Enantioselective C-H lactonization of unactivated methylenes directed by carboxylic acids

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ABSTRACT: The formidable challenges of controlling site-selectivity, enantioselectivity and product chemoselectivity, make asymmetric C–H oxidation a generally unsolved problem for non-enzymatic systems. Discrimination between the two enantiotopic C–H bonds of an unactivated methylenic group is particularly demanding and so far unprecedented, given the similarity between their environments and the facile overoxidation of the initially formed hydroxylation product. Here we show that a Mn-catalyzed C–H oxidation directed by carboxylic acids can overcome these challenges to yield γ-lactones in high enantiomeric excess (up to 99%) using hydrogen peroxide as oxidant and a Brønsted acid additive under mild conditions and short reaction times. Coordination of the carboxylic acid group to the bulky Mn complex ensures the rigidity needed for high enantioselectivity and dictates the outstanding γ site-selectivity. When the substrate contains non-equivalent γ-methylenes, the site-selectivity for lactonization can be rationally predicted on the basis of simple C–H activation/deactivation effects exerted by proximal substituents. In addition, discrimination of diastereotopic C–H bonds can be modulated by catalyst design, with no erosion of enantiomeric excess. The potential of this reaction is illustrated in the concise synthesis of a tetrahydroxylated bicyclo[3.3.1]nonane enabled by two key, sequential γ-C–H lactonizations, with the latter that fixes the chirality of five stereogenic centres in one step with 96% ee.

INTRODUCTION

The increasing complexity of bioactive molecules, featuring a large number of stereogenic centers, continuously demands for the development of novel and effective enantioselective catalytic transformations. In this regard, functionalization of aliphatic C–H bonds represents the most straightforward approach, as it directly introduces a novel functionality on ubiquitous C–H bonds of the starting material.[1] Given the relevance of chiral oxygenated motifs in natural and bioactive products, enantioselective C(sp^3)–H oxidation is particularly attractive in this respect. However, such reaction requires highly reactive species to cleave strong, unactivated secondary C–H bonds and yet a very fine control over three key challenging features: discrimination of one among many C-H bonds, typically characterized by similar bond strengths and steric environments (site-selectivity or intramolecular chemoselectivity); discrimination between two enantiotopic C–H bonds (enantioselectivity); and prevention of the facile oxidation of the first formed chiral secondary alcohol product to an achiral ketone (product chemoselectivity). The difficulty of addressing all these issues at once translates into a meager toolbox of methodologies for asymmetric aliphatic C–H bond oxidation, with the available examples that are essentially limited to the oxidation of relatively weak, activated C–H bonds (benzylic or α-to-heteroatom).[2–7] The only example of asymmetric, unactivated C-H oxidation is the recently described enantioselective desymmetrization of monosubstituted cyclohexane derivatives *via* ketonization of enantiotopic methylenic carbons (Figure 1).[8] To the best of our knowledge, there are no reports for non-enzymatic asymmetric hydroxylation of enantiotopic C–H bonds in a prochiral methylenic group (Figure 1a). Even in the broader context of C(sp^3)–H functionalization, there are only few examples of enantioselective methylene C–H discrimination, limited to the realm of late, noble transition metals[9,10] (Pd,[11] Rh,[12] Ru,[13] Ir[14,15]).

Over the last decade, bioinspired nonheme Fe and Mn complexes have emerged as catalysts for site-selective and stereoselective oxidations.[16–18] These complexes activate H_2O_2

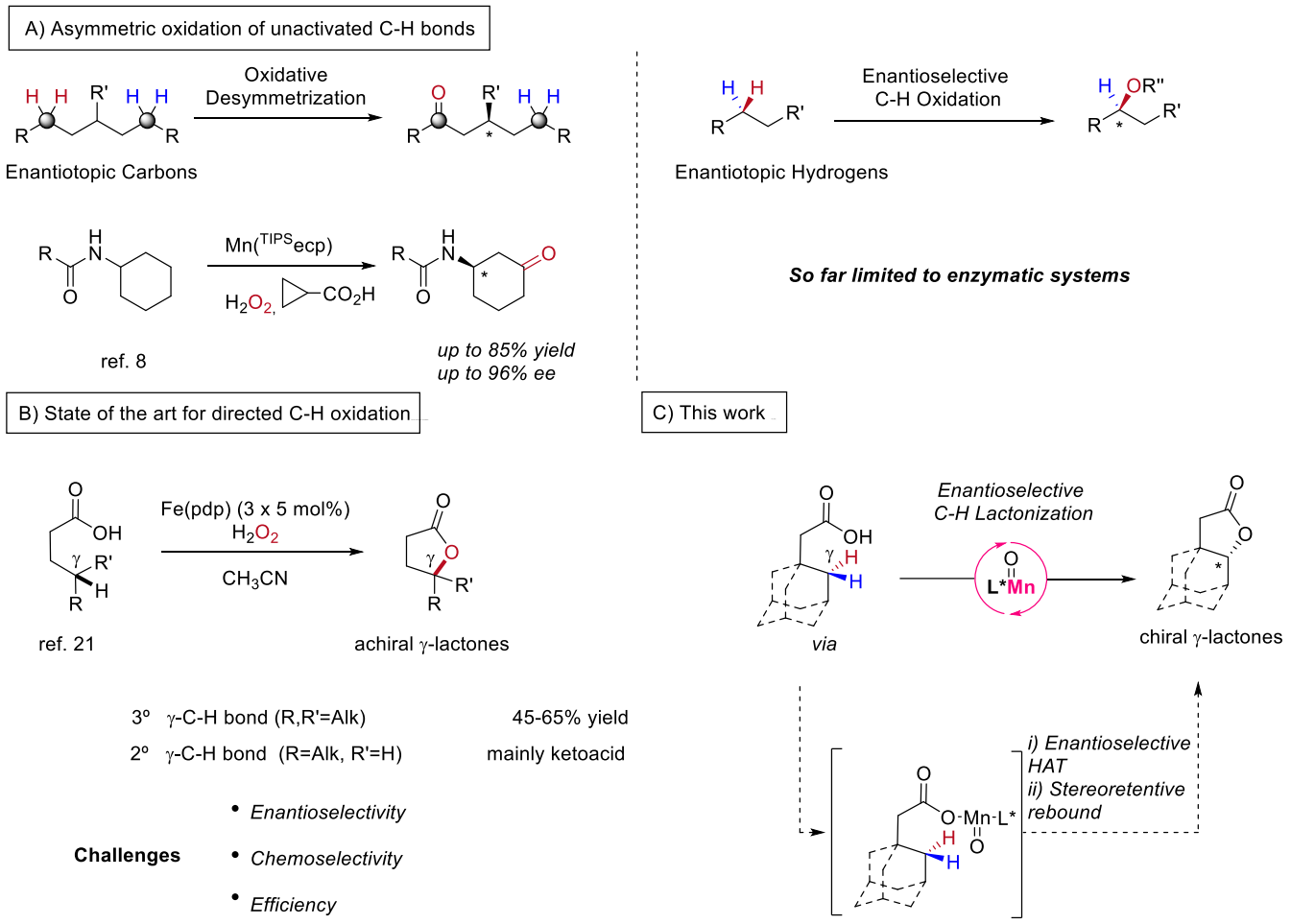


Figure 1. A) Overview of the strategies for asymmetric oxidation of unactivated aliphatic C–H bonds. B) State of the art for directed C–H oxidation, with the relative open challenges. C) Design of the present work.

to generate a powerful yet selective oxidant, an electrophilic high- valent metal-oxo species, competent for challenging C–H hydroxylations *via* a stereospecific Hydrogen Atom Transfer (HAT)/hydroxyl rebound mechanism, akin to the enzymatic path.[17] Remarkably, their structure can be modulated to rationally tune enantioselectivity both in olefin epoxidations and *syn*-dihydroxylations[17] and, more recently, in C–H oxidations *via* enantioselective desymmetrization (Fig. 1A).[8] In the latter case, key to high enantioselectivity has been the development of a well-defined pocket (cavity) around the catalytic center to precisely define substrate orientation.

We envisioned that this versatile class of catalysts may constitute a promising option to pursue enantioselective C–H oxidation of unactivated methylenic groups, provided that a far higher degree of control over the transition state geometry is exerted. We surmised that the use of a directing group could supply such control by fixing substrate orientation to the catalyst and rigidifying the transition state, as observed with heavier metals.[9,19] Carboxylic acids are known to bind the metal center in Fe and Mn catalyzed C–H oxidation where they have been shown to act as co-ligands assisting in the cleavage of H_2O_2 to give a high-valent metal-oxo carboxylate species.[17] Moreover, in Fe catalyzed C–H oxidations, carboxylic acids have been shown to act as directing groups,[20–23] enabling selective intramolecular hydroxylation of tertiary C–H bonds to provide valuable γ-lactones (albeit with low stereoinduction, max 35% ee in the kinetic resolution of a racemate),[21] with a γ-selectivity orthogonal to Pd catalyzed β-C–H functionalization.[24–26] Of notice, such a predictable γ-lactonization is a Fe-catalyzed C–H oxidation that has found application in total synthesis.[27–31] However, when applied to secondary γ-C–H bonds the reaction is not very efficient, leading to very low lactone yields[32] or overoxidation, to the ketoacid product.[21]

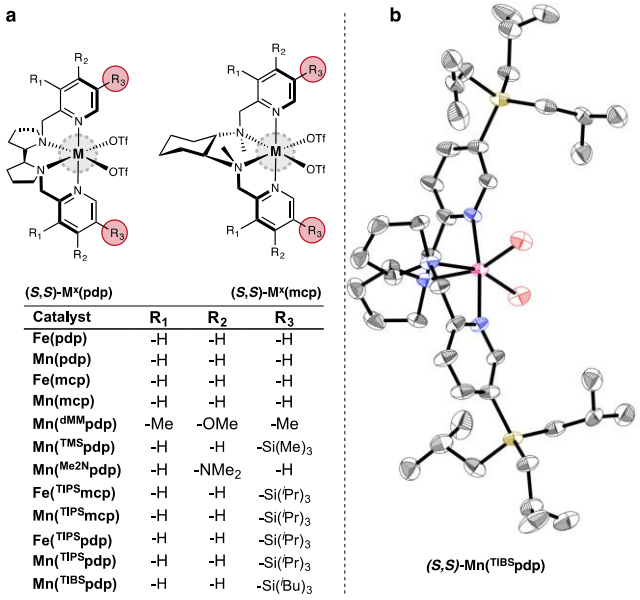
Within this framework, we hypothesized that the use of fluorinated alcohols as strong hydrogen bond donor (HBD) solvents may reduce or prevent such overoxidation, preserving the chirality.[33–35] Furthermore, fluorinated alcohols may assist H_2O_2 activation[36] as well as the subsequent spontaneous cyclization of the hydroxyacid[21] to afford the enantioenriched γ-lactone acting as hydrogen bond donors. Following this design, we herein describe the first example of Mn catalyzed enantioselective directed oxidation of non-activated C(sp^3)-H bonds on adamantaneacetic acids as a case study.

RESULTS AND DISCUSSION

Adamantaneacetic acid **1** was selected as a model substrate for its rigidity and the presence of three accessible γ-methylenes for

directed oxidation. Moreover, the defined shape, steric bulkiness, lipophilicity and chemical inertness of the adamantane core make this structural motif particularly attractive in multiple fields, from drug design to catalyst development and material science.[37] From an organic synthesis perspective, the appeal of adamantane cores could be even greater after the realization that their deconstruction *via* C–C bond cleavage pathways[38,39] can provide an easy entry into complex and densely functionalized bicyclic [3.3.1] structures that are found in molecules with notable biological activity .[39–42] Directed lactonization of **1** would enable challenging functionalization of secondary γ-C–H bonds, with a selectivity orthogonal to common bridgehead derivatizations that target the more reactive tertiary sites.[9,16,17]

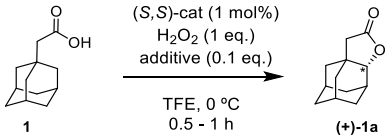
*Optimization of the oxidation of **1**:* Oxidation of **1** (25 mM) with 1 equivalent of H_2O_2, delivered over 30 minutes by syringe pump, was performed in 2,2,2-trifluoroethanol (TFE), employing 1 mol% of catalyst, at 0 °C, in the absence of an external carboxylic acid co-ligand (Table 1). The catalysts used are chiral Fe and Mn tetradentate complexes of general formula (*S*,*S*)-[M(L)(OTf)$_2$] (L = (*S*,*S*)-pdp and (*S*,*S*)-mcp, pdp = *N*,*N*′-bis(2-pyridylmethyl)-2,2′-bipyrrolidine, mcp = *N*,*N*′-dimethyl *N*,*N*′-bis(2-pyridylmethyl)-1,2-*trans*-diamino cyclohexane, OTf = CF_3SO_3, Fig. 2a).[8] At first, we tested the Fe(pdp) complex, previously shown to promote tertiary C–H lactonization on a number of carboxylic acids.[20,21] We were pleased to observe the formation of the corresponding chiral γ-lactone **1a** with good enantioselectivity (75% ee) albeit in poor yield (6%, entry 1). Modification of the diamine backbone from



Catalyst	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
Mn(^{dMM}pdp)	-Me	-OMe	-Me
Mn(^{TMS}pdp)	-H	-H	-Si(Me)$_3$
Mn(^{Me2N}pdp)	-H	-NMe$_2$	-H
Fe(^{TIPS}mcp)	-H	-H	-Si(^{i}Pr)$_3$
Mn(^{TIPS}mcp)	-H	-H	-Si(^{i}Pr)$_3$
Fe(^{TIPS}pdp)	-H	-H	-Si(^{i}Pr)$_3$
Mn(^{TIPS}pdp)	-H	-H	-Si(^{i}Pr)$_3$
Mn(^{TIBS}pdp)	-H	-H	-Si(^{t}Bu)$_3$

Figure 2. a, Schematic representation of the catalysts used in this work (see SI for their synthesis and characterization). Substituents on position 5 of the pyridines, highlighted in red, modulate the catalyst steric bulk. b, ORTEP diagram of the solid state structure of (*S*,*S*)-(Mn^{TIBS}pdp). Note the structured cavity defined by the TIBS substituents. With the exception of the Mn bound oxygen atoms, triflate groups are omitted for clarity.

Table 1. Optimization of adamantaneacetic acid (**1**) directed oxidation.[a]



Entry	Catalyst	Additive	Conv. (%)	Yield (%)	ee (%)
1	Fe(pdp)	-	59	6	75
2	Fe(mcp)	-	53	5	67
3	Fe(^{TIPS}pdp)	-	75	12	84
4	Mn(pdp)	-	72	26	89
5	Mn(^{TIPS} pdp)	-	81	28	94
6	Mn(^{TIBS}pdp)	-	74	29	95
7[b]	"	-	54	14	93
8[c]	"	-	89	28	95
9	Mn(^{TIPS}mcp)	-	38	8	65
10	Mn(^{dMM} pdp)	-	85	38	90
11	Mn(^{NMe2}pdp)	-	86	43	90
12[d]	Fe(^{TIPS}pdp)	TfOH	97	36	94
13[d]	Mn(pdp)	TfOH	80	56 (64)[e,f]	96
14	Mn(^{NMe2}pdp)	TfOH	60	35	91
15[d]	Mn(^{dMM}pdp)	TfOH	>99	63	93
16	Mn(^{TMS}pdp)	TfOH	89	51	96
17	Mn(^{TIPS}pdp)	TfOH	88	52	97
18[d]	Mn(^{TIBS}pdp)	TfOH	85	70 (68)[e]	98

[a] Reaction conditions: substrate (25 mM) and (*S*,*S*)-cat. 1 mol% were dissolved in TFE, 1.0 eq. of H_2O_2 (and, when indicated, a 0.09 M TfOH solution (0.1 eq.), delivered independently) was added as a 0.9 M TFE solution over 30 minutes by syringe pump, at 0°C. Workup as described in the SI. Conversion, yield and ee were determined by chiral GC analysis of two or three different runs with biphenyl as internal standard. n.d. = not detected. Traces (<5%) of hydroxyacids have been detected in the oxidations. [b]CH_3CN solvent. [c]HFIP solvent. [d]Additional 30 minutes of stirring to promote lactonization. [e]Isolated yield. [f] 0.8 g (4.5 mmol) scale. [g]ee determined by chiral GC analysis after $LiAlH_4$ reduction and acetylation of the resulting diol. Absolute configuration was determined by X-Ray diffraction (see SI).

bipyrrolidine to 1,2-cyclohexanediamine (entry 2) decreases the enantioselectivity, while increase of the catalyst steric bulk[43] (which leads to a more structured cavity around the metal, Fe(^{TIPS}pdp), entry 3) slightly improves product yield (up to 12%) and enantioselectivity (up to 84% ee). Considering that Fe and Mn may operate *via* common mechanisms,[44] we turned our attention to the corresponding Mn catalysts, which lead to a net improvement in both yield and ee (Mn(pdp),[45] entry 4, 26% and 89%, respectively). Again, increase of the catalyst steric bulk improves the reaction up to 28% yield and 94% ee (Mn(^{TIPS}pdp), entry 5). To further pursue this effect, we designed and synthesized a novel catalyst with a greater steric hindrance: complex Mn(^{TIBS}pdp) (Fig. 2b). Its solid state structure is very similar to those reported for other Mn(pdp) catalysts,[8] but its

larger triisobutylsilyl substituents define an even more sterically restricted cavity around the catalytic center. Accordingly, the new catalyst Mn(^{TIBS}pdp) furnished lactone **1a** in slightly improved yield and ee (entry 6, 29% and 95%, respectively). Inversion of the chirality of the catalyst affords the opposite enantiomer (see Table S2). The use of CH_3CN or HFIP (1,1,1,3,3,3-hexafluoro-2-propanol) solvents leads to worse or comparable results (entries 7-8), respectively, while change of the diamine backbone from pdp to mcp or ecp has a detrimental effect, as observed with Fe catalysts (entry 9 and Table S2). All of these reactions suffer however from a low mass balance, where high conversions are accompanied by modest product yields, as previously observed in analogous Fe-catalyzed C–H lactonization reactions.[21,27–32] Interestingly, increase in the catalyst electron density significantly improves the efficiency of the reaction, up to 43% yield for Mn^{Me2N}pdp (entries 10-11). We attribute this increase in yield to a more efficient generation of the active metal-oxo species, since electron-rich complexes have been proposed to facilitate heterolytic O–O cleavage *via* a push-pull mechanism.[46] Along this line, we reasoned that addition of a Brønsted acid could further improve the reaction outcome (*vide infra*), as protons are also known to facilitate heterolytic O–O cleavage in stoichiometric reactions.[47–49] Indeed, we were pleased to observe that slow addition of 0.1 eq of trifluoromethanesulfonic acid (triflic acid, TfOH), whose conjugate base is the same as the counteranion of the complex, proved to be key to significantly enhance product yield and, to a lower extent, reaction enantioselectivity in a general manner (entries 12-20 and Table S2. The beneficial effect of TfOH eliminates the requirement of electron-rich catalysts for efficient H_2O_2 activation (entries 14-15). Systematic increase in size of the pyridine substituent in position 5 (entries 16-18) enhances product yield and enantioselectivity up to a 68% isolated yield and an outstanding 98% ee for Mn(^{TIBS}pdp) (entry 18 and Table S2). The reaction can be easily scaled up to 0.8 g of substrate (4.5 mmol) without any loss in efficiency and selectivity (entry 13). The optimized conditions were then applied to the oxidation of 2,2-dimethyladamantaneacetic acid **2** (Figure 3A). To our delight, oxidation led to the exclusive formation of γ-lactone **2a** in very high isolated yield (88%) and excellent ee (97% ee).

Mechanistic considerations: In all cases, this directed oxidation shows an excellent site-selectivity that overrides the innate reactivity pattern of the substrate, with γ-lactone as the only product. For instance, while oxidation of **2** exclusively furnishes lactone **2a**, with the corresponding methyl ester **3** oxidation selectively occurs at the most activated tertiary sites to give hydroxyester **3a** in 76% yield (Figure 3A). Along the same line, in the oxidation of **1**, traces of oxidized lactone, likely at the tertiary C–H bonds, are detected only when employing excess H_2O_2 (Table S4), suggesting that intermolecular overoxidation occurs only after the lactonization.

Then, we elucidated in further detail the influence of the acid additive on reaction efficiency. It has to be remarked that an acid environment is known to catalyze the lactonization of hydroxy acids, which occurs spontaneously even in CH_3CN.[21] Besides this effect, we investigated the assistance of acid

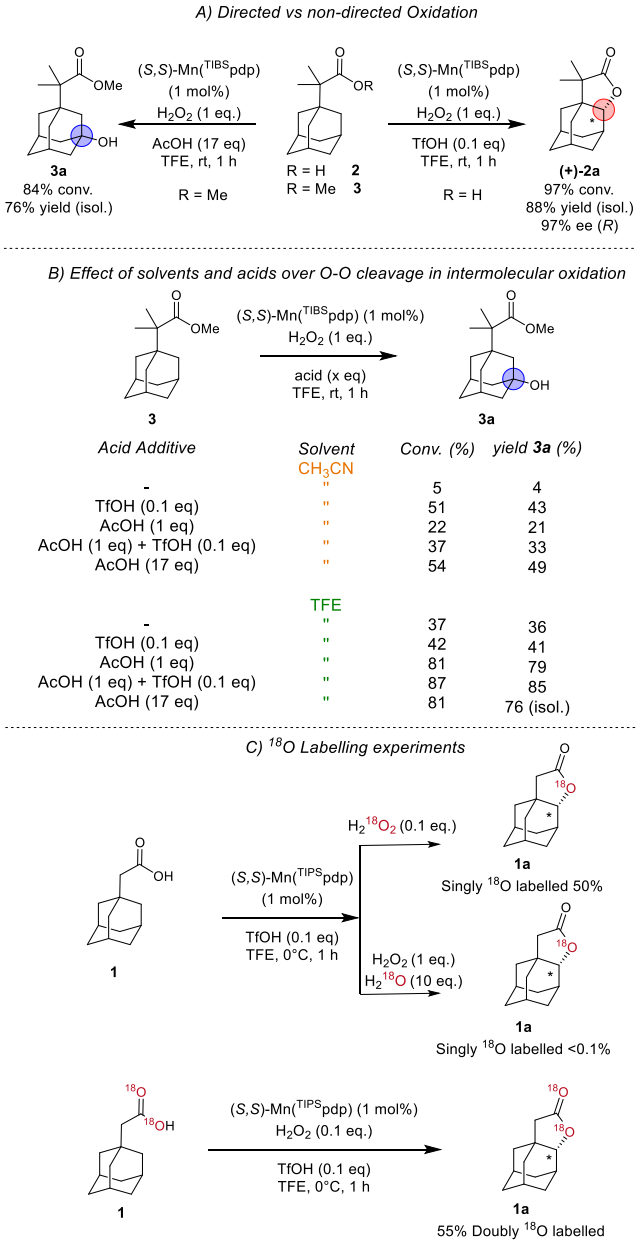


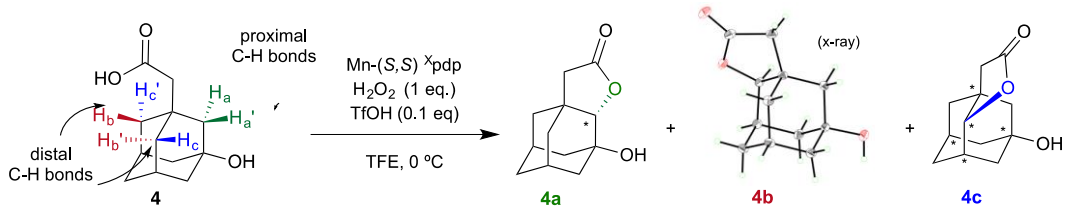
Figure 3. A: Oxidation of 2,2-dimethyladamantaneacetic acid **2**. B) Oxidation of the corresponding methyl ester **3** with different amounts and types of acid additives (GC yields and conversions). C) Isotope labelling experiments to ascertain the origin of the O-atom incorporated into the lactones (GC-MS analysis via chemical ionization with CH_4). The reported ^{18}O incorporations are obtained after correction of the isotopic purity of the labelled reactants.

additives in H_2O_2 activation for the intermolecular oxidation of **3** (Figure 3B) to avoid any possible interference from the carboxylic acid moiety. With no external acids, **3a** is formed in 4% yield in CH_3CN. In TFE, the yield increases up to 36%, suggesting an assistance of the hydrogen bond donor solvent in H_2O_2 activation.[36] Addition of TfOH (0.1 eq) improves the yield up to 43% and 41% in CH_3CN and TFE, respectively, consistently with our hypothesis of a more facile H_2O_2 activation with Brønsted acid additives. Replacement of TfOH for AcOH (1 eq), known to facilitate O-O cleavage *via* the carboxylic acid

assisted pathway,[17] leads to **3a** in 21% and 81% yield in CH_3CN and TFE, respectively. While in CH_3CN a higher carboxylic acid loading is required for efficient oxidation,[8,45] the assistance of TFE in H_2O_2 activation enables the reaction to proceed in high yield even at low AcOH loadings. Moreover, TfOH, TFE and the carboxylic acid can act synergistically to improve reaction efficiency up to an 85% yield of **3a** (Figure 3B), a scenario that is fully consistent with that observed in the intramolecular oxidation of **2** (Figure 3A), suggesting an effective H_2O_2 activation under these experimental conditions.

At last, we undertook ^{18}O labelling experiments to gain more insight into the oxidation mechanism. 88% of O-atom incorporation from H_2O_2 has been previously reported for Fe-catalyzed lactonization.[21] However, when the experiment was carried out employing the Mn(^{TIBS}pdp) catalyst, O-incorporation dropped to 50%, with the remainder 50% of the O-atom that derives from the carboxylic moiety (Figure 3C). These results imply that as compared to the Fe system a different mechanism is operating in the lactonization promoted by the Mn one. After initial HAT,[8,17] the carbon centered radical can undergo competitive rebound of either the OH or the carboxylate ligand. These two paths are in competition (1:1 ratio) but lead to the same enantiomer of the final γ-lactone product.

*Oxidation of 3'-hydroxy adamantaneacetic acid **4**:* With these results in hand, we set out to study the oxidation of substituted adamantaneacetic acids. Insertion of a substituent at position 3' breaks the C3 symmetry of the adamantane core, differentiating the three γ methylenic groups into one proximal and two distal sites (see Fig. 4, where the substituent is OH, substrate **4**). Each of the distal methylenes bears, in turn, two diastereotopic C-H bonds, pointing towards (*endo*, H_c and $H_{c'}$) or away (*exo*, H_b and $H_{b'}$) from the substituent. Therefore, three possible enantiomeric pairs can be formed upon lactonization, one proximal, **4a**, and two diastereomeric distal *exo* and *endo* lactones, **4b** and **4c**, respectively, with the simultaneous formation of up to five stereogenic centers in the latter cases (the indication of all possible products is displayed in Figure S1). 3'-Substituted adamantaneacetic acids thus provide a unique set of six non-equivalent C-H bonds to investigate the interplay between catalyst and substrate structure over enantio-, diastereo- and site-selectivity. Oxidation of **4** under optimized conditions with complex Mn(^{TIBS}pdp) furnishes the three lactones **4a**, **4b** and **4c** in a 1:2.7:1 ratio, each



Entry	1	2	3	4	5
Catalyst	Mn(^{TIBS}pdp)	Mn(^{TIPS}pdp)	Mn(^{TMS}pdp)	Mn(^{dMM}pdp)	Mn(pdp)
	← BULKINESS →				
d.r.	2.7 : 1	1.5 : 1	1 : 1.1	1 : 1.8	1 : 2.5
r.r.	1 :3.9	1 : 4.4	1 : 5.2	1 : 5.4	1 : 7.4
Total Yield	55%	58%	61%	64%	50%
Major product yield(ee,%)	**4b** 32(99)	**4b** 28(99)	**4c** 27(83)	**4c** 35(88)	**4c** 31(89)

Figure 4. Oxidation of 3'-hydroxyadamantaneacetic acid (**4**), showing the three lactone products formed and the impact of catalyst steric bulk on selectivity. Diastereomeric ratio (d.r.) corresponds to *exo*:*endo* (**4b:4c**) ratio. Regioisomeric ratio (r.r.) refers to the ratio of proximal over distal oxidation products (**4a**):(**4b** + **4c**). Conversions, yields and ee of minor products are shown in Table S7. Absolute chirality of **4b** was assigned by its X-ray structure; taking into account that the oxidation does not occur on the same carbon, absolute configuration of **4c** can be also assigned, while that of **4a** is assigned for similarity to **2a**.

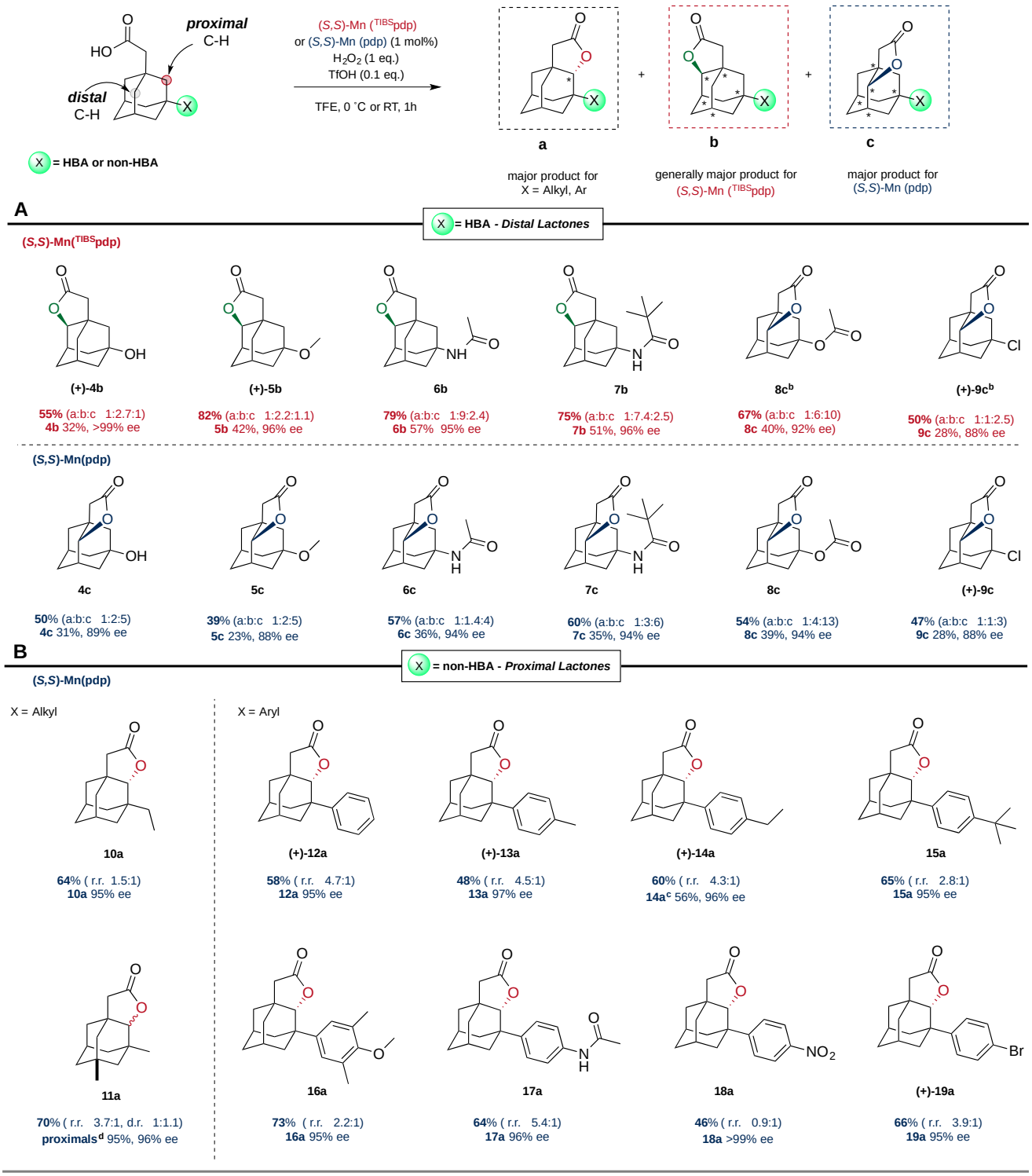


Figure 5. Enantioselective lactonization of bridgehead substituted adamantaneacetic acids (conditions as described in Typical Oxidation Procedure). For each reaction, the major product is drawn (with its ee displayed in the second row, along with its GC yield for section A), and the total yield of the three lactones is displayed in the first row (GC yield for section A, isolated yield for section B), together with the distribution of products in the crude mixture (a:b:c ratio or r.r. ratio). Further details, such as conversions, yields and ee of minor products, whenever determined, and results with Mn(TIBSpdp) catalyst are reported in Table S8 and Figure S3. [b]With substituents OAc and Cl the main product is the *endo* lactone c with both catalysts. [c]Two diastereomeric proximal lactones are formed. [d]Isolated single lactone yield.

one with good to excellent enantioselectivity (91, 99 and 67% ee, respectively), without formation of non-directed oxidation products (Fig. 4). Distal lactonization (**4b** + **4c**) is favored over proximal (**4a**), giving a regioisomeric ratio (r.r.) of 1:3.9, likely due to deactivation of the proximal site by solvent hydrogen bonding to the hydroxyl group[33] and, to a lesser extent, by steric effects. *Exo*-product **4b**, is formed in larger amount than its *endo* counterpart **4c**, as a result of the slightly favored steric accessibility. Most importantly, the main product **4b** (32% yield) is formed with the highest enantioselectivity (99% ee). Diastereomers **4b** and **4c** derive from oxidation of two different carbons (see Figure S2). Remarkably, the *exo*:*endo* diastereoselectivity can be tuned by manipulation of catalyst structure. Systematic decrease of steric bulk on position 5 of the pyridine moieties in the catalyst regularly decreases the *exo*:*endo* ratio (**4b:4c**) from 2.7:1 with Mn(^{TIBS}pdp) (Fig. 4) up to a complete inversion with Mn(pdp) (1:2.5), whilethe enantioselectivity of the main product **4c** remains high (89% ee), thus implementing a rare example of catalyst-controlled selectivity.

Oxidation of 3'-substituted adamantaneacetic acids: We then extended our study to other adamantaneacetic acids substituted at 3' (Figure 5). Ether, amide, ester and halogen substituents are all well tolerated, affording lactones in modest to good yields and excellent enantioselectivities (Figure 5, section A). The use of Mn(^{TIBS}pdp), generally provides the best results. In all cases, distal lactonization is favored over proximal one, and the preference for the *exo* **b** or *endo* **c** diastereomer can be tuned by changing catalyst structure from Mn(^{TIBS}pdp) (in red) to Mn(pdp) (in blue), respectively. Amide substituents, as previously observed in other C–H oxidation reactions,[8] give high yields and selectivities (up to 79% yield and a d.r. of 3.7:1, with 95-96% ee and r.r. ≤ 1:9.9 for **6** (X = $NHCOCH_3$) and **7** ($NHCOC(CH_3)_3$). Catalyst tuning allows complete inversion of the *exo*:*endo* ratio for hydroxyl (**4**), methoxy (**5**) and amido (**6** and **7**) substituents. With acetoxy (**8**) and chlorine (**9**) substituents the *endo* lactone product **c** was favored over the *exo* product **b**, and, in line with the results obtained with the other substrates, a decrease in d.r. was observed upon catalyst switch. The steric bulk of these substituents alone cannot account for this difference in diastereoselectivity, since groups with similar sizes, such as hydroxyl (**4**) and chlorine (**9**) or acetamido (**6**) and acetoxy (**8**), influence the d.r. to a significantly different extent. We hypothesize that solvent hydrogen bonding to the substituent can affect not only its electronics, but also its size, thus influencing diastereoselectivity. In line with this hypothesis, in the oxidation of **4** the use of a non-HBD solvent such as CH_3CN, depletes any *exo*:*endo* selectivity, while the use of HFIP gives results that are similar to those found in TFE (Table S7).

We then moved to alkyl substituents (Figure 5, section B, left), which display a weak electron-donating character *via* inductive effects. Accordingly, we observed that the presence of an ethyl substituent at 3' (**10**) favors proximal oxidation, with a r.r. of 1.5:1 and an excellent enantioselectivity for the proximal lactone product **10a** (95% ee). The distal lactones are now formed in nearly equal amounts, irrespective of the catalyst used. Although the same preference is observed for Mn(^{TIBS}pdp), the bulky trialkylsilyl moieties attenuate the proximal selectivity probably because of steric clash. For this reason, we selected the less hindered Mn(pdp) as the catalyst of choice for proximal lactonization (the results for Mn(^{TIBS}pdp) are reported in Figure S3). The insertion of two methyl substituents (**11**) does not change the reaction outcome, with the two diastereomeric proximal lactones **11a** representing again the main products.

Replacement of ethyl (**11**) for phenyl (**12**) greatly enhanced the proximal selectivity up to a 4.7:1 r.r., without altering the enantioselectivity (95% ee), a behavior that can be explained on the basis of proximal C–H bond activation *via* stereoelectronic effects. These bonds benefit from homobenzylic stabilization that slightly decreases their BDE as compared to non-activated

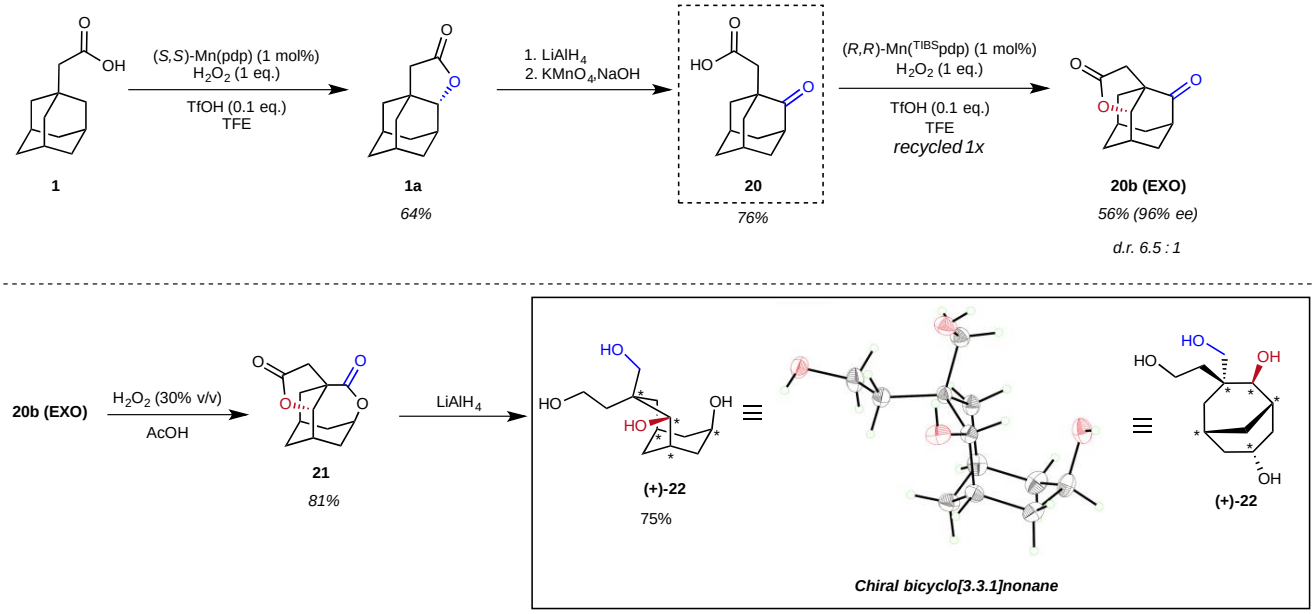


Figure 6. Synthesis of chiral tetrahydroxylated bicyclo[3.3.1]nonane core (**22**) *via* stepwise directed C-H oxidations with full enantiocontrol. Absolute configuration of (+)-22 could not be unequivocally assigned by X-ray diffraction. Results for Mn(pdp) catalyzed oxidation of **20** are shown in Figure S5.

C–H bonds.[50] Encouraged by this result, we expanded the scope of proximal γ-lactonization to a series aryl-substituted adamantaneacetic acids (substrates **13**-**19** in Figure 5b). In all cases the proximal lactone is the main product, obtained in good yield (33-61%) and excellent ee (95-97%). The reaction is completely chemoselective for the lactonization of unactivated γ-C–H bonds, with no traces of products deriving from aromatic oxidation even with electron-rich arene substituents. Moreover, no competitive oxidation on benzylic primary (**13**) or secondary (**14**) C-H bonds is observed, in spite of their significantly lower BDE as compared to adamantane C–H bonds.[50] This is indeed one of the few cases in which oxidation occurs selectively at non-activated–H bonds over intrinsically more activated benzylic ones.[51,52] Increase of the steric bulk of the *p*-substituent of the aryl ring leads to a regular erosion of the proximal selectivity (r.r. decreases from 4.7 for **13** to 4.5 for **14** up to 2.8 for **15**). Along a similar line, the insertion of *meta* substituents in **16** affords an even lower proximal selectivity (r.r. 2.2; see also the lower r.r. obtained with Mn(^{TIBS}pdp), Figure S3). On the other hand, increase of the electron-density of the aryl ring improves the proximal selectivity, with a r.r. that decreases from 5.4 for **17** to 4.7 for **13** to 3..9 for **19** up to 0.9 for the strong electron-withdrawing *p*-nitrophenyl group (**18**). To sum up, these reactions disclose a rational impact of substrate and catalyst structure over site- and diastereoselectivity in asymmetric Mn-catalyzed γ-lactonization of carboxylic acids, setting the stage for prediction of the reaction selectivity.

*Functionalization of lactones and synthesis of (+)-**22**:* The propensity of γ-lactones to undergo a vast array of different transformations makes such compounds versatile intermediates in organic synthesis. Their main reactivity path consists in a nucleophilic addition to the carbonyl group, followed by ring opening to furnish hydroxyacids, hydroxyesters, hydroxyamides and 1,4-diols, without affecting the chirality of the first formed γ-CH–OH bond. As an example of the viability of these derivatizations with our oxidation products, we reduced lactone**2a** to the corresponding 1,4-diol in excellent 95% yield and 97% ee (see Figure S4). To further demonstrate the synthetic potential of our directed lactonization procedure, we prepared 2-oxo-1-adamantaneacetic acid **20** (bearing a valuable 1,2-disubstituted adamantane motif, Figure 6) from commercial **1** in three steps, to be compared with its shortest 7 step synthesis reported so far.[53] Lactonization of **1** to yield **1a** is followed by ring-opening reduction and re-oxidation to provide **20** in a combined 53% yield over the three steps. The CH_2CO_2H motif can be regarded as a handle to sequentially forge a novel γ-C–O bond on a different methylenic group with high enantioselectivity, increasing molecular complexity in a stepwise fashion. In fact, ketoacid **20** can undergo a second round of directed γ-C–H lactonization, where the presence of the ketone function now restricts oxidation to two positions, with formation of two diastereomeric *exo* and *endo* lactones (**20b** and **20c**, respectively). Mn(^{TIBS}pdp) shows the highest diastereoselectivity, providing **20b** and **20c** in a combined 56% yield, a 6.8:1 d.r. and an excellent enantioselectivity for **20b** (96% ee), with 5 stereogenic centres again formed in a single step. The increased level of diastereoselectivity likely derives from the closer proximity of the oxo group to the carboxylic acid moiety compared to the bridgehead substituted adamantanes displayed in Figure 5. The ketone moiety in **20b** offers in turn a useful handle for the deconstruction of the adamantane core, with retention of configuration at all the chiral centers.[39] Baeyer-Villiger oxidation[41] of **20b** yields *bis*-lactone product **21** by selective insertion of an oxygen atom into the most electron rich C–C bond. Reductive ring-opening of the tetracycle affords tertahydroxylated chiral bicyclo[3.3.1]nonane **22** in a combined 75% yield over three steps. Its carbon skeleton is found in several biologically active products/metabolites. It is an intermediate along the biosynthetic pathway of sesquiterpenes, and represents as well a portion of a simplified analogue of taxol.[39–42,54] Summarizing, directed Mn-catalyzed lactonization enables a novel synthetic route to this structure with two key C–H lactonization steps, the latter of which fixes the chirality of 5 stereocenters with 96% ee.

CONCLUSIONS

Herein, we describe the first enantioselective C–H oxidation of unactivated methylenic groups to yield γ-lactones by means of a novel catalytic system that addresses the multiple selectivity challenges associated with this reaction. Our strategy entails a HAT-based C–H bond oxidation , promoted by a chiral Mn catalyst, a carboxylic acid directing group in combination with hydrogen peroxide, a fluorinated alcohol solvent and triflic acid in catalytic amount to obtain chiral γ-lactones as the exclusive products. Key to the high enantioselectivity is the combination of a carboxylic acid and a rigid adamantane core, which act synergistically to define the spatial orientation of the γ-methylenic C–H bonds to the catalytic center. The reaction is robust and tolerates several functional groups. When the three methylenic sites are rendered non-equivalent by introduction of substituents in the tertiary sites, multiple lactone products become accessible. Remarkably, in these cases site-selectivity can be predicted on the basis of activating and deactivating effects exerted by the substituents as well as their interaction with the hydrogen bond donor solvent. In addition, the diastereoselectivity of the reaction can be systematically manipulated in a predictable manner by rational choice of the catalyst. We envision that the principles for effective, asymmetric lactonization presented in this work will be a starting point for the development of novel enantioselective C–H functionalizations and for the implementation of stereoselective γ-C–H lactonization in organic synthesis.

ASSOCIATED CONTENT

The Supporting Information is available free of charge via the Internet at http://pubs.acs.org.
Experimental details for the preparation and characterization of ligands and metal complexes, substrates, catalytic reactions, and for product isolation and characterization. NMR spectra and crystallographic information files (cif 1, cif 2, cif 3, cif 4 and cif 5).

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SYNOPSIS TOC A Mn-catalyzed method for the enantioselective lactonization of rigid carboxylic acids *via* asymmetric C-H oxidation is presented. Lactones can be obtained in good yields and excellent ees, with a high, predictable site-selectivity and, whenever possible a catalyst-controlled diastereoselectivity.