Bioinspired Catalysis

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Readily Accessible Bulky Iron Catalysts exhibiting Site Selectivity in the Oxidation of Steroidal Substrates

David Font, Mercè Canta, Michela Milan, Olaf Cussó, Xavi Ribas, Robertus J. M. Klein Gebbink, and Miquel Costas**

Abstract: *Bulky iron complexes are described that catalyze the site-selective oxidation of alkyl C–H bonds with hydrogen peroxide under mild conditions. Steric bulk at the iron center is introduced by appending trialkylsilyl groups at the meta-position of the pyridines in tetradentate aminopyridine ligands, and this effect translates into high product yields, an enhanced preferential oxidation of secondary over tertiary C–H bonds, and the ability to perform site-selective oxidation of methylenic sites in terpenoid and steroidal substrates. Unprecedented site selective oxidation at C6 and C12 methylenic sites in steroidal substrates is shown to be governed by the chirality of the catalysts.*

Selective alkyl C–H functionalization is envisioned as a very powerful reaction in organic synthesis.[1] Regioselectivity exhibited by most oxidizing reagents is governed by the innate reactivity of C–H groups, and advances in understanding the factors that determine their relative reactivity have introduced some degree of predictability in the site selectivity of alkane oxidation reactions with non-enzymatic reagents.[2] However, in enzymatic oxidations a combination of directing elements can diverge site selectivity towards less-reactive C–H bonds. Contributions towards producing selective oxidations not governed by the innate reactivity of C–H bonds have started to appear, but are mainly restricted to enzymes. For example, directed evolution of P450s can be exploited to produce mutants that favor specific site selectivities.[3] Other recent approaches involve derivatization of substrates with elements that can be precisely recognized by enzymatic active sites, governing substrate positioning, so specific C–H bonds are directed towards the reactive site.[4] Synthetic reagents and catalysts are highly desirable for practical reasons but in the absence of the elaborate structures of enzymes, their ability to tune C–H site selectivity is still modest. Sterically bulky oxidants and iron catalysts with aminopyridine ligands have been recently shown to promote preferential oxidation of 2° over 3° C–H bonds because the 3° C–H bonds are sterically more encumbered.[5] However, reagents that can override intrinsic relative reactivities among not-activated methylene sites are very rare.[5c,6] This remains a very relevant and challenging problem because these strong and inert bonds are the most abundant C–H sites in organic molecules.

In the quest for iron catalysts that could regulate regioselectivity, and that are synthetically accessible in a straightforward manner, we considered installing bulky trialkylsilyl moieties to tetradentate chiral aminopyridine ligands. We envisioned that the bulky nature of the catalysts will modulate their regioselectivity, and may also enhance stereoselectivity in C–H oxidation reactions. Furthermore, from a practical point of view, the silyl derivatization offers a simple synthetic strategy to obtain modular scaffolds suitable for systematic tuning. Following these ideas, we herein show chiral iron catalysts with sterically bulky centers that mediate regioselective oxidation of alkane moieties. The catalysts oxidize preferentially 2° over 3° C–H bonds but most remarkably, their chirality endows them with the ability to determine site selectivity among distinct methylene sites in the oxidation of complex molecules, as shown for steroids.

Chiral tetradentate ligands (L = ^{tips}MCP and ^{tips}PDP, Scheme 1, giving the iron complexes **1** and **2**, respectively) in which the two pyridines are substituted with bulky *tris*-(isopropyl)silyl (tips) moieties at the 5-position were targeted. Silyl-substituted picolyl aldehyde precursors were obtained in multigram scale in a one pot sequence of reactions (See Supporting Information for details). The product yield and simplicity of the procedure compare very favorably with regard to methods required for preparing building blocks for other bulky catalysts.[5a,7] Standard procedures served to assemble the corresponding tetradentate ligands, which were then used to prepare the corresponding iron complexes of general formula (Δ or Λ)-[Fe(CF_3SO_3)$_2$((R,R' or S,S')-L)], L = ^{tips}MCP or ^{tips}PDP, (L = (S,S')-MCP, **Λ-^{tips}1**; L = (R,R')-MCP, **Δ-^{tips}1**; L = (S,S')- ^{tips}PDP, **Λ-^{tips}2**; L = (R,R')-PDP, **Δ-^{tips}2**). For illustrative purposes, a schematic diagram of the structure of the complexes is shown in Scheme 1, top. Complexes are chiral at the metal (Λ or Δ), which in turn is determined by the chirality of the diamine backbone (S,S' and R,R', respectively). Space-filling diagrams corresponding to (R,R')-[Fe(CF_3SO_3)$_2$(MCP)] (**Δ-1**),[8] [Fe(CF_3SO_3)$_2$(PDP)] (**Δ-2**),[9] **Λ-^{tips}1** and **Δ-^{tips}2** are also shown in Scheme 1, bottom. Comparison of the silylated catalysts with that of the parent **1**[8] and **2**,[9] indicates only minor differences between their respective structural parameters of the first

[*] Dr. D. Font, Dr. M. Canta, M. Milan, O. Cussó, Dr. X. Ribas, Dr. M. Costas
Institut de Química Computacional I Catàlisi (IQCC)
Departament de Química, Universitat de Girona
Campus Montilivi, 17071 Girona (Catalonia, Spain)
E-mail: miquel.costas@udg.edu
Dr. R. J. M. Klein Gebbink
Organic Chemistry & Catalysis
Debye Institute for Nanomaterials Science, Utrecht University
Universiteitsweg 99, 3584 CG Utrecht (The Netherlands)
E-mail: r.j.m.kleingebbink@uu.nl
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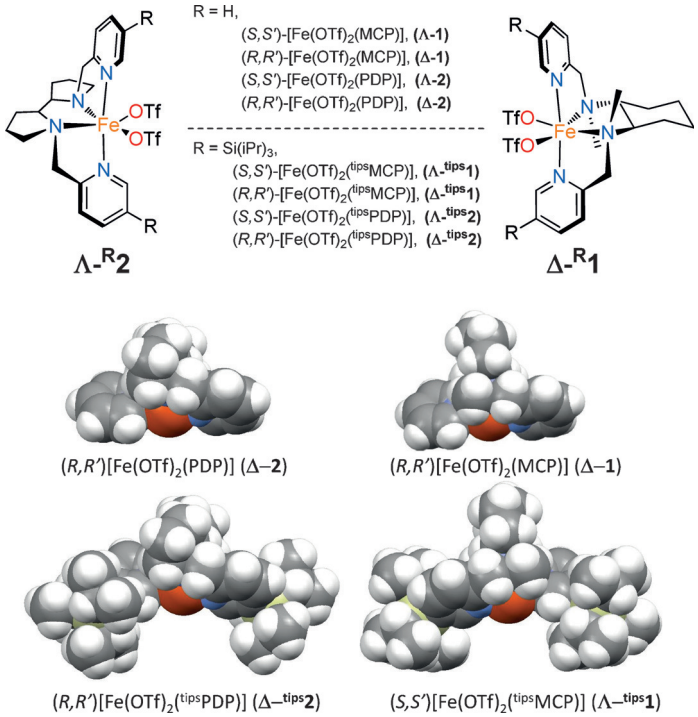


Scheme 1. Top: Schematic diagram of the series of iron catalysts employed. Bottom: Space-filling diagrams of the FeL fragments corresponding to **Δ-1**,[8] **Δ-2**,[9] **Λ-^{tips}1** and **Δ-^{tips}2** (CCDC 1456927–1456928). Triflate and water ligands in the X-ray structures have been removed for clarity. White H, gray C, blue N, yellow Si, orange Fe.

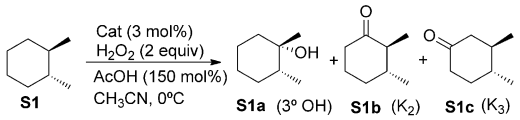
coordination sphere. Most interestingly, complexes **Λ-^{tips}1** and **Λ-^{tips}2** exhibit a well-defined and constrained envelope (Scheme 1, bottom) around the *cis* labile position of the iron center, where the putative reactive Fe=O unit forms upon reaction with H_2O_2.

A series of standard substrates were chosen as test platforms to estimate the ability of the catalysts to differentiate among 2° and 3° C–H bonds (2°/3°), and also among different methylenic sites differing in their relative steric hindrance (K3/K2; Table 1 and Supporting Information).[10] Reactions were performed at 0°C under air, by delivering aqueous H_2O_2 (2 equiv) via syringe pump (30 min) to an acetonitrile solution of the catalyst (3 mol%), the substrate, and 150 mol% of acetic acid (AcOH). Irrespective of the catalyst, oxidation of 3° C–H bonds provides the corresponding tertiary alcohol (3-OH), while oxidation of methylenic sites yields the corresponding ketone products, resulting from oxidation of the secondary alcohol that forms after initial C–H oxidation at these sites. Of note is that the hydroxylation of the tertiary site occurs with stereoretention. A perusal of Table 1 and Table S1 shows that **Λ-^{tips}1** and **Λ-^{tips}2** systematically provide improved product yields compared to the parent catalysts **Λ-1** and **Λ-2**.

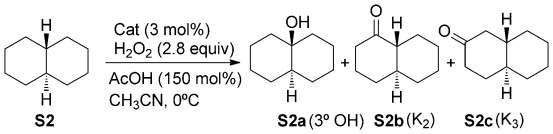
Most substantial is the systematic increase in selectivity towards the oxidation of 2° over 3° sites responding to the steric bulk of the catalysts. For example, the 2°/3° ratios change from 3 (with **S1**) and 24 (with **S2**) using **Λ-1** to 13 and 96 when using **Λ-^{tips}1**. Moreover, discrimination between methylenic sites is also enhanced when **Λ-^{tips}1** is employed as catalyst; in the oxidation of **S1** and **S2**, the K3/K2 ratio (3.0 and 1.9, entries 1 and 5) denotes a preferential oxidation at the sterically more exposed methylene site to produce ketone K3. As previously noticed for catalysts **Λ-1** and **Λ-2**,[5c,h] comparison between **Λ-^{tips}1** and **Λ-^{tips}2** shows that the nature of the backbone systematically has a contributing role in enhancing selectivity towards the less sterically hindered C–H bond (compare entries 1 vs. 2, and 5 vs. 6). In conclusion, **Λ-^{tips}1** and **Λ-^{tips}2** discriminate C–H oxidations among 3° and 2° alkyl C–H bonds on the basis of steric effects, with **Λ-^{tips}1** being particularly selective.

The ability of **^{tips}1** and **^{tips}2** to catalyze site-selective oxidations in complex organic molecules was tested for terpenoids and steroidal substrates, as representative cases. As these substrates are chiral, the two enantiomeric forms of the catalysts (**Λ** and **Δ**) were tested. Menthol derivatives have been studied as test substrates for C–H oxidation with iron and manganese catalysts, and also with P450 enzymes.[2b,4a,5b,c,11] Unlike menthyl and isomenthyl esters, where oxidation at the tertiary C1 is strongly favored because of intrinsic stereoelectronic factors, for (+)-neomenthyl esters a preferred site is absent. Consistently, (+)-neomenthyl pivalate (**S3**) was oxidized to a roughly 1:1 mixture of tertiary alcohol **S3a** and ketone **S3b** with unbiased catalysts **Λ-1**, **Δ-1**, **Λ-2** and **Δ-2**.[5c] Reactions also exhibit poor mass balance (see Supporting Information). Instead, reaction catalyzed by **Λ-^{tips}2** showed improved product yields, and mass balance, with ketone **S3b** being the major product. Instead **Δ-^{tips}2** delivered poorer yields and mass balance, highlighting a key role of chirality in determining the regioselectivity of the reaction. When performed in preparative scale, oxidation of

Table 1: Catalytic reactivity.



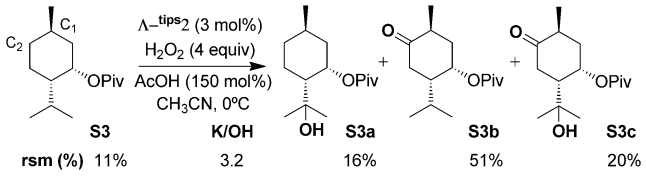
Entry	Cat.	Conv [%][a]	Yield [%][a]	3° OH/K2/K3[b]	K3/K2	2°/3°
1	**Λ-^{tips}1**	83	61	7/23/70	3.0	13
2	**Λ-^{tips}2**	87	55	20/26/54	2.1	4
3	**Λ-1**	84	41	24/26/50	1.9	3
4	**Λ-2**	65	37	48/22/30	1.3	1



5	**Λ-^{tips}1**	68	58	1/34/65	1.9	96
6	**Λ-^{tips}2**	83	58	3/36/61	1.7	31
7	**Λ-1**	83	53	4/37/59	1.6	24
8	**Λ-2**	88	48	15/38/46	1.2	5.6

[a] Conversion and yields determined from crude reaction mixtures by GC. Values are the average of at least three reactions. [b] Normalized ratios.

S3 with **Λ-^{tips}2** proceeds with excellent mass balance and provides ketone **S3b** as the major product in 51% yield (Scheme 2, 87% total yield of oxidized products, 98% mass balance). For comparison, the best yield of **S3b** described so far in the literature is 33%[5b] and in that reaction the total product yield was 48% and mass balance was 50%.

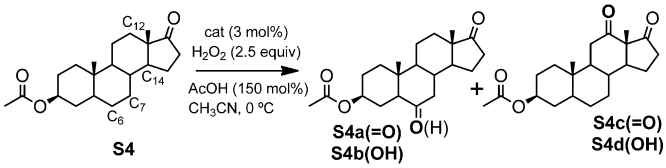


Scheme 2. Selective oxidation of (+)-neomenthyl pivalate. rsm = recovered starting material.

Steroidal substrates are particularly interesting because of their molecular complexity, containing multiple 3° and 2° C–H sites, and because of their biological importance. Oxidation patterns in steroids are very diverse and it has been argued that they regulate their physical and biological properties.[12] Seminal examples of regio and diastereoselective hydroxylation of steroidal substrates at C6 and C12 methylenic sites have been described by Breslow (Scheme 3a)[13] and Schönecker (Scheme 3b),[14] and both rely on elegant positioning of the reactive metal fragment in close proximity to the target C–H bond by either employing supramolecular or covalent interactions. Oxidation at C12 is particularly challenging. The Schönecker method remains as the only viable path for oxidation at this position, and has found use in total synthesis.[15]

Most interestingly, when *trans*-androsterone acetate was subjected to oxidation with **Λ-^{tips}1**, **Δ-^{tips}1**, **Λ-^{tips}2**, and **Δ-^{tips}2** site selectivity was shown to be dictated by the chirality of the catalysts (Table 2). Oxidation with **Λ-^{tips}1**, and **Λ-^{tips}2** proceeded predominantly (72–82% selectivity) at C6 providing the corresponding ketone **S4b** in 49–50% isolated yield. Instead, when **Δ-^{tips}1** and **Δ-^{tips}2** were used, preferential site selectivity was reversed towards C12, (**S4c** and **S4d**) in moderate (33%) and excellent (71%) isolated yields with **Λ-^{tips}2** and **Λ-^{tips}1**, respectively. Mass balance are remarkably high (72–95%), highlighting the extraordinary selectivity properties of the catalysts. In the absence of the bulky silyl moieties site selectivity is lost, low product yields and poor mass balance is obtained.[5h] Particularly unusual is the selectivity exhibited in these reactions by **Δ-^{tips}1** and **Λ-^{tips}2** (entries 2 and 3); C6 oxidized ketone accounts for 82% of oxidized products with **Λ-^{tips}2** , but only 11% with **Δ-^{tips}1**. Likewise, C12 oxidized ketone represents 88% of the oxidized products with **Δ-^{tips}1** and only 3% with **Λ- ^{tips}2**. Analogous selectivities were obtained when *cis*-androsterone was employed as substrate (see Supporting Information).

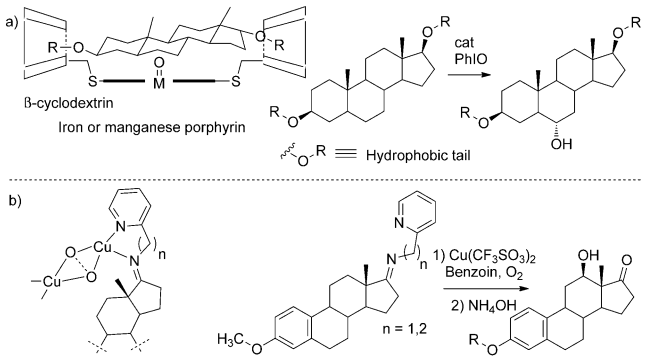
Table 2: Oxidation of *trans*-androsterone acetate (**S4**).



Entry	Cat.	Conv [%][a]	Total Yield (isol.yield) [%][a]	C6[b]/C7/C12/C14
1	**Λ-^{tips}1**	85	70(50)	72/5/23/–
2	**Δ-^{tips}1**	86	80(71)	11/1/88/–
3	**Λ-^{tips}2**	83	60(49)	82/12/3/3
4	**Δ-^{tips}2**	50	48(33)	22/6/69/3

[a] Conversion, total yield, and relative selectivities determined by GC of crude reaction mixtures. In parenthesis the isolated yield of the major ketone product. [b] Regioselectivity according to C–H oxidized site. Traces amounts of corresponding 2° alcohols are also observed in the GC but could not be isolated.

In conclusion, the present work describes straightforward accessible bulky iron catalysts for the oxidation of alkyl C–H bonds with remarkable regioselectivity, dictated by a combination of their bulky and chiral nature. To our knowledge, the switch in methylene site selectivity oxidation of steroidal substrates has only been previously documented for enzymes. Thus, the current work constitutes the first case where this effect has been demonstrated with synthetic catalysts, providing oxidized products in good yields. Future efforts will address the study and development of the stereoselective properties of these catalysts in challenging oxidation reactions.



Scheme 3. Representative examples of site selective oxidation of steroidal substrates, illustrating the basis for site selectivity.

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