Palladium-Carbene Catalysts for Aerobic, Intramolecular Wacker-Type Cyclisation Reactions

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Abstract: A catalyst derived from *in situ* complexation of N-heterocyclic carbenes to palladium bistrifluoroacetate promotes efficient intramolecular Wacker-type cyclisation reactions under aerobic conditions. A variety of 2-allylphenols undergo oxidative conversion to dihydrobenzofurans.

Keywords: alkenes; cyclization; dihydrobenzofurans; intramolecular oxidation; N-heterocyclic carbenes; palladium

Recently, palladium-catalysed intramolecular Wacker-type cyclisations such as the formation of compound **2** from phenol **1** have emerged as a versatile strategy in the construction of oxygenated stereocentres in both enantiopure and racemic form (Scheme 1).[1–3] Unfortunately, most contributions in this area rely on rather undesirable reoxidants ranging from copper chloride to benzoquinone, the latter used in high amounts of up to four equivalents. Reactions employing these reoxidants require lengthy work-up and/or complicated purification procedures to remove over-stoichiometric amounts of by-products. Thus, aerobic oxidation would obviously be an attractive alternative. A first step in this direction was recently realised by Stoltz and co-workers who reported on Pd(II)/sparteine as a catalyst system for this kind of transformation.[4] The field of catalytic aerobic oxidation has largely developed with the recent elegant work by Stoltz, Stahl and Shannon.[5]

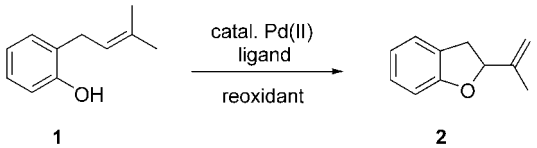
On the other hand, the recent development of stable N-heterocyclic carbenes[6] and their successful incorporation into transition metal complexes[7] has led to the development of significant new reactivity in the area of homogeneous catalysis. Still, application of these compounds has been mainly restricted to C–C bond formation reactions and related chemistry.

To the best of our knowledge, there are only two related reports on the oxidative conversion of secondary alcohols to ketones that employ a metal carbene complex.[8,9] Obviously, applications of Pd-carbene catalysts in oxidation chemistry have been prevented by the immanent concern about oxidative decomposition of the organometallic species.[10]

Herein, we report an environmentally benign intramolecular Wacker-type cyclisation that is catalysed by a Pd(II)-carbene complex and relies on molecular oxygen as terminal oxidant.

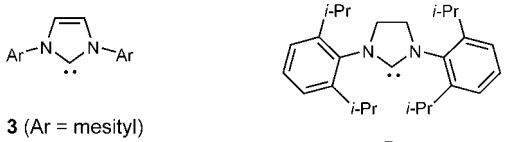
Extensive screening experiments with **1** as substrate and carbene **3** as ligand (Fig. 1), which is commercially available, revealed that several Pd/carbene combinations are capable of catalysing this type of transformation under aerobic conditions [Scheme 1 (reoxidant = O_2), Table 1]. In all cases, basic reaction media were necessary in order to prevent side reactions and to maintain catalyst activity, and a combination of DMAP (20 mol %) and sodium carbonate (2 equivs., relative to **1**) was used. Generally, catalysts from Pd sources bearing chloride or acetate counterions were of low efficiency. In addition, these catalysts gave mixtures of the desired five-membered product **2** and its six-membered isomer. While the dependence of the ratio for five- and six- membered products on the Pd source was not investigated in detail, formation of the latter was increased significantly for palladium catalysts derived from chloride precursors. Gratifyingly, it was completely suppressed by use of Pd trifluoroacetate (entries 5, 7–10). In particular, this Pd source gives rise to much more reactive catalysts.

It is noteworthy that allyl-Pd complexes were found to be significantly less efficient (entries 4, 12, 13). This



1 2

Scheme 1. Intramolecular Wacker-type cyclisation.



3 (Ar = mesityl)
4 (Ar = 2,6-diisopropylphenyl) **5**

Figure 1. Carbene ligands.

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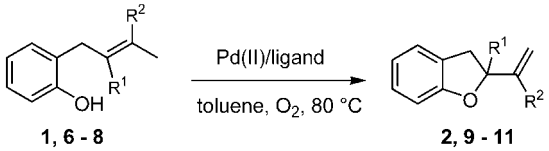
Table 1. Evaluation of Pd sources for aerobic Wacker-type cyclisations.

Entry	Pd Source[a]	Ligand[b]	Solvent	Conversion [%][c]	Yield [%][d]
1	$PdCl_2$	**3**	toluene	34	22
2	$Pd(OAc)_2$	**3**	toluene	80	42
3	$Pd(OAc)_2$[f]	**3**	toluene	65	38
4	$[PdCl(allyl)]_2$	**3**	toluene	90	66
5	$Pd(TFA)_2$	**3**	toluene	>95	91
6	$Pd(TFA)_2$[e]	**3**	toluene	56	42
7	$Pd(TFA)_2$	**3**	THF	85	82
8	$Pd(TFA)_2$	**3**	$CHCl_3$	90	88
9	$Pd(TFA)_2$	**4**	toluene	>95	92
10	$Pd(TFA)_2$	**5**	toluene	>95	88
11	$Pd(TFA)_2$[f]	**3**	toluene	60	41
12	$[PdCl(allyl)]_2$	**3**	toluene	75	57
13	$[PdCl(allyl)]_2$	**3**	toluene	60	41

[a] S/C ratio of 20.
[b] 1.2 equivs. with respect to Pd. Overall reaction times 12–14 h.
[c] Estimated from the crude ^1H NMR spectra.
[d] Isolated yield after purification.
[e] 2.4 equivs. with respect to Pd.
[f] With an additional amount of 10 mol % $Cu(OAc)_2$.

holds true for *in situ* generated allyl-Pd-carbene complexes as well as for preformed ones, which were described recently.[11] Addition of copper salts to the reaction mixture led to a pronounced drop in reactivity (entries 3 and 11) indicating that molecular oxygen as a direct oxidant is preferred over metal-mediated oxygen transfer systems. For the sake of preparative ease, all catalysts were generated *in situ* by complexation of the free carbene to the appropriate Pd(II) precursor. Within this context, an NMR control experiment in toluene-d_8 confirmed the formation of a defined Pd-carbene complex under these conditions.[12] A cyclisation of **1** carried out with the Pd catalyst from the NMR sample gave an almost identical reaction outcome as that reported in Table 1, entry 5. In addition to the use of **3**, related carbenes **4** and **5** yielded similar results (entries 9, 10). Importantly, use of 1.2 equivalents of carbene was found to be the optimum. Higher carbene/palladium ratios led to significantly lower reactivity (entry 6).



1, 6 - 8 **2, 9 - 11**

Scheme 2. Intramolecular Wacker-type cyclisation.

The $Pd(TFA)_2$/**3** combination represents a catalyst precursor which is also suitable for related Wacker cyclisation reactions (Scheme 2, Table 2). For example, substrates **6**–**8** were converted into the desired dihydrobenzofurans in high yields. In all cases, no or only tiny amounts of by-products were detected in the proton NMR of the crude reaction mixture. After work-up, pure cyclised products were obtained in high yields.

The overall cyclisation process is believed to proceed with coordination of the olefin to the carbene-palladium catalyst. Nucleophilic attack of the hydroxy group to the

Table 2. Aerobic Wacker-type cyclisations.[a]

Compound	R^1	R^2	Product	Conversion [%][b]	Yield [%][c]
1	H	CH_3	**2**	>95	91
6	CH_3	H	**9**	>95	92
7	CH_3	CH_3	**10**	100	96
8	H	H	**11**	>95	89
6[d]	CH_3	H	**9**	>95	87
7[d]	CH_3	CH_3	**10**	>95	88

[a] Conditions as described. Overall 12 h reaction time.
[b] Estimated from the crude ^1H NMR spectra.
[c] Isolated yield after purification.
[d] With carbene ligand **5**.

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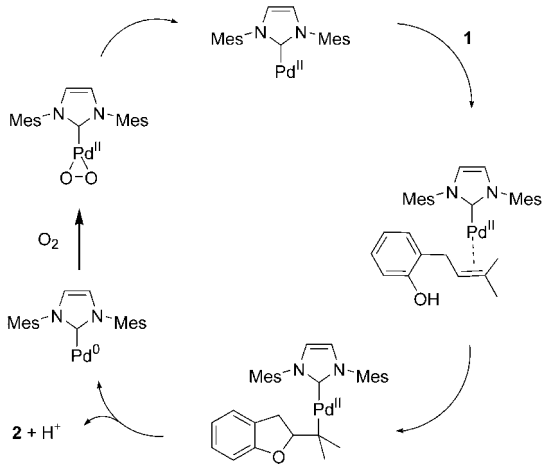

Figure 2. Proposed catalytic cycle.

double bond produces the dihydrobenzofuran ring with concomitant formation of a palladium-alkyl bond. Apparently, the degree of five- over six-membered product is influenced by both the carbene ligand and the formal counterion. Reductive β-hydride elimination releases cyclised product **2**. The remaining Pd-HX species is deprotonated within the basic reaction medium to form a carbene-palladium(0) intermediate (Figure 2). The active Pd(II) catalyst is then regenerated under the aerobic oxidation conditions, presumably *via* a peroxo-palladium intermediate. A related compound bearing a bathocuproine ligand was isolated in mechanistic studies by Stahl and shown to be a reasonable intermediate in dioxygen activation for aerobic catalytic cycles.[13]

We have described the *in situ* formation of carbene-palladium catalysts that tolerate oxidative conditions. A first application of these compounds in catalytic intramolecular Wacker-type cyclisation has led to the establishment of suitable conditions for the rapid and highly efficient synthesis of dihydrobenzofurans.

Experimental Section

Typical Experimental Procedure (Tables 1 and 2)

A solution of freshly prepared carbene **3**[11] (0.06 mmol) in toluene (2 mL) was transferred *via* cannula to a Schlenk vial containing a 1 M toluene solution of Pd trifluoroacetate (17 mg, 0.05 mmol) and the resulting mixture was stirred at room temperature for 15 min. 4-(*N*,*N*-Dimethylamino)-pyridine (25 mg), sodium carbonate (212 mg) and 4 Å MS (0.5 g) were added under a positive stream of argon and the resulting mixture was stirred for 5 min before addition of phenol **1** (1 mmol). The reaction mixture was submitted to three freeze and thaw cycles employing molecular oxygen (***Caution!*** Molecular oxygen may spontaneously ignite, especially in the presence of organic solvents and precious metals. Special care and adequate security precaution are strongly recommended). Finally, the Schlenk vial was connected to an external balloon containing molecular oxygen and the reaction mixture was heated to 80 °C over a period of 12 hours. After this, it was concentrated under vacuum, and the residue was taken up in dichloromethane, washed with water, dried and evaporated under reduced pressure. If required, column chromatography (silica gel, *n*-hexane/ethyl acetate, 4/1, v/v) gave the pure product **2** as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.78 (s, 3H), 3.05 (dd, *J* = 8.2, 15.6 Hz, 1H), 3.34 (dd, *J* = 9.4, 15.6 Hz, 1H), 4.92 (m, 1H), 5.10 (m, 1H), 5.17 (t, *J* = 8.9 Hz, 1H), 6.82 (m, 2H), 7.17 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.22, 34.74, 85.60, 109.22, 111.97, 120.33, 124.77, 126.58, 128.03, 144.06, 159.76.[14]

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