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Mechanistic Investigations

Catalytic Functionalization of Styrenyl Epoxides via 2-Nickela(II)oxetanes

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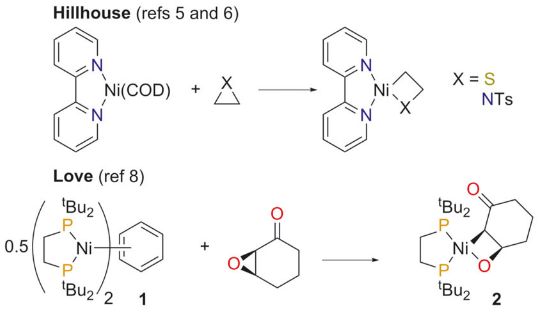
Abstract: Low-valent nickel is shown to preferentially isomerize mono- or disubstituted epoxides into their corresponding aldehydes. Experiments with tetrasubstituted epoxides demonstrate that these reactions proceed via reactive 2-nickelaoxetane intermediates, and that the oxidative addition step likely occurs with retention of configuration. The monosubstituted aldehyde isomerization products were found to rapidly react with HBpin to form boronate esters. These hydroboration reactions could be performed catalytically.

2-Metallaheterocyclobutanes are an unusual structural motif that have frequently been invoked as reactive intermediates during organometallic transformations, yet well-defined examples have been only recently reported.[1] Ongoing research in our group has been focused on exploring the development of new catalytic transformations that feature these metallaheterocycles as intermediates.[2] Key to achieving such processes is to develop an understanding of the fundamental reactivity of these complexes. As such, we have demonstrated that 2-rhodaoxetanes undergo transmetallation with aryl-and alkenylboronic acids,[3] and ring expansion with various other organic electrophiles.[4] More recently, we have become interested in exploring the feasibility of substituting a cheaper, more earth-abundant metal, such as nickel, for rhodium. This is appealing not only for economic reasons, but also because it could lead to complementary reactivity of these nickelaheterocycles from their rhodium counterparts.

In particular, Hillhouse has demonstrated that (bpy)Ni(COD) (bpy = 2,2′-bipyridyl, COD = 1,5-cyclooctadiene) can oxidatively add to both aziridines[5] and thiiranes[6] to generate the corresponding nickelaheterocyclobutanes. The Jamison group has also invoked the formation of nickelaoxetanes through an S_N2-type oxidative addition of nickel(0) during the catalytic reductive coupling of epoxides and alkynes.[7] Our group has since demonstrated the oxidative addition of a different low-valent nickel source, $[(dtbpe)Ni]_2(\mu\text{-}\eta^2{:}\eta^2\text{-}C_6H_6)$ **1** (dtbpe = 1,2-bis{di-*tert*-butyl}phosphinoethane), into the C–O bond of epoxides[8] (Scheme 1, bottom). Notably, the oxidative addition to form **2** occurs with retention of configuration, in contrast with Hillhouse's synthesis of azanickelacyclobutanes[5] (Scheme 1, top) and Jamison's reductive coupling strategy,[7a,b] both of which occur with inversion of configuration.



Scheme 1. Synthesis of nickelaheterocyclobutanes from nickel(0).

Doyle and co-workers have recently reported nickel-catalyzed cross-coupling of styrenyl epoxides with boronic acids.[9] The authors propose that catalysis occurs through a tandem process: first, the isomerization of the epoxide to the corresponding aldehyde via a nickelaoxetane intermediate, followed by a 1,2-arylation to give the final product. Both of these cycles are proposed to be catalyzed by nickel(0). We were thus intrigued to explore the reactivity of **1** towards styrenyl epoxides. We report herein that **1** can rapidly isomerize styrenyl epoxides preferentially to their corresponding aldehydes via nickelaoxetane intermediates, that the oxidative addition step occurs with retention of configuration, and that the aldehyde complexes can undergo catalytic hydroboration with HBpin, demonstrating proof-of-concept that these reactions can be applied towards catalysis.

Addition of styrene oxide **3** to an orange–red solution of **1** in C_6D_6 results in the formation of a mixture of products as determined by $^{31}P\{^1H\}$ NMR spectroscopy (Scheme 2). The major product, formed in 73 % yield, displays two doublets at 94.6 and 83.9 ppm that show large $^2J_{P,P}$ values of 74 Hz, indicative of an asymmetric coordination geometry at a nickel(0) centre.[10] The minor product (12 % yield by ^1H NMR spectroscopy) displays similar spectroscopic features, that is, two [AB]

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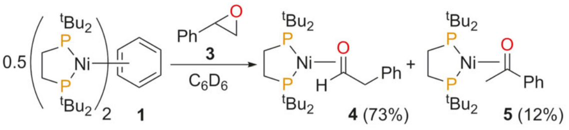
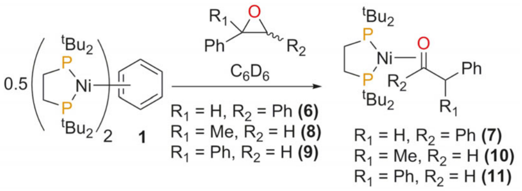


Scheme 2. Synthesis of complexes **4** and **5**. ^{1}H NMR yields in parentheses.



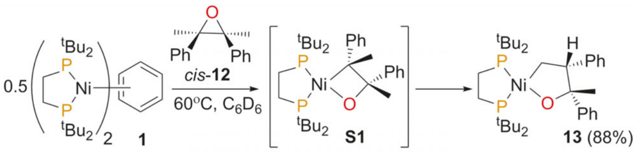
Scheme 3. Synthesis of complexes **7**, **10** and **11**.

doublets at 87.1 and 85.9 ppm with $^2J_{P,P}$ values of 75 Hz. The major and minor products were identified as the η^2-bound aldehyde complex **4** and ketone complex **5**, respectively, formed by isomerization of the epoxide.[11] The isomerization products were also prepared independently through the addition of the appropriate organic carbonyl to complex **1**, and were fully characterized by a variety of NMR spectroscopic experiments, mass spectrometry and elemental analysis.

The ^{31}P{^{1}H} and ^{1}H NMR spectra of **4** show an asymmetric phosphine ligand, since each of the *tert*-butyl groups are inequivalent. The aldehydic proton resonance ($\delta = 4.98$ ppm) is remarkably shielded, demonstrating a significant extent of backbonding from the metal centre to the π^* orbital of the C=O group. Complex **4** was recrystallized from Et_2O at −35 °C to yield orange crystals suitable for diffraction analysis (Figure 1). The C−O bond of the phenylacetaldehyde ligand is long at 1.332(3) Å, again demonstrating a high degree of back-bonding. The ^{1}H NMR spectrum of **5** also displays a C_1 symmetric complex. Cooling a concentrated toluene solution of **5** allowed for the growth of dark red crystals which were suitable for X-ray diffraction (Figure 1). To probe the lability of these π-bound ligands, we reacted **4** with an excess of acetophenone, and **5** with an excess of phenylacetaldehyde. In both cases, no reaction was observed over several days at room temperature, and heating to 80 °C was required for ligand exchange to occur.[12] Thus, ligand exchange is quite slow in these complexes.

In an attempt to gain insight into the mechanism of these isomerization reactions, we then reacted a variety of substituted epoxides with complex **1** (Scheme 3). The *cis*- and *trans*-stilbene oxides (**6**) rapidly isomerize at room temperature to give the same organometallic species (in 97% ^{1}H NMR yield from *cis*-**6**, and 88% ^{1}H NMR yield from *trans*-**6**), which was identified as the ketone complex **7** (X-ray structure in Figure 1). 1,1-Disubstituted epoxides **8** and **9** also reacted cleanly with **1** to generate aldehyde complexes **10** (93% ^{1}H NMR yield) and **11** (78% ^{1}H NMR yield; see Supporting Information for solid-state structures). Complex **10** forms as an equimolar mixture of diastereomers when prepared by reacting **1** with **8** or 2-phenylpropionaldehyde.[12] Importantly, reacting enantiopure epoxide (*R*)-**8** with **1** also results in an equimolar mixture of the diastereomers of **10**, which indicates that some step along the conversion of **1** to **10** proceeds with scrambling of configuration.

The formation of aldehydes from epoxides is well known to proceed by Lewis acid catalysis.[13] However, Ni^0 is a notably poor Lewis acid, especially when chelated by an electron-donating phosphine ligand.[11] In contrast, recent work with both Al/Co[14] and Rh[15] has demonstrated epoxide isomerization that proceeds through nucleophilic attack typically form ketones, although a notable exception is the Pd system reported by Kulsagaram and Kulawiec[16] To explore the ring-opening step, we prepared epoxide *cis*-**12** and reacted it with **1**. Monitoring the reaction at 60 °C using ^{31}P{^{1}H} NMR spectroscopy reveals the formation of an asymmetric intermediate ($^2J_{P,P} = 29$ Hz) as well as a final nickel(II) product, **13** ($^2J_{P,P} = 13$ Hz). Complete conversion to **13** was observed after 10 hours. Surprisingly, the ^{1}H NMR spectrum of **13** showed an ABX spin system inconsistent with the expected nickelaoxetane product. Further analysis by HMBC and HSQC experiments reveal that **13** is the five-membered metallacycle shown in Scheme 4. 2D-NOESY and X-ray diffraction experiments demonstrates that **13**



Scheme 4. Synthesis of complexes **13**. Isolated yields in parentheses.

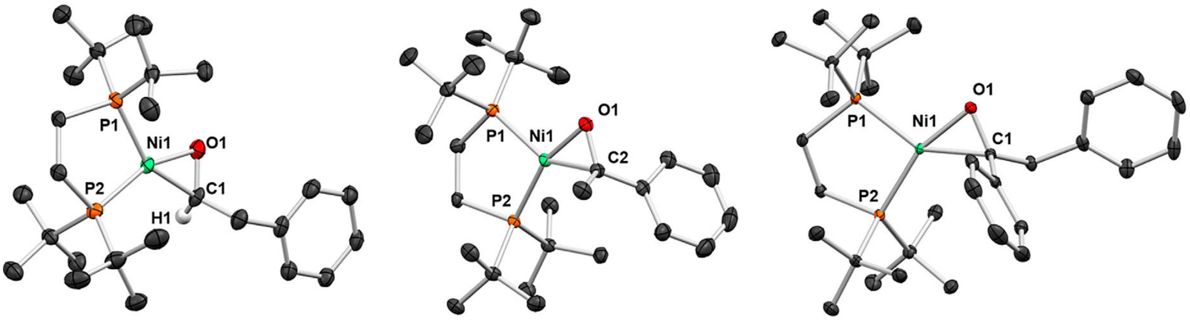


Figure 1. POV-Ray (50% probability ellipsoids) diagrams of complexes **4** (left), **5** (middle) and **7** (right). All hydrogen atoms except H1 of complex **4** have been omitted for clarity.

is formed as a single diastereomer (Figure 2), indicating that the oxidative addition step likely proceeds with retention of configuration. Although our previously isolated nickelaoxetanes were also formed with retention of configuration,[8] earlier work by Jamsion invoked the formation of nickelaoxetane intermediates via an S_N2-type mechanism (i.e., with inversion of configuration).[7] We propose that **13** is formed by oxidative addition of nickel(0) into the C–O bond of *cis*-**12**, followed by β-hydride elimination of a methyl C–H bond and insertion of the hydride into the newly-formed styrenyl group (see Supporting Information). Notably, the insertion of the hydride into the styrenyl group must be more rapid than bond rotation in order to account for the observed diasteroselectivity of the formation of **13**.

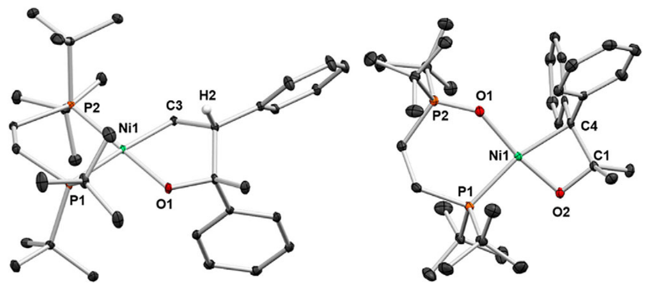
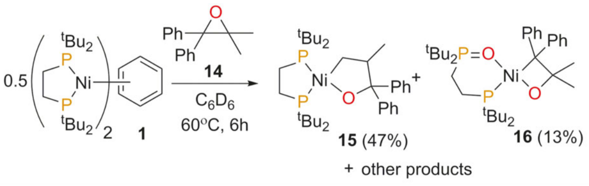


Figure 2. POV-Ray (50 % probability ellipsoids) diagrams of complexes **13** (left) and **16** (right) All hydrogen atoms except H2 of complex **13** have been omitted for clarity.

We also prepared tetrasubstituted epoxide **14** and reacted it with **1**. Heating the solution at 60 °C for 6 hours results in the formation of a complex mixture of products, including oxidized dtbpe ligand (dtbpeO), as well as two major new organometallic species. The main product, complex **15**, was found by NMR experiments to be the five-membered nickelacycle in Scheme 5, analogous to **13**. The second product, complex **16**, displays two doublets in the $^{31}P\{^1H\}$ NMR spectrum, one of which ($\delta = 29.4$ ppm) is remarkably upfield for (dtbpe)nickel complexes.[12]

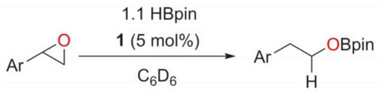
Complexes **15** and **16** could be separated by repeated extractions of the crude reaction mixture with cold pentanes. Gratifyingly, cooling a concentrated Et_2O solution of complex **16** resulted in crystals that were of sufficient quality to be analyzed by X-ray diffraction (Figure 2). The structure was determined to be the nickelaoxetane shown in Scheme 5. Curiously, the dtbpe ligand of **16** was oxidized by a single O atom, giving a rare example of a dtbpeO complex of nickel.



Scheme 5. Synthesis of complexes **15** and **16**. Isolated yields in parentheses.

Given the rapid rate of the reaction of **1** with **3**, we sought to find a way to close a potential catalytic cycle for the functionalization of epoxides featuring this isomerization step. Nickel-catalyzed hydroboration has recently been reported,[17] and we proposed that the aldehyde moiety could be cleaved from the nickel upon reduction by a borane. Addition of HBpin to a solution of **3** and 5 mol % **1** (i.e., 10 mol % in nickel) resulted in the formation of boronate ester $PhCH_2CH_2OBpin$ **17** in 31 % ^1H NMR yield, which could be increased to 72 % upon heating for 22 hours at 80 °C. Interestingly, only **4** reacts with HBpin under these conditions. As observed by $^{31}P\{^1H\}$ NMR spectroscopy, the resting state of these catalytic reactions is complex **5**. We then probed the scope of styrene oxide derivatives that could undergo this hydroboration process with HBpin (Table 1). Although electron-rich epoxides (entries 2 and 3) produced better yields than electron-poor epoxides (entries 4 and 5) at room temperature, moderate yields of boronate esters were observed for all the *para*-substituted derivatives tested upon heating. Bulkier epoxides such as xylyloxirane (entry 6) gave only trace hydroboration product under the typical reaction conditions, demonstrating a sensitivity to the sterics of the substrate.

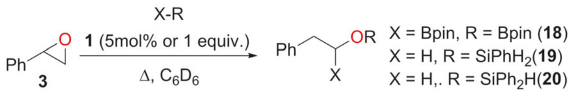
Table 1. Hydroboration of aryl epoxides with **1** and HBpin.



Entry	Ar	Yield[a] [%]
1	Ph	72 (31)
2	*p*-MeC_6H_4	43 (15)
3	*p*-$MeOC_6H_4$	46 (6)
4	C_6F_5	41 (trace)
5	*p*-ClC_6H_4	39 (trace)
6	Xyl	2 (trace)

[a] Yields determined by ^1H NMR spectroscopy after 22 hours at 80 °C. Values in brackets are yields after 10 minutes at room temperature.

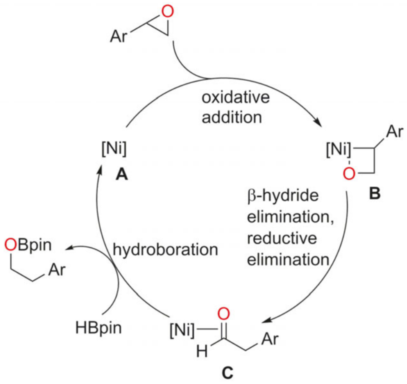
Upon prolonged heating, catalytic diboration of **3** with B_2pin_2 was also found to give functionalized product $PhCH_2CH(Bpin)OBpin$ **18** in 45 % yield (Scheme 6), along with a significant amount of protodeboronation product $PhCH_2CH_2OBpin$ **17** (14 % yield).[12] Catalytic hydroboration reactions with epoxides **8** or **9** resulted in complex mixtures that contained only trace yields of the desired products. We attribute this to a greatly reduced rate of reaction of complexes **10** and **11** with HBpin. Indeed, equimolar amounts of HBpin and **11** require 16 hours before reaching completion at room temperature. We also found that complex **1** could facilitate stoi-



Scheme 6. Functionalization of styrene oxide with B_2pin_2 or silanes.

chiometric hydrosilation of **3** (i.e., forming **19** in 44 % yield and **20** in 57 % yield), at elevated temperatures.[12]

Based on the available data, we propose the following mechanism for the isomerization and hydroboration of epoxides (Scheme 7): first, oxidative addition of the (dtbpe)nickel(0) fragment **A** into the more substituted C–O bond of the epoxide yields 2-nickelaoxetane intermediate **B**, likely with retention of configuration. Subsequent β-hydride elimination and reductive elimination reduces the metal centre and forms the η^2-aldehyde complex **C** along with scrambling of configuration. Reaction of this species with HBpin regenerates the nickel(0) catalyst **A** and releases the product boronate ester. Overall, our data and mechanism here support that proposed by Doyle and co-workers for the cross-coupling of boronic acids with styrenyl epoxides.[9]



Scheme 7. Proposed catalytic cycle for the hydroboration of epoxides. [Ni] = (dtbpe)Ni.

In conclusion, we have demonstrated that complex **1** can isomerize styrenyl epoxides to the corresponding aldehydes, likely via 2-nickelaoxetane intermediates. Functionalization of the resulting aldehyde complexes was possible using HBpin, silanes or B_2pin_2, and catalytic turnover could be achieved for these boration reactions by elevating the reaction temperatures. Efforts are underway to determine the origins of selectivity in epoxide ring-opening with different Ni^0 complexes.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: epoxides · hydroboration · isomerization · metallaheterocycles · nickel

[1] A. Dauth, J. A. Love, *Chem. Rev.* **2011**, *111*, 2010 – 2047.
[2] a) A. Dauth, J. A. Love, *Angew. Chem. Int. Ed.* **2012**, *51*, 3634 – 3637; *Angew. Chem.* **2012**, *124*, 3694 – 3697; b) A. Dauth, C. Rigling, J. Tsoung, J. A. Love, *Chem. Eur. J.* **2013**, *19*, 17180 – 17191.
[3] A. Dauth, J. A. Love, *Angew. Chem. Int. Ed.* **2010**, *49*, 9219 – 9224; *Angew. Chem.* **2010**, *122*, 9405 – 9410.
[4] A. N. Desnoyer, A. Dauth, B. O. Patrick, J. A. Love, *Dalton Trans.* **2014**, *43*, 30 – 33.
[5] B. L. Lin, C. R. Clough, G. L. Hillhouse, *J. Am. Chem. Soc.* **2002**, *124*, 2890 – 2891.
[6] P. T. Matsunaga, G. L. Hillhouse, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1748 – 1749; *Angew. Chem.* **1994**, *106*, 1841 – 1843.
[7] a) C. Molinaro, T. F. Jamison, *J. Am. Chem. Soc.* **2003**, *125*, 8076 – 8077; b) M. G. Beaver, T. F. Jamison, *Org. Lett.* **2011**, *13*, 4140 – 4143; c) For a related cobalt system, see G. Prina Cerai, B. Morandi, *Chem. Commun.* **2016**, *52*, 9769 – 9772.
[8] A. N. Desnoyer, E. G. Bowes, B. O. Patrick, J. A. Love, *J. Am. Chem. Soc.* **2015**, *137*, 12748 – 12751.
[9] D. K. Nielsen, A. G. Doyle, *Angew. Chem. Int. Ed.* **2011**, *50*, 6056 – 6059; *Angew. Chem.* **2011**, *123*, 6180 – 6183.
[10] J. J. Garcia, N. M. Brunkan, W. D. Jones, *J. Am. Chem. Soc.* **2002**, *124*, 9547 – 9555.
[11] S. Ogoshi, K.-I. Tonomori, M.-A. Oka, H. Kurosawa, *J. Am. Chem. Soc.* **2006**, *128*, 7077 – 7086.
[12] See the Supporting Information for more details.
[13] M. W. C. Robinson, K. S. Pillinger, I. Mabbett, D. A. Timms, A. E. Graham, *Tetrahedron* **2010**, *66*, 8377 – 8382.
[14] J. R. Lamb, Y. Jung, G. W. Coates, *Org. Chem. Front.* **2015**, *2*, 346 – 349.
[15] E. Jürgens, B. Wucher, F. Rominger, K. W. Tornroos, D. Kunz, *Chem. Commun.* **2015**, *51*, 1897 – 1900.
[16] S. Kulasegaram, R. J. Kulawiec, *Tetrahedron* **1998**, *54*, 1361 – 1374.
[17] A. E. King, S. C. E. Steiber, N. J. Henson, S. A. Kozimor, N. C. Smythe, A. D. Sutton, J. C. Gordon, *Eur. J. Inorg. Chem.* **2016**, 1635 – 1640.

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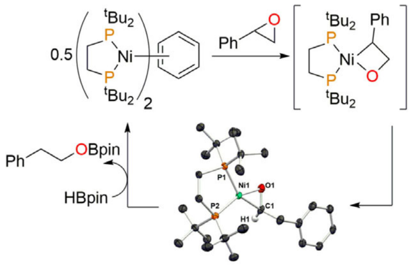
COMMUNICATION

Nickel squares up: Low-valent nickel(0) is shown to isomerize styrenyl epoxides to aldehydes in high yields. Mechanistic studies indicate that these isomerizations occur via 2-nickelaoxetane intermediates. Catalytic hydroboration of styrene oxide with HBpin was also demonstrated to be facile.



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