## Propane Activation by Palladium Complexes with Chelating Bis(NHC) Ligands and Aerobic Cooxidation\*\*

Dominik Munz and Thomas Strassner\*

**Abstract:** The development of efficient aerobic oxidation methods remains a challenge for the selective functionalization of C–H bonds in alkanes. Herein we report the development of a C–H functionalization procedure for propane by using a palladium catalyst with chelating bis(N-heterocyclic carbene) ligands in trifluoroacetic acid together with a vanadium cocatalyst. Halides play a decisive role in the reaction. The experimental results are presented together with supporting kinetic data and an isotope effect. The reaction can be run with dioxygen as the oxidant if vanadium salts and halides are present in the reaction mixture. Experimental as well as computational results favor a mechanism involving C–H activation by palladium(II), followed by oxidation to palladium(IV) by bromine.

he selective functionalization of hydrocarbons and especially methane has proven to be a formidable challenge and has been deemed to be the "holy grail" of transition-metal catalysis.<sup>[1]</sup> Methane and lower hydrocarbons constitute an enormous reservoir of comparably clean fossil energy, and a potential feedstock for the chemical industry. From an economic perspective, oxidative C-H functionalization approaches offer an attractive alternative to conventional gas-to-liquids processes, as they do not rely on the energyintensive formation of syngas.<sup>[2]</sup> We reported earlier that *cis*chelated palladium(II)-bis(NHC) (NHC = N-heterocyclic carbene) complexes catalyze the conversion of methane into methyl trifluoroacetate in trifluoroacetic acid (HOTFA).<sup>[3]</sup> The catalytic activity was found to be comparable to the platinum(II) system with bispyrimidine ligands in oleum reported by Catalytica.<sup>[4]</sup> In subsequent studies we investigated the influence of the transition metal (Pt versus Pd), the halogenido counterions, the chelating bis(NHC) ligand, and extended our investigations from methane to propane (Scheme 1).<sup>[5]</sup> Whereas the catalytic activity turned out to be highly dependent on the ligand design and the transition metal employed (TON = 0-30), we only observed very



**Scheme 1.** Trifluoroacetoxylation of propane catalyzed by chelated palladium-bis (NHC) complexes.

moderate differences for the chemo- and regioselectivity (isopropyl trifluoroacetate: ca. 90%, Scheme 1).

Other research groups explored the reactivity with alkyl esters and evaluated the industrial relevance of closely related systems.<sup>[6]</sup> C–H functionalization usually relies on economically unfavorable oxidants, such as  $K_2S_2O_8$  in our case.<sup>[2c]</sup> Therefore, further development has to focus on the realization of aerobic oxidation procedures.

Although there has been substantial progress in the field of homogeneous, transition-metal-catalyzed activation of sp<sup>2</sup>hybridized C–H bonds,<sup>[7]</sup> the selective conversion of alkane C–H bonds using sustainable oxidants<sup>[8]</sup> still remains a challenge 40 years after the seminal work by Shilov and Shulpin.<sup>[9]</sup> The related palladium-catalyzed oxidation of C–H bonds in the presence of a directing group usually relies on strong oxidants such as peroxides, F<sup>+</sup> reagents, halogens, or hypervalent iodine species to generate palladium(III) or palladium(IV) intermediates.<sup>[10]</sup> However, whereas the reactivity of palladium(0)<sup>[8a,11]</sup> with molecular oxygen is comparably well understood, examples of the oxidation of palladium(II) compounds by dioxygen remain extremely rare.<sup>[8b,12]</sup> Thus we reasoned that a strategy based on a redox co-catalyst for the activation of dioxygen should be a versatile strategy.<sup>[2c,9]</sup>

DFT calculations have proven to be a valuable tool for the investigation of C–H activation mechanisms.<sup>[13]</sup> Thus, we decided to study by DFT calculations the functionalization of methane by a palladium-bis(NHC) catalyst.<sup>[14]</sup> We proposed, on the basis of previous work on the synthesis and reactivity of potential intermediates,<sup>[15]</sup> that the reaction involves a palladium catalyst in the oxidation states of + II and + IV, and that the oxidation step is mediated by bromine (Scheme 2).

Therefore, we envisioned a combination of the catalytic cycle for the C–H activation with a second redox cycle involving oxygen activation.

Based on the experimental observation of bromine fumes at a high catalyst loading as well as, in the case of methane, the

 <sup>[\*]</sup> Dr. D. Munz, Prof. T. Strassner
 Physikalische Organische Chemie, Technische Universität Dresden
 01069 Dresden (Germany)
 E-mail: thomas.strassner@chemie.tu-dresden.de

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Scheme 2. Proposed mechanism.

inhibition of the reaction on addition of  $\text{KBr}^{[5b]}$  we decided to study the influence of halides in the reaction with  $K_2S_2O_8$  as the oxidant. Consequently, the catalytic activity of a series of bis(NHC) catalysts with different halogenido counterligands (Figure 1) was investigated in the reaction with propane.



Figure 1. Dependence of catalytic activity on counterligands. Reaction conditions: 4.2  $\mu$ mol catalyst, 210  $\mu$ mol K<sub>2</sub>S<sub>2</sub>O<sub>8</sub>, 1 bar propane, 2.5 mL HOTFA, 60°C, 17 h.

We found a comparable catalytic activity for the catalysts  $1_Br_2$  (TON = 18) and  $1_Cl_2$  (TON = 17) but a significantly lower activity for  $\mathbf{1}_{I_2}$  (TON = 6), while all the catalysts led to a comparable regio- and chemoselectivity. This is expected, as bromine and chlorine are known to oxidize 1 Br<sub>2</sub> to the corresponding palladium(IV) complex, whereas the oxidation strength of iodine is not sufficient for this reaction. The catalytic activity of  $1_{OTFA}_2$  and  $Pd(OAc)_2$  (TON = 5 and TON = 6) was found to be substantially lower. In those catalyst systems, and likewise for  $1_I_2$ , a different mechanism for the reoxidation of the palladium centers is clearly operative. The tetrafluoroborate complex  $1_{(MeCN)_2(BF_4)_2}$ with coordinating acetonitrile ligands (TON = 1) as well as the corresponding platinum complex  ${}^{Pt}\mathbf{1}_{Br_2}$  (TON = 0) turned out to be inactive. The last result in particular underlines the significance of the nature of the transitionmetal center.

As in the case of methane,<sup>[5b]</sup> the reaction with propane is strongly inhibited by the addition of two or five equivalents of potassium bromide to the reaction mixture (4.2 µmol catalyst, 8.4 µmol or 21 µmol KBr, 210 µmol K<sub>2</sub>S<sub>2</sub>O<sub>8</sub>, 1 bar propane, 2.5 mL HOTFA, 60 °C, 17 h: TON = 4 and TON = 2) or by the addition of water. The addition of trifluoroacetic anhydride only led to a slight inhibition (for details see the Supporting Information). These observations taken together highlight the importance of generating free coordination sites at the palladium catalyst. Catalysis by a heterogeneous palladium catalyst appears unlikely considering the large differences in the catalytic activity of the different catalysts investigated herein and those reported before with different bis(NHC) ligands.<sup>[5c]</sup>

Next, we examined a series of oxidants which are well known to oxidize bromide rapidly under acidic conditions. As anticipated, we found catalytic turnover with the oxidants HAuCl<sub>4</sub>, KMnO<sub>4</sub>, H<sub>2</sub>O<sub>2</sub>, Pb(OAc)<sub>4</sub>, and F<sup>+</sup> reagents. Select-fluor<sup>[10b]</sup> gave the same results as  $K_2S_2O_8$ . Oxidants with a lower redox potential than the bromine/bromide redox couple, but which have been reported to oxidize palladium(0), such as, for example Cu(OAc)<sub>2</sub> + O<sub>2</sub>, NaVO<sub>3</sub>, Ag(OTFA), or tetrachloro-1,4-benzoquinone, turned out to be completely inactive!

Peroxodisulfate and polyhalides can react with alkanes and trifluoroacetic acid by radical pathways.<sup>[16,17]</sup> To exclude that carbon-centered radicals participate in the reaction and to check whether polyhalomethanes mediate the C–H functionalization we added the radical-transfer reagents CBrCl<sub>3</sub> and CCl<sub>4</sub> in large excess to the reaction mixture (4.2 µmol catalyst, 210 µmol CX<sub>4</sub>, 210 µmol K<sub>2</sub>S<sub>2</sub>O<sub>8</sub>, 1 bar propane, 2.5 mL HOTFA, 60 °C, 17 h). We did not observe the formation of considerable amounts of chloro- and bromopropane (CCl<sub>4</sub>: TON = 16; CCl<sub>3</sub>Br: TON = 9), as has been reported for radical mechanisms under comparable reaction conditions.<sup>[18]</sup> Furthermore, as the reaction seems not to be sensitive to the presence of dioxygen, we conclude that radicals do not play a role during the course of the reaction.

Inspired by the work of Hirao and co-workers,<sup>[19]</sup> who showed that vanadium salts catalyze the aerobic oxidation of bromide under acidic conditions, we then explored the oxidation of propane in the presence of NaVO<sub>3</sub> and dioxygen. As expected, isopropyl trifluoroacetate formed at 90°C in trifluoroacetic acid (25 mL, HOTFA, 84 µmol 1\_Br<sub>2</sub>; 840 µmol NaVO<sub>3</sub>, 17 h, 6 bar propane, 4 bar dioxygen: TON = 3). The addition of related vanadium precatalysts such as  $NH_4VO_3$  or  $VO(OAc)_2$  led to a comparable level of catalytic activity. The product distribution obtained matched the regio- and chemoselectivity when K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> and Selectfluor were used as oxidants (Figure 1), although we also identified the formation of traces of methyl and ethyl trifluoroacetate as well as isopropyl bromide. During the course of the reoxidation process, one equivalent of water forms per molecule of ester. As described above, water inhibits the C-H activation cycle. We therefore examined the effect of the addition of trifluoroacetic anhydride (21 mL HOTFA + 4 mL  $TFA_2O$ ) and found, as expected, a remarkable increase in activity (90 °C: TON = 10, 100 °C: TON = 12). Only traces of  $CO_2$  were detected at the end of the reaction, which points toward negligible decomposition of HOTFA by radical pathways. The catalytic activity is highly preserved at lower catalyst loadings and TONs of over 60 for the palladium catalyst could be obtained (Figure 2). The reaction is also clearly catalytic in NaVO<sub>3</sub> (TON = 8). The catalytic activity remained high after 65 h as long as not too much water had accumulated in the reaction mixture and not all the dioxygen had been consumed.



Figure 2. Variation of the concentration of the palladium catalyst  $1_Br_2$  and the reaction time. 21 mL HOTFA+4 mL TFA<sub>2</sub>O, 168 µmol NaVO<sub>3</sub>, 6 bar propane, 4 bar dioxygen, 90 °C.

In agreement with reports in the literature,<sup>[18a]</sup> we also observed a blue-colored, paramagnetic reaction mixture when all the dioxygen had been consumed. This blue color, which rapidly vanished upon exposure to air, has been attributed to a reduced vanadium(III) or vanadium(IV) species,<sup>[18a]</sup>

To verify that the same C–H activation mechanism is operative with the vanadium co-catalyst as in the case of the oxidants  $K_2S_2O_8$  or Selectfluor, we examined the catalytic activity of different catalysts and KBr in the presence of the vanadium co-catalyst. No significant catalytic activity (TON  $\approx 0$ ) was obtained for the platinum complex  $^{Pt}\mathbf{1}_{-}Br_2$ , the palladium trifluoroacetate complex  $\mathbf{1}_{-}(OTFA)_2$ , palladium acetate, palladium bromide, or in the absence of any palladium catalyst. In the presence of KBr (84 µmol KBr: TON = 1, 84 µmol Pd(OAc)<sub>2</sub> + 0.17 mmol KBr: TON = 1) we determined minor background reactions, which we attribute to vanadium catalysis and/or radical reactivity. Evidently, the concomitant presence of a palladium catalyst with a bis(NHC) ligand, a halide source, and the vanadium salt are necessary for an efficient oxidation reaction.

On the basis of all of our results we therefore propose that the palladium catalyst is responsible for the C–H functionalization, while the vanadium catalyst mediates the dioxygen activation (Scheme 3). We expect that both catalytic cycles are connected by a bromide/bromine redox pair, which mediates the oxidation step of the alkane functionalization.



Scheme 3. Proposed redox cycles.

Finally, we looked at various aspects of the reaction with the oxidant  $K_2S_2O_8$  to assess the plausibility of the proposed mechanism: We found that the reaction follows a pseudolinear kinetic model, at least for the first 15 h (ca. 50% yield based on the oxidant). We observed neither a significant induction period nor signs of decomposition of the palladium catalyst after a reaction time of 23 h. Remarkably, the reaction proceeded with a comparable initial reaction rate if we added new oxidant after 23 h. The reaction rate shows a first order dependence on the catalyst and the  $substrate^{\left[20\right]}$  concentration. We were able to determine the Arrhenius relationship to get an estimate of the reaction barrier and important information on the rate-determining step of the catalytic cycle. From the experimental data we calculated a reaction barrier of  $(29.0 \pm 1.6)$  kcal mol<sup>-1</sup>, which is in good agreement with reported values for related reactions.<sup>[13a]</sup> To gain more information on the rate-determining state of the reaction, we then measured the isotope effect for the model substrate cyclohexane.  $^{[20]}$  We obtained an isotope effect (IE) of 3.4  $\pm$ 0.8, which is indicative of a primary IE. This value does not only confirm that the C-H bond is broken in the ratedetermining step of the reaction, but is also in good agreement with reports in the literature<sup>[21]</sup> on the carbonylation of cyclohexane by palladium catalysts (IE = 3.2) and our DFT calculations (IE = 3.9).

In conclusion, the mechanism of the palladium-bis(NHC)catalyzed functionalization of propane has been studied in detail. There is a very strong indication that the catalytic cycle proceeds via palladium in the oxidation state + IV and that neither radical nor heterogeneous reactivity play an important role. Furthermore, there is evidence that halides are involved in the reaction. We demonstrated that the palladium-catalyzed C–H activation can be coupled through a bromide/bromine redox pair to an aerobic cooxidation procedure based on NaVO<sub>3</sub>. We therefore present a very promising and new cooxidation concept for the development of catalytic reactions with palladium in high oxidation states (+ III, + IV) and dioxygen used as the terminal oxidant.

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