Article

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Tuning Selectivity in Aliphatic C–H Bond Oxidation of *N*-Alkylamides and Phthalimides Catalyzed by Manganese Complexes

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ABSTRACT. Site selective C–H oxidation of *N*-alkylamides and phthalimides with aqueous hydrogen peroxide catalyzed by manganese complexes is described. These catalysts are shown to exhibit substantially improved performance in product yields and substrate scope when compared with their iron counterparts. The nature of the amide and imide group and of the *N*-alkyl moiety are shown to be effective tools in order to finely tune site-selectivity between proximal (adjacent to the nitrogen) and remote C–H bonds on the basis of steric, electronic and stereoelectronic effects. Moreover, formation of the α-hydroxyalkyl product in good yield and with excellent product chemoselectivity was observed in the reactions of the pivalamide and acetamide derivatives bearing an α-CH_2 group pointing again towards an important role played by stereoelectronic effects and supporting the hypothesis that these oxidations proceed via hydrogen atom transfer (HAT) to a high valent manganese-oxo species. Good product yields and mass balances are obtained in short reaction times and under mild experimental conditions when using relatively low loadings of an electron rich manganese catalyst. The potential utility of these reactions for preparative purposes is highlighted in the site-selective oxidation of the pivalamide and phthalimide derivatives of substrates of pharmaceutical interest.

KEYWORDS: C–H oxidation, manganese and iron catalysts, hydrogen atom transfer, stereoelectronic effects, selectivity, amides, phthalimides

INTRODUCTION

The selective functionalization of aliphatic C–H bonds in organic molecules represents one of the main challenges of modern synthetic organic chemistry because of their inert character and because selectivity is hampered by the multitude of C–H bonds, that differ only slightly in terms of their electronic and steric properties. Increasing efforts have been devoted towards meeting this

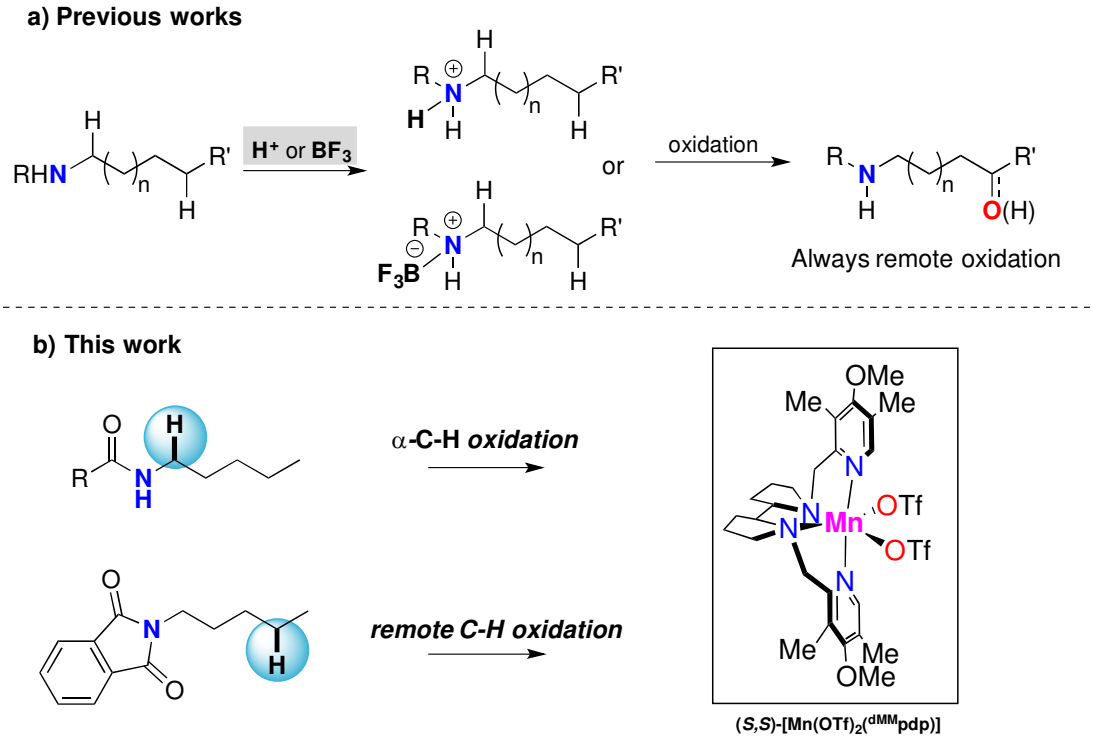
rewarding research goal, by pursuing metal catalyzed reactions that could implement site-selectivity in C–H functionalization reactions.[1-6]

A breakthrough towards the development of selective aliphatic C–H oxidation methodologies for organic synthesis was disclosed in the studies of White and coworkers, using nonheme nitrogen-ligated iron coordination complexes as catalysts, and hydrogen peroxide as oxidant.[7-8] Selectivity rules for the C–H oxidation reaction were clearly defined on the basis of steric, electronic and stereoelectronic effects, and a reaction mechanism proceeding through an initial hydrogen abstraction step was proposed.[9-10] By taking into consideration these elements, a reliable prediction of oxidation sites could be deduced in several substrates, including complex natural products. Related manganese complexes have been more recently shown to follow the same selectivity patterns, but their use remains much less explored.[11-12] Catalyst dependent selectivity distinct from the innate relative reactivity of C–H bonds can also be introduced by employing highly structured catalysts.[13-16] On one hand, sterically crowded catalysts favor oxidation of secondary over tertiary C–H bonds, because, despite being weaker, the latter are sterically more demanding.[13-15] On the other hand, chiral bulky catalysts can also exhibit chirality dependent site selectivity in the oxidation of steroids.[13]

Amines represent an especially important class of organic compounds, that serve in particular as the basic structure of a variety of natural products, bioactive molecules and organic materials. The tolerance of this functional group to metal catalyzed oxidation reactions is however particularly critical. Besides of their strong tendency to bind and deactivate metal centers, amines can be also easily oxidized.[17] Quite importantly, functionalization of amine substrates, when achieved, selectively occurs at the strongly activated C–H that is α to the nitrogen center.[18-30] Remote aliphatic C–H bond oxidation of amines with iron and manganese catalysts was recently reported.[31-33] In these works protonation of the amine, or formation of Lewis acid-base amine-BF_3 adducts, electronically deactivated the amine moiety and the C–H bonds that are adjacent to the nitrogen center, favoring selective oxidation at remote positions (Scheme 1a).

Along this vein, amide functionalities are also very interesting because, by decreasing nucleophilicity at the nitrogen center, they can be employed as protecting groups for primary and secondary amines, and the functionalization of these substrates can thus expand the structural elaboration of amine-containing targets. Moreover, highly efficient C–H oxidation of monosubstituted cyclohexanes has been recently described with manganese catalysts, where an *N*-cyclohexyl amide moiety was the key to enable high levels of regio- and enantioselectivity,[34] highlighting a very powerful role of this functional group in defining selective C–H oxidation

reactions. In this study it was proposed that enantioselectivity arises in the C–H cleavage step via hydrogen atom transfer (HAT) to a chiral high valent manganese-oxo species, followed by a fast hydroxyl rebound towards the incipient carbon centered radical.



Scheme 1. The influence of medium (a) and structural (b) effects on site-selectivity in aliphatic C–H bond functionalization of amine and amine-derived substrates

Besides the utility of the amide moiety as an amine protecting group, selective oxidation of the aliphatic C–H bonds of these substrates is also of considerable interest in modern organic synthesis. With secondary and tertiary amides bearing *N*-alkyl groups and with *N*-acyl cyclic amines, oxidation generally occurs at the C–H bonds that are α to nitrogen yielding α-hydroxylated products that are rapidly converted into imides, a useful functional group that has multiple applications.[26, 35-40] Quite importantly, isolation of the first formed α-hydroxy derivatives was only achieved in a very limited number of cases,[41-43] despite of the fact that such products can represent versatile intermediates for further synthetic elaboration.[44] Therefore, amide substrates constitute a very promising platform for the development of selective C–H oxidation procedures, where control over site (intramolecular) and product (intermolecular) selectivity can be particularly challenging but highly rewarding.

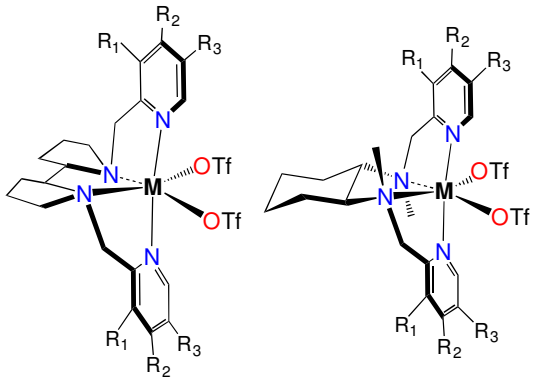
Within this framework, we reasoned that amide moieties have the potential to be developed into powerful directing groups for site-selective C–H functionalization because their electronic properties and steric demand can be uniquely tuned. For example, the acyl moiety can be changed from a strong electron withdrawing group such as trifluoroacetyl to the weaker acetyl one, and the electron withdrawing character can be further increased by conversion into an imide derivative. On the other hand, sterically demanding acyl moieties, such as pivaloyl, can be envisioned to impact on the accessibility of the different C–H bonds of the substrate, translating into site-selectivity. With these considerations in mind, in this work aliphatic C–H bond oxidation of *N*-alkylpivalamides, acetamides, trifluoroacetamides and phthalimides bearing 1-pentyl, 2-(5-methylhexyl) and 1-(3-methylbutyl) groups bound to nitrogen (structures **S1**-**S12** displayed below in Table 1), has been explored using iron and manganese catalysts and hydrogen peroxide as the oxidant. The three series of substrates were chosen in order to allow a thorough evaluation of the role of structural and electronic effects on the C–H functionalization selectivity, taking advantage of the methylenic C–H bonds present in the *N*-pentyl derivatives (**S1**-**S4**), the combination of a tertiary α-C–H bond with a tertiary δ-C–H bond in the *N*-2-(5-methylhexyl) derivatives (**S5**-**S8**), and the combination of an α-CH_2 group with a tertiary γ-C–H bond in the *N*-1-(3-methylbutyl) derivatives (**S9**-**S12**).

The results obtained show that with manganese catalysts the nature of the amide and imide group and of the *N*-alkyl moiety effectively tunes site-selectivity between proximal (adjacent to the nitrogen) and remote C–H bonds on the basis of steric, electronic and stereoelectronic effects (Scheme 1b). Good product yields and mass balances are obtained in short reaction times and under mild experimental conditions when using relatively low loadings of an electron rich manganese catalyst, highlighting the potential utility of these reactions for preparative purposes. Quite importantly, in the reactions of the pivalamide and acetamide derivatives bearing a CH_2 group α to nitrogen, good yields and excellent selectivities were observed for the formation of the α-hydroxyalkyl product.

RESULTS AND DISCUSSION

The oxidation of *N*-pentylpivalamide (**S1**) with hydrogen peroxide catalyzed by different iron and manganese complexes was initially explored. Catalysts tested are based on chiral iron and manganese complexes bearing tetradentate ligands, and with general formula $[M(CF_3SO_3)_2(L)]$ (L = mcp, and pdp, mcp = *N*,*N*′-dimethyl *N*,*N*′-bis(2-pyridylmethyl)-1,2-*trans*-diamino cyclohexane, pdp = *N*,*N*′-bis(2-pyridylmethyl)-2,2′-bipyrrolidine), whose structures are displayed in Scheme 2, all of

which have been recently described to be particularly efficient in aliphatic C–H oxidation reactions.[7-8, 11-13, 16, 34, 45-48] The results of these reactions are shown in Table 1.

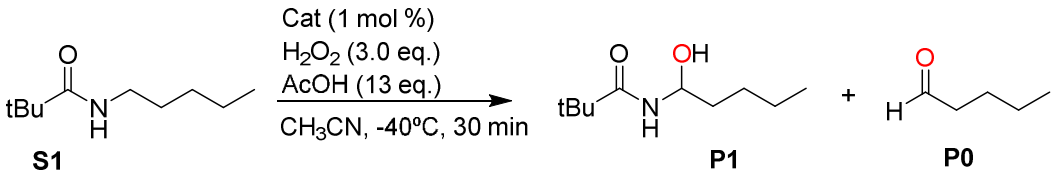


M(Xpdp) M(Xmcp)

M^x	R_1	R_2	R_3
Fe(pdp)	-H	-H	-H
Mn(pdp)	-H	-H	-H
Fe(mcp)	-H	-H	-H
Mn(mcp)	-H	-H	-H
Fe(^{dMM}pdp)	-Me	-OMe	-Me
Mn(^{dMM}pdp)	-Me	-OMe	-Me
Mn(^{dMM}mcp)	-Me	-OMe	-Me
Mn(^{Cl}mcp)	-H	-Cl	-H
Fe(^{Me2N}pdp)	-H	-NMe_2	-H
Mn(^{Me2N}pdp)	-H	-NMe_2	-H
Fe(^{TIPS}mcp)	-H	-H	-$Si(^iPr)_3$
Mn(^{TIPS}mcp)	-H	-H	-$Si(^iPr)_3$
Mn(^{TIPS}pdp)	-H	-H	-$Si(^iPr)_3$
Mn(^{BzIm}pdp)	-BzIm[a]		
Mn(^{CF3}mcp)	-H	-H	-$Ph(CF_3)_2$

Scheme 2. Diagram of the iron and manganese complexes studied. [a]*N*-methylbenzimidazole instead of pyridine.

Table 1. Oxidation of *N*-pentylpivalamide (S1) with Different Catalysts



S1 P1 P0

Entry	Catalysts	Conv %[a]	Yield P1 %[a]	Yield P0 %[a]
1[b]	**Fe (pdp)**	< 2%	-	-
2	**Mn (pdp)**	64	41	15
3[b]	**Fe (mcp)**	10	-	-
4	**Mn (mcp)**	36	10	4
5[b]	**Fe (^{dMM}pdp)**	15	6	5

6	**Mn (^{dMM}pdp)**	**99**	**60**	**11**
7	**Mn (^{dMM}mcp)**	97	42	10
8	**Mn (^{Cl}mcp)**	22	8	11
9[b]	**Fe (^{Me2N}pdp)**	4	-	-
10	**Mn (^{Me2N}pdp)**	60	14	12
11[b]	**Fe (^{TIPS}mcp)**	11	-	-
12	**Mn (^{TIPS}mcp)**	65	58	4
13	**Mn (^{TIPS}pdp)**	52	31	13
14	**Mn (^{BzIm}pdp)**	98	40	10
15	**Mn (^{CF3}mcp)**	63	15	12
16[c]	**Mn (^{dMM}pdp)**	60	45	12

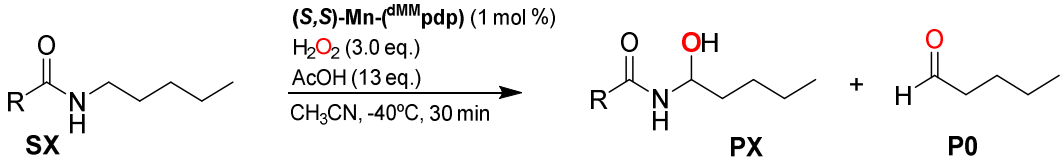
[a]Conversions and yields determined from crude reaction mixtures by GC or ^{1}H NMR. [b]Reaction conditions: Fe catalyst (3 mol %), H_2O_2 (2.5 equiv), AcOH (1.5 equiv) in CH_3CN at 0 °C during 30 min. [c]Cyclopropanecarboxylic acid was used instead of acetic acid.

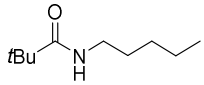
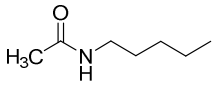
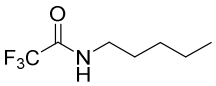
Standard conditions for the reactions catalyzed by the manganese complexes involved syringe pump delivery of H_2O_2 (3.0 equiv) to an acetonitrile solution of the catalyst (1 mol %) and AcOH (13 equiv) in CH_3CN at −40 °C during 30 min. Exploration of the simplest catalysts of the series, **Fe(pdp)**, **Mn(pdp)**, **Fe(mcp)** and **Mn(mcp)** (entries 1-4) reveals that only the manganese catalysts oxidize the substrate, with the bipyrrolidine **Mn(pdp)** catalyst being more efficient than the cyclohexanediamine **Mn(mcp)** one. The negligible conversion observed with **Fe(pdp)** and **Fe(mcp)** highlights the challenge that these substrates represent for the iron complexes. With the two manganese catalysts the product deriving from C–H hydroxylation in α to nitrogen (**P1**) was obtained in poor (10%, entry 4) to moderate (41%, entry 2) yield, together with smaller amounts of pentanal. Despite of the electron withdrawing character of the amide group, the nitrogen atom in pivalamide **S1** is still sufficiently electron rich to activate the α-C–H bonds. No products deriving from oxidation at C2-C5, nor from oxidation of the primary *t*-Bu C–H bonds were observed.

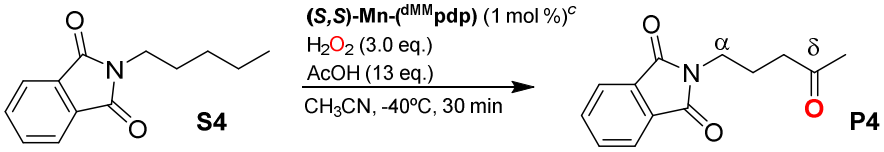
Remarkably, no evidence for the formation of the corresponding imide, which is the most common product resulting from oxidation of the C–H bonds that are α to nitrogen in *N*-alkylamides,[38] was observed. Pentanal presumably arises from oxidative C–N bond cleavage. Control experiments showed that **P1** does not convert into pentanal under the reaction conditions, indicating that the latter is formed via a path that competes with α-C–H hydroxylation.[49] Improved yields, from moderate to good, were obtained when electron donating methyl and methoxy groups (**Mn(**$^{\mathbf{dMM}}$**pdp)** and **Mn (**$^{\mathbf{dMM}}$**mcp)**) were introduced at pyridine positions 3, 4 and 5 of the manganese complexes (entries 6 and 7). Making the catalyst more electron rich partially rescues activity also in the case of iron catalysts, thus **Fe(**$^{\mathbf{dMM}}$**pdp)** provides oxidation products but in low yield (entry 5), far from the values obtained with the manganese analogue (entry 6). On the other hand, the more electron poor catalyst **Mn(**$^{\mathbf{Cl}}$**mcp)** delivered only very low product yields (entry 8). This apparent correlation between catalytic activity and electron donating ability of the ligand follows that observed in epoxidation reactions.[50-51] However, the use of the electron-rich **Fe(**$^{\mathbf{Me2N}}$**pdp)** and **Mn(**$^{\mathbf{Me2N}}$**pdp)** catalysts, which have proven particularly active in olefin epoxidation reactions,[51] but are quite sensitive to harsh oxidation conditions, affords no product or only 14% of the α-C–H hydroxylation product (entries 9 and 10). Improvement in product yield was also observed by the use of manganese catalysts where bulky groups like the *tris*-(isopropyl)silyl (TIPS) were introduced at positions 3 of the pyridine rings (entries 12-13). In this case, the cyclohexanediamine system **Mn(**$^{\mathbf{TIPS}}$**mcp)** performs substantially better than the bipyrrolidine one **Mn(**$^{\mathbf{TIPS}}$**pdp)**, in line with our previous observations on the oxidation of *N*-cyclohexyl amides.[34] In addition, other manganese complexes were included in the catalyst screening; namely **Mn(**$^{\mathbf{BzIm}}$**pdp)**, where the pyridine rings were replaced by *N*-methylbenzimidazole (BzIm) rings, and **Mn(**$^{\mathbf{CF3}}$**mcp)** where 2,6-bis-trifluoromethylphenyl groups were appended to position 3 of the pyridines of the mcp ligand (entries 14 and 15). None of these catalysts improved the outcome of the reaction. Finally, cyclopropanecarboxylic acid was used instead of acetic acid in reactions with the **Mn(**$^{\mathbf{dMM}}$**pdp)** catalyst (entry 16). This acid is sterically more demanding than acetic acid and has recently proven particularly effective in regio and enantioselective C–H oxidation of *N*-cyclohexyl amides with similar manganese catalysts.[34] As compared to acetic acid, the reaction furnished reduced yields of **P1** and pentanal as the only products, in similar relative ratios, although the mass balance of the reaction was particularly good. Therefore, on the basis of this screening, **Mn(**$^{\mathbf{dMM}}$**pdp)** in combination with acetic acid was selected as the catalyst and carboxylic acid partner of choice for the oxidation of the three series of *N*-alkylamide and phthalimide substrates, in order to study in detail the effect of *N*-alkyl structure and of functional group structure and electronics on yield and site-selectivity of the reaction. The product

distributions observed in the oxidation of the *N*-pentyl (**S1**-**S4**), *N*-2-(5-methylhexyl) (**S5**-**S8**) and *N*-1-(3-methylbutyl) derivatives (**S9**-**S12**) catalyzed by **Mn(**^{dMM}**pdp)** are displayed in Tables 2, 3 and 4, respectively.

Table 2. Oxidation of Different *N*-Pentyl Derivatives



Entry/ Substrate (SX)		Conv %[a]	Yield PX %[a] (Isolated)	Yield P0 %[a]
1	 **S1**	99	60 (48)	11
2	 **S2**	89	40[b]	13
3	 **S3**	64	26	6



[a]Conversions and yields determined from crude reaction mixtures by GC or ^{1}H NMR. [b]In a larger scale catalysis experiment driven to complete substrate conversion, 36% yield of product **P2** and 36% yield of the overoxidized imide product were isolated together with pentanal (determined by GC) in 11% yield. [c]Iterative addition (2x): cat (1 mol %), H_2O_2 (3.0 equiv), AcOH (13 equiv) in CH_3CN at -40 °C during 30 min.

Starting from the reactions of the *N*-pentyl derivatives, the results displayed in Table 2 show that replacement of the sterically demanding pivaloyl (**S1**) for acetyl (**S2**) and for the more electron withdrawing trifluoroacetyl (**S3**) (Table 2, entries 1-3) did not alter site selectivity, as clearly shown for all three substrates by the formation of products **P1**, **P2** and **P3**, respectively deriving from α-C–H bond hydroxylation. Interestingly, the imide product was only observed in the oxidation of **S2**, when the reaction was driven to full substrate conversion. Under these conditions formation of the α-hydroxylation and imide products in a 1:1 ratio was observed, supporting the hypothesis of a

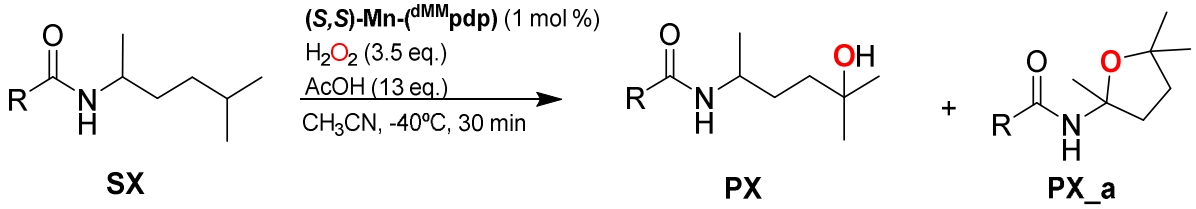
higher reactivity of the substrate **S2** as compared to first formed product **P2** in the **Mn(**^{dMM}**pdp)** catalyzed reaction, and indicating that the imide product derives from overoxidation of **P2**. Pentanal, that as mentioned above presumably derives from oxidative C–N bond cleavage, was again identified in the reaction mixtures as side product. The decrease in conversion and product yield observed on going from **S1** and **S2** to **S3** is in line with the electrophilic character of the intermediate manganese oxo complex and the electron withdrawing effect of the CF_3 group that, as compared to *t*-Bu and Me groups, deactivates the α-C–H bonds toward oxidation.

Most interestingly, on going from the *N*-pentylamides to *N*-pentylphthalimide (**S4**), a dramatic change in site selectivity was observed in the reactions catalyzed by **Mn(**^{dMM}**pdp)** (Table 2, entry 4), where exclusive formation of the δ-ketoamide product resulting from oxidation at the most remote methylene site of the pentyl moiety was detected. This behavior can be explained on the basis of the increased electron withdrawing ability of the phthalimido group that, as compared to the acyl ones, strongly deactivates the α-C–H bonds, as well as the β- and γ- ones, towards oxidation, showing in particular that in these reactions site-selectivity can be drastically changed through a simple synthetic modification of a parent amine substrate. The remote functionalization observed in the reaction of **S4** is in agreement with the results of recent studies on aliphatic C–H bond oxidation of *N*-pentyl, *N*-cyclohexyl and *N*-cycloheptyl derivatives, where in all cases, the phthalimido group provided the highest selectivity for the most remote methylene group.[34, 52-54] However, in partial contrast to the present study, Alexanian and coworkers have recently shown that sterically demanding amidyl radicals, generated photochemically from *N*-bromo and *N*-chloroamides, react with *N*-pentylphthalimide leading, in addition to the δ-haloimide, to the formation of sizable amounts (18-19%) of products deriving from halogenation at other sites.[52-53] This comparison points towards an important role of the **Mn(**^{dMM}**pdp)** catalyst in defining this exquisite C–H oxidation selectivity that may reflect a higher steric demand of the reactive manganese-oxo species as compared to the amidyl radicals, but it may also denote a higher and less discriminate HAT reactivity of the later, a hypothesis that is well supported by the observation of small amounts of products deriving from halogenation of the terminal methyl group.[52-53]

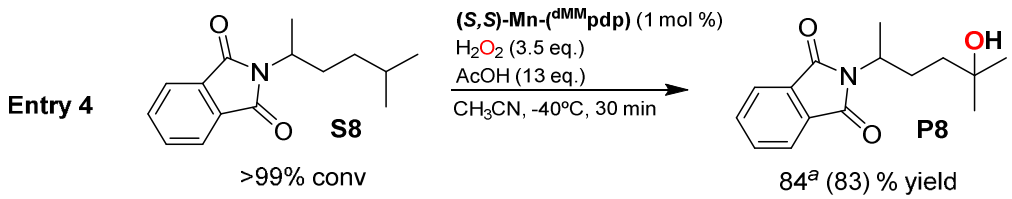
Moving then to the oxidation of the *N*-2-(5-methylhexyl) derivatives (**S5**-**S8**), characterized by the presence of a tertiary α-C–H bond and a tertiary C–H bond at the remote δ-position, the main product observed is in all cases the hydroxylated product **PX** that derives from oxidation at the δ-C–H bond (Table 3, entries 1-4). This result is in sharp contrast with the oxidations of **S1**-**S3**, that selectively occurred at the proximal α-methylene site (Table 2, entries 1-3). A second compound, **PX_a** appears as a significant side product in the reactions of the least deactivated pivalamide (**S5**)

and acetamide (**S6**) substrates and as a minor product in the reaction of the trifluoroacetamide one (**S7**). Formation of this cyclic product can be explained on the basis of α-C–H oxidation of the first formed product **PX** followed by cyclization. The observation that the relative importance of product **PX_a** over **PX** increases with increasing conversion, together with the increased yield in **PX_a** observed on going from **S5** to **S6**, and the very low yield or lack of this product observed in the reactions of **S7** and **S8**, respectively, strongly support this hypothesis, reflecting the contribution of steric (faster α-C–H oxidation of **P6** as compared to **P5**) and electronic effects (slower α-C–H oxidation of **P7** as compared to **P5** and **P6**) on the formation of this product.

Table 3. Oxidation of Different *N*-2-(5-methylhexyl) Derivatives

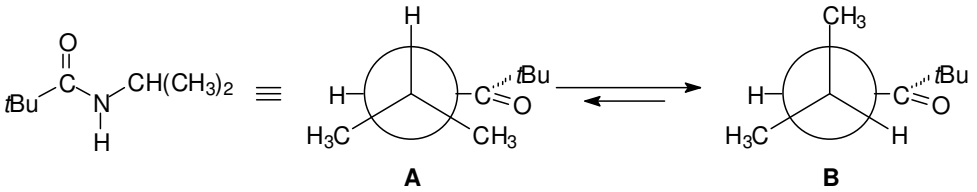


Entry	Substrate	Conv %[a]	Yield PX %[a] (isolated)	Yield PX_a %[a] (isolated)
1	**S5**	93	77 (52)	13
2	**S6**	99	41 (36)	34 (33)[b]
3	**S7**	90	84 (58)	2



[a]Conversions and yields determined from crude reaction mixtures by GC or ^{1}H NMR. [b]**P6_a** was isolated with 11% yield of a non-identified impurity that could not be separated.

The lack of products deriving from tertiary α-C–H bond oxidation in **S5**-**S7** can be reasonably explained on the basis of the operation of stereoelectronic effects. As described in a recent time-resolved kinetic study on HAT from *N*-alkylamides to a representative oxygen centered radical such as cumyloxyl (CumO$^{\bullet}$), a ~9-fold decrease in the k_H value for HAT from the α-C–H bonds was measured on going from *N*-ethylpivalamide to *N*-isopropylpivalamide.[55] It was proposed that the introduction of a methyl group on the α-carbon increases the energy barrier required to reach the most suitable conformation for HAT where the α-C–H bonds are aligned with the amide π-system (structure **A** in Scheme 3), accounting for the observed decrease in reactivity.



Scheme 3. Conformational equilibrium for rotation around the N–CH(CH$_3$)$_2$ bond in *N*-isopropylpivalamide.

Along these lines, a similar explanation can be put forward to account for the regioselectivity observed in the present study in the **Mn(**$^{\mathbf{dMM}}$**pdp)** catalyzed oxidation of **S5**-**S7**. Quite importantly, this observation supports the hypothesis that the reactions of alkanamides with CumO$^{\bullet}$ and the oxidations catalyzed by manganese complexes described in this work involve a common HAT step.

Of notice, an analogous regioselective oxidation of a trifluoroacetamide substrate strictly related to **S7**, namely *N*-(2-(6-methylheptyl)trifluoroacetamide, with the [Fe(pdp)(CH$_3$CN)$_2$](SbF$_6$)$_2$ catalyst was previously described and rationalized on the basis of the electron withdrawing α-C–H deactivation determined by the trifluoroacetyl group.[7] The current results indicate instead that stereoelectronic effects are at the basis of the observed regioselectivity.

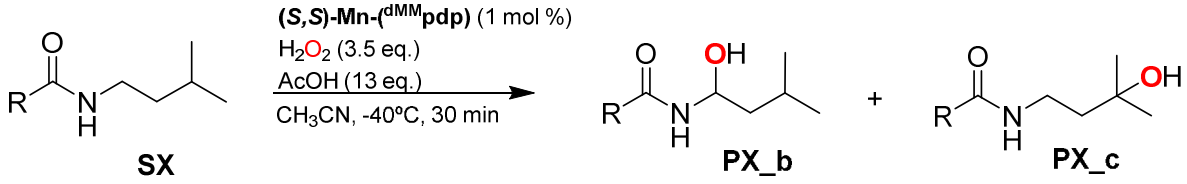
Along the same vein, a very recent study on the aliphatic α-C–H functionalization of *N*-Boc protected ethyl methyl amine and isopropyl methyl amine via the combination of photoredox, nickel and HAT catalysis, pointed towards steric effects as a rationale for the predominant alkylation of the primary α-C–H bonds of the methyl groups over the weaker secondary and tertiary ones.[56] Also in this case, stereoelectronic effects can be reasonably invoked to account for this peculiar selectivity, pointing once again towards the very important role played by these effects in governing site-selectivity in HAT based functionalization of aliphatic C–H bonds that are α to sp^2 nitrogen atoms, such as those of amide and carbamate substrates.

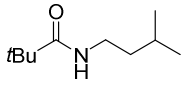
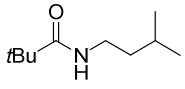
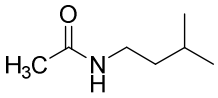
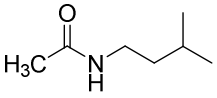
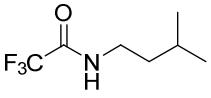
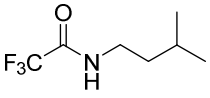
Particularly relevant in the context of the oxidation of *N*-2-(5-methylhexyl) derivatives is the observation that with the phthalimide derivative **S8** the reaction progresses with excellent yield and mass balance (Table 3, entry 4), leading to exclusive oxidation at the remote tertiary position, with no formation of the secondary oxidation product **P8_a**.

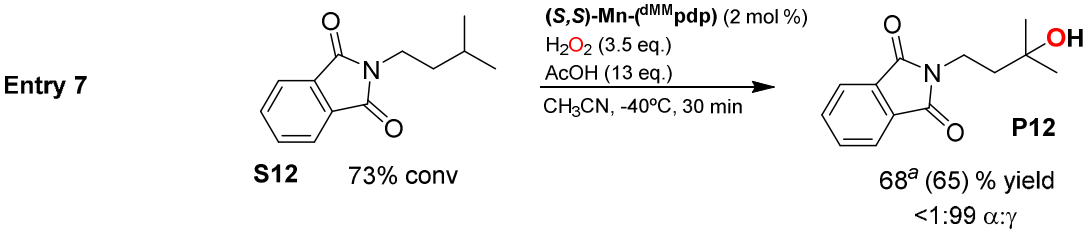
Finally, the oxidation of *N*-1-(3-methyl)butyl derivatives **S9**-**S12** was evaluated. In this case, the proximal position is a methylenic site, that was envisioned to compete with the oxidation of a tertiary C–H bond at a remote γ-position. In line with the previous observations (Tables 2 and 3), in the reactions of the pivalamide (**S9**) and acetamide (**S10**) derivatives the α-CH_2 position is activated toward oxidation, and the proximal hydroxylated products **P9_b** and **P10_b** were preferentially obtained in good isolated yield (Table 4, entries 1 and 3), while the remote oxidized products **P9_c** and **P10_c** were observed only in low or very low amount. This can be explained on the basis of a stronger activation of the α-C–H bonds as compared to the remote tertiary C–H bonds determined by the presence of the amide nitrogen atom. It is possible to notice that the presence of the bulkier pivaloyl group as compared to acetyl can reduce the extent of α-oxidation, however a good to excellent selectivity for this oxidation site was observed for both substrates (**PX_b**:**PX_c** = 4.7:1 and 33:1; Table 4, entries 1 and 3, respectively). The formation of **P9_b** and **P10_b**, with no evidence of overoxidation to the corresponding imide products, highlights once again the ability of this catalyst to perform oxidation of amide C–H bonds with very high levels of product selectivity. The origin of this unusual chemoselectivity can be explained on the basis of the stereoelectronic effects discussed above (see Scheme 3), where α-hydroxylation increases the energy barrier required to reach the most suitable conformation for HAT from this position where the α-C–H bonds are aligned with the amide π-system. It can also be proposed that intramolecular hydrogen-bonding between the α-hydroxyl and carbonyl groups plays a role in this respect, preventing optimal overlap of the α-C-H bond with the amide π system.

On the other hand, the presence of EWG groups led to a dramatic change in site selectivity. The predominant or exclusive formation of the product deriving from remote tertiary C–H bond hydroxylation **PX_c** was obtained with the trifluoroacetamide or phthalimide substrates (**S11** and **S12**, respectively, Table 4, entries 5 and 7) with modest to good isolated yields and very good to outstanding levels of selectivity (**PX_b**:**PX_c** from 1:22 to <1:99, Table 4, entries 5 and 7, respectively). Very striking is the observation that the phthalimide derivative **S12** undergoes exclusive oxidation at the remote position, highlighting once again the powerful role of this functional group in governing site-selectivity.

Table 4. Oxidation of Different *N*-1-(3-methylbutyl) Derivatives



Entry	Substrate	Conv %[a]	Yield PX_b %[a] (isolated)	Yield PX_c %[a] (isolated)	Selectivity PX_b / PX_c[b]
1	 **S9**	93	66 (64)	7	4.7:1
2[c]	 **S9**	<2	-	-	-
3	 **S10**	95	66 (65)	1	33:1
4[c]	 **S10**	<2	-	-	-
5	 **S11**	91	7	77 (48)	1:22
6[c]	 **S11**	55	11	36	1:6.5

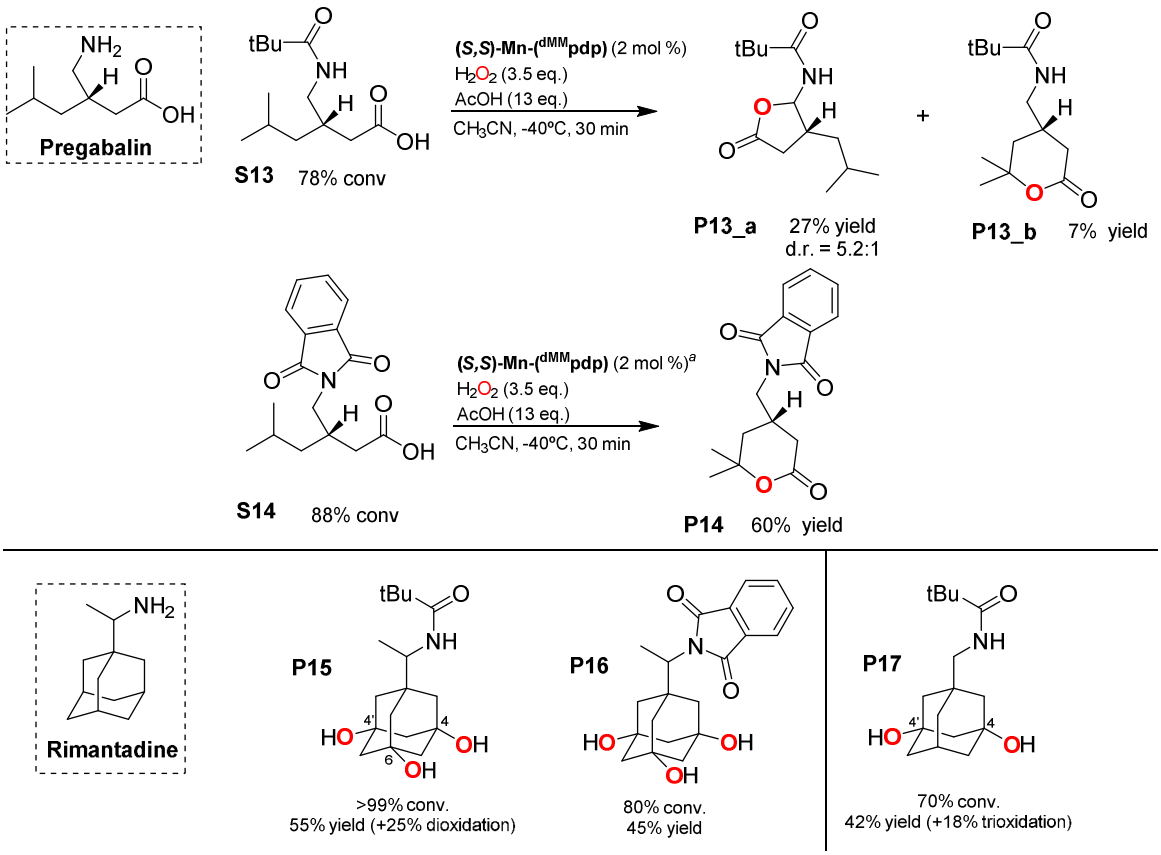


[a]Conversions and yields determined from crude reaction mixtures by GC or ^{1}H NMR. [b]Normalized Ratio. [c]Reaction conditions: **Fe(pdp)** (3 mol %), H_2O_2 (2.5 equiv), AcOH (1.5 equiv) in CH_3CN at 0 °C during 30 min.

Finally, the poor performance of the iron analogues of the **Mn(pdp)** and **Mn(**^{dMM}**pdp)** catalysts was further investigated. It was noticed that with the **Fe(pdp)** and **Fe(**^{dMM}**pdp)** catalyst catalytic oxidation of amide substrates bearing activated α-C–H bonds (**S1, S9** and **S10**) did not proceed or provided very low product yields (Table 1, entries 1 and 5; Table 4, entries 2 and 4). Instead, oxidation of amide substrates where oxidation takes place preferentially at remote positions (**S4**, see Supporting Information, and **S11**, Table 4, entry 6) occurred with improved (albeit still modest) yields. We reasoned that the α-hydroxylated product may inhibit the catalyst, presumably by chelation through the O-carbonyl and the α-OH groups. Consistent with this proposal, no oxidation products were obtained when a typical catalytic oxidation reaction of **S10** (50 equiv with respect to the catalyst) with **Fe(pdp)** was performed in the presence of **P10** (50 equiv with respect to the catalyst). Furthermore, reaction mixtures of the oxidation of **S1**, **S9** and **S10** with the iron catalysts rapidly turned intense purple/blue following addition of hydrogen peroxide, suggesting the immediate formation of iron species that exhibit low energy charge transfer transitions. Charge transfer from extended π systems of the ligand to a Fe^{III} center are usually associated with these spectroscopic features.[57-61] In addition, high resolution mass spectrometry monitoring of the reaction of **Fe(pdp)** with **S10** under standard conditions showed cluster ions at m/z = 261.1294 that can be assigned to $\{[Fe(pdp)(\mathbf{S10})+O-H]\}^{+2}$ ions**.** Taken together, these observations suggest that **P10** chelates and effectively deactivates the iron catalysts, while manganese counterparts do not appear to be affected suggesting that they are more labile and less sensitive to chelation.

With these results in hand we decided to probe the versatility of this approach in the oxidation of more complex bioactive molecules bearing primary amine moieties as a main structural feature. For this purpose, pivalamide and phthalimide derivatives of drug molecules such as pregabalin (Lyrica) and the antiviral drug rimantadine (Flumadine), whose structures are shown in Scheme 4, were chosen as substrates.

As expected, the **Mn(**^{dMM}**pdp)** catalyst performs the oxidation of these molecules in satisfactory yields, with site selectivity that can be predicted on the basis of the amine derivatization. In line with the results shown in Table 4, oxidation of the pivalamide derivative of pregabalin (**S13**, Scheme 4) occurs preferentially at the most activated CH_2 position that is α to nitrogen, yielding amido γ-lactone compound **P13_a** derived from cyclization of the first formed product, that results from hydroxylation at this methylenic site, with the carboxylic group.



Scheme 4. Oxidation of bioactive molecules. [a]Iterative addition (3x): cat (2 mol %), H_2O_2 (3.5 equiv), AcOH (13 equiv) in CH_3CN at -40 °C during 30 min. Isolated yields.

The oxidized amido δ-lactone product resulting from hydroxylation at the remote tertiary C–H site (**P13_b**) was observed only in lower amount (**P13_a/P13_b** = 3.9). No evidence for functionalization at the tertiary C–H bond that is β to both the amido and carboxyl groups was observed, in line with the deactivation of this site determined by the presence of the latter group. On the other hand, when pregabalin is derivatized with the strong electron withdrawing phthalimido group (**S14**, Scheme 4), oxidation catalyzed by **Mn(dMMpdp)** provides exclusively the amido δ-lactone product (**P14**) deriving from remote tertiary C–H hydroxylation, in good isolated yield (60%). On the other hand, the nature of the amine protecting group did not alter site selectivity in the oxidation of rimantadine derivatives **S15** and **S16** (Scheme 4). In both cases, products deriving from hydroxylation of two and/or three tertiary C–H bonds of the adamantane skeleton were observed. Moreover, removal of the methyl group that is α to nitrogen (**S17**, Scheme 4), did not change the reaction regioselectivity. Product **P17**, resulting from hydroxylation of two adamantane tertiary C–H bonds, is the mayor product, along with a smaller amount of the trihydroxylated one. Products deriving from oxidation at the α-C–H bonds were not observed, pointing towards the strong activation of adamantane tertiary C–H bonds and suggesting moreover an important

contribution of steric and stereoelectronic effects imposed by the presence of the bulky adamantly moiety towards deactivation of the α-CH_2 site.

CONCLUSIONS

The present work describes the oxidation of aliphatic amides and phthalimides with aqueous H_2O_2 using manganese catalysts. Amides are demonstrated to be superior functional groups for modulating site selectivity in these reactions, playing an activating or deactivating role on proximal C–H bonds on the basis of electronic, steric and stereoelectronic factors. The phthalimido group constitutes a unique case because its powerful electron withdrawing character strongly deactivates proximal C–H bonds and consistently directs oxidation towards the most remote position. Also remarkably, amides that present a methylenic site that is α to nitrogen are hydroxylated at this position with excellent product chemoselectivity, providing a straightforward entry into this challenging class of molecules. This hydroxylation reaction is remarkable because most oxidation methods reported in the literature consistently lead to the imide product and highlights in particular the powerful role of the manganese catalyst in governing selectivity. Presumably, the HAT nature of the current reactions and the associated stereoelectronic effects lay at the basis of this unusual chemoselectivity. Taken together, the current work discloses a site- and product selective and predictable C–H oxidation methodology with potential applicability to molecules of interest in modern organic chemistry, including substrate platforms of pharmaceutical relevance.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website. Experimental details on the preparation and characterization of the catalysts, experimental procedures for the catalytic reactions, spectroscopic data for the products.

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REFERENCES

1. Newhouse, T.; Baran, P. S., *Angew. Chem. Int. Ed.* **2011,** *50*, 3362–3374.
2. Brückl, T.; Baxter, R. D.; Ishihara, Y.; Baran, P. S., *Acc. Chem. Res.* **2012,** *45*, 826-839.
3. Sun, C.-L.; Li, B.-J.; Shi, Z.-J., *Chem. Rev.* **2011,** *111*, 1293-1314.
4. Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachal, P.; Krska, S. W., *Chem. Soc. Rev.* **2016,** *45*, 546-576.
5. Liu, W.; Groves, J. T., *Acc. Chem. Res.* **2015,** *48*, 1727-1735.
6. Hartwig, J. F.; Larsen, M. A., *ACS Cent. Sci.* **2016,** *2*, 281-292.
7. Chen, M. S.; White, M. C., *Science* **2007,** *318*, 783-787.
8. Chen, M. S.; White, M. C., *Science* **2010,** *327*, 566-571.
9. Bigi, M. A.; Reed, S. A.; White, M. C., *Nat. Chem.* **2011,** *3*, 216-222.
10. Bigi, M. A.; Reed, S. A.; White, M. C., *J. Am. Chem. Soc.* **2012,** *134*, 9721-9726.
11. Ottenbacher, R. V.; Samsonenko, D. G.; Talsi, E. P.; Bryliakov, K. P., *Org. Lett.* **2012,** *14*, 4310–4313.
12. Shen, D. Y.; Miao, C. X.; Xu, D. Q.; Xia, C. G.; Sun, W., *Org. Lett.* **2015,** *17*, 54-57.
13. Font, D.; Canta, M.; Milan, M.; Cussó, O.; Ribas, X.; Klein Gebbink, R. J. M.; Costas, M., *Angew. Chem. Int. Ed.* **2016,** *55*, 5776-5779.
14. Prat, I.; Gomez, L.; Canta, M.; Ribas, X.; Costas, M., *Chemistry* **2013,** *19*, 1908-13.
15. Gormisky, P. E.; White, M. C., *J. Am. Chem. Soc.* **2013,** *135*, 14052-14055.
16. Gomez, L.; Canta, M.; Font, D.; Prat, I.; Ribas, X.; Costas, M., *J. Org. Chem.* **2013,** *78*, 1421-33.
17. Topczewski, J. J.; Cabrera, P. J.; Saper, N. I.; Sanford, M. S., *Nature* **2016,** *531*, 220-224.
18. Khusnutdinova, J. R.; Ben-David, Y.; Milstein, D., *J. Am. Chem. Soc* **2014,** *136*, 2998-3001.
19. Legacy, C. J.; Wang, A.; O'Day, B. J.; Emmert, M. H., *Angew. Chem. Int. Ed.* **2015,** *54*, 14907-14910.
20. Wu, X.-F.; Bheeter, C. B.; Neumann, H.; Dixneuf, P. H.; Beller, M., *Chem. Comm.* **2012,** *48*, 12237-12239.
21. Xu, W.; Jiang, Y.; Fu, H., *Synlett* **2012,** *23*, 801-804.
22. Preedasuriyachai, P.; Chavasiri, W.; Sakurai, H., *Synlett* **2011,** *2011*, 1121-1124.
23. Kim, J. W.; Yamaguchi, K.; Mizuno, N., *Angew. Chem. Int. Ed.* **2008,** *47*, 9249-9251.
24. Klobukowski, E. R.; Mueller, M. L.; Angelici, R. J.; Woo, L. K., *ACS Catal.* **2011,** *1*, 703-708.
25. Genovino, J.; Lütz, S.; Sames, D.; Touré, B. B., *J. Am. Chem. Soc* **2013,** *135*, 12346-12352.
26. Liu, P.; Liu, Y.; Wong, E. L.-M.; Xiang, S.; Che, C.-M., *Chem. Sci.* **2011,** *2*, 2187-2195.
27. Murahashi, S.; Naota, T.; Yonemura, K., *J. Am. Chem. Soc* **1988,** *110*, 8256-8258.
28. Mitchell, E. A.; Peschiulli, A.; Lefevre, N.; Meerpoel, L.; Maes, B. U. W., *Chemistry–Eur. J.* **2012,** *18*, 10092-10142.
29. Griffiths, R. J.; Burley, G. A.; Talbot, E. P. A., *Org. Lett.* **2017,** *19*, 870-873.
30. Milan, M.; Salamone, M.; Bietti, M., *J. Org. Chem.* **2014,** *79*, 5710-5716.
31. Lee, M.; Sanford, M. S., *J. Am. Chem. Soc* **2015,** *137*, 12796-12799.
32. Howell, J. M.; Feng, K.; Clark, J. R.; Trzepkowski, L. J.; White, M. C., *J. Am. Chem. Soc.* **2015,** *137*, 14590-14593.
33. Mbofana, C. T.; Chong, E.; Lawniczak, J.; Sanford, M. S., *Org. Lett.* **2016,** *18*, 4258-4261.
34. Milan, M.; Bietti, M.; Costas, M., *ACS Cent. Sci.* **2017,** *3*, 196-204.
35. Nicolaou, K. C.; Mathison, C. J. N., *Angew. Chem. Int. Ed.* **2005,** *44*, 5992-5997.
36. Bjorsvik, H.-R.; Fontana, F.; Liguori, L.; Minisci, F., *Chem. Comm.* **2001,** *0*, 523-524.
37. Itoh, I.; Matsusaki, Y.; Fujiya, A.; Tada, N.; Miura, T.; Itoh, A., *Tetrahedron Lett.* **2014,** *55*, 3160-3162.
38. Sperry, J., *Synthesis* **2011,** *2011*, 3569-3580.
39. Minisci, F.; Punta, C.; Recupero, F.; Fontana, F.; Pedulli, G. F., *J. Org. Chem.* **2002,** *67*, 2671-2676.
40. Ito, R.; Umezawa, N.; Higuchi, T., *J. Am. Chem. Soc.* **2005,** *127*, 834-835.
41. Capdevielle, P.; Maumy, M., *Tetrahedron Lett.* **1991,** *32*, 3831-3834.
42. Ivashkin, P. E.; Lukyanov, K. A.; Lukyanov, S.; Yampolsky, I. V., *J. Org. Chem.* **2011,** *76*, 2782-2791.
43. Braña, M. F.; Rodriquez, M. L. L., *J. Het. Chem.* **1981,** *18*, 869-871.

44. Osberger, T. J.; Rogness, D. C.; Kohrt, J. T.; Stepan, A. F.; White, M. C., *Nature* **2016,** *537*, 214-219.
45. Adams, A. M.; Du Bois, J.; Malik, H. A., *Org. Lett.* **2015,** *17*, 6066-6069.
46. Murphy, A.; Dubois, G.; Stack, T. D. P., *J. Am. Chem. Soc.* **2003,** *125*, 5250-5251.
47. Shen, D.; Miao, C.; Wang, S.; Xia, C.; Sun, W., *Org. Lett.* **2014,** *16*, 1108-1111.
48. Canta, M.; Font, D.; Gómez, L.; Ribas, X.; Costas, M., *Adv. Synth. Catal.* **2014,** *356*, 818-830.
49. Hull, J. F.; Balcells, D.; Sauer, E. L. O.; Raynaud, C.; Brudvig, G. W.; Crabtree, R. H.; Eisenstein, O., *J. Am. Chem. Soc.* **2010,** *132*, 7605-7616.
50. Cussó, O.; Garcia-Bosch, I.; Ribas, X.; Lloret-Fillol, J.; Costas, M., *J. Am. Chem. Soc.* **2013,** *135*, 14871-14878.
51. Cussó, O.; Garcia-Bosch, I.; Font, D.; Ribas, X.; Lloret-Fillol, J.; Costas, M., *Org. Lett.* **2013,** *15*, 6158-6161.
52. Schmidt, V. A.; Quinn, R. K.; Brusoe, A. T.; Alexanian, E. J., *J. Am. Chem. Soc.* **2014,** *136*, 14389-14392.
53. Quinn, R. K.; Könst, Z. A.; Michalak, S. E.; Schmidt, Y.; Szklarski, A. R.; Flores, A. R.; Nam, S.; Horne, D. A.; Vanderwal, C. D.; Alexanian, E. J., *J. Am. Chem. Soc.* **2016,** *138*, 696-702.
54. Kawamata, Y.; Yan, M.; Liu, Z.; Bao, D.-H.; Chen, J.; Starr, J. T.; Baran, P. S., *J. Am. Chem. Soc.* **2017,** *139*, 7448-7451.
55. Salamone, M.; Basili, F.; Mele, R.; Cianfanelli, M.; Bietti, M., *Org. Lett.* **2014,** *16*, 6444-6447.
56. Le, C.; Liang, Y.; Evans, R. W.; Li, X.; MacMillan, D. W. C., *Nature* **2017,** doi:10.1038/nature22813
57. Cox, D. D.; Benkovic, S. J.; Bloom, L. M.; Bradley, F. C.; Nelson, M. J.; Que, L., Jr.; Wallick, D. E., *J. Am. Chem. Soc.* **1988,** *110*, 2026-2032.
58. Mehn, M. P.; Fujisawa, K.; Hegg, E. L.; Que, L., Jr., *J. Am. Chem. Soc.* **2003,** *125*, 7828-7842.
59. Solomon, E. I.; Brunold, T. C.; Davis, M. I.; Kemsley, J. N.; Lee, S.-K.; Lehnert, N.; Neese, F.; Skulan, A. J.; Yang, Y.-S.; Zhou, J., *Chem. Rev.* **2000,** *100*, 235-349.
60. Makhlynets, O. V.; Rybak-Akimova, E. V., *Chem. Eur. J.* **2010,** *16*, 13995-14006.
61. Serrano-Plana, J.; Oloo, W. N.; Acosta-Rueda, L.; Meier, K. K.; Verdejo, B.; García-España, E.; Basallote, M. G.; Münck, E.; Que, L.; Company, A.; Costas, M., *J. Am. Chem. Soc.* **2015,** *137*, 15833-15842.

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