Aerobic C–C and C–O bond formation reactions mediated by high-valent nickel species†

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Nickel complexes have been widely employed as catalysts in C–C and C–heteroatom bond formation reactions. While Ni(0), Ni(I), and Ni(II) intermediates are most relevant in these transformations, recently Ni(III) and Ni(IV) species have also been proposed to play a role in catalysis. Reported herein is the synthesis, detailed characterization, and reactivity of a series of Ni(II) and Ni(IV) metallacycle complexes stabilized by tetradentate pyridinophane ligands with various N-substituents. Interestingly, while the oxidation of the Ni(II) complexes with various other oxidants led to exclusive C–C bond formation in very good yields, the use of O2 or H2O2 as oxidants led to formation of appreciable amounts of C–O bond formation products, especially for the Ni(II) complex supported by an asymmetric pyridinophane ligand containing one tosyl N-substituent. Moreover, cryo-ESI-MS studies support the formation of several high-valent Ni species as key intermediates in this uncommon Ni-mediated oxygenase-type chemistry.

Introduction

The formation of C–C and C–heteroatom bonds plays a fundamental role in organic transformations, and C–C cross-coupling reactions are among the most powerful tools for the construction of new C–C bonds.1–3 In this context, nickel catalysts have been commonly used for more than four decades in cross-coupling reactions such as Negishi, Kumada and Suzuki couplings.4–9 The most common oxidation states involved in these catalytic transformations are Ni0, NiI, and NiII, although more recent studies show that NiIII and NiIV oxidation states can also play a role in C–C bond formation.10–28 By comparison, stoichiometric and catalytic Ni-mediated C–heteroatom bond formation reactions have been developed mostly in the past two decades.21–26

In the past several years we have employed tetradeutate pyridinophane ligands to stabilize uncommon organometallic PdIIIIV and NiIIIIV complexes,37–44 which can undergo C–C and C–heteroatom bond formation reactions. In addition, we have recently reported the use of the ligand 1,4,7-trimethyl-1,4,7-triazaacyclonane (Me3tacn) to stabilize high-valent NiIIIIV complexes that undergo C–C and C–heteroatom bond formation reactions.35 With this ligand, small amounts of C–O bond formation products (~5%) were observed upon oxidation of [Me3tacn]NiII(CH2CMe2-tosyl, Ts) with O2.35 Herein, we report the use of modified pyridinophane ligands that directly affects that stability and reactivity of the corresponding high-valent Ni complexes. We tested the effect of the amine N-substituents by replacing the methyl groups with a more electron-withdrawing toluenesulfonyl (tosyl, Ts) group or a bulkier tert-butyl (tBu) group. By employing a Ni-cycloneophyl structure motif, we have been able to isolate NiIII species and also perform uncommon oxidatively-induced C–C and C–O bond formation reactions using O2 or H2O2 as the oxidants. The ability to control the relative reactivity of C–C vs. C–heteroatom bond formation should have important implications in various organic transformations.

Results and discussion

Synthesis and characterization of NiIIIIV complexes

The ligands N,N'-dimethyl-2,11-diaza[3.3](2,6)pyridinophane (MeN4), N,N'-tosylmethyl-2,11-diaza[3.3](2,6)pyridinophane (TosN4), N,N'-ditosyl-2,11-diaza[3.3](2,6)pyridinophane (T2N4) and N,N'-di-tert-butyl-2,11-diaza[3.3](2,6)pyridinophane (tBuN4) were synthesized according to literature procedures.45,46 With these ligands a series of cycloneophyl complexes were synthesized through a ligand exchange of (py)2Ni][cycloneophyl].47,48 The orange NiII complex (MeN4)NiII(cycloneophyl), 1, was
prepared in a 72% yield (Scheme 1), while the yellow NiII complex \(\text{TmSMeN}4\text{NiIII(cycloneophyl)}\), 2, was prepared in 81% yield and fully characterized. The cyclic voltammetry (CV) characterization of 2 reveals two main oxidation events at \(-990\) \(mV\) and \(750\) \(mV\) vs. \(\text{Fc}/\text{Fc}\), along with a smaller oxidation wave at \(70\) \(mV\) (Table 1). The two main oxidation events are tentatively assigned to the NiIII/II and NiIV/III redox couples, while the oxidation wave at \(70\) \(mV\) is proposed to correspond to a conformer of complex 2 in which the TmSMeN4 ligand adopts a \(\kappa^1\) binding mode, while the oxidation wave at \(-990\) \(mV\) likely corresponds to the confirmation of 2 with TmSMeN4 in a \(\kappa^4\) binding mode. The third complex, \(\text{TmSMeN}4\text{NiIII(cycloneophyl)}\), 3, was prepared in a 67% yield and was fully characterized by \(^1\)H NMR and \(^{13}\)C NMR. Its CV shows an oxidation potential at \(-400\) \(mV\), which is tentatively assigned to the NiIII/II couple. Finally, the yellow NiIII complex \(\text{Bu}^+\text{N4NiIII(cycloneophyl)}\), 4, was prepared in 73% yield and was also characterized by \(^1\)H NMR and \(^{13}\)C NMR. The CV of 4 shows a first oxidation potential at \(200\) \(mV\) vs. \(\text{Fc}/\text{Fc}\), which is higher than those observed for 2 and 3, likely due to the steric bulk of the \(\text{t}-\text{butyl}\) group, and as observed previously.

Given their accessible oxidation potentials, complexes 1–4 can easily be oxidized with one equivalent of acetylferrocenium \(\text{BF}_4\) or silver hexafluorophosphate \(\text{AgBF}_4\) in THF at \(-50\) \(\degree\)C to yield \(\text{Bu}^+\text{N4NiII(cycloneophyl)}\), \(\text{TmSMeN}4\text{NiII(cycloneophyl)}\), \(\text{Bu}^+\text{N4NiII(cycloneophyl)}\), and \(\text{TmSMeN}4\text{NiII(cycloneophyl)}\). The X-ray structures of both six-coordinate NiIII centers in distorted octahedral geometries (Fig. 1). For 2\(^*\), the Ni-N bond length 2.527 \(\AA\) is larger than the Ni-NMe bond length 2.199(4) \(\AA\), given that the N-tosyl group is more electron withdrawing vs. the N-methyl group. The Ni-Ni bond length of 2.182(5) \(\AA\) is larger than the Ni-N2 bond of 1.867(4) \(\AA\) due to a stronger trans effect of the C(sp\(^2\)) vs. the C(sp\(^2\)) donor atom. Similar trends are observed for 3\(^*\), while the Ni-NTs distances are significantly longer than the axial interactions observed for 2\(^*\) (Fig. 1).

The EPR spectrum of 2\(^*\) exhibits a rhombic signal with a superhyperfine coupling observed in the \(g_z\) direction due to one axial N donors (\(I = 1\)) coupling to the NiIII center (Fig. 2), suggesting that the NTs atom only weakly coordinates in the axial position. By comparison, complex 3\(^*\) exhibits a rhombic signal with a weak superhyperfine coupling to two N atoms in the \(g_z\) direction (\(A_{2N} = 8\) \(G\)), suggesting that both NTs atoms weakly bind to the Ni center (Fig. 2). Also, a small amount of unknown NiIII impurity is present in complex 3\(^*\), and simulation of the experimental spectrum suggests this impurity amounts to \(~5\)% of the entire EPR signal. Complex 4\(^*\) also exhibits a rhombic EPR signal, with superhyperfine coupling to two axial N donors in the \(g_z\) direction (\(A_{2N} = 11\) \(G\)), suggesting that the \(\text{t}-\text{butyl}\) groups interact with the Ni center to a greater extent than the NTs groups in 3\(^*\).

C–C and C–X bond formation reactivity of \(\text{Bu}^+\text{N4NiII(cycloneophyl)}\) complexes

With the new \(\text{Bu}^+\text{N4NiII(cycloneophyl)}\) complexes in hand, we set out to probe their reactivity in C–C and C–heteroatom bond formation reactions. First, we studied the oxidation of complexes 1–4 with 1-fluoro-2,4,6-trimethylpyridinium triflate (NFTPT), 5-(trifluoromethyl)dibenzothiophenium trifluoromethanesulfonate (TDTT), xenon difluoride (XeF\(_2\)) and (diacetoxyiodo)benzene (Phl(OAc))\(_2\), since these oxidants have been commonly employed in high-valent transition metal chemistry, including Ni complexes. While no C–heteroatom bond formation was detected, the C–C coupled product 1,1-dimethylbenzocyclobutene was obtained in various yields (Table 2). Comparing the reactivity of complexes 1–4, it appears that the presence of electron withdrawing NTs groups leads to higher C–C product yields, with up to 99% conversion.

Table 1: Cyclic voltammetry (CV) data for \(\text{Bu}^+\text{N4Ni(cycloneophyl)}\) complexes

<table>
<thead>
<tr>
<th>Complex</th>
<th>(E(\text{NiIII/II})) (mV)</th>
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<tbody>
<tr>
<td>1</td>
<td>-1700</td>
</tr>
<tr>
<td>2</td>
<td>-990</td>
</tr>
<tr>
<td>3</td>
<td>-400</td>
</tr>
<tr>
<td>4</td>
<td>200</td>
</tr>
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\(a\) \(E(\text{NiIII/II})\) values reported vs. \(\text{Fc}/\text{Fc}\). The CV shows an oxidation potential at \(100\) \(mV\) s\(^{-1}\) scan rate.

Fig. 1 ORTEP representation of 2\(^*\) (left) and 3\(^*\) (right) with 50% probability thermal ellipsoids. Selected bond distances (Å): 2\(^*\): Ni1–C1, 1.938(9); Ni1–C4, 1.938(4); Ni1–N1, 2.182(5); Ni1–N2, 1.867(4); Ni1–N3, 2.199(4); Ni1–N4, 2.527. 3\(^*\): Ni1–C1, 1.933(3); Ni1–C8, 1.982(3); Ni1–N1, 1.993(3); Ni1–N2, 2.010(3); Ni1–N3, 2.360(3); Ni1–N4, 2.436(3).
observed when 3 was oxidized with XeF₂. This reactivity trend is likely due to the coordination of the amine arms to create a six-coordinate high-valent Ni species that is less reactive towards reductive elimination than a five- or four-coordinate Ni species formed in the presence of the ligands with weakly interacting N-Ts groups. Since the reagents employed above are considered to usually act as two-electron oxidants, we tentatively propose the formation of transient \((\text{N}^4)\text{Ni}^\text{IV}(\text{cycloneophyl})\) species that then undergo C–C reductive elimination to generate the 1,1-dimethylbenzocyclobutene product and a \((\text{N}^4)\text{Ni}^\text{IV}\)-bis-solvento species, similar to what we observed recently for the (Me₂taecn) Ni\text{IV}(cycloneophyl) system. ²⁵

We have also investigated the oxidation of complexes 1–4 with O₂ and H₂O₂. The use of O₂ and H₂O₂ as an oxidant obviates the requirement for strong and hazardous oxidants which generate undesired stoichiometric byproducts, and thus making O₂ and H₂O₂ “greener” reagents for C–C and C–O bond formation reactions. The exposure of solutions of complexes 1–4 to O₂ quickly generates orange or red solutions. To our delight, heating these reaction mixtures for 14 hours at 70 °C followed by acidic workup and GC-MS analysis reveals the formation of C–O bond formation products. For example, oxidation of 1 and 3 with O₂ generates C–O bond formation products in 12–17% combined yield, while complex 2 shows up to 41% combined yield of C–O products (Table 3). By comparison, no C–O bond formation was formed for 4, suggesting that the steric bulk of the tert-butyl groups precludes exogenous reactivity, and thus 4 was not employed in any further reactivity studies. The GC-MS analysis also confirmed the presence of C–C coupled product 1,1-dimethylbenzocyclobutene for all four complexes, with up to 69% yield observed for 3. In addition, the oxidants H₂O₂ and m-chloroperoxybenzoic acid (mCPBA) are also capable of promoting C–C and C–O bond formation, although lower C–O product yields were observed,²⁶ likely due to the formation of more stable high-valent Ni species that undergo reductive elimination more slowly or undergo unspecific decomposition (see below). The lower C–O and C–C bond formation product yields might be attributed to the presence of water in the H₂O₂ solution that likely leads to unspecific decomposition of the high-valent Ni species before being able to undergo reductive elimination.²⁶ Overall, complex 2 seems to be the optimal system to generate the highest yields of C–O products, likely by providing the sweet spot of stability vs. reactivity to allow for the oxidation by O₂, and the formation of high-valent Ni species that persists long enough to undergo C–O reductive elimination.

To further probe the mechanism of oxidation, the reaction of \((\text{N}^4)\text{Ni}^\text{III}(\text{cycloneophyl})\) complexes 1–3 with O₂ or H₂O₂ was monitored at −50 °C in 9 : 1 acetone-\(d_6\) : D₂O. While no Ni\text{IV} intermediates were observed by \(^1\text{H}\) NMR, the formation of more than one Ni\text{III} species was suggested by EPR spectroscopy. In addition, cryo-electrospray mass spectrometry (cryo-ESI-MS)
was employed in an attempt to detect any high-valent Ni intermediates formed during the oxidation process.\textsuperscript{30,55} First, the oxidation of (TsMeN\textsubscript{4})Ni\textsuperscript{II}(cycloneophyl) complex with O\textsubscript{2} was probed by cryo-ESI-MS at 80°C in 9 : 1 acetone : H\textsubscript{2}O, followed by addition of HClO\textsubscript{4} as the proton source. The most intense signal corresponds to the [(TsMeN\textsubscript{4})Ni\textsuperscript{III}(cycloneophyl)]\textsuperscript{+} species (m/z 598.1912), confirming the detection of Ni\textsuperscript{III} species by EPR. In addition, two less intense species were observed that correspond to the mass of species \textsuperscript{2+} plus two or one O atoms, C\textsubscript{32}H\textsubscript{36}N\textsubscript{4}NiO\textsubscript{4}S (m/z 630.1811), and C\textsubscript{32}H\textsubscript{36}N\textsubscript{4}NiO\textsubscript{3}S (m/z 614.1856), respectively. While we cannot unambiguously assign the structure of these species,\textsuperscript{50} they are strongly suggesting an inner-sphere aerobic oxidation mechanism that eventually leads to formation of the detected C–O bond formation products.

Interestingly, oxidation of 2 at –80°C with H\textsubscript{2}O\textsubscript{2} in 9 : 1 acetone : H\textsubscript{2}O generates a number of transient and persistent species that can be observed by cryo-ESI-MS. The first two transient species that are observed are tentatively assigned to a Ni\textsuperscript{III}–hydroperoxo and a Ni\textsuperscript{IV}–hydroxo complex (A, m/z 631.1884, and B, m/z 615.1934, Fig. 3).\textsuperscript{50} The decay of the two transient species leads to the formation of a persistent species that likely corresponds to a hydroxylated Ni-cycloneophyl species (C, m/z 614.1856). This Ni\textsuperscript{III} species C is then proposed to undergo reductive elimination to form a cationic Ni\textsuperscript{I} species, which was detected by ESI-MS, and the cyclized C–O product (Scheme 2). Alternatively, the Ni\textsuperscript{IV} species B can

### Table 2 Oxidation of (\textsuperscript{1}N\textsubscript{4})Ni\textsuperscript{II}(cycloneophyl) with various oxidants in MeCN

<table>
<thead>
<tr>
<th>Complex</th>
<th>PhI(OAc)\textsubscript{2}</th>
<th>NFTPT</th>
<th>TDTT</th>
<th>XeF\textsubscript{2}</th>
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<td>17; 39</td>
<td>7; 19</td>
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<td>ND\textsuperscript{b}</td>
<td>14; 44</td>
<td>6; 9</td>
<td>ND\textsuperscript{b}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reaction conditions: MeCN, 70°C, 14 h. Yields (%) were determined by GC-FID vs. 1,3,5-trimethoxybenzene as internal standard. The first yield shown is for 1,1-dimethylbenzocyclobutene, while the second yield is for is tert-butylbenzene.\textsuperscript{a} Not determined.

### Table 3 Oxidation of (\textsuperscript{1}N\textsubscript{4})Ni\textsuperscript{II}(cycloneophyl) with O\textsubscript{2} in 9 : 1 MeCN : H\textsubscript{2}O

<table>
<thead>
<tr>
<th>Complex</th>
<th>Yields\textsuperscript{a} (%)</th>
<th>Total yield (%)</th>
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<tr>
<td>1</td>
<td>35 12 8 3 6 64</td>
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</tr>
<tr>
<td>2</td>
<td>41 12 2 17 22 94</td>
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</tr>
<tr>
<td>3</td>
<td>69 12 2 5 5 93</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>27 6 0 0 0 33</td>
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</tbody>
</table>

\textsuperscript{a} Reaction conditions: 9 : 1 MeCN : H\textsubscript{2}O, 70°C, 14 h. Yields (%) were determined by GC-FID vs. 1,3,5-trimethoxybenzene as internal standard.

Fig. 3 Cryo-ESI-MS spectra (top) and simulations (bottom) showing the isotopic patterns of cationic Ni\textsuperscript{III} and Ni\textsuperscript{IV} intermediates found during the oxidation of 2 with H\textsubscript{2}O\textsubscript{2} in 10% H\textsubscript{2}O/acetone and HClO\textsubscript{4} at –80°C. From top to bottom: A, [(\textsuperscript{1}T\textsubscript{Me}N\textsubscript{4})Ni\textsuperscript{III}(cycloneophyl)(OOH)]\textsuperscript{+} m/z 631.1884 (transient species, simulated as a 49 : 51 mixture with a \textsuperscript{2+} + O\textsubscript{2} species with m/z 630.1805), B, [(\textsuperscript{1}T\textsubscript{Me}N\textsubscript{4})Ni\textsuperscript{IV}(cycloneophyl)(OH)]\textsuperscript{+} m/z 615.1934 (transient species, simulated in a 39 : 61 ratio with species C) and C, [(\textsuperscript{1}T\textsubscript{Me}N\textsubscript{4})Ni\textsuperscript{III}(-CH\textsubscript{2}CMe\textsubscript{2}-o-C\textsubscript{6}H\textsubscript{4}–O)]\textsuperscript{+} m/z 614.1856 (persistent species).\textsuperscript{50}
undergo C–C reductive elimination to generate the 1,1-dimethylbenzocyclobutene product and the [{(TsMeN4)NiII(MeCN)}2]2+ complex, which is observed in the ESI-MS as the [{(TsMeN4)NiII(ClO4)}] species D. Analysis by cryo-ESI-MS of the oxidation of complexes 1 and 3 with H2O2 also reveals the formation of the persistent Ni complexes, although no high-valent Ni intermediates were observed in these cases, likely due to their decreased stability. When comparing the product yields for complexes 1–3 and the various oxidants employed, the general trend is observed in which the less stable the high-valent Ni species are, the higher are the yields of C–C and/or C–O bond formation products. Overall, these results are very promising, suggesting that with an appropriately tailored multidentate ligand the corresponding organoametallic Ni complexes can be oxidized with mild oxidants such as O2 and H2O2 and promote C–C and/or C–O bond formation reactivity that is usually possible only under stringent anaerobic and anhydrous conditions. Interestingly, high-valent Ni–oxo species supported by the multidentate amine ligands have also been reported recently, lending support to the transient species proposed above. It is also important to note that similar reactivity with O2 and H2O2 has been observed previously for both Pt and Pd complexes.

Conclusion

In conclusion, we report herein the use of four different pyridinophane ligands to stabilize organoametallic Ni complexes, including high-valent Ni species. All isolated complexes were fully characterized and their C–C and C–heteroatom bond formation reactions investigated. The [(N4)NiII(cycloneophyl)] derivatives have accessible oxidation potentials and thus can easily be oxidized with a variety of oxidants. Interestingly, oxidation of [(N4)NiII(cycloneophyl)] complexes with O2 and H2O2 generates both C–C and C–O bond formation products. For example, the [(TsMeN4)NiII(cycloneophyl)] complex yields C–O bond formation products in 41% yield, along with the C–C coupled product for an overall conversion of 94%. Cryo-ESI-MS studies were employed to detect high-valent Ni–oxygen species and a mechanism was proposed for the oxidatively-induced C–C and C–O bond formation reactions. Overall, the [(TsMeN4)NiII(cycloneophyl)] complex seems to be at the sweet spot of stability vs. reactivity for C–O bond formation, while the [(N4)NiII(cycloneophyl)] complex gives the highest yield of C–C coupled product. All these results are very promising, suggesting that organoametallic Ni complexes supported by multidentate ligands can exhibit bioinspired aerobic oxidation chemistry, which could be further developed into catalytic aerobic oxidative transformations.

Conflicts of interest

The authors declare no competing financial interest.

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