Manganese-catalyzed benzylic C(sp³)–H amination for late-stage functionalization

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Abstract

Reactions that directly install nitrogen into C–H bonds of complex molecules are significant because of their potential to change the chemical and biological properties of a given compound. Although selective intramolecular C–H amination reactions are known, achieving high levels of reactivity, while maintaining excellent site-selectivity and functional-group tolerance, remains a challenge for intermolecular C–H amination. Herein, we report a manganese perchlorophthalocyanine catalyst [Mn^{III}(ClPc)] for intermolecular benzylic C–H amination of bioactive molecules and natural products that proceeds with unprecedented levels of reactivity and site-selectivity. In the presence of Brønsted or Lewis acid, the [Mn^{III}(ClPc)]-catalyzed C–H amination demonstrates unique tolerance for tertiary amine, pyridine and benzimidazole functionalities. Mechanistic studies suggest that C–H amination likely proceeds through an electrophilic metallonitrene intermediate via a stepwise pathway where C–H cleavage is the rate-determining step of the reaction. Collectively these mechanistic features contrast previous base-metal catalyzed C–H aminations and provide new opportunities for tunable selectivities.

Introduction of nitrogen into natural products and biologically active small molecules has the potential to drastically change the physical and biological properties of a given molecule.[1] For example, ampicillin, the first broad spectrum penicillin derivative, differs from

penicillin G by the presence of a benzylic amine (Figure 1a).[2] In fact, the importance of nitrogen in the benzylic position of pharmacophores can be gleaned by its appearance in top selling FDA approved drugs such as imatinib, meclizine, clopidogrel, sertraline, rivastigmine, donepezil, and many others.[3] In nature, such nitrogen functionality is installed through oxygenated intermediates.[4] For example, in the biosynthesis of L-*p*-hydroxyphenylglycine, a crucial component of several peptidic natural products, the benzylic amine is installed from the benzylic ketone.[5] Analogously, standard synthetic methods to install nitrogen rely on functional group transformations from pre-oxidized carbon-heteroatom (C–O, C–X, X = halogens) precursors.[6–8] This approach limits direct installation of nitrogen into topologically and functionally complex molecules, often necessitating *de novo* syntheses. The ability to effect late-stage functionalization via direct and selective installation of nitrogen in complex molecules may expedite discovery processes for biologically active small molecules and re-invigorate exploration of natural product derived drug candidates.[9,10]

Significant reactivity and selectivity challenges exist in the late-stage C–H amination of natural products and pharmaceuticals as many similar C–H bond types may be present in a molecule. Noble metal rhodium catalysis via metallonitrene intermediates is well-established for the intramolecular C–H amination of a wide range of C–H bond types.[11–13] One advantage of proceeding via metallonitrene intermediates is that both C–H cleavage and functionalization are tightly regulated at the metal and therefore are amenable to tuning via ligand/metal modifications. Intermolecular rhodium catalyzed C–H aminations are emerging for benzylic, tertiary and allylic C–H aminations;[14–17] however, chemo-and site-selectivity challenges exist in molecules having multiple reactive functionalities or C–H bonds. For example, in molecules having both tertiary and benzylic C–H bonds, inseparable product mixtures are formed (Figure 1b).[14,15] Moreover, the ability to effect remote C–H amination in molecules having basic amines or heterocyclic functionality has not been demonstrated for this type of C–H amination (Figure 1c). Tertiary amine-containing natural products undergo α-amination/oxidation sequences to give amidines or direct *N*-amination to furnish hydrazine sulfamate zwitterions, with protection of nitrogen as an amine salt not shown to be tolerated.[18]

Recently, base-metal catalysts have emerged for highly selective intramolecular C–H aminations;[19–21] however, analogous intermolecular processes are scarce.[22,23] For example, cobalt-catalyzed intermolecular benzylic C–H aminations are not suitable for late-stage applications as they have formidable reactivity challenges requiring solvent quantities of substrates (Figure 1d), and intramolecular processes do not appear to discriminate C–H bonds based on electronic properties (Figure 1e).[24,25] Copper-catalyzed processes can have significant site-and chemoselectivity issues, furnishing mixtures of aminated products with substrates as simple as ethylbenzene.[26,27] Iron and manganese catalyzed intermolecular C–H azidations have been reported having tolerance for nitrogen heterocyclic functionality, but these proceed via free radical pathways that result in poor site-selectivities and long-lived substrate radicals which scramble stereochemistry and may lead to skeletal rearrangements (Figure 1f).[28,29] Herein, we report a manganese perchlorophthalocyanine [Mn^{III}(ClPc)] catalyst for a highly site-selective and functional group tolerant intermolecular benzylic C(sp^3)–H amination. This methodology enables preparative base-metal nitrene mediated

late-stage amination on a broad range of natural products and pharmaceuticals, including ones containing multiple benzylic sites and basic nitrogen (tertiary amines, pyridines, and benzimidazole) functionality.

Results and discussion

Reaction development.

Reaction development commenced by examining commercially available first row transition metal catalysts previously demonstrated to be effective in intramolecular C–H amination via metallonitrene intermediates.[19,20,30] The combination of 2,2,2-trichloroethyl sulfamate (TcesNH$_2$) and PhI(OPiv)$_2$ oxidant in the presence of iron phthalocyanine gave no product whereas manganese phthalocyanines gave trace product (Table 1, entries 1–4). In the presence of cobalt (II) tetraphenylporphyrin (Co^{II}(TPP)), no reactivity was observed under *in situ* iminoiodinane conditions or previously reported TrocN$_3$ conditions (entry 5).[24] Mechanistic studies for intramolecular C–H amination processes promoted by manganese phthalocyanines suggested that *in situ* formation of iminoiodinane, an equilibrium process that favors the sulfamate ester, may be partially rate-determining.[20] Examining if elimination of this step could enhance reactivity by using preformed iminoiodinane (PhI=NTces) gave improved yields of benzylic amination across all the phthalocyanine catalysts examined, with [Mn^{III}(Pc)]SbF$_6$ giving the best results (entries 6–8). The use of non-coordinating hexafluoroantimonate (SbF$_6^-$) counterion is thought to increase reactivity in these systems by furnishing a cationic metal complex with enhanced electrophilicity.[19,20] We further hypothesized that electron withdrawing ligand modifications may promote formation of an electrophilic metallonitrene that is more reactive towards intermolecular C–H amination. Gratifyingly, a novel perchlorinated manganese phthalocyanine catalyst [Mn^{III}(ClPc)] **4** [[Mn^{III}(ClPc)] **4** = [Mn^{III}(Cl$_{16}$Pc)]SbF$_6$], readily accessed in one step from commercial reagents, significantly improved the yield of desired amination to 53% (Table 1 entry 9, Fig. 2a).[31] Increasing the reaction temperature from 23 °C to 40 °C further increased the yield of aminated product to 68% (entry 10). Lowering the catalyst loading to 5 mol% or cutting the PhI=NTces to 1.0 equivalent led to a 47% and 42% yield, respectively (entries 11–12). Replacing the benzene solvent with 1,2-dichloroethane, a polar aprotic solvent compatible with polar substrates and complex molecules (*vide infra*), gave a synthetically useful 60% yield (entry 13). In the absence of AgSbF$_6$, a synthetically useful 50% yield is still obtained (entry 14); whereas elimination of [Mn^{III}(ClPc)] **4** resulted in no product formation (entry 15). Re-examination of Co^{II}(TPP) with iminoiodinane under the optimal [Mn^{III}(ClPc)] **4** conditions did not lead to a productive reaction (entry 16). *In situ* iminoiodinane formation under these optimal conditions was unproductive (entry 17). It is important to note however that iminoiodinane (PhI=NTces) can be readily synthesized from commercial starting materials and upon isolation can be stored for months (see Supplementary Information section II).[32] Interestingly, using preformed iminoiodinane for rhodium-catalyzed intermolecular benzylic C–H amination was reported to result in a significant decrease in yield relative to the *in situ* method.[14]

Reaction scope.

We next evaluated the substrate scope of this transformation under preparative conditions (all examples are with 1 equiv. of substrate) using the novel and readily accessible [Mn[III](ClPc)] **4** catalyst, synthesized in one step as the chloride [Mn[III](ClPc)]Cl **3** from commercial starting materials (95% yield, multi-gram scale, Figure 2a) followed by an *in situ* metathesis with equimolar AgSbF$_6$. In contrast to results with previously reported base-metal catalysts, ethyl benzene furnished good yields and selectivities of aminated product (Figure 2b, **5**, 72%).[24,27] Significantly substituting the *para* position with electron-withdrawing functionality (Cl, σ_{para}= 0.23, CF$_3$, σ_{para}= 0.54) led to diminished yields as the sigma value of the substituent increased (**6**, 57%; **7**, 30%). A similar trend is observed when varying the aromatic ring electronics on screening substrate **1** where a bias for electron-neutral and electron-rich aromatic systems can be observed (**2, 8–10,** 55–68% yields). Remote electron-withdrawing aliphatic functionality is well tolerated in this reaction as seen with ester and trifluoroacetamide containing compounds undergoing [Mn[III](ClPc)] **4** catalyzed aminations in good yields (**11–13,** 65–69% yields).

We explored the selectivity of the [Mn[III](ClPc)] **4**-catalyzed benzylic C–H amination in substrates containing more than one potential site for functionalization. In substrates containing both a benzylic and a tertiary site, we observed selective amination at the benzylic position with no tertiary amination observed by LC-MS and/or ^{1}H NMR analysis (Figure 2c, **14**, 53% yield, >100:1 benzylic:tertiary (B:T) amination; **15**, 59% yield, >20:1 B:T). These results are orthogonal to noble metal catalyzed methods where mixtures (often inseparable) of benzylic and tertiary amination products are routinely observed (Figure 1b).[14,15,17] In substrates containing multiple benzylic sites, we found an amination preference for the least sterically encumbered and most electron-rich site. For example, evaluation of 5-acetoxytetralin bearing two methylene benzylic sites (C$_1$ and C$_4$) revealed preferential amination at the C$_1$ site over the C$_4$ site, likely because of the 1,3 strain present at C$_4$ (**16**, 70% yield). Oxygen substitution in cyclic ethers activates adjacent C–H bonds towards amination via hyperconjugation (**17**, 60% yield). In contrast oxygen with an electron withdrawing substituent like acyl deactivates the proximal C–H bond toward amination (**18**, 60% yield, 1:1 d.r.), likely due to a combination of electronic and steric deactivation. Electronic substitution on the aromatic ring can have substantial effects on site-selectivity and reactivity in this reaction. For example, 6-methoxytetralin contains two potential sites for oxidation, differentiated by the electron-donating *para*-methoxy group on the phenyl ring. We isolate amination product at C$_1$ (**19**, 58%), the more electronically favored site, with only trace diaminated product detected in the crude reaction mixture (determined by HPLC). In contrast, under rhodium catalysis an inseparable 7:1 mixture of C$_1$:C$_4$ amination products is reported alongside a 15% yield of diamination product.[14] The methoxy substitution on 7-methoxytetralone provides electronic activation to the benzylic methylene C–H bonds to achieve a synthetically useful 51% yield of aminated tetralone **20** (Figure 2d). It is significant to note that an unsubstituted α-tetralone affords only trace amounts of aminated product.

Evaluation of nitrogen containing heterocycles commenced using strongly electron-withdrawing protecting groups for secondary amine functionality. Tetrahydroquinoline is a

viable substrate for C–H amination when the nitrogen is protected as a trifluoroacetamide (Figure 2d, **21**, 76% yield). Carbazole, a key heterocycle in many alkaloids, was aminated at the pendent benzylic site in good yield (**22**, 65%) when the secondary amine was protected with a phenylsulfonyl group. Moderately basic amide-containing heterocycles were also examined under [Mn^{III}(ClPc)] **4** catalysis: a *N*-aryl lactam derived substrate underwent benzylic C–H amination in good yield (**23**, 63% yield, 1:1 d.r.) and *N*-aryl oxazolidinone, a structural motif found in pharmaceuticals like linezolid, was aminated to form **24** in 51% yield (1:1 d.r.). The lack of diastereoselectivity observed with these substrates is likely attributed to the substrate's stereogenic center being distal to the site of C–H amination.

Despite the high prevalence of basic tertiary amines and basic heterocycles in pharmaceuticals and natural products, previous methods for metal-catalyzed C–H amination proceeding via metallonitrene intermediates have not demonstrated tolerance for this functionality in remote C–H aminations. Indeed, examining this amination protocol in a substrate containing a tertiary piperidine yielded no benzylic amination product with 47% recovered starting material (Figure 2e, entry 1). We hypothesized that the basic amine may bind strongly to the metal, inhibiting catalysis and/or undergo α-amination or direct *N*-amination to furnish polar products that are not easily isolated.[18] We examined Brønsted acid and Lewis acid complexation strategies that have been demonstrated to circumvent such issues in the context of aliphatic C–H hydroxylations.[33–35] Both protection methods produced the desired product in good yield (**26**, 58% and 51% yields, entries 2–3). Analogous to previous reports, HBF$_4$ has proven to be more effective for tertiary amines having steric bulk. However, the BF$_3$ protecting method enhances substrate solubility and is beneficial with more polar substrates facing isolation challenges (*vide infra*).

This strategy was evaluated with four basic amine-containing substrates containing pharmaceutically common motifs. The linear 3° amine and *N*-methylpiperidine containing substrates were aminated using HBF$_4$/[Mn^{III}(ClPc)] **4** to afford **27** (Figure 2e, 50% yield) and **28** (57% yield), respectively. Pyridine, the most prevalent heteroaromatic in pharmaceuticals,[36] was also tolerated using the HBF$_4$ protonation strategy. A useful yield was observed for 2° benzylic amination in a pyridyl substituted tetrahydronaphthalene with no 3° benzylic C–H amination observed likely due to sterics and the strong electron-deactivation of the pyridyl ring upon nitrogen protonation (**29**, 42% yield, 1:1 d.r.). A primary amine-containing substrate can also be conveniently protected as a BF$_3$ salt and aminated using the [Mn^{III}(ClPc)] **4** catalyst to afford a product that can be readily isolated via silica gel chromatography (**30,** 56% yield), stored as a bench stable solid, and easily deprotected using a hydroxide base or fluoride anion.[34]

Late-stage benzylic C–H amination of bioactive molecules.

Site-selective intermolecular C–H functionalization processes that may be used at a late-stage constitute powerful methods because of their capacity to make atomistic changes that may profoundly impact a molecule's biological and physical properties.[37,38] We sought to evaluate the [Mn^{III}(ClPc)] **4**-catalyzed benzylic C–H amination in such pharmaceutical settings where late-stage amination may be beneficial (Figure 3a). FKGK11, a group VIA calcium-independent phospholipase A$_2$, with a pentafluoroethyl carbonyl underwent

benzylic amination to afford **31** in 51% yield. A retinoic acid receptor agonist analog[39] having a biaryl moiety underwent benzylic amination to afford **32** in 76% yield, which could be readily deprotected using a Zn/Cu couple to afford the primary amine (**33**, 88% yield).[14] Analogous to previous substrates, electron deficient nitrogen is well-tolerated: a P-glycoprotein inhibitor containing an imide functionality and a spiropiperidine σ receptor agonist precursor containing a 2° amine protected as a trifluoroacetamide were efficiently aminated in excellent yields to afford **34** (84% yield) and **35** (85% yield), respectively.[40,41] Citalopram, a widely used antidepressant containing a linear 3° amine, was evaluated for late-stage C—H amination with $HBF_4/[Mn^{III}(ClPc)]$ **4**. Benzylic amination product **36** was obtained as a single diastereomer in 71% yield. It is significant to note that no intermolecular C–H amination methods have thus far demonstrated the capacity to preparatively aminate such a broad range of medicinally relevant substrates.

We next evaluated bioactive molecules with multiple benzylic C–H bond sites that differ primarily in their steric environments. In a dopamine receptor agonist analog having both 2° and 3° benzylic sites, the $HBF_4/[Mn^{III}(ClPc)]$ **4** catalyzed amination protocol was effective at selectively functionalizing the more exposed 2° benzylic position to afford **37** (Figure 3b, 59% yield, 5:1 d.r.).[42] Remarkably, even a glucocorticoid receptor agonist analog having two sterically differentiated 2° benzylic sites was selectively aminated at the less hindered site flanked by a methylene, rather than the one adjacent to a quaternary center, to furnish **38** as one regioisomer in 56% yield (8:1 d.r.).[43] Anti-depressant sertraline **40** was accessed from **39** via a high yielding 3-step synthetic sequence. Site-selective amination of a 2° benzylic C–H bond in the presence of a sterically encumbered but highly activated 3° dibenzylic C–H bond proceeded in 73% yield (1:1 d.r. of an easily separable mixture of *cis* and *trans* diastereomers). *N*-methylation of the *cis*-diastereomer proceeded quantitatively followed by Tces removal with Zn/Cu couple (95% yield) to afford sertraline **40**. These examples serve to highlight the high sensitivity of this C—H amination method to the steric environments of benzylic C–H bonds.

Bioactive molecules with electronically differentiated 2° benzylic C–H sites, proximal and distal to electron-withdrawing functionality were evaluated (Figure 3c). In an alkylated analog of the antibiotic sulbactam, a 50% yield (1:1 d.r.) of aminated product **41** was isolated at the more electron rich benzylic site distal from the ester linkage. A 5,7-dibromoisatin analog, shown to have anti colon cancer activity,[44] was preferentially aminated at the benzylic site remote from the electron deficient nitrogen moiety to furnish **42** in 64% yield. We evaluated our C–H amination protocol in a CYP11B1 inhibitor analog[45] having a benzimidazole functionality. Use of the BF_3 complexation strategy led to an increase in substrate solubility, and we found amination occurred at the benzylic site remote from the electron deficient heteroaromatic to furnish **43** in 53% yield. These examples further underscore the $[Mn^{III}(ClPc)]$ **4**-catalyzed benzylic C–H amination's sensitivity to electronics with preparatively meaningful site-selectivities being achieved for amination at electron rich benzylic C–H bonds relative to sites proximal to electron withdrawing functionality. Such sensitivity to electronics is consistent with an electrophilic metallonitrene intermediate and inconsistent with a nonelectrophilic metalloradical

intermediate, evoked in Co-mediated intramolecular C–H aminations that demonstrate poor sensitivity to substrate electronics (Figure 1e, *vide infra*).[25]

We explored the capacity for the [Mn^{III}(ClPc)] catalyst to effect late-stage benzylic C–H amination in complex natural product settings (Figure 4). The COCF$_3$-leelamine analog, a diterpene amine with two sterically differentiated 2° and 3° benzylic sites, was selectively aminated at the 2° benzylic site to afford **44** (62% yield, 6:1 dr) as a single regioisomer. The Zn/Cu couple Tces deprotection is chemoselective for the Tces amine in the presence of the COCF$_3$-amine and furnished **45** in 70% yield. The 2,8-dioxabicyclo[3.3.1]nonane skeleton is contained in biflavonoid natural product motifs that exhibit intriguing medicinal properties which include antiviral, anti-inflammatory and antitumor properties.[46] Benzylic amination in the presence of this biflavonoid natural product core was achieved to give **46** in a 73% yield (1:1 d.r.). Further diversification of the biflavonoid natural product core with a pyridine was performed, and using the HBF$_4$/amination protocol, a 57% yield (1:1 d.r.) of benzylic amination product **47** was ultimately realized. Significantly, the acid sensitive ketal functionality remains intact under the HBF$_4$ complexation protocol.

Previously, low yields or highly complex mixtures of products were furnished from the C—H azidation of estrone analogs (Figure 1f).[28,29] We evaluated a formylated OAc-estradiol analog and a structurally analogous pyridyl containing abiraterone analog, both having two potential amination sites (2° and 3° benzylic C(sp^3) –H bonds) (Figure 4). In both cases, we observed highly site-selective 2° benzylic amination (3° benzylic amination was not observed) in synthetically useful yields (65% yield (1.6:1 d.r.) **48**; 51% yield (1.6:1 d.r.) **49**). In the case of the pyridyl containing steroid, complexation with BF$_3$ was found to be beneficial in generating a BF$_3$-pyridine complex soluble in 1,2-dichloroethane. These examples further underscore the ability of the [Mn^{III}(ClPc)] **4** catalyst to discriminate between small differences in the steric environments of benzylic sites.

Previous efforts to diversify the 3° amine-containing alkaloid dextromethorphan using a rhodium nitrene provided amination at the 3° amine and the methyl group adjacent to the 3° amine (Figure 1c).[18] We postulated that base-metal nitrene catalyzed amination at a benzylic site remote from the 3° amine would be possible after irreversible protonation of dextromethorphan with HBF$_4$, as the protonated 3° amine renders the nearby C–H bonds electron deficient. Gratifyingly, our protonated dextromethorphan analog was aminated in 44% yield (1:1 d.r.) at the benzylic site most remote from the 3° amine (Figure 4).

Mechanistic studies.

We hypothesized the [Mn^{III}(ClPc)] **4**-catalyzed intermolecular benzylic C–H amination reaction proceeds via formation of an electrophilic metallonitrene followed by a rate-determining C–H cleavage step to afford a benzylic radical that undergoes rebound from the Mn-imido intermediate to form the benzylic aminated product (Figure 5a). Whereas in the intramolecular [Mn^{III}(^{t}BuPc)]-catalyzed C–H amination, a step prior to C–H cleavage, such as iminoiodinane formation, was found to be partially rate-determining,[20] we envisioned that preforming the iminoiodinane would now render C–H cleavage as the rate-determining step. To assess this hypothesis, the intermolecular kinetic isotope effect (KIE) was measured to evaluate the effect of C–H cleavage on the overall reaction rate and compared to the

intramolecular KIE that directly probes the C–H cleavage step (Figure 5b). Initial rates measured on parallel reactions with substrates **1** and **1**-d$_2$ gave a primary KIE of 2.5 ± 0.2. This value was closely matched with the intramolecular KIE of 3.0 ± 0.1 measured on monodeuterated substrate **51**, suggesting that C–H cleavage is likely the rate-determining step of this intermolecular benzylic C–H amination. The intramolecular KIE is similar to those obtained with other base metal phthalocyanine catalysts (Mn and Fe) that catalyze intramolecular benzylic C–H aminations (KIE = 4.2 and 4.8, respectively),[20] however is appreciably lower than that reported for cobalt porphyrins that catalyze intramolecular allylic C–H aminations (KIE = 6.2).[47] Therefore, while this data supports our hypothesis that [Mn^{III}(ClPc)] **4** proceeds through a stepwise mechanism, C–H bond breakage appears to occur to a much lesser extent in the transition structure than with Co porphyrin catalysis where such a stepwise mechanism has also been evoked.[25,47]

We next evaluated the proposed rebound step of the Mn-imido with the substrate benzylic radical intermediate (Figure 5c). C–H amination at a defined benzylic stereocenter in **52** proceeds with complete erosion in stereochemistry with [Mn^{III}(ClPc)] **4**, supporting the intermediacy of a stabilized carbon-centered radical. Importantly, intramolecular C–H amination with [Mn^{III}(ClPc)] **4** at a defined aliphatic stereocenter in **54** proceeds with complete stereoretention, as had been previously reported with [Mn^{III}(^{t}BuPc)].[20] These results support a step-wise mechanism and suggest that the rate of the rebound step is dependent on the stability of the carbon-centered radical intermediate.

We sought to probe the nature of the aminating species to distinguish between an electrophilic metallonitrene that has been suggested for rhodium, manganese, and iron catalysis versus a nonelectrophilic metalloradical intermediate evoked in cobalt catalysis (Figure 5d). In intramolecular C–H amination studies, rhodium, manganese, and iron mediated C–H aminations preferred the more electron rich C–H site whereas cobalt mediated C–H aminations were relatively insensitive to electronics and exhibited site-selectivity based primarily on differences in bond dissociation energies (BDE, Figure 1e).[11,20,25] We directly probed this by examining [Mn^{III}(ClPc)] **4**-catalyzed C–H amination in substrate **56**, having two benzylic sites that are electronically distinct and have different BDEs (Figure 5d).[48] [Mn^{III}(ClPc)] **4** demonstrates a strong preference for amination at the more electron rich benzylic site having the higher BDE versus the electron deficient benzylic site α to a carbonyl having a lower BDE, furnishing **57** in 52% isolated yield with 17:1 site-selectivity (**57:58**). This outcome contrasts site-selectivity trends reported with nonelectrophilic metalloradical mediated cobalt reactions that preferentially aminate even highly electron deficient C–H bonds α to carbonyls because of their low BDEs (Figure 1e).[25] Collectively, this data suggests that Mn phthalocyanine catalyzed benzylic C–H aminations proceed through a stepwise mechanism via electrophilic metallonitrene intermediates where C–H bond cleavage is tightly regulated at the metal center and occurs preferentially at the most electron rich and sterically accessible site.

Conclusion

A base-metal catalyzed intermolecular benzylic C–H amination is reported that proceeds with unprecedented levels of reactivity, site-selectivity and functional group tolerance. The

[Mn^{III}(ClPc)] **4** catalyst is synthesized in a one step, scalable reaction from abundant and sustainable commercial starting materials.[49] The [Mn^{III}(ClPc)] **4** catalyzed C–H amination demonstrates high site-selectivity in molecules containing multiple reactive C–H bonds based on steric and electronic differentiation.[50] Moreover, the catalyst is compatible with both Brønsted and Lewis acid complexed basic nitrogen functionality, enabling remote C–H amination in molecules containing tertiary amines and heterocycles that cannot effectively be masked via alternative methods. Collectively, the combination of reactivity and selectivity makes this [Mn^{III}(ClPc)] **4**-catalyzed intermolecular benzylic C(sp^3)–H amination uniquely effective at late-stage functionalization of bioactive molecules and natural products. Mechanistic studies suggest that this method proceeds via a stepwise C–H amination pathway with C–H cleavage as the rate-determining step. A competition study and empirical data on the impact of electronic effects on site-selectivities suggest that the nature of the key intermediate is that of an electrophilic metallonitrene. Collectively, these features significantly contrast with other base-metal catalyzed C–H aminations that are poorly reactive intermolecularly and generally proceed via intermediates with more free radical character that exhibit less control on site-selectivity. We envision that the high reactivity and selectivity of this reaction will make it uniquely effective for late-stage installation of valuable nitrogen functionality in complex molecule settings. Moreover, we anticipate that the mechanistic features will enable tunable control of site-selectivity when the reactivity is increased for intermolecular amination of other C(sp^3)–H bond types.

Methods

A general procedure for the manganese-catalyzed benzylic amination is as follows. In a 10 mL round-bottom flask, 5Å powdered molecular sieves (40 mg) and a Teflon stir bar were added. The flask was sealed with a Suba Seal rubber septum, placed under vacuum, flame-dried for 45 seconds to activate the molecular sieves, cooled under a purged and completely air-free argon balloon and wrapped in foil to exclude light. Once cooled, solvent (0.40 mL, 0.5 M to substrate) and substrate (0.20 mmol, 1 equiv) were added and stirred for 10 minutes. Manganese (III) perchlorophthalocyanine chloride **3** (23.1 mg, 0.020 mmol, 0.1 equiv) and silver hexafluoroantimonate (6.9 mg, 0.020 mmol, 0.1 equiv) were weighed in a foil-wrapped 1 dram vial in the glove box and sealed with a Teflon cap. The vial was removed from the glove box and the contents added directly to the round bottom flask while maintaining an argon atmosphere, then stirred for 10 minutes at room temperature. In a 1 dram vial open to air, 2,2,2-trichloroethyl (phenyl-λ^3-iodanylidene)sulfamate (172.2 mg, 0.40 mmol, 2 equiv) was weighed and added directly to the round bottom flask while maintaining an argon atmosphere. The Suba Seal rubber septum was replaced by a polyethylene cap, sealed tightly and placed in a 40 °C oil bath for 8 hours with stirring. Upon reaction completion, the reaction was filtered through a 1 inch silica gel plug using diethyl ether or ethyl acetate as the eluent. The crude material was concentrated and dry-loaded directly onto a silica gel column.

A general procedure for the manganese-catalyzed benzylic amination of basic nitrogen-containing substrates is as follows. In a 1-dram vial equipped with a stir bar were added the nitrogen-containing substrate (0.20 mmol, 1 equiv) and methylene chloride (DCM) (0.8 mL). Tetrafluoroboric acid diethyl ether complex (HBF$_4$•OEt$_2$) (30.2 μL, 35.6 mg, 0.22

mmol, 1.1 equiv) or boron trifluoride diethyl etherate (BF$_3$•OEt$_2$) (27.2 μL, 31.2 mg, 0.22 mmol, 1.1 equiv) was added dropwise while stirring at room temperature. The reaction mixture was stirred for 1 h. Upon reaction completion, the stir bar was removed, and the mixture was concentrated *in vacuo* and placed on vacuum overnight. A 10 mL round-bottom flask containing 3Å powdered molecular sieves (40 mg) and a Teflon stir bar was set up and flame-dried according to the general procedure above. In the 1-dram vial carrying the protonated substrate was added 0.2 mL of anhydrous 1,2-dichloroethane (DCE). The resulting solution or suspension was added into the round-bottom flask containing the 3Å molecular sieves. This process was repeated 2x with 0.1 mL DCE each time to ensure complete transfer. The amination reaction was then set up according to the general procedure above. The reaction was then placed in a 40 °C oil bath for 15 hours with stirring. Upon completion, the flask was removed from the oil bath. Sodium hydroxide solution (1M, 3 mL) and CH$_2$Cl$_2$ (3 mL) were added and the reaction mixture was vigorously stirred for 15 min (for HBF$_4$ deprotection) or 4 h (for BF$_3$ deprotection of amines), and the layers were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (3×5 mL). The organic layers were combined, dried over anhydrous potassium carbonate, filtered and concentrated via rotary evaporation. The crude material was purified by flash chromatography to afford the aminated product. For deprotection of BF$_3$ in pyridine and benzimidazole containing substrates, tetramethylethylenediamine (TMEDA) (150 μL, 116 mg, 1.0 mmol, 5 equiv) was added instead of NaOH, followed by CH$_2$Cl$_2$ (1 mL). The resulting mixture was stirred for 4 h and loaded directly onto a silica column.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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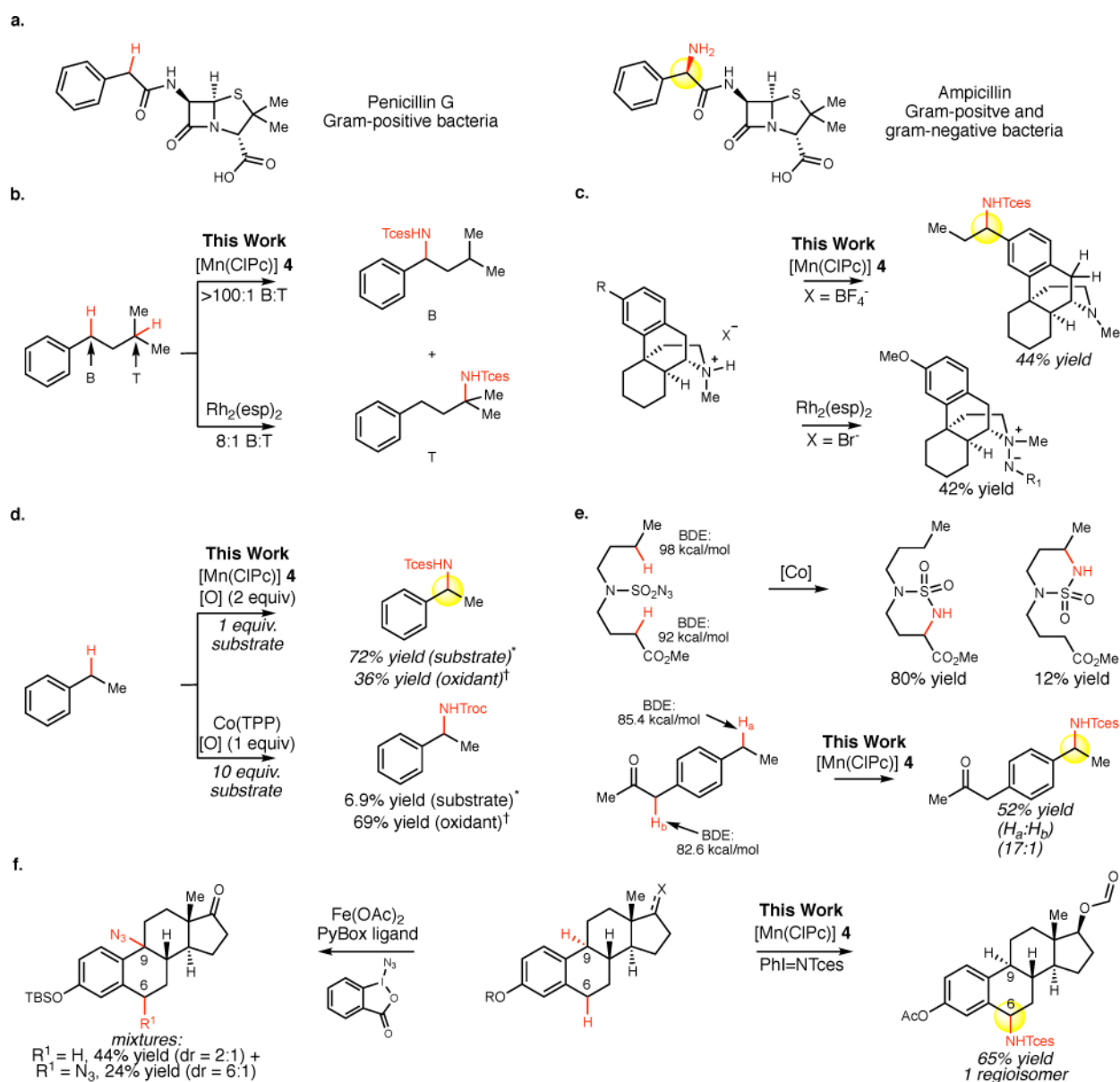
Figure 1. Converting C–H bonds to C–N bonds.
a. Ampicillin, a broad spectrum antibacterial drug differs from penicillin by an atomistic change of a benzylic C–H to C–N. **b.** Comparison of site-selectivities for benzylic versus tertiary C–H amination of Mn versus Rh catalyzed C–H aminations. Tces = 2,2,2-trichloroethoxysulfonamide. **c.** Chemoselectivity in a tertiary amine containing natural product of Mn versus Rh catalyzed C–H aminations. **d.** Comparison of reactivity of Mn versus Co catalyzed benzylic C–H aminations. *Yield based on equivalents of substrate used. †Yield based on equivalents of oxidant used. Troc = 2,2,2-trichloroethoxycarbonyl. **e.** Observed site-selectivity of Mn versus Co catalyzed C–H aminations. **f.** Comparison of site-selectivities among sterically differentiated benzylic C–H bonds on estrone/estradiol derivatives of a Mn-catalyzed reaction proceeding via a metallonitrene with previously reported Fe-catalyzed C–H azidation proceeding via a free radical intermediate.
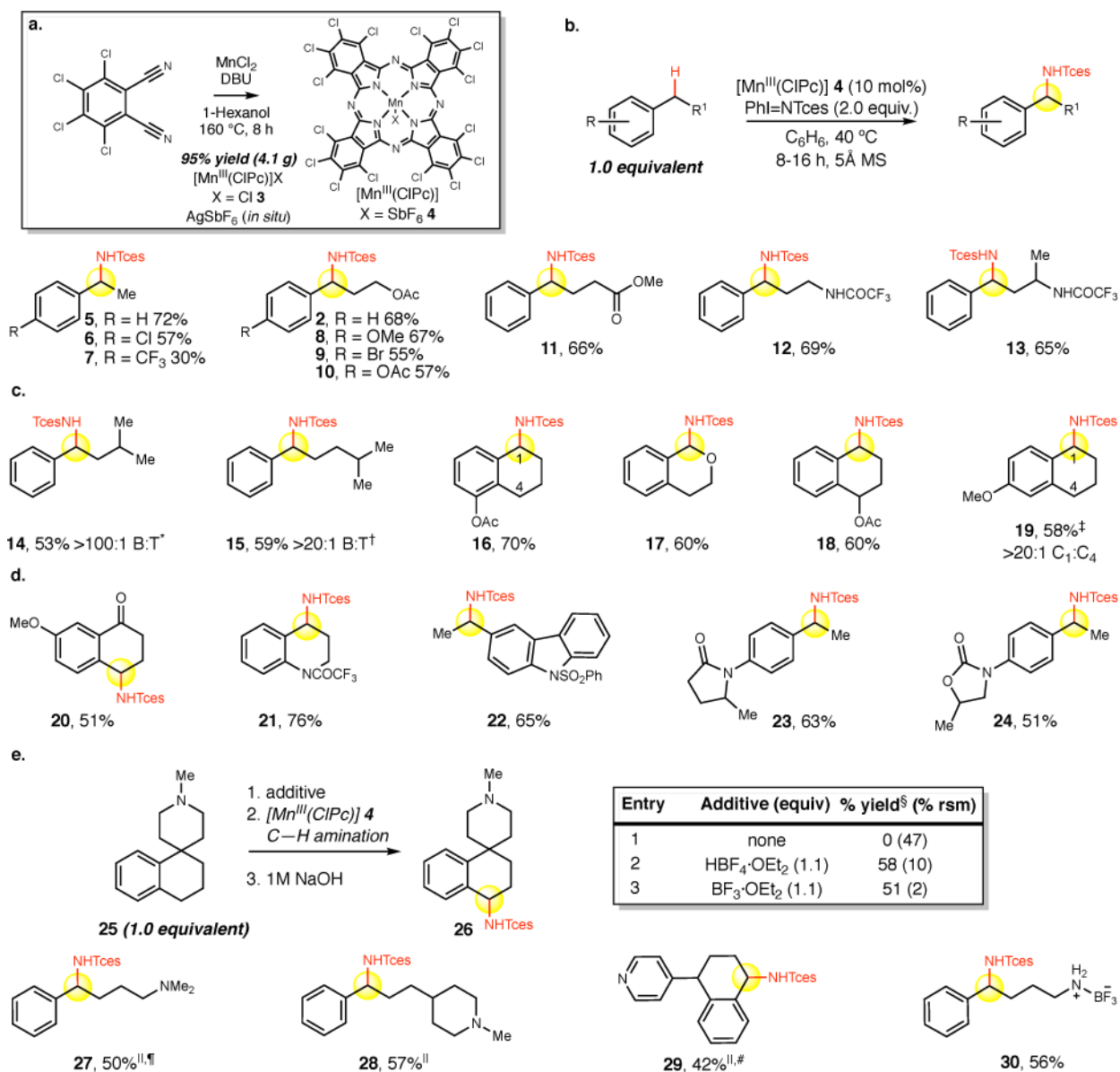
Figure 2. Intermolecular benzylic C–H amination substrate scope.
a. One-step, gram-scale synthesis of [Mn^{III}(ClPc)]Cl from commercial materials. **b.** General reaction conditions and evaluation of aryl and alkyl electronic effects. Reaction conditions: substrate (0.2 mmol, 1 equiv), [Mn^{III}(ClPc)]Cl **3** (10 mol%), AgSbF$_6$ (10 mol%), PhI=NTces (2 equiv), C$_6$H$_6$ (0.5M), 5Å molecular sieves (40 mg), 40 °C, 8–16 h. Isolated yields are average of three runs. Diastereomeric ratios are 1:1 unless otherwise noted **c.** Evaluation of site-selectivity: benzylic versus tertiary and sterically and electronically differentiated benzylic C–H bonds. **d.** Nitrogen-containing heterocyclic substrates with electron-withdrawing groups on nitrogen. **e.** Brønsted and Lewis acid protection strategy for basic tertiary amine and pyridine-containing substrates. *No tertiary product detected by HPLC (detection limit 0.0002 mg/mL using authentic product). †No tertiary product detected in ^{1}H NMR crude or after purification. ‡No monoamination product detected at C$_4$
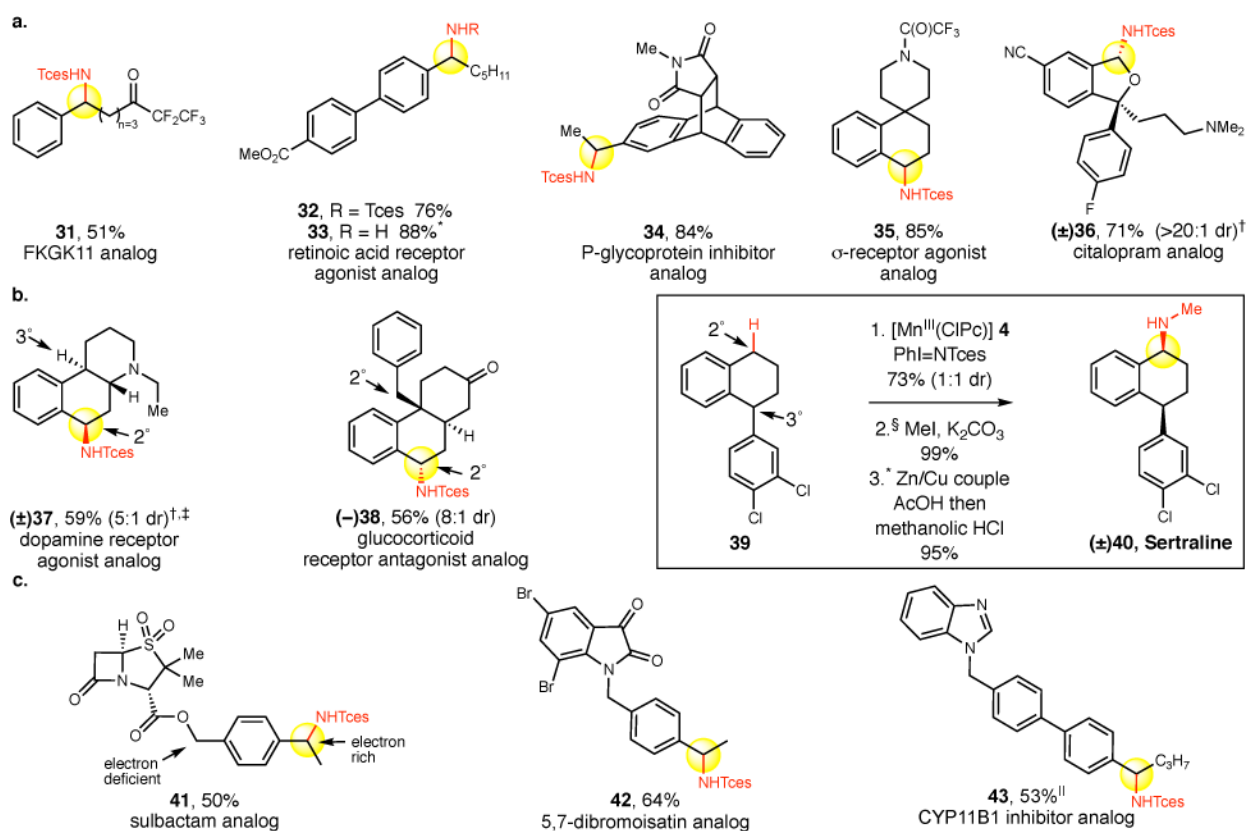
by HPLC (detection limit 0.00015 mg/mL using an authentic product); trace diamination detected using authentic product by HPLC, not seen by ^{1}H NMR. An imine product at C_1 was isolated in 12% yield. [§]Overall three step yield (1,2-DCE (0.5M): acid complexation, amination and decomplexation. [‖]3 equivalents of PhI=NTces. [¶]15 mol% catalyst used. [#]3Å molecular sieves.

**Figure 3. Late-stage benzylic C–H amination of bioactive molecules.**
a. [Mn^{III}(ClPc)] **4** catalyzed benzylic C–H amination (reaction conditions in Figure 2, isolated yields are average of three runs, diastereomeric ratios are 1:1 unless otherwise noted) selectively installs Tces-protected amines into bioactive molecules that can be converted to primary amines (**32→33**) **b.** Bioactive molecules with multiple reactive benzylic C–H bonds are selectively aminated at the most sterically accessible site. **c.** Bioactive molecules are selectively aminated at the most electron rich site. *Tces deprotection performed using Zn/Cu couple (10 equiv), MeOH:AcOH (1:1). After filtration through celite plug the concentrated white solid was stirred in methanolic HCl at 40 ˚C for 12 h to yield the corresponding amine. [†]3Å molecular sieves (40 mg) used. Substrate protonated with HBF$_4$•OEt$_2$ (1.1 equiv) in CH$_2$Cl$_2$ prior to amination then deprotonated with 1M NaOH in CH$_2$Cl$_2$ after amination. [‡]3 equiv of iminoiodinane used. [§]Only the *cis*-isomer used for alkylation, deprotection. [||]3Å molecular sieves (40 mg) used. Substrate complexed with BF$_3$•OEt$_2$ (1.1 equiv) in CH$_2$Cl$_2$ prior to amination and decomplexed with tetramethylethylenediamine (TMEDA) in CH$_2$Cl$_2$.
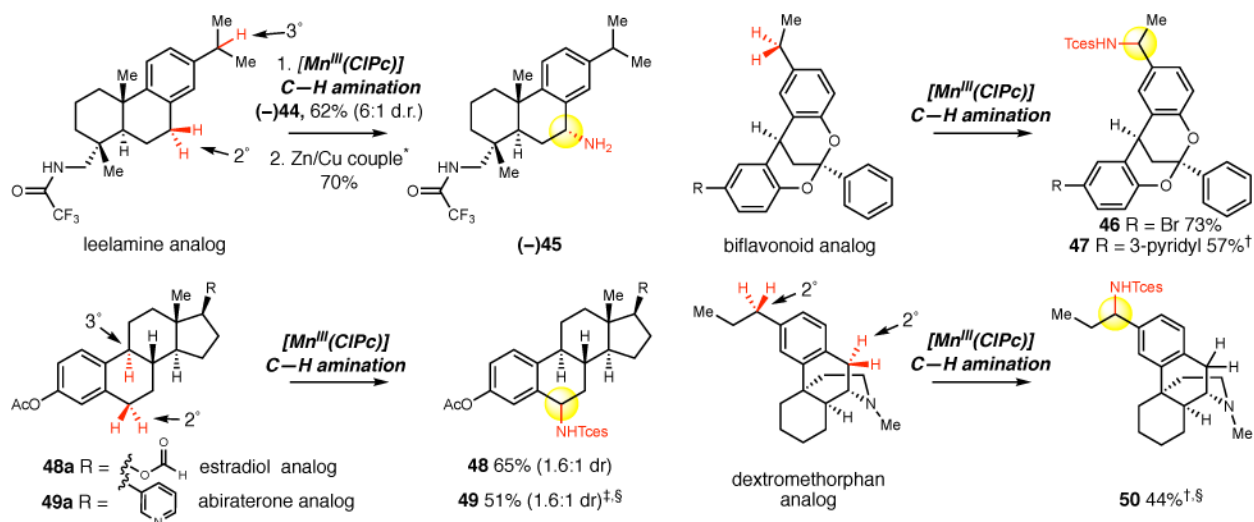
**Figure 4. Late-stage benzylic C–H amination of natural products.**
The late-stage functionalization of six natural product analogs is demonstrated with [Mn^{III}(ClPc)] **4** catalysis (reaction conditions in Figure 2, isolated yields are average of three runs, diastereomeric ratios are 1:1 unless otherwise noted) to give preparative yields and excellent levels of site-selectivity. *Tces deprotection: Zn/Cu couple protocol (Figure 3). [†]3Å molecular sieves (40 mg) used. HBF$_4$•OEt$_2$ (1.1 equiv, CH$_2$Cl$_2$) amine protection followed by 1M NaOH (CH$_2$Cl$_2$) deprotection after amination. [‡]3Å molecular sieves (40 mg) used. BF$_3$•OEt$_2$ (1.1 equiv, CH$_2$Cl$_2$) pyridine protection prior to amination, then deprotection with tetramethylethylenediamine in CH$_2$Cl$_2$ after amination. [§]3 equiv of iminoiodinane used.
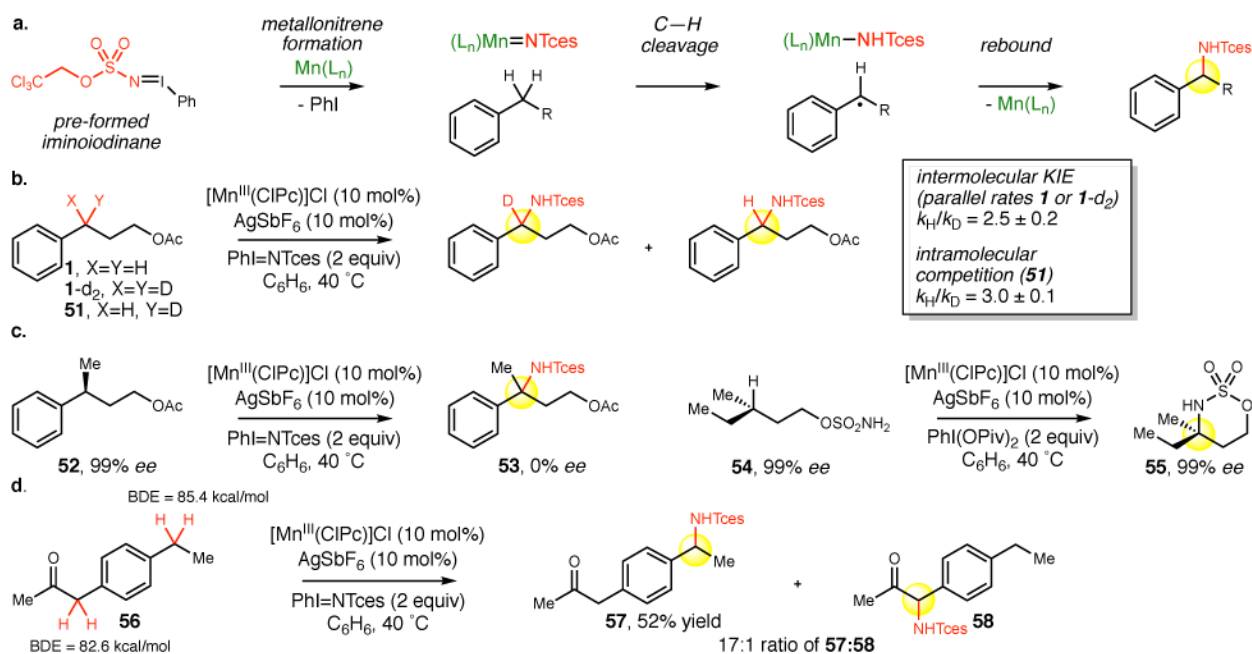
Figure 5. Mechanism of [Mn^{III}(ClPc)] catalyzed benzylic C–H amination.
a. Proposed stepwise mechanism for the [Mn^{III}(ClPc)] catalyzed benzylic C–H amination. **b.** C–H cleavage step is rate-determining step. Intermolecular kinetic isotope effect (KIE), evaluating the effect of C–H cleavage on overall reaction rates, closely matches the intramolecular KIE that directly probes the C–H cleavage step. **c.** The intermolecular rebound of the Mn-imido with a stabilized benzylic radical proceeds with racemization of stereogenic centers. Intramolecular rebound with an aliphatic carbon-centered radical proceeds with complete retention of stereochemistry. **d.** Site-selectivity of [Mn^{III}(ClPc)] catalyzed C–H amination is probed in a substrate containing two 2° benzylic C(sp^3)–H sites that differ electronically and in bond dissociation energies (BDE). The high site-selectivity for the most electron rich site having a higher BDE suggests that the reaction proceeds via an electrophilic metallonitrene intermediate. The 17:1 ratio of **57:58** was measured by HPLC.

Table 1.

Development of [Mn^{III}(ClPc)]-catalyzed intermolecular benzylic C–H amination.
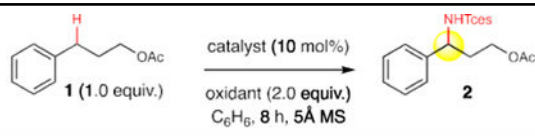
Entry*	Sulfamate Ester	Oxidant	Catalyst	Temp	% yield (% rsm)
1	NH$_2$Tces	PhI(OPiv)$_2$	[Fe^{III}(Pc)]SbF$_6$	23 °c	0% (100%)
2	NH$_2$Tces	PhI(OPiv)$_2$	[Mn^{III}(Pc)]SbF$_6$	23 °c	trace (96%)
3[†]	NH$_2$Tces	PhI(OPiv)$_2$	[Mn^{III}(Pc)]SbF$_6$	23 °c	trace (95%)
4	NH$_2$Tces	PhI(OPiv)$_2$	[Mn^{III}(BuPc)]SbF$_6$	23 °c	trace (94%)
5[‡]	NH$_2$Tces	PhI(OPiv)$_2$	Co^{II}(TPP)	23 °c	0%(99%)
6		PhI=NTces	[Fe^{III}(Pc)]SbF$_6$	23 °c	9%(85%)
7		PhI=NTces	[Mn^{III}(^{t}BuPc)]SbF$_6$	23 °c	12%(88%)
8		PhI=NTces	[Mn^{III}(Pc)]SbF$_6$	23 °c	17%(83%)
9		PhI=NTces	[Mn^{III}(ClPc)]SbF$_6$	23 °c	53%(41%)
10		PhI=NTces	[Mn^{III}(ClPc)]SbF$_6$	40 °c	68%(32%)
11[§]		PhI=NTces	[Mn^{III}(ClPc)]SbF$_6$	40 °c	47%(49%)
12[//]		PhI=NTces	[Mn^{III}(ClPc)]SbF$_6$	40 °c	42%(58%)
13[¶]		PhI=NTces	[Mn^{III}(ClPc)]SbF$_6$	40 °c	60%(24%)
14		PhI=NTces	[Mn^{III}(ClPc)]Cl	40 °c	0%(100%)
15		PhI=NTces	AgSbF$_6$	40 °c	trace(100%)
16		PhI=NTces	Co^{II}(TPP)	40 °c	trace(95%)
17	NH$_2$ Tces	PhI(OPiv)$_2$	[Mn^{III}(ClPc)]SbF$_6$	40 °c	trace(87%)

*
Reaction conditions: **1** (0.2 mmol, 1 equiv), catalyst (10 mol%), AgSbF$_6$ (10 mol%), oxidant (2 equiv), C$_6$H$_6$ (0.5M), 5Å molecular sieves (40 mg), 8 h. Yields are of isolated products. Trace yield (<5%) and recovered starting material (rsm) are reported based on ^{1}H NMR analysis of the crude reaction using 1,3,5-trimethylbenzene as an internal standard.

†
2.2 equiv of MgO used as an additive in the reaction.

‡
A separate reaction with **1** (1 equiv), TrocN$_3$ (2 equiv), Co^{II}(TPP) (10 mol%), C$_6$H$_6$ (0.5M), 40 °C, 5Å molecular sieves (40 mg), 8 h resulted in 0% yield (88% rsm). TPP = tetraphenylporphyrin.

§
5 mol% catalyst used.

//
1 equiv of PhI=NTces used.

¶
3Å molecular sieves used. 1,2-DCE used as solvent.