JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
pubs.acs.org/JACS



Article

# Highly Enantioselective Catalytic Lactonization at Nonactivated Primary and Secondary γ-C−H Bonds

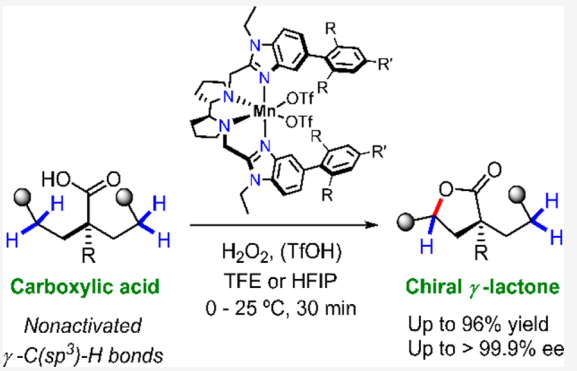
Arnau Call,* Giorgio Capocasa, Andrea Palone, Laia Vicens, Eric Aparicio, Najoua Choukairi Afailal, Nikos Siakavaras, Maria Eugènia López Saló, Massimo Bietti,* and Miquel Costas*

Cite This: J. Am. Chem. Soc. 2023, 145, 18094−18103

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

**ABSTRACT:** Chiral oxygenated aliphatic moieties are recurrent in biological and pharmaceutically relevant molecules and constitute one of the most versatile types of functionalities for further elaboration. Herein we report a protocol for straightforward and general access to chiral γ-lactones via enantioselective oxidation of strong nonactivated primary and secondary C($sp^3$)−H bonds in readily available carboxylic acids. The key enabling aspect is the use of robust sterically encumbered manganese catalysts that provide outstanding enantioselectivities (up to >99.9%) and yields (up to 96%) employing hydrogen peroxide as the oxidant. The resulting γ-lactones are of immediate interest for the preparation of *inter alia* natural products and recyclable polymeric materials.




## INTRODUCTION

One of the long-standing challenges in chemistry is the efficient synthesis of highly added-value chiral molecules from readily available, cheap, and simple hydrocarbon frameworks with minimal waste generation.[1] In this context, given the biological relevance and the high chemical versatility of chiral oxygenated motifs,[2] methods that can enable site and enantioselective C($sp^3$)−H oxidation are particularly valuable.[3] Despite their interest, these methods remain mostly inaccessible because their realization has to overcome major challenges: (1) the significantly lower reactivity of these bonds compared with most functional groups and (2) the need to control chemo- and stereoselectivity in molecules containing multiple nonactivated nonequivalent C($sp^3$)−H bonds.[4] Consequently, chiral oxygenated aliphatic frames are still customarily built via the laborious transformation of preexisting functional groups. Such limitation has resulted in the design of alternative multistep synthetic routes, often involving the use of readily available chiral building blocks deriving from natural sources (i.e., the "chiral pool"), thus restricting the use of simple hydrocarbon scaffolds as starting materials.[5]

State-of-the-art site- and enantioselective oxidation of nonactivated C($sp^3$)−H bonds is basically restricted to heme and nonheme oxygenases, often optimized via directed evolution (Figure 1A).[6] On the other hand, small-molecule oxidation catalysts that operate via mechanisms related to iron-dependent oxygenases[7] oxidizing enantioselectively methylenic and tertiary C−H bonds have been recently described[3,8] demonstrating the potential of these reactions to expand chemical space and the chiral pool. In these reactions, $H_2O_2$ is used as an environmentally benign oxidant to generate electrophilic high-valent metal-oxo species, which react by a mechanism akin to the generally accepted hydrogen atom transfer (HAT)/hydroxyl rebound one displayed by natural metalloenzymes.[9]

A major challenge for full development of synthetically useful enantioselective C−H oxidations is control over site-selectivity.[10] As a consequence of this constraint, successful examples described so far have a narrow substrate scope. Use of directing groups offers a valuable handle on navigating this challenge and exerting precise control. Installation and removal of the directing groups constitute the major limitations of this approach that can be circumvented by using native substrate functionalities. Carboxylic acid groups constitute a privileged functionality for this purpose: they are very common in organic molecules, can be chemically manipulated by a wide diversity of reactions, and if necessary can be tracelessly removed.[11] The poor binding ability of carboxylic acid moieties to precious metals limits their use in organometallic enantioselective C−H functionalization reactions.[12] However, using carboxylic acids as directing groups, we have recently described examples of highly enantioselective intramolecular γ-lactonization of *N*-phthalimido-protected α-amino acids[13] and adamantaneacetic

Received: June 13, 2023
Published: August 4, 2023







https://doi.org/10.1021/jacs.3c06231
J. Am. Chem. Soc. 2023, 145, 18094−18103

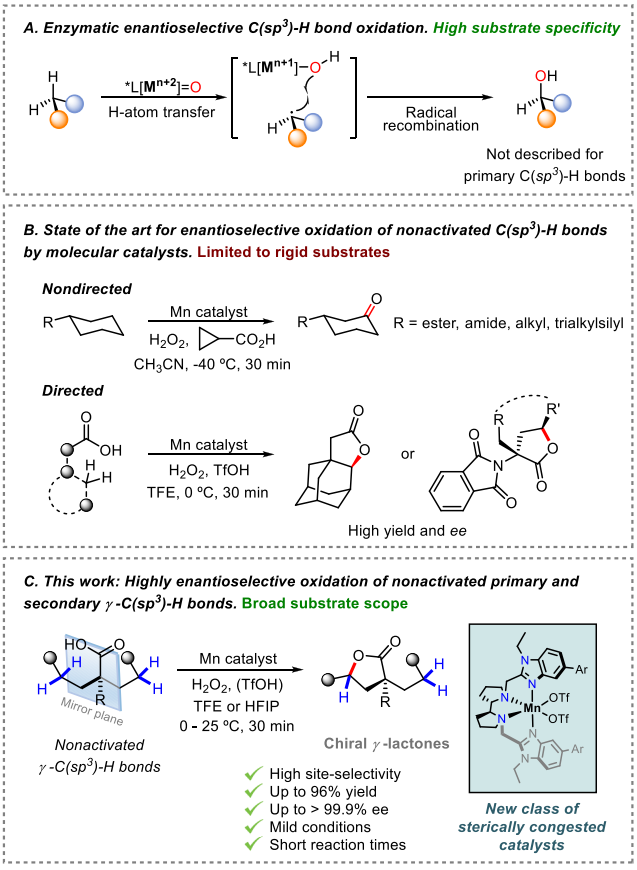



**Figure 1.** (A) Enantioselective oxidation of C−H bonds by enzymatic metal-oxo species. (B) Enantioselective oxidation of nonactivated C($sp^3$)−H bonds by metal complexes. (C) Summary of the main features of the present work.

acids[14] using Mn catalysts based on bulky trialkylsilyl-substituted pyridine moieties (Figure 1B). A detailed mechanistic investigation of carboxylic acid directed γ-lactonization[15] and intermolecular acyloxylation reactions[12d,16] catalyzed by Mn systems has been recently carried out. These reactions provide good yields and excellent ee's, but their narrow substrate scope showcases the current limitations of the reaction.

Overcoming the limitations of state-of-the-art methods and uncovering the extraordinary potential of this reaction require the identification of novel catalysts. Paradigmatically, this challenge parallels the main difficulties faced when using biotechnological tools to address this class of reactions, which lie in the identification of competent enzymes and in their evolution to optimize selectivity and product yield.[6a−c,17] The high specificity of C−H oxidation enzymes and their sensitivity against oxidative degradation constitute often insurmountable problems. We envision that this class of reactions may constitute a chemical problem for which small-molecule catalysts represent a powerful and far-reaching alternative. The challenge in the design of such systems resides not only in building structurally rich and spatially stringent ligands but also in their ability to access the highly electrophilic hypervalent metal oxo species competent for cleavage of strong C−H bonds (BDE > 100 kcal·mol$^{-1}$), while resisting immolative self-oxidation.

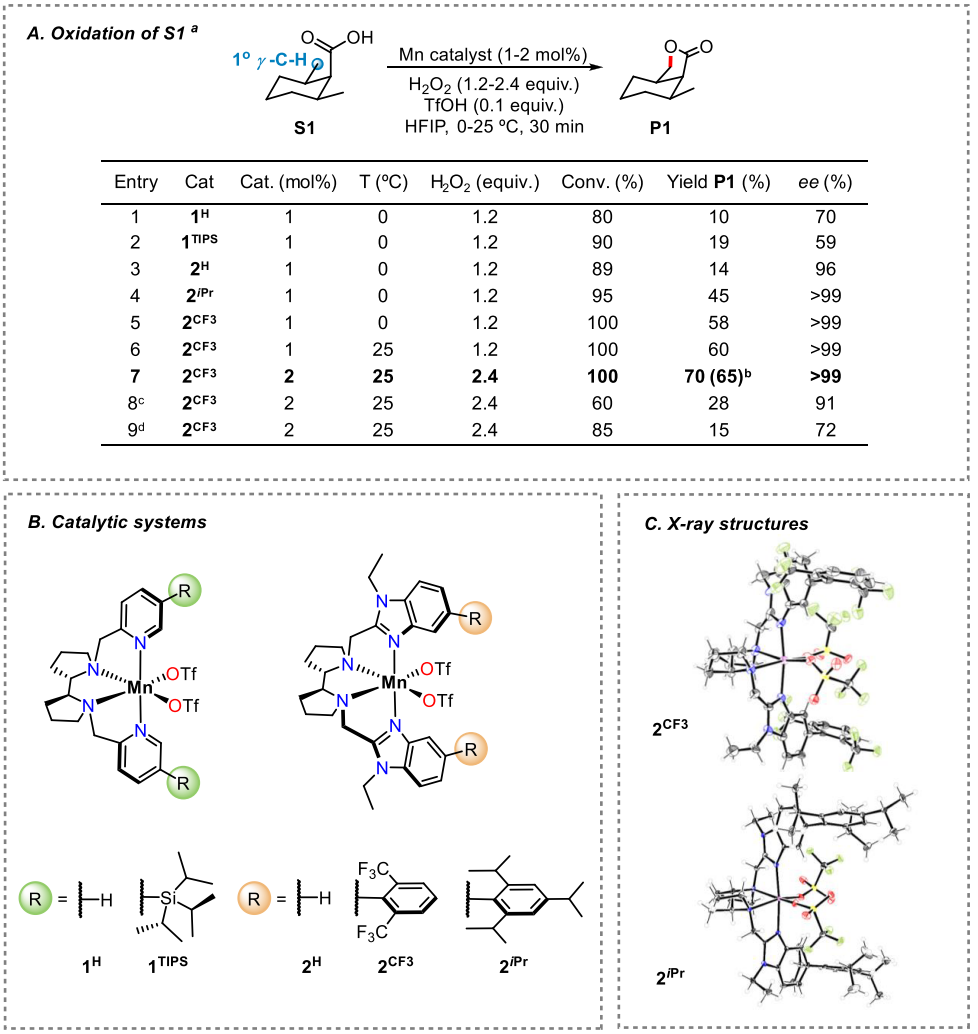
Herein we describe a solution to this challenge and describe a new class of sterically congested chiral Mn catalysts that enable the desymmetrization of carboxylic acids via highly enantioselective γ-lactonization at nonactivated primary and secondary C−H bonds using $H_2O_2$ as the oxidant (Figure 1C). This is a broad, readily accessible class of substrates that can be converted, through site and enantioselective lactonization, into precious oxygenated cyclic skeletons with innumerable synthetic applications ranging from natural products to multifunctional materials. Reactions occur with low catalyst loadings under mild conditions and in short reaction times. The system enables the efficient formation (yields up to 96%) of chiral γ-lactones with outstanding site-selectivity and unprecedented levels of enantioselectivity (up to >99.9% ee). The potential of this methodology in enabling powerful retrosynthetic strategies is showcased in the streamlining of synthetic routes of important natural products, in the access to strained lactones of interest in recyclable polymers, and in the systematic site- and stereoselective polyfunctionalization of cyclohexane skeletons.

## RESULTS AND DISCUSSION

Building on a recently developed procedure for diastereoselective γ-lactonization of *gem*-dimethyl groups in chiral substrates,[15] *cis,cis*-2,6-dimethylcyclohexanecarboxylic acid (**S1**) containing six primary and four secondary γ-C−H bonds (Figure 2A) was chosen as model substrate to initiate the exploration of the enantioselective γ-lactonization of cyclohexanecarboxylic acids, a class of substrates for which selective oxidation at the methyl groups, resulting in desymmetrization, is a synthetically relevant problem.[18] Addition of 1.2 molar equivalents of $H_2O_2$ as the oxidant and 0.1 equivalents of triflic acid (TfOH) as additive via syringe pump to a 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) solution of the substrate and the (*S,S*)-Mn(pdp) ($\mathbf{1^H}$) catalyst (1 mol %) at 0 °C resulted in 80% substrate conversion, yielding lactone **P1** originated from primary γ-C−H bond oxidation, as the single detectable product in low yield (10%). Interestingly, formation of this product occurs with a notable enantioselection (70% ee) (entry 1). Use of the bulkier *tris*-isopropylsilyl-substituted catalyst (*S,S*)-Mn($^{TIPS}$pdp) ($\mathbf{1^{TIPS}}$) afforded **P1** with a slight increase in yield (19%) and diminished enantioselectivity (59% ee) (entry 2). Crucially, replacing the pyridine donors in the catalyst structure with *N*-ethylbenzimidazoles (i.e., (*S,S*)-Mn(bpeb) ($\mathbf{2^H}$))[19] resulted in an extraordinary increase in enantioselectivity (96% ee) without affecting to a significant extent the yield (14%) (entry 3). The outstanding enantioselectivity observed led us to explore additional benzimidazole-based manganese catalysts. Inspired by the visionary strategy initially designed by Meggers[20] and later explored by Xiao,[21] we synthesized the chiral complexes (*S,S*)-Mn($^{CF3}$bpeb) ($\mathbf{2^{CF3}}$) and (*S,S*)-Mn($^{iPr}$bpeb) ($\mathbf{2^{iPr}}$) bearing substituted aryl groups in position 5 of the benzimidazole rings (Figure 2B). X-ray crystallographic analysis confirmed the chiral octahedral geometries with the steric groups distant from the plane comprising Mn and O atoms (Figure 2C). Gratifyingly, by testing them as catalysts in the model reaction we found that use of $\mathbf{2^{iPr}}$ increased the yield of the desired product **P1** to 45% (entry 4) while affording outstanding enantioselection (>99% ee). Catalyst $\mathbf{2^{CF3}}$ further improved the reaction yield to 58% while retaining ee (entry 5) and was therefore chosen as the standard catalyst for the primary C−H bond oxidation scope (Figure 3).

Increasing the temperature to 25 °C (entry 6) did not determine any significant change in yield and ee, whereas an


https://doi.org/10.1021/jacs.3c06231
J. Am. Chem. Soc. 2023, 145, 18094−18103




| Entry | Cat | Cat. (mol%) | T (°C) | $H_2O_2$ (equiv.) | Conv. (%) | Yield **P1** (%) | *ee* (%) |
|---|---|---|---|---|---|---|---|
| 1 | $\mathbf{1}^{H}$ | 1 | 0 | 1.2 | 80 | 10 | 70 |
| 2 | $\mathbf{1}^{TIPS}$ | 1 | 0 | 1.2 | 90 | 19 | 59 |
| 3 | $\mathbf{2}^{H}$ | 1 | 0 | 1.2 | 89 | 14 | 96 |
| 4 | $\mathbf{2}^{iPr}$ | 1 | 0 | 1.2 | 95 | 45 | >99 |
| 5 | $\mathbf{2}^{CF3}$ | 1 | 0 | 1.2 | 100 | 58 | >99 |
| 6 | $\mathbf{2}^{CF3}$ | 1 | 25 | 1.2 | 100 | 60 | >99 |
| **7** | $\mathbf{2}^{CF3}$ | **2** | **25** | **2.4** | **100** | **70 (65)[b]** | **>99** |
| 8[c] | $\mathbf{2}^{CF3}$ | 2 | 25 | 2.4 | 60 | 28 | 91 |
| 9[d] | $\mathbf{2}^{CF3}$ | 2 | 25 | 2.4 | 85 | 15 | 72 |

**Figure 2.** (A) Initial experiments and optimization for the development of an enantioselective primary γ-C−H bond lactonization reaction on *cis,cis*-2,6-dimethylcyclohexanecarboxylic acid (**S1**). [a]Reaction conditions: substrate (25 mM) and Mn catalysts (1−2 mol %) were dissolved in HFIP; 1.2 equiv. of $H_2O_2$ (0.9 M solution in HFIP) and 0.1 equiv. of TfOH (0.09 M solution in HFIP) were independently delivered over 30 min with a syringe pump, at 0 °C, unless otherwise indicated. Workup is indicated in the Supporting Information. Conversion, yield, and ee were determined by GC analysis of two or three different runs with biphenyl as internal standard. [b]Isolated yield. [c]Using TFE:$CH_2Cl_2$ (9:1) as a solvent mixture. [d]In the absence of TfOH. (B) Structure of the catalysts studied in this work based on pyridines and benzimidazoles. (C) ORTEP diagram of the solid state structure of $\mathbf{2}^{CF3}$ and $\mathbf{2}^{iPr}$.

increase in both $H_2O_2$ (2.4 molar equiv.) and catalyst loading (2 mol %) furnished **P1** in 70% yield as a single enantiomer (ee >99%, entry 7). Substituting HFIP with a 2,2,2-trifluoroethanol (TFE)/$CH_2Cl_2$ mixture (the substrate was only partially soluble in neat TFE) had detrimental effects on the reaction yield (entry 8), as did running the reaction in the absence of TfOH (entry 9). Surprisingly, although in all reactions some mass loss was observed, with catalysts $\mathbf{1}^{TIPS}$, $\mathbf{2}^{H}$, $\mathbf{2}^{CF3}$, and $\mathbf{2}^{iPr}$ no other lactone product was detected, indicating that lactonization at primary γ-C−H bonds is strongly favored over that at γ-methylenic ring sites.

In terms of practicality, it is important to remark that the newly prepared $\mathbf{2}^{CF3}$ and $\mathbf{2}^{iPr}$ catalysts are air-stable, with no significant degradation observed over six months and that the oxidation reactions could be performed in open-to-air vessels with no precautions to exclude oxygen or humidity. With the optimized conditions in hand, the reaction scope for primary C−H bond oxidation was investigated (reaction overview and products shown in Figure 3). The introduction of a *cis*-methyl group in position 4 as in **S2** resulted in the smooth formation of lactone **P2** without affecting the yield and enantioselectivity. Of interest, this compound is a key intermediate in Baran's synthesis of (−)-maximiscin, where it was obtained in two steps and overall 49% yield (90% ee) from **S2** via installation of a chiral directing group and Pd-catalyzed C−H methoxylation, followed by cyclization.[18] Gratifyingly, our approach furnished the same product in 71% isolated yield with 99% ee in a single step starting from the parent carboxylic acid. We note on passing that these constitute the first examples of desymmetrization of carboxylic acids via C−H bond oxidation at methyl groups, generating up to four stereocenters in a single step with high enantioselectivity.

Inversion of the relative configuration at C1 as in *cis,trans*-2,6-dimethylcyclohexanecarboxylic acid (**S3**) only resulted in a slight decrease in yield and ee, furnishing product **P3** with a *trans* bicyclo[4.3.0] junction in 54% isolated yield and 93% ee, showing that for the reaction to proceed efficiently, the target methyl groups must not necessarily be *cis* to the carboxylic acid


https://doi.org/10.1021/jacs.3c06231
J. Am. Chem. Soc. 2023, 145, 18094−18103

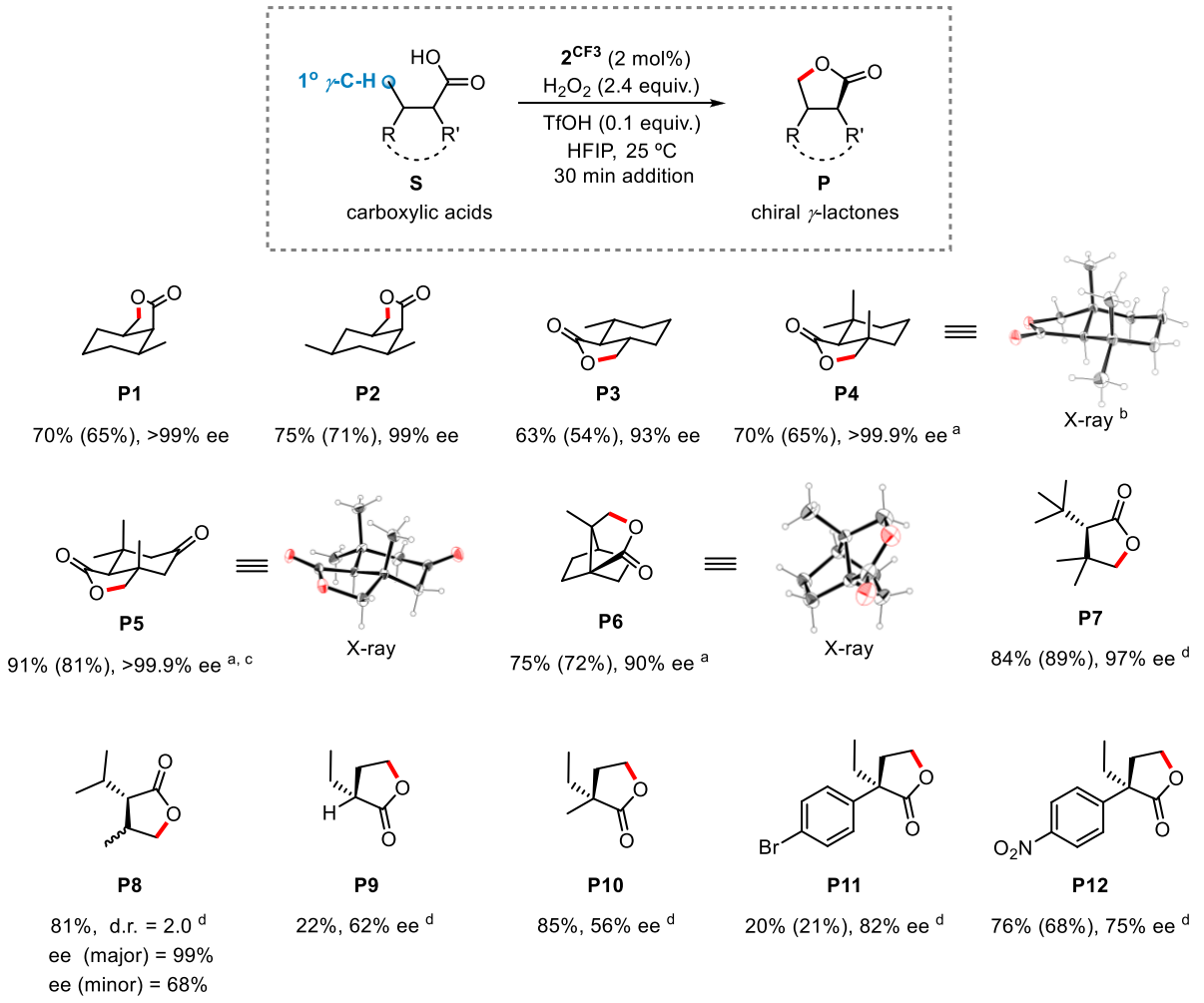


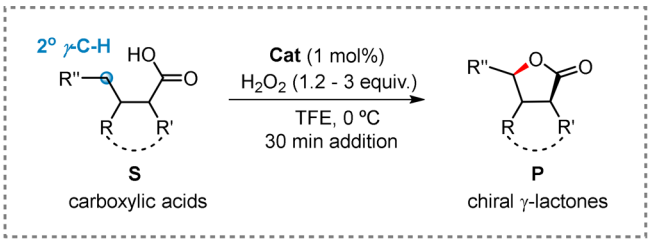

**Figure 3.** General scheme for γ-lactonization at the primary C−H bonds of different carboxylic acid substrates. [a]Triple addition of $H_2O_2$ (1.2 equiv.) + $\mathbf{2}^{CF3}$ (1 mol %).[b]Product was isolated using (*R,R*)-Mn($^{CF3}$bpeb). [c]Without TfOH. [d]$\mathbf{2}^{CF3}$ (1 mol %) and $H_2O_2$ (1.5 equiv.) without TfOH at 0 °C. Isolated yields in parentheses. d.r. = diastereoisomeric ratio.

moiety. At this point, in order to check possible reactivity differences between methyl groups that are *cis* and *trans* to the carboxylic acid moiety, 2,2,6,6-tetramethylcyclohexanecarboxylic acid (**S4**) was tested in catalysis. The reaction proceeded with the exclusive formation of the *trans* lactone **P4** in satisfactory isolated yield (65%) and excellent ee (>99.9%). We speculate that such selectivity may arise from the better accessibility of the *trans* over *cis* methyl C−H bonds. Importantly, we note on passing that the present reaction enables the functionalization of the primary sites in the *trans* [6+5] junction to the directing group, which is orthogonal to the functionalization of the primary sites in the *cis* [6+5] junction typically achieved by synthetically useful O-centered radical oxidation reactions.[22] We were pleased to find out that the presence of a carbonyl group in position 4 as in 4-oxo-2,2,6,6-tetramethylcyclohexanecarboxylic acid (**S5**) did not depress reactivity: indeed, product **P5** was formed in an outstanding 91% yield, again furnishing the lactone with a *trans* bicyclo[4.3.0] junction as a single enantiomer. As such, the present observation sets the stage to further elaborate such an optically active γ-lactone at position 4 of the cyclohexane framework. Lactones **P4** and **P5** are of interest because they feature the A ring of labdane-related diterpenoids,[23] offering a new path to access this stereochemically complex ring distinct from the natural polyene cyclizations.[24]

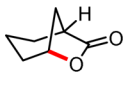
Furthermore, despite a complex bicyclic structure, oxidation of 7,7-dimethyl-1-norbornanecarboxylic acid (**S6**) under standard conditions delivered lactone **P6** in good yield (75%) and excellent ee (90%). Such a result is especially noteworthy when taking into account that the oxofunctionalization of the *gem*-dimethyls of camphor derivatives is notoriously difficult and usually requires either free radical or rearrangement reactions.[25] Camphane structures with this uncommon functionalization appear in natural products such as oliganthyl cinnamate, which is a component of curcuma.[26] In addition, camphor-based terpenes are important members of the chiral pool that are commonly used in the syntheses of relevant natural products.[5b,25b]

Desymmetrization of acyclic α-alkyl-substituted carboxylic acids was then undertaken. The oxidation of 2-(*tert*-butyl)-3,3-dimethylbutanoic acid (**S7**) bearing 18 primary γ-C−H bonds occurs in high isolated yield (89%) and excellent enantioselectivity (97% ee). Analogously, γ-lactonization of 2-isopropyl-3-methylbutanoic acid (**S8**) occurs selectively at the primary sites in overall 81% yield (d.r. = 2.0) with an outstanding enantioselectivity (99% ee) for the major diastereoisomer, leaving the weaker and *a priori* more reactive tertiary β-C−H


https://doi.org/10.1021/jacs.3c06231
J. Am. Chem. Soc. 2023, 145, 18094−18103

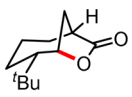



**Structural requirements**



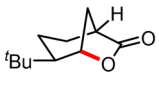
**P13**

$2^{CF3}$: 5%, 85% ee [a]
$2^{iPr}$: 10%, 84% ee [a]



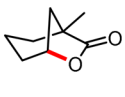
**P14**

$2^{CF3}$: 7%, 15% ee [a]
$2^{iPr}$: (12%) 89% ee [a]



**P15**

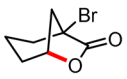
$2^{CF3}$: n.d. [a]
$2^{iPr}$: n.d. [a]



**P16**

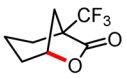
$2^{CF3}$: 76%, 96% ee [a]
$2^{iPr}$: (88%), 94% ee [a]

**Functional group tolerance**



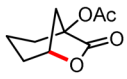
**P17**

$2^{CF3}$: (78%), 99% ee [b]
$2^{iPr}$: 69%, 99% ee [b]



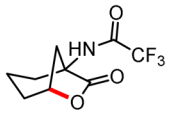
**P18**

$2^{CF3}$: 82%, 86% ee [a]
$2^{iPr}$: (80%), 91% ee [a]



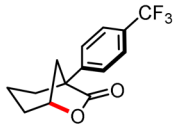
**P19**

$2^{CF3}$: 62%, 86% ee [b]
$2^{iPr}$: (63%), 86% ee [b]



**P20**

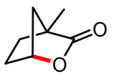
$2^{CF3}$: 58%, 92% ee [c,d]
$2^{iPr}$: (85%), 92% ee [c,d]



**P21**

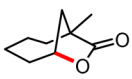
$2^{CF3}$: (50%), >99.9% ee [e]
$2^{iPr}$: 46%, >99.9% ee [e]

**Expanded scope**



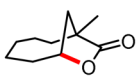
**P22**

$2^{CF3}$: (52%), 70% ee [e]
$2^{iPr}$: 72%, 75% ee [e]



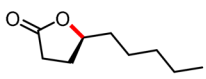
**P23**

$2^{CF3}$: (74%), 95% ee [e]
$2^{iPr}$: 82%, 93% ee [e]



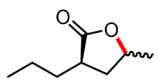
**P24**

$2^{CF3}$: (76%), 82% ee [e]
$2^{iPr}$: 73%, 85% ee [e]



**P25**

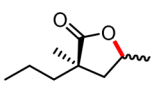
$2^{CF3}$: 40%, 3% ee [e]
$2^{iPr}$: 48%, 46% ee [e]



**P26**

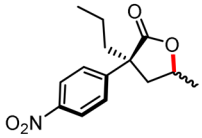
$2^{CF3}$: (44%), d.r. = 1.4
80% ee (minor) [e]
$2^{iPr}$: 44%, d.r. = 1.1
84% ee (minor) [e]

**Competitive γ-C-H bonds**



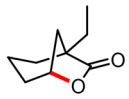
**P27**

$2^{CF3}$: (80%), d.r. = 5.0
91% ee (major),
54% ee (minor) [e]
$2^{iPr}$: 75%, d.r. = 5.2
94% ee (major),
33% ee (minor) [e]



**P28**

$2^{CF3}$: (80%), d.r. = 7.2
>99.9% ee (major)
47% ee (minor) [e]
$2^{iPr}$: 92%, d.r. = 3.3
>99.9% ee (major)
56% ee (minor) [e]



**P29**

$2^{CF3}$: 77%, 98% ee [a]
$2^{iPr}$: (74%), 98% ee [a]

**P30a** **P30b**

$2^{CF3}$: 73%, (**P30a** : **P30b** = 1 : 1)
>99.9% ee (**P30a**), 36% ee (**P30b**) [a]
$2^{iPr}$: (77%), (**P30a** : **P30b** = 5 : 1)
>99.9% ee (**P30a**), 43% ee (**P30b**) [a]

**Figure 4.** continued



https://doi.org/10.1021/jacs.3c06231
J. Am. Chem. Soc. 2023, 145, 18094−18103

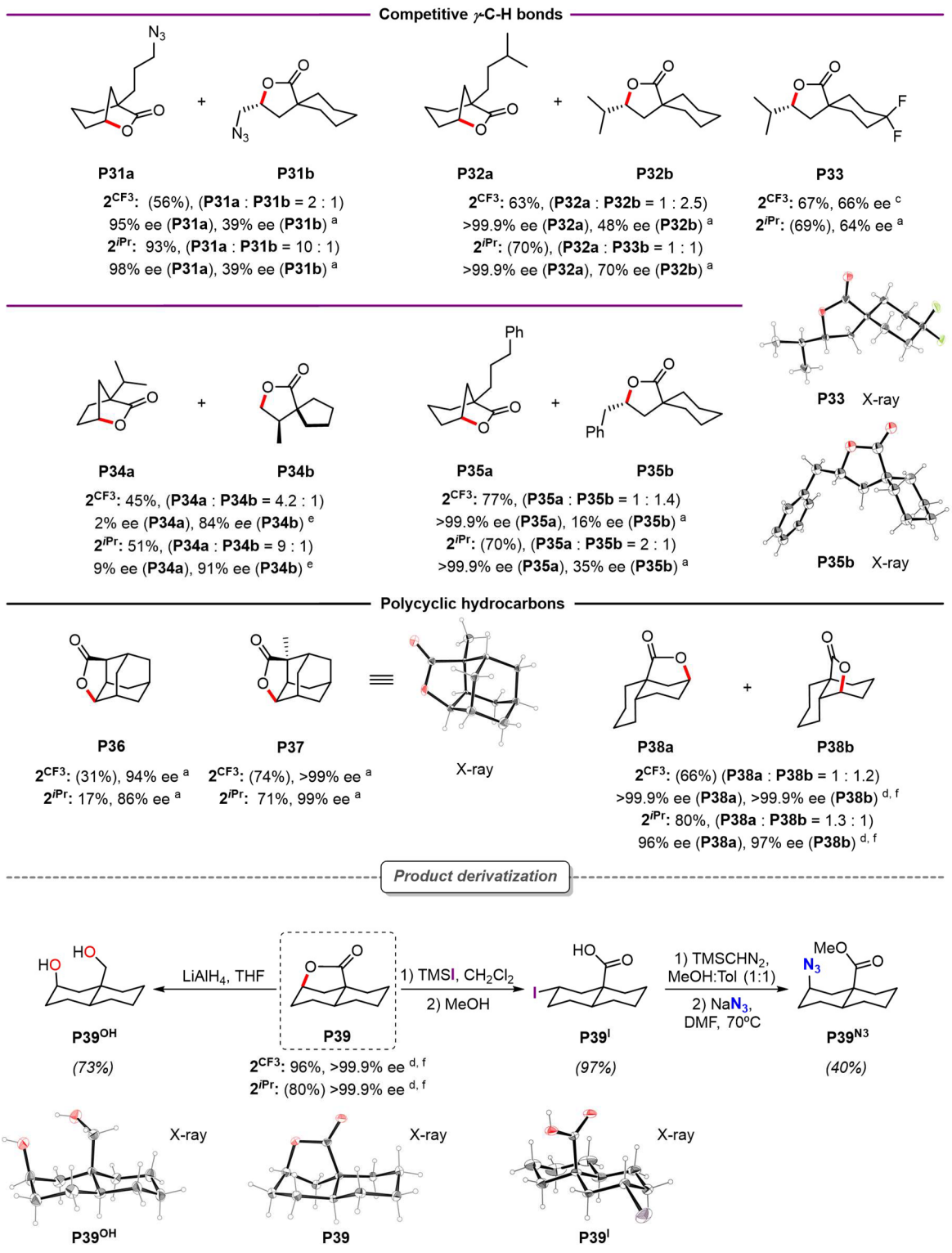



**Figure 4.** Enantioselective γ-lactonization of the substituted carboxylic acids. Reaction conditions: substrate (25 mM) and Mn catalyst (1 mol %) using TFE as a solvent at 0 °C. $H_2O_2$ (0.9 M solution in TFE) was delivered over 30 min with a syringe pump. [a]$H_2O_2$ (1.2 equiv.). [b]$H_2O_2$ (2 equiv.). [c]$H_2O_2$ (3 equiv.). [d]In the presence of TfOH (0.1 equiv.). [e]$H_2O_2$ (1.5 equiv.). [f]$H_2O_2$ (1.6 equiv.) and triple addition of catalyst (0.3 mol % × 3). Isolated yield in parentheses. n.d. = not detected. d.r. = diastereoisomeric ratio. Bottom: Chemical derivatization of lactone **P39**.

bonds untouched. Further removal of the β-methyl groups (**S9**) substantially erodes both yield (22%) and enantioselectivity (62% ee) and may suggest the existence of competitive paths. However, when a methyl group is incorporated at the α-position of the carboxylic acid as in **S10**, the activity is restored (**P10**, 85% yield) while maintaining similar enantioinduction (56% ee), a behavior that reflects the operation of the Thorpe−Ingold effect.[27] In this scenario, the present methodology also enables γ-C−H bond lactonization at primary sites in carboxylic acids bearing aryl bromides (**S11**), which are usually incompatible in C−H activation reactions catalyzed by noble metals due to



https://doi.org/10.1021/jacs.3c06231
J. Am. Chem. Soc. 2023, 145, 18094−18103

hydrodehalogenation,[28] as well as electron-poor aromatic moieties (**S12**). Importantly, the products thus formed, **P11** and **P12**, provide the opportunity to access important structural motifs present in a variety of approved drugs, such as C3-quaternary azepanes.[29]

With the identification of $\mathbf{2}^{CF3}$ and $\mathbf{2}^{iPr}$ as preferential catalysts for highly enantioselective primary C−H oxidation, γ-lactonization at secondary sites was investigated (Figure 4). The oxidation of cyclohexanecarboxylic acid (**S13**), which contains two enantiotopic γ-methylenic units, results in full substrate conversion with formation of only a small amount of γ-lactone **P13**. No significant increase in yield and ee was observed following introduction of a bulky *cis* $^{t}$Bu group at position 4 of the cyclohexane ring (**S14**). Notably, lactone formation is observed only when the carboxylic group is forced in the axial position in the most stable chair conformation (compare **S14** and **S15**, see also Section 6.4 in the Supporting Information), although the high conversion attained with both substrates showcases that some unidentified side-reactions can override the γ-lactonization pathway.

However, when the α-position of the carboxylic acid is quarternarized as in 1-methylcyclohexanecarboxylic acid (**S16**), the reaction becomes chemoselective for γ-lactonization (**P16**, 88% isolated yield) with high enantiodiscrimination (94% ee). The reaction again proceeds cleanly with no traces of products deriving from nondirected oxidations. Capitalizing on this finding, we tested different 1-substituted cyclohexanecarboxylic acids. Halogen, trifluoromethyl, ester, amide, and aromatic substituents are all well tolerated, affording γ-lactones with excellent ee's while maintaining good yields (**P17**−**P21**). Of interest, such lactones display a [3.2.1]bicyclic structure, hybrid between an ε-caprolactone and a γ-butyrolactone, which are valuable monomers for building infinitely recyclable polymers.[30] Their access, exclusively in racemic form, requires multistep processes starting from 3-cyclohexene-1-carboxylic acid derivatives. Furthermore, the exquisite γ-site-selectivity is maintained when modifying the flanking cycle of the acid to 5, 7, and 8 carbons, affording bicyclic lactones **P22**−**P24** in moderate to high ee.

The study was then extended to the oxidation of linear and less rigid architectures, in which the differentiation of the two enantiotopic γ-C−H bonds is particularly challenging. Within this frame, γ-lactonization of nonanoic (**S25**) and valproic acids (**S26**) occurs with a moderate yield and from moderate to high ee (up to 84%). However, quaternarization of the α-position of **S26** as in **S27** and **S28** significantly improves the yield (up to 92%), diastereoselectivity (d.r. up to 7.2), and enantioselectivity (up to >99.9% ee) (**P27** and **P28**).

With these results in hand, we set out to study the oxidation of 1-alkylcyclohexanecarboxylic acids displaying competitive exocyclic γ-C−H bonds. Indeed, we found that the ee of the γ-lactone product deriving from endocyclic oxidation increases with increasing alkyl chain length (i.e., on going from **P16** to **P29** and **P30a**), ultimately affording, with **S30**, bicyclic lactone **P30a** as a single enantiomer, accompanied however by the spirocyclic γ-lactone **P30b** resulting from alkyl chain oxidation in moderate ee (36−43%). Interestingly, the site-selectivity appears to be influenced by catalyst structure; while the oxidation of the cyclohexane ring is clearly favored when sterically congested $\mathbf{2}^{iPr}$ is used (**P30a**:**P30b** = 5), oxidation of the endocyclic γ-$CH_2$ unit is attenuated with $\mathbf{2}^{CF3}$ (**P30a**:**P30b** = 1). Remarkably, the present method also enables the synthesis of chiral azido compounds (**P31a** and **P31b**), which are building blocks of interest for azide−alkyne Huisgen cycloaddition and elaboration into chiral amines.

We then explored the desymmetrization of substrates **S32** and **S34**, bearing weaker tertiary δ- and β-C−H bonds adjacent to the targeted exocyclic secondary and primary γ-C−H bonds. Pleasantly, the reaction led to the exclusive formation of the two γ-lactones deriving from endo- and exocyclic oxidation without the formation of any oxidation product at the tertiary sites. Interestingly, the oxidation of **S34** results in the formation of the spirocyclic γ-lactone **P34b** derived from primary C−H bond oxidation with high enantioinduction (91% ee). Furthermore, the competition between exo- and endocyclic γ-C−H bond oxidation can be completely suppressed by electronic deactivation without significantly affecting the ee (**P33**). The outstanding γ-site-selectivity attained in the present system is maintained also in the presence of benzylic δ-C−H bonds, which *a priori* may be expected to compete because of their lower BDE (**P35a** and **P35b**). A rationale for this selectivity has been recently provided on the basis of DFT calculations which pointed to a comparatively lower activation barrier for intramolecular HAT from the γ-C−H compared to the β- and δ-C−H bonds.[15]

The potential of this methodology is also highlighted by the selective oxidation of complex fused polycyclic hydrocarbon settings: adamantanecarboxylic acids (**S36** and **S37**) and *cis*- and *trans*-decalin-9-carboxylic acids (**S38** and **S39**, respectively). The directed oxidation of the rigid and bulky substrates **S36** and **S37** occurs with a high ee, albeit in relatively low yield for **P36**. We note on passing that the oxidation of the adamantane core results in the simultaneous formation of six stereogenic centers. Furthermore, the system enables the efficient site-selective oxidation of decalin structures with outstanding enantioselectivity (>99.9% ee). Oxygenated decalin skeletons are very important structural features in a wide variety of natural products. Their importance is witnessed by the large number of multistep strategies aimed at the synthesis and functionalization of decalin units.[31] Lactones **P38a**, **P38b**, and **P39** can be valuable strategic intermediates en route to the synthesis of a wide variety of diterpenoids.[32] Notably, the reaction could be readily scaled up (500 mg quantity) to obtain lactone **P39** in a high yield (80%) and in an enantiopure form, highlighting the practicability of the present protocol.

γ-Lactones represent ideal versatile platforms to expand the chiral pool due to their propensity to undergo a vast array of different chemical transformations.[33] This is illustrated by the straightforward elaboration of decalin lactone **P39** (Figure 4). Lactone ring opening by reduction offers stereoretentive access to important chiral oxygenated motifs. For instance, the enantiopure diol $\mathbf{P39}^{OH}$, obtained in 73% isolated yield, is a common structural motif in triterpenoids[34] and a valuable starting material that can provide access to chiral cyclohexanes and γ-ketoacids by dehydration and oxidation, respectively, as well as to chiral pyrrolidines.[35] Alternatively, lactones can be straightforwardly opened in a stereospecific fashion with trimethylsilyl iodide (TMSI), enabling the installation of iodine at the oxidized γ-position with inversion of configuration ($\mathbf{P39}^{I}$, obtained in 97% isolated yield). Through this strategy, such iodo compounds can be intermediates of interest en route to the synthesis of chiral compounds, such as γ-azido ester $\mathbf{P39}^{N3}$, prone to further elaboration. Products such as $\mathbf{P39}^{N3}$ can also be strategic intermediates for the synthesis of chiral compounds with the 6-azabicyclo[3.2.1]octane core,


https://doi.org/10.1021/jacs.3c06231
J. Am. Chem. Soc. 2023, 145, 18094−18103

which are highly valued because of their bioactivity.[36] Finally, the free carboxylic acid of **P39**$^{I}$ can be regarded as a handle to sequentially generate a novel $\gamma$-C−O bond, increasing the molecular complexity as well as the number of stereocenters.

## CONCLUSIONS

We report sterically congested manganese catalysts that enable a general, economical, and practical synthesis of chiral $\gamma$-lactones by a highly enantioselective directed oxidation of strong primary and secondary C($sp^3$)−H bonds under mild conditions and in short reaction times. The method reported here provides the straightforward conversion of cheap and simple carboxylic acids into highly added-value chiral compounds with unprecedented levels of enantioselectivity. Besides pioneering highly enantioselective functionalization of primary C−H bonds, the use of catalysts based on an earth-abundant metal singularizes the current system with respect to asymmetric C($sp^3$)−H oxidation reactions that rely on precious metals. In addition, the use of hydrogen peroxide as an oxidant confers to the system a high atom economy, which combined with the mild experimental conditions makes the reaction particularly appealing from sustainability and large-scale applicability perspectives. The simplicity of the reaction, composed by low loading of a manganese catalyst and hydrogen peroxide in a fluorinated alcohol solvent at ambient temperature, contrasts with the state-of-the-art systems constituted by multiple reagents and additives often accompanied by prolonged heating at high temperature, producing large amounts of waste. The availability of the substrates and the immediate importance of the resulting products in natural product synthesis and materials combined with their facile follow-up elaboration constitute a distinctive aspect of the current reactions. We envision that the high structural versatility and powerful oxidation ability of the novel family of catalysts disclosed in this work will find utility in the development of novel enantioselective C−H functionalization reactions.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c06231.

Materials and methods describing preparation of complexes and substrates, characterization of the isolated oxidation products and experimental procedures for the catalytic reactions; NMR spectra; SFC and GC traces (PDF)

### Accession Codes

CCDC 2269610−2269622 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

## AUTHOR INFORMATION


### Corresponding Authors

**Arnau Call** − *Institut de Química Computacional i Catàlisi (IQCC) and Departament de Química, Universitat de Girona, Girona E-17071 Catalonia, Spain;* orcid.org/0000-0003-0970-7195; Email: arnau.call@udg.edu

**Massimo Bietti** − *Dipartimento di Scienze e Tecnologie Chimiche, Università "Tor Vergata", I-00133 Rome, Italy;* orcid.org/0000-0001-5880-7614; Email: bietti@uniroma2.it

**Miquel Costas** − *Institut de Química Computacional i Catàlisi (IQCC) and Departament de Química, Universitat de Girona, Girona E-17071 Catalonia, Spain;* orcid.org/0000-0001-6326-8299; Email: miquel.costas@udg.edu

### Authors

**Giorgio Capocasa** − *Institut de Química Computacional i Catàlisi (IQCC) and Departament de Química, Universitat de Girona, Girona E-17071 Catalonia, Spain*

**Andrea Palone** − *Institut de Química Computacional i Catàlisi (IQCC) and Departament de Química, Universitat de Girona, Girona E-17071 Catalonia, Spain;* orcid.org/0000-0001-8482-6085

**Laia Vicens** − *Institut de Química Computacional i Catàlisi (IQCC) and Departament de Química, Universitat de Girona, Girona E-17071 Catalonia, Spain*

**Eric Aparicio** − *Institut de Química Computacional i Catàlisi (IQCC) and Departament de Química, Universitat de Girona, Girona E-17071 Catalonia, Spain;* orcid.org/0000-0002-8905-4640

**Najoua Choukairi Afailal** − *Institut de Química Computacional i Catàlisi (IQCC) and Departament de Química, Universitat de Girona, Girona E-17071 Catalonia, Spain*

**Nikos Siakavaras** − *Institut de Química Computacional i Catàlisi (IQCC) and Departament de Química, Universitat de Girona, Girona E-17071 Catalonia, Spain*

**Maria Eugènia López Saló** − *Institut de Química Computacional i Catàlisi (IQCC) and Departament de Química, Universitat de Girona, Girona E-17071 Catalonia, Spain*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.3c06231


### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

We acknowledge economic support from European Research Council (AdvG 883922 to M.C.), Spain Ministry of Science (MINECO, IJC2020-046115-I to A.C., PRE2019-090149 to A.P., PID2021-129036NB-I00 to M.C.), and Generalitat de Catalunya (ICREA Academia to M.C., 2021 SGR 00475). N.C.A. acknowledges UdG for the Ph.D. grant IFUdG2021. We acknowledge STR of UdG for experimental support.

## REFERENCES

(1) Nugent, W. A.; RajanBabu, T. V.; Burk, M. J. Beyond Nature's Chiral Pool: Enantioselective Catalysis in Industry. *Science* **1993**, *259*, 479−483.

(2) (a) White, M. C.; Zhao, J. Aliphatic C-H Oxidations for Late-Stage Functionalization. *J. Am. Chem. Soc.* **2018**, *140*, 13988−14009. (b) Genovino, J.; Sames, D.; Hamann, L. G.; Toure, B. B. Accessing Drug Metabolites via Transition-Metal Catalyzed C-H Oxidation: The Liver as Synthetic Inspiration. *Angew. Chem., Int. Ed.* **2016**, *55*, 14218−14238. (c) D'Accolti, L.; Annese, C.; Fusco, C. Continued Progress towards Efficient Functionalization of Natural and Non-natural Targets under Mild Conditions: Oxygenation by C-H Bond Activation with Dioxirane. *Chem.—Eur. J.* **2019**, *25*, 12003−12017.

(3) Milan, M.; Bietti, M.; Costas, M. Enantioselective aliphatic C−H bond oxidation catalyzed by bioinspired complexes. *Chem. Commun.* **2018**, *54*, 9559−9570.
(4) (a) Bergman, R. G. C−H activation. *Nature* **2007**, *446*, 391−393. (b) White, M. C. Adding aliphatic C-H bond oxidations to synthesis. *Science* **2012**, *335*, 807−809. (c) Newhouse, T.; Baran, P. S. If C-H bonds could talk: selective C-H bond oxidation. *Angew. Chem., Int. Ed.* **2011**, *50*, 3362−3374.
(5) (a) Blaser, H. U. The chiral pool as a source of enantioselective catalysts and auxiliaries. *Chem. Rev.* **1992**, *92*, 935−952. (b) Brill, Z. G.; Condakes, M. L.; Ting, C. P.; Maimone, T. J. Navigating the Chiral Pool in the Total Synthesis of Complex Terpene Natural Products. *Chem. Rev.* **2017**, *117*, 11753−11795.
(6) (a) Kille, S.; Zilly, F. E.; Acevedo, J. P.; Reetz, M. T. Regio- and stereoselectivity of P450-catalysed hydroxylation of steroids controlled by laboratory evolution. *Nat. Chem.* **2011**, *3*, 738−743. (b) Roiban, G. D.; Agudo, R.; Reetz, M. T. Cytochrome P450 catalyzed oxidative hydroxylation of achiral organic compounds with simultaneous creation of two chirality centers in a single C-H activation step. *Angew. Chem., Int. Ed.* **2014**, *53*, 8659−8663. (c) Zhang, K.; Shafer, B. M.; Demars, M. D., 2nd; Stern, H. A.; Fasan, R. Controlled oxidation of remote $sp^3$ C-H bonds in artemisinin via P450 catalysts with fine-tuned regio- and stereoselectivity. *J. Am. Chem. Soc.* **2012**, *134*, 18695−18704. (d) Chakrabarty, S.; Wang, Y.; Perkins, J. C.; Narayan, A. R. H. Scalable biocatalytic C-H oxyfunctionalization reactions. *Chem. Soc. Rev.* **2020**, *49*, 8137−8155. (e) Zwick, C. R.; Renata, H. Harnessing the biocatalytic potential of iron- and alpha-ketoglutarate-dependent dioxygenases in natural product total synthesis. *Nat. Prod. Rep.* **2020**, *37*, 1065−1079.
(7) (a) Gormisky, P. E.; White, M. C. Catalyst-controlled aliphatic C-H oxidations with a predictive model for site-selectivity. *J. Am. Chem. Soc.* **2013**, *135*, 14052−14055. (b) Chen, M. S.; White, M. C. A Predictably Selective Aliphatic C−H Oxidation Reaction for Complex Molecule Synthesis. *Science* **2007**, *318*, 783−787. (c) Vicens, L.; Olivo, G.; Costas, M. Rational Design of Bioinspired Catalysts for Selective Oxidations. *ACS Catal.* **2020**, *10*, 8611−8631.
(8) (a) Sun, W.; Sun, Q. Bioinspired Manganese and Iron Complexes for Enantioselective Oxidation Reactions: Ligand Design, Catalytic Activity, and Beyond. *Acc. Chem. Res.* **2019**, *52*, 2370−2381. (b) Milan, M.; Bietti, M.; Costas, M. Highly Enantioselective Oxidation of Nonactivated Aliphatic C-H Bonds with Hydrogen Peroxide Catalyzed by Manganese Complexes. *ACS Cent. Sci.* **2017**, *3*, 196−204.
(9) (a) Kal, S.; Xu, S.; Que, L., Jr Bio-inspired Nonheme Iron Oxidation Catalysis: Involvement of Oxoiron(V) Oxidants in Cleaving Strong C-H Bonds. *Angew. Chem., Int. Ed.* **2020**, *59*, 7332−7349. (b) Bryliakov, K. P.; Talsi, E. P. Active sites and mechanisms of bioinspired oxidation with $H_2O_2$, catalyzed by nonheme Fe and related Mn complexes. *Coord. Chem. Rev.* **2014**, *276*, 73−96.
(10) (a) Chu, J. C. K.; Rovis, T. Complementary Strategies for Directed C($sp^3$)-H Functionalization: A Comparison of Transition-Metal-Catalyzed Activation, Hydrogen Atom Transfer, and Carbene/Nitrene Transfer. *Angew. Chem., Int. Ed.* **2018**, *57*, 62−101. (b) Kurganskiy, V. I.; Ottenbacher, R. V.; Shashkov, M. V.; Talsi, E. P.; Samsonenko, D. G.; Bryliakov, K. P. Manganese-Catalyzed Regioselective C-H Lactonization and Hydroxylation of Fatty Acids with $H_2O_2$. *Org. Lett.* **2022**, *24*, 8764−8768.
(11) Pichette Drapeau, M.; Goossen, L. J. Carboxylic Acids as Directing Groups for C-H Bond Functionalization. *Chem.—Eur. J.* **2016**, *22*, 18654−18677.
(12) (a) Zhuang, Z.; Yu, J. Q. Lactonization as a general route to b-C($sp^3$)-H functionalization. *Nature* **2020**, *577*, 656−659. (b) Chan, H. S. S.; Yang, J.-M.; Yu, J.-Q. Catalyst-controlled site-selective methylene C−H lactonization of dicarboxylic acids. *Science* **2022**, *376*, 1481−1487. (c) Dutta, S.; Bhattacharya, T.; Geffers, F. J.; Bürger, M.; Maiti, D.; Werz, D. B. Pd-catalysed C−H functionalisation of free carboxylic acids. *Chem. Sci.* **2022**, *13*, 2551−2573. (d) Kuhn, L.; Vil, V. A.; Barsegyan, Y. A.; Terent'ev, A. O.; Alabugin, I. V. Carboxylate as a Non-innocent L-Ligand: Computational and Experimental Search for Metal-Bound Carboxylate Radicals. *Org. Lett.* **2022**, *24*, 3817−3822.
(13) Vicens, L.; Bietti, M.; Costas, M. General Access to Modified $\alpha$-Amino Acids by Bioinspired Stereoselective $\gamma$-C−H Bond Lactonization. *Angew. Chem., Int. Ed.* **2021**, *60*, 4740−4746.
(14) Cianfanelli, M.; Olivo, G.; Milan, M.; Klein Gebbink, R. J. M.; Ribas, X.; Bietti, M.; Costas, M. Enantioselective C-H Lactonization of Unactivated Methylenes Directed by Carboxylic Acids. *J. Am. Chem. Soc.* **2020**, *142*, 1584−1593.
(15) Call, A.; Cianfanelli, M.; Besalú-Sala, P.; Olivo, G.; Palone, A.; Vicens, L.; Ribas, X.; Luis, J. M.; Bietti, M.; Costas, M. Carboxylic Acid Directed $\gamma$-Lactonization of Unactivated Primary C−H Bonds Catalyzed by Mn Complexes: Application to Stereoselective Natural Product Diversification. *J. Am. Chem. Soc.* **2022**, *144*, 19542−19558.
(16) (a) Ottenbacher, R. V.; Bryliakova, A. A.; Shashkov, M. V.; Talsi, E. P.; Bryliakov, K. P. To Rebound or···Rebound? Evidence for the "Alternative Rebound" Mechanism in C−H Oxidations by the Systems Nonheme Mn Complex/$H_2O_2$/Carboxylic Acid. *ACS Catal.* **2021**, *11*, 5517−5524. (b) Galeotti, M.; Vicens, L.; Salamone, M.; Costas, M.; Bietti, M. Resolving Oxygenation Pathways in Manganese-Catalyzed C($sp^3$)-H Functionalization via Radical and Cationic Intermediates. *J. Am. Chem. Soc.* **2022**, *144*, 7391−7401.
(17) (a) Peters, M. W.; Meinhold, P.; Glieder, A.; Arnold, F. H. Regio- and Enantioselective Alkane Hydroxylation with Engineered Cytochromes P450 BM-3. *J. Am. Chem. Soc.* **2003**, *125*, 13442−13450. (b) Narayan, A. R.; Jimenez-Oses, G.; Liu, P.; Negretti, S.; Zhao, W.; Gilbert, M. M.; Ramabhadran, R. O.; Yang, Y. F.; Furan, L. R.; Li, Z.; Podust, L. M.; Montgomery, J.; Houk, K. N.; Sherman, D. H. Enzymatic hydroxylation of an unactivated methylene C-H bond guided by molecular dynamics simulations. *Nat. Chem.* **2015**, *7*, 653−660.
(18) McClymont, K. S.; Wang, F. Y.; Minakar, A.; Baran, P. S. Total Synthesis of (−)-Maximiscin. *J. Am. Chem. Soc.* **2020**, *142*, 8608−8613.
(19) Sun, Q.; Sun, W. Catalytic Enantioselective Methylene C($sp^3$)-H Hydroxylation Using a Chiral Manganese Complex/Carboxylic Acid System. *Org. Lett.* **2020**, *22*, 9529−9533.
(20) Zhang, L.; Meggers, E. Steering Asymmetric Lewis Acid Catalysis Exclusively with Octahedral Metal-Centered Chirality. *Acc. Chem. Res.* **2017**, *50*, 320−330.
(21) Zhang, K.; Lu, L. Q.; Jia, Y.; Wang, Y.; Lu, F. D.; Pan, F.; Xiao, W. J. Exploration of a Chiral Cobalt Catalyst for Visible-Light-Induced Enantioselective Radical Conjugate Addition. *Angew. Chem., Int. Ed.* **2019**, *58*, 13375−13379.
(22) (a) Čeković, Z. Reactions of $\delta$-carbon radicals generated by 1,5-hydrogen transfer to alkoxyl radicals. *Tetrahedron* **2003**, *59*, 8073−8090. (b) Hung, K.; Condakes, M. L.; Novaes, L. F. T.; Harwood, S. J.; Morikawa, T.; Yang, Z.; Maimone, T. J. Development of a Terpene Feedstock-Based Oxidative Synthetic Approach to the Illicium Sesquiterpenes. *J. Am. Chem. Soc.* **2019**, *141*, 3083−3099.
(23) (a) Peters, R. J. Two rings in them all: the labdane-related diterpenoids. *Nat. Prod. Rep.* **2010**, *27*, 1521−1530. (b) Rudolf, J. D.; Chang, C. Y. Terpene synthases in disguise: enzymology, structure, and opportunities of non-canonical terpene synthases. *Nat. Prod. Rep.* **2020**, *37*, 425−463.
(24) Feilner, J. M.; Plangger, I.; Wurst, K.; Magauer, T. Bifunctional Polyene Cyclizations: Synthetic Studies on Pimarane Natural Products. *Chem.—Eur. J.* **2021**, *27*, 12410−12421.
(25) (a) Shokova, E. A.; Kim, J. K.; Kovalev, V. V. Camphor and its derivatives. Unusual transformations and biological activity. *Russ. J. Org. Chem.* **2016**, *52*, 459−488. (b) Lusi, R. F.; Sennari, G.; Sarpong, R. Total synthesis of nine longiborneol sesquiterpenoids using a functionalized camphor strategy. *Nat. Chem.* **2022**, *14*, 450−456.
(26) Sun, W.; Wang, S.; Zhao, W.; Wu, C.; Guo, S.; Gao, H.; Tao, H.; Lu, J.; Wang, Y.; Chen, X. Chemical constituents and biological research on plants in the genus Curcuma. *Crit Rev. Food Sci. Nutr* **2017**, *57*, 1451−1523.


https://doi.org/10.1021/jacs.3c06231
J. Am. Chem. Soc. 2023, 145, 18094−18103

(27) DeLomba, W. C.; Stone, E. A.; Alley, K. A.; Iannarone, V.; Tarsis, E.; Ovaska, S.; Ovaska, T. V. Utilization of the Thorpe-Ingold Effect in the Synthesis of Cyclooctanoid Ring Systems via Anionic 6-*exo-dig* Cyclization/Claisen Rearrangement Sequence. *J. Org. Chem.* **2020**, *85*, 9464−9474.
(28) He, J.; Wasa, M.; Chan, K. S. L.; Shao, Q.; Yu, J. Q. Palladium-Catalyzed Transformations of Alkyl C-H Bonds. *Chem. Rev.* **2017**, *117*, 8754−8786.
(29) Babl, T.; Reiser, O. Asymmetric Total Synthesis of Meptazinol. *J. Org. Chem.* **2022**, *87*, 6410−6417.
(30) Shi, C.; Li, Z.-C.; Caporaso, L.; Cavallo, L.; Falivene, L.; Chen, E. Y. X. Hybrid monomer design for unifying conflicting polymerizability, recyclability, and performance properties. *Chem.* **2021**, *7*, 670−685.
(31) Gromov, A.; Enev, V.; Mulzer, J. A Desymmetrization Approach toward Highly Oxygenated *cis*-Decalins. *Org. Lett.* **2009**, *11*, 2884−2886.
(32) Cao, W.; Deng, H.; Sun, Y.; Liu, B.; Qin, S. Asymmetric Synthesis of Hispidanin A and Related Diterpenoids. *Chem.—Eur. J.* **2018**, *24*, 9120−9129.
(33) (a) Nájera, C.; Foubelo, F.; Sansano, J. M.; Yus, M. Stereodivergent routes in organic synthesis: marine natural products, lactones, other natural products, heterocycles and unnatural compounds. *Org. Biomol. Chem.* **2020**, *18*, 1279−1336. (b) Paryzek, Z.; Skiera, I. Synthesis and cleavage of lactones and tiolactones. Applications in organic synthesis. A review. *Org. Prep. Proced. Int.* **2007**, *39*, 203−296.
(34) Mu, T.; Xu, P.; Yu, B. Facile Synthesis of Oleanane-type Pentacyclic Triterpenoids Bearing Hydroxy Groups on D/E Rings. *Asian J. Org. Chem.* **2021**, *10*, 1752−1755.
(35) Liu, Y.; Diao, H.; Hong, G.; Edward, J.; Zhang, T.; Yang, G.; Yang, B. M.; Zhao, Y. Iridium-Catalyzed Enantioconvergent Borrowing Hydrogen Annulation of Racemic 1,4-Diols with Amines. *J. Am. Chem. Soc.* **2023**, *145*, 5007−5016.
(36) (a) Verhoest, P. R.; Basak, A. S.; Parikh, V.; Hayward, M.; Kauffman, G. W.; Paradis, V.; McHardy, S. F.; McLean, S.; Grimwood, S.; Schmidt, A. W.; Vanase-Frawley, M.; Freeman, J.; Van Deusen, J.; Cox, L.; Wong, D.; Liras, S. Design and discovery of a selective small molecule kappa opioid antagonist (2-methyl-N-((2'-(pyrrolidin-1-ylsulfonyl)biphenyl-4-yl)methyl)propan-1-amine, PF-4455242). *J. Med. Chem.* **2011**, *54*, 5868−5877. (b) Roy, A.; Roberts, F. G.; Wilderman, P. R.; Zhou, K.; Peters, R. J.; Coates, R. M. 16-Aza-ent-beyerane and 16-Aza-ent-trachylobane: Potent Mechanism-Based Inhibitors of Recombinant ent-Kaurene Synthase from Arabidopsis thaliana. *J. Am. Chem. Soc.* **2007**, *129*, 12453−12460.


https://doi.org/10.1021/jacs.3c06231
*J. Am. Chem. Soc.* 2023, 145, 18094−18103