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Synthesis of 2-Nickela(II)oxetanes from Nickel(0) and Epoxides: Structure, Reactivity, and a New Mechanism of Formation

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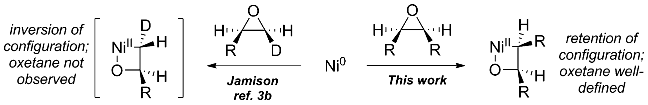
Ⓢ *Supporting Information*

ABSTRACT: 2-Nickelaoxetanes have been frequently invoked as reactive intermediates in catalytic reactions of epoxides using nickel, but have never been isolated or experimentally observed in these transformations. Herein, we report the preparation of a series of well-defined nickelaoxetanes formed via the oxidative addition of nickel(0) with epoxides featuring ketones. The stereochemistry of the products is retained, which has not yet been reported for nickelaoxetanes. Theoretical calculations support a bimetallic ring-opening/closing pathway over a concerted oxidative addition. Initial reactivity studies of a nickelaoxetane demonstrated protonolysis, oxidatively induced reductive elimination, deoxygenation, and elimination reactions when treated with the appropriate reagents.

The 2-metallaoxetanes, most notably invoked as reactive intermediates during catalytic olefin oxidation reactions, remain relatively rare chemical species.[1] The classic example of a nickelaoxetane in the literature is a report by de Pasquale on the formation of cyclic carbonates from epoxides and CO_2.[2] The nickelaoxetane is proposed to arise from the oxidative addition of nickel(0) to the epoxide. More recently, the Jamison group has reported on the reductive coupling of alkynes and epoxides catalyzed by nickel(0) complexes.[3] The proposed mechanism of this transformation involves S_N2-type attack of the nickel(0) complex onto the epoxide, with inversion of configuration, followed by ring closure to form a nickelaoxetane (Scheme 1); subsequent insertion of the alkyne occurs exclusively into the M−C bond of the oxetane. The Doyle group has also suggested the formation of nickelaoxetanes as intermediates during the transmetalation of aryl epoxides with boronic acids using a nickel(0) catalyst.[4] Although all of these reports invoke the formation of a nickelaoxetane from nickel(0) and an epoxide, the nickelacycles have not been isolated or observed experimentally. Indeed, to date the only examples of well-defined nickelaoxetanes belong to the Hillhouse group, where the oxetanes are formed by the reaction of a nickel alkylidene[5a] or imido[5b] with a ketene. The authors proposed that these nickelaoxetanes arise from pathways that proceed via [2 + 2] cyclization.

Scheme 1. Syntheses of Nickelaoxetanes from Nickel(0)

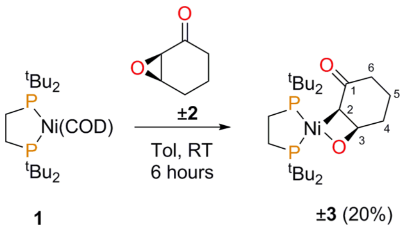


Recently, efforts in our group have been focused on the development of new chemical transformations based on the reactivity of well-defined metallaoxetanes of rhodium.[6] We have reported that a 2-rhodaoxetane can undergo transmetalation with aryl- and alkenylboronic acids[6b] as well as insertion with a variety of unsaturated electrophiles to give ring-expanded metallacycles.[6c] Ring expansion occurred exclusively into the M−O bond of the rhodaoxetane, which contrasts with reported insertion into the M−C bond of nickelaoxetanes. This complementary reactivity of nickel versus rhodium inspired us to investigate the synthesis of a well-defined nickelaoxetane and explore its reactivity. We report our initial findings herein.

Ogoshi has demonstrated that carbonyl groups can be used as directing groups for a wide array of nickel-mediated transformations.[7] Inspired by these reports, we prepared epoxide *rac*-**2** and reacted it with (dtbpe)Ni(COD) (**1**, dtbpe =1,2-bis(di-*tert*-butyl)phosphinoethane, COD = 1,5-cyclooctadiene). Monitoring the reaction by ^{31}P NMR spectroscopy reveals the formation of a mixture of products over the course of 6 h. The major product appears as two doublets (δ = 72.7 and 71.5 ppm) with small $^2J_{P,P}$ values of 6 Hz, indicative of coupling through a nickel(II) center.[8] Removing the volatiles *in vacuo* and extracting the residue with pentanes allowed for the isolation of the major product **3** as the racemate in 20% yield as an analytically pure orange powder (Scheme 2). A variety of NMR techniques and X-ray crystallography were employed to determine the structure of **3**, which is the first example of an isolable nickela(II)oxetane derived from nickel(0) and epoxides.

The ^1H NMR spectrum of **3** displays a downfield multiplet for H3 (δ = 5.78 ppm; see Scheme 2 for numbering). A COSY

Scheme 2. Initial Synthesis of 3[a]



[a] Isolated yield in parentheses. Relative stereochemistry shown for clarity.

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experiment shows that this resonance is coupled to another at 2.87 ppm, which is assigned as the resonance for H2. Importantly, a NOESY experiment shows strong correlations between the H2 and H3 protons, indicative of *cis* stereochemistry. Each of the methylene resonances of the cyclohexyl ring are diastereotopic, which complicates the aliphatic region of the ^{1}H NMR spectrum. However, they can each be assigned on the basis of COSY, HSQC, and HMBC experiments. The presence of the free ketone is shown by the downfield shift of the C1 resonance in the ^{13}C NMR spectrum (δ = 211.7, apparent t, J = 2 Hz). The slow evaporation of a cold Et_2O solution of **3** allowed for the growth of dark red crystals, and the structure of **3** was confirmed by an X-ray diffraction study (Figure 1). The geometry at the nickel is square planar, with a Ni−O distance of 1.832(1) Å and a Ni−C distance of 2.014(2) Å. The metallacycle bond lengths are similar to those of Hillhouse's oxetanes.[5]

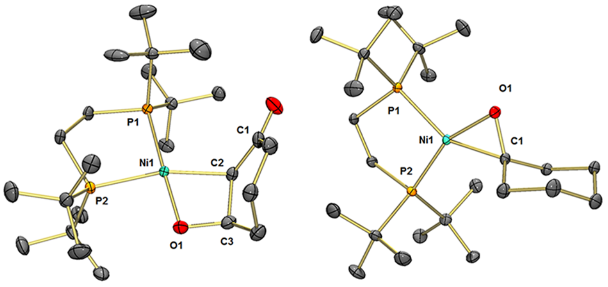
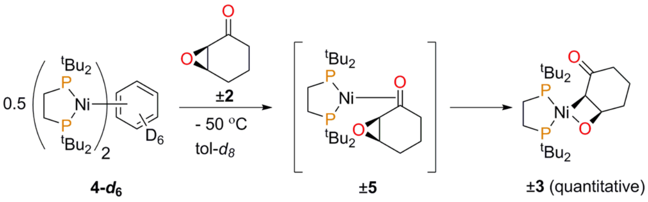


Figure 1. POV-Ray (50% ellipsoids) diagrams of **3** and **6**. Hydrogen atoms omitted for clarity.

With **3** in hand, we sought to explore the mechanism of formation and reactivity of this species. We speculated that COD could be competing with **2** at the nickel(0) center, resulting in low yields of **3**.[9] Thus, we explored other sources of (dtbpe)nickel(0) as starting materials. While (dtbpe)Ni(C_2H_4) was found to be unreactive with **2**, the arene adduct [(dtbpe)Ni]$_2$(μ−η^2:η^2-C_6H_6) **4**[10] was found to rapidly generate **3** at room temperature in 60% isolated yield. In an attempt to observe any intermediates during this transformation, we performed low-temperature NMR studies on the reaction of **4** with **2**.[7b] Even at −50 °C, the main species in solution is **3**, which highlights the facile oxidative addition process. In addition, ^{31}P and ^{13}C NMR experiments reveal the transient existence of a nickel(0) complex, which we assign as the asymmetric η^2-ketone complex **5** (Scheme 3). Warming the solution to −15 °C resulted in the disappearance of the resonances of **5** in the ^{31}P NMR spectrum and the complete conversion to **3**. This shows that **5** is either an intermediate along the pathway to **3** or possibly in an off-path equilibrium with some intermediate along the reaction pathway to **3**. In contrast, the reaction of **1** with **2** was found to not proceed below room temperature.

Scheme 3. Low-Temperature Synthesis of 3[a]

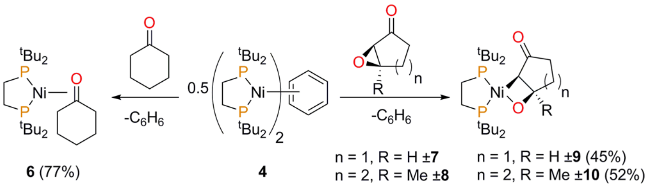


[a] Relative stereochemistry shown for clarity.

As **5** proved too reactive to isolate, we sought to prepare an analogue that did not contain the epoxide moiety. Addition of cyclohexanone to a solution of **4** resulted in an immediate color change from red to yellow. Crystallization of the crude product from pentanes afforded the η^2-ketone adduct, **6** (see Figure 1 for solid-state structure). As expected, **5** and **6** are spectroscopically similar, in particular with regard to the coupling constants in the ^{13}C and ^{31}P NMR spectra.[11] In addition, we found that equimolar amounts of either **1** or **4** and cyclohexene oxide in C_6D_6 resulted in no reaction over the course of several days, which highlights the importance of the ketone in this transformation (*vide infra*). Furthermore, the yield of **3** was found to be unaffected by the presence of 1,4-cyclohexadiene, which indicates to us that a radical-based mechanism is unlikely.[11]

We also prepared complexes **9** and **10** using an analogous synthetic route to that of **3** (Scheme 4).[11] To explore the potential reversibility of nickelaoxetane formation, an excess of **7** was added to a solution of **3** in C_6D_6. No formation of **9** was detected after 3 days at room temperature, which indicates that the reaction is irreversible under these conditions.

Scheme 4. Synthesis of 6, 9, and 10[a]



[a] Isolated yields in parentheses. Relative stereochemistry shown for clarity.

The Jamison group has previously proposed that low-valent nickel can react with epoxides via an S_N2-type attack, resulting in an inversion of configuration at the carbon.[3b] Hillhouse has also reported a similar mechanism for the oxidative addition of (bpy)Ni(COD) (bpy = 2,2′-bipyridyl) to a variety of *N*-tosylaziridines to generate azanickelacyclobutanes.[9,13] We believe that in our system **3** is formed by a different mechanism, as the oxetane retains the *cis* configuration of the epoxide. In order to further probe the mechanism of our transformation, DFT calculations were performed, and two possible mechanistic pathways are shown in Figure 2.[14] Ligand dissociation from **A** or **B** leads to the formation of the unsaturated nickel(0) complex **C**, which is trapped by the free epoxide to form an η^2-ketone complex **D** that is stabilized by 11.7 kcal/mol (ΔG) relative to **B**. Two conformers are possible for the η^2-ketone complex: **D**, where the epoxide oxygen is located on the same face of the six-membered ring as the Ni center, and **D′**, where the oxygen atom is found on the opposing face. Attempts to locate a concerted C−O oxidative addition pathway directly from intermediate **D** were unsuccessful. Instead, an intermediate **E** (ΔG = 10.2 kcal/mol) was located on the potential energy surface (PES), best described as an η^5-O,C,C,C,H complex.[11] Oxidative addition proceeds through transition state **EF**^{TS} (ΔG = 24.5 kcal/mol, **D** → **EF**^{TS}) to generate the metallaoxetane **F**. The connectivity of **D** with **E** was not established, and therefore it is possible that the η^2-ketone complex is formed in an off-pathway equilibrium, and intermediate **E** is formed directly from free **C** and epoxide.

Although we were unable to locate a transition state for S_N2-type cleavage from conformer **D′**, the zwitterionic ring-opened product of such as process was found to be high in energy (+27.9

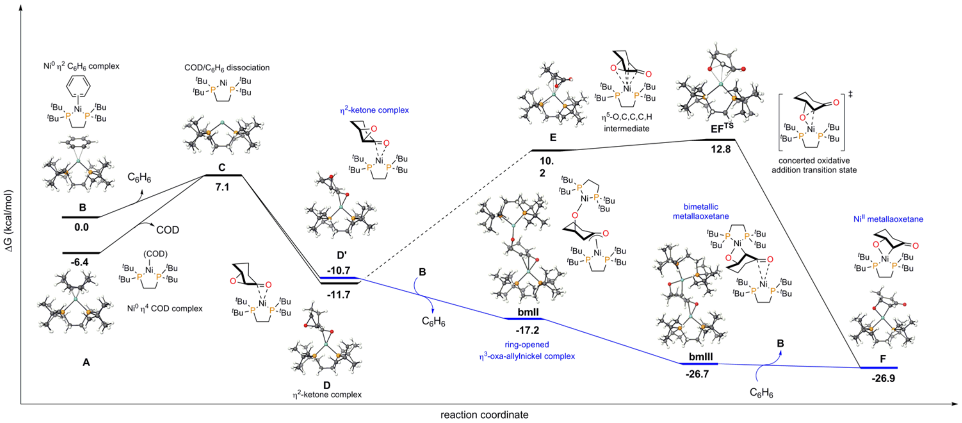
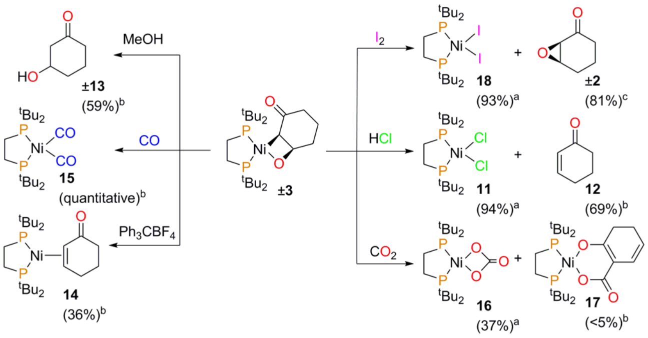


Figure 2. DFT-calculated reaction pathway for stepwise (blue) and concerted (black) metallaoxetane formation. Energies (ΔG) are reported in kcal/mol relative to **B**.

kcal/mol relative to **D′**). We were surprised to find that (dtbpe)nickel(0) could act effectively to stabilize this intermediate, lowering its relative energy by 24.7 kcal/mol.[11] In light of this, we explored the possibility of a stepwise ring-opening/closing mechanism that would allow for retention of stereochemistry. In model calculations involving a truncated dmpe (dmpe = 1,2-bis(dimethyl)phosphinoethane) ligand, a bimetallic ketone complex was identified in which the epoxide oxygen binds a second (dmpe)nickel(0) fragment. For the energetics in this discussion we assume the second nickel(0) fragment is generated by dissociation from **B**.[11] Formation of the bimetallic species is endergonic (+8.0 kcal/mol compared to the η^2-ketone complex), and the intermediate exists in a shallow well on the PES, with epoxide opening proceeding through a transition state that was calculated to have a slightly negative ΔG value.[11] In calculations involving the dtbpe ligand, no epoxide complex was located, and ring opening was found to be barrierless upon approach of the nickel(0) fragment toward the epoxide oxygen of **D′**. The resultant ring-opened structure **bmII** ($\Delta G = -17.2$ kcal/mol) is an η^3-oxa-allylnickel complex, analogous to those previously described.[7a,15] No transition state was located for subsequent ring closure leading to metallaoxetane **bmIII** ($\Delta G = -26.7$ kcal/mol), but we expect this process to be facile.[11] In the formation of **bmIII** the oxa-allylic nickel readopts a η^2-ketone binding mode. Formation of the observed product **F** and regeneration of **B** by loss of nickel(0) from the carbonyl is calculated to have a negligible free energy change. Notably, no conversion to **bmIII** was observed experimentally upon addition of arene complex **4** to **3**. The lack of reactivity between complexes **1** and **4** with cyclohexene oxide demonstrates that the ketone group plays a crucial role in this transformation. DFT analysis reveals that the transition-state energy ($\Delta G^\ddagger = 15.4$ kcal/mol) for concerted C–O oxidative addition of cyclohexene oxide is similar to that for **2**.[11] This observation is consistent with a bimetallic stepwise mechanism, as precoordination of one of the metal centers as well as formation of the η^3-oxa-allylnickel motif upon ring-opening are expected to lower the reaction barrier. In addition, the lower energetics of the bimetallic pathway are more consistent with the rapid rate of formation of **3** that we observe. Although our DFT calculations favor a stepwise mechanism, we cannot conclusively rule out a concerted mechanism at this time, and further mechanistic studies are ongoing within our group.

We then sought to probe the reactivity of **3** (Scheme 5). Protonolysis of **3** with an excess of HCl in C_6D_6 resulted in the rapid precipitation of a red solid, identified as (dtbpe)$NiCl_2$ (**11**)[16] and isolated in 94% yield. The organic product was identified by GC-MS and ^1H NMR spectroscopy as 2-cyclohexenone **12** (69% yield), presumably formed via acid-induced elimination from liberated 3-hydroxycyclohexanone (**13**).[17] Indeed, using less acidic sources of protons such as MeOH results in the formation of **13** in 59% yield by ^1H NMR spectroscopy. Treatment of **3** with Ph_3CBF_4 gave complex **14** as the major organometallic product via deoxygenation of the nickelaoxetane ring. Complex **14** was formed in 36% yield, and singly oxidized phosphine ligand (dtbpeO) was also observed by ^{31}P NMR spectroscopy.[18] The crude reaction mixture also contained **12** (26% yield), free dtbpe, and a dark precipitate presumed to be Ni black. Alkene extrusions have been reported for a few other 2-metallaoxetanes.[19] Complex **14** was also prepared independently (see Figure 3 for solid-state structure).[11]

Scheme 5. Preliminary reactivity of 3. (a) isolated yield (b) NMR yield (c) GC yield.[11]



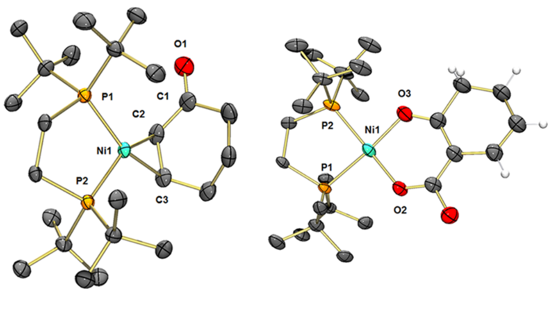


Figure 3. POV-Ray diagrams of **14** (50% ellipsoids) and **17** (30% ellipsoids). Certain hydrogen atoms omitted for clarity.

Stirring a solution of **3** in C_6D_6 under 1 atm of CO for 16 h resulted in a color change from orange-red to pale yellow. Analysis of the reaction mixture by ^{31}P NMR spectroscopy revealed the complete formation of (dtbpe)Ni$(CO)_2$ (**15**). In contrast, reacting **3** with CO_2[20] in CD_2Cl_2 yields (dtbpe)Ni(CO_3)[21] (**16**) as the major product (>90% yield by ^{31}P NMR spectroscopy) along with **12** (75% yield by ^1H NMR spectroscopy).[11] If the reaction is performed in aromatic solvents at 50 °C, orange crystals of **17** which are suitable for X-ray diffraction analysis (Figure 3) can also be obtained from the reaction mixture. While the insertion of a CO_2 unit does result in ring expansion, the bicyclic moiety of **3** appears to have undergone an elimination reaction to form an alkene. This group is clearly seen in the ^1H NMR spectrum of **17**.[11] We have been unable to characterize complex **17** fully, as it is formed in low yields (<5% by ^1H NMR spectroscopy) and readily decomposes.

Oxidatively induced reductive elimination has been well-documented for first-row transition metals, including nickel.[13,22] Addition of I_2 to **3** results in a color change from red-orange to dark green. Analysis of the resulting solution by EI-MS and UV−vis spectroscopy reveals the formation of paramagnetic (dtbpe)-NiI_2[23] (**18**), isolated in 93% yield. GC analysis of the crude mixture shows the presence of **2** in 81% yield.

In conclusion, we have demonstrated that ketones act as directing groups for the oxidative addition of nickel(0) with epoxides to give rare examples of well-defined 2-nickelaoxetanes. DFT calculations were performed to probe the mechanism of formation of these nickelaoxetanes, which support a bimetallic ring-opening/closing pathway over a concerted oxidative addition. Complex **3** was found to be susceptible to protonolysis, oxidatively induced reductive elimination, deoxygenation, and elimination reactions when treated with the appropriate reagents. We are currently undertaking further mechanistic studies on the reactions reported herein and are also exploring the possibility of catalytic reactivity with these complexes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b06735.

Computational coordinates and full experimental details (PDF)

Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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