Site-Selective α-C-H functionalization of Trialkylamines via Reversible Hydrogen Atom Transfer Catalysis

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Trialkylamines are widely found in naturally-occurring alkaloids, synthetic agrochemicals, biological probes, and especially pharmaceuticals agents and pre-clinical candidates. Despite the recent breakthrough of catalytic alkylation of dialkylamines, the selective α-C(sp^3)–H bond functionalization of widely available trialkylamine scaffolds holds promise to streamline complex trialkylamine synthesis, accelerate drug discovery and execute late-stage pharmaceutical modification with complementary reactivity. However, the canonical methods always result in functionalization at the less-crowded site. Herein, we describe a solution to switch the reaction site through fundamentally overcoming the steric control that dominates such processes. By rapidly establishing an equilibrium between α-amino C(sp^3)-H bonds and a highly electrophilic thiol radical via reversible hydrogen atom transfer, we leverage a slower radical-trapping step with electron-deficient olefins to selectively forge a C(sp^3)-C(sp^3) bond with the more-crowded α-amino radical, with the overall selectivity guided by Curtin-Hammett principle. This subtle reaction profile has unlocked a new strategic concept in direct C-H functionalization arena for forging C–C bonds from a diverse set of trialkylamines with high levels of site-selectivity and preparative utility. Simple correlation of site-selectivity and ^{13}C NMR shift serves as a qualitative predictive guide. The broad consequences of this dynamic system, together with the ability to forge *N*-substituted quaternary carbon centers and implement late-stage functionalization techniques, holds tremendous potential to streamline complex trialkylamine synthesis and accelerate drug discovery.

Trialkylamine-containing pharmaceuticals are ubiquitous, with the amine functionality incorporated to mimic the multiple functions of biogenic amines or to provide desirable pharmacokinetic properties[1]. Against this backdrop, there is an immense interest in the development and improvement of methods to catalytically construct complex trialkylamine-scaffolds in synthetic and medicinal chemistry[2,3]. Traditional approaches to trialkylamines use alkylation of secondary amines, with some noteworthy catalytic examples recently disclosed[4-7]. Alternatively, the direct α-C-H functionalization of widely available trialkylamines would enable facile access to functionally diverse libraries, and consequently allow for streamlined routes for the catalytic synthesis of structurally complex trialkylamines with complementary reactivity, amenable to late-stage functionalization strategies[8]. However, α-C-H bonds of unsymmetrical unfunctionalized trialkylamines often have nearly identical bond dissociation energies (for example, *N*-methyl piperidine: 91 kcal/mol for the secondary vs 92 kcal/mol for the primary site)[9]. Thus, their selective activation on the basis of enthalpic differences will be doomed to failure. Currently, the vast majority of strategies based on fundamentally different reactive intermediates, including carbene insertion[10], direct hydride[11] or hydrogen abstraction[12,13] or single electron oxidation/deprotonation processes[12,14,15] predominantly rely on steric control to activate the more accessible and least substituted position selectively (Fig.1, A). One type of exception that has recently appeared involves benzylic amines where selectivity is apparently governed by obvious differences in acidity or bond dissociation energies[16,17]. The other exception involves diaryl ketone as catalyst under irradiation with high energy UV light in presence of large excess of the trialkylamines (20 eq. or more)[18,19], which largely limits the synthetic potential and makes late-stage applications nearly impossible.[20] Thus, a general approach to functionalize the more substituted and less accessible α-C-H bond of a wide range of trialkylamines with enhanced structural complexity therefore constitutes an elusive and long-standing synthetic challenge.

Thiyl radicals have had a transformative impact in modern synthetic chemistry[21]. The electrophilicity of thiyl radicals make them preeminent and efficient species for a broad range of biological and chemical processes, especially those involving hydrogen atom transfer (HAT)[22]. Recently, MacMillan and co-workers demonstrated the isotope

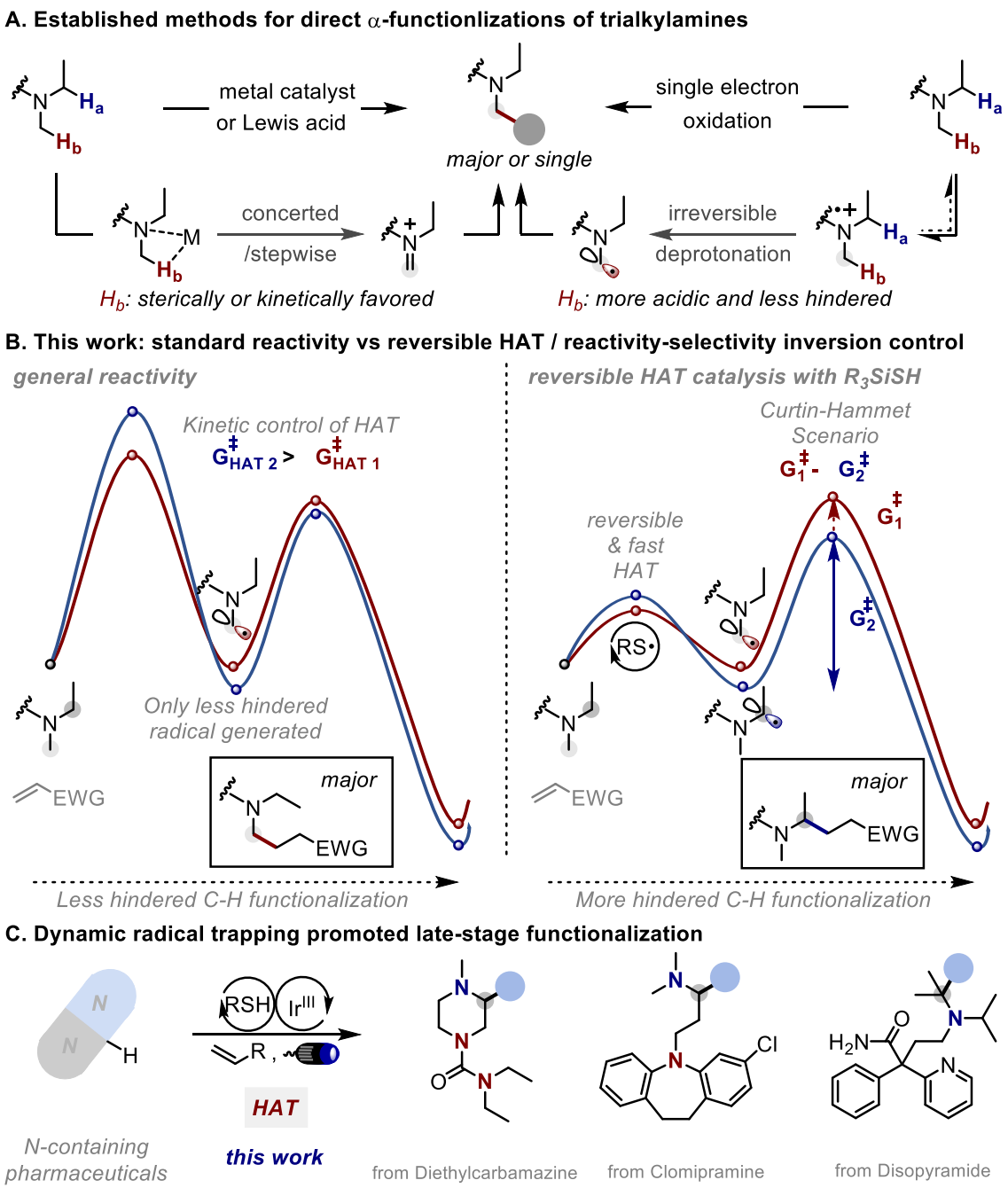

Figure 1. (**A**) Canonical methods for trialkylamine α-functionalization. (**B**) Energy profile of trialkylamine α-functionalization enabled by standard photoredox catalysis *vs* reverisible HAT catalysis. (**C**) Late-stage modification of trialkylamine-containing pharmaceuticals.

labeling utility of silyl thiyl radicals as HAT catalysts to perform photoredox-catalyzed α-deuteration and tritiation of trialkylamine-containing pharmaceuticals[23]. Diagnostically, this strategy results in exhaustive α-C-H isotopic labeling. Our continuing interest in photoredox promoted amine functionalization[15] led us to examine the feasibility of selective C(sp^3)-C(sp^3) bond formation at the more-substituted position of trialkylamines. If successful, this

strategy would offer a pathway complementary to existing methods for complex trialkylamine construction and late-stage functionalization of pharmaceuticals.

Results and discussion

Specifically, under photoredox conditions, we envisioned using thiol catalyst to generate a highly electrophilic thiyl radical via a single electron transfer (SET) and subsequent deprotonation process. The resultant thiyl radical would then ideally participate in an unselective, fast and reversible HAT of the C(sp^3)-H bond adjacent to the basic nitrogen atoms[24], an equilibrium reminiscent of the racemization step in dynamic kinetic resolution and other Curtin-Hammett controlled processes[25-27]. However, under equilibrium conditions, the primary radical might be expected to react preferentially as it is kinetically more accessible. Thus, the key to this strategy is to find a suitable electrophilic coupling partner that inverts that natural trend and reacts preferentially at the more-substituted (and more-nucleophilic) position of the α-amino radical. To do so, fine tuning of reaction barriers is required since the initial HAT should be fully reversible and the subsequent steps should be irreversible and rate-determining to kinetically control the selectivity in a Curtin-Hammet mechanistic scenario (Fig.1, B right).

In line with this notion, we considered that radical trapping with electron-deficient olefins— the Giese reaction — would meet the requirements for the inversion of selectivity, (Fig.1, C)[28]. To achieve the proposed mechanism, we sought a thiol catalyst capable of unselective, fast and reversible HAT. After testing a series of thiol catalysts, we found that commercially available triphenyl silanethiol (TPS-SH, $E_{1/2}^{ox}$ = 0.43 V vs Ag/AgCl in MeCN) and triisopropyl silanethiol (TIPS-SH, $E_{1/2}^{ox}$ = 0.28 V vs Ag/AgCl in MeCN), were particularly suited for selective alkylation of *N*-methyl piperidine with tert-butyl acrylate (see Supplementary Section II for details). By contrast, omitting TPS-SH leads to mixtures favoring C–H functionalization at the less hindered position as previously reported[14,15] (see Table S2 for details).

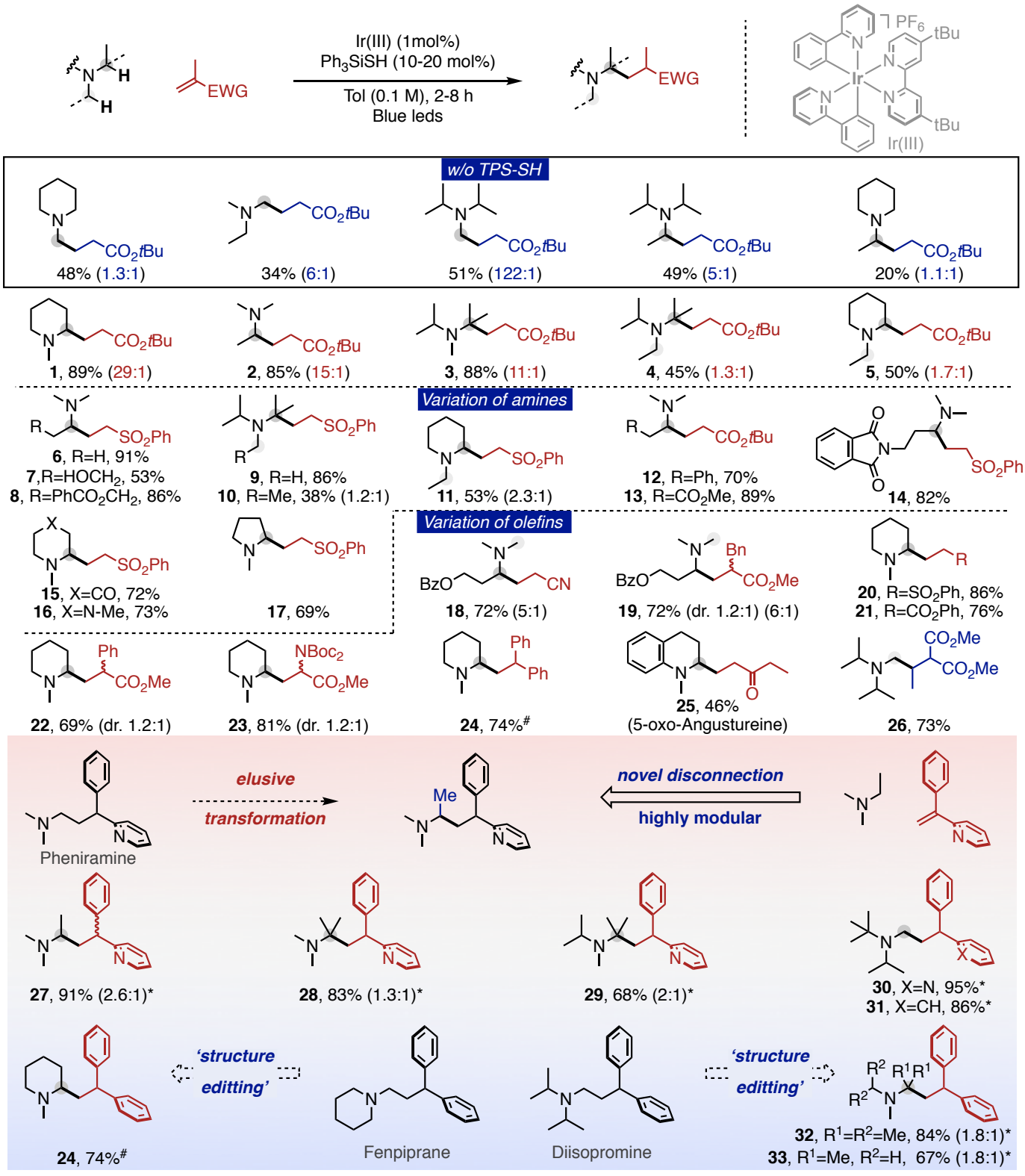

Figure 2. Site-selective alkylation of simple trialkylamines and novel disconnection. Reaction conditions: trialkylamine (3.0 eq.), olefin (1.0 eq.), $Ir(ppy)_2(dtbby)PF_6$ (1 mol%), Ph_3SiSH (20 mol%), Tol (0.1 M), Blue LED (32W), 28 °C, 2-8 h. *TPS-SH (5 mol%) and Dioxane (0.1 M) were used instead. #2-*tert*-butyl-1,1,3,3- tetramethylguanidine (50 mol%) used as additive.

After optimization, a combination of 1 mol% $Ir(ppy)_2(dtbbpy)PF_6$ (ppy, 2-phenylpyridinato; dtbbpy, 4,4'-di-tert-butyl-2,2'-bipyridyl) and 20 mol% TPS-SH in toluene (0.1 M) in presence of vinyl phenyl sulfone, under blue light-emitting diode (LED) irradiation provides the best results, giving rise to compound **20** in 86% isolated yield with excellent

site-selectivity. Next, we aimed to study the generality of our protocol. As shown in Fig. 2, a wide variety of trialkylamines undergo the targeted sp^3 C–H alkylation with vinyl sulfone, acrylate, acrylonitrile, 1,1-diarylethylene and vinyl ketone. Strikingly, our catalytic system selectively alkylates *N*-ethyl piperidine on the ring, albeit with moderate selectivity (**5**, **11**). Indeed, the method generally displays an excellent site-selectivity profile, and is tolerant of multiple functional groups, such as alcohol (**7**), ester (**8**, **13**), imide (**14**), ketone (**15**) and saturated *N*-heterocycles such as piperazine (**16**), pyrrolidine (**17**) and piperidine (**20**-**24**). As expected, the reactivity can be smoothly extended to aniline derivatives (**25**). We found that the selectivity is affected by the steric bulk of both olefin acceptor and bulky amines; in an extreme case, diisopropyl methyl amine affords tertiary-alkylation with unsubstituted Michael acceptors but methyl-alkylation when the olefin bears a β-substituent (**3** *vs*. **26**), indicating the fast reversibility of HAT step is tempered by increased steric crowding in the selectivity-determining alkylation event (see Supplementary Fig. S18 for details).

With our approach, we considered whether it also may provide an orthogonal solution to strategic derivatization efforts of trialkylamine-containing biologically active compounds. The biological activity of 3,3-Diarylpropylamines, critical units widely found in H1-antihistamines, can vary from antiallergic to antispasmodic, antipyretic, and choleretic by fine-tuning of the structure[29]. Editing the structure by selective introduction of methyl groups remains a daunting challenge[30], with several recent noteworthy solutions[31,32]. We considered a retrosynthetic disconnection involving the corresponding trialkylamine motif alkylated with diarylethylenes. The strategy provides facile access to methylated (**27**-**31**) versions of pheniramine, albeit with moderate selectivity. Even more noteworthy is the structural reorganization that is enabled by this approach – a pheniramine analogue is easily assembled by reacting N-methyl piperidine with diphenyl ethylene (**24**) while an isostructural diisopromine is formed from diisopropyl methyl amine (**32**). From a chemical perspective, these reactions are distinguished by a superb reaction profile with simple precursors being converted to products of significantly increased complexity that are difficult to access with existing methods, thus showcasing the preparative potential of this transformation.

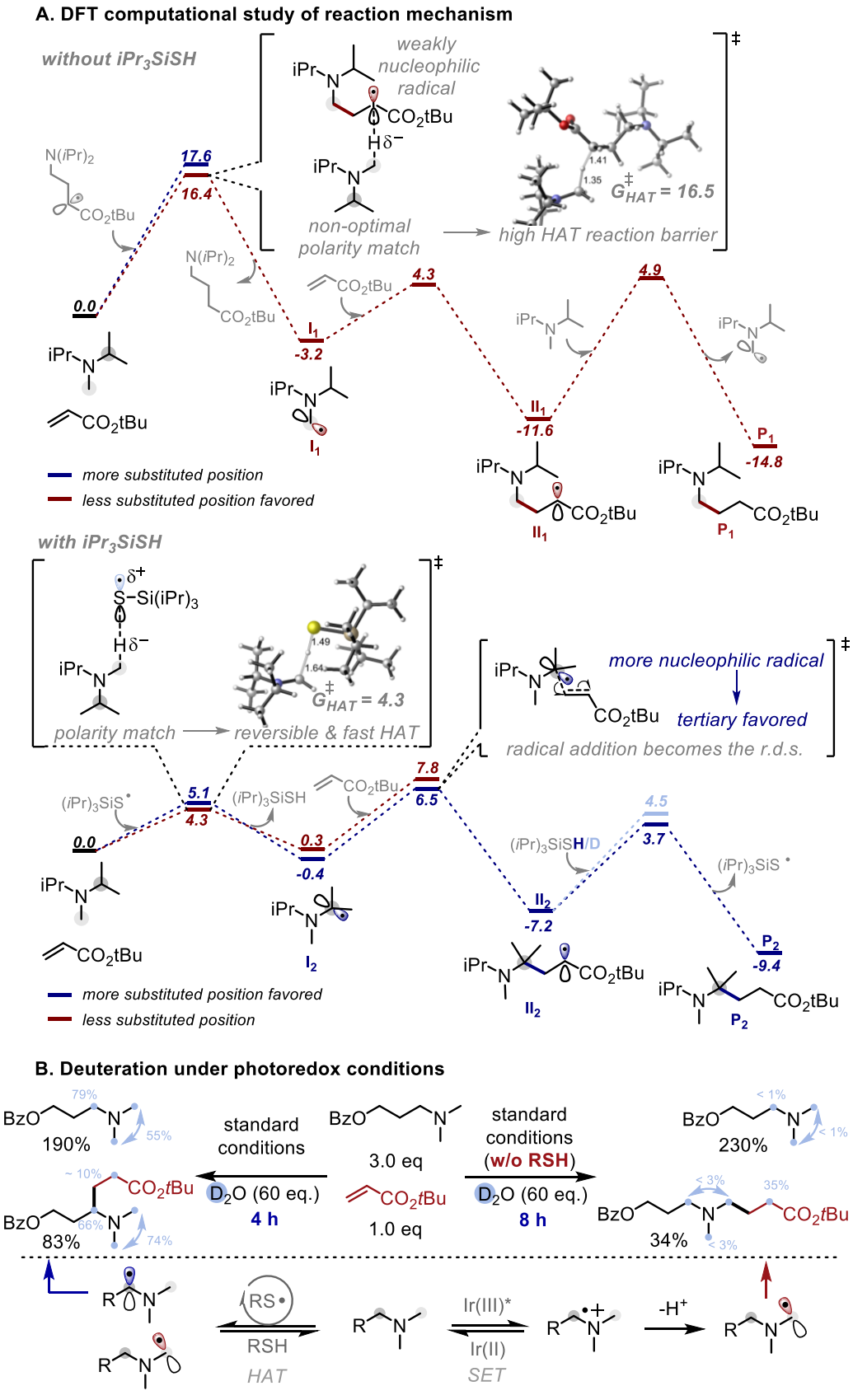

Figure 3. DFT calculations and mechanistic studies. (A) DFT computational studies of the reaction mechanism. (B) Deuteration studies under photoredox (Ir) reaction conditions.

To gain insight into the reaction mechanism and understand the origin of the high levels of selectivity attained with our system, we performed a series of computational and experimental studies. Our control study indicates

that a radical chain mechanism is operative, as both photoredox and traditional radical initiation with azobisisobutyronitrile (AIBN) give essentially the same results for *N*-methyl piperidine(see Supplementary Fig. S1 for details). Under thiol-free conditions (Fig. 3, A), the radical is generated (and later re-generated) via an irreversible HAT to a carbon-centered radical, which is of relatively high activation barrier (ΔG‡= 16.4-17.6 kcal/mol) and kinetically favors the least substituted site (by ΔΔG‡ = 1.2 kcal/mol). This is followed by rapid radical addition (C-C bond formation). In stark contrast, when the thiol is present, initial formation of a thiyl radical is favored, which triggers H-atom abstraction with roughly a third of the activation barrier (ΔG‡= 4.3-5.1 kcal/mol) as compared to the carbon centered radical, and essentially without driving force (ΔGrxn = -0.4 (tertiary) / 0.3 (primary) kcal/mol), rendering the process fully reversible. As such, the calculated profile fully supports that the HAT process is unselective, fast and reversible under thiol-conditions, in line with the deuteration experiments (Fig 3. B) (see Supplementary Table S8 and Fig. S2-S5 for details). Our calculations suggest that this different behavior in HAT is due to an excellent polarity match of the electrophilic thiyl radical with the relatively electron-rich α-N C-H bond. On the contrary, the α-ester radical II1 under thiol-free conditions is also weakly nucleophilic[33,34] in character and there is hence a barrier-enhancing polarity mismatch (see Supplementary Section IV for details).

Thus, while HAT is the selectivity-determining step under thiol-free conditions, in the presence of R_3Si-SH, the later slower C-C bond-forming step becomes the rate determining step and determines the product outcome. Interestingly, the more substituted radical (tertiary) reacts via a slightly lower activation barrier (ΔΔG‡ = 1.3 kcal/mol). Our data indicate that this is primarily due to the electronic impact of the adjacent nitrogen in these radicals and the resulting pyramidalization. Additionally, our calculation of the corresponding nitrogen-free system predicts inverted reactivities (i.e. primary radical reacts with lower barrier than tertiary, see Supplementary Information for details). To further corroborate this point, we calculated the corresponding barrier of a series of α-C, α-N and α-O tertiary radicals, which follow the trend of *the more pyramidal the radical, the lower the barrier*

(see Supplementary Fig. S14, S15 for details). Finally, regeneration of the thiyl radical occurs irreversibly through HAT from the resulting α-ester radical. This process is influenced by the deuteration of silanethiol: the free energy barrier of deuterium transfer is 0.8 kcal/mol higher in energy than HAT from R_3Si-S(H/D), explaining the low deuterium incorporation in the α-ester position of the acrylate.

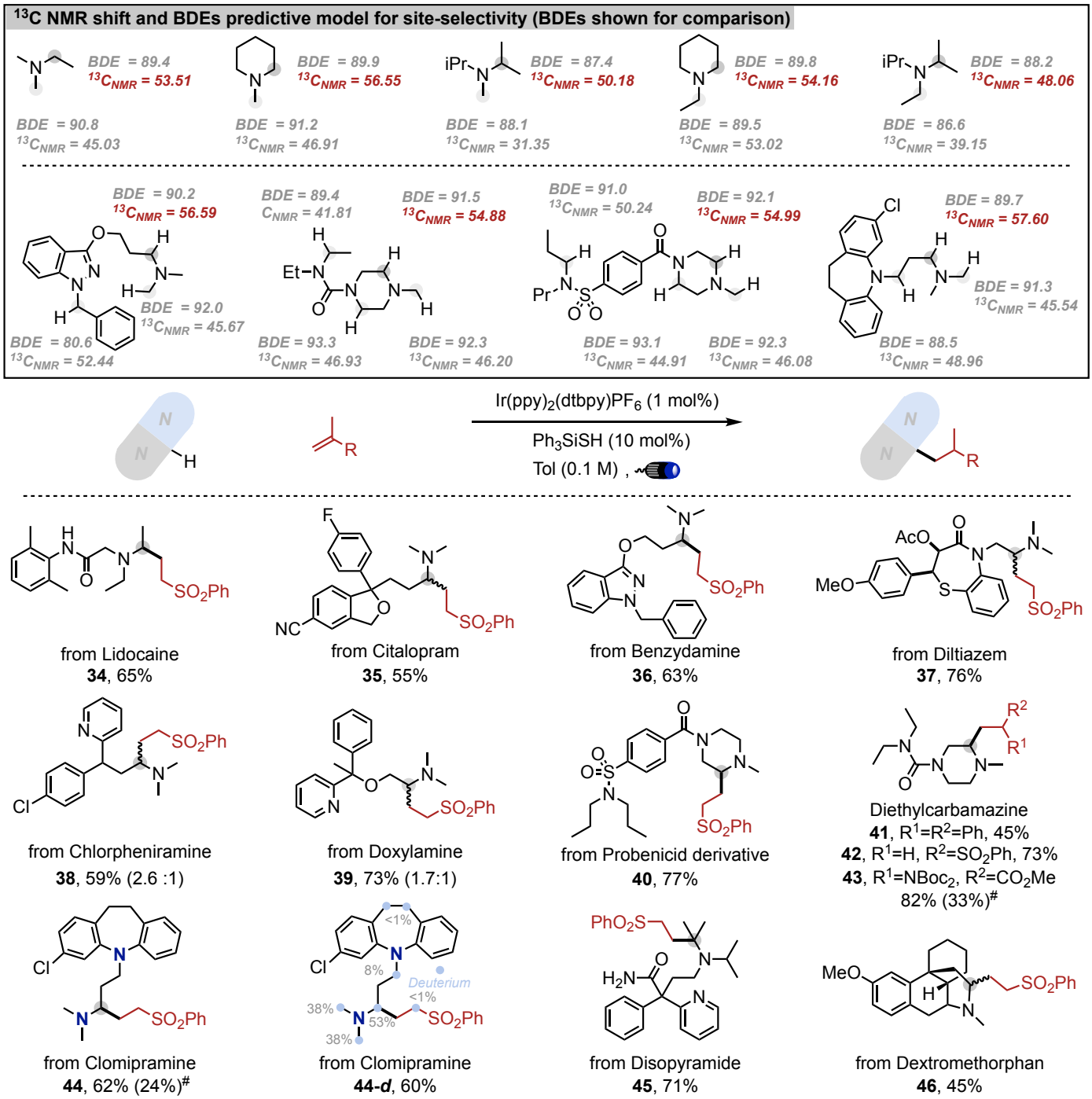

Fig. 4. Qualitative reaction site prediction and Late-stage alkylation of pharmaceuticals. BDEs listed are in kcal/mol. ^{13}C NMR shifts are in ppm. Reaction conditions: trialkylamine (3.0 eq.), olefin (1.0 eq.), $Ir(ppy)_2(dtbby)PF_6$ (1 mol%), Ph_3SiSH (10 mol%), Tol (0.1 M), Blue LED (32W), 28 °C, 8 h. # ^1H NMR yield, amine (1.0 eq.) used instead.

With a rationalization of the underlying reactivity and selectivity in hand, we wondered whether certain simple molecular parameters could potentially correlate with the overall site-selectivity even in the context of late-stage functionalization of complex pharmaceuticals. As expected, bond dissociation energies (BDE) do not correlate with the observed reactivity (Fig. 4). However, our calculations of a variety of parameters for simple amines revealed that the site-selectivity has a qualitative relationship with the ^{13}C NMR shift of the α-amino carbon signal*; alkylation occurs selectively at the carbon bearing the higher ^{13}C NMR shift*.

We then extrapolated this predictive model to a library of commercially available drugs containing trialkylamine scaffolds and other potential reactive sites. As evident from the results compiled for **32-44** in Fig. 4 and as predicted by our simple model (Fig. 4), all these trialkylamine-containing complex molecules underwent effective site-selective alkylation under our conditions. Importantly, the α-amino C-H bonds of aniline (**40**), amide (**37**), sulfonamide (**37**) and urea (**38**- **40**), α-C-H bonds to oxygen (**33**, **34**, **36**) and benzylic C-H bonds (**33**, **34**, **35**, **41**) all remained untouched under the reaction conditions, highlighting the potential of the current transformation in the rapid and efficient late-stage modification of medicinally relevant molecules. Trialkyl *N*- substituted quaternary carbon centers, which are challenging to form with conventional methods[35], are readily accessible even in the context of late-stage functionalization (**8**, **9**, **42**). Strikingly, selective alkylation of secondary α-amino C-H bonds in dextromethorphan was observed with good yield (**35**). Isotope labelling is a paramount diagnostic tool in pharmacokinetics[36], and in the presence of D_2O, almost all alkylated drug molecules presented in Fig. 4 should undergo decent isotope incorporation[23]. As a testament, clomipramine was selected to perform the desired alkylation/D-labelling sequence with good yield, and deuterium incorporation (**44-*d***), a result that underscores our mechanistic conclusions – HAT is rapid and equilibrating leading to per-deuteration of the substrate while the alkylation event is selective and product-determining leading to a monoalkylation.

Conclusion

In summary, we have developed a general regioselective α-C(sp^3)-H functionalization of the least accessible site of trialkylamines via reversible HAT catalysis. Using silanethiols as reversible HAT catalysts under visible light photoredox conditions, this transformation has proven to be mild, efficient, and tolerant to a wide variety of functionalities present in complex amines. The key to success is the rapid reversibility of the HAT process and subsequent selective trapping of the more substituted and nucleophilic α-amino radical under Curtin-Hammett control. Conceptually, we expect that the broader consequences of the inversion of canonical selectivity in trialkylamine functionalization will foster systematic investigations for more challenging site-selective transformations involving radical species.

References

1. Blakemore, D. C. *et al.* Organic synthesis provides opportunities to transform drug discovery. *Nature Chem* **10**, 383–394 (2018).
2. Trowbridge, A., Walton, S. M. & Gaunt, M. J. New strategies for the transition-metal catalyzed synthesis of aliphatic amines. *Chem. Rev.* **120**, 2613–2692 (2020).
3. Matheau-Raven, D. *et al.* Catalytic reductive functionalization of tertiary amides using Vaska's complex: synthesis of complex tertiary amine building blocks and natural products. *ACS Catal.* **10**, 8880–8897 (2020).
4. Yang, Y., Shi, S.-L., Niu, D., Liu, P. & Buchwald, S. L. Catalytic asymmetric hydroamination of unactivated internal olefins to aliphatic amines. *Science* **349**, 62–66 (2015).
5. Musacchio, A. J. *et al.* Catalytic intermolecular hydroaminations of unactivated olefins with secondary alkyl amines. *Science* **355**, 727–730 (2017).
6. Li, M.-L., Yu, J.-H., Li, Y.-H., Zhu, S.-F. & Zhou, Q.-L. Highly enantioselective carbene insertion into N–H bonds of aliphatic amines. *Science* **366**, 990–994 (2019).
7. Kumar, R., Flodén, N. J., Whitehurst, W. G. & Gaunt, M. J. A general carbonyl alkylative amination for tertiary amine synthesis. *Nature* **581**, 415–420 (2020).

8. Beatty, J. W. & Stephenson, C. R. J. Amine functionalization via oxidative photoredox catalysis: methodology development and complex molecule synthesis. *Acc. Chem. Res.* **48**, 1474–1484 (2015).
9. Wayner, D. D. M., Clark, K. B., Rauk, A., Yu, D. & Armstrong, D. A. C−H bond dissociation energies of alkyl amines: radical structures and stabilization energies. *J. Am. Chem. Soc.* **119**, 8925–8932 (1997).
10. He, J., Hamann, L. G., Davies, H. M. L. & Beckwith, R. E. J. Late-stage C–H functionalization of complex alkaloids and drug molecules via intermolecular rhodium-carbenoid insertion. *Nat Commun* **6**, 5943 (2015).
11. Chan, J. Z., Chang, Y. & Wasa, M. $B(C_6F_5)_3$-Catalyzed C–H alkylation of *N*-alkylamines using silicon enolates without external oxidant. *Org. Lett.* **21**, 984–988 (2019).
12. Catino, A. J., Nichols, J. M., Nettles, B. J. & Doyle, M. P. The oxidative mannich reaction catalyzed by dirhodium caprolactamate. *J. Am. Chem. Soc.* **128**, 5648–5649 (2006).
13. Barham, J. P., John, M. P. & Murphy, J. A. Contra-thermodynamic hydrogen atom abstraction in the selective c–h functionalization of trialkylamine *N*–CH_3 groups. *J. Am. Chem. Soc.* **138**, 15482–15487 (2016).
14. Aycock, R. A., Pratt, C. J. & Jui, N. T. Aminoalkyl radicals as powerful intermediates for the synthesis of unnatural amino acids and peptides. *ACS Catal.* **8**, 9115–9119 (2018).
15. Thullen, S. M. & Rovis, T. A mild hydroaminoalkylation of conjugated dienes using a unified cobalt and photoredox catalytic system. *J. Am. Chem. Soc.* **139**, 15504–15508 (2017).
16. Ide, T. *et al.* Regio- and chemoselective Csp^3–H arylation of benzylamines by single electron transfer/hydrogen atom transfer synergistic catalysis. *Chem. Sci.* **9**, 8453–8460 (2018).
17. Leng, L., Fu, Y., Liu, P. & Ready, J. M. Regioselective, photocatalytic α-functionalization of amines. *J. Am. Chem. Soc.* **142**, 11972–11977 (2020).
18. Bertrand, S., Hoffmann, N. & Pete, J.-P. Highly efficient and stereoselective radical addition of tertiary amines to electron‐deficient alkenes − application to the enantioselective synthesis of necine bases. *Eur. J. Org. Chem.* 12 (2000).

19. Hoffmann, N., Bertrand, S., Marinković, S. & Pesch, J. Efficient radical addition of tertiary amines to alkenes using photochemical electron transfer. *Pure and Applied Chemistry* **78**, 2227–2246 (2006).

20. As mentioned in ref. 18, the use of simple acrylate or acrylonitrile as coupling partner resulted in polymerization, which could be avoided by conduting the reaction in neat amine (0.1 M).

21. Dénès, F., Pichowicz, M., Povie, G. & Renaud, P. Thiyl radicals in organic synthesis. *Chem. Rev.* **114**, 2587–2693 (2014).

22. Jin, J. & MacMillan, D. W. C. Alcohols as alkylating agents in heteroarene C–H functionalization. *Nature* **525**, 87–90 (2015).

23. Loh, Y. Y. *et al.* Photoredox-catalyzed deuteration and tritiation of pharmaceutical compounds. *Science* **358**, 1182–1187 (2017).

24. Escoubet, S. *et al.* Thiyl radical mediated racemization of benzylic amines. *Eur. J. Org. Chem.* **2006**, 3242–3250 (2006).

25. Shin, N. Y., Ryss, J. M., Zhang, X., Miller, S. J. & Knowles, R. R. Light-driven deracemization enabled by excited-state electron transfer. *Science* 7 (2019).

26. DeHovitz, J. S. *et al.* Static to inducibly dynamic stereocontrol: The convergent use of racemic β-substituted ketones. *Science* 7 (2020).

27. Seeman, J. I. Effect of conformational change on reactivity in organic chemistry. Evaluations, applications, and extensions of Curtin-Hammett Winstein-Holness kinetics. *Chem. Rev.* **83**, 83–134 (1983).

28. Giese, B. Formation of C–C Bonds by Addition of Free Radicals to Alkenes. *Angew. Chem. Int. Ed. Engl.* **22**, 753–764 (1983).

29. Ahmed, M. *et al.* Hydroaminomethylation with novel rhodium–carbene complexes: an efficient catalytic approach to pharmaceuticals. *Chem. Eur. J.* **13**, 1594–1601 (2007).

30. Schönherr, H. & Cernak, T. Profound methyl effects in drug discovery and a call for new c-h methylation reactions. *Angew. Chem. Int. Ed.* **52**, 12256–12267 (2013).

31. Feng, K. *et al.* Late-stage oxidative C(sp^3)–H methylation. *Nature* **580**, 621–627 (2020).

32. Friis, S. D., Johansson, M. J. & Ackermann, L. Cobalt-catalysed C–H methylation for late-stage drug diversification. *Nat. Chem.* **12**, 511–519 (2020).

33. De Vleeschouwer, F., Van Speybroeck, V., Waroquier, M., Geerlings, P. & De Proft, F. Electrophilicity and Nucleophilicity Index for Radicals. *Org. Lett.* **9**, 2721–2724 (2007).

34. Separation of polar and enthalpy effects in radical addition reactions using polar (σ) and radical (σ·) sigma scales. *J. Phys. Org. Chem.* 6 (2000).

35. Hager, A., Vrielink, N., Hager, D., Lefranc, J. & Trauner, D. Synthetic approaches towards alkaloids bearing α-tertiary amines. *Nat. Prod. Rep.* **33**, 491–522 (2016).

36. Elmore, C. S. & Bragg, R. A. Isotope chemistry; a useful tool in the drug discovery arsenal. *Bioorganic & Medicinal Chemistry Letters* **25**, 167–171 (2015).

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Author contributions

T.R. and Y.S. conceived the concept. T.R. and F.S. directed the investigation. Y.S. performed the experiments and analysed the data. I.F.A. carried out computational studies. T.R., F.S., Y.S. and I.F.A. collated the data, discussed the implications and prepared the manuscript.

Competing interests

The authors declare no competing interests.

Methods

General procedure for simple trialkylamines with electron deficient olefin

A 8.0 mL disposable borosilicate glass tube with screw cap containing a stir bar was charged with TPS-SH (20 mol%, 11.7 mg, 0.04 mmol), $Ir(ppy)_2(dtbbpy)PF_6$ (1 mol%, 1.8 mg, 0.002 mmol), trialkylamine (0.6 mmol, added after solvent if volatile) and olefin (0.2 mmol, added after solvent if liquid). The tube was transferred to a nitrogen-filled glove-box where the dry Tol (2.0 mL, 0.1 M) was added. Then the reaction was stirred for 1 minute and transferred outside, placing ~10 cm away from a Kessil blue LED (34W maximum, 24 VDC) and vigorously stirred for the mentioned time (4~16 h) with cooling by fan. After completion of the reaction, the product was directly purified by flash column chromatography on silica gel with $CHCl_3$/MeOH.

General procedure for simple trialkylamines with 1,1-diaryl ethylene

A 8.0 mL disposable borosilicate glass tube with screw cap containing a stir bar was charged with TPS-SH (5 mol%, 2.9 mg, 0.01 mmol), $Ir(ppy)_2(dtbbpy)PF_6$ (1 mol%, 1.8 mg, 0.002 mmol), trialkylamine (0.6 mmol, added after solvent if volatile) and diaryl styrene (0.2 mmol, added after solvent if liquid). The tube was transferred to a nitrogen-filled glove-box where the dry 1,4-Dioxane (2.0 mL, 0.1 M) was added. Then the reaction was stirred for 1 minute and transferred outside, placing ~10 cm away from a Kessil blue LED (34W maximum, 24 VDC) and vigorously stirred for 8h with cooling by fan. After completion of the reaction, the product was directly purified by flash column chromatography on silica gel with $CHCl_3$/MeOH.

General procedure for pharmaceuticals with vinyl phenyl sulfone

A 8.0 mL disposable borosilicate glass tube with screw cap containing a stir bar was charged with TPS-SH (20 mol%, 5.8 mg, 0.02 mmol), $Ir(ppy)_2(dtbbpy)PF_6$ (1 mol%, 0.9 mg, 0.001 mmol), pharmaceutical (0.3 mmol) and vinyl phenyl sulfone (0.1 mmol, added after solvent if liquid). The tube was transferred to a nitrogen-filled glove-box where the dry toluene (1.0 mL, 0.1 M) was added. Then the reaction was stirred for 1 minute and transferred outside, placing ~10 cm away from a Kessil blue LED (34W maximum, 24 VDC) and vigorously stirred for 8 h with cooling by fan. After completion of the reaction, the product was directly purified by flash column chromatography on silica gel with $CHCl_3$/MeOH.

Data availability

All data generated or analysed during this study are included in this published article and its supplementary information file.