Journal of Catalysis 283 (2011) 55–67

Contents lists available at ScienceDirect

Journal of Catalysis

journal homepage: www.elsevier.com/locate/jcat

Methyltrioxorhenium-catalyzed oxidation of pseudocumene for vitamin E synthesis: A study of solvent and ligand effects

Mónica Carril [a], Philipp Altmann [a], Markus Drees [a], Werner Bonrath [b], Thomas Netscher [b], Jan Schütz [b], Fritz E. Kühn [a,*]

[a] Technische Universität München, Faculty of Chemistry, Chair of Inorganic Chemistry and Molecular Catalysis, Catalysis Research Center, Ernst-Otto-Fischer-Str. 1, 85747 Garching bei München, Germany
[b] Research and Development, DSM Nutritional Products, P.O. Box 2676, 4002 Basel, Switzerland

ARTICLE INFO

Article history:
Received 15 April 2011
Revised 2 July 2011
Accepted 5 July 2011
Available online 12 August 2011

Keywords:
Vitamin E
Oxidation
MTO
Arenes
Hydrogen peroxide
Lewis base
Schiff base
DFT
Mechanism

ABSTRACT

Vitamin E is an essential food component of major economical relevance with important antioxidant properties and biological activity. The oxidation of pseudocumene to trimethyl-1,4-benzoquinone would be a key transformation in an alternative industrial production of α-tocopherol that is important for the antioxidant activity of vitamin E. The methyltrioxorhenium (MTO)-catalyzed oxidation of pseudocumene has been revisited to offer a more environmentally friendly, economically beneficial and milder approach to this important industrial product. It has been observed that by choosing the solvent and Lewis base additives (as ligands of MTO), both yield and chemoselectivity are considerably improved, allowing milder reaction conditions compared to previously reported protocols.

1. Introduction

Vitamins are essential food components which are either not synthesized in the human or animal organism or not formed in sufficient amounts. Among them, vitamin E is of particular economical relevance and industrial interest due to its antioxidizing properties and its biological activity. The term "vitamin E" comprises a group of four tocopherols and four tocotrienols with a characteristic chroman core (Scheme 1). Tocopherols have received more attention than tocotrienols on account of their superior biological relevance [1].

Adequately substituted hydroquinone or benzoquinone derivatives, in particular 2,3,5-trimethyl substituted ones, are important intermediates in the early stages of the industrial synthesis of α-tocopherol that is the most active component of vitamin E. Therefore, the design of selective catalytic methods for α-tocopherol large-scale production is particularly appealing from an industrial point of view [2].

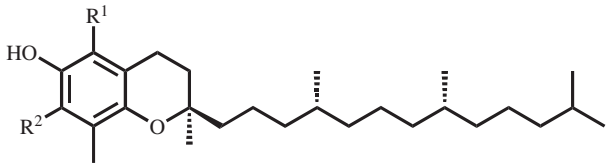
A number of diverse methods for the synthesis of 2,3,5-trimethylhydroquinone (**2**) or its corresponding benzoquinone derivative **3** are documented in the literature. Such methods usually start from a conveniently substituted phenol derivative and often involve costly transition metal catalysts (e.g., cobalt, titanium, or vanadium) in high loadings or heteropolyacids. Despite the remarkable performance of some of them, the latter substances are still economically disadvantageous and yield substantial amounts of waste by-products [3,4]. On an industrial scale, the production of 2,3,5-trimethylquinone is performed under air or oxygen atmosphere, 332–380 K, and copper chloride-based catalysts. With optimized conditions, the oxidation reaches yields between 86% and 95% [2d].

The most interesting but at the same time most challenging approaches are those starting from inexpensive pseudocumene (**1**) that is submitted to selective oxidation in the presence of a catalyst [5]. Although certainly appealing, the difficulty of selective arene oxidations when starting from non-hydroxylated substrates, such as pseudocumene, must be taken into account. Furthermore, the intrinsic reactivity of the so-obtained hydroquinone **2**, which is not isolated and usually easily further oxidized under the reaction conditions to the corresponding benzoquinone derivative **3** (Scheme 2), renders this process particularly challenging.

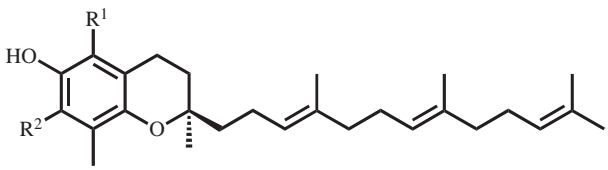
During the last two decades, methyltrioxorhenium (MTO) has been used as a powerful catalyst for hydrogen peroxide-promoted oxidations, particularly in the epoxidation of olefins

* Corresponding author. Fax: +49 (0)89 289 13473.
E-mail address: fritz.kuehn@ch.tum.de (F.E. Kühn).

0021-9517/$ - see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.jcat.2011.07.003

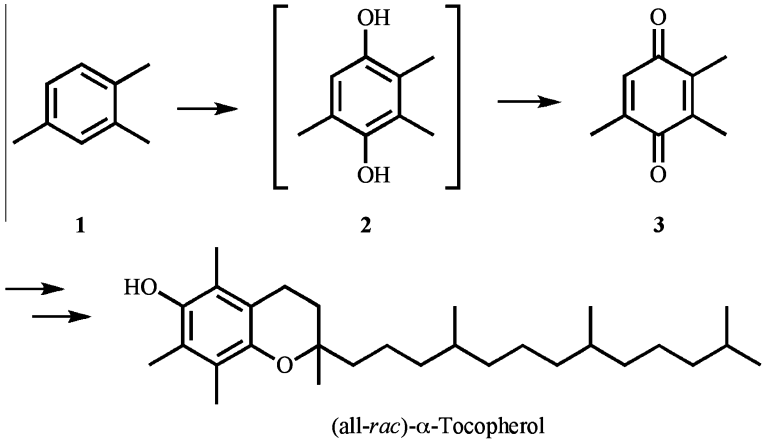


tocopherol-	α	β	γ	δ
R^1	Me	Me	H	H
R^2	Me	H	Me	H



tocotrienol-	α	β	γ	δ
R^1	Me	Me	H	H
R^2	Me	H	Me	H

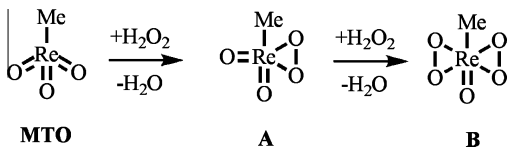
Scheme 1. Compounds with vitamin E activity.



Scheme 2. Synthesis of tocopherol from pseudocumene.

[6]. Furthermore, MTO has also been successfully applied to the oxidation of electron-rich arenes, delivering the corresponding quinone derivatives [3i,p,t,7]. The active catalyst is produced by *in situ* reaction of MTO with hydrogen peroxide, yielding a monoperoxo complex **A**, which further reacts to a bisperoxo species **B** in the presence of large excesses of H_2O_2. Both peroxo species **A** and **B** have been shown to be active in oxidation reactions (Scheme 3) [6a–f].

Herrmann et al. were the first to report an efficient and novel pathway to synthesize vitamin K_3 based on the MTO-catalyzed selective oxidation of methyl-substituted naphthalene derivatives to deliver the corresponding quinones (Scheme 4) [7b]. Further extensions of this methodology involved the MTO-catalyzed oxidation of phenol, anisol, and phenyl derivatives, including pseudocumene and 2,3,5-trimethylphenol [3i,p,t,4k,5b]. However, although promising, the so far reported MTO-based protocols require a large excess of often highly concentrated hydrogen peroxide, highly activated starting materials such as naphthalene or phenoxy derivatives for achieving good selectivities and they are frequently carried out in acetic acid and/or anhydride, with concomitant formation of potentially hazardous peracetic acid.



Scheme 3. Mono- and bisperoxo species of MTO.

Accordingly, to date, none of the published routes meets industrial requirements.

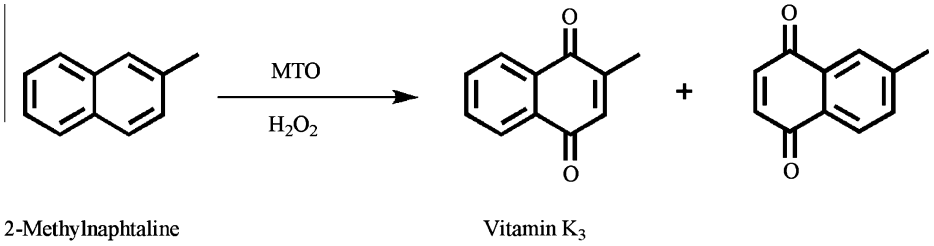
Hence, the search for milder reaction conditions for the oxidation of pseudocumene (**1**) involving catalytic amounts of MTO in combination with inexpensive hydrogen peroxide remains a challenge of substantial interest. Due to its importance, we set out to revisit the MTO-catalyzed oxidation of arenes, especially pseudocumene, for the synthesis of **2**, which is one of the two major building blocks for the synthesis of α-tocopherol.

2. Experimental

2.1. General

All oxidants, solvents, ligands **L1**–**4**, aniline, and salicylaldehyde derivatives are commercially available and were used as received, except for MTO that was prepared following a standard literature procedure [8]. Ligand **L5** was prepared by reaction of the corresponding ketone with hydroxylamine following a common procedure [9], and **L6**–**13** were prepared through standard condensation reactions between an aldehyde and an amine derivative in ethanol and are well-known in the literature [6g–m]. Ligands **L15** and **L16** are known in the literature and have been previously prepared in our group [6g,h,m].

Reactions were monitored by GC–MS in a Hewlett–Packard HP-6890 instrument with a mass selective detector and a DB-225 column, and yields were measured using 4-methylbiphenyl and decane as internal standards. Those standards were added to the samples after the reactions were quenched to prevent their oxidation under the reaction conditions and possible interference with



Scheme 4. Vitamin K_3 synthesis.

the study of the solvent effect. No inert atmosphere was employed for the oxidation reactions.

The spectra ^1H, ^{13}C, and ^{17}O NMR were measured in a Bruker Avance DPX-400 spectrometer.

2.2. Ligand-assisted MTO-catalyzed oxidation of pseudocumene (1)

To a solution of MTO (2 mol%), Ligand **L1**–**25** (2 mol%, see Tables 5 and 6), **1** (1 equiv.) and the solvent of choice (1 mL $mmol^{-1}$), were added H_2O_2 30% or 50% (4 equiv.). The reaction was stirred at the selected temperature for at least 6 h. For the characterization of **3**, after the reaction was stopped, the crude mixture was extracted three times with diethyl ether. Subsequently, a catalytic amount of MnO_2 was added to destroy traces of peroxide if necessary, and the resulting solution was dried over anhydrous sodium sulfate, filtered, and the solvent carefully removed under vacuum. 2,3,5-Trimethyl-1,4-benzoquinone **3** was purified through flash chromatography (dichloromethane/pentane 4:6) and obtained as a pale orange solid. Spectroscopic data are in accordance with literature data [3h].

2.3. General procedure for the synthesis of ligands *L14* and *L17–25*

A solution of salicylaldehyde derivative **6** (1.0 equiv.) in ethanol (5.0 mL $mmol^{-1}$) was added into a solution of aniline derivative **7** (1.0 equiv.) in ethanol (5.0 mL $mmol^{-1}$). After stirring at room temperature for 1 h, the mixture was refluxed until complete consumption of the starting materials. Subsequently, ethanol was removed under reduced pressure and the so-obtained imines were purified by crystallization.

***N*-(3,5-Dichlorosalicylidene)aniline (L14)** [10]. The general procedure was followed using 3,5-dichlorosalicylaldehyde (634.6 mg, 3.29 mmol) and aniline (0.3 mL, 3.29 mmol) to afford 724.4 mg (83% yield) of the product as an orange solid after crystallization in ethanol. ^1H NMR (400 MHz, $CDCl_3$): δ = 14.27 (s, 1H), 8.58 (s, 1H), 7.47–7.44 (m, 3H), 7.36–7.30 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.3, 156.1, 146.8, 132.7, 129.7, 129.6, 127.9, 123.3, 122.9, 121.2, 120.2; anal. calcd. for $C_{13}H_9Cl_2NO$: C 58.67, H 3.41, N 5.26, Cl 26.64; found: C 58.31, H 3.34, N 5.21, Cl 26.77.

***N*-Salicylidene-3-chloroaniline (L17)** [11]. The general procedure was followed using salicylaldehyde (0.35 mL, 3.22 mmol) and 3-chloroaniline (0.34 mL, 3.22 mmol) to afford 524.8 mg (70% yield) of the product as a yellow solid after crystallization in hexane. ^1H NMR (400 MHz, $CDCl_3$): δ = 12.91 (s, 1H), 8.62 (s, 1H), 7.45–7.40 (m, 2H), 7.37 (d, J = 8.07 Hz, 1H), 7.31–7.27 (m, 2H), 7.20–7.17 (m, 1H), 7.06 (d, J = 8.19 Hz, 1H), 6.98 (dt, J = 7.51, 1.03 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.7, 161.2, 149.9, 135.1, 133.6, 132.5, 130.4, 126.8, 121.2, 119.7, 119.2, 118.9, 117.3; anal. calcd. for $C_{13}H_{10}ClNO$: C 67.39, H 4.35, N 6.05, Cl 15.30; found: C 67.11, H 4.08, N 5.90, Cl 15.38.

***N*-(3,5-Dichlorosalicylidene)-2-chloroaniline (L18)** [12]. The general procedure was followed using 3,5-dichlorosalicylaldehyde (634.6 mg, 3.29 mmol) and 2-chloroaniline (0.35 mL, 3.29 mmol) to afford 628.4 mg (64% yield) of the product as an orange solid after crystallization in ethanol. ^1H NMR (400 MHz, $CDCl_3$): δ = 13.88 (s, 1H), 8.48 (s, 1H), 7.42–7.38 (m, 2H), 7.28–7.15 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.0, 160.9, 155.97, 143.9, 133.1, 130.4, 129.9, 128.7, 127.8, 123.5, 123.1, 120.2, 118.9; anal. calcd. for $C_{13}H_8Cl_3N$: C 51.95, H 2.68, N 4.66, Cl 35.39; found: C 51.55, H 2.69, N 4.55, Cl 35.39.

***N*-Salicylidene-4-fluoroaniline (L19)** [13]. The general procedure was followed using salicylaldehyde (0.35 mL, 3.22 mmol) and 4-fluoroaniline (0.31 mL, 3.22 mmol) to afford 553.9 mg (80% yield) of the product as a yellow solid after crystallization in hexane. ^1H NMR (400 MHz, $CDCl_3$): δ = 13.07 (s, 1H), 8.59 (s, 1H), 7.40–7.36 (m, 2H), 7.27–7.24 (m, 2H), 7.11 (t, J = 8.54 Hz, 2H), 7.02 (d, J = 8.67 Hz, 1H), 6.95 (t, J = 7.45 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.5, 162.4, 161.7 (d, J = 246.49 Hz), 161.1, 144.7 (d, J = 2.94 Hz), 133.2, 132.3, 122.6 (d, J = 8.28 Hz), 119.1, 117.3, 116.2 (d, J = 22.74 Hz); anal. calcd. for $C_{13}H_{10}FNO$: C 72.55, H 4.68, N 6.51, F 8.83; found: C 72.11, H 4.66, N 6.44, F 9.00.

***N*-Salicylidene-2-chloro-4-fluoroaniline (L20)**. The general procedure was followed using salicylaldehyde (0.35 mL, 3.22 mmol) and 2-chloro-4-fluoroaniline (0.43 mL, 3.22 mmol) to afford 782.5 mg (97% yield) of the product as a yellow solid after crystallization in hexane. ^1H NMR (400 MHz, $CDCl_3$): δ = 13.20 (s, 1H), 8.78 (s, 1H), 7.61–7.57 (m, 2H), 7.44–7.40 (m, 2H), 7.25–7.21 (m, 2H), 7.14 (t, J = 7.48 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.1, 161.3, 160.9 (d, J = 249.89 Hz), 141.9 (d, J = 3.46 Hz), 133.8, 132.5, 130.4 (d, J = 10.46 Hz), 119.8 (d, J = 8.87 Hz), 119.2, 118.9, 117.6 (d, J = 12.72 Hz), 114.8 (d, J = 22.49 Hz); anal. calcd. for $C_{13}H_9ClFNO$: C 62.54, H 3.63, N 5.61, F 7.61; found: C 62.93, H 3.64, N 5.66, F 7.80.

***N*-Salicylidene-4-trifluoromethylaniline (L21)** [14]. The general procedure was followed using salicylaldehyde (0.35 mL, 3.22 mmol) and 4-trifluoromethylaniline (0.41 mL, 3.22 mmol) to afford 791.4 mg (93% yield) of the product as a yellow solid after crystallization in hexane. ^1H NMR (400 MHz, $CDCl_3$): δ = 12.79 (s, 1H), 8.62 (s, 1H), 7.74–7.63 (m, 1H), 7.44–7.41 (m, 2H), 7.35 (d, J = 8.41 Hz, 2H), 7.05 (d, J = 8.78 Hz, 1H), 6.97 (t, J = 7.49 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.4, 161.2, 151.7, 133.9, 132.7, 128.7 (q, J = 32.79 Hz), 126.6 (q, J = 7.15 Hz), 124.1 (q, J = 271.71 Hz), 121.4, 119.3, 117.4; anal. calcd. for $C_{14}H_{10}F_3NO$: C 63.40, H 3.80, N 5.28, F 21.49; found: C 63.49, H 3.60, N 5.27, F 21.20.

***N*-(5-Bromosalicylidene)aniline (L22)** [15]. The general procedure was followed using 5-bromosalicylaldehyde (667.8 mg, 3.29 mmol) and aniline (0.3 mL, 3.29 mmol) to afford 844 mg (93% yield) of the product as an orange solid after crystallization in ethanol. ^1H NMR (400 MHz, $CDCl_3$): δ = 13.26 (s, 1H), 8.54 (s, 1H), 7.50 (d, J = 1.90 Hz, 1H), 7.45–7.41 (m, 3H), 7.32–7.26 (m, 3H), 6.93 (d, J = 8.92 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.1, 160.2, 147.9, 135.7, 134.2, 129.5, 127.3, 121.2, 120.6, 119.3, 110.5; anal. calcd. for $C_{13}H_{10}BrNO$: C 56.55, H 3.65, N 5.07, Br 28.94; found: C 56.30, H 3.59, N 5.02, Br 29.33.

***N*-(5-Bromosalicylidene)-2-chloroaniline (L23)** [16]. The general procedure was followed using 5-bromosalicylaldehyde (667.8 mg, 3.29 mmol) and 2-chloroaniline (0.35 mL, 3.29 mmol) to afford 667.9 mg (65% yield) of the product as a dark yellow solid after crystallization in a mixture of diethylether and hexane. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.16 (s, 1H), 8.56 (s, 1H), 7.53–7.46 (m, 3H), 7.35–7.31 (m, 1H), 7.25–7.21 (m, 2H), 6.95 (d, J = 8.83 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.8, 160.4, 144.9, 136.2, 134.4, 130.4, 129.7, 128.2, 127.8, 120.5, 119.5, 119.1, 110.5; anal. calcd. for $C_{13}H_9BrClNO$: C 50.27, H 2.92, N 4.51, Br 25.73, Cl 11.42; found: C 50.04, H 2.85, N 4.51, Br 25.93, Cl 11.82.

***N*-Salicylidene-4-nitroaniline (L24)** [17]. The general procedure was followed using salicylaldehyde (0.35 mg, 3.22 mmol) and 4-nitroaniline (453.7 mL, 3.22 mmol) to afford 313.3 mg (40% yield) of the product as a brown solid after crystallization in hexane. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.56 (s, 1H), 8.63 (s, 1H), 8.28 (d, J = 8.68 Hz, 2H), 7.46–7.42 (m, 2H), 7.35 (d, J = 8.72 Hz, 2H), 7.04 (d, J = 8.65 Hz, 1H), 6.98 (t, J = 7.37 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3, 161.32, 154.2, 146.1, 134.5, 132.9, 125.2, 121.8, 119.5, 118.7, 117.5; anal. calcd. for $C_{13}H_{10}N_2O_3$: C 64.46, H 4.16, N 11.56; found: C 64.08, H 3.99, N 11.25.

***N*-(5-Nitrosalicylidene)aniline (L25)** [18]. The general procedure was followed using 5-nitrosalicylaldehyde (560.8 mg, 3.29 mmol) and aniline (0.3 mL, 3.29 mmol) to afford 568.6 mg (72% yield) of the product as a pale orange solid after crystallization in ethanol. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 14.43 (s, 1H), 8.71 (s, 1H), 8.38 (d, J = 2.74 Hz, 1H), 8.25 (dd, J = 9.18, 2.76 Hz, 1H), 7.49–7.44 (m, 2H), 7.38–7.32 (m, 3H), 7.08 (d, J = 9.17 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.8, 160.6, 146.7, 139.9, 129.7, 128.3, 128.1, 121.2, 118.3, 118.1; anal. calcd. for $C_{13}H_{10}N_2O_3$: C 64.46, H 4.16, N 11.56; found: C 64.35, H 4.05, N 11.41.

2.4. Computational details

All calculations were performed with Gaussian-03 [19] using the density functional/Hartree–Fock hybrid model Becke3LYP [20–23] and the split valence double-z (DZ) basis set 6-31+G** [24]. Re atoms have to be treated with an effective core potential, and we chose the Hay-Wadt LANL2DZ [25] basis set for this metal. No symmetry or internal coordinate constraints were applied during optimizations. All reported intermediates were verified as being true minima by the absence of negative eigenvalues in the vibrational frequency analysis. Transition-state structures (indicated by TS) were located using the Berny algorithm [26] until the Hessian matrix had only one imaginary eigenvalue. The identities of all transition states were confirmed by IRC calculations and by animating the negative eigenvector coordinate with MOLDEN [27] and GaussView [28].

Approximate free energies (ΔG) and enthalpies (ΔH) were obtained through thermochemical analysis of frequency calculations, using the thermal correction to Gibbs free energy as reported by Gaussian-03. This takes into account zero-point effects, thermal enthalpy corrections, and entropy. All energies reported in this paper, unless otherwise noted, are free energies or enthalpies at 298 K, using unscaled frequencies. All transition states are maxima on the electronic potential energy surface (PES), which may not correspond to maxima on the free energy surface. Solvation effects are added with the application of the PCM method [29,30] as implemented in Gaussian-03. The solvents used are methanol (dielectric constant ϵ = 32.63), dichloromethane (ϵ = 8.93), dimethyl carbonate (ϵ = 3.09), and nitromethane (ϵ = 38.20), according to the experimental study. All calculated data are available as supporting information upon request from the authors.

3. Results and discussion

3.1. Solvent effects

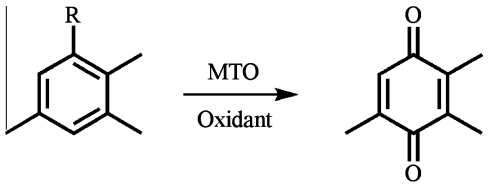
As mentioned above, MTO-catalyzed oxidations of arenes are often carried out in highly diluted solutions of acetic acid or in combination with acetic anhydride in the presence of usually high catalyst loadings (8 mol%) and large excesses of oxidant (up to 20 equiv.), especially when non-hydroxylated starting materials are utilized [5b]. Though efficient and certainly of some academic interest, these reaction conditions are considered too harsh and economically disadvantageous for industrial applications. Accordingly, the main goal of the present research was to improve the conditions for the oxidation of pseudocumene (**1**) in the presence of MTO to pave the way for economically appealing applications. Firstly, the effect of solvents other than those already reported, as well as the use of lower amounts of inexpensive and commercially available hydrogen peroxide (30% and 50%) was studied for the target reaction. In all cases, formation of the corresponding benzoquinone **3** is observed due to the known over-oxidation of hydroquinone **2**, often accompanied by oxidation of the methyl groups, or partially oxidized forms (phenols) of **1**, which act as intermediates toward the formation of benzoquinone **3**. When the target oxidation is carried out in different solvents, but in the absence of MTO, no reaction takes place and the starting material is recovered unreacted. For the sake of comparison, several experiments using 2,3,5-trimethylphenol (**4**) as substrate were also performed (Table 1).

When the reaction is carried out in a diluted aqueous solution of hydrogen peroxide in the absence of organic solvent or in the presence of methanol, the highest selectivities for benzoquinone **3** are obtained, although the yields are low (Table 1, entries 1 and 7). Interestingly, when methanol is replaced by other alcohols, such as EtOH, ^{t}BuOH, or ^{i}PrOH, the reaction barely takes place and nearly no conversion of **1** is observed. Likewise, the use of neither apolar hexane nor relatively polar CH_3CN or DMF affords the target compound **3** (Table 1, entries 15–17). However, in the presence of other types of solvents such as nitromethane and chloroform, yields are higher and selectivities are relatively good (Table 1, entries 18–20). Taking the higher amount of catalyst into account, the catalytic performance with dimethyl carbonate (DMC) or MeOH as solvents is nearly equal (Table 1, entries 7 and 9).

When the reported conditions for the oxidation of **4** in DMC [3h] are applied to both pseudocumene (**1**) and 2,3,5-trimethylphenol (**4**), different results are obtained. The selectivity data obtained for the oxidation of **4** are excellent regardless of the concentration of hydrogen peroxide, although conversions are lower than those reported by Bernini et al. (Table 1, entries 12 and 13) [3h]. However, when **1** is submitted to similar conditions, both selectivities and yields drop significantly relative to those observed for the oxidation of **4** (Table 1, entries 9 and 10). This result is in accordance with the oxidation of pseudocumene (**1**) to intermediate hydroquinone **2** being a more challenging transformation than the benzoquinone formation from an already hydroxylated starting material, such as **4**.

Additionally, when more diluted hydrogen peroxide (30% vs. 50%) is employed in the oxidation of **1**, the yield decreases (Table 1, entry 9 vs. 10). This is certainly the main reason why literature procedures usually use over 80% hydrogen peroxide [3t,7]. Furthermore, several decomposition pathways for MTO in diluted aqueous solutions are known [6,31]. Batch-wise MTO addition also leads only to low yields. Compared to nitromethane, using DMC as solvent leads to lower activities. The yields and selectivities being almost equal, however, with the catalyst and oxidant equivalents are at least twice as high for the DMC system (Table 1, entry 10 vs. 20).

Table 1
Solvent influences in the MTO-catalyzed oxidation of **1**.[a]



1 R = H
4 R = OH

3

Entry	MTO (mol%)	Oxidant	Equiv. oxidant	Solvent	*T* (°C)	Conv. (%)[b]	Yield **3** (%)	Sel. **3** (%)
1	2	H_2O_2 (30%)	4	–	50	13	13	100
2	2	H_2O_2 (30%)	5	Ac_2O	60	63	37	59
3	2	SPC	4	CH_3COOH	r.t.	Tr.	Tr.	–
4	2	H_2O_2 (30%)	4	CH_3COOH	r.t.	n.c.	36	–
5	2	H_2O_2 (27%)	4	$MeSO_3H/CH_3COOH$	0–r.t.	n.c.	26	–
6	2	H_2O_2 (27%)	4	H_2SO_4/CH_3COOH	r.t.	n.c.	13	–
7	2	H_2O_2 (30%)	4	MeOH	50	10	9	90
8	2	UHP	4	MeOH	40	24	10	42
9	5	H_2O_2 (30%)	10	DMC	60	35	15	43
10	5	H_2O_2 (50%)	10	DMC	60	62	26	42
11	5	UHP	4	DMC	60	70	Tr.	–
12[b]	2	H_2O_2 (30%)	4	DMC	60	67	66	98.5
13[b]	2	H_2O_2 (50%)	4	DMC	60	73	69	94.5
14[b]	2	UHP	4	DMC	60	47	24	51
15	2	H_2O_2 (50%)	4	DMF	60	5	Tr.	–
16	2	H_2O_2 (50%)	4	CH_3CN	60	13	Tr.	–
17	2	H_2O_2 (30%)	4	Hexane	60	0	0	0
18	2	H_2O_2 (50%)	4	$CHCl_3$	55	38	23	60.5
19	2	H_2O_2 (30%)	4	$MeNO_2$	60	25	15	60
20	2	H_2O_2 (50%)	4	$MeNO_2$	60	46	25	54
21[b]	2	H_2O_2 (50%)	4	$MeNO_2$	60	92	61	66

Tr. = trace amount, n.c. = not calculated, UHP = urea hydrogen peroxide, DMC = dimethyl carbonate, DMF = dimethylformamide, SPC = sodium percarbonate.
[a] Reaction conditions: **1** (1 equiv.), solvent (1 mL $mmol^{-1}$), 6–24 h.
[b] **4** was used as starting material instead of **1**.

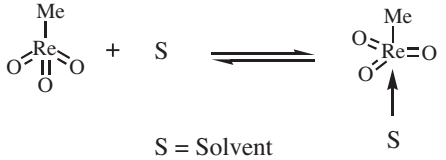
Nevertheless, the use of water-free hydrogen peroxide sources such as urea hydrogen peroxide (UHP), or sodium percarbonate (SPC) does not afford better results (Table 1, entries 3, 8, 11, and 14). However, the reactions starting from **4** do not seem to be affected by the amount of water present in the system in contrast to the oxidation of pseudocumene. The negative effect of water must therefore be limited to the first oxidation step to form a hydroxylated intermediate from pseudocumene (**1**).

As a benchmark, the reaction is carried out in acetic anhydride and acetic acid as solvent, as well as in acetic acid solutions containing H_2SO_4 and $MeSO_3H$ (Table 1, entries 2–6), to elucidate how high the yield under mild reaction conditions is in comparison with previously published procedures [3i,p,t,4k,5b]. When the desired reaction is carried out in acetic anhydride without MTO, benzoquinone **3** is obtained in 31% yield, being a very similar value to that obtained when the same reaction is carried out in the presence of MTO (Table 1, entry 2). This observation suggests that peracetic acid is the real oxidant under these conditions, and MTO does not play a major role. When the reaction is performed in acetic acid, the oxidation takes place not only because of *in situ* formed peracid, but also due to a MTO contribution [3t]. Indeed, when the reaction is performed in acetic acid but in the absence of MTO, **3** only 15% yield is obtained. However, attempts to improve the product yield by increasing the amount of peracid formed by the addition of acid catalysts such as methanesulfonic [32] or sulfuric acid [33], only lead to very exothermic reactions and decomposition of both starting material and catalyst (Table 1, entries 5, 6).

In an attempt to rationalize the solvent effect with respect to the solvent coordinating properties to MTO forming MTO·S, ^{17}O NMR investigations of ^{17}O-labeled MTO in different solvents were performed and compared to the catalytic performance of MTO in these solvents in the oxidation of pseudocumene (**1**) (Table 2). The coordination ability of the solvent to MTO can be evaluated by the chemical shift of the terminal oxygen atoms of MTO. According to the equilibrium shown in Scheme 5, the more the signals are shifted to low field, the higher is the degree of solvent coordination [6c,34].

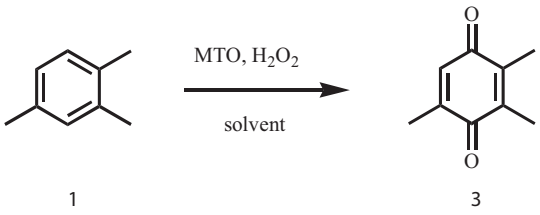
In the range of solvents analyzed, methanol would rank as the best coordinating solvent and acetonitrile would be that of lowest coordination ability [6c,34]. Based on the obtained results, MeOH coordination provides the best selectivity but very low conversion (Table 2, entry 1). Less coordinating solvents such as $CHCl_3$ and $MeNO_2$ afford improved conversions and still good selectivities for the benzoquinone formation (Table 2, entries 3–5). Interestingly, solvents such as CH_3CN and *n*-hexane, with similar coordinating ability toward MTO as chloroform and nitromethane, only furnish target benzoquinone **3** in traces and no significant yield (Table 2, entries 2 and 4).

When the coordination ability of the solvent is expressed in a more general way with donor numbers (DN) and not exclusively



Scheme 5. Adduct formation of MTO with solvent molecules.

Table 2
Relationship between the coordinating ability of solvent and MTO catalytic performance in the oxidation of **1**.



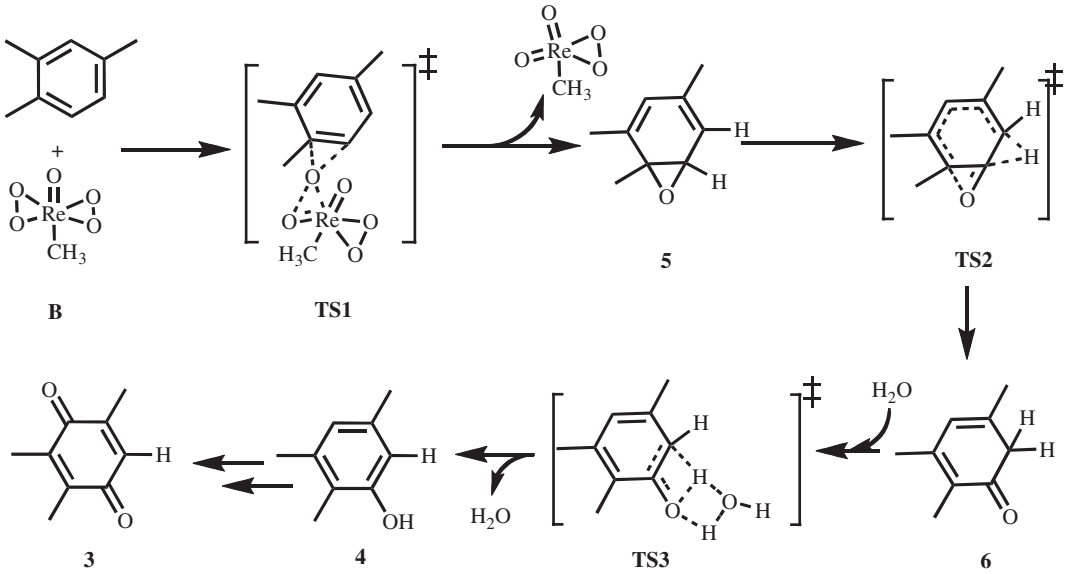
1 3

Entry	Solvent	$\delta(^{17}O)$ (ppm)	Oxidation conditions (from Table 1)	Conversion (%)	**3** (%)	Selectivity **3** (%)
1	MeOH	861 [6c]	**1** (1 equiv.), MTO (2 mol%), H_2O_2 (30%, 4 equiv.), MeOH, 50 °C (Table 1, entry 7)	10	9	90
2	*n*-Hexane	835 [6c]	**1** (1 equiv.), MTO (2 mol%), H_2O_2 (30%, 4 equiv.), ^{n}Hexane, 50 °C (Table 1, entry 17)	0	0	0
3	$MeNO_2$	833	**1** (1 equiv.), MTO (2 mol%), H_2O_2 (30%, 4 equiv.), $MeNO_2$, 60 °C (Table 1, entry 19)	25	15	60
4	$MeNO_2$	833	**1** (1 equiv.), MTO (2 mol%), H_2O_2 (50%, 4 equiv.), $MeNO_2$, 60 °C (Table 1, entry 20)	46	25	54
5	$CHCl_3$	829 [34a,b]	**1** (1 equiv.), MTO (2 mol%), H_2O_2 (50%, 4 equiv.), $CHCl_3$, 60 °C (Table 1, entry 18)	38	23	60.5
6	CH_3CN	824 [6c]	**1** (1 equiv.), MTO (2 mol%), H_2O_2 (50%, 4 equiv.), CH_3CN, 60 °C (Table 1, entry 16)	13	Trace	–

toward MTO, they rank as followed: MeOH (DN = 30) > DMF (DN = 26.6) > DMC (DN = 17.2) > CH_3CN (DN = 14.1) > CH_3Cl (DN = 4) > $MeNO_2$ (DN = 2.7) > *n*-hexane (DN = 0) [35]. But with this general approach, no correlation with reaction performance is detectable.

The solvent effect was also examined in relation to the polarity of the media employed. According to their normalized empirical parameter of solvent polarity, the solvents examined for this reaction rank from more polar to less polar in the order: water > MeOH > EtOH > ^{i}PrOH > $MeNO_2$ > CH_3CN > ^{t}BuOH > DMF > $CHCl_3$ > *n*-hexane [36]. Acetic acid and acetic anhydride have not been taken into account for this comparison due to their particular role in this reaction through *in situ* formation of peracetic acid. Unfortunately, no trend is obvious and neither the coordination ability nor the polarity seems to account for the significantly different catalytic performance of MTO in different solvents. This might indicate that there are other influences that are more difficult to evaluate, e.g., the solubility of intermediate species.

The mechanism of the reaction is thought to proceed through the formation of an arene oxide **5** [3t]. As previously stated, MTO forms the catalytically active species **B** upon addition of excess of hydrogen peroxide. Peroxorhenium(VII) **B** is electrophilic and would be attacked by electron-rich nucleophilic arenes to form an intermediate epoxide as shown in Scheme 6. Such an epoxide would open under the reaction conditions producing a very nucleophilic phenolic intermediate, which would further oxidize to the corresponding ketonic derivative, following the same reaction pathway. As part of this study, we look at the first half of the mechanism from the first epoxidation of the aromatic ring to the phenolic intermediate. There is no experimental observation of the formation of such an arene oxide thus far, but its presence is confirmed to some extent through the analysis of by-products (e.g., phenols) and DFT calculations on this mechanism (Scheme 6). The mechanism was adjusted from the benzene oxidation mechanism of Kudrik and Sorokin [37] and shows clearly that the arene oxide route is reasonable under certain conditions. The calculated Gibbs free energies obtained for gas phase and different solvents are summarized in Table 3, especially the calculations for the solvents support the experimental results. Therein, nitromethane is the only solvent able to lower ΔG of transition state **TS1** significantly in comparison with methanol, dichloromethane, or dimethyl carbonate. This would be a reason why the catalytic reaction shows higher activities in nitromethane than in other solvents. Similar to the experimental data, the energies of **TS1** for the different solvents do not show a correlation with solvent parameters like coordination ability or polarity.



Scheme 6. Proposed mechanism of pseudocumene oxidation.

Table 3
Gibbs free energies of the calculated mechanism.

	Gas phase	Nitromethane	Methanol	DCM	DMC
Pseudocumene					
+B	0.0	0.0	0.0	0.0	0.0
TS1	35.3	14.8	32.7	32.7	33.4
5	−21.6	−24.9	−30.3	−24.5	−26.0
TS2	14.5	2.4	−7.5	3.6	2.4
6	−53.0	−57.6	−61.6	−57.0	−58.0
TS3 (H_2O)	−26.1	−26.4	−27.1	−26.4	−26.3
4	−66.6	−66.5	−73.3	−69.1	−69.9

B3LYP/6-31+G**; Re-ECP (Hay–Wadt); PCM (UAKS radius); ΔG (Gibbs free energy, kcal/mol).

Table 4
Comparison of the different epoxidation barriers.

Position	Gas phase	Nitromethane
1,6 (**TS1**)	35.3	14.8
5,6	36.7	33.4
2,3	35.1	16.9
3,4	37.5	33.6

B3LYP/6-31+G**; Re-ECP; ΔG (Gibbs free energy, kcal/mol).

The reaction mechanism starts with the attack of the aromatic substrate on the bisperoxo MTO complex. The oxidation might occur on different positions of pseudocumene. The barrier for **TS1** shown in Table 3 is corresponding to an epoxidation of the phenyl ring in 1,6 position. The barriers for the epoxidations on other positions at the pseudocumene have also been calculated. The free energies of these barriers for gas-phase conditions and for nitromethane as solvent are summarized in Table 4.

Based on the obtained values, we conclude that the mechanism in nitromethane yielding product **3** proceeds as shown in Scheme 6. It starts with **TS1** in position 1,6 leading to the interim product **4** via **5**, **TS2**, **6,** and **TS3**. **TS2** features the concerted formation of a carbonyl group and H transfer to a neighboring ring atom to form a sp^3 carbon in intermediate **6**. **TS3** is water assisted and restores the aromatic system, while transforming the ketone to a phenol through H transfer. Starting from intermediate **4,** another epoxidation is likely to occur at the 2,3 position according to Table 4. Via two similar H transfers, a hydroquinonic system is generated, being able to undergo a conversion to the desired quinone **3**.

However, it cannot be ruled out that the 2,3 position is also available at the beginning of the reaction, as the barrier for both possibilities in the gas phase is equal. However, for nitromethane, it is different by 2 kcal/mol. Anyway, the reaction cycle has to be repeated on the opposite side of the aromatic ring in order to obtain, starting from **4** (or the corresponding alternative at the other side of the aromatic ring), the desired quinone **3**. As the other two possibilities show higher epoxidation barriers, it might be concluded that both the 1,6 and the 2,3 epoxidation occur at the phenyl ring during the reaction and proceeds via a set of two H transfers on each side to yield product **3**.

3.2. Ligand influence

In order to reach improved reaction conditions and selectivities for the MTO-catalyzed oxidation of pseudocumene (**1**) to its corresponding quinone derivative **3**, the next step was to explore the ligand influence on the catalytic performance [6g–m,38]. Among the most easily accessible ligands, pyridine derivatives [6i,38b–d,f,g] and Schiff bases [6g,h,j–m] have afforded the most promising results by displaying increased selectivities and reaction rates. Several ligands have not been applied as additives for the MTO-catalyzed oxidation of **1** before (see Table 5).

As shown above, when the oxidation is carried out in the presence of MTO, but without the addition of a ligand, the results are very dependent on the solvent. In order to obtain selectivities higher than 90%, the reaction has to be run either without solvent or in methanol, although the yields obtained under those reaction conditions are low. By using other solvents such as nitromethane, however, yields increase but unfortunately the selectivity values observed are often between only 50% and 60% (see Tables 1 and 2). Nevertheless, by addition of some ligands, it has been possible to increase the yields to more than 20% and to obtain selectivities of around 70% (see Table 5).

It is known that excess of aromatic Lewis bases such as pyridine lead to significantly higher activities and selectivities than MTO alone. While literature reports on the optimal pyridine excess differ from 5- to 24-fold [4j], we found that a ligand/MTO ratio of 2:1 or 1:1 leads to the best results for the reaction under examination (see Table 5, entries 1–4).

When the oxidation of **1** is carried out in the presence of oxime derivatives **L4** and **L5** and particularly in nitromethane, selectivity values ranging from 55% to 71% are obtained (Table 5, entries 5–10). When using **L4** as ligand, the use of either H_2O_2 (30% or 50%) with a MTO/**L** ratio of 1:1 affords very similar results in terms of both yield and selectivity, (Table 5, entry 5 vs. 7). Interestingly, when the reaction is allowed to run for 72 h instead of 6 h, the conversion barely changes but the selectivity increases slightly from 66% to 71% (Table 5, entries 5 and 6). Additionally, when a 1:2 ratio of MTO/**L** is employed, the yield improves without selectivity loss (Table 5, entry 9).

Furthermore, we examined the target oxidation with some (*N*-salicylidene)aniline derived Schiff bases such as **L6–L8**.[6h,j–l].

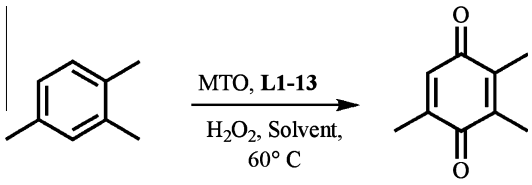
When the reaction is run in the presence of ligands **L6** and **L7**, the obtained selectivity values are moderate and very similar regardless of the solvent (Table 5, entries 11 and 13). However, the results obtained in the presence of ligand **L8**, which is known to be very active in epoxidation reactions [6h], are slightly better yielding selectivities over 60% (Table 5, entry 14). While the oxidation of **1** is generally improved by the addition of ligands, the oxidation starting from 2,3,5-trimethylphenol (**4**), delivers both lower yields and selectivities with a Lewis base present (Table 1, entry 21; Table 5, entry 12). In some cases, the imine bond of the ligands hydrolyzes during the course of the reaction. Despite the higher basicity of ligand **L10**, which is known to be detrimental to MTO lifetime [6a–d], the results afforded with **L10** are similar to those obtained by its oxidized analog **L6**. When performing the reaction in chloroform, **L10** delivers much higher selectivity than **L6**, 64% *vs.* 35%, respectively (Table 5, entry 16 *vs*. 11).

Recently, it was shown that MTO can coordinate to salen-type ligands [6g]. Dependent on the ligand/MTO ratio, salen compounds can ligate one or two MTO molecules, with both types of complexes active in epoxidation reactions. Hence, some related salen-type ligands were tested in the oxidation of pseudocumene (**1**) in both 1:1 and 1:2 ratios with respect to MTO (Table 5, entries 17–20). The selectivities obtained in the presence of **L12** and **L13** are 85% and 75%, respectively, but the yields are just above 10% (Table 5, entries 19 and 20). Additionally, a combination of MTO, imidazol as ligand, Oxone® as oxidant in ethylacetate as solvent at room temperature, based on similar conditions reported by Wei and Liu [39], was tested but starting material **1** was recovered unreacted.

3.3. Schiff base ligands

Schiff bases bearing chlorine substituents in certain aromatic positions generally afford better results in the oxidation of

Table 5
Ligand assisted MTO-catalyzed oxidation of **1**.[a]



1 **3**

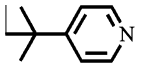
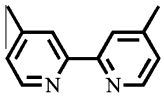
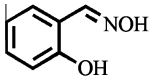
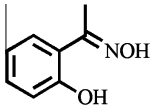
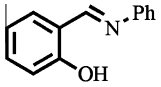
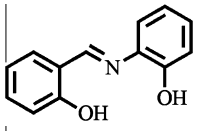
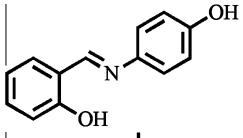
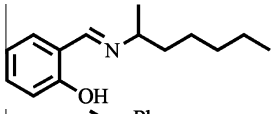
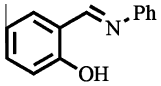
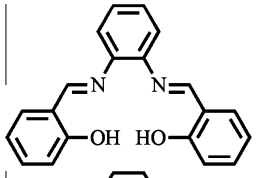
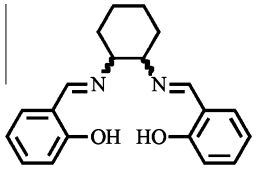
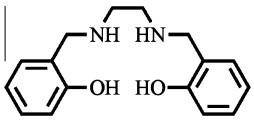
Entry	Ligand **L**		Methanol		Nitromethane		Chloroform	
			Yield **3** (%)	Sel. **3** (%)	Yield **3** (%)	Sel. **3** (%)	Yield **3** (%)	Sel. **3** (%)
1[d]		**L1**	13	54	3	43	1.5	30
2[e]		**L1**	23	57.5	–	–	–	–
3[d]		**L2**	7	47	–	–	–	–
4		**L3**	10	33	6	25	8	50
5		**L4**	22	44	21	66	14	32
6[f]		**L4**	–	–	24	71	–	–
7[f,g]		**L4**	–	–	22	59.5	–	–
8[f,g,h]		**L4**	–	–	33	55	–	–
9[e,f]		**L4**	–	–	32	67	–	–
10		**L5**	28	53	28	68	15.5	48
11		**L6**	25	50	16	43	12	35
12[i]		**L6**	–	–	54	61	–	–
13		**L7**	23.5	51	20	51	15	45.5
14		**L8**	28	64	24	63	–	–
15		**L9**	10	43.5	10	41	8	31
16		**L10**	19	63	18	50	9	64
17		**L11**	4	21	8	46	–	–
18[j]		**L11**	15	67	–	–	–	–
19		**L12**	–	–	11	85	–	–

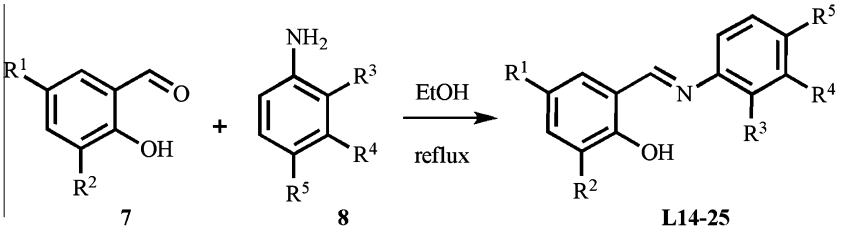
Table 5 (*continued*)

Entry	Ligand **L**		Methanol		Nitromethane		Chloroform	
			Yield **3** (%)	Sel. **3** (%)	Yield **3** (%)	Sel. **3** (%)	Yield **3** (%)	Sel. **3** (%)
20		**L13**	–	–	12	75	–	–

[a] Reaction conditions: **1** (1 equiv.), MTO (2 mol%), **L1–13** (2 mol%), H_2O_2 (50%, 4 equiv.), solvent (methanol, nitromethane or chloroform) (1 mL $mmol^{-1}$), 60 °C, 6–24 h.
[d] MTO:**L** = 1:24.
[e] MTO:**L** = 1:2.
[f] Reaction time 72 h.
[g] H_2O_2 (30%) was employed.
[h] MTO (10 mol%) was employed.
[i] 2,3,5-Trimethylphenol (**4**) was used as starting material instead of pseudocumene (**1**).
[j] MTO:**L** = 2:1. Sel. = Selectivity.

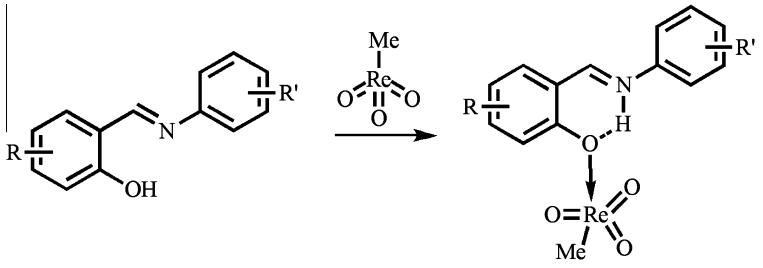
pseudocumene (**1**) in comparison with those ligands bearing electron donating groups or hydrogen. Similar effects in the presence of electron withdrawing substituents have been observed previously, especially with Lewis bases [38e,40,41], but never studied in detail for Schiff bases [6g,h,m]. A number of salicyladehyde and aniline derivatives **7** and **8,** respectively, bearing fluorine, chlorine, bromine, nitro, and trifluoromethyl groups were selected and subsequently condensed in a solution of refluxing ethanol, to obtain the corresponding Schiff bases **L14–25** in yields ranging from 40% to 97% (Scheme 7).

The ligands, **L15** and **L16**, have already proven to be beneficial additives in MTO-catalyzed epoxidation reactions [6h,m]. As it has been shown, (*N*-salicylidene)aniline Schiff bases coordinate to MTO through the oxygen atom (Scheme 8) [6h,l,m]. The interaction of MTO with such ligands results in a small shift of the methyl protons in MTO to higher field in the ^1H NMR spectra in $CDCl_3$. Among other options, such a shift can be a simple and easy way to determine the degree of MTO ligand coordination. Donor ligands lead to greater high field shifts of around 0.15 ppm of the methyl protons. Weaker coordinating ligands cause smaller high field shifts of approximately 0.05 ppm and deliver more active catalysts. In the ^{17}O NMR spectra of MTO with Schiff bases, a comparatively small shift change of 2–3 ppm can be observed for the MTO oxygen atoms compared to those of free MTO recorded in the same solvent [6h,l,m]. For the oxidation of **1**, a weakly coordinating ligand being able to deliver a very active MTO derivative would be needed. Likewise, the chosen ligand should also be able to reduce the Lewis acidity of the metal center and enable



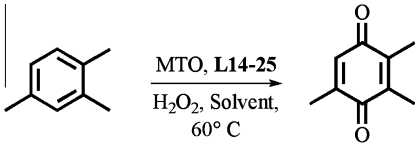
L14 R^1,R^2 = Cl; R^3, R^4, R^5 = H
L15 R^1, R^2, R^4, R^5 = H; R^3 = Cl
L16 R^1, R^2, R^3, R^4 = H; R^5 = Cl
L17 R^1, R^2, R^3, R^5 = H; R^4 = Cl
L18 R^1, R^2, R^3 = Cl; R^4, R^5 = H
L19 R^1, R^2, R^3, R^4 = H; R^5 = F
L20 R^1, R^2, R^4 = H; R^3 = Cl; R^5 = F
L21 R^1, R^2, R^3, R^4 = H; R^5 = CF_3
L22 R^1 = Br; R^2, R^3, R^4, R^5 = H
L23 R^1 = Br; R^2, R^4, R^5 = H; R^3 = Cl
L24 R^1, R^2, R^3, R^4 = H; R^5 = NO_2
L25 R^1 = NO_2; R^2, R^3, R^4, R^5 = H

Scheme 7. Synthesized Schiff bases.

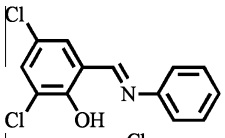
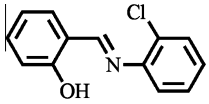
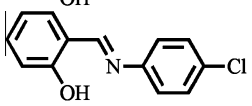
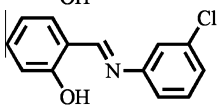
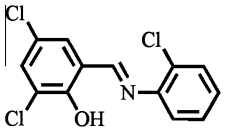
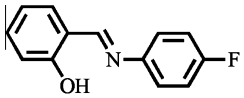
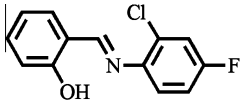
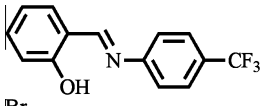
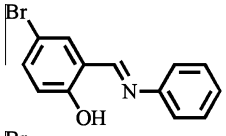
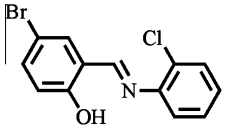
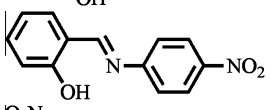
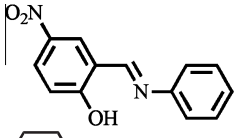
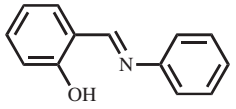


Scheme 8. MTO-Schiff base complex.

Table 6
Ligand assisted MTO-catalyzed oxidation of **1**.[a]



1 **3**

Entry	Ligand **L**		Methanol		Nitromethane		Chloroform	
			Yield **3** (%)	Sel. **3** (%)	Yield **3** (%)	Sel. **3** (%)	Yield **3** (%)	Sel. **3** (%)
1		**L14**	32.5	53	35	56.5	28	60
2[d]		**L14**	–	–	66.5	87.5	–	–
3[d,e]		**L14**	–	–	57	95	–	–
4		**L15**	30	79	28	68	20	56
5		**L16**	32	65	30	59	22.5	59
6		**L17**	24	61.5	30	73	16	70
7		**L18**	33	63	32	62	25	66
8		**L19**	27	48	20	67	21	67
9		**L20**	35	64	29	62	22	58
10		**L21**	31	69	29	66	23	64
11		**L22**	20	57	21	64	18	64
12		**L23**	31.5	62	28	70	17	59
13		**L24**	27	69	20	67	17	59
14		**L25**	31	60	27	84	24	80
15		**L6**	25	50	16	43	12	35

[a] Reaction conditions: **1** (1 equiv.), MTO (2 mol%), **L6**, **L14–25** (2 mol%), H_2O_2 (50%, 4 equiv.), solvent (methanol, nitromethane or chloroform) (1 mL $mmol^{-1}$), 60 °C, 6–22 h.
[d] 2,3,5-Trimethylphenol (**4**) was used as starting material instead of pseudocumene (**1**) and 3 equiv. of oxidant were employed.
[e] H_2O_2 (27%) was employed as oxidant.

Table 7
Comparison of different pseudocumene oxidations.

Entry	Reaction conditions	Time (h)	Temp. (°C)	Conversion (%)	Yield (%)
1[5d]	Catalyst: Pd(II)–SP resin (0.24 wt%); solvent: AcOH; H_2O_2 (60%) 3 eq.	10	70	77.6	3.3
2[5c]	Catalyst: –; solvent: $CHCl_3$; MCPBA 2.2 eq.	0.5	60–70	–	16.5
3[5b]	Catalyst: MTO (8 mol%); solvent: AcOH; H_2O_2 (30%) 20 eq.	4	57	75	67
4[4l]	Catalyst: $FeCl_3$ + additives (7.5 mol%); solvent: *t*-amyl alcohol; H_2O_2 (30%) 4 eq.	1.5	0	69	Sel.: 38
5	Catalyst: MTO + **L17** (2 mol%); solvent: nitromethane; H_2O_2 (50%) 4 eq.	20	60	30	73

increased chemoselectivity toward benzoquinone **3**. Hence, the employment of electron withdrawing ligands **L14–25** should decrease the donating ability of the Schiff bases creating optimized ligands.

In order to check whether such weakly coordinating ligands **L14–25** could actually link to MTO, some NMR experiments were performed. Spectroscopic data obtained from ^{1}H NMR spectra of equimolecular mixtures of MTO and **L14–25** confirm the existence of coordination between MTO and the ligands. For the methyl protons of MTO in its adducts with ligands **L14–25,** a chemical shift of 2.61 or 2.62 ppm has been observed in $CDCl_3$, which is within the expected range for relatively weakly coordinating ligands [42]. Likewise, the ^{17}O NMR of MTO and **L18** in nitromethane was recorded affording a 2.5 ppm shift change in comparison with free MTO ($\delta(^{17}O)$ = 833 ppm), which is also consistent with reported data for similar compounds [6g,l,m,43].

According to previous results from solvent studies on the oxidation of pseudocumene, the best results are obtained when using 2 mol% of MTO and 4 equiv. H_2O_2 (50%) in the presence of methanol, nitromethane, or chloroform as solvents at 60 °C. The newly prepared ligands **L14–25** were applied in the oxidation of pseudocumene (**1**) under those reaction conditions and compared to previous results with non-substituted Schiff base **L6**. The most relevant results are included in Table 6. Oxidation attempts starting from 2,3,5-trimethylphenol (**4**) have also been performed.

As it can be seen from Table 6, ligands **L14–25** in combination with MTO afford the best selectivity values (compared to results depicted in Table 5). The selectivities obtained by using such ligands are higher than 60%, in some cases around 80%, with yields of around 30%. When comparing with non-substituted Schiff base **L6**, the most pronounced differences in selectivity values are observed when the reaction takes places in non-coordinating nitromethane and chloroform, although in general the best results in terms of both yield and selectivity are obtained in nitromethane as solvent. Nevertheless, the use of ligands in the oxidation of **4** does only have a small beneficial effect and the reaction proceeds almost as in the absence of ligand (Table 5, entry 12; Table 6, entries 2 and 3). In the case of the ligands bearing exclusively chlorine atoms as substituents (Table 6, entries 1–7), the best selectivities are observed when the chlorine atom is in the aromatic ring derived from the aniline counterpart, particularly in the *ortho* or *meta* position (Table 6, entry 4). According to the coordination mode of these types of ligands (shown in Scheme 5), the substituents present on that part of the molecule should not directly affect the coordination ability of the salicylic oxygen. However, they can also have an electronic effect on the iminic nitrogen and therefore on the strength of the intramolecular hydrogen bond. Indeed, previous research on the MTO-Schiff base complexes shows very different values for the N–H bond lengths for two MTO adducts, one with a chlorine atom (**L16**) and another with a donating methoxy substituent, both in the *para* position to the iminic nitrogen. The chlorine substituted adduct displays a shorter N–H bond than the methoxy one [6m]. How such an intra-molecular hydrogen bond affects the adduct formation or the resulting catalyst performance is not clear yet.

Additionally, the presence of a fluorine atom *para* to the iminic nitrogen (**L19**) results in improved selectivity and yield with respect to **L6** in non-coordinating nitromethane or chloroform as solvents. However, it makes virtually no difference when using the coordinating solvent methanol (Table 6, entry 8 *vs.* 15). Interestingly, the presence of an *ortho*-chlorine in addition to a *para*-fluorine (**L20**) does affect the selectivity to a significant extent for MeOH and it increases the yield to 35% (Table 6, entries 8 *vs.* 9). Likewise, bromine atoms *para* to the hydroxyl moiety (**L22**) have a moderate effect on the yield, but deliver selectivities of ca. 60% (Table 6, entry 11 *vs.* 15). Once again, when there is an additional *ortho*-chlorine, a selectivity of 70% is obtained (Table 6, entry 12).

Very strongly electron withdrawing groups in *para* position to the iminic nitrogen, such as trifluoromethyl (**L21**) or nitro substituents (**L24**), have both a similar effect, affording high selectivities of nearly 70% depending on the solvent and yields close to 30% (Table 6, entries 10 and 13). Nonetheless, the best results are obtained when using **L25** bearing a nitro group in the *para* position to the hydroxyl group on the salicylic counterpart. Yields of around 30% and selectivity values of 80% and 84% are obtained in the presence of **L25** when using chloroform and nitromethane as solvents, respectively (Table 6, entry 14). It must be emphasized that given the great economical and industrial relevance of the target oxidation, these results can indeed be considered as an important step forward, despite the seemingly moderate yields (Table 6, entry 14). The high selectivity values would allow an easier purification of the product during large-scale production, as well as recovery of the unreacted starting material, if desired. Compared to other catalytic systems (Table 7) using pseudocumene as starting material, the selectivity is again the most striking point. Although the catalyst loading is the smallest, the highest selectivity values are reached. It is also obvious that no harsh conditions like acetic acid as solvent or *m*-chloroperbenzoic acid (MCPBA) as oxidant are used in our experiments. Nevertheless, the presented data in Table 7 are only a qualitative comparison as the experimental setup is not identical.

4. Conclusion

Among the examined catalytic systems, MTO is most efficient for the oxidation of pseudocumene in terms of both yield and selectivity. The performance of MTO in the oxidation of pseudocumene is strongly solvent influenced. The solvent effect appears to be related to the solubility of the reaction intermediates. Calculations on the possible mechanism reveal a significant barrier drop of **TS1** with nitromethane as solvent. By shifting from the previously reported solvents for the oxidation of non-hydroxylated arenes (mainly AcOH and Ac_2O) to nitromethane, chloroform, or dimethyl carbonate, it is possible not only to considerably reduce the number of equivalents of oxidant per catalyst (from up to 20 to 4) in the presence of 2 mol% of MTO, but also the concentration of H_2O_2 (from 85% to 50% or 30%), leading to results comparable to those already reported under far less favorable conditions. The use of Lewis basic ligands in the MTO-catalyzed oxidation of pseudocumene (**1**) to the corresponding benzoquinone derivative **3** has a beneficial effect on both yield and selectivity. The use of salicylaldoxime **L4** and its derivative **L5** is particularly efficient when nitromethane is applied as the solvent, delivering selectivities of around 70% and yields of around 30% within 72 h. Additionally, se-

lected salen-type ligands also lead to a highly selective oxidation of pseudocumene (up to 84% selectivity), although the obtained yields are low. These results are nevertheless remarkable considering the difficulty of selective oxidations of simple unactivated arenes, where several ring carbon atoms are equally prone to oxidation. The use of (*N*-salicylidene)aniline derived Schiff bases bearing electron withdrawing substituents as ligands in the MTO-catalyzed oxidation of pseudocumene increases the selectivity of the reaction toward the formation of benzoquinone **3**. In particular, the presence of a nitro group in *trans* position to the hydroxyl moiety in the salicylaldehyde derived part of the ligand leads to selectivities as high as 84%. The Schiff base ligands coordinate only weakly to the rhenium center of MTO. This results in active catalysts with reduced Lewis acidity, leading to increased chemoselectivity. The presence of electron withdrawing groups in the ligands might not only affect coordination strength but also intra-molecular hydrogen bond formation.

References

[1] (a) T. Netscher, Vitamins and Hormones, 76 (2007) 155;
[b] T. Netscher, F. Mazzini, R. Jestin, Eur. J. Org. Chem. (2007) 1176;
(c) T. Rosenau, E. Kloser, L. Gille, F. Mazzini, T. Netscher, J. Org. Chem. 72 (2007) 3268;
(d) K.U. Baldenius, L. von dem Bussche-Hünnefeld, E. Hilgemann, P. Hoppe, R. Stürmer, Ullmann's Encylopedia of Industrial Chemistry, vol. A27, VCH, Weinheim, 1996. p. 478.

[2] (a) For recent advances in the field of tocopherols and analogues, see: C. Rein, P. Demel, R.A. Outten, T. Netscher, B. Breit, Angew. Chem. 119 (2007) 8824; Angew. Chem. Int. Ed. 46 (2007) 8670;
(b) A. Wildermann, Y. Foricher, T. Netscher, W. Bonrath, Pure Appl. Chem. 79 (2007) 1839;
(c) W. Bonrath, M. Eggersdorfer, T. Netscher, Catal. Today 121 (2007) 45;
(d) W. Bonrath, T. Netscher, Appl. Catal. A 280 (2005) 55.

[3] (a) For some examples, see: O.V. Zalomaeva, I.D. Ivanchikova, O.A. Kholdeeva, A.B. Sorokin, New J. Chem. 33 (2009) 1031;
(b) C. Wang, W. Guan, P. Xie, X. Yun, H. Li, X. Hu, Y. Wang, Catal. Commun. 10 (2009) 725;
(c) T.A. Trubitsyna, O.A. Kholdeeva, Kinet. Catal. 49 (2008) 371;
(d) Y. Çimen, H. Türk, Appl. Catal. A 340 (2008) 52;
(e) Y. Li, W. Liu, M. Wu, Z. Yi, J. Zhang, J. Mol. Catal. A: Chem. 261 (2007) 73;
(f) O.A. Kholdeeva, I.D. Ivanchikova, M. Guidotti, N. Ravasio, Green. Chem. 9 (2007) 731;
(g) A.B. Shishmakov, Y.V. Mikushina, M.S. Valova, O.V. Koryakova, L.A. Petrov, Russ. J. Appl. Chem. 80 (2007) 2029;
(h) R. Bernini, E. Mincione, M. Barontini, F. Crisante, G. Fabrizi, A. Gambacorta, Tetrahedron 63 (2007) 6895;
(i) R. Bernini, E. Mincione, M. Barontini, G. Fabrizi, M. Pasqualetti, S. Tempesta, Tetrahedron 62 (2006) 7733;
(j) S. Iwasa, A. Fakhruddin, H.S. Widagdo, H. Nishiyama, Adv. Synth. Catal. 347 (2005) 517;
(k) V. Tesevic, J.A. Gladysz, Green Chem. 7 (2005) 833;
(l) A.Y. Yermakov, T.A. Feduschak, M.A. Uimin, A.A. Myisik, V.S. Gaviko, Y.A. Kotov, A.V. Vosmerikov, A.V. Korolyov, Solid State Ionics 172 (2004) 317;
(m) C. Rocaboy, J.A. Gladysz, Chem. Eur. J. 9 (2003) 88;
(n) O.A. Kholdeeva, N.N. Trukhan, M.P. Vanina, V.N. Romannikov, V.N. Parmon, J. Mrowiec-Bialon, A.B. Jarzebski, Catal. Today 75 (2002) 203;
(o) X. Menga, Z. Suna, S. Lin, M. Yang, X. Yang, J. Suna, D. Jiang, F.-S. Xiao, S. Chen, Appl. Catal. A 236 (2002) 17;
(p) R. Saladino, V. Neri, E. Mincione, P. Filippone, Tetrahedron 58 (2002) 8493;
(q) R. Maasen, S. Krill, K. Huthmacher, EP1132367 (2001);
(r) S. Ficht, M. Mülbaier, A. Giannis, Tetrahedron 57 (2001) 4863;
(s) H. Togo, T. Nabana, K. Yamaguchi, J. Org. Chem. 65 (2000) 8391;
(t) W. Adam, W.A. Herrmann, J. Lin, C.R. Saha-Möller, J. Org. Chem. 59 (1994) 8281.

[4] (a) For some related oxidations of arenes or phenol derivatives, see M.E.L. Preethi, S. Revathi, T. Sivakumar, D. Manikandan, D. Divakar, A.V. Rupa, M. Palanichami, Catal. Lett. 120 (2008) 56;
(b) J.L. van Wyka, S.F. Mapolie, A. Lennartson, M. Håkansson, S. Jagner, Inorg. Chim. Acta 361 (2008) 2094;
(c) M.R. Maurya, A.K. Chandrakar, S. Chand, J. Mol. Catal. A: Chem. 263 (2007) 227;
(d) K.M. Parida, S.S. Dash, J. Colloid Interface Sci. 316 (2007) 541;
(e) D. Bianchi, L. Balducci, R. Bortolo, R. D'Aloisio, M. Ricci, G. Spanò, R. Tassinari, C. Tonini, R. Ungarelli, Adv. Synth. Catal. 349 (2007) 979;
(f) K. Yube, M. Furuta, K. Mae, Catal. Today 125 (2007) 56;
(g) H. Sun, X. Li, J. Sundermeyer, J. Mol. Catal. A: Chem. 240 (2005) 119;
(i) H.H. Monfared, Z. Amouei, J. Mol. Catal. A: Chem. 217 (2004) 161;
(j) B. Tamami, H. Yeganeh, Eur. Polym. J. 35 (1999) 1445;
(k) W. Adam, W.A. Herrmann, C.R. Saha-Möller, M. Shimizu, J. Mol. Catal. A: Chem. 97 (1995) 15;
(l) K. Möller, G. Wienhöfer, K. Schröder, B. Join, K. Junge, M. Beller, Chem. Eur. J. 16 (2010) 10300.

[5] (a) S. Li, J. Fu, Shihua Jishu Yu Yingyong 26 (2008) 234;
(b) J. Jacob, J.H. Espenson, Inorg. Chim. Acta 270 (1998) 55;
(c) Y. Asakawa, R. Matsuda, M. Tori, M. Sono, J. Org. Chem. 53 (1988) 5453;
(d) S. Yamaguchi, M. Inoue, S. Enomoto, Bull. Chem. Soc. Jpn. 59 (1986) 2881;
(e) G.A. Olah, A.P. Fung, T. Keumi, J. Org. Chem. 46 (1981) 4305.

[6] (a) For general reviews see: F.E. Kühn, A. Scherbaum, W.A. Herrmann, J. Organomet. Chem. 689 (2004) 4149;
(b) F.E. Kühn, A.M. Santos, W.A. Herrmann, Dalton Trans. (2005) 2483;
(c) C.C. Romão, F.E. Kühn, W.A. Herrmann, Chem. Rev. 97 (1997) 3197;
(d) W.A. Herrmann, F.E. Kühn, Acc. Chem. Res. 30 (1997) 169;
(e) For MTO–H_2O_2 equilibrium, see:S. Yamazaki, J.H. Espenson, P. Huston, Inorg. Chem. 32 (1993) 4683;
(f) P.J. Hansen, J.H. Espenson, Inorg. Chem. 34 (1995) 5839;
(g) For some recent applications of MTO, see:Z. Xu, M.-D. Zhou, M. Drees, H. Chaffey-Millar, E. Herdtweck, W.A. Herrmann, F.E. Kühn, Inorg. Chem. 48 (2009) 6812;
(h) M.-D. Zhou, Y. Yu, A. Capapé, K.R. Jain, E. Herdtweck, X.-R. Li, J. Li, S.-L. Zang, F.E. Kühn, Chem. Asian J. 4 (2009) 411;
(i) P. Altmann, F.E. Kühn, J. Organomet. Chem. 694 (2009) 4032;
(j) M.-D. Zhou, K.R. Jain, A. Günyar, P.N.W. Baxter, E. Herdtweck, F.E. Kühn, Eur. J. Inorg. Chem. (2009) 2907;
(k) C.-J. Qiu, Y.-C. Zhang, Y. Gao, J.-Q. Zhao, J. Organomet. Chem. 694 (2009) 3418;
(l) A. Capapé, M.-D. Zhou, S.-L. Zang, F.E. Kühn, J. Organomet. Chem. 693 (2008) 3240;
(m) M.-D. Zhou, J. Zhao, J. Li, S. Yue, C.-N. Bao, J. Mink, S.-L. Zang, F.E. Kühn, Chem. Eur. J. 13 (2007) 158.

[7] (a) W.A. Herrmann, J.J. Haider, R.W. Fischer, J. Mol. Catal. A: Chem. 138 (1999) 115;
(b) W. Adam, W.A. Herrmann, J. Lin, C.R. Saha-Möller, R.W. Fischer, J.D.G. Correia, Angew. Chem. 106 (1994) 2545; Angew. Chem. Int. Ed. 33 (1994) 2476.

[8] (a) J.K.M. Mitterpleininger, N. Szesni, S. Sturm, R.W. Fischer, F.E. Kühn, Eur. J. Inorg. Chem. (2008) 3929;
(b) W.A. Herrmann, A.M.J. Rost, J.K.M. Mitterpleininger, N. Szesni, S. Sturm, R.W. Fischer, F.E. Kühn, Angew. Chem. 119 (2007) 7440; Angew. Chem. Int. Ed. 46 (2007) 7301.

[9] N. Gharah, S. Chakraborty, A.K. Mukherjee, R. Bhattacharyya, Inorg. Chim. Acta 362 (2009) 1089.

[10] H. Fukuda, K. Amimoto, H. Koyama, T. Kawato, Org. Biomol. Chem. 1 (2003) 1578.

[11] E. Roberts, E.E. Turner, J. Chem. Soc. (1927) 1832.

[12] M.M. Ismail, Indian J. Pharm. Sci. 48 (1986) 121.

[13] D.-P. Song, Y.-G. Li, R. Lu, N.-H. Hu, Y.-S. Li, Appl. Organomet. Chem. 22 (2008) 333.

[14] J.-C. Zhuo, Magn. Res. Chem. 37 (1999) 259.

[15] N.H. Patel, H.M. Parekh, M.N. Patel, Transition Met. Chem. 30 (2005) 13.

[16] C.M. Brewster, L.H. Millam, J. Am. Chem. Soc. 55 (1933) 763.

[17] K.K. Upadhyay, A. Kumar, S. Upadhyay, P.C. Mishra, J. Mol. Struct. 873 (2008) 5.

[18] J.-C. Zhuo, Magn. Reson. Chem. 34 (1996) 595.

[19] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, J.A. Montgomery, T. Vreven, K.N. Kudin, J.C. Burant, J.M. Millam, S.S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G.A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J.E. Knox, H.P. Hratchian, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, P.Y. Ayala, K. Morokuma, G.A. Voth, P. Salvador, J.J. Dannenberg, V.G. Zakrzewski, S. Dapprich, A.D. Daniels, M.C. Strain, O. Farkas, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J.V. Ortiz, Q. Cui, A.G. Baboul, S. Clifford, J. Cioslowski, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, C. Gonzalez, J.A. Pople, Gaussian-03, Rev. C.02, Gaussian Inc., Wallingford, CT, 2004.

[20] A.D. Becke, J. Chem. Phys. 98 (1993) 5648.

[21] C. Lee, W. Yang, R.G. Parr, Phys. Rev. B.: Condens. Matter 37 (1988) 785.

[22] P.J. Stephens, F.J. Devlin, C.F. Chabalowski, M.J. Frisch, J. Phys. Chem. 98 (1994) 11623.

[23] S.H. Vosko, L. Wilk, M. Nusair, Can. J. Phys. 58 (1980) 1200.

[24] W.J. Hehre, R. Ditchfield, J.A. Pople, J. Chem. Phys. 56 (1972) 2257.

[25] W.R. Wadt, P.J. Hay, J. Chem. Phys. 82 (1985) 284.

[26] H.B. Schlegel, J. Comput. Chem. 3 (1982) 214.

[27] G. Schaftenaar, J.H. Noordik, J. Comput. Aided Mol. Des. 14 (2000) 123.

[28] R. Dennington II, T. Keith, J. Millam, K. Eppinnett, W.L. Hovell, R. Gilliland, GaussView, Version 3.09, Shawnee Mission, KS, 2003.

[29] J. Tomasi, B. Mennucci, R. Cammi, Chem. Rev. 135 (2005) 2999.

[30] M. Cossi, G. Scalmani, N. Rega, V. Barone, J. Chem. Phys. 117 (2002) 43.

[31] M.M. Abu-Omar, P.J. Hansen, J.H. Espenson, J. Am. Chem. Soc. 118 (1996) 4966.

[32] L.S. Silbert, E. Siegel, D. Swern, J. Org. Chem. 27 (1962) 1336.

[33] W.E. Parker, C. Ricciuti, C.L. Ogg, D. Swern, J. Am. Chem. Soc. 77 (1955) 4037.

[34] (a) W.A. Herrmann, F.E. Kühn, P.W. Roesky, J. Organomet. Chem. 485 (1995) 243;
(b) W.A. Herrmann, P. Kiprof, K. Rypdal, J. Tremmel, R. Blom, R. Alberto, J.

Behm, R.W. Albach, H. Bock, B. Solouki, J. Mink, D. Lichtenberger, N.E. Gruhn, J. Am. Chem. Soc. 113 (1991) 6527;
(c) W.A. Herrmann, W.A. Wojtczak, G.R.J. Artus, F.E. Kühn, M.R. Mattner, Inorg. Chem. 36 (1997) 465;
(d) W.A. Herrmann, J.D.G. Correia, M.U. Rauch, G.R.J. Artus, F.E. Kühn, J. Mol. Catal. A: Chem. 118 (1997) 33.
[35] Y. Marcus, Chem. Soc. Rev. (1993) 409.
[36] C. Reichardt, in: C. Reichardt (Ed.), Solvents and Solvent Effects in Organic Chemistry, third ed., Wiley-VCH, Weinheim, 2003, pp. 472–474.
[37] E.V. Kudrik, A.B. Sorokin, Chem. Eur. J. 14 (2008) 7123.
[38] (a) A. Barandov, U. Abram, Inorg. Chem. 48 (2009) 8072;
(b) E. da Palma Carreiro, G. Yong-En, A.J. Burke, J. Mol. Catal. A: Chem. 235 (2005) 285;
(c) E. da Palma Carreiro, A.J. Burke, M.J.M. Curto, A.J.R. Teixeira, J. Mol. Catal. A: Chem. 217 (2004) 69;
(d) S. Stankovic, J.H. Espenson, Chem. Commun. (1998) 1579;
(e) W.A. Herrmann, R.M. Kratzer, H. Ding, W.R. Thiel, H. Glas, J. Organomet. Chem. 555 (1998) 293;
(f) C. Copéret, H. Adolfsson, K.B. Sharpless, Chem. Commun. (1997) 1565;
(g) J. Rudolph, K.L. Reddy, J.P. Chiang, K.B. Sharpless, J. Am. Chem. Soc. 119 (1997) 6189.
[39] S.-H. Wei, S.-T. Liu, Catal. Lett. 127 (2009) 143.
[40] C. Copéret, H. Adolfsson, J.P. Chiang, A.K. Yudin, J. Org. Chem. 65 (2000) 8651.
[41] (a) S.M. Nabavizadeh, M. Rashidi, J. Am. Chem. Soc. 128 (2006) 351;
(b) J.H. Espenson, W.W. Wang, J. Am. Chem. Soc. 120 (1998) 11335.
[42] Chemical shifts (ppm) for the methyl protons of MTO in ^{1}H NMR ($CDCl_3$) spectra: for free MTO $\delta(CH_3)$ = 2.67 ppm, see Ref. [6f]; for MTO + L15, L16 and L6 $\delta(CH_3)$ = 2.63–2.62 ppm, see Ref. [6f]; for MTO + L14, L17, L18 and L24 $\delta(CH_3)$ = 2.62 ppm; for MTO + L19, L20, L21, L22, L23 and L25 $\delta(CH_3)$ = 2.61 ppm.
[43] Chemical shifts (ppm) for the oxygens of MTO in ^{17}O NMR (CH_3NO_2) spectra: for free MTO $\delta(O)$ = 833 ppm; for MTO + L18 $\delta(O)$ = 835.5 ppm.