

## **Recent Advances in the Homogeneous Palladium-Catalyzed Aerobic Oxidation of Alcohols**

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This review is dedicated to Professor Habib Firouzabadi on the occasion of his 65<sup>th</sup> birthday and also his honorable retirement

The use of palladium catalysts for the oxidation of alcohols to aldehydes and ketones in the presence of various types of oxidants is well known. Recently, the advantages of using molecular oxygen as the oxidant in the Pd-catalyzed oxidation of alcohols have been explored. The aim of this review is to provide an overview on the most important homogeneous palladium-catalyzed aerobic oxidation of alcohols without a co-catalyst during last decade until the end of 2007.

**Keywords:** Aerobic oxidation, Palladium, Molecular oxygen, Alcohols, Homogenous Catalysts, Oxidation, Carbonyl Compounds

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### **INTRODUCTION**

The oxidation of organic compounds is an important and widely used reaction in laboratory scale organic synthesis as well as in large scale chemical industry [1]. There are hundreds of different reagents and methods available for the oxidation of organic chemicals. Although these methods exist and are very applicable for a laboratory scale, most of them share common disadvantages from an industrial point of view. Many industrial oxidation reactions are currently performed with stoichiometric amounts of oxidants such as peroxides, nitric acid or high oxidation state metal oxides. These oxidants are expensive and the processes where these oxidants are used generate organic and heavy metal wastes [2]. When reactions are scaled to tons instead of grams, the use of stoichiometric oxidants would not be an attractive option at all. For these kinds of reactions an alternative and environmentally benign oxidant is welcome.

An ideal oxidant for any large scale oxidation reaction should be easily accessible, cheap and non-toxic. As it happens, the best oxidant to fit this description is dioxygen [3]. It is easily available since it is present in air and the only by-product produced from its decomposition is water. There are few things however which make the use of molecular oxygen challenging: 1) although dioxygen has a high oxidation potential, it is not very reactive towards organic molecules. 2) the reactions where dioxygen is present are often radical reactions, which are hard to control. What is needed for efficient use of dioxygen is the appropriate catalyst which activates the dioxygen molecule and mediates the oxidation potential to right oxidation reaction.

Nowadays, a number of industrial processes are utilizing catalytic methods for aerobic oxidation, but their scope is limited, and chemical reagents such as transition metal oxides and chlorine based oxidants remain in common use. However, recent developments in homogeneous palladium catalysis point toward new opportunities for selective aerobic oxidation chemistry [4]. The aim of this review is to provide an

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overview on the most important homogeneous palladium-catalyzed aerobic oxidation of alcohols without a co-catalyst.

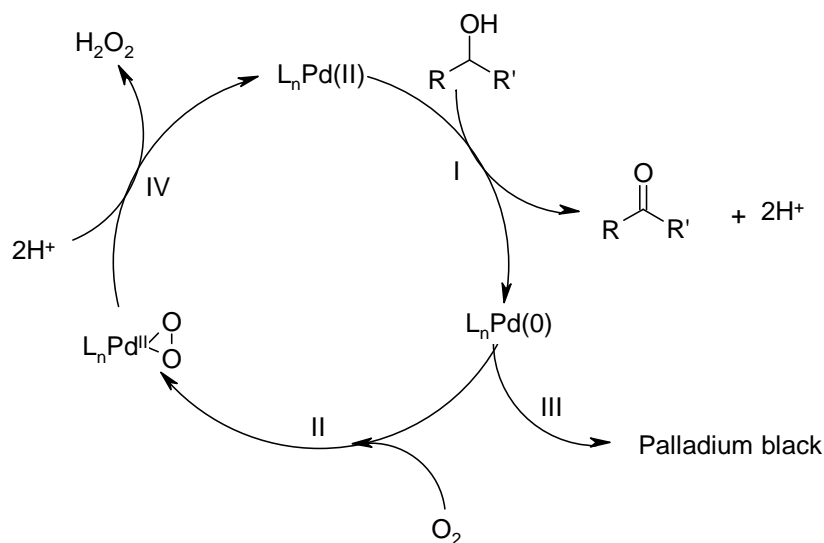
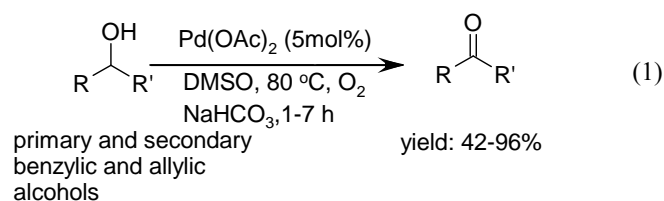
## Non-Asymmetric Aerobic Oxidation of Alcohols

### Initial works

In 1977, Blackburn and Schwartz reported the first example of palladium-catalyzed alcohol oxidation that underwent dioxygen-coupled turnover in the absence of a co-catalyst [5]. Echavarren and co-workers discovered that  $[\text{Pd}(\text{dba})_2](10\%)/\text{PPh}_3(30\%)$  catalyzes the oxidation of allylic alcohols in toluene under air atmosphere. Although modest yields were generally obtained (38–56%, 90% for cinnamyl alcohol) [6], but these methods can be considered as the first example of palladium catalyzed aerobic oxidation of alcohols.

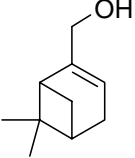
### $\text{Pd}(\text{OAc})_2$ / DMSO system

In 1998, Peterson and Larock disclosed an efficient oxidation of primary and secondary benzylic alcohols to the corresponding aldehydes and ketones using 5 mol% of  $\text{Pd}(\text{OAc})_2$  in DMSO at 80 °C under an atmosphere of oxygen (Table 1) [7]. It was shown that the presence of an inorganic base ( $\text{NaHCO}_3$ ) generally improved the rates and yields. The



**Scheme 1.** Oxidation mechanism for the aerobic oxidation of alcohols in  $\text{Pd}(\text{OAc})_2/\text{DMSO}$  system

**Table 1.** Oxidation of alcohols by  $\text{Pd}(\text{OAc})_2/\text{DMSO}^a$

entry	alcohol	time/h	yield/% <sup>b</sup>
1	benzyl alcohol	2	90
2	benzhydrol <sup>c</sup>	1	95
3	cinnamyl alcohol	1.5	69
4		2	50

<sup>a</sup>  $\text{Pd}(\text{OAc})_2$  (5 mol %), alcohol (1mmol) DMSO (1 mL), 80 °C,  $\text{O}_2$

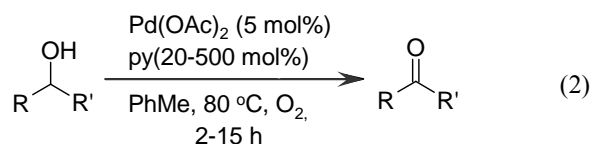
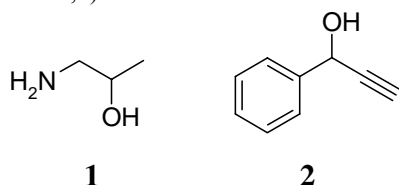
<sup>b</sup>GLC yield, <sup>c</sup> $\text{NaHCO}_3$  (2equiv.)

reactions were clean, and the corresponding carbonyl compounds are produced in moderate to excellent yields (42–96%) (Eq.1). This system was not successful for aerobic oxidation of allylic alcohols (Table 1, entries 3, 4).

In 2002 Stahl and co-workers proposed that the  $\text{Pd}(\text{II})$ -catalyzed aerobic oxidation of alcohols proceeded through a reduction of  $\text{Pd}(\text{II})$  to  $\text{Pd}(0)$  by the alcohol (Scheme 1) [8].  $\text{Pd}(0)$  then reacts with dioxygen to produce a palladium peroxo intermediate (step II). The role of DMSO as the solvent is also to coordinate  $\text{pd}(0)$  and prevent the formation of palladium black (step III).

**Pd(OAc)<sub>2</sub> / pyridine system**

Meanwhile, Uemura and co-workers reported a catalyst systems; Pd(OAc)<sub>2</sub> (5 mol%)/pyridine (py, 20 mol%)/Molecular Sieve 3Å (MS3A) for the aerobic oxidation of alcohols in toluene at 80 °C [9]. This efficient system can oxidize all types of alcohols generally in high yields (80–100%)(Eq. 2). Palladium black formation can be accelerated by complexation of the alkenes to palladium so oxidation of alcohols containing C=C bond, require the use of excess pyridine (500 mol%) (Table 2, entries 4, 5). Vicinal alcohols **1** and **2** appear to be ineffective substrates, possibly reflecting substrate chelation. Several alcohol-protecting groups including tetrahydropyranyl, *tert*-butyldimethylsilyl, and benzyl ethers were compatible with the reaction conditions, (Table 2, entries 6,7).



primary and secondary  
benzylic, aliphatic and  
allylic alcohols

yield: 58-100%

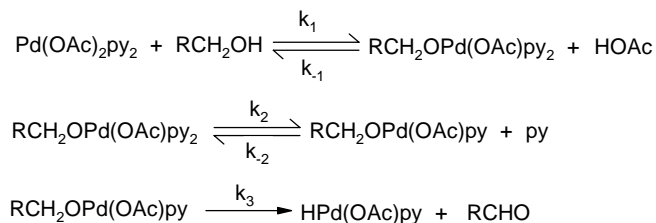
It was proposed that the catalytic cycle proceeds via a Pd(II)-alcoholate formed from the substrate and the starting Pd(II)-pyridine complex (Scheme 2). Kinetic studies [8] indicated that (py)<sub>2</sub>Pd(OAc)<sub>2</sub> reacted with the alcohol in a pre-equilibrium step to produce the palladium(II) alkoxide (*k*<sub>1</sub>, Scheme 2) and coordinated acetate serves as an internal base in this step. Subsequently, one of the two pyridine ligands must dissociate (*k*<sub>2</sub>) prior to the rate-limiting β-hydride elimination of the alkoxide ligand (*k*<sub>3</sub>). Two principle mechanisms have been proposed for the dioxygen-coupled oxidation of the reduced catalyst: 1) oxygenation of Pd(0) to form a η<sup>2</sup>-peroxo species (Scheme 3, pathway **A**) [10], and 2) direct reaction of molecular oxygen with a Pd(II)-hydride intermediate (Scheme 3, pathway **B**) [8, 11].

**Table 2.** Oxidation of alcohols by Pd(OAc)<sub>2</sub> /Pyridine<sup>a</sup>

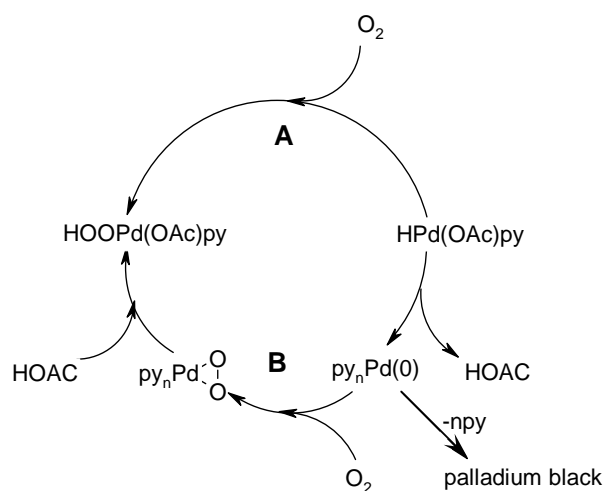
entry	alcohol	pyridine(mmol)	time/h	yield/% <sup>b</sup>
1	benzyl alcohol	0.2	2	100
2	1-phenylethanol	0.2	2	100
3	dodecan-1-ol	0.2	2	98
4	cinnamyl alcohol	5	4	69
5		5	6	88
6		1	4	89
7		1	4	86

<sup>a</sup> Pd(OAc)<sub>2</sub> (0.05 mol), alcohol (1mmol), toluene (10 mL), 80 °C, O<sub>2</sub>,  
<sup>b</sup>GLC yield.

Some times later on, Stahl and his co-workers showed that molecular sieves can enhance the rate of the Pd(OAc)<sub>2</sub>/pyridine-catalyzed reaction by serving as a heterogeneous Brønsted base. On the other hand, molecular sieves increases the catalyst stability. The latter effect seems to arise from the ability of MS3A to provide a heterogeneous surface that hinders bulk aggregation of palladium metal [12].



**Scheme 2.** Oxidation mechanism for the aerobic oxidation of alcohols with Pd(OAc)<sub>2</sub>/ pyridine system

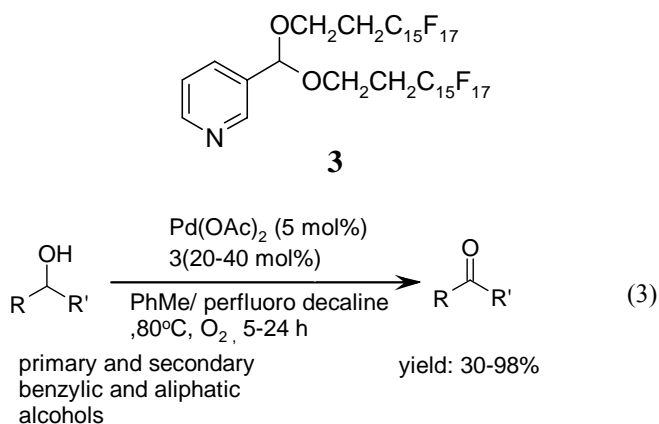


**Scheme 3.** Differences between Stahl and Uemura's mechanisms

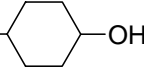
### **Pd(OAc)<sub>2</sub> / perfluoroalkylated pyridine system**

The development of environmentally friendly technologies is nowadays a critical point for the chemical industry. Some of the aspects related to this problem are concerning the use of nontoxic, safe solvents and reagents as well as the possibility of catalyst recycling. In this respect, there is an increasing demand for new methods which can meet these needs [13]. The Fluorous Biphasic System technique represents an important solution to these problems [14]. The fluorous medium is especially suitable for oxidation reactions as the solubility of dioxygen is very high in fluorous solvent and perfluoroalkanes are extremely resistant to oxidation [15].

Uemura *et al.* successfully oxidized various types of primary and secondary alcohols using molecular oxygen, catalyzed by palladium acetate in the presence of a novel perfluoroalkylated pyridine **3** as a ligand in a fluorous biphasic (toluene/perfluorodecalin) system [16] (Eq. 3). Oxidation of primary and secondary benzylic alcohols with an electron-withdrawing group is very efficient under these conditions (Table 3, entries 1, 2). On the other hand, the oxidation of chlorobenzyl alcohols, in particular, the *ortho*-substituted one proceeded more slowly than that of benzyl alcohol (Table 3, entries 3). In addition, in the oxidation of allylic alcohols such as cinnamyl alcohol and geraniol extensive catalyst deactivation was occurred. The recycling of the catalyst was possible at least 5 times without a significant loss of its catalytic activity. This catalytic system was also applied to the oxidation of aliphatic alcohols as well (Table 3, entries 5-7) although a longer reaction time was generally required.



**Table 3.** Oxidation of alcohols by Pd(OAc)<sub>2</sub> /perfluoroalkylated-pyridine<sup>a</sup>

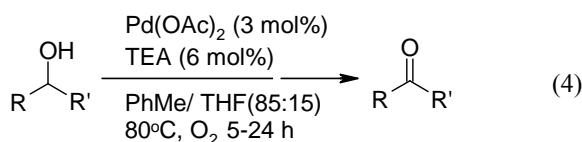
entry	alcohol	Time(h)	Yield(%) <sup>b</sup>
1	benzyl alcohol	5	94
2	<i>p</i> -chlorobenzyl alcohols	5	71
3	<i>o</i> -chlorobenzyl alcohols	24	65
4	1-phenylethanol	5	98
5	dodecan-1-ol	10	76
6	dodecan-2-ol	9	90
7	t-Bu-  -OH	24	89

<sup>a</sup>Alcohol (0.5 mmol), Pd(OAc)<sub>2</sub>, **4** (0.025 mmol), **2** (0.1 mmol), MS3A(200 mg), toluene (2 mL), perfluorodecalin(2 mL), 80°C, O<sub>2</sub>. <sup>b</sup>GLC yield

### **Pd(OAc)<sub>2</sub> / triethylamine system**

The scope of previous Pd-catalyzed aerobic oxidations are often limited by the use of high temperatures, and therefore,

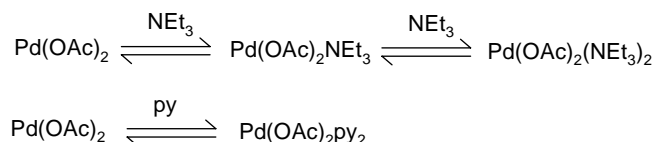
the development of more active Pd-catalysts which are effective at low temperature is highly desirable for improving the utility of these oxidation reactions. In 2002, Sigman and co-workers reported a new reagent system composing of Pd(OAc)<sub>2</sub>(3%) and triethylamine (TEA, 6%). This method is an effective alternative to the Pd(OAc)<sub>2</sub>/pyridine catalyst system and allows alcohol oxidation reactions to be conducted at room temperature [17] (Eq. 4). Primary and secondary benzylic and aliphatic alcohols were oxidized by this system but cinnamyl alcohol was a poor substrate for the oxidation (even by 5 mol% of Pd(OAc)<sub>2</sub> and 300 mol% of TEA) causing the precipitation of palladium metal.



primary and secondary  
benzylic, aliphatic and  
allylic alcohols

yield: 50-98%

To help elucidate the role of TEA, the dependence of TEA concentration on the initial rate of benzyl alcohol oxidation was evaluated. Initially increasing TEA concentration led to enhanced rates, but further increasing of TEA concentration beyond 8 mol% reduced the observed oxidation rate. While TEA was necessary for oxidation at room temperature, these results indicated that high concentrations of TEA inhibit the reaction. <sup>1</sup>H NMR analysis indicate that there is an equilibrium between three Pd species that includes free Pd(OAc)<sub>2</sub> along with both Pd(OAc)<sub>2</sub>NEt<sub>3</sub> and Pd(OAc)<sub>2</sub>(NEt<sub>3</sub>)<sub>2</sub> (Scheme 4). As the concentration of TEA was increased, the equilibrium favors Pd(OAc)<sub>2</sub>(NEt<sub>3</sub>)<sub>2</sub>. So Pd(OAc)<sub>2</sub>NEt<sub>3</sub> is the catalytically active species at room temperature (Scheme 4).



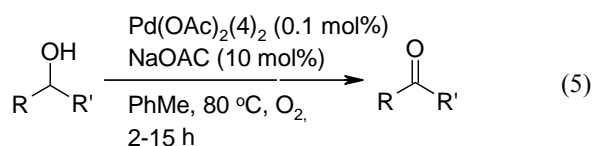
**Scheme 4.** Proposed equilibria are based on NMR experiments

In contrast to the use of TEA, the use of pyridine results in a single Pd-species, Pd(OAc)<sub>2</sub>py<sub>2</sub>, at room temperature and 80 °C. From these results, it is apparent that the nature and

number of nitrogen-based ligands on Pd play a vital role in catalyst activity.

### Pd(OAc)<sub>2</sub> / nano-sized pyridine system

Nano-sized pyridine ligands having tetraphenylphenyl-moiety were synthesized (Scheme 5) [18]. These ligands showed a remarkable effect in homogeneous transition metal catalyzed reactions. Pd(II) complexes with tetraphenylphenyl substituted pyridine ligands showed high catalytic activity in alcohol oxidation suppressing Pd black formation and maintains the catalytic activity for a long time (Eq. 5). The result of Pd(OAc)<sub>2</sub>(**4**)<sub>2</sub> catalyzed air oxidation of various alcohols are shown in Table 4 [19].



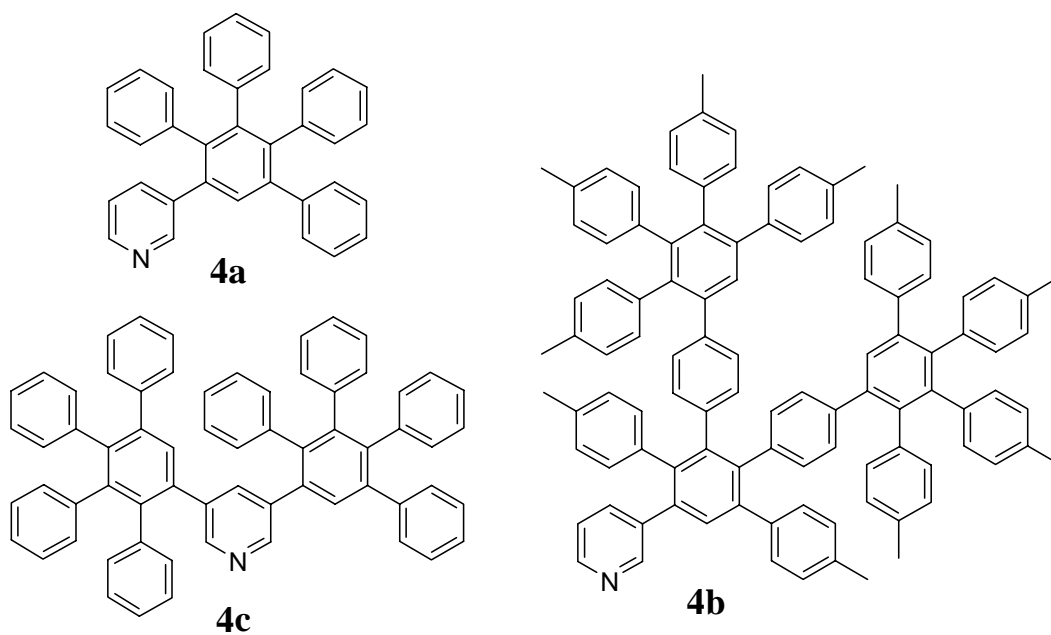
primary and secondary  
benzylic and aliphatic  
alcohols

24-96% yield

As shown in Table 4, Pd(OAc)<sub>2</sub> and Pd(OAc)<sub>2</sub>(Py)<sub>2</sub> (Py = pyridine) showed no or low catalytic activity in the oxidation of 1-phenylethanol and the Pd catalyst decomposed completely into Pd black (entries 1-2). Similarly, Pd(OAc)<sub>2</sub>(3-PhPy)<sub>2</sub> and Pd(OAc)<sub>2</sub>(3,5-diPhPy)<sub>2</sub> resulted in complete Pd black formation within 6 h and yielded acetophenone in ca. 30% (Table 4, entries 3-4). In contrast, Pd(OAc)<sub>2</sub>(**4a**) afforded acetophenone in 87% yield without the Pd black formation (Table 4, entry 5). It was also shown that the higher dendritic analogue Pd(OAc)<sub>2</sub>(**4b**) is even a more efficient catalyst (Table 4, entry 6), achieving the highest TON=1480 (TON: Turn over number) (entry 7). Pd(OAc)<sub>2</sub>(**4c**) also catalyzed the reaction without the Pd black formation (Table 4, entry 8). The marked effects of **4a** and **4b** over pyridine (Py) ligands were also observed in the oxidation of various alcohols under air.

### Pd(OAc)<sub>2</sub> / bathophenanthroline system

In many examples of homogeneous oxidative systems, toluene is used as solvent. However if these oxidations could be performed in water, they would be considerably safer,



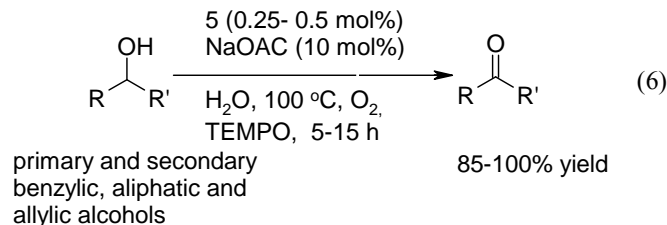
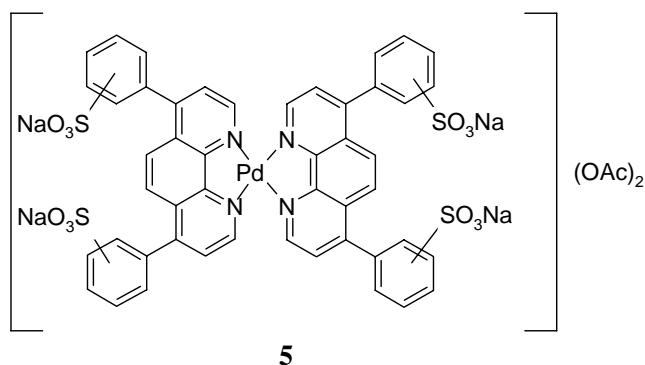
Scheme 5. Pyridine ligands having 2,3,4,5-tetraphenylphenyl moiety

Table 4. Effect of pyridine ligands on palladium-catalyzed air oxidation of alcohols

entry	alcohol	ligand <sup>a</sup>	time/h	yield/% <sup>b</sup>	Pd black formation <sup>c</sup>
1	1-phenylethanol <sup>d</sup>	none	24	trace	+
2		Py	24	23	+
3		3-PhPy	6	34	+
4		3,5-diPhPy	6	32	+
5		<b>4a</b>	72	87	-
6		<b>4b</b>	72	>99 (95)	-
7 <sup>e</sup>		<b>4b</b>	96	74	-
8		<b>4c</b>	72	63	-
9	2-octanol <sup>e</sup>	Py	2	21	+
10		<b>4a</b>	96	69	-
11		<b>4b</b>	96	79 (75)	-

<sup>a</sup> The ligand of the Pd(OAc)<sub>2</sub>(ligand)<sub>2</sub>. <sup>b</sup> Determined by GC. Isolated yields in parentheses. <sup>c</sup> +: Complete Pd black formation. -: No Pd black formation. <sup>d</sup>1-Phenylethanol (2 mmol), Pd(OAc)<sub>2</sub>(ligand)<sub>2</sub> (0.002 mmol), NaOAc (0.2mmol), and toluene (1 mL), 80 °C. <sup>e</sup>2-Octanol (2.5 mmol), Pd(OAc)<sub>2</sub>(ligand)<sub>2</sub> (0.0025 mmol), NaOAc (0.25 mmol), and toluene (0.8 mL), 80 °C.

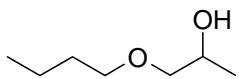
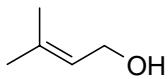
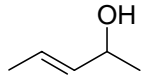
cheaper, and more environmentally friendly. Sheldon and co-workers described the aerobic oxidation of alcohols using a water soluble palladium(II) bathophenanthroline complex **5** as a stable, recyclable catalyst [20]. They demonstrated that using 0.25-0.5 mol % of catalyst with 30 bar air at 100 °C, selectivity of >95% was generally obtained with complete conversion in 5-15 h (Table 5, Eq. 6).



Secondary alcohols generally afforded the corresponding ketones in essentially quantitative yield (Table 5, entries 2, 4). However, primary aliphatic alcohols afforded the corresponding carboxylic acids (Table 5, entries 1, 3). In the case of aliphatic alcohols, addition of catalytic amounts of 2,2,6,6-tetramethylpiperidinyl-1-oxyl (TEMPO) were suppressed the overoxidation to the carboxylic acid (Table 5, entry 3). Using the same protocol, oxidation of primary allylic and benzylic alcohols afforded the corresponding aldehydes in high selectivity without the need for addition of TEMPO.

Since the reaction takes place in the aqueous phase, where the catalyst resides, the alcohol substrate should be at least sparingly soluble in water. Most alcohols were only partially soluble in water, which means that the alcohol concentration

**Table 5.** Oxidation of alcohols by Pd(OAc)<sub>2</sub> / bathophenanthroline<sup>a</sup>

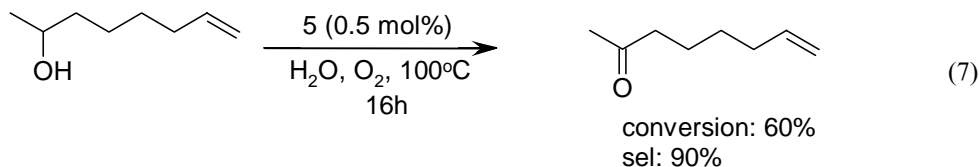
entry	alcohol	time(h)	yield (%) <sup>b</sup>
1	benzyl alcohol	10	99.8
2	1-phenylethanol	10	100
3	1-pentanol <sup>c</sup>	15	97
4		10	100
5		10	96
6		9	83

<sup>a</sup> Alcohol (10 mmol), **5** (0.25 mol%), water (50 g), NaOAc (1 mmol), pH=11.5, 100°C, O<sub>2</sub> (30 bar). <sup>b</sup> Selectivity to aldehyde (GC yield). <sup>c</sup> TEMPO (4 equiv. to Pd).

and, hence, the rate remain constant throughout most of the reaction. For the smaller (more soluble) alcohols, such as pentan-2-ol, cyclopentanol, cyclohexanol, etc., rates have an order of magnitude higher (TOF= 100 h<sup>-1</sup>) than those of other aerobic alcohol oxidations reported earlier [21]. In a homologous series of alkanols, the rate decreases with increasing chain length, consistent with the decreasing solubility in water. Nonetheless, even higher alcohols were oxidized at reasonable rates; e.g., octan-2-ol and nonan-2-ol gave TOFs of 20 and 14 h<sup>-1</sup>, respectively. Higher rates could be achieved with these less soluble alcohols through the addition of co-solvents or additives, such as alkanesulfonates or anthraquinone-2-sulfonate, which increase the concentration of the alcohol in the water phase through a micellar effect.

Analogous to most other homogeneous oxidation catalysts, this protocol seems to suffer from the low tolerance for (coordinating) functional groups in the solvent or the substrate. Catalyst **5** could only tolerated a single ether functionality (in butyl proxitol, Table 5, entry 4), and all other functional groups proved insurmountable, as these coordinated more tightly to palladium (Eq. 7) [20b].

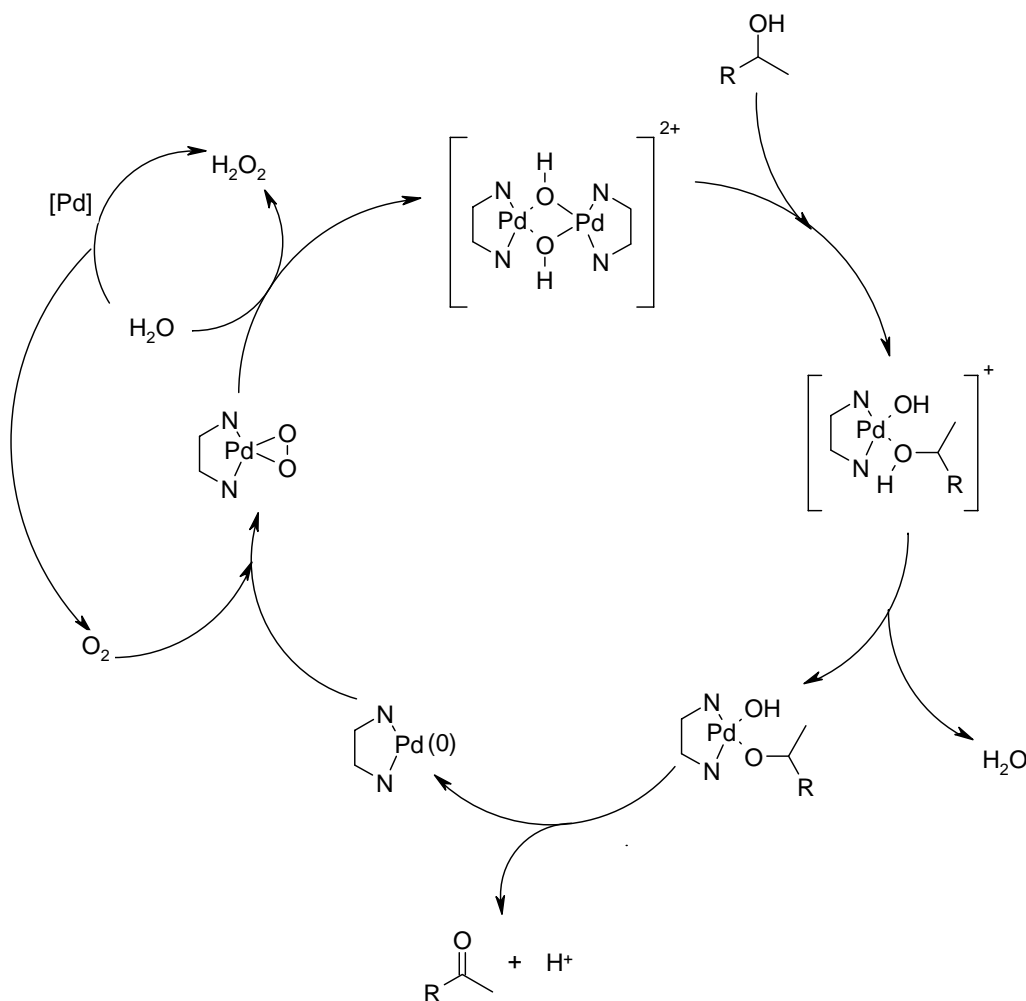
On the basis of the results of kinetic studies and investigations of the nature of the catalyst, authors proposed



the catalytic cycle depicted in scheme 6 for aerobic oxidation of alcohols using **5** as catalyst. In the first step, the hydroxyl-bridged-dimer dissociates, via reaction with the alcohol substrate, to form a monomeric complex containing a hydroxide ligand and a coordinated alcohol molecule [20b].

Loss of water from this complex, which is not base dependent, would afford a labile alkoxy-palladium(II) complex, which would undergo facile  $\beta$ -hydride elimination to afford the carbonyl product and either a palladium hydride species or palladium(0) and a proton. Subsequent reaction of the

palladium(0) complex with dioxygen will afford an  $\eta$ -peroxypalladium(II) complex. Reaction of the latter species with water affords hydrogen peroxide, via an intermediate hydroperoxopalladium(II) complex, and regenerates the hydroxyl-bridged dimer. Since the catalyst is present in the water phase, it will cause rapid decomposition of the hydrogen peroxide. In contrast, when the palladium catalyst resides in the organic phase (chlorobenzene solvent),  $\text{H}_2\text{O}_2$  forms a separate, aqueous phase, thus circumventing its decomposition by the catalyst.



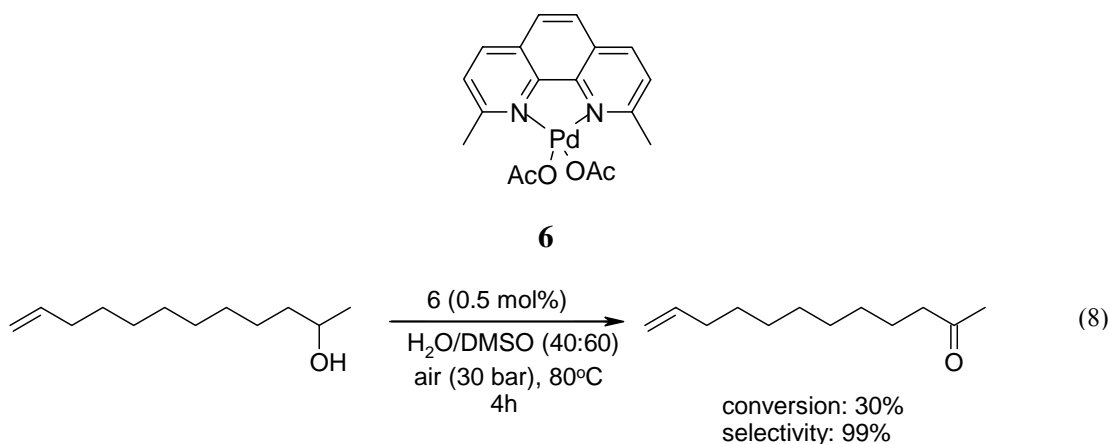
**Scheme 6.** Mechanism of the **5** catalyzed oxidation of alcohols.

**Pd(OAc)<sub>2</sub>/ neocuproine**

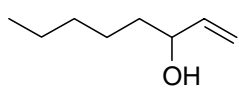
By Pd(OAc)<sub>2</sub>/ neocuproine **6** as catalyst in water/ DMSO mixtures Sheldon and co-workers have oxidized a wide range of alcohols and also functionalized alcohols with high selectivity (Eq. 8) [22]. Secondary and primary aliphatic alcohols reacted very quickly to give the corresponding ketones by a loading as low as 0.1 mol% of catalyst (Table 6). It is noteworthy that under these conditions 2-hexanol was converted at rates two orders of magnitude faster in comparison with previous catalytic methods (Table 6, entries, 1). With 0.005 mmol (0.025 mol%) (neocuproine)/Pd(OAc)<sub>2</sub> catalyst, the turnover frequency increased even further to ca. 1800 h<sup>-1</sup>. Allylic primary alcohols can be oxidized smoothly (Table 6, entries, 5, 6), whereas primary aliphatic alcohols are oxidized to a mixture of aldehydes and acids (Table 6, entry, 2).

Notably, aldehydes can be produced selectively by adding TEMPO.

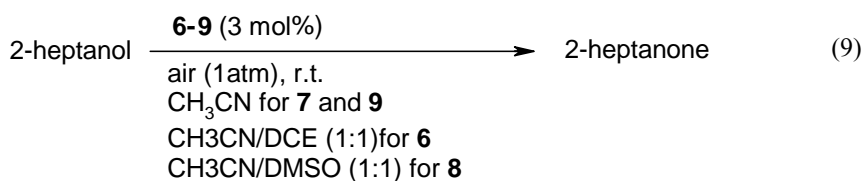
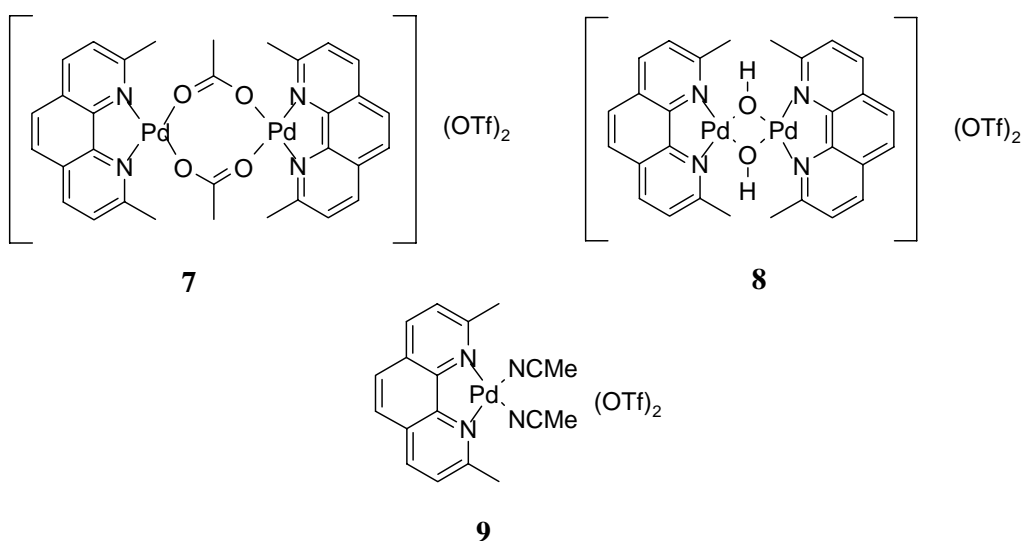
Way mouth and co-workers have investigated complexes **6-9** for the catalytic oxidation of 2-heptanol to 2-heptanone in acetonitrile at room temperature under an ambient pressure of air (Eq. 9) [23]. Under these mild conditions, complex **7** (3 mol % Pd) exhibited a fast initial TOF (TOF<sub>i</sub>) (TOF<sub>i</sub> = 78 Pd atom<sup>-1</sup> h<sup>-1</sup>) for the oxidation of 2-heptanol but the rate was decreased rapidly to afford a 36% yield of 2-heptanone after 24 h. The  $\mu$ -hydroxo Pd dimer **8** showed behavior similar to that of the mixed acetate/triflate Pd dimer **7** but exhibited lower initial rates (TOF<sub>i</sub> = 2.0 (Pd atom<sup>-1</sup>) h<sup>-1</sup>) and yield. In contrast, under these conditions, both (neocuproine)Pd(OAc)<sub>2</sub> **6** and (neocuproine)Pd(MeCN)<sub>2</sub>(OTf)<sub>2</sub> **9** were ineffective catalysts (TOF<sub>i</sub> = 0.24 and 0.16 (Pd atom<sup>-1</sup> h<sup>-1</sup>), respectively).



**Table 6.** Oxidation of alcohols by Pd(OAc)<sub>2</sub> / neocuproine <sup>a</sup>

entry	alcohol	time(h)	TOF (h <sup>-1</sup> )	conv. (%) <sup>b</sup>	sel.(%)
1	2-hexanol	2	>>500	100	100
2	1-heptanol	2.5	200	40	75
3	cycloctanol	3	400	93	99
4	1-phenylpropananol	3	300	80	99
5	cinnamaldehyde	10	135	88	99
6		3	400	95	96

<sup>a</sup> **6** (0.1 mol%), 100 °C, 50 bar 8% O<sub>2</sub>, water/DMSO (1:1).

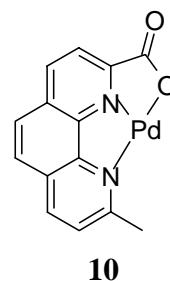


Waymouth proposed that the presence of both triflate and acetate counter ions in complex **7** allows for fast alcohol binding and fast deprotonation of the palladium-bound alcohol species, followed by  $\beta$ -hydride elimination. The slow rate observed with the diacetate **6** suggests that an open coordination site for the alcohol is a key feature leading to fast oxidation with **7**. The slow rate observed with the ditriflate **9** implies that the presence of a suitable base to deprotonate the palladium-bound alcohol is also important. They attributed the slower rate of **8** (relative to **7**) to the slow dissociation of the  $\mu$ -OH dimer in the absence of acetic acid. These data suggest that a weakly coordinating ligand and an intramolecular base are necessary to achieve high TOFs with the neocuproine/palladium(II) system under mild conditions.

Despite the fast initial rates of alcohol oxidation with complexes **7** and **8**, the rates decrease rapidly with conversion, implicating that these catalysts are deactivated, even under these mild reaction conditions. The time course of the reaction reveals that the rate of alcohol oxidation decreases linearly with percent yield of 2-heptanone. Palladium black was not observed in the catalysis with **7** during the time in which the

reaction was monitored and, therefore, cannot account for this loss of activity.

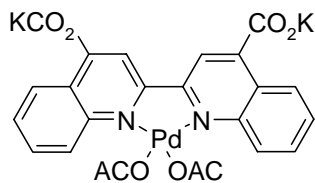
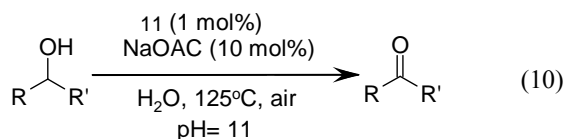
Analysis of the palladium-containing products revealed the presence of the cationic palladium carboxylate **10** indicating that one of the methyl groups of the 2,9-dimethylphenanthroline ligands is oxidized to the carboxylate. This complex was inactive as a catalyst for alcohol oxidation. Complex **10** was also formed in the aerobic oxidation of 2-heptanol with the  $\mu$ -hydroxo Pd dimer **8**.



#### Pd(OAc)<sub>2</sub>/biquinoline

Buffine and co-workers have shown Pd(OAc)<sub>2</sub>/biquinoline **11** as a water-soluble catalyst system can be used for the aerobic oxidation of secondary and primary alcohols (Eq. 10)

[24]. Secondary alcohols afforded the corresponding ketones in high yield with selectivities greater than 90% (Table 7, entries 1-3). Aliphatic primary alcohols were fully oxidized to carboxylic acid products under the same reaction conditions, with various amounts of ester byproduct (Table 7, entry 4). Benzyl alcohol can be converted to a mixture of benzaldehyde and benzoic acid, where the relative amounts were dependent on the reaction conditions, while substituted benzylic alcohols gave primarily benzaldehyde derivatives. In contrast to the related systems, the catalyst used in this study is tolerant of additional coordinating groups on the benzyl alcohol substrate (e.g. 4-methylthiobenzyl alcohol and 3,4-dimethoxybenzyl alcohol, Table 7, entries 5, 6). In all examples of alcohol oxidation, air was used as primary oxidant.

**11**

primary and secondary  
benzylic and aliphatic  
alcohols

conversion: 63-100%  
selectivity: 82-100%

### **Pd(OAc)<sub>2</sub>/N-heterocyclic carbene system**

In recent years, *N*-heterocyclic carbenes (NHCs) have received increasing attention as possible alternative ligands for the widely used air sensitive phosphine ligands in Pd-catalyzed cross-coupling reactions [25]. The primary advantage of these ligands appears to be that they do not easily dissociate from the metal center and therefore result in high

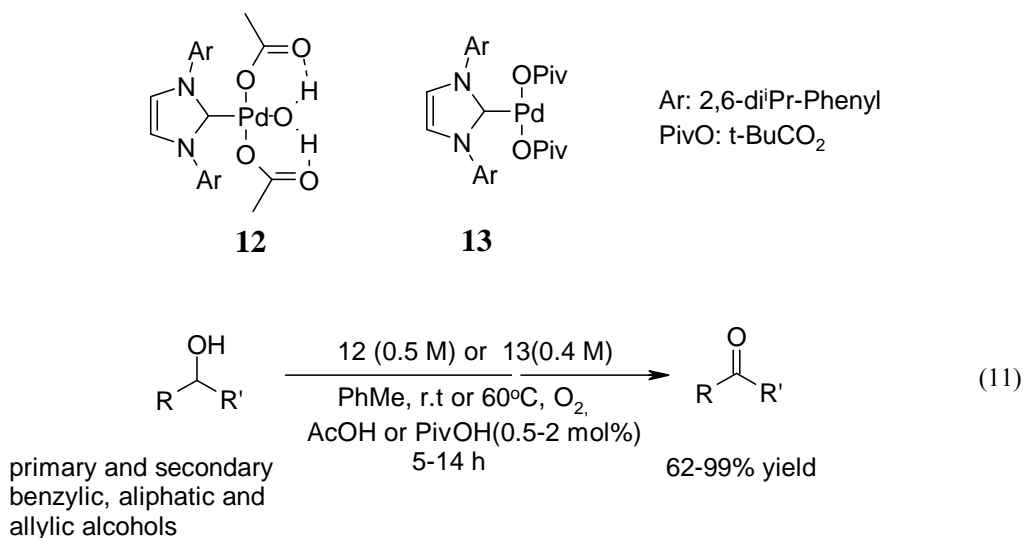
**Table 7.** Oxidation of alcohols by Pd(OAc)<sub>2</sub> / neocuproine<sup>a</sup>

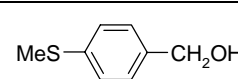
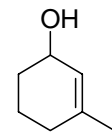
entry	alcohol	TOF (h <sup>-1</sup> )	conv. (%) <sup>b</sup>	sel.(%)
1	2-hexanol	5.4	100	92
2	1-phenylethanol	5.1	97	100
3	cyclopentanol	4.1	100	94
4	1-hexanol	3.5	92	90 <sup>b</sup>
5		3.8	100	87
6		5.4	98	95

<sup>a</sup> Alcohol (10 mmol), **11** (1 mol%), water (50 ml), NaOAc (10 mol%), O<sub>2</sub> (300 psi), 125°C, pH= 11. <sup>b</sup> Major product is hexanoic acid.

stability of the active Pd species. Moreover, the strong  $\sigma$ -donation of NHCs, their low toxicity, as well as their tunable steric bulk and topology makes them superior ligands compared to the traditional tertiary phosphines. Sigman and co-workers reported an *N*-heterocyclic carbene coordinated catalysts **12** and **13** that successfully oxidize alcohols at quite low catalyst loadings (0.5-1 mol%) [26]. The catalysts is most effective in the presence of catalytic quantities of acetic acid (2 mol%) or pivalic acid (PivOH) (0.5 mol%) (Eq. 11). A crystal structure of the pre-catalyst **12** revealed hydrogen-bonding interactions between the acetate and water ligands, supporting earlier hypotheses that acetate could serve as an internal base to facilitate the formation of a palladium alkoxide intermediate.

Among the catalysts, **13** used the mildest reaction conditions (room temperature, 1 mol % of catalyst, and air as oxidant) but the substrate scope of this catalyst was the most limited (Table 8). The advantages of catalyst **12** were (1) low catalyst loadings for a Pd-catalyzed alcohol oxidation (0.1 to 1.0 mol %), (2) replacement of O<sub>2</sub> with ambient air by raising [AcOH] (2 to 5 mol %), (3) a diastereoselective oxidation of substituted cyclohexanols, and (4) effective oxidation of allylic alcohols. However, catalyst **12** showed the greatest ability to be modulated through changing temperature, the oxygen concentration, and amounts of additive AcOH or Bu<sub>4</sub>NOAc.

**Table 8.** Oxidation of alcohols by Pd(OAc)<sub>2</sub> / N-heterocyclic carbene

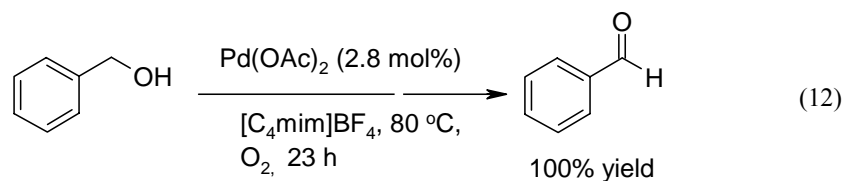
entry	alcohol	cat. <sup>a</sup> (mol%)	oxidant	additive (mol%)	temp. (°C)	time (h)	yield (%) <sup>b</sup>
1		<b>12</b> (0.5)	O <sub>2</sub>	AcOH(2)	60	13	90
2		<b>12</b> (0.75)	O <sub>2</sub>	Bu <sub>4</sub> NOAc(5)	60	14	95
3		<b>13</b> (1)	Air	PivOH(0.5)	rt	14	92
4	1-phenylethanol	<b>12</b> (0.5)	O <sub>2</sub>	AcOH(2)	60	5	99
5		<b>12</b> (0.5)	Air	AcOH(5)	60	14	99
6		<b>13</b> (1)	Air	PivOH(0.5)	rt	14	99
7	2-decanol	<b>12</b> (0.5)	O <sub>2</sub>	AcOH(0.5)	60	13	99
8		<b>13</b> (1)	Air	PivOH(0.5)	rt	14	97
9		<b>12</b> (0.5)	O <sub>2</sub>	AcOH(2)	60	12	92
10		<b>13</b> (1)	Air	PivOH(0.5)	rt	14	99

<sup>a</sup> Reaction with **12**: 0.5 M in toluene. Reactions with **13**: 0.4 M in toluene. <sup>b</sup>GLC yield.

### Pd(OAc)<sub>2</sub>/ionic liquid system

Over the last decade, growing attention has been devoted to the use of ionic liquids (ILs) as solvents for organic synthesis, a fact manifested by the increasing rate at which papers and reviews on this topic are being published [27]. The strong interest in ILs for catalyzed reactions is due to the

expected immobilization of the catalyst in the IL that would allow the recycling of the tandem catalyst/solvent. Furthermore, ILs have a rate acceleration effect on some catalytic reactions, and they are often considered as green alternatives to volatile organic solvents although their toxicity and biodegradability are yet to be fully determined [28].

**Table 9.** Pd catalyzed aerobic oxidation of benzyl alcohol in ionic liquids

entry	ionic liquid <sup>a</sup>	Pd(OAc) <sub>2</sub> (mol%)	time (h)	yield(%)		
				benzaldehyde	benzoic acid	dibenzyl ether
1	[C <sub>6</sub> mim]Cl	0.5	28	12.8	5.2	10.8
2	[C <sub>4</sub> mim]BF <sub>4</sub>	0.9 <sup>b</sup>	18	13.4	0	12.7
3	[C <sub>4</sub> mim]Br	2.8	23	0	0	0
4	[C <sub>4</sub> mim]BF <sub>4</sub>	2.8	23	100	0	0
5	[C <sub>4</sub> mim]BF <sub>4</sub>	5	15	90	0	0

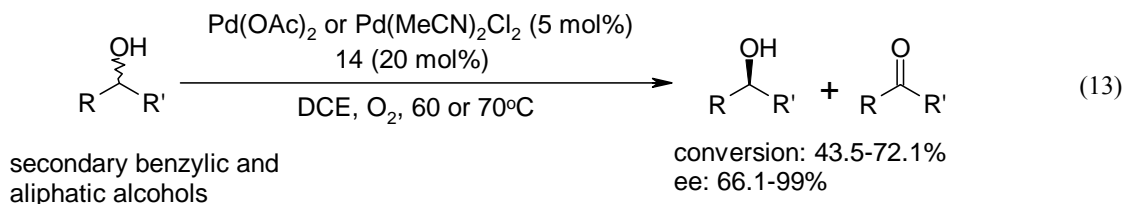
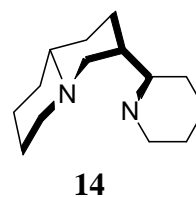
<sup>a</sup>[C<sub>4</sub>mim] = Butylmethylimidazolium cation. <sup>b</sup>[C<sub>4</sub>mim]<sub>2</sub>[PdCl<sub>4</sub>] was used,

Seddon and Stark have quantitatively oxidized benzyl alcohol and 1-phenylethanol to benzaldehyde and acetophenone respectively, using Pd(OAc)<sub>2</sub> as the catalyst and 1 atm of O<sub>2</sub> in an ionic liquid, [C<sub>4</sub>mim][BF<sub>4</sub>], at 80°C (Eq. 12 and Table 9) [29]. Both the catalyst and the ionic liquid were claimed to be re-used for at least five recycles, but, to preclude overoxidation of the benzaldehyde to benzoic acid, the catalytic system has to be dried from time to time to remove the water that accumulated during the reaction and work-up.

reported by two independent teams led by Sigman [30] and Stoltz [31]. The Sigman group reported that the use of Pd(OAc)<sub>2</sub> in conjunction with **14** and O<sub>2</sub> resulted in highly enantioselective oxidations of secondary benzylic and aliphatic alcohols in dichloroethane at 60 °C (Table 10, Eq. 13). Alternatively, Stoltz reported that a catalyst comprised of Pd(nbd)Cl<sub>2</sub> (nbd: norbornyl diene) and **14** produced similar results in toluene (Table 11, Eq. 14).

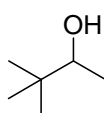
### Pd(II)-Catalyzed Aerobic Oxidative kinetic resolution of Alcohols

In early 2001, the successful application of Pd(II) catalysts to the oxidative kinetic resolution of secondary alcohols using Pd(II) salts and a natural diamine, (-)-sparteine **14**, was

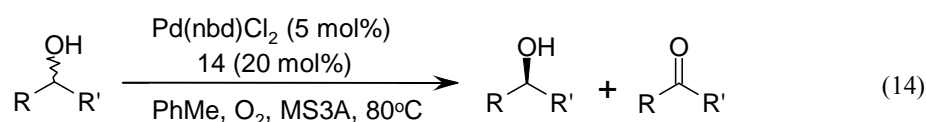


secondary benzylic and  
aliphatic alcohols

**Table 10.** Sigman's method in aerobic oxidative kinetic resolution of secondary alcohols

entry	alcohol	conditions <sup>a</sup>	conv.(%) ee(%) <sup>b</sup>	k <sub>rel</sub>
1	1-phenylethanol	A	65.9 (98.2)	13.0
2		B	53.9 (86.9)	17.5
3	1-( <i>p</i> -Me-phenyl)ethanol	A	60.8 (96.6)	14.0
4		B	57.0 (94.3)	17.1
6	1-( <i>p</i> -F-phenyl)ethanol	A	52.9(80.7)	12.2
7 <sup>c</sup>		A	58.5 (77.8)	7.6

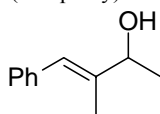
<sup>a</sup>Conditions A: Pd(OAc)<sub>2</sub> at 60 °C and 0.5M substrate, **14** (20 mol%); Condition B: Pd(MeCN)<sub>2</sub>Cl<sub>2</sub> at 70 °C and 0.25M substrate in DCE, **14** (20 mol%). <sup>b</sup>Enantioselectivity and conversion were determined by GC using commercial chiral columns and tetradecane as an internal standard. <sup>c</sup>The reaction was performed at 80 °C.



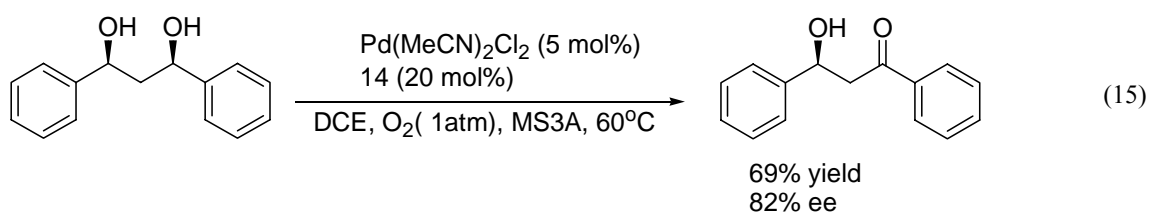
secondary benzylic and allylic alcohols

conversion: 48.4-70.4%  
ee: 68.7-99.8%

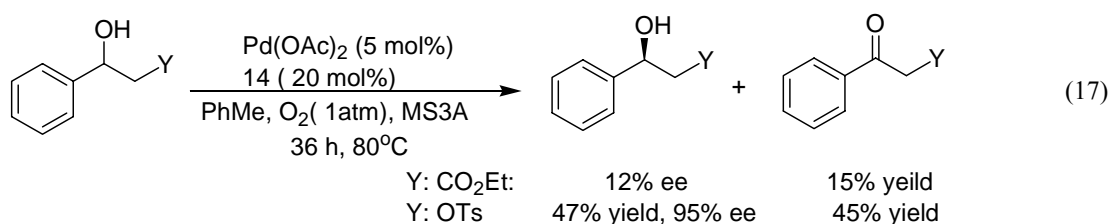
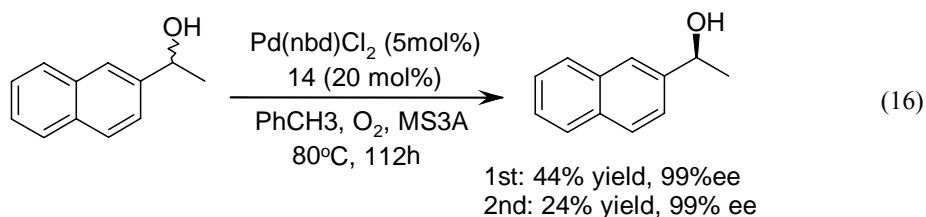
**Table 11.** Stoltz's method in aerobic oxidative kinetic resolution of secondary alcohols<sup>a</sup>

entry	alcohol	time(h)	conv./% (ee/%) <sup>b</sup>	k <sub>rel</sub>
1	1-phenylethanol	96	59.9 (98.7)	23.1
2	1-( <i>p</i> -F-phenyl)ethanol	54	63.3 (97.4)	14.4
3	1-( <i>p</i> -MeO-phenyl)ethanol	96	66.6 (98.1)	12.3
4	1-(1-naphthyl)ethanol	192	55.9 (78.4)	9.8
5		120	70.4 (91.8)	6.6

<sup>a</sup>Conditions A: Pd(nbd)Cl<sub>2</sub> (5 mol%), **14** (20 mol%), O<sub>2</sub> (1 atm), at 80 °C and 0.1M substrate in PhMe. <sup>b</sup> Enantioselectivity and conversion were determined by GC using commercial chiral columns and tetradecane as an internal standard.



Recent Advances in the Homogeneous Palladium-Catalyzed



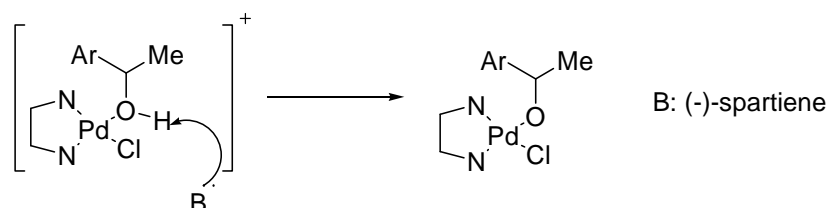
Furthermore, the PdCl<sub>2</sub>/(-)-sparteine catalytic system has also been employed in the desymmetrization of meso diols. For example, desymmetrization of 1,3-meso-diol (Eq. 15) provided the enantiomerically enriched hydroxy-ketone product in 69% yield and 82% ee (59% yield, 93% ee after recrystallization) [30].

The isolation of enantiomerically enriched alcohols with over 50% total yield were achieved by the oxidative kinetic resolution as the ketones are recyclable, as demonstrated by Stoltz and Ferreira [31]. For example, in the oxidative kinetic resolution of (±)-2-naphthylethanol, the first cycle gave a 44% yield of (-)-2-naphthylethanol in 99% ee. After isolation of the enantiomerically enriched alcohol, the ketone was reduced back to the racemic alcohol by treatment with NaBH<sub>4</sub> (99% yield). A second oxidative kinetic resolution cycle gave a 24% yield in 99% ee (Eq. 16).

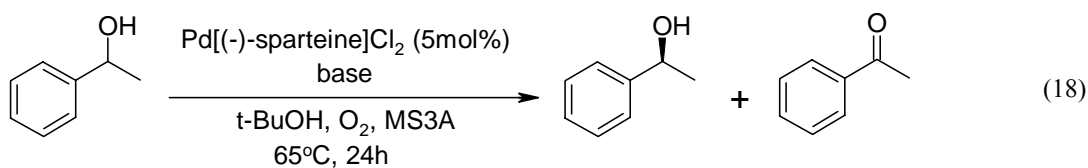
Later on, Sudalai *et al.* showed the influence of the β-function on the efficiency of the resolution (Eq. 17) [32]. One example of the kinetic resolution of an allylic alcohol, 4-phenyl-3-methyl-but-3-en-2-ol, has been disclosed. The recovered alcohol was obtained with 91.8% ee at 70.4% conversions. The resolution of saturated alcohols was less selective by this protocol.

Mechanistic work from Sigman's group provided a framework for the elimination of exogenous sparteine [33]. In these studies, exogenous (-)-sparteine was observed to act as a Brønsted base to deprotonate Pd-bound alcohol. High concentrations of **14** provided faster rates and higher *k<sub>rel</sub>* values. Under these conditions, kinetic experiments were consistent with rate limiting β-hydride elimination (Scheme 7). Asymmetric induction is proposed to arise from a combination of two factors: a thermodynamic difference in diastereomeric alkoxides formed, and a kinetic difference in the reaction of these alkoxides. In this scenario, exogenous **14** is acting purely as Brønsted base and not directly influencing the asymmetric induction of the process.

Therefore, identification of an achiral base that allows for equilibration of the alkoxides and rate-limiting β-hydride elimination should give similar *k<sub>rel</sub>* values as above and the need for exogenous **14** should be avoided. Sigman (Table 12, Eq. 18) and Stoltz (Table 13, Eq. 19) indicated that several carbonate and fluoride sources produce comparable *k<sub>rel</sub>* values (*k<sub>rel</sub>*: 17-25) [34]. The carbonate bases are especially interesting due to their convenience and low cost. Also Stoltz found that a mixture of Cs<sub>2</sub>CO<sub>3</sub> and *t*-BuOH led to an increase in the reaction rate (Table 13, Eq. 19) [34b].

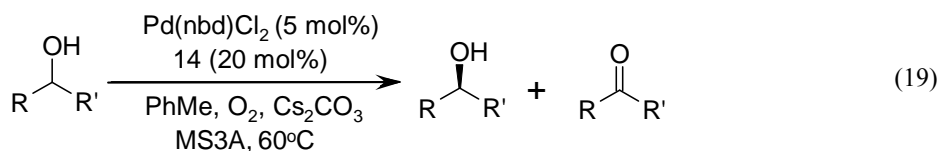


Scheme 7. β-hydride elimination

**Table 12.** Screening of achiral bases in Sigman's protocol<sup>a</sup>

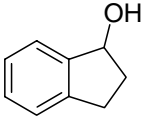
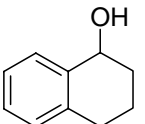
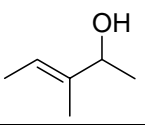
entry	base	loading, (mol %)	% conv (% ee) <sup>b</sup>	k <sub>rel</sub>
1	10	20	66.1 (94.2)	16
2	KF	20	35.0 (46.3)	21
3	Cs <sub>2</sub> CO <sub>3</sub>	20	38.1 (51.3)	18
4	K <sub>2</sub> CO <sub>3</sub>	50	58.3 (95.3)	19
5	Na <sub>2</sub> CO <sub>3</sub>	50	59.0 (96.6)	20
6	KHCO <sub>3</sub>	20	30.7 (38.8)	22
7	NaHCO <sub>3</sub>	20	20.9 (21.7)	13

<sup>a</sup> Pd[(-)-sparteine]Cl<sub>2</sub> (5mol%), O<sub>2</sub>, t-BuOH, MS3A, 65 °C, 24h. <sup>b</sup> Enantioselectivity.



Secondary benzylic  
and allylic alcohols

**Table 13.** Cs<sub>2</sub>CO<sub>3</sub>/ t-BuOH as rate-accelerator of oxidative kinetic resolution in Stoltz's protocol<sup>a</sup>

entry	R <sup>1</sup>	time(h)	conv./% (ee/%) <sup>b</sup>	k <sub>rel</sub>
1	1-phenylethanol	12.5	63.9 (99.6)	20.0
2	1-( <i>p</i> -F-phenyl)ethanol	9.5	67.4 (99.5)	14.9
3	1-( <i>p</i> -MeO-phenyl)ethanol	12.5	65.7(97.4)	12.1
4		12	74.0 (99.5)	10.1
5		12	61.5 (99.0)	20.9
6		12	65.1 (87.9)	7.5

<sup>a</sup> Pd(nbd)Cl<sub>2</sub> (5 mol%), 14 (20 mol%), MS3A, O<sub>2</sub> (1 atm), 0.5M substrate in PhMe, t-BuOH(1.5 eq.), Cs<sub>2</sub>CO<sub>3</sub> (0.5 eq.), 60°C. <sup>b</sup> Enantioselectivity and conversion were determined by GC using commercial chiral columns and tetradecane as an internal standard.

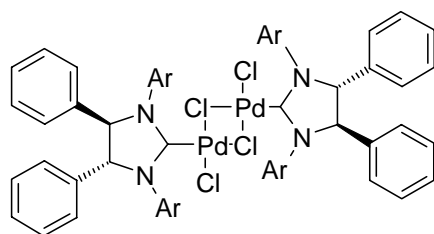
Recent Advances in the Homogeneous Palladium-Catalyzed

Jensen and Sigman have also disclosed the use of various  $\text{PdCl}_2(\text{N-heterocyclic carbene})_2$  complexes as catalysts for which the ligand was not displaced by **14** [35]. Achiral Pd-catalyst such as **16** used with 0.15 equiv. of **14** to mediate the kinetic resolution of benzylic alcohols, affording up to 96% ee (Eq. 20). With a chiral carbene ligand **15**, 'matched' diastereoisomeric interactions with the chiral exogenous base have allowed increases in the kinetic resolution (Eq. 21).

Mechanistic studies of Goddard and Nielsen [36] showed that in the aerobic oxidation of alcohols by Palladium complexes of *N*-Heterocyclic carbenes, reversible  $\beta$ -hydride

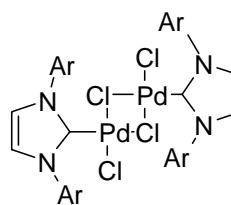
elimination may provide a mechanism for the racemization of chiral alcohols, which would undermine attempts at an enantioselective oxidation.

Shi and co-workers were prepared a new axially chiral *N*-heterocyclic carbene (NHC) Pd(II) (**17** and **18**) complexes and applied in the oxidative kinetic resolution of secondary alcohols using molecular oxygen (Table 14, Eq. 22) [37]. Compared to (-)-sparteine/Pd(II) system, the catalyst system enabled the authors to get *sec*-alcohols of different configuration readily through modulating the configuration of NHC-Pd(II) complex.



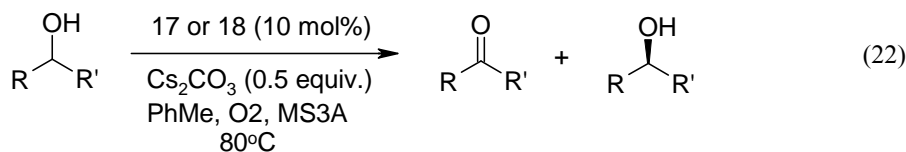
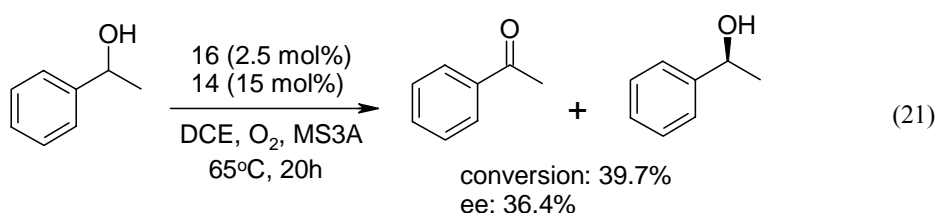
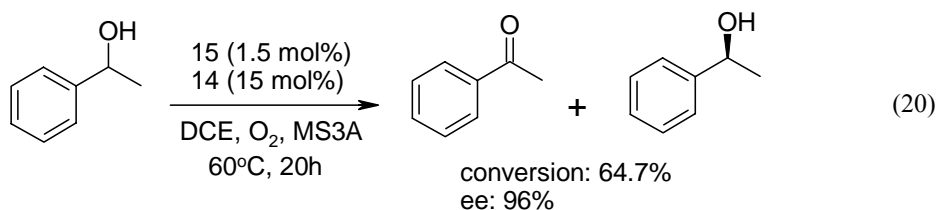
Ar:2,3,5,6-tetra-methyl phenyl

**15**

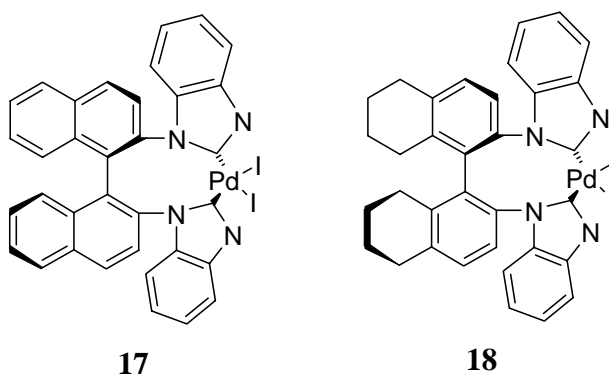


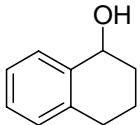
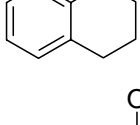
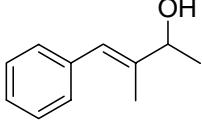
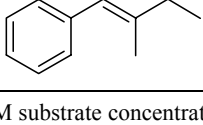
Ar: 2,6-di-isopropyl phenyl

**16**

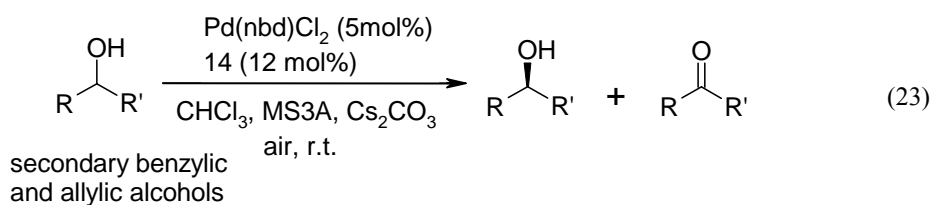


secondary benzylic  
and allylic alcohols

**Table 14.** NHC-Pd(II) complexes catalyzed oxidative kinetic resolution of secondary alcohols<sup>a</sup>

entry	R <sup>1</sup>	cat.	time(h)	conv. <sup>b</sup> / (ee/%) <sup>c</sup>	k <sub>rel</sub>
1	1-( <i>p</i> -F-phenyl)ethanol	<b>17</b>	48	75 (86)	4.38
2		<b>18</b>	5	69 (93)	7.46
3	1-( <i>p</i> -Cl-phenyl)ethanol	<b>17</b>	48	64 (77)	5.53
4		<b>18</b>	5	64 (66)	4.08
5	1-( <i>p</i> -Br -phenyl)ethanol	<b>17</b>	48	60 (80)	7.69
6		<b>18</b>	48	68 (93)	7.88
7	1-( <i>p</i> -MeO-phenyl)ethanol	<b>17</b>	7	63 (89)	8.95
8		<b>17</b>	7	68 (99)	15.52
9		<b>18</b>	7	64(99)	19.80
10		<b>17</b>	7	66 (77)	5.02
11		<b>18</b>	5	64 (77)	5.53

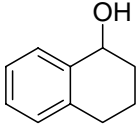
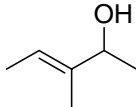
<sup>a</sup> 1.0 atm of O<sub>2</sub>, 0.1 M substrate concentration in PhMe. <sup>b</sup> Measured by GC. <sup>c</sup> Measured by chiral HPLC.



In 2004 Stoltz investigated a wide array of solvents and found that CHCl<sub>3</sub> was uniquely effective as a solvent for the oxidative kinetic resolution [38]. Excellent selectivities were observed by employing CHCl<sub>3</sub> as the solvent. Furthermore, the

use of CHCl<sub>3</sub> allowed these resolutions to be performed for the first time at 23 °C and under low pressures of molecular oxygen (i.e., normal air) (Table 15, Eq. 23). Under these improved conditions, alcohols were resolved with as little as a 5% O<sub>2</sub> in N<sub>2</sub>.

**Table 15.** Stoltz's room temperature/ambient air oxidative kinetic resolution in  $\text{CHCl}_3$ <sup>a</sup>

entry	alcohol	time(h)	conv./% (ee/%) <sup>b</sup>	$k_{\text{rel}}$
1	1-( <i>p</i> -MeO-phenyl)ethanol	24	62.3 (99.8)	25.4
2	1-( <i>p</i> -F-phenyl)ethanol	24	56.7(93.0)	19.5
3	1-naphthyl ethanol	24	55.5 (98.0)	37.3
4		16	60.2 (99.6)	28.0
5	1-phenyl propanol	48	56.8 (94.2)	21.7
6		44	64.7 (98.9)	15.7

<sup>a</sup> Pd(nbd)Cl<sub>2</sub> (5 mol%), 14 (12 mol%), MS3A, air (1 atm),  $\text{CHCl}_3$ ,  $\text{Cs}_2\text{CO}_3$  (0.4 eq.), r.t.. <sup>b</sup>Enantioselectivity and conversion were determined by GC using commercial chiral columns and tetradecane as an internal standard.

At the moment, limited access to the (+)-sparteine isomer limits the generality of this methodology. However, a readily accessible (+)-sparteine analogue was synthesized recently, and moderate selectivities were obtained in the oxidative kinetic resolution reaction [39]. The development of new chiral ligands for palladium-catalyzed aerobic oxidation reactions represents an important target for future research.

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