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Rapid and Selective Catalytic Oxidation of Secondary Alcohols at Room Temperature by Using (N-Heterocyclic Carbene)–Ni^0 Systems

Christophe Berini,[a] Ole H. Winkelmann,[a] Jennifer Otten,[b] David A. Vicic,[a] and Oscar Navarro*[a]

Abstract: The selective, anaerobic catalytic oxidation of secondary alcohols at room temperature by using an in situ (N-heterocyclic carbene)–Ni^0 system is presented. The use of non-anhydrous, non-degassed 2,4-dichlorotoluene as both the oxidant and the solvent allows for very short reaction times and very high yields. In addition, a well-defined (N-heterocyclic carbene)–Ni^0 complex was synthesized and applied to these oxidation reactions.

Keywords: alcohols · anaerobic conditions · nickel · nitrogen heterocycles · oxidation

Introduction

In recent years, the transition-metal-catalyzed oxidation of alcohols has attracted a great deal of interest.[1] While this very common transformation can be performed in stoichiometric proportions using traditional methods (Dess–Martin, Jones, Swern, etc.), the use of efficient catalytic systems allows for a reduction of waste and toxic reagents, as well as less harsh conditions.[2] Although many metals have been used for this reaction, palladium is arguably the most studied,[1,2] especially in aerobic systems in which molecular oxygen (or air) is used as oxidant. Seminal work by Swartz and Blackburn in aerobic systems in the late 1970s[3] provided the foundation for more recent and extensive developments by Sigman,[4] Stahl[5] and Stoltz,[6] among others,[7] in what has been called the renaissance of Pd^{II}-catalyzed oxidation chemistry.[1,8]

In theory, the use of molecular oxygen or air as oxidant for these reactions is ideal because of its availability, price and ease of handling. In a practical sense and especially on large scale, this approach is problematic due to the hazard of oxygen pressures when running oxidations in flammable organic solvents.[5b,8b] Herein, we describe the use of (NHC)–Ni (NHC=N-heterocyclic carbene)[9] catalytic systems for the selective oxidation of secondary alcohols at room temperature under anaerobic conditions.

Results and Discussion

Recently, our group disclosed the use of an (NHC)–Pd catalytic system for the oxidation of secondary alcohols using aryl chlorides as oxidants, at ambient temperature and under anaerobic conditions.[10] The dehalogenation of the aryl chloride leads to the formation of an unreactive by-product that becomes part of the solvent. The use of an NHC ligand allowed for a drastic reduction in reactions times when compared with analogous phosphine-based systems.[11] Moreover, we also reported on a novel and more interesting system using much less expensive[12] mixtures of the imidazolium salt IPr·HCl (IPr·HCl = 1,3-bis-(2,6-diisopropylphenyl)imidazolium chloride) and $[Ni(cod)_2]$ to perform the same reaction, albeit requiring higher temperature (60 °C) and longer reaction times than the Pd system. In order to study this difference in behavior between our Pd and Ni systems, we recently carried out experiments at room temperature with the Ni system using the corresponding free carbene instead of the imidazolium salt (Table 1). Reaction times were drastically reduced and close to those

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[a] Dr. C. Berini, Dr. O. H. Winkelmann, Prof. D. A. Vicic,+
Prof. O. Navarro
Department of Chemistry, University of Hawaii at Manoa
2545 McCarthy Mall, Honolulu, HI 96825 (USA)
Fax: (+1) 808-956-5908
E-mail: oscarnf@hawaii.edu

[b] J. Otten
Visiting student: Carrol University, 100 N. East Ave.
Waukesha, WI 53186 (USA)

[+] To whom inquiries regarding the crystal structure of **3b** should be addressed.

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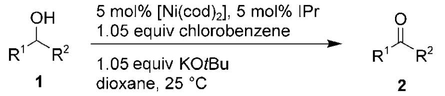
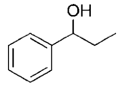
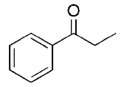
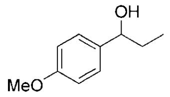
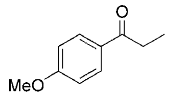
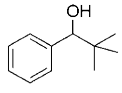
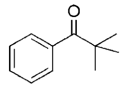
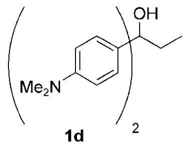
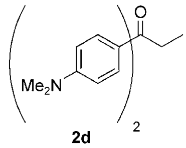
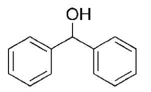
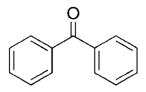
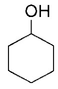
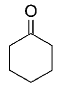
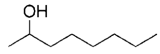
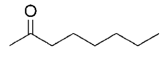
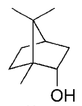
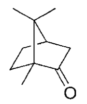
Table 1. Catalytic oxidation of secondary alcohols using [Ni(cod)$_2$] and IPr carbene.



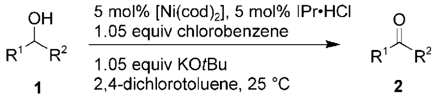
Entry	Alcohol	Product	t [h]	Yield [%][a]
1	 **1a**	 **2a**	13	96
2	 **1b**	 **2b**	10	98
3	 **1c**	 **2c**	5	96
4	 **1d**	 **2d**	6	92
5	 **1e**	 **2e**	14	98[b]
6	 **1f**	 **2f**	12	58[b]
7	 **1g**	 **2g**	11	74[b]
8	 **1h**	 **2h**	3	91

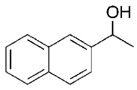
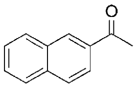
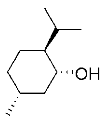
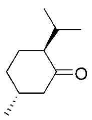
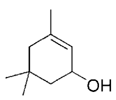
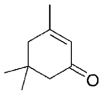
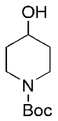
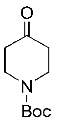
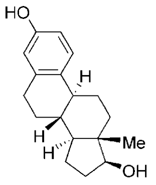
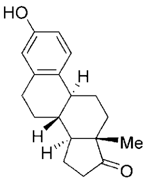
[a] Isolated yields, average of two runs. [b] Catalyst loading was doubled.

of our (NHC)–Pd system, albeit still using 5 mol% catalyst loading.[13] These results indicate that the "high" temperature required in our earlier work was needed only to deprotonate the imidazolium salt to generate the corresponding carbene ligand that coordinates to nickel, initiating the catalytic cycle.

The ability of performing oxidations without the need of a strong oxidant, at very mild temperature and without generating species potentially harmful to the substrate and/or of difficult removal makes this catalytic system attractive not only for multistep synthesis, but also for large scale reactions. With this premise in mind, we turned our attention to the use of an inexpensive chlorinated solvent for the reaction that could play the roles of both oxidant and solvent. Dichlorotoluenes, for example, are commonly used as high boiling-point solvents in industry due to their price, stability and ease of handling. We decided to use bulk non-anhydrous, non-degassed 2,4-dichlorotoluene (2,4-DCT) for the oxidation of 4-methoxy-α-methylbenzyl alcohol, using a mixture of 5 mol% [Ni(cod)$_2$] and 5 mol% IPr·HCl as catalyst precursor and 1.05 equivalents of KO*t*Bu (Table 2).

Table 2. (NHC)Ni-catalyzed oxidation of secondary alcohols in 2,4-DCT at room temperature.



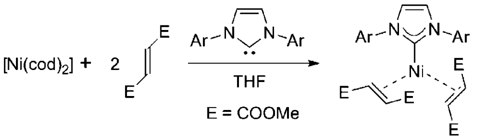
Entry	Alcohol	Product	t [min]	Yield [%][a]
1	**1a**	**2a**	90	92
2	**1b**	**2b**	15	97
3	**1c**	**2c**	30	96
4	**1d**	**2d**	15	90
5	**1e**	**2e**	15	98[b]
6	**1f**	**2f**	90	84[b]
7	**1g**	**2g**	15	95[b]
8	**1h**	**2h**	15	99
9	 **1i**	 **2i**	30	97
10	 **1j**	 **2j**	15	88[c]
11	 **1k**	 **2k**	120	99[b]
12	 **1l**	 **2l**	30	95
13	 **1m**	 **2m**	90	96

[a] Isolated yields, average of two runs. [b] Catalyst loading was doubled. [c] Reaction was performed at 40 °C.

To our delight, the results surpassed our expectations and the desired ketone was obtained in excellent yield after 15 min (Table 2, entry 1). When compared to our previous set of conditions (dioxane as solvent and chlorobenzene as oxidant), this reaction takes places two orders or magnitude faster. Under these conditions, a variety of secondary alcohols were easily oxidized to the corresponding ketones in high yields and in a matter of minutes. The substrates display varying degrees of bulk and include functionalities such as ether (Table 2, entry 2), tertiary amine (Table 2, entries 4, 12) and alkene (Table 2, entry 11). Natural products such as borneol, menthol and β-estradiol (Table 2, entries 8, 10 and 13, respectively) were also smoothly oxidized to the corresponding ketones in excellent yields. It is worth mentioning that, in agreement with the dioxane/chlorobenzene system, primary benzylic and alkylic alcohols were unreactive under these reaction conditions and cleanly and quantitatively recovered after work-up. The development of selective catalytic systems that discriminate one specific class of alcohols over another has been identified as one of the ultimate goals in alcohols oxidations.[8b]

Keeping in mind our desire to develop a user-friendly system that could potentially be used in large-scale reactions, our next goal was to circumvent the use of the very sensitive and highly flammable [Ni(cod)$_2$] in the reactions, and therefore became interested in the use of a well-defined NHC–Ni^0 complex, ideally air-stable, instead of the previously used in situ system. Cavell and co-workers recently reported on the synthesis of a number of NHC–Ni^0 complexes, employing dimethyl fumarate (dmfu) and the NHC-ligand IMes (IMes = 1,3-bis(2,4,6-trimethylphenyl)-imidazol-2-ylidene) in varying ratios.[14] [(IMes)Ni(dmfu)$_2$] (**3a**) caught our attention, representing an air-stable nickel(0) complex that, however, had not been tested for its catalytic performance in any reaction. Since we used the more bulky NHC-ligand IPr throughout our previous examinations, we synthesized the analogous complex [(IPr)Ni(dmfu)$_2$] (**3b**) to explore its potential in the anaerobic oxidation of secondary alcohols.

The synthesis of **3b** was carried out in an analogous fashion to that reported for **3a** by simply mixing [Ni(cod)$_2$] with two equivalents of dmfu, followed by addition of the preformed carbene (Scheme 1). Following this procedure [(IPr)Ni(dmfu)$_2$] (**3b**) was isolated in 90% yield. ^{1}H and ^{13}C NMR spectroscopic data of **3b** were in good agreement with those reported for **3a**, with the carbene carbon atom resonating at 189.5 ppm. The olefinic protons of the fumarates resonate at δ 4.72 and 4.07 ppm ($^3J = 10.6$ Hz), respectively. Single-crystals suitable for X-ray diffraction were grown by slow diffusion of hexanes into a solution of **3b** in THF. The crystal structure of **3b** is depicted in Figure 1.



3a: Ar = 2,4,6-trimethylphenyl
3b: Ar = 2,6-diisopropylphenyl

Scheme 1. Synthesis of [(NHC)Ni(dmfu)$_2$] complexes.

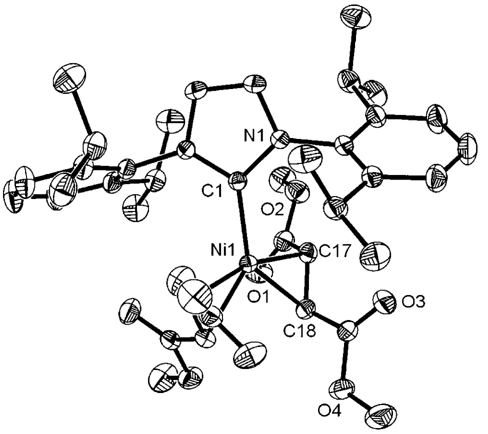
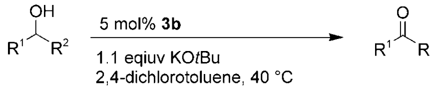


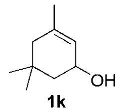
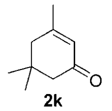
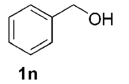
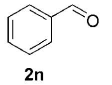
Figure 1. Crystal structure of [(IPr)Ni(dmfu)$_2$] (**3b**) with thermal ellipsoids drawn at the 50% probability level. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å]: Ni1–C1 1.9661(16), Ni1–C17 2.0240(12), Ni1–C18 1.9934(11), C17–C18 1.4057(17); selected bond angles [°]: C1-Ni1-C17 98.55(3), C1-Ni1-C18 137.09(4), N1-C1-N1A 102.91(12).

We evaluated the performance of **3b** in the anaerobic oxidation of 1-phenyl-1-propanol at different temperatures. Although **3b** allowed to perform this reaction at 25 °C, a considerably longer time was needed for the reaction to reach completion (12 h) when compared to the previously used IPr·HCl/[Ni(cod)$_2$] catalytic system that requires 1.5 h using similar catalyst loading. Running the reaction at 40 °C led to a more comparable reaction time (2.5 h), while at 60 °C the reaction was completed in less than 1 h. A reduction of the catalyst loading to 2.5 mol% resulted in a reaction time of 12 h at 40 °C. It is noteworthy that, although **3b** may be handled in air without any detectable decomposition[15] and 2,4-DCT can be used in reagent grade, the oxidation reactions had to be conducted under an inert atmosphere. No product formation was observed by gas chromatography when the reactants were loaded in air.

Thus, we examined the anaerobic oxidation of a variety of secondary alcohols employing 5 mol% of **3b** in 2,4-dichlorotoluene at 40 °C. Some representative results are depicted in Table 3. High yields of the respective ketones were obtained

Table 3. Catalytic oxidation of secondary alcohols in 2,4-DCT using **3b**.



Entry	Alcohol	Product	*t* [min]	Yield [%][a]
1	**1a**	**2a**	150	97
2	**1b**	**2b**	120	96
3	**1c**	**2c**	60	97
4	**1e**	**2e**	90	98
5	**1g**	**2g**	120	92[b]
6	**1h**	**2h**	30	95
7	 OH **1k**	 **2k**	90	69[b]
8	 OH **1n**	 **2n**	180	<5[b,c]

[a] Isolated yields, average of two runs. [b] Reaction performed at 60 °C. [c] Estimated by ^{1}H NMR of the recovered starting material.

from secondary aryl–alkyl and aryl–aryl alcohols (Table 3, entries 1–4). Except for borneol, which was oxidized particularly well (Table 3, entry 6), alkyl–alkyl substrates required higher reaction temperature (60 °C) to reach completion in comparable reaction times (Table 3, entries 5–7). As for the in situ system, primary alcohols are not oxidized to the respective aldehydes and also the use of **3b** produced only trace amounts of benzaldehyde from benzyl alcohol, being the starting material recovered almost quantitatively after work-up (Table 3, entry 8).

Conclusion

In summary, we have presented highly active, anaerobic (NHC)–Ni catalytic systems for the selective oxidation of secondary alcohols at room temperature. These constitute, to our knowledge, the first nickel-catalyzed reactions to accomplish this task under these mild conditions. The use of non-anhydrous, non-degassed 2,4-DCT as both solvent and oxidant allows for a drastic reduction of the reaction temperature and time. Yields of products are comparable to those of the most common state-of-the-art Pd-catalyzed aerobic oxidations,[16] although reaction times are significantly shorter and using inexpensive nickel. In addition to this activity, these NHC–Ni^0 catalysts are very selective toward secondary alcohols, and primary aliphatic and benzylic alcohols subjected to the same reaction conditions remain unchanged even after prolonged exposure to reaction conditions. The use of a new air-stable, well-defined (NHC)–Ni^0 complex as pre-catalyst avoids the use of flammable [Ni(cod)$_2$] in the oxidation reactions. Studies to expand the scope of the reaction and applying it to enantioselective systems are currently ongoing in our laboratories.

Experimental Section

General procedure for the catalytic oxidation of secondary alcohols: In the glovebox, KO*t*Bu (59 mg, 0.53 mmol) and either **3b** (18 mg, 0.025 mmol, 5 mol %) or bis(cyclooctadiene)nickel(0) (7 mg, 0.025 mmol, 5 mol %) and 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (11 mg, 0.025 mmol, 5 mol %) were added to a vial equipped with a magnetic stirbar. The vial was sealed with a screw cap fitted with a septum. Outside the glovebox, 2,4-dichlorotoluene (1 mL) and the alcohol (0.50 mmol) were added sequentially via syringe. The resulting mixture was allowed to stir the corresponding temperature until completion or no further conversion was observed by gas chromatography. The mixture was then purified by flash column chromatography on silica gel (hexane/ethyl acetate mixtures) affording the corresponding product, whose identity and purity was confirmed by ^{1}H NMR spectroscopy.

Acknowledgements

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