A Light-Activated Hypervalent Iodine Agent Enables Diverse Aliphatic C–H Functionalization

Zhipeng Lu, John Putziger, Song Lin*

Department of Chemistry and Chemical Biology, Cornell University, Ithaca, NY 14853, USA. *Correspondence to: songlin@cornell.edu

Abstract

The functionalization of aliphatic C–H bonds is a crucial step in the synthesis and transformation of complex molecules relevant to medicinal, agricultural, and materials chemistry. As such, there is significant interest in the development of general synthetic platforms that will enable efficient diversification of aliphatic C–H bonds. Here, we report a new hypervalent iodine reagent that releases a potent hydrogen atom abstractor for C–H activation under mild photochemical conditions. Using this reagent, we demonstrate the selective (*N*-phenyltetrazole)thiolation of aliphatic C–H bonds for a broad scope of substrates. The synthetic utility of the thiolated products is showcased through various derivatizations. Simply by altering the radical trapping agent, our method can be used to directly transform C–H bonds into diverse functionalities, including C–S, C–Cl, C–Br, C–I, C–O, C–N, and C–C bonds.

Introduction

The direct conversion of inert aliphatic C–H bonds to useful functional groups is a desirable strategy for synthesizing pharmaceuticals, agrochemicals, and other functional molecules using readily available starting materials[1–4]. Particularly in the realm of drug discovery, late-stage diversification of drug-like molecules allows for the generation of broad chemical diversity from materials in existing compound libraries, bypassing the need for time-consuming de novo syntheses[5,6]. However, site-selective functionalization of strong aliphatic C–H bonds remains challenging in complex settings in the absence of directing groups[7–9]. As such, innovative solutions are in high demand to unlock the full synthetic potential of C–H bonds.

Notable progress has been made in the development of new methods for undirected C(sp^3)–H bond functionalization that rely on hydrogen atom transfer (HAT)[10–12], enabling diverse transformations including C–H bond oxidation[13–15], amination[16–19], halogenation[20–23], and thiolation[24–26]. However, these functionalizations generally require distinct reaction strategies and different reaction conditions. The development of modular platforms that can be applied to a range of C–H functionalization reactions remains highly desirable (Fig. 1a)[27–30]. In this context, previous work from Nicewicz, Alexanian, and coworkers employed an acridinium photoredox catalyst and phosphate salt to homolytically cleave C–H bonds, followed by diverse functionalization using radical traps[29]. Similarly, Hu *et al.* used a Cu catalyst in combination with an *N*-F sulfonamide-based HAT reagent to functionalize C–H bonds with a suite of carbon-, nitrogen-, sulfur-, selenium-, and halide-based functional groups[27]. Recently, Alexanian *et al.* developed a radical chain transfer reaction based on an *O*-alkenylhydroxamate reagent to diversify aliphatic C–H bonds in small molecules and polyolefins[28]. In these seminal contributions, however, the radical trapping agents (RTAs) also play the role of turning over the catalyst or sustaining the radical chain, which limits the choice of suitable RTAs and thus the functional groups that are accessible through these methods.

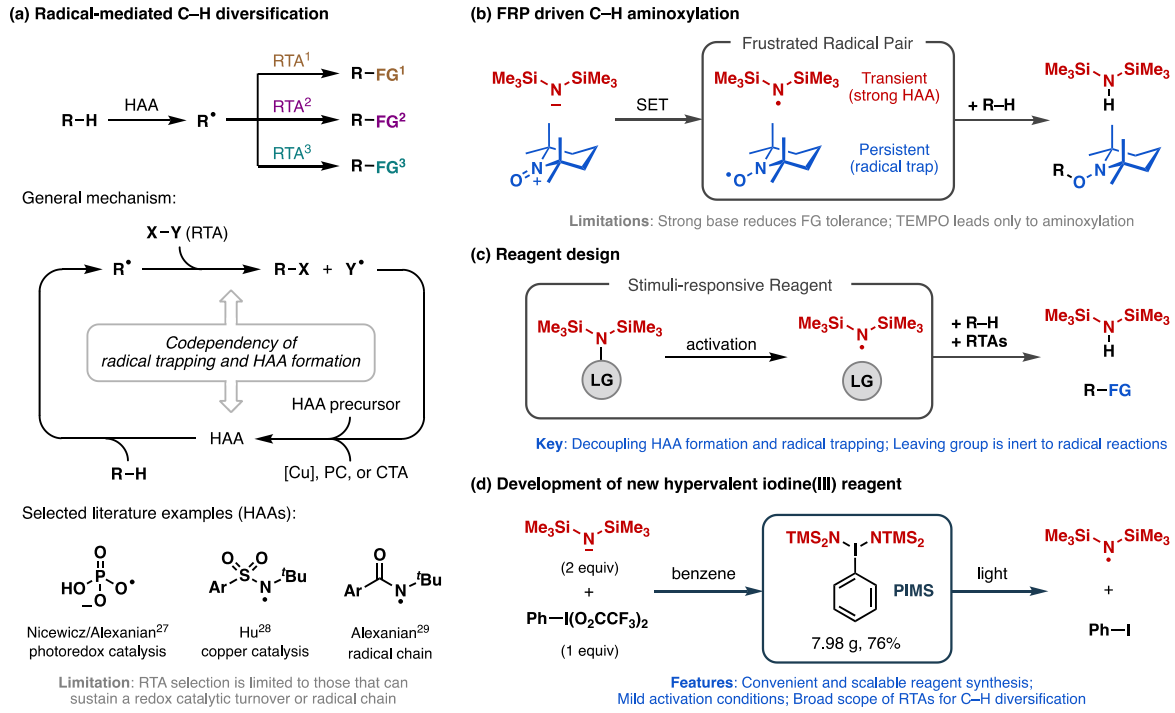

Fig. 1 | Undirected diversification of aliphatic C–H bonds via hydrogen atom transfer. a, Prior art on diverse aliphatic C–H bonds functionalizations. In these reports, radical trapping is not fully decoupled from the HAA formation. **b**, Aliphatic C–H aminoxylation using frustrated radical pairs of HMDS• and TEMPO•. The reaction requires the use of a strong base and cannot be extended beyond aminoxylation. **c**, Our strategy of developing a stimuli-responsive reagent that allows for independent HAT and radical trapping. **d**, Preparation and photochemical reactivity of a novel hypervalent iodine (III) regent, which possesses weak I–N bonds that readily homolyze under light irradiation to release HMDS•. Abbreviations: HAA: hydrogen-atom abstractor, RTA: radical trapping agent, PC: photocatalyst, CTA: chain transfer agent, LG: leaving group, FG: functional group, PIMS: phenyliodine(III) bis(hexamethyldisilazide).

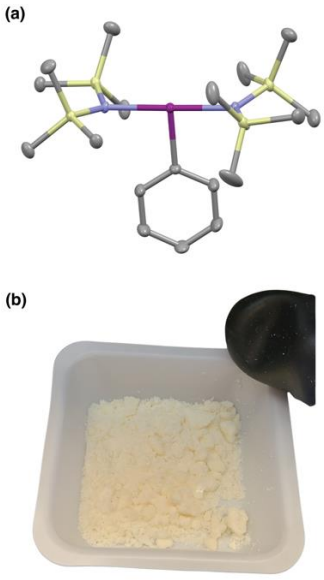

Fig. 2 | Crystal structure (a) and appearance (b) of PIMS.

We recently reported a strategy for regiodivergent C–H functionalization that utilizes a frustrated radical pair consisting of a transient hexamethyldisilaminyl radical (HMDS$^{\bullet}$) and a persistent (2,2,6,6-tetramethylpiperidin-1-yl)oxyl radical (TEMPO$^{\bullet}$), generated via single-electron transfer from hexamethyldisilazide (HMDS^{-}) to TEMPO^{+} (Fig. 1b)[31]. We have also shown that it is possible to control the regioselectivity of this reaction by changing the disilazide donor. However, the strong basicity of HMDS^{-} limits the substrate functional group tolerance; furthermore, because TEMPO^{+} is required to generate HMDS$^{\bullet}$ and simultaneously yields TEMPO as an excellent radical trap, the reaction only provides aminoxylated products. To adapt this reactivity for C–H diversification, we sought to develop a neutral reagent that, in response to an external stimulus, would generate HMDS$^{\bullet}$ along with a byproduct that is inert to radical reactions. Using such an approach, there would be no need for HMDS^{-} or TEMPO^{+}, and importantly, the formation of the H-atom abstractor and the subsequent radical trapping step would be fully decoupled, in principle facilitating the use a more diverse suite of radical trapping agents (Fig. 1c). Here, we describe the synthesis and characterization of a hypervalent iodine reagent phenyliodine(III) bis(hexamethyldisilazide) (PIMS) that, upon visible light irradiation, generates innocuous iodobenzene and two equivalents of HMDS$^{\bullet}$ radical. We further demonstrate that this reagent is competent for the diversification of C–H bonds under simple and mild reaction conditions.

The PIMS reagent was synthesized in one step on a multigram scale from commercially available lithium bis(trimethylsilyl)amide and [bis(trifluoroacetoxy)iodo]benzene (Fig. 1d) (see Supplementary Information for full synthesis and characterization details). Single-crystal X-ray diffraction analysis (Fig. 2) of PIMS revealed a T-shaped geometry at the iodine center with an N–I–N angle of 179.08(5)° and N–I–C bond angles ranging from 90.08(6) to 90.81(6)°. The I–N bond distances are 2.2069(13) and 2.1953(13) Å, both longer than the sum of the atomic covalent radii (2.10 Å), and density functional theory calculations predicted a mean I–N bond energy of 20 kcal/mol, suggesting that these bonds are prone to homolysis (see section 10 of the Supplementary Information). Indeed, differential scanning calorimetry analysis revealed that PIMS melts at 82.6 °C and subsequently degrades to iodobenzene (Fig. S2). The ultraviolet-visible spectrum of PIMS exhibits an absorption feature in the ultraviolet region with a tail that extends into the visible range (Fig. S3). As such, we hypothesized that visible light irradiation could drive I–N bond homolysis to generate two hexamethyldisilaminyl radicals for C–H activation. Related to this proposed mode of reactivity, previous literature has documented photoinduced generation of chlorine atom or trifluoroacetoxy radical from iodobenzene dichloride and [bis(trifluoroacetoxy)iodo]benzene, respectively, for the functionalization of activated C–H bonds[32–35].

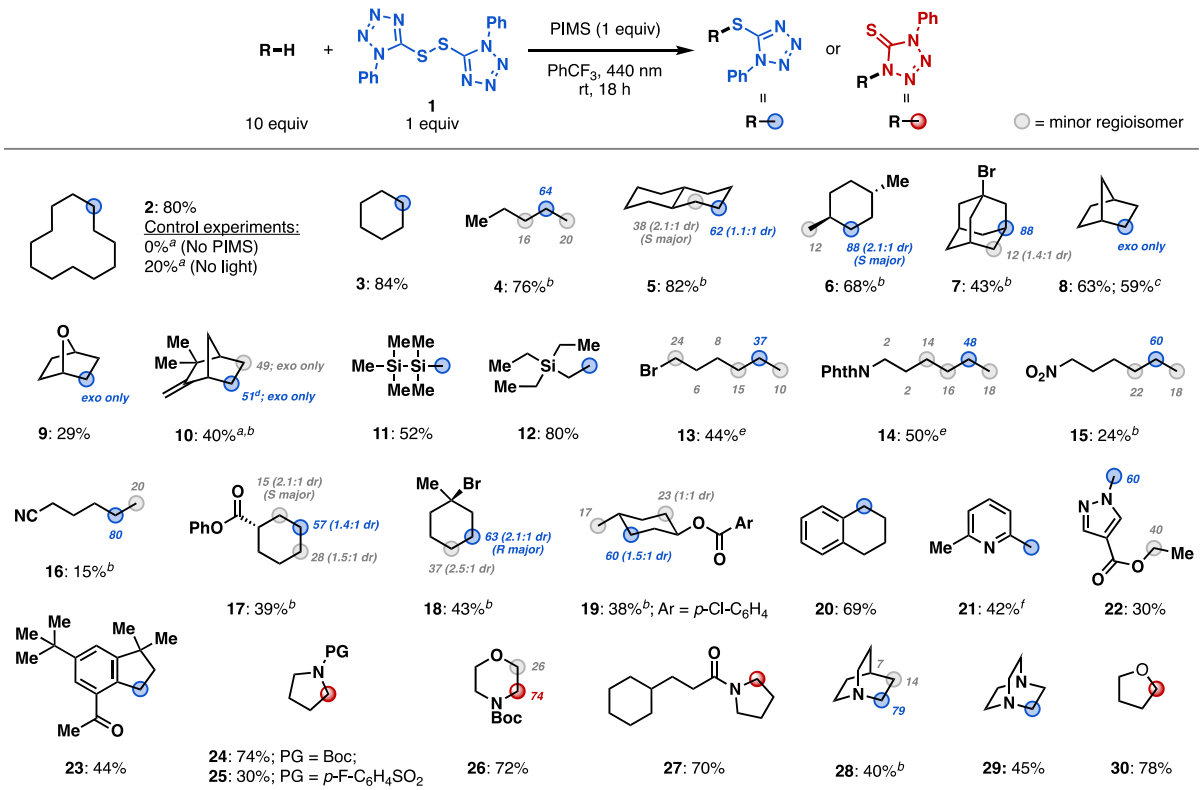

Fig. 3 | Optimization and substrate scope of aliphatic C–H (*N*-phenyltetrazole)thiolation. Reactions were performed on a 0.2-mmol scale unless otherwise noted. All yields are isolated yields calculated per equivalent of HMDS• generated, assuming both equivalents can participate in HAT. [a]Yields and [b]regioselectivity determined by quantitative ^{1}H NMR spectroscopy. [c]4-mmol scale. [d]Intramolecular cyclization observed, see Supplementary Information for details. [e]Yields and regioselectivity determined by quantitative ^{13}C NMR spectroscopy. [f]40 equiv substrate.

As a proof-of-concept, we targeted aliphatic C–H bond thiolation using 1,2-bis(1-phenyl-1H-tetrazol-5-yl)disulfane (**1**, hereafter SPT–SPT) as the radical trapping agent. For simple and readily available hydrocarbons, we performed the reaction using PIMS as the limiting reagent in the presence of excess alkane (Fig. 3). When cyclododecane (**2**) was used as the substrate, irradiation with 440-nm blue light for 18 hours afforded the desired product in an optimized 80% yield (per HMDS• equivalent; see Table S2). Of note, we found the reaction occurred rapidly, and depending on the light source and intensity, could reach full conversion within 4 hours (Table S3). However, to maximize productivity and reproducibility, we used a reaction time of 18 h for the optimized model reaction and all subsequent experiments. Control experiments revealed that PIMS and constant light irradiation are necessary for achieving high reaction yield. When the experiment was performed in the absence of PIMS, product was not observed, indicating SPT–SPT alone cannot promote the observed reactivity[36]. The reaction provided a substantially lower 20% yield in the dark, presumably through slow thermal decomposition of PIMS to generate HMDS•.

Using our optimized conditions, we found that the reaction affords thiolated products in synthetically useful yields starting from other cycloalkanes (**3**, **6**), linear alkanes (**4**), and bicyclic alkanes (**5**). In the case of *trans*-decalin (**5**) and *trans*-1,4-dimethylcyclohexane (**6**), stronger yet more accessible primary and secondary C–H bonds were preferentially activated over substantially weaker yet more hindered tertiary C–H bonds, likely due to the steric bulk of HMDS•. We note that very recently, Alexanian *et al.* published a protocol for C(sp^3)–H (*N*-phenyltetrazole)thiolation[36] via a radical chain mechanism using

SPT–SPT as the sole reagent in a hexafluoroisopropanol solvent: light irradiation generates an H-bonded *N*-phenyltetrazolethiyl radical (SPT$^{\bullet}$) that abstracts an H atom from the substrate, and the resulting alkyl radical is trapped by SPT–SPT, generating the product and propagating the reaction. In the case of *trans*-decalin, tertiary C–H thiolation was favored, in contrast to our system. The difference in regioselectivity indicates that our reaction is not a radical chain process initiated by PIMS and maintained by SPT$^{\bullet}$, and that HMDS$^{\bullet}$ rather than SPT$^{\bullet}$ acts as the HAA.

Adamantane (**7**) and a series of bridged bicyclic hydrocarbons (**8**–**9**) were thiolated with high regioselectivity and stereoselectivity. Organosilanes (**11**, **12**) were also effectively functionalized. For linear alkanes, electron-withdrawing substituents deactivate adjacent C–H bonds, leading to preferential thiolation at the ω–1 position (adjacent to the terminal methyl group; **13** to **16**). Further, a variety of functional groups were found to be tolerated, including phthalimide (**14**), bromide (**7**, **13**, **18**), nitro (**15**), nitrile (**16**), ester (**17, 19**) groups. When (hetero)aromatic substrates (**20**–**23**) bearing benzylic C–H bonds were subjected to the optimal conditions, moderate yields were obtained. We also observed selective functionalization of α-heteroatom-substituted C–H bonds in saturated heterocycles such as pyrrolidine (**24**, **25**, **27**), morpholine (**26**), furane (**30**), quinuclidine (**28**), and 1,4-diazabicyclo[2.2.2]octane (**29**). From some of these substrates, we obtained 1-substituted-4-phenyl-1,4-dihydro-5*H*-tetrazole-5-thione (**24**–**27**, **30**), which presumably arose from an *S*-to-*N* rearrangement via the formation of iminium and oxocarbenium intermediates[36–38]. It is worth noting that this method is compatible with base-sensitive (**15**–**17, 23, 27**) functional groups, in contrast to our previous frustrated radical pair approach. Lastly, starting from norbornane, it was possible to synthesize the functionalized product (**8**) on a gram-scale, although the reaction yield was slightly diminished (59% vs. 63%).

We modified the protocol to enable the use of more complex substrates as limiting reagents (Fig. 4a). Natural products and pharmaceutically relevant molecules such as methyl dehydroabietate (**31**), octahydropyrrolo[3,4-c]pyrrole (**32**), proline-derived amide (**33**), azetidine (**34**), oxazolidinone (**35**), bicyclic morpholine (**36**), and (–)-ambroxide (**37**) afforded products with high regioselectivity at benzylic or α-heteroatom-substituted sites. In addition, this method is suitable for functionalizing sugar derivatives, including protected β-D-fructopyranose (**38**) and dapagliflozin tetraacetate (**39**). Additionally, moderate yield but high regio- and stereoselectivity was achieved using cyclohexane (**3**) and (+)-longifolene (**40**), which feature only unactivated C–H bonds.

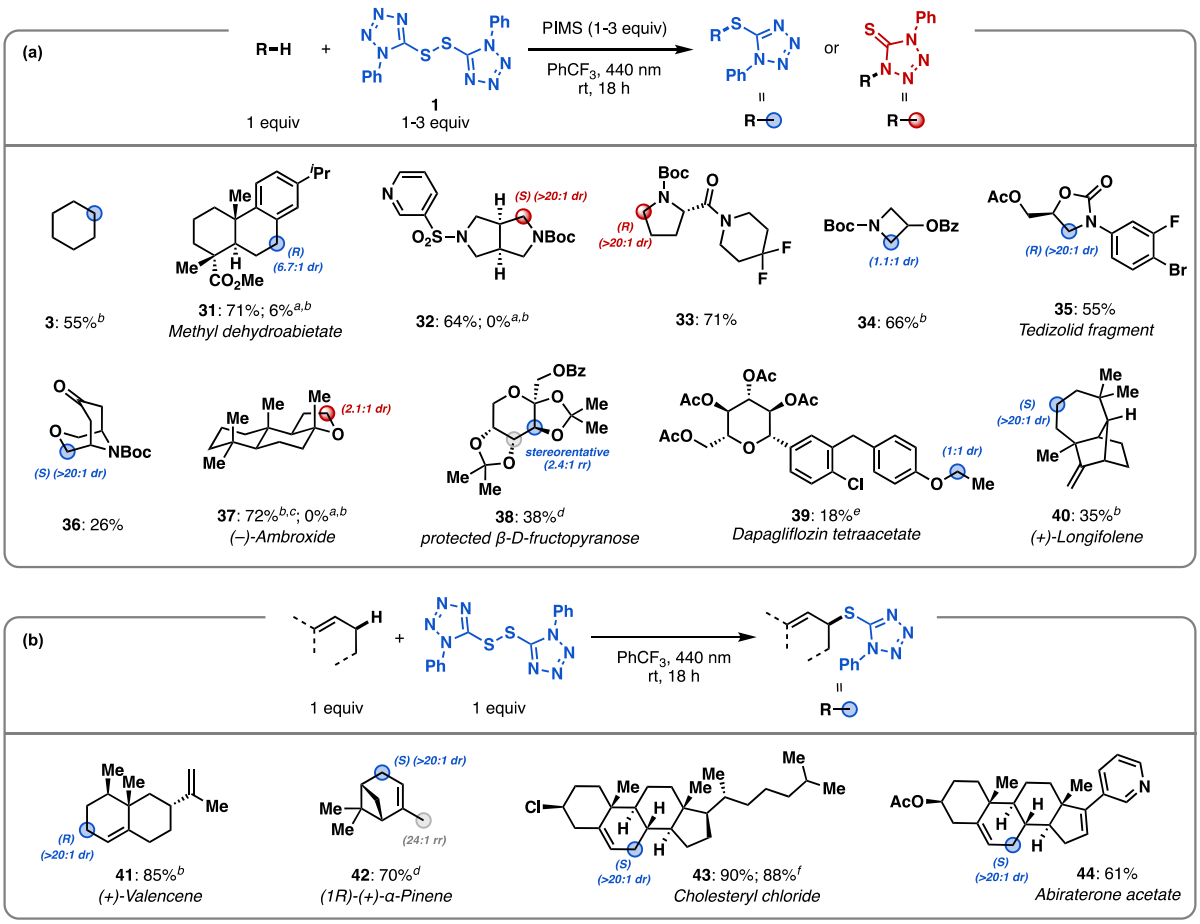

Fig. 4 | Aliphatic C–H (*N*-phenyltetrazole)thiolation of complex substrates. Reactions were performed on a 0.2-mmol scale unless otherwise noted. All yields are isolated yields unless otherwise noted. [a]Without PIMS. [b]Yields and [d]regioselectivity determined by quantitative ^{1}H NMR spectroscopy. [c]Relative stereochemistry of the major diastereomer unassigned. [e]Only regioisomer identified. [f]3-mmol scale.

The thiolation of allylic C–H bonds remains a challenge in transition metal catalysis, both because strong sulfur–metal interactions can induce catalyst poisoning[39,40] and low-valent sulfur is readily oxidized[41–43]. Accordingly, HAT-based strategies have been developed recently for allylic C–H thiolation[44,45], although these reactions require a large excess of alkenes or are limited in scope. We found the allylic thiolation works efficiently with one equiv of substrate for a diverse panel of alkenes (Fig. 4b). Unlike in the parent reaction system with unactivated (**2**), benzylic (**31**), and α-heteroatom-substituted C–H bonds (**32**, **37**), the addition of PIMS is unnecessary. We hypothesize that the SPT$^\bullet$ formed *in situ* from irradiation of SPT–SPT is capable of abstracting an H atom from allylic C–H bonds ($BDE_{S–H}$ = 83 kcal/mol for SPT–H and $BDE_{C–H}$ = 83 kcal/mol for cyclohexene, both calculated using density functional theory). Subsequently, the incipient allylic radical would react with another equivalent of SPT–SPT to generate the product and SPT$^\bullet$, which would sustain a radical chain. This modified procedure works effectively for a variety of complex natural products and drug molecules, including (+)-valencene (**41**), (1R)-(+)-α-pinene (**42**), cholesteryl chloride (**43**; gram-scale) and anti-cancer drug abiraterone acetate (**44**) all with excellent diastereoselectivity.

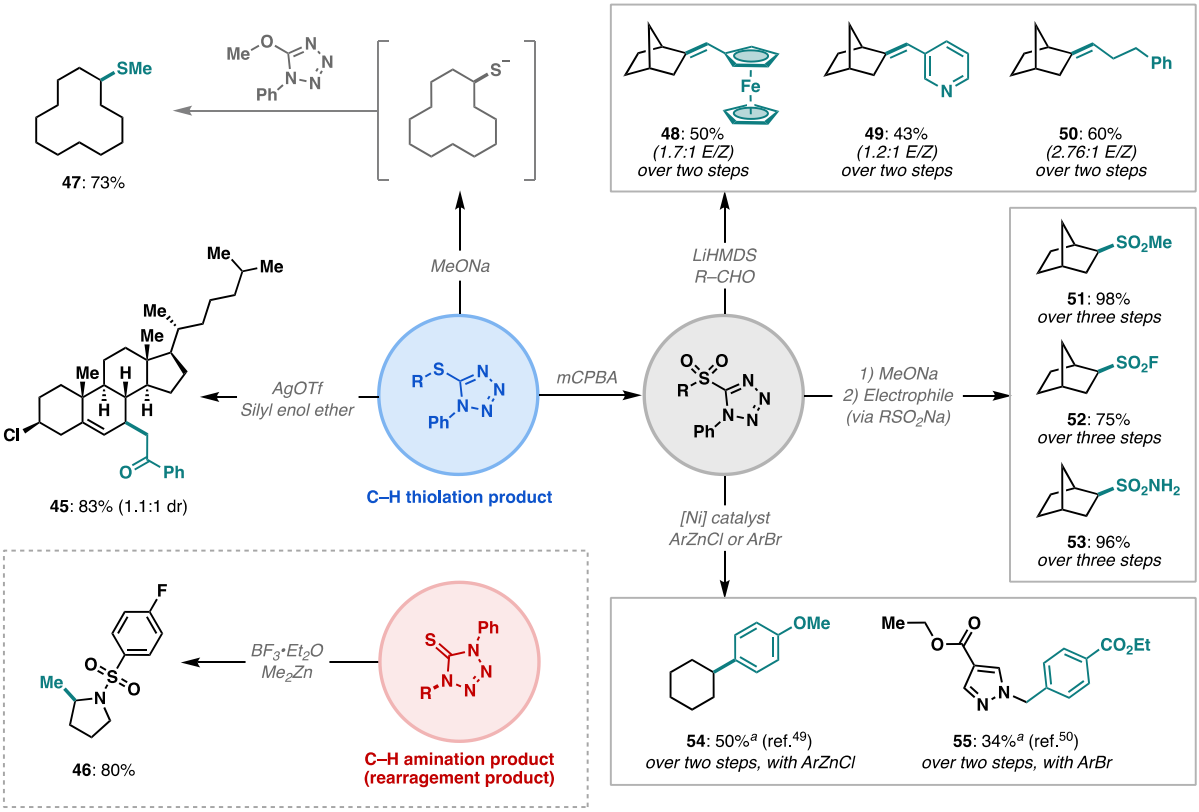

Fig. 5 | Derivatizations of (*N*-phenyltetrazole)thioethers and tetrazolothiones. The SPT and corresponding tetrazolothione groups can participate in various substitution reactions. Upon oxidation with *m*CPBA, the resultant SPT sulfones can also engage in diverse transformations including olefination, substitution, and nickel-catalyzed cross-couplings. Isolated yields are given unless otherwise noted. [a]Yields are based on literature report. See Supplementary Information for details.

We next explored the synthetic utility of the C–H (phenyltetrazole)thiolation products, leveraging the versatile reactivity of the SPT moiety in polar and radical pathways (Fig. 5). Under Lewis-acid promotion[46,47], nucleophilic substitution took place to generate compound **45** from **43–SPT** (thiolation product from **43**) and a silyl enol ether nucleophile. Similar reactivity was also observed by treating tetrazolothione product of **25** with dimethyl zinc, affording **46** in high yield. Additionally, in a one-pot reaction, the tetrazole group in **2–SPT** can be removed by sodium methoxide ($NaOCH_3$) via nucleophilic aromatic substitution (S_NAr), and the sodium alkyl thiolate generated *in situ* was subsequently methylated to furnish sulfide **47**. Furthermore, the SPT group can be oxidized to a sulfone, which can engage in a diverse range of further transformations including coupling with an aldehyde (i.e., Julia-Kocienski olefination; **48–50**)[48]. Alternatively, the sulfone can undergo an S_NAr reaction with $NaOCH_3$ to generate a sodium alkyl sulfinate intermediate, which can then be converted to an alkyl sulfone (**51**), sulfonyl fluoride (**52**), or primary sulfonamide (**53**) in a one-pot process. Finally, while not directly investigated in this work, the same intermediates have been shown to undergo cross-coupling or radical addition reactions to forge C–C bonds. For example, Baran[49] and Fier[50] developed nickel-catalyzed radical cross-coupling reactions with aryl zinc reagents (**54**) and aryl bromides (**55**), respectively. In addition, SPT sulfones have been engaged in radical additions to electron-deficient alkenes[51–53].

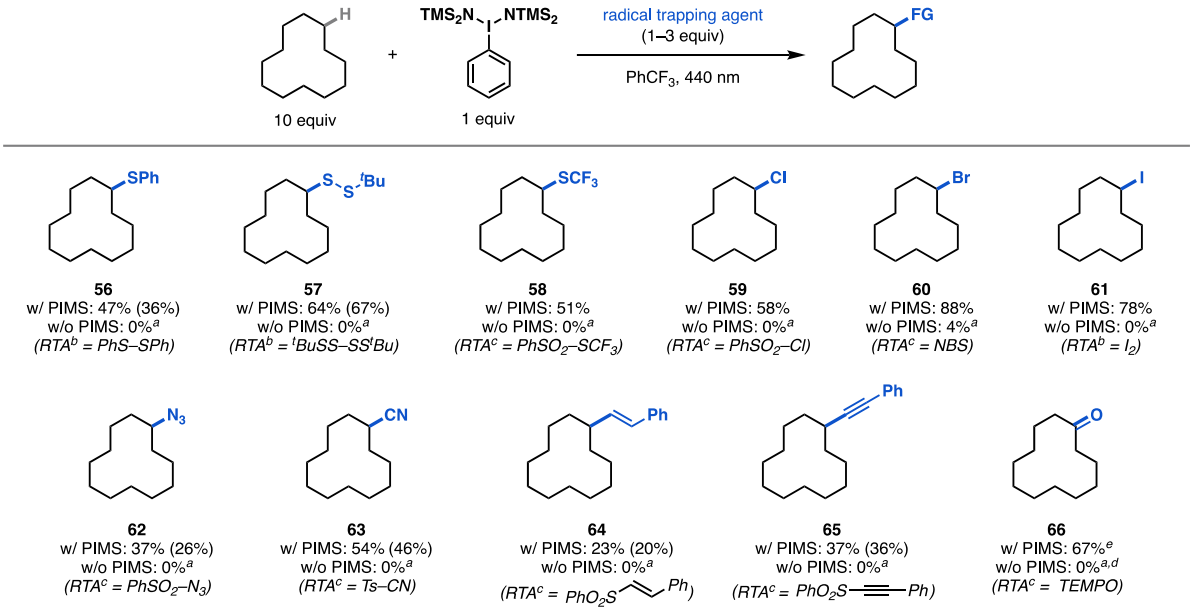

Fig. 6 | C–H diversification using PIMS. Yields determined by quantitative ^{1}H NMR spectroscopy and calculated per equivalent of HMDS$^\bullet$ generated, assuming both equivalents can participate in HAT, with isolated yields given in parentheses. [a]Yields determined by quantitative ^{1}H NMR spectroscopy and calculated based on the RTA. [b]1 equiv of RTA. [c]2 equiv of RTA. [d]Yield of the aminoxylated product determined by quantitative ^{1}H NMR spectroscopy. [e]Yield after *m*CPBA oxidation. NBS: *N*-bromosuccinimide. Ts: tosyl. *m*CPBA: *meta*-chloroperoxybenzoic acid.

Our method employing PIMS can readily be adapted for diverse C–H functionalization reactions, simply by varying the radical trapping agents (Fig. 6). Importantly, this approach is distinct from previous methods[27–29] in that the generation of the HAA is completely decoupled from the radical trapping step. Therefore, the choice of RTA is in principle nearly unlimited, as there is no need to consider its ability to turn over a photocatalyst[29], metal catalyst[27], or sustain a radical chain[28], as is the case in related prior reports. To demonstrate this versatility, we carried out a series of reactions using cyclododecane as the substrate under the original optimized reaction conditions. In addition to various related thiolation reactions (**56**–**58**) using diphenyl disulfide, di-*tert*-butyl tetrasulfide, or *S*-(trifluoromethyl) benzenesulfonothioate as the radical trap, halogenation (**59**–**61**) was also shown to be possible using readily available reagents such as benzenesulfonyl chloride, *N*-bromosuccinimide, and iodine. Furthermore, C–H azidation (**62**), cyanation (**63**), vinylation (**64**), and alkynylation (**65**) were achieved with corresponding arylsulfonyl-based radical traps. The use of persistent TEMPO$^\bullet$ as an RTA led to the aminoxylated product in good yield, which was readily converted to a ketone (**66**) in one pot. We note that in all cases shown here, little to no product formation was found to occur in the absence of PIMS, indicating that the involvement of HMDS$^\bullet$ as an HAA is key.

Conclusion

In conclusion, we have developed a new hypervalent iodine reagent, phenyliodine(III) bis(hexamethyldisilazide), for the diversification of C–H bonds under mild conditions. Thiolation with SPT–SPT proceeds well with hydrocarbons containing inert and activated aliphatic C–H bonds and is suitable for late-stage modification of complex drug molecules and natural products. Ultimately, our method represents a general and modular strategy for diverse C–H functionalizations as demonstrated in the construction of new C–S, C–Cl, C–Br, C–I, C–O, C–N, and C–C bonds.

Acknowledgements

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