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Combining Ligand Deuteration with Ligand Bulkiness in Non-Heme Iron Oxidation Catalysis: Enhancing Catalyst Lifetime and Site-Selectivity

Fanshi Li,[a] Isabelle Meijer,[a] Bauke Kniestedt,[a] Martin Lutz,[b] Daniël L. J. Broere,[a] and Robertus J. M. Klein Gebbink*[a]

Bulky tri-isopropyl silyl (TIPS) substituents and deuterium atoms in the ligand design have been shown to enhance the site-selective oxidation of aliphatic C–H bonds and the epoxidation of C=C bonds in non-heme iron oxidation catalysis. In this work, a series of non-heme iron complexes were developed by combining TIPS groups and deuterium atoms in the ligand. These bulky deuterated complexes show a significant increase in catalytic performance compared to their counterparts containing only TIPS groups or deuterium atoms. A broad range of substrates was oxidized with excellent yields, particularly, using [Fe(OTf)$_2$((*S*,*S*)-^{TIPS}BPBP-D$_4$)] (**1-TIPS-D$_4$**) (0.1 mol% to 1 mol%) via a fast or slow oxidant addition protocol, resulting in an overall improvement in catalytic performance. Notably, in the oxidation of the complex substrate *trans*-androsterone acetate, the use of a slow addition protocol and a lower catalyst loading of **1-TIPS-D$_4$** resulted in significant increases in reaction efficiency. In addition, kinetic and catalytic studies showed that deuteration does not affect the catalytic activity and the secondary C–H site-selectivity but increases the catalysts' lifetime resulting in higher conversion/yield. Accordingly, the yield of selectively oxidized secondary C–H products also increases with the overall yield by using the bulky deuterated iron complexes as catalysts. These catalytic improvements of the bulky deuterated complexes exemplify the enhanced design of ligands for homogeneous oxidation catalysis.

Introduction

The selective oxidation of aliphatic C–H bonds and (enantioselective) epoxidation of alkene functionalities are important transformations in nature and chemical synthesis. Aliphatic oxidation products are not only typical intermediates in detoxification pathways in the human body but also represent an important class of building blocks in organic synthesis.[1–6] Likewise, epoxides are important intermediates in synthesis, that are readily transformed into other common functional groups and derivatives.[1,7,8]

The catalytic synthesis of hydroxyl compounds and epoxides using molecular iron, as well as manganese complexes derived from linear bis-amino-bipyridyl (N2Py2) ligands has undergone a gratifying development in the past two decades (Figure 1). More general, iron is a promising metal for the development of catalytic oxidations and other reactions because iron is plentiful, affordable, and commercially available on a large scale and is relatively nontoxic.[9]

Que et al. reported the first bio-inspired non-heme iron catalyst based on the BPMEN ligand able to hydroxylate aliphatic substrates utilizing H_2O_2 as the oxidant in 1993.[10] Ever since, numerous iron complexes were investigated for the catalytic oxidation utilizing H_2O_2 as the oxidant. By increasing the rigidity of the ligand, iron catalysts based on the BPMCN (Que, 2001)[10] and BPBP ligands (White, 2007)[11] were found to have improved reactivity and selectivity in oxidation reactions. Building on the success of the BPBP ligand, many variants of this ligand have been developed which either comprise substituted pyridine donor groups or modified aliphatic diamine backbones.[12–16] For instance, a bulky iron complex derived from the (*R*,*R*)-^{2CF3Ph}BPBP ligand bearing 1,3-bis(trifluoromethyl)phenyl substituents at the 5-position of the pyridine moieties was reported to provide high site-selectivity in the oxidation of secondary aliphatic C–H bonds.[16] Interestingly, the introduction of bulky TIPS groups (TIPS = tris-(isopropyl)silyl) at the 5-position of the pyridine donors was found to also result in improved overall product yield and mass balances in many oxidation reactions ((*S*,*S*)-^{TIPS}BPBP ligand

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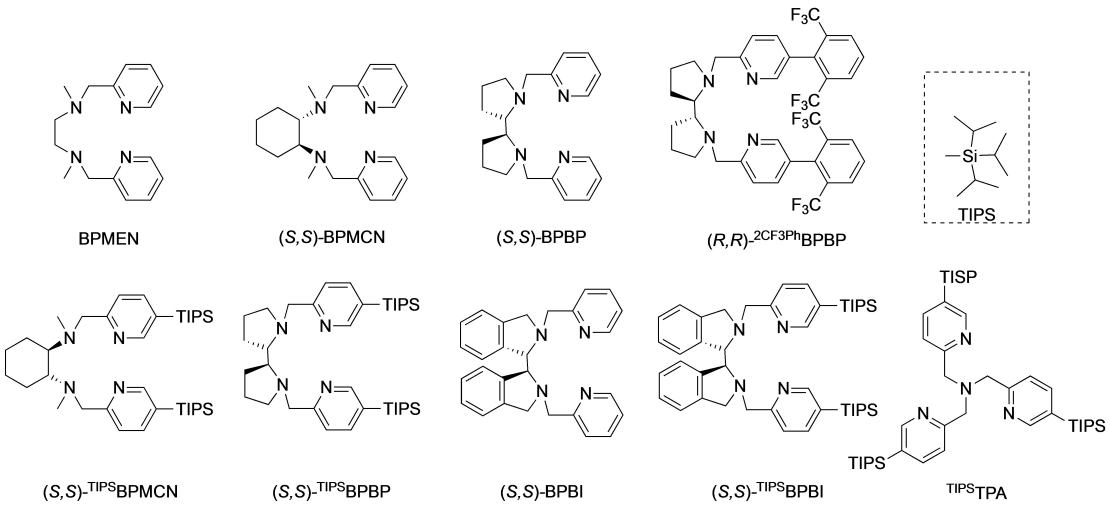
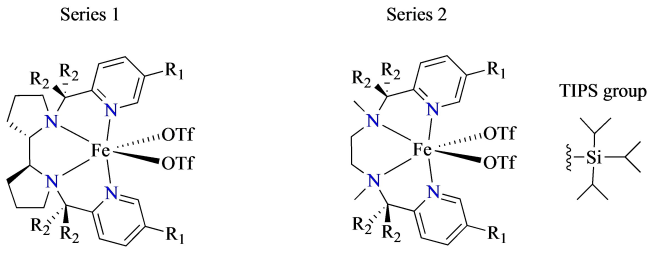


Figure 1. Selected examples of bio-inspired (bulky) amino-pyridine ligands used in iron oxidation catalysis.

reported by Costas and Klein Gebbink, 2016).[13,17,18] The use of such bulky ligands also resulted in an enhanced preference to oxidize more accessible secondary C–H bonds with respect to more sterically encumbered tertiary C–H bonds in terpenoid and steroidal substrates. For example, in the oxidation of *trans*-androsterone acetate 48% yield of oxidized products was obtained using non-TIPS complex [Fe(OTf)$_2$(*S,S*-BPBP)], including 15% of C6, 15% of C7 and 11% of C14 oxidized products.[18] Using the bulky complex [Fe(OTf)$_2$(*S,S*-^{TIPS}BPBP)] in this reaction resulted in an increased total product yield of 60%, including 49% of C6 oxide as the main product.[13] In agreement with the report from Costas and Klein Gebbink, another bulky catalyst [Fe(OTf)$_2$(*S,S*-^{TIPS}BPBI)] was reported by Chen and Klein Gebbink in 2017,[14] which showed an improved product yield and preference for secondary over tertiary C–H oxide products compared to the catalyst [Fe(OTf)$_2$(*S,S*-BPBI)] that lacks TIPS groups. Other examples of the use of bulky TIPS groups in oxidation catalysis include the use of [Fe(OTf)$_2$(tris($^{5-TIPS}$(2-methylpyridyl)amine)] in the catalytic dihydroxylation of olefins[19] and of [Mn(OTf)$_2$((*S,S*)-^{TIPS}BPMCN)] in the hydroxylation of aromatic C–H bonds.[20]

An important aspect of catalytic oxidation reactions using non-heme iron and manganese complexes is that the oxidant (mostly H_2O_2) is added slowly to the reaction mixture, typically over a period of 10–30 minutes. Although it is a significant factor affecting catalyst performance, the stability of such complexes under oxidizing conditions remains an issue and has received relatively little attention. Two deactivation pathways are currently considered for non-heme metal complexes in combination with H_2O_2 as the oxidant and a carboxylic acid additive. The first pathway involves the dimerization of non-heme iron complexes to produce catalytically inactive oxo-bridged $Fe^{III}_2(\mu\text{-O})(L)_2$ dimers (L = TPA,[21,22] BPMEN,[23] *S,S*-BPBP[12,24]). Slow oxidant addition protocols[24,25] or iterative catalyst addition protocols,[11,18,26] as well as the incorporation of bulky ligand substituents[27,28] have been applied to suppress this dimerization pathway. The second catalyst decomposition pathway is oxidative ligand degradation. For example, (benzylic) methylene positions of the ligand may be hydroxylated under catalytic conditions and even cleaved at the C–N bond upon further oxidation.[27,29–32] One approach that has been investigated to prevent oxidative ligand degradation is the deuteration of benzylic methylene groups in the ligand.[33,34] In view of the lower zero-point energy of a C–D bond with respect to a C–H bond, the replacement of a C–H bond by a C–D bond is expected to lead to slower oxidative activation of the bond.[35] Our earlier investigations have indeed shown that this may lead to non-heme oxidation catalysts with longer lifetimes and increased catalytic properties.[33] For instance, the epoxidation of *cis*-cylooctene using 0.25 mol% [Fe(OTf)$_2$(BPMEN-D$_4$)] provided a more than 2-fold improvement in conversion and yield (70% and 57%) compared to using the non-deuterated catalyst [Fe(OTf)$_2$(BPMEN)], which gave 34% conversion and 27% yield, respectively.[33a]

Taking these considerations into account we have set out to investigate the catalytic oxidation properties of a series of non-heme iron catalysts in which the incorporation of bulky ligand substituents (TIPS groups) has been combined with deuterated methylene moieties (Figure 2). To investigate if there is an



1	R_1=H, R_2=H	**2**	R_1=H, R_2=H
1-D$_4$	R_1=H, R_2=D	**2-D$_4$**	R_1=H, R_2=D
1-TIPS	R_1=TIPS, R_2=H	**2-TIPS**	R_1=TIPS, R_2=H
1-TIPS-D$_4$	R_1=TIPS, R_2=D	**2-TIPS-D$_4$**	R_1=TIPS, R_2=D

Figure 2. Non-heme iron complexes used in this study.

incremental effect on the catalytic performance of these ligand modifications, a series of complexes derived from the BPBP and BPMEN ligand (as shown in Figure 2) were tested in a series of alkene epoxidation and aliphatic C–H oxidation reactions. These investigations show that the combination of ligand bulk and deuteration results in enhanced product yields with good mass balances for epoxidations and good product yields with the enhanced preferential oxidation of secondary over tertiary C–H bonds for aliphatic oxidations. Remarkably, the bulky deuterated iron catalysts not only show a high site selectivity in the oxidation of methylenic sites in terpenoid and steroidal substrates, which typically results from the incorporation of TIPS groups, but also allow for the use of lower catalyst loadings due to a further improvement in catalytic lifetime resulting from ligand deuteration. Accordingly, the two ligand modifications act in concert to enhance the performance of non-heme iron oxidation catalysts even further.

Results and Discussion

Synthesis of N_2Py_2-D_4 Ligands and Iron Complexes.

The bulky undeuterated iron complexes, [Fe(OTf)$_2$((*S,S*)-^{TIPS}BPBP)][13] (**1-TIPS**) and [Fe(OTf)$_2$(^{TIPS}BPMEN)] (**2-TIPS**), as well as parent complexes [Fe(OTf)$_2$((*S,S*)-BPBP)][11] (**1**) and [Fe(OTf)$_2$(BPMEN)][10] (**2**) were prepared using reported methods.[33a] Two different deuteration methods have been explored for the synthesis of deuterated bulky complexes, **1-TIPS-D$_4$** and **2-TIPS-D$_4$**. First, the bulky deuterated ligand ^{TIPS}BPMEN-D$_4$ was synthesized using a reported method for the deuteration of the parent BPMEN ligand.[34] Following this method (method i, green synthesis route in Figure 3), the ligand ^{TIPS}BPMEN was heated for 24 h at 70 °C in anhydrous CD_3CN in the presence of 4.0 equiv. of sodium hydride under N_2. After workup and purification, ^{TIPS}BPMEN-D$_4$ was obtained in 66% yield (see SI for synthesis details). ^{1}H-NMR characterization indicated that this method led to 97% deuterium incorporation at the methylene positions of the ligand (Figure S5). ESI-MS analysis showed the presence of 2 isotopologues of the ligand, ^{TIPS}BPMEN-D$_4$ and ^{TIPS}BPMEN-D$_3$H$_1$ in a 9/1 ratio, respectively (Figure S7).

Applying this same method to the synthesis of (*S,S*)-^{TIPS}BPBP-D$_4$ failed to give the targeted deuterated ligand. Therefore, we turned to the deuteration method described by Chen et al. in which deuteration is accomplished using $NaBD_4$ reduction of a picolinate ester intermediate (method ii, blue synthesis route in Figure 3).[33a] Applying this method to the reduction of methyl 5-(triisopropylsilyl)picolinate (^{TIPS}Py-COOMe) gave access to the corresponding deuterated alcohol ^{TIPS}Py-CD$_2$OH in 86% yield with a typical deuteration percentage of 90% on the basis of ^{1}H-NMR analysis (based on different synthesis batches). Following this step, ^{TIPS}Py-CD$_2$OH was used to prepare the (*S,S*)-^{TIPS}BPBP-D$_4$ ligand following the standard route for BPBP ligand synthesis (see SI for synthesis details). ^{1}H-NMR characterization indicated that this method led to 90% deuterium

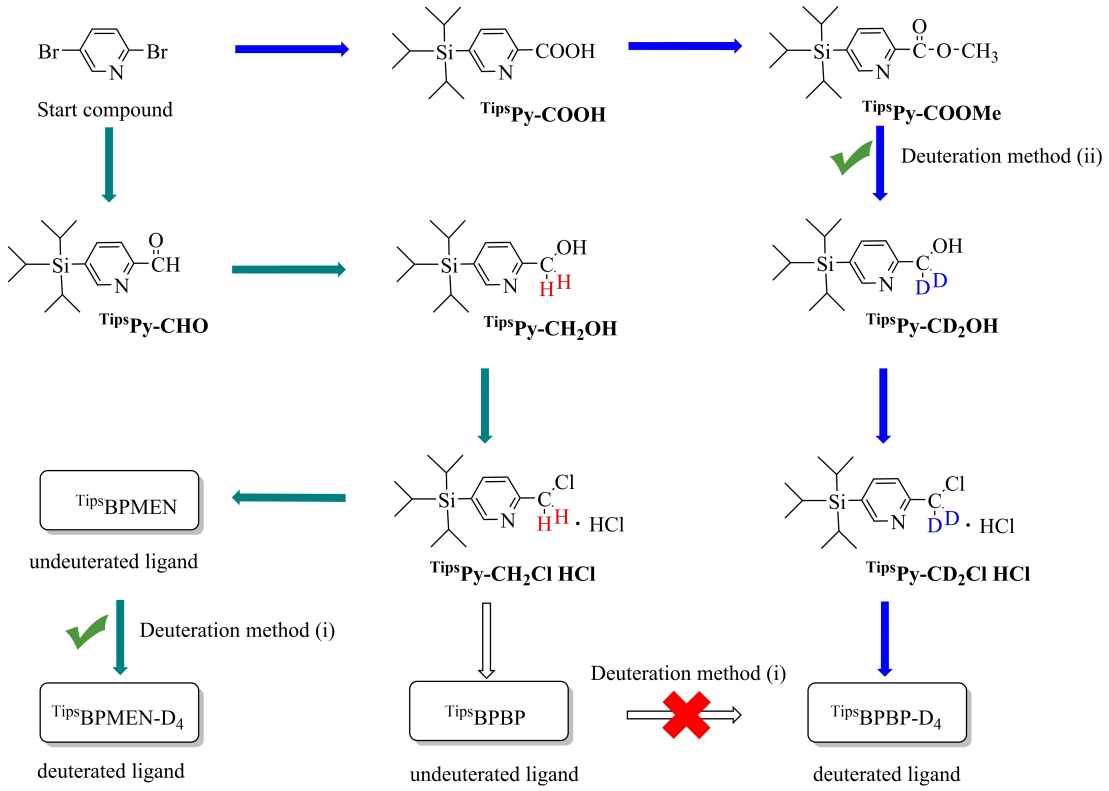


Figure 3. Synthesis routes towards bulky ligands and bulky deuterated ligands. Two deuteration methods, deuteration method i (NaH, green synthesis route) and method ii (using $NaBD_4$, blue synthesis route), are shown.

incorporation at the methylene positions of the ligand (Figure S2). ESI-MS analysis showed the presence of 4 isotopologues of the ligand, ^{TIPS}BPBP-D_4, ^{TIPS}BPBP-D_3H_1, ^{TIPS}BPBP-D_2H_2, and ^{TIPS}BPBP-D_1H_3 in a 65/25/5/5 relative ratio, respectively (Figure S6). After the synthesis of ligands, the corresponding iron triflate complexes were prepared as crystalline solids following reported procedures[13] and the structure of the complexes was confirmed based on HR-MS, ESI-MS and X-ray crystal structure determination. ESI-MS analysis of iron complex [Fe(OTf)$_2$((*S,S*)-^{TIPS}BPBP-D_4)] (**1-TIPS-D$_4$**) showed a molecular ion peak at m/z 747.9, corresponding to the [Fe(Cl)(H$_2$O)((*S,S*)-^{TIPS}BPBP-D_4)]$^+$ ion (calculated m/z 747.4) (Figure S6). The analysis also showed that the relative ratio of isotopologues is the same as found for the free ligand. Accordingly, the relative percentage of the isotopologues is not influenced by the complexation process. ESI-MS analysis of [Fe(OTf)$_2$(^{TIPS}BPMEN-D_4)] (**2-TIPS-D$_4$**) showed a molecular ion peak at m/z 694.5, corresponding to the [Fe(Cl)(H$_2$O)((*S,S*)-^{TIPS}BPMEN-D_4)]$^+$ ion (calculated m/z 695.3). The relative percentage of fully deuterated complex **2-TIPS-D$_4$** was 90% (Figure S7). [Fe(OTf)$_2$((*S,S*)-BPBP-D_4)] (**1-D$_4$**) and [Fe(OTf)$_2$BPMEN-D_4] (**2-D$_4$**) were prepared following a reported procedure.[33a] Based on ESI-MS analysis, the amounts of fully deuterated isotopologues of **1-D$_4$** and **2-D$_4$** are 93% and 88%, respectively (Table S1, details shown in SI).

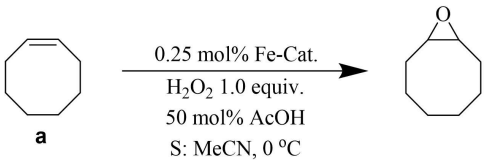
Catalytic Performances.

To investigate the catalytic performance of the deuterated bulky iron complexes, the oxidation of several alkane and olefin substrates was explored using H_2O_2 as the oxidant. In order to benchmark the performances of **1-TIPS-D$_4$** and **2-TIPS-D$_4$**, their catalytic performance was compared to that of the parent complexes devoid of the ligand modifications and to complexes that contain either one of the modifications (see Figure 2).

In line with a previous study from our group,[9,33a] and an optimization of the oxidation conditions (Table S2 and Table S3, SI), we have tested the performance of iron complexes in the epoxidation of *cis*-cyclooctene following catalytic method A, in which a limiting amount of 1.0 equiv. aqueous H_2O_2 was added at once to substrate (1.0 equiv.), iron complex (0.1–1.0 mol%), and AcOH (50 mol%) in MeCN (2 mL) at 0 °C, in order to show the maximum difference in the catalyst lifetime (the general catalytic procedure is shown in the Experimental section, the details on catalytic method A–E are provided in the SI). Under this condition, as shown in Table 1, complexes **1** (entry 1.1) and **1-D$_4$** (entry 1.2) generated the epoxide product in 66 and 73% yield, respectively. Notably, complexes **1-TIPS** (entry 1.3) and **1-TIPS-D$_4$** (entry 1.4) produced the epoxide product in 96% yield.

In order to provide a more detailed picture of the catalytic activity of the complexes, the catalyst loading was lowered to 0.1 mol%, while keeping the other reaction parameters the same (Table 2). Under these conditions, complexes **1** (entry 2.1) and **1-D$_4$** (entry 2.2) yield the epoxide product in 10% (12%) to 17% (20%) yield (conversion). For the TIPS-substituted complexes, the yield (conversion) ranges from 20% (23%) to 51% (54%) using non-deuterated bulky catalyst **1-TIPS** (entry 2.3) and deuterated catalyst **1-TIPS-D$_4$** (entry 2.4), respectively. In this case, the yield and conversion increased 2.5-fold for the deuterated analogue **1-TIPS-D$_4$**, showing that deuteration as well as the incorporation of TIPS groups have a significant impact on the epoxidation reaction. Interestingly, by comparing entry 2.2 and entry 2.4, the conversion and yield increased by a factor of 2.7 and 3.0, respectively, upon the incorporation of TIPS groups in deuterated complexes.

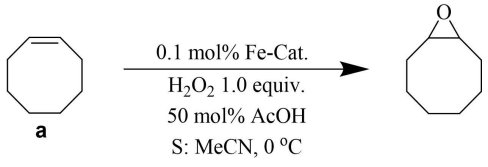
Table 1. Epoxidation of *cis*-cyclooctene using BPBP-based catalysts at 0.25 mol% loading[a]



Entry	Catalyst	Conv. (mol%)	Yield (mol%)	Mass Balance (mol%)[b]
1.1	**1**	71(1)	66(1)	95(0)
1.2	**1-D$_4$**	80(1)	73(2)	93(1)
1.3	**1-TIPS**	100(0)	96(1)	96(0)
1.4	**1-TIPS-D$_4$**	100(0)	96(2)	95(1)

[a] The experiment was carried out by following catalytic Method A. Reported analysis data represent the outcome of at least two independent catalysis experiments and were determined by GC analysis. The numbers in parentheses represent the error of multiple independent experiments. [b] The mass balance (MB) was calculated according to: MB = (1 − Conv. + Yield)×100%.

Table 2. Epoxidation of *cis*-cyclooctene[a]



Entry	Catalyst	Conv. (%)	Yield (%)	Mass Balance (%)[b]
2.1	**1**	12(1)	10(1)	98(0)
2.2	**1-D$_4$**	20(2)	17(2)	97(0)
2.3	**1-TIPS**	23(2)	(3)	97(1)
2.4	**1-TIPS-D$_4$**	54(3)	51(2)	97(1)
2.5	**2**	8(2)	5(2)	97(0)
2.6	**2-D$_4$**	17(1)	13(1)	96(0)
2.7	**2-TIPS**	22(1)	19(1)	97(0)
2.8	**2-TIPS-D$_4$**	40(2)	35(1)	95(1)

[a] The experiment was carried out by following catalytic Method A. Reported analysis data represent the outcome of at least two independent catalysis experiments and were determined by GC analysis. The numbers in parentheses represent the error of multiple independent experiments. [b] The mass balance (MB) was calculated according to: MB = (1 − Conv. + Yield)×100%.

Next, the catalytic epoxidation of *cis*-cyclooctene was examined for a related series of iron complexes based on the BPMEN framework. Under the same reaction conditions, complexes **2** (entry 2.5) and **2-D$_4$** (entry 2.6) showed lower activity compared to their BPBP congeners, but showed an increase in yield (conversion) from 5% (8%) and to 13% (17%) upon deuteration. Complexes **2-TIPS** (entry 2.7) and **2-TIPS-D$_4$** (entry 2.8) showed improved epoxide yields (conversions) of 19% (22%) and 35% (40%), which means a 1.8-fold increase in comparison with the effect of deuteration. Remarkably, a small difference in yield (conversion) between the use of **1-TIPS** (entry 2.3) and **2-TIPS** (entry 2.7) was found in the epoxidation of *cis*-cyclooctene under these conditions. Therefore, these observations point out that the epoxide yield can be improved by deuterating the ligand and by including bulky TIPS groups. More importantly, these findings point to an additive effect on catalysis by including both methylene deuteration and TIPS-functionalization within the same N2Py2 ligand framework.

Kinetic Studies

At this point, kinetic studies were carried out to determine whether the bulky deuterated complexes have a higher intrinsic activity or a longer lifetime compared to the bulky complexes. In a previous investigation, we have shown that deuterated catalysts have a longer lifetime compared to non-deuterated catalysts.[33a] Therefore, the catalytic performance of the four bulky complexes in this study has been followed over time. By using *cis*-cyclooctene as the model substrate, catalytic epoxidation was performed following catalytic method B using 0.1 mol% iron complex. As shown in Figure 4A, when **1-TIPS-D$_4$** was used a product yield of 51% at 54% conversion was attained after 60 min and only minor substrate conversion to epoxide product was observed afterward. In contrast, when **1-TIPS** was employed, substrate conversion stopped after about 40 min at a maximum product yield of 19% at 25% conversion. The initial rate of substrate conversion and product formation (in the first few minutes) seems to be rather similar for the two catalysts. The same kinetic study using **2-TIPS** and **2-TIPS-D$_4$** (Figure 4B) showed a maximum 35% epoxide yield at 40% conversion after 60 min for **2-TIPS-D$_4$**, while a maximum product yield of 19% at 22% conversion was obtained in 40 min using **2-TIPS**. These observations indicate that the deuterated bulky catalysts have a longer lifetime than the non-deuterated bulky catalysts: they continue to convert substrate for longer and, accordingly, give higher epoxide yields. In addition, the performance of **1-TIPS-D$_4$** is significantly better than that of **2-TIPS-D$_4$**, confirming the earlier reported higher catalytic competence of BPBP-type complexes with respect to BPMEN-type complexes. These findings are in agreement with the catalytic results described in Table 2.

Substrate scope in epoxidation

To further show the combined effect of deuteration and bulky pyridine groups, two cycloalkene and three styrene substrates were tested in epoxidation reactions. For cyclohexene and cyclohexanone similar trends in catalytic performance were found as for *cis*-cyclooctene (Table 3); the reactions with deuterated bulky iron-complexes **1-TIPS-D$_4$** and **2-TIPS-D$_4$** showed the best conversions and yields. Based on the reaction conditions used for the epoxidation of *cis*-cyclooctene, different catalyst loadings were applied for the other catalytic epoxidation reactions in order to demonstrate the incremental effect of ligand deuterium and the incorporation of bulky groups, while ultimately achieving high product yields.

As shown in Table 3, the epoxidation of cyclohexene was carried out following catalytic method A using 0.2 mol% catalyst loading. Complexes **1-TIPS-D$_4$** (entry 3.4) and **2-TIPS-D$_4$** (entry 3.8) showed excellent epoxide yields of 91% and 85%,

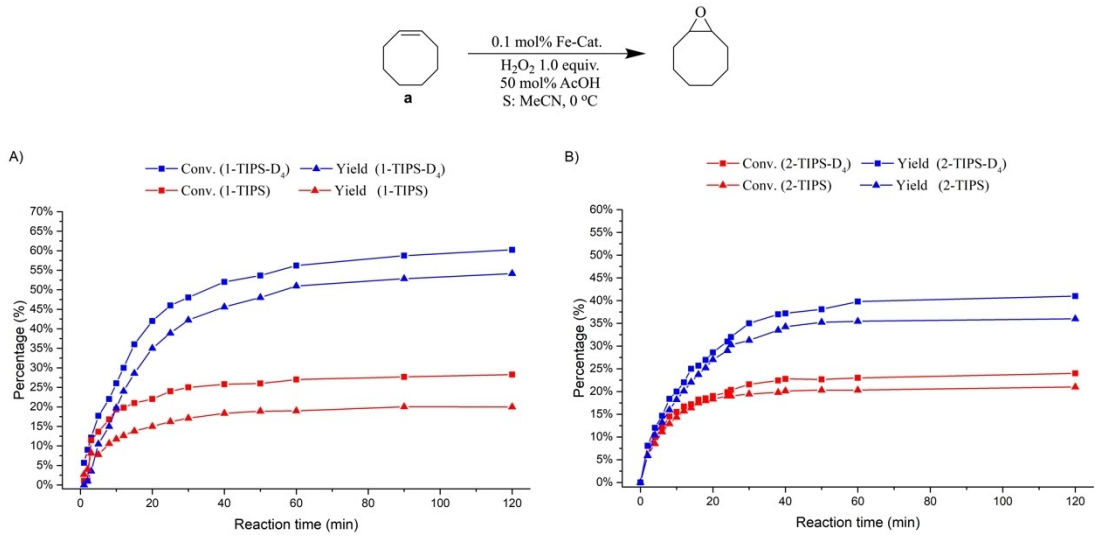
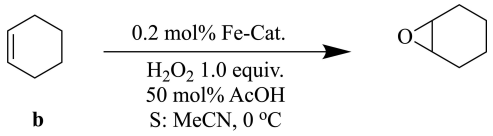


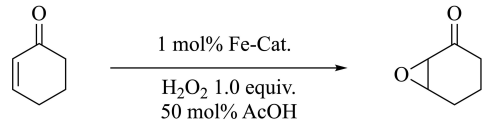
Figure 4. Kinetic profiles of substrate conversion and product formation in the epoxidation of cis-cyclooctene: A) using complexes **1-TIPS** (red traces) and **1-TIPS-D$_4$** (blue traces); B) using complexes **2-TIPS** (red traces) and **2-TIPS-D$_4$** (blue traces).

Table 3. Epoxidation of cyclohexene and cyclohexenone[a]



b

Entry	Cat.	Conv. (%)	Yield (%)	Mass balance (%)[b]
3.1	**1**	31(1)	24(2)	93(1)
3.2	**1-D$_4$**	60(2)	50(1)	90(1)
3.3	**1-TIPS**	75(2)	68(2)	93(1)
3.4	**1-TIPS-D$_4$**	100(0)	91(2)	91(2)
3.5	**2**	30(2)	21(1)	91(1)
3.6	**2-D$_4$**	58(1)	47(1)	89(1)
3.7	**2-TIPS**	88(1)	73(2)	85(1)
3.8	**2-TIPS-D$_4$**	100(0)	85(2)	85(2)



c

Entry	Cat.	Conv. (%)	Yield (%)	Mass balance (%)[b]
3.9	**1**	35(1)	15(3)	80(2)
3.10	**1-D$_4$**	55(1)	34(3)	79(2)
3.11	**1-TIPS**	60(1)	39(3)	79(2)
3.12	**1-TIPS-D$_4$**	90(1)	67(3)	77(2)
3.13	**2**	30(2)	13(2)	83(0)
3.14	**2-D$_4$**	40(1)	13(3)	73(2)
3.15	**2-TIPS**	42(1)	19(2)	77(1)
3.16	**2-TIPS-D$_4$**	63(1)	38(2)	75(1)

[a] The experiment was carried out by following catalytic Method A. Reported analysis data represent the outcome of at least two independent catalysis experiments. The results were determined by GC analysis. The numbers in parentheses represent the error of multiple independent experiments. [b] The mass balance (MB) was calculated according to: MB = (1−Conv.+Yield)×100%.

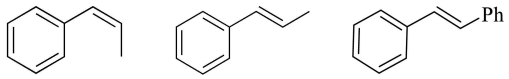
respectively, at full substrate conversion. The yield and conversion for this substrate build up incrementally upon the introduction of deuterons and bulky groups, starting at 24% yield at 30% conversion when **1** was used as a catalyst for the BPBP-based complexes (entries 3.1–3.4), and at only 21% yield at 30% conversion when **2** was used for the BPMEN-based complexes (entries 3.5–3.8). In the epoxidation of cyclohexene, the introduction of bulky pyridine groups seems to have a more pronounced effect than the deuteration of the ligand; compare entries 3.2.and 3.3. and entries 3.6 and 3.7.

Similarly, in the epoxidation of cyclohexenone, we found that the highest yield (67%) and conversion (90%) was obtained using 1.0 mol% **1-TIPS-D$_4$** (entry 3.12). In addition, complex **2-TIPS-D$_4$** exhibited the highest yield (conversion) of 38% (63%) in the series of BPMEN complexes (entries 3.13–3.16). Despite the higher catalyst loading (1 mol%), lower yields and conversations were obtained than in the epoxidation of cyclohexene using the same complexes. This observation is related to the electron-poor character of the C=C double bond in cyclohexenone. In addition, the mass balances obtained in the epoxidation of cyclohexenone are rather low, which we attributed to the work-up procedure. The results on the catalytic epoxidation of these cyclic aliphatic alkenes corroborate that a combination of ligand deuteration and bulky pyridine groups leads to an incremental increase in the catalytic performance of the non-heme iron catalysts in epoxidation reactions.

Next, the catalytic epoxidation of three styrenes was studied following catalytic method A using 0.5 mol% catalyst loading. As shown in Table 4, in the epoxidation of *cis*- and *trans*-β-methylstyrene, the best results in terms of 17% epoxide yield at 37% conversion and 20% epoxide yield at 38% conversion were obtained when using **1-TIPS-D$_4$** as the catalyst. Additionally, in the epoxidations of *cis*- and *trans*-β-methylstyrene using BPMEN-based iron catalysts, **2-TIPS-D$_4$** provided the best results in terms of 10% yield at 25% conversion for *cis*-β-methylstyrene and 17% yield at 36% conversion for *trans*-β-methylstyrene. In each case, full retention of the alkene configuration was found in the epoxide products, as shown by the mass balance indicated in Table 4. Based on these observations, we can conclude that although the yields and conversions under the employed reaction conditions are not very high and the mass balance was slightly decreased using deuterated bulky complexes, the bulky deuterated catalysts again showed the best performance amongst both series of complexes.

In the catalytic epoxidation of *trans*-stilbene a different trend in the catalytic performance of the complexes was found

Table 4. The catalytic epoxidation of styrenes.[a]



Catalyst	*Cis*-β-methylstyrene Conv./Yield/MB[b]	*Trans*-β-methylstyrene Conv./Yield/MB	*Trans*-stilbene Conv./Yield/MB
1	15%/5.1%/90%	19%/5.8%/87%	66%/58%/92%
1-D$_4$	19%/8.2%/91%	24%/10%/86%	94%/90%/96%
1-TIPS	28%/14%/86%	30%/16%/86%	58%/49%/91%
1-TIPS-D$_4$	37%/17%/80%	38%/20%/82%	80%/72%/92%
2	11%/3.1%/92%	10%/5.1%/95%	44%/35%/91%
2-D$_4$	15%/7.6%/92%	23%/9.6%/87%	62%/51%/89%
2-TIPS	21%/9.2%/88%	24%/11%/87%	35%/26%/91%
2-TIPS-D$_4$	25%/10%/85%	36%/17%/81%	44%/37%/93%

[a] The experiment was carried out by following catalytic Method A. Reported analysis data represent the outcome of at least two independent catalysis experiments. The results were determined by GC analysis. Full retention of alkene configuration was found in the epoxide products. [b] The mass balance (MB) was calculated according to: MB = (1−Conv.+Yield)×100%.

in comparison to the trends in epoxidation reactions found thus far in this study (see Table 4). In this case, the best result was obtained using deuterated non-bulky complexes **1-D$_4$** (90% yield at 94% conversion) and full retention of the *trans*-configuration was found for the epoxidation product. It was found that an increase in both yield and conversion was observed upon the introduction of deuterium atoms on the ligand scaffold, but the introduction of bulky silyl groups at the pyridine donor groups resulted in a decrease in yield and conversion in the epoxidation of *trans*-stilbene. Similar observations for the catalytic epoxidation of *trans*-stilbene were also made for the series of BPMEN complexes (see Table 4). These results suggest that steric hindrance becomes a limiting factor when combining a bulky substrate like *trans*-stilbene and catalysts that provide a bulky C_2-symmetric ligand envelope, resulting in a lower catalytic competence of the bulky complex.

Interestingly, during experiments involving *cis*- and *trans*-β-methylstyrene reaction mixtures developed a deep-blue color. After filtration of the reaction mixtures through a short plug of silica gel to remove the catalyst during the workup, it was found that this blue color stayed at the top of the silica plug and turned to yellow after being exposed to air for a few minutes. We have observed similar color formations in a recent study on aromatic oxidation reactions and attribute these to the formation of phenolate complexes.[20] Accordingly, these colors may be indicative of concurrent aromatic oxidation reactions taking place alongside the epoxidation reactions. The occurrence of such side-reactions may impart the overall efficiency of the epoxidation reactions.

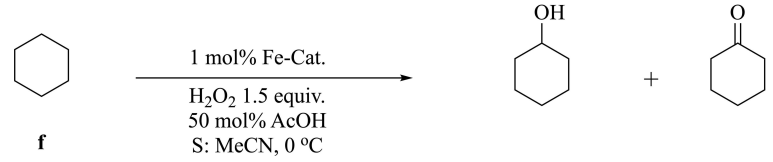
Aliphatic oxidation

Next, we explored the catalytic activity of the bulky deuterated catalysts in the oxidation of aliphatic C–H bonds in cyclohexanes. In the biochemistry and biomedical fields, cyclohexane moieties represent a basic structural unit that is commonly found in drugs and biological metabolites;[13,36,37] examples include artemisinin and androsterone. For this reason, the regio- and stereo-selective oxidation of aliphatic C–H bonds in cyclohexane structures has attracted a lot of attention in the field of organic synthesis. Therefore, we explored the oxidation of a series of standard cyclohexane substrates to establish the catalytic activity of bulky deuterated catalysts toward these substrates and to study the regio-selectivity of these catalysts in terms of their ability to discriminate between 3° and 2° C–H bonds in the substrates.

Reviewing the literature, most studies use 1–5 mol% of iron catalyst for aliphatic oxidation reactions. For example, in the oxidation of *trans*-1,2-dimethylcyclohexane (*trans*-DMCH),[13,14,18,33a] 3 mol% of catalyst was used in the presence of AcOH (1.5 equiv.) in MeCN and the H_2O_2 oxidant (1.2 to 2 equiv.) was delivered over 30 min. Under these oxidation conditions, using complexes **1** and **1-TIPS** give 37% (65%) to 55% (87%) combined yield (conversion) of the cyclohexanol and cyclohexanone products, respectively.[13] Notably, only 23% total yield at 27% conversion was obtained when 1 mol% of complex **1** was used for the oxidation of *trans*-DMCH.[14] In our current study, we have used 1 mol% catalyst loading since this would allow us to properly monitor the anticipated incremental activity within the series of iron complexes.

Accordingly, the catalytic oxidation of cyclohexane was explored following catalytic method A using 1.5 equiv. aqueous H_2O_2 and 1 mol% of catalyst (Table 5). For all eight catalysts, the cyclohexanone product was obtained as the major product

Table 5. Oxidation of Cyclohexane.[a]



Entry	Catalyst	Conv. (%)	Yield (%) Ketone/alcohol	K/A[b]	Total Yield (%)	Mass Balance [c] (%)
5.1	**1**	35(1)	1.9/1.5	1.3	3(1)	68(0)
5.2	**1-D$_4$**	41(1)	9.6/6.9	1.4	16(2)	75(1)
5.3	**1-TIPS**	37(1)	8.5/4.4	1.9	13(1)	76(0)
5.4	**1-TIPS-D$_4$**	49(2)	16/8.4	1.9	24(1)	75(2)
5.5	**2**	34(1)	2.1/1.6	1.3	4(2)	70(1)
5.6	**2-D$_4$**	39(2)	4.6/3.5	1.3	8(2)	69(0)
5.7	**2-TIPS**	39(1)	6.7/4.2	1.6	11(2)	72(1)
5.8	**2-TIPS-D$_4$**	42(1)	11/6.9	1.6	18(1)	76(0)

[a] The experiment was carried out by following catalytic Method A. Reported analysis data represent the outcome of at least two independent catalysis experiments. The results were determined by GC analysis. The numbers in parentheses represent the error of multiple independent experiments. [b] Ration of ketone and alcohol products. [c] The mass balance (MB) was calculated according to: MB = (1 − Conv. + total Yield)×100%.

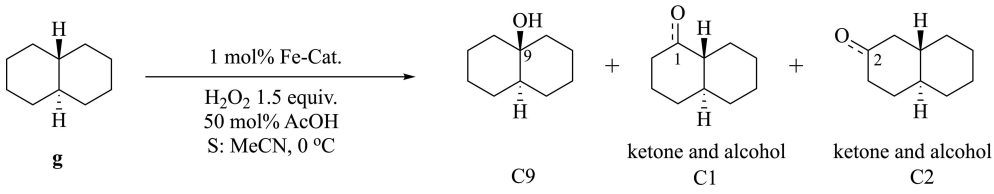
next to cyclohexanol (entry 5.1 till 5.8). Reactions using the deuterated bulky catalysts **1-TIPS-D$_4$** (entry 5.4) and **2-TIPS-D$_4$** (entry 5.8) give the highest yield (conversion), 24% (49%) and 18% (42%), respectively, in the series of BPBP and BPMEN complexes. Reactions using a bulky catalyst (e.g. **1-TIPS** and **1-TIPS-D$_4$**) give a large K/A ratio and a better mass balance than reactions using a non-bulky catalyst, which is in agreement with previous results from our group.[14]

Similar to our observations for the epoxidation reactions, cyclohexane oxidation reactions using BPMEN-type catalysts provide lower product yields than reactions using BPBP-type catalysts. In addition, lower K/A ratios were observed for the BPMEN-based catalysts. Overall, the data shown in Table 5 point to an increased catalytic activity in C–H oxidation for bulky deuterated catalysts and an incremental effect on catalysis of ligand deuteration and bulky pyridine substituents.

To further investigate catalyst lifetimes in aliphatic oxidation reactions, as well as the site selectivity, *trans*-decaline, *trans*-1,2-dimethyl-cyclohexane (see SI) and *cis*-1,2-dimethyl-cyclohexane, and adamantane were tested under the same catalytic conditions (Tables 6–8). In the oxidation of *trans*-decaline, complexes **1** (entry 6.1) and **1-D$_4$** (entry 6.2) gave 14% (19%) to 28% (37%) yield (conversion), showing a 2-fold improvement in yield and conversion, whereas the site-selectivity (3°/2° ratio) remained at 2.2. Similarly, between complexes **1-TIPS** (entry 6.3) and **1-TIPS-D$_4$** (entry 6.4) the yield (conversion) improved from 38% (45%) to 55% (60%) and these bulky catalysts gave a lower 3°/2° product ratio at 0.71 and 0.75, respectively. Accordingly, both deuteration and incorporation of steric bulk lead to an increase in catalyst lifetime, whereas only the incorporation of bulky groups results in different regioselectivity. These effects are incremental once combined, as in **1-TIPS-D$_4$**. Very similar trends were observed for the oxidation of *trans*-decaline using the BPMEN-type complexes (entries 6.5–6.8). The best yield (conversion) of 38% (43%) and 3°/2° product ratio at 0.68 was observed when using **2-TIPS-D$_4$** as the catalyst (entry 6.8). Earlier results showed a 58% total yield of *trans*-decaline oxides at 83% conversion when using 3 mol% complex **1-TIPS** using the slow oxidant addition protocol.[13] Now, our data show that using only 1 mol% of deuterated bulky complex **1-TIPS-D$_4$** gives a similar total yield and an excellent mass balance even though the oxidant was added at once.

The ability of the catalysts to differentiate between 2° and 3° C–H bonds was further explored in the oxidation of *trans*-1,2-dimethylcyclohexane (*trans*-DMCH, results are shown in Table S4, SI) and *cis*-1,2-dimethylcyclohexane (*cis*-DMCH) (Table 7). When using **1- TIPS-D$_4$** in the oxidation of these substrates using our standard conditions, *trans*-DMCH, containing only axial tertiary sites, affords the highest, yet medium yield (43% total yield) with the lowest 3°/2°ratio (1.4) at 65% conversion (entry S4.4, SI). In contrast, *cis*-DMCH, containing both axial and equatorial tertiary sites, undergoes preferential tertiary hydroxylation to result in 59% total yield (5.1 3°/2°ratio) at 79% conversion (entry 7.4). Additionally, the same trends were found in the oxidation by using iron complexes based on the BPMEN ligand. Another interesting observation from these experiments is the rather similar performance in *trans*-DMCH oxidation by **2-TIPS-D$_4$** in comparison to **1-TIPS-D$_4$** (entries S4.8 and S4.4, SI). In contrast, the overall performance in *cis*-DMCH oxidation by **2-TIPS-D$_4$** is significantly lower than by **1-TIPS-D$_4$**. This could be caused by a combination of different steric effects on site selectivity in the selective oxidation of substrates with enhanced conformational rigidity.[26,38]

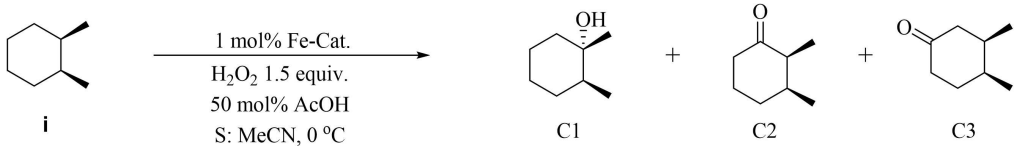
Table 6. Oxidation of *trans*-decaline.[a]



Entry	Catalyst	Conv. (%)	Yield. (%) C9/C1/C2	Yield (%)	3°/2°[b]	Mass Balance (%)[c]
6.1	**1**	19(1)	3/6/5	14(1)	2.2	95(0)
6.2	**1-D$_4$**	37(1)	6/12/10	28(2)	2.2	91(1)
6.3	**1-TIPS**	45(1)	3/15/20	38(2)	0.71	93(1)
6.4	**1-TIPS-D$_4$**	60(1)	5/20/30	55(2)	0.75	95(1)
6.5	**2**	17(1)	2/6/5	13(1)	1.5	96(0)
6.6	**2-D$_4$**	28(2)	3/9/7	19(2)	1.5	91(0)
6.7	**2-TIPS**	30(2)	2/10/12	24(2)	0.73	94(0)
6.8	**2-TIPS-D$_4$**	43(1)	3/15/20	38(2)	0.68	95(1)

[a] The experiment was carried out by following catalytic Method A. Reported analysis data represent the outcome of at least two independent catalysis experiments. The results were determined by GC analysis. The numbers in parentheses represent the error of multiple independent experiments. [b] 3°/2° = ratio between tertiary C–H and secondary C–H oxidation products. [c] The mass balance (MB) was calculated according to: MB = (1 − Conv. + total Yield)×100%.

Table 7. Oxidation of *cis*-dimethylcyclohexane.[a]

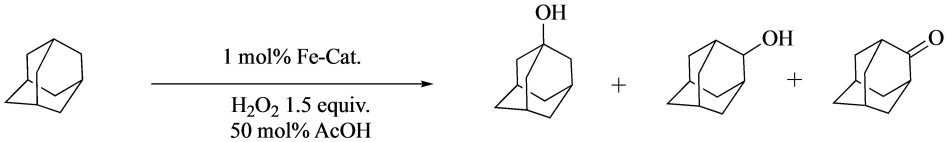


i C1 C2 C3

Entry	Catalyst	Conv. (%)	Yield (%) C1/C2/C3	Yield (%)	3°/2°[b]	Mass Balance (%)[c]
7.1	**1**	31(2)	12/0/2	14(2)	24	83(2)
7.2	**1-D$_4$**	43(1)	18/0/3	21(1)	24	78(1)
7.3	**1-TIPS**	66(2)	30/8/14	52(1)	5.5	86(2)
7.4	**1-TIPS-D$_4$**	79(3)	33/10/16	59(2)	5.1	80(3)
7.5	**2**	33(2)	10/1/1	12(1)	20	79(2)
7.6	**2-D$_4$**	40(1)	15/1/2	18(2)	20	78(1)
7.7	**2-TIPS**	41(1)	10/3/5	18(1)	5.0	77(0)
7.8	**2-TIPS-D$_4$**	50(1)	14/4/7	25(3)	5.1	75(2)

[a] The experiment was carried out by following catalytic Method A. Reported analysis data represent the outcome of at least two independent catalysis experiments and were determined by GC analysis. The numbers in parentheses represent the error of multiple independent experiments. [b] 3°/2° = ratio between tertiary C–H and secondary C–H oxidation products. [c] The mass balance (MB) was calculated according to: MB = (1 − Conv. + total Yield)×100 %.

Table 8. Oxidation of Adamantane.[a]



j C1 C2-ol C2-one

Entry	Catalyst	Conv. (%)	Yield (%) **C1**/C2-ol/C2-one	Total Yield (%)	3°/2°[b]	Mass balance (%)[c]
8.1	**1**	17(2)	7.9/1.0/0.9	10(2)	12	93(0)
8.2	**1-D$_4$**	29(1)	16/3.0/1.1	20(2)	12	91(1)
8.3	**1-TIPS**	35(1)	15/2.2/3.1	20(2)	8.6	85(1)
8.4	**1-TIPS-D$_4$**	44(2)	20/3.0/4.1	27(1)	8.6	83(1)
8.5	**2**	13(1)	6.2/1.1/1.0	8.3(1)	8.9	95(0)
8.6	**2-D$_4$**	20(3)	9.1/2.1/0.9	12(2)	9.1	92(2)
8.7	**2-TIPS**	19(3)	8.0/1.2/2.1	11(2)	7.3	92(2)
8.8	**2-TIPS-D$_4$**	33(2)	16/2.6/3.9	23(1)	7.4	90(1)

[a] The experiment was carried out by following catalytic Method A. Reported analysis data represent the outcome of at least two independent catalysis experiments and were determined by GC analysis. The numbers in parentheses represent the error of multiple independent experiments. [b] 3°/2° = ratio between tertiary C–H and secondary C–H oxidation products. [c] The mass balance (MB) was calculated according to: MB = (1 − Conv. + total Yield)×100 %.

Similar results were obtained for the oxidation of adamantane, as shown in Table 8. The best conversion (44 %) and yield (27 %) were obtained by using **1-TIPS-D$_4$** (entry 8.4), as a result of an incremental increase in catalytic performance in the series of complexes. In terms of the regioselectivity of the reaction, the 3°/2° ratio decreased from 12 for **1-D$_4$** (entry 8.2) and 8.9 for **2-D$_4$** (entry 8.6), to 8.6 for **1-TIPS-D$_4$** (entry 8.4) and 7.4 for **2-TIPS-D$_4$** (entry 8.8), respectively. For the adamantane substrate, no matter which catalyst was used, the tertiary C–H oxide was always obtained as the main product, which is in line with observations in the literature.

Overall, the oxidation of five aliphatic cyclohexane substrates provided very consistent trends in the catalytic ability of the iron complexes in terms of substrate conversion, product yield, and site-selectivity of the reactions. These trends point out that the use of bulky ligands greatly improves catalyst activity and the ability to oxidize less encumbered secondary C–H bonds based, and that an incremental effect on conversion and yield can be achieved by deuteration of the ligand.

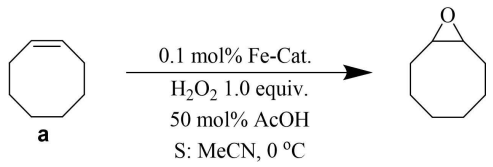
Catalytic performance using the slow oxidant addition protocol

According to the above results, the catalyst lifetime of deuterated bulky catalysts is significantly increased. In the catalytic protocol used in the studies to probe lifetime and performance of these catalysts, we were able to obtain almost 100% yields in the epoxidation of some substrates despite that the oxidant was added at once. Examples include the epoxidation of *cis*-cyclooctene (entry 1.4), cyclohexene (entry 3.4), and cyclohexanone (3.16). Compared to the literature, even if the oxidant was added slowly in the presence of 0.25 mol% of catalyst **1** and 1.5 mol% carboxylic acid, the epoxidation of *cis*-cyclooctene only reached 75% yield at 84% conversion.[33a] In our current study, the use of 0.25 mol% **1-TIPS-D$_4$** showed 96% yield and 100% conversion even though we added the oxidant at once (entry 1.4). Nevertheless, we were interested to investigate if the efficiency of C–H oxidation and epoxidation using the deuterated bulky catalysts could be further improved by adding the oxidant slowly to the reaction mixture. Accordingly, we have explored the catalytic performance for the BPBP-based complexes used in this study using a slow oxidant addition protocol. To this end, we initially investigated the epoxidation of *cis*-cyclooctene (Table 9) following the catalytic method C (slow oxidant addition reaction protocol, details are shown in the SI) using 1.0 equiv. H_2O_2 and 0.1 mol% catalyst loading.

Under these reaction conditions, a remarkable and incremental improvement in catalytic performance was found for bulky and deuterated complexes, reaching the highest yield of 83% at 95% conversion using catalyst **1-TIPS-D$_4$** (entry 9.4). The yield obtained when using only 0.1 mol% of **1-TIPS-D$_4$** increased more than 9-fold at a more than 4-fold increase in conversion going from **1** to **1-TIPS-D$_4$** (entries 9.1. to 9.4). Overall, the slow oxidant addition protocol provides a 1.6-fold higher yield in *cis*-cyclooctene epoxidation with **1-TIPS-D$_4$**, compared to the catalytic protocol in which the oxidant was added at once (compare entry 2.4 and entry 9.4).

Next, the oxidation of *cis*-DMCH and adamantane was investigated using the same slow addition protocol catalytic method C, but in the presence of 1 mol% of catalyst (Tables 10 and 11). As shown in Table 10, the trends in product yields and conversion for the oxidation of *cis*-DMCH are similar to our previous observations (Table 7), and the total product yield and substrate conversion increased because of the slow addition protocol of the oxidant. For the best catalyst in this series, **1-TIPS-D$_4$**, both the yield and conversion increased when comparing the instant oxidant addition (entry 7.4) and slow oxidant addition protocols (entry 10.4); *i.e.* the combined yield of oxidized products increased from 59% to 73% at a conversion increase from 79% to 97%. Between these two protocols, the 3°/2° product ratio remained at 5.1, showing that the catalyst site-selectivity is barely affected by the change in oxidant addition protocol. Compared with the results reported in the literature,[12,18,39,40] for instance the 45% total yield at 65% conversion that was obtained with 1 mol% iron complex based on the (*S,S*)-^{TIPS}BPBI ligand[14] (see Figure 1), the performance of

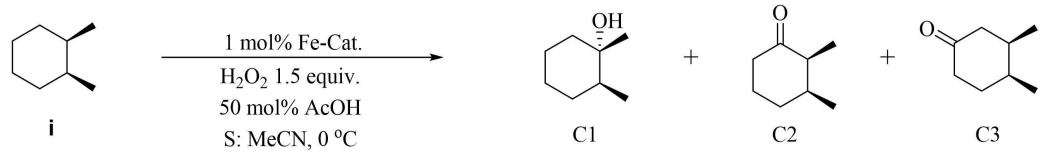
Table 9. Epoxidation of *cis*-cyclooctene (slow oxidant addition protocol).[a]



Entry	Catalyst	Conv. (%)	Yield (%)	Mass Balance (%)[b]
9.1	**1**	22(2)	9(2)	87(0)
9.2	**1-D$_4$**	44(1)	30(2)	86(1)
9.3	**1-TIPS**	54(2)	40(1)	86(1)
9.4	**1-TIPS-D$_4$**	95(2)	83(1)	88(1)

[a] The experiment was carried out by following catalytic Method C. Reported analysis data represent the outcome of at least two independent catalysis experiments and were determined by GC analysis. The numbers in parentheses represent the error of multiple independent experiments. [b] The mass balance (MB) was calculated according to: MB = (1 − Conv. + Yield)×100%.

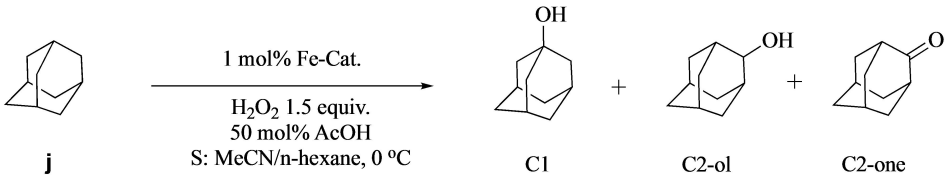
Table 10. Oxidation of *cis*-dimethylcyclohexane using a slow oxidant addition protocol.[a]



Entry	Catalyst	Conv.(%)	Yield (%) C1/C2/C3	Yield (%)	3°/2°[b]	Mass Balance (%)[c]
10.1	**1**	49(2)	24/1.2/2.8	28(2)	24	83(2)
10.2	**1-D$_4$**	60(1)	30/1.5/3.7	35(1)	23	78(1)
10.3	**1-TIPS**	86(2)	39/10/17	66(2)	5.8	80(0)
10.4	**1-TIPS-D$_4$**	97(3)	41/12/20	73(2)	5.1	76(1)

[a] The experiment was carried out by following catalytic Method C. Reported analysis data represent the outcome of at least two independent catalysis experiments and were determined by GC analysis. The numbers in parentheses represent the error of multiple independent experiments. [b] 3°/2° = ratio between tertiary C–H and secondary C–H oxidation products. [c] The mass balance (MB) was calculated according to: MB = (1 − Conv. + total Yield)×100%.

Table 11. Oxidation of Adamantane using a slow oxidant addition protocol.[a]



j C1 C2-ol C2-one

Entry	Catalyst	Conv. (%)	Yield (%) C1/C2-ol/C2-one3	Total Yield (%)	3°/2°[b]	Mass balance (%)[c]
11.1	**1**	37(2)	17/2.3/1.8	21(2)	12	84(0)
11.2	**1-D_4**	49(1)	27/4.8/1.8	34(2)	12	85(1)
11.3	**1-TIPS**	58(1)	24/3.5/5.0	33(2)	8.5	75(1)
11.4	**1-TIPS-D_4**	70(2)	32/4.8/6.6	43(1)	8.4	73(1)

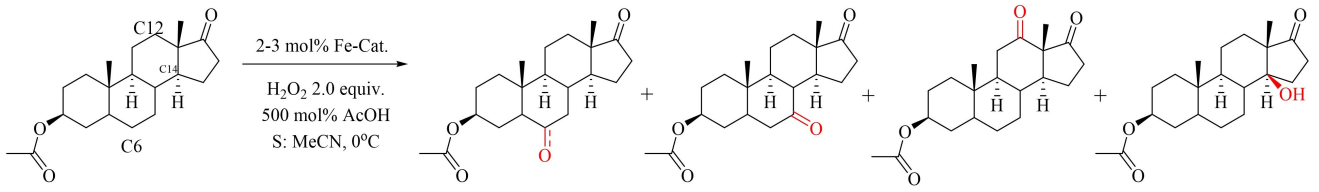
[a] The experiment was carried out by following catalytic Method C. Reported analysis data represent the outcome of at least two independent catalysis experiments and were determined by GC analysis. The numbers in parentheses represent the error of multiple independent experiments. [b] 3°/2° = ratio between tertiary C–H and secondary C–H oxidation products. [c] The mass balance (MB) was calculated according to: MB = (1 − Conv. + total Yield)×100 %.

1-TIPS-D_4 using the slow addition protocol represents the highest values reported to date using a non-heme iron catalyst at 1 mol% loading.

Moreover, Table 11 shows that similar observations were made for the oxidation of adamantane. Complex **1-TIPS-D_4** gives the highest yield (43%) and conversion (70%) at a 3°/2° product ratio of 8.4 in the slow oxidant addition protocol (entry 11.4). Deuteration of the ligand gives an improvement of the catalytic lifetime to obtain a higher total yield, and the effect of the TIPS groups enhanced the steric effect to increase the site-selectivity and the total yield (conversion). However, no matter whether the oxidant was added at once or added in 30 min, the site-selectivity of C–H is not affected and all catalysts perform better in the slow addition protocol (compare Tables 8 and 11).

To investigate whether the incremental improvements outlined above also translate to more challenging substrates, we selected *trans*-androsterone acetate as substrate, because of its complex geometrical structure and its biological importance.[1,13,14,18] The oxidation of this substrate was studied following catalytic method D using the two bulky complexes. When the oxidant was added at once in the presence of 3 mol% catalyst loading, oxidation proceeded with a low conversion (21% and 30%) and a low yield (4% and 10%) (Table 12, entries 12.1 and 12.2). For this challenging substrate, catalyst decomposition at higher oxidant concentrations therefore seems competitive with substrate conversion. Changing to

Table 12. Oxidation of trans-androsterone acetate.



k C6 (C6-ol & C6-one) C7-one C12-one C14-ol Not found

Entry	Catalyst	Catalyst loading (mol%)	Conv. (%)	Yield (%) C6/C7/C12/C14	Total Yield (%)	Mass balance (%)[c]
12.1[a]	**1-TIPS**	3	21(1)	4/0/0/0	4(1)	83(0)
12.2[a]	**1-TIPS-D_4**	3	30(1)	10/0/0/0	10(1)	80(0)
12.3[b]	**1-TIPS**	3	83(2)	38/11/11/0	60(1)	72(1)
12.4[b]	**1-TIPS-D_4**	3	87(3)	39/13/12/0	59(2)	72(1)
12.5[b]	**1-TIPS**	2	55(2)	22/7/7/0	36(2)	81(0)
12.6[b]	**1-TIPS-D_4**	2	81(2)	35/11/10/0	56(1)	75(1)

[a] The experiment was carried out by following catalytic Method D. [b] The experiment was carried out by following catalytic Method E. Reported analysis data represent the outcome of at least two independent catalysis experiments. The results were determined by GC analysis. The numbers in parentheses represent the error of multiple independent experiments. [c] The mass balance (MB) was calculated with the following function: MB = (1 − Conv. + total Yield)×100 %.

a slow addition protocol (30 min by syringe pump, catalytic method E, see SI), but keeping all other reaction parameters the same, lead to a significant increase in reaction efficiency. Under these conditions, total product yields up to 60% were achieved for both **1-TIPS** and **1-TIPS-D$_4$** at good conversions of 83% and 87%, respectively, providing 38–39% of C6 ketone and alcohol products (entries 12.3 and 12.4). These results are in agreement with our earlier observations[13] and show no significantly enhanced performance for the deuterated complex. However, lowering the catalyst loading to 2 mol% resulted in significantly different catalytic performances between the use of the two complexes. The use of **1-TIPS-D$_4$** maintained a good total yield of 56% at 81% conversion (entry 12.6), while the performance of **1-TIPS** exhibited a significant decrease to a 36% yield at 55% conversion (entry 12.5). This indicates that **1-TIPS-D$_4$** demonstrated better performance than **1-TIPS** due to the longer catalyst lifetime of deuterated complexes. It is worth noticing that even at a loading of 2 mol% (entry 12.6) deuterated bulky complex **1-TIPS-D$_4$** showed only a minor decrease in performance compared to the reaction using 3 mol% catalyst loading (entry 12.4), to reach a total product yield of 56% at 81% substrate conversion. For both complexes, the ratio of oxidation products remained constant, providing C6 oxidation products as the major products. Therefore, a good yield (conversion) could be obtained by using only 2 mol% of deuterated bulky catalyst **1-TIPS-D$_4$**. It certifies that **1-TIPS-D$_4$** is an efficient catalyst with a good catalytic lifetime and high site-selectivity.

Overall, based on these observations we can conclude that the efficiency performance of the deuterated bulky catalysts can be further enhanced by a slow oxidant addition protocol. Compared with the protocol of adding the oxidant at once, the same trends in terms of conversion, yield and regioselectivity were obtained using the slow oxidant addition protocol.

Conclusions

In summary, this study has combined the advantages of two earlier reported ligand modification strategies for improving the performance of bio-inspired non-heme iron oxidation catalysts, *i.e.* the introduction of bulky TIPS-groups at the 5-position of the pyridine donors and the deuteration of the benzylic positions in the ligand. Extended investigations on a variety of epoxidation and C–H oxidation reactions have shown that, remarkably, these ligand modification strategies work in concert when applied to the same ligand scaffold. Based on our kinetic and catalysis studies, the catalysts that combine the two strategies, **1-TIPS-D$_4$** and **2-TIPS-D$_4$**, demonstrate a notable and incremental enhancement in lifetime and efficiency in these reactions. In comparison to the catalysts which only applied one or none of the two strategies, the combined catalysts consistently exhibit excellent performance in several cases that outperform literature examples. From a broad screening of substrates, it was shown once more that the TIPS-modified bulky catalysts show very high regioselectivity. Furthermore, it is noteworthy that the utilization of the slow oxidant addition protocol contributes to further enhancing the performance of catalyst **1-TIPS-D$_4$** compared to non-functionalized catalysts in catalytic oxidation. Overall, a higher product yield and regioselectivity can be obtained using a (significantly) lower amount of bulky deuterated catalysts.

Based on these findings, the development of other deuterated bulky catalysts derived from other (chiral) backbones may aid the development of (enantioselective) oxidation catalysis in general and can provide the tools for catalytic oxidation protocols of more challenging substrates, e.g. in late-stage functionalization of pharmaceuticals. In addition, the combined strategy of ligand deuteration and the inclusion of bulk can be beneficial in synthetic chemistry beyond the realm of oxidation catalysis.

Experimental Section

The preparation of ligands and complexes

The synthesis of the bulky precursor ^{TIPS}Py-$CD_2Cl\cdot HCl$ and ^{TIPS}Py-$CH_2Cl\cdot HCl$ were prepared according to literature procedures.[4,5,13] The target ligands were synthesized according to reported procedures.[5,13,34] The final complexes **1-TIPS**, **1-TIPS-D$_4$**, **2-TIPS** and **2-TIPS-D$_4$** were synthesized by adding a suspension of Fe-$(OTf)_2\cdot 2CH_3CN$ (0.19 mmol) to a vigorously stirred solution of ligand (0.19 mmol) in dry THF (2 mL). The reaction mixture was stirred at room temperature overnight. Then, the complex was precipitated as a yellow precipitate by adding diethyl ether (1 mL) dropwise. At this point, the supernatant was carefully pipetted off, and the remaining solid was dried under reduced pressure, resulting in the crude complex as a powder. The resulting solid was recrystallized by slow diethyl ether diffusion into a DCM solution. All the procedures of complexation and recrystallization are carried out under an inert atmosphere, using standard Schlenk techniques or in a nitrogen-filled M. Braun glovebox. Full synthetic and analytical details are presented in the SI.

General catalytic method

A 20 mL vial was charged with the substrate (1.0 equiv.), iron complex (0.1–3.0 mol%), and AcOH (50 mol%) in of MeCN (2 mL). The vial was cooled to 0 °C for 5 min in a water/ice bath while stirring. At this point, H_2O_2 solution in MeCN (1.0–1.5 equiv., 1.0 M, diluted from a 35% H_2O_2 aqueous solution) was added at once/slowly. After that, the resulting solution was stirred at 0 °C for an extended time, the total reaction time was 60 min. Then, internal standard (0.1 mL, 0.1 mmol, 1 M stock solution of nitrobenzene in MeCN) was added to the mixture. The solution was diluted with Et_2O to precipitate the iron catalyst, and the solution was filtered through a silica plug. The filtrate was analyzed by GC. Full details on the catalytic procedures are presented in the SI.

Supporting Information

The data that support the findings of this study are available in the Supporting Information of this article.[4,5,13,34,41–46]

Author Contributions

F.L., D.L.J.B. and R.J.M.K.G. devised the project and designed experiments. F.L., I.M. and B.K. performed the experiments and analyzed the data. F.L. and R.J.M.K.G. wrote the manuscript. M. L. performed X-ray crystal structure determination. All authors provided comments on the experiments and manuscript during its preparation.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: bioinspired catalysis · iron complexes · deuterated ligands · bulky ligands · catalyst lifetime · catalytic oxidation

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