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A manganese catalyst for highly reactive yet chemoselective intramolecular C(sp^3)–H amination

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C–H bond oxidation reactions underscore the existing paradigm wherein high reactivity and high selectivity are inversely correlated. The development of catalysts capable of oxidizing strong aliphatic C(sp^3)–H bonds while displaying chemoselectivity (that is, tolerance of more oxidizable functionality) remains an unsolved problem. Here, we describe a catalyst, manganese *tert*-butylphthalocyanine [Mn(^{t}BuPc)], that is an outlier to the reactivity–selectivity paradigm. It is unique in its capacity to functionalize all types of C(sp^3)–H bond intramolecularly, while displaying excellent chemoselectivity in the presence of π functionality. Mechanistic studies indicate that [Mn(^{t}BuPc)] transfers bound nitrenes to C(sp^3)–H bonds via a pathway that lies between concerted C–H insertion, observed with reactive noble metals such as rhodium, and stepwise radical C–H abstraction/rebound, as observed with chemoselective base metals such as iron. Rather than achieving a blending of effects, [Mn(^{t}BuPc)] aminates even 1° aliphatic and propargylic C–H bonds, demonstrating reactivity and selectivity unusual for previously known catalysts.

High-valent metal heteroatom species (that is, oxos and nitrenes) oxidize inert C–H bonds with tunable site-selectivity and stereospecificity, but typically do not tolerate more readily oxidizable π functionality[1–6]. Intramolecular metallonitrene-based C(sp^3)–H amination of sulfamate esters, which installs medicinally important amino alcohol motifs, showcases the inverse correlation between reactivity and chemoselectivity for such catalysis[7–10]. Noble metal rhodium catalysts that stereospecifically functionalize robust aliphatic C–H bonds (secondary, 2°; tertiary, 3°) lack chemoselectivity due to the competitive oxidation of π bonds (Fig. 1a)[1,7–10]. Conversely, base metal iron catalysts that chemoselectively aminate allylic C–H bonds over competing aziridination are only moderately reactive toward stronger aliphatic C–H bonds (Fig. 1a)[11–15]. Here, we describe the discovery of an outlier catalyst, manganese *tert*-butylphthalocyanine [Mn(^{t}BuPc)] (**3**), which is the first to achieve both high reactivity and chemoselectivity for a C–H oxidation reaction. Catalyst [Mn(^{t}BuPc)] preparatively aminates all C(sp^3)–H bond types encompassed by rhodium, and maintains the high chemoselectivity for allylic C–H amination observed with iron, all while demonstrating stereospecificity, site selectivity and high functional group tolerance (Fig. 1b). Additionally, [Mn(^{t}BuPc)] aminates primary (1°) aliphatic and propargylic C–H bonds, demonstrating reactivity and selectivity that is typically difficult to achieve with metallonitrene-based catalysis. Importantly, we show this reaction enables rapid and scalable late-stage diversification of bioactive molecules. The unique generality of [Mn(^{t}BuPc)] is partially attributed to its mechanistically distinct pathway for nitrene transfer that lies between the stepwise mechanism of iron and the concerted mechanism of rhodium. Discovery of an Earth-abundant base metal catalyst that is capable of aminating all types of C(sp^3)–H bonds, including those challenging to access with precious noble metals, underscores the potential benefits in the continued development of these inexpensive, underexplored metals as catalysts for important synthetic reactions[5,6,11–14,16–19].

Noble metal rhodium catalysts functionalize strong aliphatic C–H bonds via a concerted asynchronous C–H insertion mechanism[1]. Conversely, base metal iron catalysts access mechanistically distinct single-electron pathways for nitrene transfer, affording excellent chemoselectivity with diminished reactivity for stronger C–H bond types[11–14]. We hypothesized that a metal catalyst capable of transferring bound nitrenes to C(sp^3)–H bonds via a stepwise mechanism with attenuated radical character of the metallonitrene oxidant relative to iron would achieve higher reactivity while maintaining chemoselectivity[20]. The low reactivity observed under iron catalysis with aliphatic C(sp^3)–H bonds coupled with reports that sulfamate ester *N*-centred free radicals are unreactive towards intramolecular aminations of 3° C(sp^3)–H bonds[21] suggested to us that a metallonitrene with diminished radical character would be more reactive. Although nature rarely uses manganese metal species to mediate oxidations, early studies using synthetic metalloporphryins as models for cytochrome P450 demonstrated that manganese and iron oxos react via mechanistically analogous one-electron pathways, with manganese exhibiting significantly higher C–H hydroxylation reactivity[22]. Importantly, the manganese catalysts were found to have smaller kinetic isotope effects (KIE) than their iron counterparts, suggestive of attenuated radical behaviour[23]. Moreover, well-characterized nitridomanganese(v) porphyrin complexes have been shown to stoichiometrically transfer nitrenes when the nitrogen is rendered electron-deficient, much like with iron[24–26].

Results

Reaction development. We first compared a series of manganese complexes with their iron counterparts for the C–H amination of challenging 3° aliphatic substrate **4** (bond dissociation energy (BDE) of ~96 kcal mol^{-1})[27]. Improved yields of aminated product **5** were observed with the manganese complexes across all ligand classes (Table 1, entries 1–8). The previously reported phthalocyanine ligand was most effective[11], so catalyst **2** was used for further optimization. Notably, both iron and manganese porphyrin catalysts, among the first catalysts shown to be competent for metallonitrene-based C–H amination[28], exhibited

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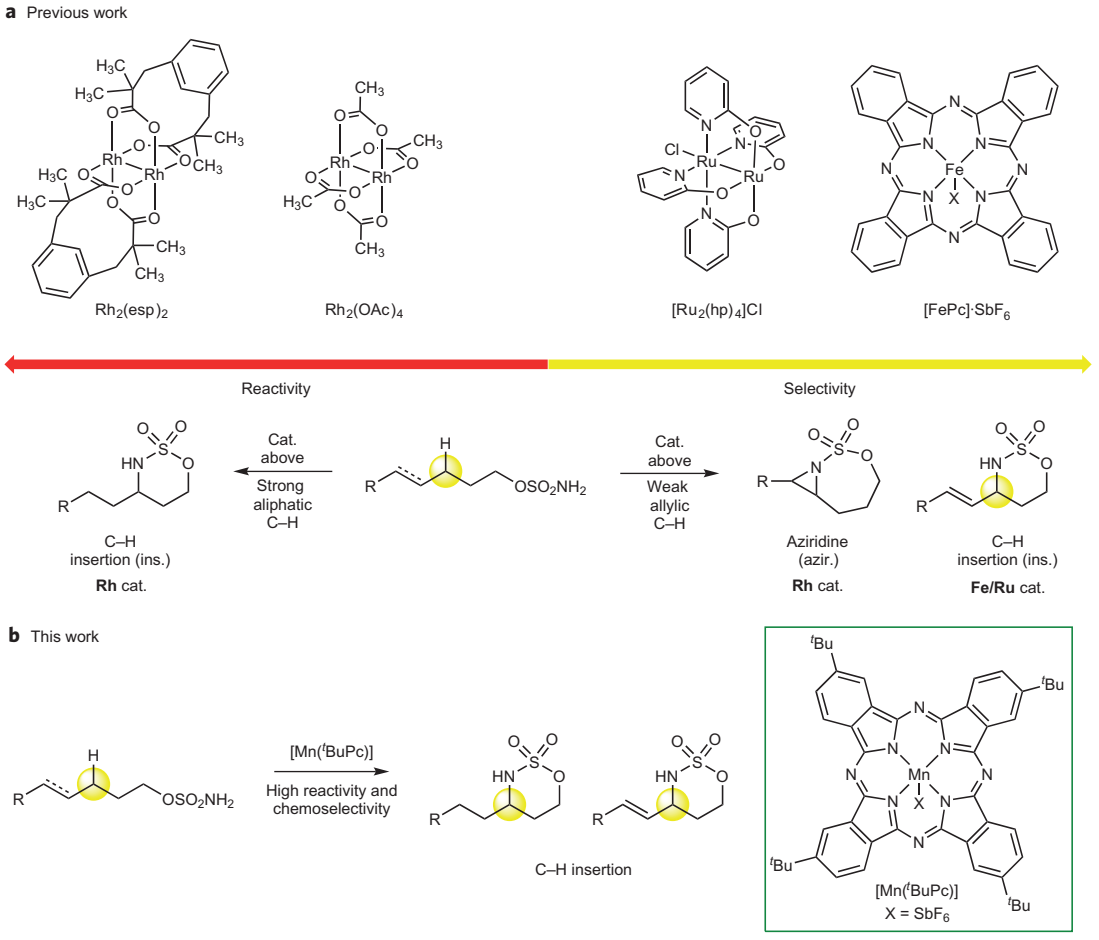

Figure 1 | The C–H oxidation reactivity/selectivity paradigm. a, Reactivity and chemoselectivity of existing C–H amination catalysts with sulfamate ester substrates. Rhodium catalysts aminate strong 2° C–H bonds in aliphatic substrates but aziridinate reactive π functionality in allylic substrates. Iron and ruthenium catalysts aminate weak allylic bonds with high chemoselectivity, but demonstrate limited reactivity towards strong aliphatic C–H bonds. **b**, Novel [Mn(ᵗBuPc)] catalyst demonstrates both high reactivity and chemoselectivity. It is capable of aminating strong aliphatic C–H bonds while tolerating reactive π functionality in allylic substrates.

significantly lower reactivity with this challenging substrate (entries 3 and 4). The enhanced reactivity for an electrophilic C–H amination reaction may be attributed to an electronic difference between these ligands, as evidence suggests that phthalocyanines are significantly better π-acceptor ligands and may lead to enhanced electrophilicity at the metal centre[29,30]. The addition of molecular sieves significantly improved reactivity with both 10 and 5 mol% catalyst **2**, affording 60% and 58% of **5**, respectively (entries 9 and 10). Catalyst **3**, in which *tert*-butyl groups were introduced into the periphery of the phthalocyanine ligand, further improved the yield to 75% (entry 11). This modification was not similarly beneficial for the corresponding iron complex (29% yield, entry 12). The enhanced productivity of **3** enables the catalyst loading to be reduced to 5 mol% (72%, entry 13) and in some cases to 2.5 mol% (71%, entry 14). Additionally, the oxidant loading can be reduced to 1.2 equiv. while still maintaining good reactivity (68%, entry 15).

Reaction generality. This new catalytic method was examined with all other major sp^3 C–H bond types (benzylic, allylic, 2° and 1° aliphatic) using unsubstituted linear sulfamate esters, among the most difficult substrate classes for intramolecular C–H amination (Table 2). In all cases, a significant improvement in yield was observed in switching from the iron to the manganese phthalocyanine catalyst, with the benzylic and allylic substrates affording synthetically useful yields of aminated products **6** and **7** (entries 1 and 2). Catalyst **3** exhibited good reactivity across all bond types with 2° (**8**, BDE of ~98 kcal mol^{-1}) and even 1° (**9**, BDE of ~101 kcal mol^{-1})[27] C–H bonds being readily intramolecularly aminated (entries 3 and 4). Significantly, 1° C–H bonds are at the lowest end of the reactivity spectrum under rhodium catalysis, and amination of this bond type is rare (*vide infra*)[31]. Moreover, despite the high intramolecular reactivity of **3**, excellent chemoselectivity (>20:1 insertion (ins.)/aziridine (azir.)) was maintained for allylic C–H amination, as compared to 1:1 ins./azir. observed for rhodium catalyst [Rh_2(esp)$_2$] (bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)]; ref. 31) (entry 2).

Catalyst **3** is capable of aminating 3°, 2° and 1° aliphatic C–H bonds in a broad range of substrates with good functional group tolerance and site-selectivity (Table 3). Adjacent functionality, such as protected nitrogen (**10**, 79%) and silyl ethers (**11**, 71%), is well tolerated. In the presence of proximally equivalent C–H bonds, catalyst **3** discriminates according to BDE, functionalizing at the weaker β 3° C–H bond of an isopinocampheol derivative in the presence of a β 2° C–H bond (**12**, 63%; *vide infra* Fig. 2c). Amination of 3° C–H bonds is also effective for the formation of azaspirocycles (**13**, 52%) and fused bicycles (**14**, 86%). Additionally, **3** exhibits sensitivity to substrate electronics (that is, inductive effects) in the amination of 2° C–H bonds. A remote electron-withdrawing ester moiety has limited impact on amination at the *γ* position

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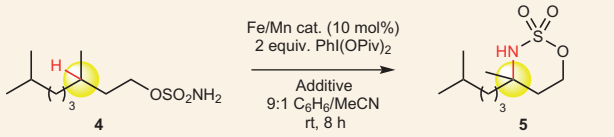
Table 1 | Reaction development with [Mn(^{t}BuPc)] catalyst.



Entry	Catalyst	Additive	% yield (% rsm)
1	[FePc]·SbF_6 (1)*	-	29 (32)
2	[MnPc]·SbF_6 (2)*	-	43 (27)
3	Fe(TPP)·SbF_6*	-	4 (85)
4	Mn(TPP)·SbF_6*	-	18 (62)
5	Fe(*R,R*-salen)·SbF_6*	-	<1 (85)
6	Mn(*R,R*-salen)·SbF_6*	-	4 (78)
7	Fe(*R,R*-PDP)$(SbF_6)_2$	-	<1 (91)
8	Mn(*R,R*-PDP)$(SbF_6)_2$	-	7 (82)
9	[MnPc]·SbF_6 (2)*	4 Å MS	60 (11)
10	[MnPc]·SbF_6 (2)*	4 Å MS	58 (20)†
11	[Mn(^{t}BuPc)]·SbF_6 (3)*	4 Å MS	75 (<5)
12	[Fe(^{t}BuPc)·SbF_6]*	4 Å MS	29 (34)
13	[Mn(^{t}BuPc)]·SbF_6 (3)*	4 Å MS	72 (14)†
14	[Mn(^{t}BuPc)]·SbF_6 (3)*	4 Å MS	71 (13)‡
15	[Mn(^{t}BuPc)]·SbF_6 (3)*	4 Å MS	68 (16)†,§

Isolated yields are an average of three runs with recovered starting material (rsm) in parentheses. Pc, phthalocyanine; TPP, tetraphenylporphyrin; salen, *N,N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine; PDP, [*N,N'*-bis(2-pyridylmethyl)]-2,2'-bipyrrolidine. *Active catalyst formed via *in situ* metathesis using equimolar $AgSbF_6$ and chloride pre-catalyst. †5 mol% each Mn catalyst and $AgSbF_6$. ‡2.5 mol% each Mn catalyst and $AgSbF_6$. §1.2 equiv. $PhI(OPiv)_2$. Piv, pivaloyl.

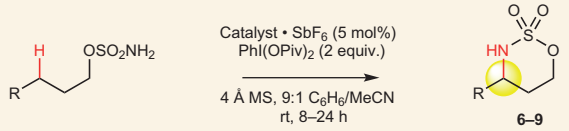
(**15**, 57%), but will attenuate reactivity when made more proximal (Supplementary Table 3 and Supplementary compound **S36**). A distal tosylate group is tolerated under the reaction conditions to afford **16** in 54% yield; this functionality can be subsequently displaced intramolecularly to generate a heterobicycle in 80% yield (Supplementary compound **S37**). In addition, 2° C–H amination in cyclohexanes can occur across the ring in a 1,3-fashion, functionalizing adjacent to a bulky *tert*-butyl group in a *cis* relationship (**17**, 90%), which would be challenging to accomplish with traditional synthetic methods.

Under [Mn(^{t}BuPc)] **3** catalysis, amination of γ C–H bonds to form six-membered oxathiazinanes is generally preferred over β C–H bonds to form five-membered oxathiazoles, regardless of the relative bond strength. For example, in the functionalization of a borneol derivative, amination selectively occurs at the stronger γ 1° C–H bond of the adjacent methyl group to afford **18** in 53% yield. Competitive C–H amination at the β 2° C–H bond is geometrically possible with this substrate and is observed in 27% yield. This ring-size selectivity has been noted with rhodium catalysis and is based on the geometric constraints imposed by the favoured N–S–O bond angles of the sulfamate tether[1]. However, the ability to aminate effectively at 1° methyl groups with metallonitrenes is rare, and the reported examples with iron[12,14] and rhodium[31,32] are low yielding. A limitation to this trend can be observed when amination to form a six-membered heterocycle requires functionalization of an exceptionally strong γ C–H bond over a much weaker β C–H bond. Amination of a cyclopropane-containing substrate occurs exclusively at the stereoelectronically activated β 2° C–H bond (BDE of ~97 kcal mol^{-1}) to form five-membered sulfamidate **19** (51%) as opposed to the six-membered oxathiazinane, which would require abstraction of a much stronger 3° cyclopropane C–H bond (BDE of ~106 kcal mol^{-1})[27].

Catalyst **3** successfully aminates at the allylic position in a variety of molecules, in all cases maintaining the excellent chemoselectivity previously observed with [Fe^{III}Pc] for olefin-containing substrates (Table 3)[11]. For example, with a challenging linear terminal olefin substrate, catalyst **3** affords C–H amination product **20** in 50% yield and in 7:1 excess over the aziridine. Iron catalyst **1** exhibits similarly high chemoselectivity (7:1 ins./azir.) but poor reactivity (22%), whereas a noble metal ruthenium catalyst [$Ru_2(hp)_4$] (tetrakis-(2-oxypyridinato)diruthenium(II, III) chloride), designed to be highly chemoselective, is less selective for insertion (2:1 ins./azir.)[15] and $Rh_2(esp)_2$ favours π functionalization (1:1.5 ins./azir.)[31]. Additionally, [Mn(^{t}BuPc)] exhibits diminished sensitivity to substrate electronics relative to its iron predecessor with weaker C(sp^3)–H bond types (Fig. 2b, *vide infra*). Catalyst **3** readily functionalizes C–H bonds proximal to an α,β-unsaturated ester (**21**, 77%), while other chemoselective catalysts **1** and [$Ru_2(hp)_4$] are less reactive (12 and 25%, respectively)[11,15]. This electronic insensitivity is further highlighted by the tolerance of electron-withdrawing nitrogen functionality (**22**, 73%) introduced via palladium-catalysed intermolecular allylic C–H amination[33]. A cyclohexene derivative readily cyclizes to form bicycle **23** in 69% yield with excellent diastereoselectivity (>20:1 *anti/syn*). The high chemoselectivity for allylic C–H amination over aziridination with [Mn(^{t}BuPc)] **3** is maintained even in cases where aziridination is geometrically preferred. The homoallylic sulfamate derivative of terpene (–)-nopol undergoes facile allylic C–H amination with catalyst **3** at the β-position to furnish the five-membered heterocycle (**24**, 60%) with no observed aziridine. This bias of **3** toward allylic C–H amination versus aziridination persists even in an acyclic styrenyl homoallylic sulfamate ester substrate (**25**, 62%, 7:1 ins./azir.). In contrast, both reactivity and chemoselectivity are lower with typically chemoselective chiral rhodium catalysts[34] ([Rh_2(*S*-nap)$_4$], 48%, 2:1 ins./azir.), and formation of the aziridine product is strongly favoured (1:20 ins./azir.) with standard $Rh_2(OAc)_4$ (ref. 1).

Although chemoselective propargylic C–H amination with carbamates to furnish 1,2-amino alcohols is precedented[35], amination using sulfamate esters to afford the 1,3-amino alcohol motif is

Table 2 | Manganese versus iron catalyst comparison with unsubstituted linear substrates.



Entry	Product	Yield (%, based on catalyst) [FePc] (1)	[MnPc] (2)	[Mn(^{t}BuPc)] (3)
1	Benzylic (6)	22	71	74
2	Allylic (7), >20:1 ins./azir.	10	61	61
3	2° C–H (8)	5†	39†	57†
4	1° C–H (9)	3†	37†	64†

Isolated yields are average of three runs. *Conditions: 5 mol% [FePc]Cl, 5 mol% $AgSbF_6$, 2 equiv. $PhI(OPiv)_2$, 4:1 PhMe/MeCN (0.5 M), rt, 8 h. †10 mol% catalyst.

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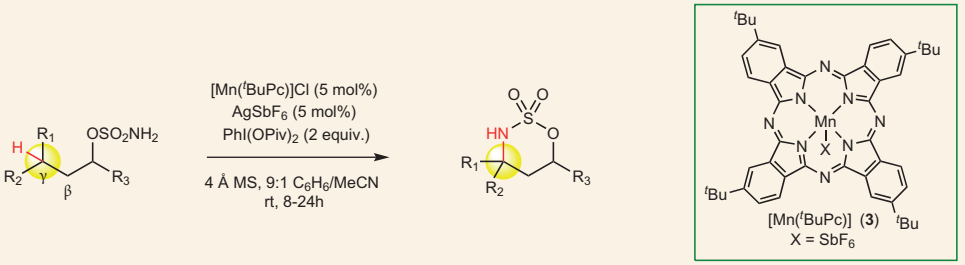
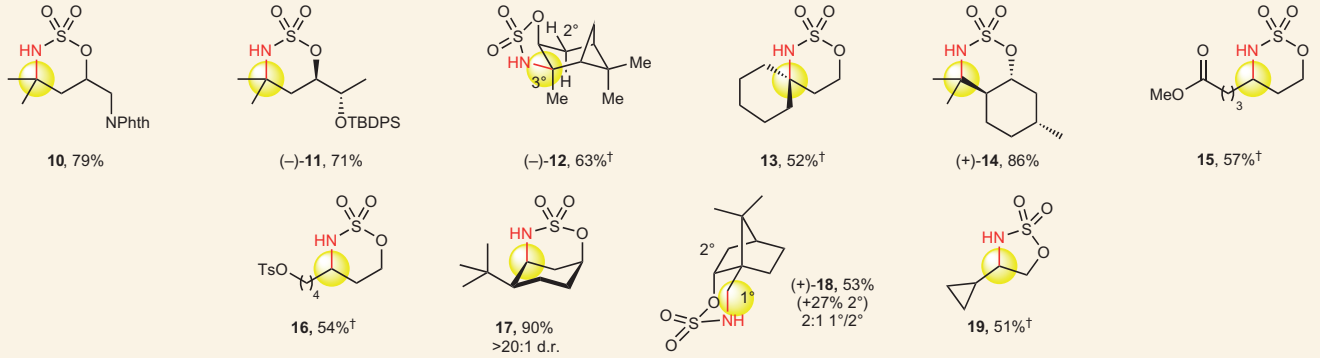
Table 3 | Substrate scope of [Mn(ᵗBuPc)]-catalysed C–H amination.



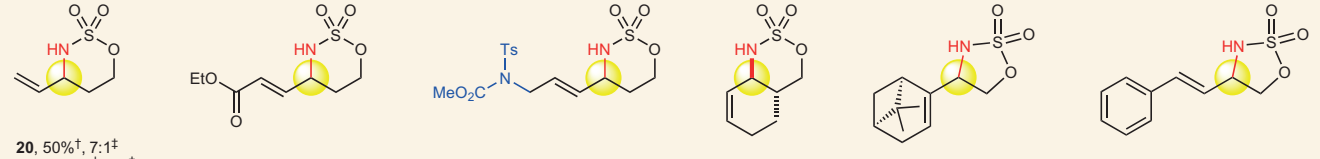
Aliphatic



10, 79% | (–)-**11**, 71% | (–)-**12**, 63%† | **13**, 52%† | (+)-**14**, 86% | **15**, 57%†

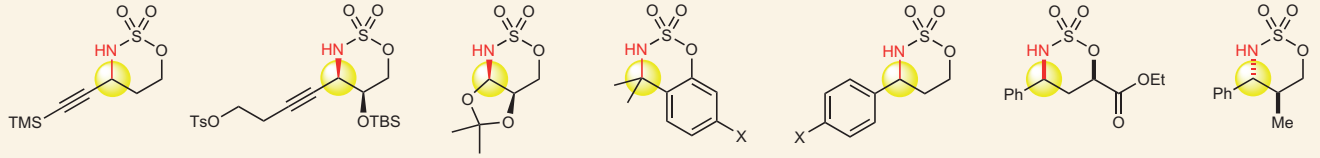
16, 54%† | **17**, 90% >20:1 d.r. | (+)-**18**, 53% (+27% 2°) 2:1 1°/2° | **19**, 51%†

Allylic

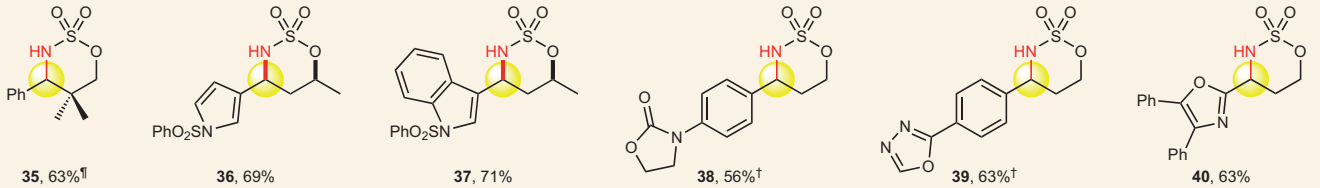


20, 50%†, 7:1‡ [FePc]: 22%*†, 7:1‡ [Ru2(hp)4]: 2:1‡,§ Rh2(esp)2: 1:1.5‡,§ | **21**, 77%† [FePc]: 12%*,† [Ru2(hp)4]: 25%§ | **22**, 73%† | **23**, 69% >20:1 d.r. | **24**, 60% 2:1 d.r. | **25**, 62%, 7:1‡ [Rh2(*S*-nap)4]: 2:1‡,§ Rh2(OAc)4: 1:20‡,§

Propargylic, ethereal, benzylic



26, 64% | (–)-**27**, 48%† 1:1 d.r. | (–)-**28**, 64% >20:1 d.r. | **29**, X = H, 69% [FePc]: 43%*,† **30**, X = OBoc, 69% | **31**, X = Br, 68% [FePc]: 30%* **32**, X = CF_3, 58%† | **33**, 64%† >20:1 d.r. | **34**, 68% >20:1 d.r.



35, 63%¶ | **36**, 69% 7:1 d.r. | **37**, 71% 12:1 d.r. | **38**, 56%† | **39**, 63%† | **40**, 63% oxaprozin derivative

Isolated yields are average of three runs. *Conditions: 5 mol% [FePc]Cl, 5 mol%$AgSbF_6$, 2 equiv. $PhI(OPiv)_2$, 4:1 PhMe/MeCN (0.5 M), rt, 8 h. †10 mol% catalyst. ‡Ins./azir. ratio. §For $Rh_2(esp)_2$ see ref. 31. For $Rh_2(OAc)_4$ and $[Rh_2(S\text{-nap})_4]$ see ref. 1. For $[Ru_2(hp)_4]$ see ref. 15. ¶10% of 1° C–H amination also isolated.

challenging as the alkyne typically undergoes alternative oxidation pathways[36]. Instead, two-step sequences have been developed that involve amination of activated ethereal C–H bonds to furnish *N*,*O*-acetals followed by Lewis acid-promoted alkylations to generate propargylic amines[1]. Further underscoring the high chemoselectivity achieved with manganese catalysis, a trimethylsilyl (TMS)-protected terminal alkyne sulfamate ester readily undergoes propargylic C–H amination (**26**, 64%). α-Substituted alkyne **27** functionalizes in moderate yields and serves as a viable intermediate for a streamlined synthesis of saxitoxin[37]. Alternatively, ethereal C–H amination can be performed in good yield and diastereoselectivity (64%; >20:1 d.r.) with catalyst **3** to furnish the sensitive oxathiazinane *N*,*O*-acetal **28**, a known precursor to alkyne **27**.

Catalyst **3** functionalizes benzylic C–H bonds in a variety of aromatic and heterocyclic compounds, further demonstrating the generality of this method (Table 3). Phenolic sulfamate esters cyclize with iron catalyst **1** in modest yields due to deleterious substrate decomposition (**29**, 43%), but these substrates are functionalized

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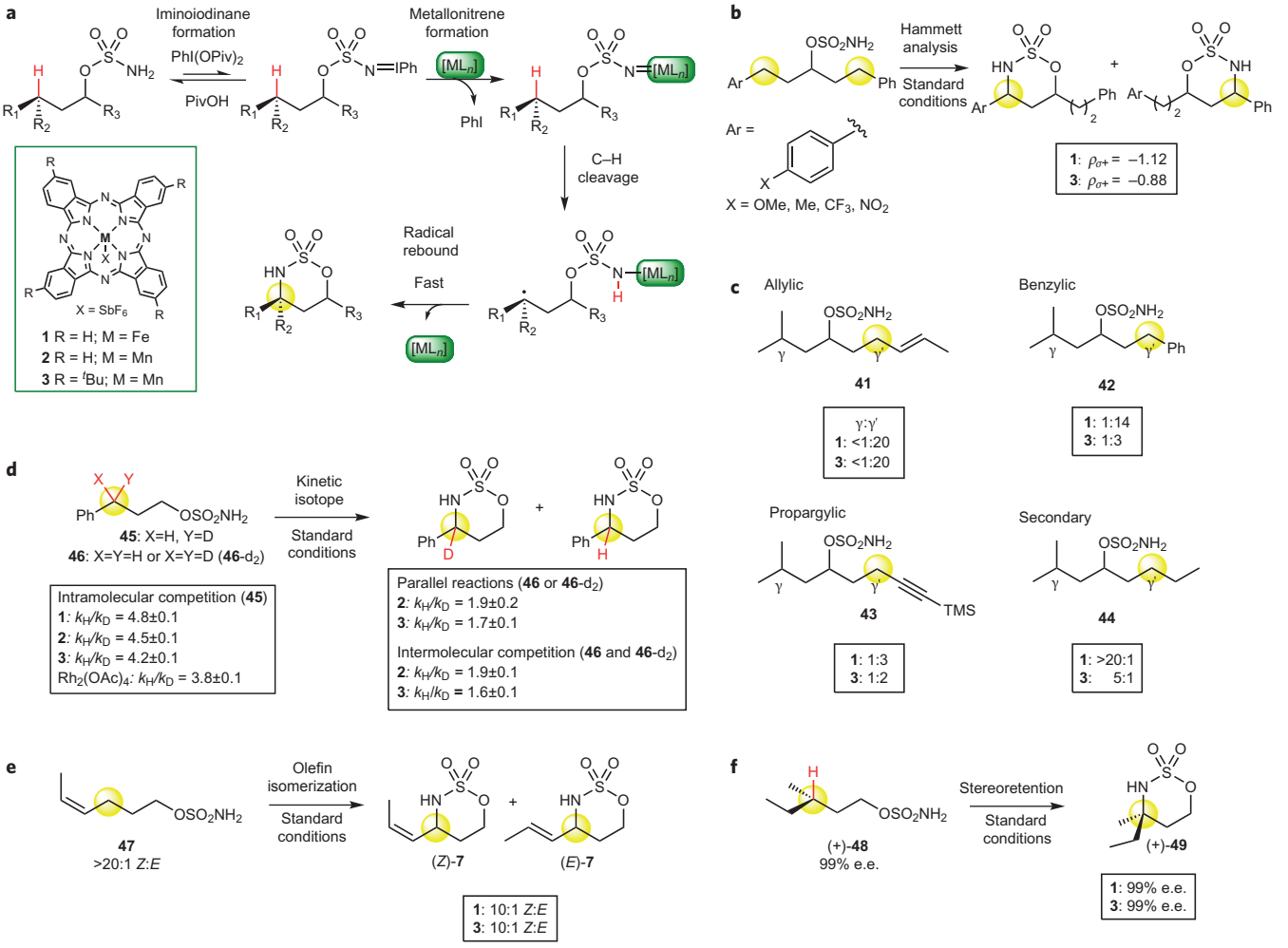

Figure 2 | Mechanistic studies of manganese and iron C–H amination catalysts. a, Proposed stepwise mechanism for manganese and iron catalysis. **b**, Intramolecular Hammett analysis (σ^+) reveals that **3** is less sensitive to the electronics of the C–H bond than **1**, but more so than reported for rhodium ($\rho = -0.55$). **c**, C–H bond reactivity trends for 3° aliphatic C–H bonds relative to other bond types show that **3** reacts according to relative C–H BDE but is less discriminating than **1**, indicating attenuated radical character in C–H cleavage. **d**, KIE values for intramolecular competition experiments for catalysts **1**, **2**, **3** and $Rh_2(OAc)_4$ (quantitative ^{13}C NMR spectroscopy) suggest manganese catalysis proceeds via a transition structure where C–H bond breakage occurs to a greater extent than with rhodium but less than with iron. Intermolecular KIE studies with catalysts **2** and **3** suggest C–H cleavage contributes to the reaction rate but is not solely rate-determining. **e**, Partial isomerization of *Z*-olefin substrate **47** with catalysts **3** and **1** support a stepwise mechanism. **f**, Complete stereoretention in C–H amination of enantiometrically enriched (+)-**48** with catalysts **3** and **1** supports a rapid radical rebound of the nitrogen from the base metal catalyst versus a free radical intermediate.

with manganese catalyst **3** in improved yields (**29**, 69%; **30**, 69%). Catalyst **3** promotes benzylic C–H amination on substrates with varying degrees of electronic deactivation, such as *para*-Br- and *para*-CF_3-substituted benzylic substrates (**31**, 68% and **32**, 58%, respectively). In contrast, iron catalyst **1** is less reactive for electronically deactivated benzylic substrates (**31**, 30%). Both α- and β-branched sulfamates readily undergo benzylic C–H amination with excellent diastereoselectivity (>20:1), favouring the conformationally preferred *syn* and *anti* oxathiazinane, respectively (**33**, 64%; **34**, 68%)[1]. Sterically encumbered benzylic substrates with quaternary centres adjacent to the site of functionalization still aminate in good yields (**35**, 63%). Given the prevalence of heterocycles in medicinally relevant compounds, we evaluated the tolerance of this method to aromatics with varying degrees of heteroatom incorporation. Pyrrole and indole substrates both afforded good yields and diastereoselectivities of the desired C–H amination products (**36**, 69%, 7:1 d.r. and **37**, 71%, 12:1 d.r., respectively). *N*-aryloxazolidinones and oxadiazoles, which contain both nitrogen and oxygen heteroatoms, proceeded smoothly under the reaction conditions (**38**, 56% and **39**, 63%, respectively). Exemplifying the potential application of this method to late-stage diversification of pharmaceuticals, an oxazole-based substrate derived from the commercial nonsteroidal anti-inflammatory drug (NSAID) oxaprozin furnished oxathiazinane **40** in 63% yield.

Mechanistic studies. We sought to investigate our hypothesis that the unique generality of catalyst **3** can be attributed to the attenuated radical character of the manganese metallonitrene oxidant relative to iron. Intramolecular competition experiments were conducted to probe the C–H amination steps of the catalytic cycle independently from the reaction kinetics (Fig. 2a). The electronic nature of the transition state for C–H cleavage was assessed by way of Hammett analysis with a series of sulfamate ester substrates having two electronically dissimilar benzylic sites (Fig. 2b and Supplementary Fig. 1). Plotting $\log(k_{Ar}/k_H)$ against substituent parameter σ^+ gave linear correlations, with manganese showing less sensitivity to the electronics of the C–H bond relative to iron ($\rho = -0.88$ for **3**, –1.12 for **1**), but significantly

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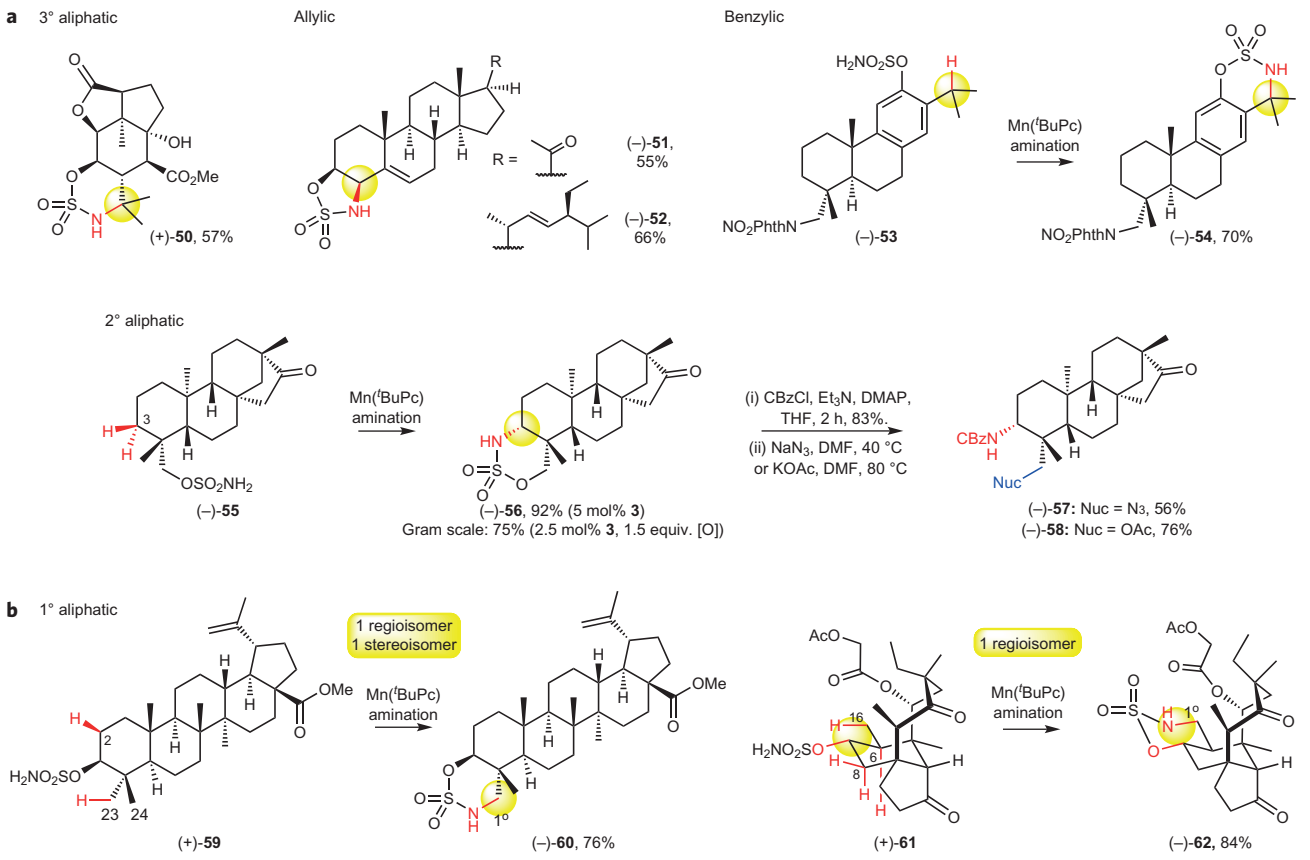

Figure 3 | Late-stage diversification of complex molecules via [Mn(ᵗBuPc)]-catalysed C–H amination. Amination of native oxygen-containing complex molecules picrotoxinin, pregnenolone, stigmasterol, isosteviol and betulinic acid, as well as those where hydroxyl functionality is readily installed, leelamine and dihydropleuromutilone. **a**, Predictably selective C–H amination occurs on allylic, benzylic and 3° and 2° aliphatic C–H bonds in the presence of alternative reactive functionality. Isosteviol derivative (–)-**55** undergoes C–H amination on a gram scale and the resulting oxathiazinane (–)-**56** is derivatized to reveal 1,3 diamine and amino alcohol motifs. DMAP, 4-dimethylaminopyridine. **b**, Site- and diastereoselective 1° aliphatic C–H amination of betulinic acid (+)-**59** and dihydropleuromutilone (+)-**61** sulfamate ester derivatives in the presence of alternative, accessible 2° and 3° C–H bonds to furnish geometrically favoured six-membered oxathiazinanes.

more than that reported for rhodium catalysts ($\rho = -0.55$)[1,15]. These data are consistent with the reactivity trends observed between manganese and iron with electronically deactivated substrates and suggest a transition structure in which C–H cleavage for manganese is less pronounced than for iron, but more so than the related transition structure for the concerted rhodium-catalysed process[15]. We also systematically compared the C–H bond reactivity trends for γ 3° aliphatic C–H bonds relative to other bond types (γ′) (**41**–**44**, Fig. 2c). The reactivity trends correlate with the homolytic C–H BDEs for both manganese and iron, but manganese shows less discrimination between the different bond types, consistent with diminished electrophilic radical character in the C–H cleavage transition state. Additionally, benzylic amination of monodeuterated substrate **45** provides an intramolecular KIE for manganese catalyst **3** (4.2 ± 0.1) that lies between iron catalyst **1** (4.8 ± 0.1) and $Rh_2(OAc)_4$ catalyst (3.8 ± 0.1) (Fig. 2d). Taken together, these data support our hypothesis that catalyst **3** proceeds through a stepwise mechanism with a transition structure in which C–H bond breakage occurs to a lesser extent than with iron[15]. Notably, catalyst **3** behaved in a manner comparable to its unsubstituted manganese analogue **2**, with the exception that a slightly smaller intramolecular KIE was observed with **3** (4.2) relative to **2** (4.5), suggesting that this ligand modification results in further attenuation of radical character.

We next evaluated the recombination step for manganese catalyst **3**. In the allylic C–H amination of *Z*-olefin substrate **47** (>20:1 *Z*/*E*), olefin isomerization was observed with manganese catalyst **3** to the same degree as with iron catalyst **1**, affording a 10:1 *Z*/*E* mixture of **7** (Fig. 2e). Characteristic of a reaction proceeding via a concerted C–H amination mechanism, an analogous substrate has been reported to proceed with no isomerization under rhodium catalysis[11]. Importantly, C–H amination at a defined aliphatic stereocentre in **48** proceeds with complete stereoretention for manganese catalysts **2** and **3** as well as for iron catalyst **1** (**49**, 99% enantiomeric excess (e.e.), Fig. 2f). These data further support a stepwise mechanism for manganese that proceeds through H atom abstraction followed by rapid radical rebound from the base metal catalyst. In contrast to aminations that proceed via free radical intermediates[21,38,39], this mechanistic feature of metallonitrene chemistry allows C–H amination reactions to proceed stereospecifically with high functional group tolerance, and enables the prospect of tuning the catalyst to control selectivity during functionalization[6].

To gain further mechanistic insight, we investigated the influence of manganese catalyst **3** on reaction kinetics. The reaction profile for a 2° aliphatic substrate suggested an overall reaction rate enhancement with **3** relative to both **1** and **2**, resulting in significantly higher product yields with **3** (Supplementary Fig. 2). Initial rate measurements for 2° and benzylic C–H amination with **3** quantitatively support catalyst involvement in the rate-determining step of the reaction, as changes in catalyst concentration (5–10 mol%) result in proportional changes in the initial rate (Supplementary Figs 3–5 and 10). This contrasts with rhodium catalysis, where there is no rate dependence on catalyst concentration, and iminoiodinane formation is hypothesized to be rate-determining[1,31].

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Moreover, measuring initial rates on parallel reactions with benzylic substrate **46** and **46**-d_2 revealed a primary KIE of 1.7 for catalyst **3** and 1.9 for catalyst **2**. Consistent with this, an intermolecular competition experiment with 1 equiv. each of **46** and **46**-d_2 gave a KIE of 1.6 for **3** and 1.9 for **2** from isolated product ratios (Fig. 2d). These two KIE experiments with manganese catalysts **2** and **3** provide values that are larger than would be expected for a rate-determining step that did not involve C–H cleavage (k_H/k_D of ~1), but smaller than if C–H cleavage was solely rate-determining (k_H/k_D of ~3.5–6)[40]. Ligand modification on the manganese catalyst results in small differences in KIE (Fig. 2d), providing support for a manganese-bound nitrene species in the C–H cleavage step. Collectively, these data suggest that the C–H cleavage step contributes significantly to the overall reactivity and selectivity observed with catalyst **3**, a mechanistic feature that enables tunable control over selectivity in oxidation.

Late-stage C–H amination. The reactivity, site- and chemoselectivity trends observed with catalyst **3** on relatively simple molecules are maintained in more topologically and functionally complex natural product settings (Fig. 3). A functionally dense picrotoxinin derivative, containing an unprotected 3° alcohol, reacted smoothly under standard reaction conditions at a 3° C–H bond to produce fused bicycle **50** in 57% yield (Fig. 3a). Allylic C–H amination of sulfamate ester-derived steroids pregnenolone and stigmasterol furnished five-membered heterocycles **51** and **52** in 55% and 66% yields, respectively, as single diastereomers. A leelamine-derived phenolic sulfamate ester **53** gave 70% yield of the 3° benzylic C–H amination product **54**. Isosteviol derivative **55** was functionalized at the equatorial γ 2° aliphatic C–H bond to furnish **56** in 92% yield as a single *syn* diastereomer. Importantly, this reaction is high yielding (75%) with reduced catalyst (2.5 mol% **3**) and oxidant (1.5 equiv.) loadings, and scales readily. The versatile oxathiazinane moiety can also be diversified easily[41]. For example, reaction of *N*-carboxybenzyl (Cbz)-protected oxathiazinane **56** with NaN_3 or KOAc affords 1,3-diamine (**57**, 56%) or amino alcohol (**58**, 76%) precursors.

Whereas C–H amination methods proceeding with noble metals (for example, iridium) via organometallic intermediates have a steric preference for functionalizing 1° methyl groups[42], electrophilic high-valent metal–heteroatom species (that is, oxos and nitrenes) typically display poor reactivity with 1° methyl C–H bonds due to their high BDEs and low basicity. Based on our observation that γ 1° methyl C–H bonds can be selectively functionalized by catalyst **3** in preference to weaker β C–H bonds, we sought to explore this exciting new reactivity and selectivity in complex molecule settings (Fig. 3b). Betulinic acid is a readily available pentacyclic triterpenoid with demonstrated mitochondrial-targeted antitumour activity[43]. Betulinic acid-derived sulfamate ester **59** may undergo amination at either the γ 1° C–H bond of a C23 methyl group to furnish a six-membered heterocycle or a β 2° C–H bond to generate a five-membered heterocycle. Consistent with selectivities observed in simpler substrates (**18**, *vide supra*), catalyst **3** preferentially aminates at the γ 1° C–H bond of the equatorial C23 methyl group with high site- and diastereoselectivity to furnish oxathiazinane **60** in 76% yield. This provides a functional handle for a range of further modifications (*vide supra*) that may attenuate betulinic acid's high lipophilicity, which has thus far limited its bioavailability.

Dihydropleuromutilone sulfamate ester derivative **61**, rapidly generated via Fe(PDP)-catalysed C–H hydroxylation and subsequent sulfamoylation at C7, presented the opportunity for additional investigation of site selectivity in a complex molecule setting[44]. For **61**, C–H amination can feasibly occur at three sites: the γ 1° C–H bond (C16), the β 2° C–H bond (C8) or the β 3° C–H bond (C6). Notably, **3**-catalysed C–H amination again resulted in the exclusive formation of 1° C–H amination oxathiazinane product **62** in 84% yield, a remarkably high level of reactivity for 1° aliphatic C–H bond amination under metallonitrene catalysis. These results establish that native alcohols present in a wide range of readily available natural products, as well as those that can be readily installed, serve as valuable handles to install nitrogen into a broad range of sp^3 C–H bonds in predictable 1,3- or 1,2-relationships.

Conclusion

We have reported a novel manganese C–H amination catalyst, readily synthesized in one step from commercial materials (see Supplementary Information), that is ten million times more abundant than its noble metal predecessor[45]. While further development of this reaction is required, [Mn(^{t}BuPc)] **3** is unique in its capacity to intramolecularly functionalize all types of C(sp^3)–H bonds (including 1° aliphatic and propargylic) while maintaining stereospecificity and broad functional group tolerance in complex molecule settings. Studies indicate that the mechanism of metallonitrene insertion into sp^3 C–H bonds for [Mn(^{t}BuPc)] lies between that of the concerted asynchronous C–H insertion observed with rhodium and the stepwise radical C–H abstraction/rebound observed for iron. Rather than demonstrating reactivity and selectivity between the two, [Mn(^{t}BuPc)] promotes intramolecular C–H amination with higher reactivity than rhodium while maintaining the high chemoselectivity observed with iron. This finding challenges the bounds of the reactivity/selectivity paradigm and informs an approach to discover other highly reactive and selective C–H oxidation reactions with catalysts that access tunable high-valent metal–heteroatom species.

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Author contributions

S.M.P., J.R.G., J.P.Z., A.L.P. and S.M.M. conducted the experiments and analysed the data. S.M.P., J.R.G. and M.C.W. conceived and designed the project, analysed the data and prepared the manuscript.

Additional information

Supplementary information and chemical compound information are available in the online version of the paper. Metrical parameters for the structure of 56 are available free of charge from the Cambridge Crystallographic Data Centre under reference CCDC-1421220. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to M.C.W.

Competing financial interests

The University of Illinois has filed a patent application on the [Mn(^{t}BuPc)] catalyst for general C–H functionalizations. The [Mn(^{t}BuPc)] catalyst (prod # 799688) will be offered by Aldrich through a licence from the University of Illinois.

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