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# Homogeneous, Anaerobic (N-Heterocyclic Carbene)−Pd or −Ni Catalyzed Oxidation of Secondary Alcohols at Mild Temperatures

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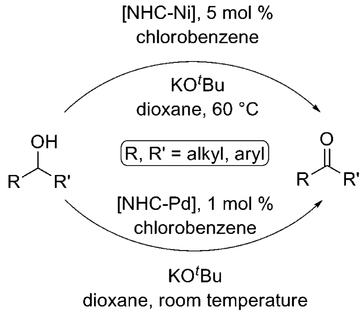
## ABSTRACT



**The use of aryl chlorides as oxidants for the selective oxidation of a variety of secondary alcohols in anaerobic conditions with (NHC)−Pd and −Ni systems (NHC = N-heterocyclic carbene) at very mild temperatures is presented.**

The oxidation of alcohols to their corresponding carbonyl products is a very important and useful organic transformation.[1] While most common traditional methods usually require the use of forcing conditions and/or toxic stoichiometric oxidants, the use of transition metal catalysts and an oxidizing agent has emerged as a very powerful tool for this reaction.[2] Since the first report on Pd-catalyzed aerobic alcohol oxidation by Schwartz and Blackburn in 1977,[3] numerous and excellent Pd-catalyzed systems in which molecular oxygen is used as the oxidant have been developed.[2,4]

The stoichiometric use of molecular oxygen, or air, is a very user-friendly, attractive, and cheap option. Unfortunately, this route is often inconvenient due to the hazard of oxygen pressures when running oxidations in flammable organic solvents.[2a] This issue is particularly important when moving from a laboratory setting to an industrial scale. In many cases, conditions that employ organic solvents with 1 atm of oxygen pressure fall within the explosive limits.[5]

A far less explored but very interesting option for the oxidation of alcohols is the use of aryl halides as oxidants.[6,7] The use of an aryl halide as a hydride acceptor results in the formation of the corresponding inert, dehalogenated aryl

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(1) (a) Bäckval, J.-E. *Modern Oxidation Methods*; Wiley-VCH: New York, 2004. (b) Tojo, G.; Fernández, M. *Oxidation of Alcohols to Aldehydes and Ketones*; Springer: Berlin, Germany, 2006. (c) Hudlicky, M. *Oxidations in Organic Chemistry*, ACS Monograph Series; American Chemical Society: Washington, DC, 1990. (d) Seldon, R. A.; Kochi, J. K. *Metal-catalyzed Oxidations of Organic Compounds*; Academic Press: New York, 1981.

(2) (a) Schultz, M. J.; Sigman, M. S. *Tetrahedron* **2006**, *62*, 8227–8241. (b) Muzart, J. *Tetrahedron* **2003**, *59*, 5789–5816.

(3) Blackburn, T. F.; Schwartz, J. *Chem. Commun.* **1977**, 157–158.

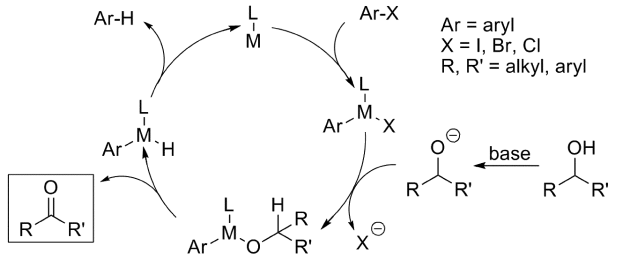
(4) (a) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400–3420. (b) Gligorich, K. M.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 6612–6615. (c) Arends, I. V. C. E.; ten Brink, G.-J.; Sheldon, R. A. *J. Mol. Catal. A: Chem.* **2006**, *251*, 246–254. (d) Ebner, D. C.; Trend, R. M.; Genet, C.; McGrath, M. J.; O'Brien, P.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 6367–6370. (e) Sigman, M. S.; Jensen, D. R. *Acc. Chem. Res.* **2006**, *39*, 221–229.

(5) Steinhoff, B. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 4348–4355.

10.1021/ol901825u CCC: $40.75

compound as a byproduct of the reaction (Scheme 1). State-of-the-art systems following this approach have described the use of aryl bromides and iodides, requiring elevated temperatures (above 100 °C) and long reaction times.[7] The use of aryl chlorides as oxidants was recently reported with use of biaryl phosphine ligands, but also requires those elevated temperatures.[8] Aryl chlorides are very appealing substrates as they are readily available and much cheaper than their bromo and iodo counterparts, although less reactive due to the relative difficulty of activation of the C−Cl bond.[9] Herein, we report on the use of aryl chlorides for the oxidation of a variety of secondary alcohols under anaerobic conditions at very mild temperatures using (NHC)Pd or (NHC)Ni systems (NHC = N-heterocyclic carbene).[10]

**Scheme 1.** Metal-Catalyzed Oxidation of Alcohols with Aryl Halides



The very effective use of (NHC)−Pd and (NHC)−Ni complexes for the dehalogenation of aryl chlorides, an important transformation in organic chemistry[11] and for environmental remediation,[12] has been previously reported with use of 2-propanol as a hydride source, leading to the formation of acetone as a byproduct.[7b,13] We decided to start from those well-established systems and target the ketone formation as a way to oxidize alcohols. We first tested the activity of a variety of commercially available NHC-bearing Pd complexes (Figure 1) in the oxidation of 1-phenyl-1-propanol to propiophenone in dioxane, using chorobenzene as the oxidant (Table 1). Complex **1** allows for oxidation to occur in high yield at 40 °C in 3 h, with a low catalyst loading (0.5 mol %). The reaction could also be carried out at room temperature, requiring nearly 24 h to reach completion. When complex **2** was used, known to be more active at lower temperatures in cross-coupling reactions,[14] the reaction time was shortened to 17 h at room temperature. Palladium dimer **3** allowed for the formation of only 45% of the desired product under the same conditions. It is worth mentioning that, for all complexes, similar results were obtained when *p*-chlorotoluene was used as oxidant, leading to the formation of toluene as a byproduct, more appealing than benzene in large-scale applications due to safety and health concerns.

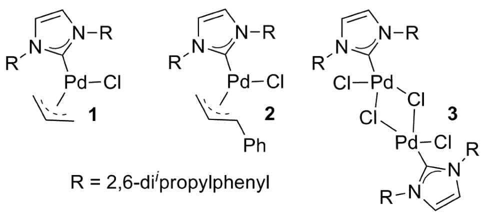
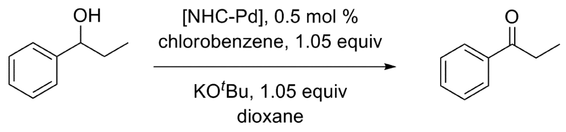


**Figure 1.** (NHC)Pd Complexes Tested

**Table 1.** Performance Comparison of Different (NHC)Pd Complexes



| entry | [NHC−Pd] | temp (°C) | time (h) | yield (%)$^a$ |
|---|---|---|---|---|
| 1 | **1** | 40 | 3 | 92 |
| 2 | **1** | 25 | 24 | 90 |
| 3 | **2** | 25 | 17 | 92 |
| 4 | **2** | 25 | 11 | 91$^b$ |
| 5 | **3** | 25 | 24 | 45 |

[a] Average of two runs, isolated yields. [b] 1 mol % of **2**.

Regarding the scope of the reaction, preliminary results are depicted in Table 2. A variety of alcohols were oxidized to the corresponding ketones at room temperature (25 °C) or slightly above in high yields. Catalyst loadings, reaction times and isolated yields of products are comparable to those reported with use of the most common state-of-the-art Pd-catalyzed aerobic oxidation systems.[15] Interestingly, with these initial reaction conditions our (NHC)Pd system did not

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(6) For some early references, see: (a) Tamaru, Y.; Yamamoto, Y.; Yamada, Y.; Yoshida, Z. *Tetrahedron Lett.* **1979**, *16*, 1401–1404. (b) Bouquillon, S.; Henin, F.; Muzart, J. *Organometallics* **2000**, *19*, 1434–1437.

(7) (a) Guram, A. S.; Bei, X.; Turner, H. W. *Org. Lett.* **2003**, *5*, 2485–2487. (b) Bei, X.; Hagemeyer, A.; Volpe, A.; Saxton, R.; Turner, H.; Guram, A. S. *J. Org. Chem.* **2004**, *69*, 8626–8633.

(8) In ref 7b, 96 different phosphines were tested as ligands with Pd(dba)$_2$ and with the exception of one substrate the best combination required 105 °C.

(9) (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176–4211. (b) Grushin, V. V.; Alper, H. *Chem. Rev.* **2000**, *100*, 3009–3066.

(10) For general reviews on NHCs, see : (a) Nolan, S. P., Ed. *N-Heterocyclic Carbenes in Synthesis*; Wiley-VCH: Weinheim, Germany, 2006. (b) Glorius, F., Ed. *Top. Organomet. Chem.* **2007**, 21.

(11) (a) Parry, R. J.; Li, Y.; Gomez, E. E. *J. Am. Chem. Soc.* **1992**, *114*, 5946–5959. (b) Dorman, G.; Olszewski, J. D.; Prestwich, G. D.; Hong, Y.; Ahem, D. G. *J. Org. Chem.* **1995**, *60*, 2292–2297.

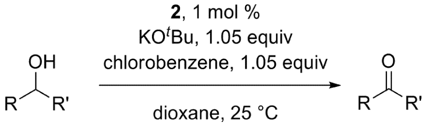
(12) (a) Hutzinger, O.; Safe, S.; Zitko, V. *The Chemistry of PCBs*; CRC Press: Cleveland, OH, 1974. (b) Morra, M. J.; Borek, V.; Koolpe, J. *J. Environ. Qual.* **2000**, *29*, 706–715.

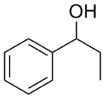
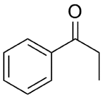
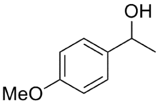
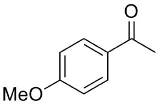
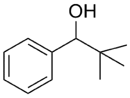
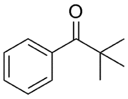
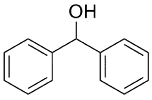
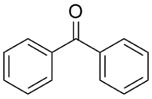
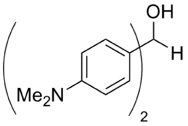
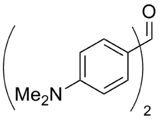
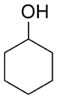
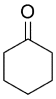
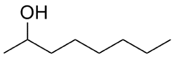
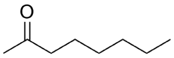
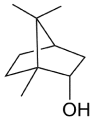
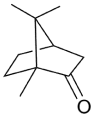
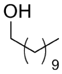
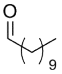
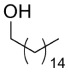
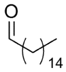
(13) (a) Navarro, O.; Marion, N.; Oonishi, Y.; Kelly, R. A.; Nolan, S. P. *J. Org. Chem.* **2006**, *71*, 685–692. (b) Navarro, O.; Kaur, H.; Mahjoor, P.; Nolan, S. P. *J. Org. Chem.* **2004**, *69*, 3173–3180. (c) Desmarets, C.; Kuhl, S.; Schneider, R.; Fort, Y. *Organometallics* **2002**, *21*, 1554–1559. (d) For a review in metal-mediated hydrodehalogenation, see: Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2002**, *102*, 4009–4091.

(14) Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. *J. Am. Chem. Soc.* **2006**, *128*, 4101–4111.

(15) For an excellent, substrate-dependent comparison of Pd-catalyzed aerobic systems, see: Schultz, M. J.; Hamilton, S. S.; Jensen, D. R.; Sigman, M. S. *J. Org. Chem.* **2005**, *70*, 3343–3352.

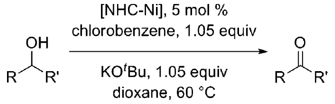
**Table 2.** Catalytic Oxidation of Secondary Alcohols with **2** and Chlorobenzene

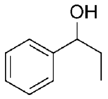
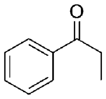
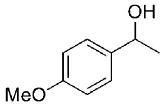
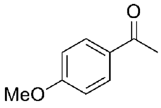
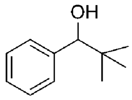
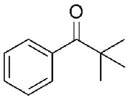
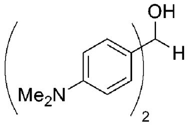
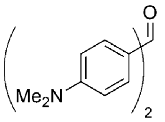
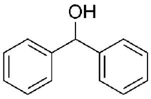
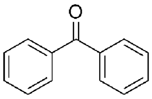
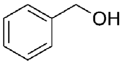
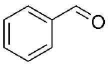
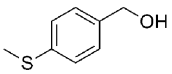
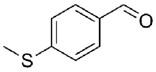
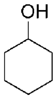
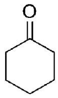
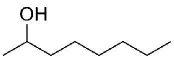
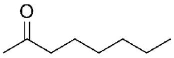
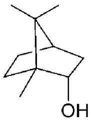
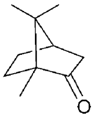


| entry | alcohol | product | time (h) | yield (%)[a] |
|---|---|---|---|---|
| 1 |  |  | 11 | 91 |
| 2 |  |  | 14 | 90 |
| 3 |  |  | 12 | 91 |
| 4 |  |  | 12 | 85[b] |
| 5 |  |  | 26 | 96[b] |
| 6 |  |  | 27 | 73 |
| 7 |  |  | 20 | 71 |
| 8 |  |  | 16 | 93 |
| 9 |  |  | 120 | <5[c] |
| 10 |  |  | 120 | <5[c] |

[a] Isolated yields, average of two runs. [b] Reaction performed at 40 °C. [c] Estimated by $^1$H NMR of the recovered starting material.

**Table 3.** Catalytic Oxidation of Secondary Alcohols with an (NHC)−Ni System and Chlorobenzene[a]



| entry | alcohol | product | time (h) | yield (%)[b] |
|---|---|---|---|---|
| 1 |  |  | 24 | 93 |
| 2 |  |  | 26 | 92 |
| 3 |  |  | 22 | 87 |
| 4 |  |  | 26 | 93 |
| 5 |  |  | 22 | 99[c] |
| 6 |  |  | 24 | <5[d] |
| 7 |  |  | 36 | <5[d] |
| 8 |  |  | 24 | 71[c] |
| 9 |  |  | 24 | 63[c] |
| 10 |  |  | 17 | 94 |

[a] [NHC−Ni] = Ni(cod)$_2$, 5 mol %; IPr•HCl, 5 mol %. [b] Isolated yields, average of two runs. [c] Catalyst loading was doubled. [d] Estimated by $^1$H NMR of the recoverd starting material.

perform the oxidation of the primary aliphatic alcohols we tested (Table 2, entries 9 and 10) and after workup we were able to recover the starting materials in nearly quantitative yield. Other (NHC)Pd systems that have been used in aerobic reactions can perform oxidation of this type of substrates in excellent yields.[16] While this could seem a limitation of our system, the development of a catalytic system that controls the ability of discriminating one specific class of alcohols has been identified as one of the ultimate goals in alcohol oxidations.[2a] Unfortunately, with these initial conditions, the oxidation of benzyl alcohol did not proceed to completion and was also accompanied by degradation of some of the aldehyde product and the formation of the corresponding ester.

Following the same approach, we moved on to the development of a Ni-based system. Due the price of this metal, about 100 times cheaper than Pd,[17] a general,

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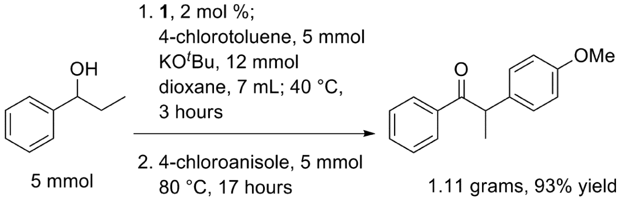
(16) Jensen, D. R.; Schultz, M. J.; Mueller, J. A.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3810–3813.

(17) PdCl$_2$: \$5/mmol. NiCl$_2$: \$0.05/mmol (Strem catalog 2008).

homogeneous Ni-based system would be of great interest, especially since the use of Ni for this reaction has been less explored and examples are scarce.[18] After a brief optimization of the reaction conditions, we determined that mixtures of 5 mol % of Ni(cod)$_2$ and 5 mol % of IPr•HCl (IPr•HCl = 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride) allowed for the oxidations to take place in good yields, albeit at higher temperature over longer reaction times than for the Pd-catalyzed reaction. We found that the system displayed similar, but not equal, versatility and functional group compatibility as the Pd-based system (Table 3). As for the Pd system, nonsterically demanding aliphatic alcohols (entries 8 and 9) led to slightly lower yields under these standard conditions than the arylated counterparts. This trend had already been noted in previous reports and attributed to a less favored elimination of the product from the metal center due to less steric hindrance.[7b] It is worth mentioning that with this Ni system, the primary benzylic alcohols that we tested did not undergo oxidation and remained unaltered after extended periods of time (Table 3, entries 6 and 7). In contrast to the Pd system, attempts to oxidize primary alipahtic alcohols led to mixtures of numerous and unidentified products.

The ability to perform oxidations without the need of a strong oxidant, at very mild temperatures, and without generating species potentially harmful to the substrate and/or difficult to remove makes these catalytic systems attractive not only for large-scale reactions, but also for multistep synthesis. To address this premise, we carried out a temperature-controlled domino oxidation/α-ketone arylation[19] with two different different aryl chlorides on a larger scale (Scheme 2). Performing the reaction at 40 °C led to a quantitative oxidation reaction in about 3 h, with no signs of α-arylation with 4-chlorotoluene. Raising the temperature and adding the second aryl halide afforded the target compound in excellent yield.

**Scheme 2.** Large-Scale Domino Oxidation/α-Ketone Arylation



In summary, we have presented the use of commercially available (NHC)Pd and (NHC)Ni systems for the selective anaerobic oxidation of a variety of secondary alcohols under very mild conditions, using aryl chlorides as oxidants. The use of NHCs as ligands allows for a dramatic decrease in the temperature required for the oxidations to take place, compared to previously reported analogous systems. Using nickel for this reaction is a novel option. Efforts toward broadening the scope of the reaction and applying it to kinetic resolutions are currently ongoing in our laboratories.

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**Supporting Information Available:** Experimental procedures and product charaterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) (a) For a heterogeneous aerobic system, see: Choudary, B. M.; Kantam, M. L.; Rahman, A.; Reddy, C. V.; Rao, K. K. *Angew. Chem., Int. Ed.* **2001**, *40*, 763–766. (b) For a heterogeneous system with Ni salts and bleach in water, see: Grill, J. M.; Ogle, J. W.; Miller, S. A. *J. Org. Chem.* **2006**, *71*, 9291–9296.

(19) For a review on this Pd-catalyzed reaction, see: Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234–235.