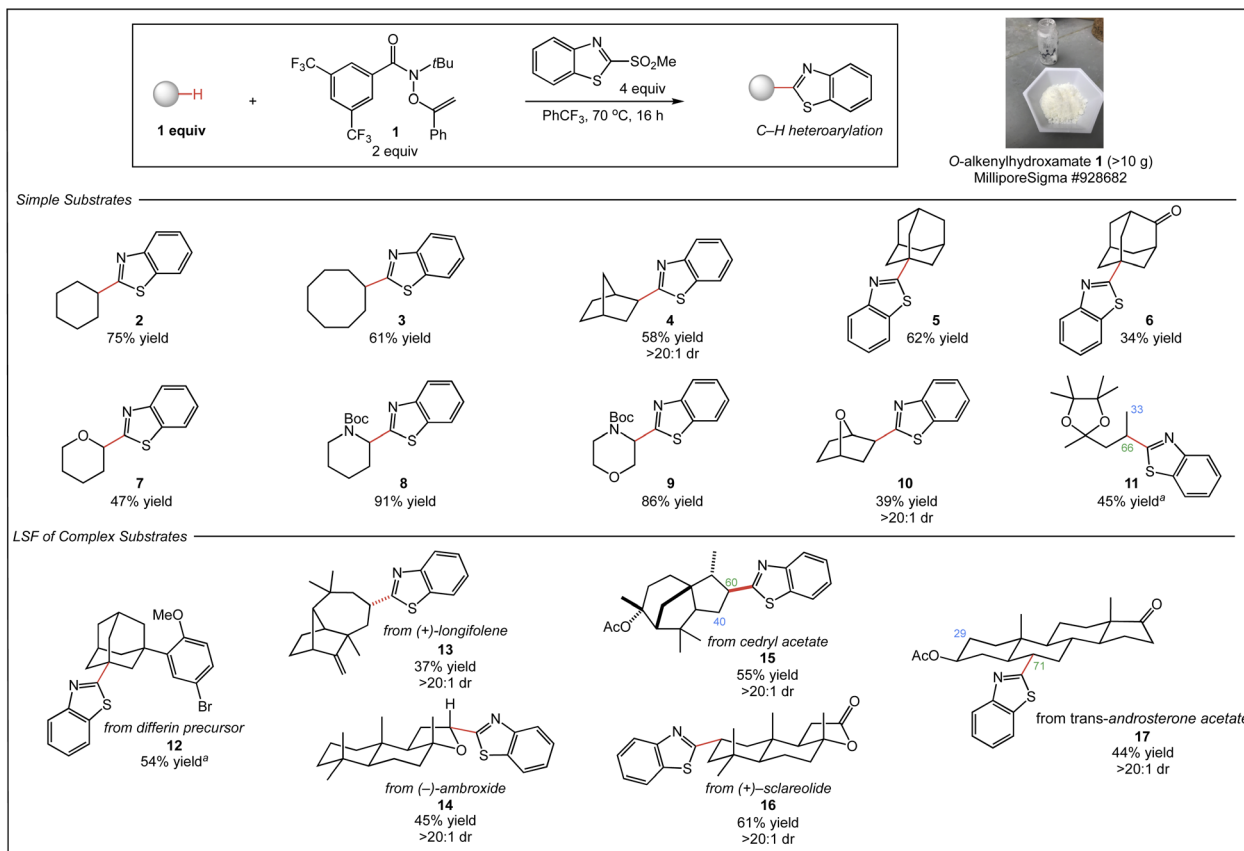


Fig. 2 C–H heteroarylation of diverse substrates using 2-(methylsulfonyl)benzothiazole as coupling partner. All yields are of isolated product unless otherwise indicated. Regio- and diastereoselectivities were determined by ¹H NMR spectroscopy of crude reaction mixture. Percent functionalization values are provided in examples containing regioisomeric mixtures. ^aReaction yield determined by NMR using an internal standard.



others¹⁴ delivered a mixture of diastereomers. Stereoselective C–H heteroarylation of the sesquiterpene cedryl acetate delivered single diastereomers of **15** in good combined yield (55%), favoring functionalization of the most accessible methylene site (1.5 : 1 rr). Terpenoid (+)-sclareolide—a benchmark substrate for intermolecular C–H functionalization—underwent reaction with substrate as limiting reagent to afford **16** in 61% isolated yield as a single diastereomer. Prior C–H heteroarylation of this substrate using nickel/polyoxometalate dual-catalysis required (+)-sclareolide in superstoichiometric amounts (5 equiv.).⁸ Steroid *trans*-androsterone acetate was also derivatized with high stereoselectivity, favoring the C6 site on the B-ring (44% yield, 2.4 : 1 rr).

We next surveyed diverse heteroaryl coupling partners in this transformation (Fig. 3).¹⁵ Benzoxazole and benzimidazole sulfones coupled with similar efficiency to benzothiazole, delivering C–H heteroarylation products of (+)-sclareolide (**18** and **19**) in good yield. Interestingly, this represents a formal approach to aliphatic C–H carboxylation as benzoxazoles can be hydrolyzed to carboxylic acids.¹⁶ 1,2-Azoles were also easily transferred, as demonstrated by the successful couplings of thiazole and oxazole to deliver products **20** and **23**, respectively. In addition, oxadiazole was an excellent coupling partner (**21**, 71% isolated yield).

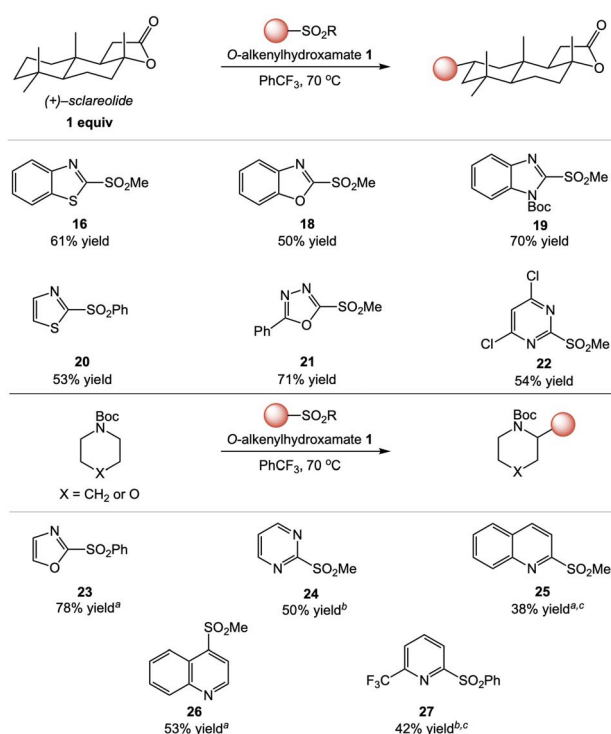
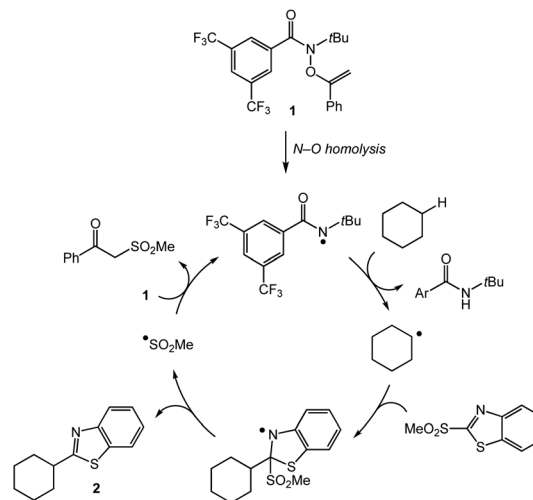


Fig. 3 C–H heteroarylations featuring a variety of heterocyclic sulfones. All reactions were performed with 1 equiv. of substrate, 2 equiv. of **1**, and 4 equiv. of the corresponding heteroaryl sulfone in PhCF₃. All yields are of isolated product unless otherwise indicated. ^aReaction using *N*-Boc piperidine as substrate. ^bReaction using *N*-Boc morpholine as substrate. ^cReaction yield determined by ¹H NMR using an internal standard.



Scheme 1 Proposed radical chain mechanism for the C–H heteroarylation.

Our studies continued with pyrimidine and quinoline heterocycles known to present regioselectivity challenges in Minisci-type radical addition processes.^{17,18} In particular, C–H heteroarylations involving pyrimidinyl sulfones proceeded with complete regioselectivity for the 2-position to deliver **22** and **24**, in contrast with Minisci-type heteroarylations of pyrimidines which produce regioisomeric mixtures.¹⁷ Furthermore, reactions of both quinolines also delivered C–H heteroarylation products (**25** and **26**) with high regioselectivity for the sulfone substituted position of the heteroarene. As with pyrimidines, Minisci-type heteroarylations involving quinolines typically produce regioisomeric mixtures or dialkylation products unless sites are blocked by substitution.^{13,18} Attempts to extend the heteroarene scope to pyridines were initially unsuccessful, as reactions using either 2-(methylsulfonyl)- or 2-(phenylsulfonyl) pyridine proceeded in low yields (<15%). We hypothesized that the use of a more electron-deficient pyridine could facilitate alkyl radical addition and heterocycle transfer, and heteroarylation with 2-(phenylsulfonyl)-6-(trifluoromethyl)pyridine was indeed more efficient (**27**, 42% yield).

We propose that the C–H heteroarylation proceeds *via* hydrogen atom abstraction by an amidyl radical followed by heteroaryl group transfer (Scheme 1). Upon heating, *N*–*O* bond homolysis delivers the amidyl radical which can abstract a strong aliphatic C–H bond in a site-selective manner. The resulting carbon-centered radical participates in a homolytic aromatic substitution with the heteroaryl sulfone partner to deliver product and the chain-carrying sulfonyl radical. The sulfonyl radical adds to the *O*-alkenylhydroxamate reagent **1** to furnish an amidyl radical and propagate the chain process.¹⁹

Conclusions

In conclusion, we have developed a practical approach to the direct C–H heteroarylation of unactivated aliphatic C–H bonds using easily accessed heteroaryl sulfones and a commercially



available *O*-alkenylhydroxamate reagent. A diverse array of synthetically and medicinally relevant heteroarenes are efficient coupling partners, providing a broad platform for molecular diversification. Importantly, all examples herein use the substrate as limiting reagent, essential to applications in the late-stage functionalization of complex molecules. We anticipate that this C–H heteroarylation will prove useful in chemical synthesis across a range of contexts.

Data availability

Experimental procedures, reaction optimization, compound characterization, NMR spectra, and additional data are located within the ESI.†

Author contributions

E. J. A. and A. S. M. conceived of the work and designed the experiments. A. S. M. performed and analyzed the experiments. All authors prepared and reviewed the manuscript. E. J. A. acquired the funding to support the work.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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