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Organometallic Catalysis

Synthesis of Five- and Six-Membered Benzocyclic Ketones through Intramolecular Alkene Hydroacylation Catalyzed by Nickel(0)/N-Heterocyclic Carbenes**

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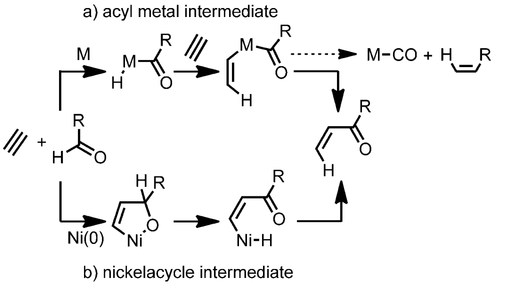
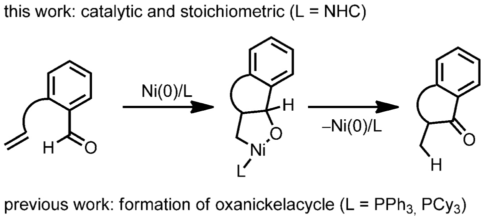
Transition-metal-catalyzed hydroacylation has been accepted as a promising synthetic method to form carbon–carbon bonds between an aldehyde and unsaturated compounds, such as alkenes, alkynes, and ketones. A number of catalyst systems have been developed, and high enatio-, regio-, and chemo-selectivity has been achieved.[1] Despite these extensive efforts and praiseworthy results, an inevitable side reaction persists: decarbonylation from an acyl metal intermediate, which causes a decrease in atom-efficiency and a deactivation of the catalyst through the coordination of carbon monoxide (Scheme 1, path a).[1,2] Major advances in hydroacylation have been associated with the development of strategies to suppress decarbonylation.[3,4] Thus, in the interest of promoting further progress, it is worthwhile to provide an alternative strategy to avoid decarbonylation.



Scheme 1. Transition-metal-catalyzed alkyne hydroacylation through a) an acyl metal intermediate or b) a nickelacycle intermediate. M = Rh, Ru, Co, Ir, Ni, or Pd.

Tsuda and Saegusa et al. reported Ni^0/PR_3-catalyzed intermolecular alkyne hydroacylation to give α,β-enones.[5,6] They proposed two possible reaction pathways: a) proceeds through an acyl nickel intermediate, and b) proceeds through an oxanickelacycle intermediate (Scheme 1). They concluded that the former was more plausible because of the formation of decarbonylated olefinic products in the reaction with benzaldehyde. On the other hand, during the course of our research on heteronickelacycles,[7] we demonstrated that an oxanickelacycle prepared by oxidative cyclization of an alkyne and an aldehyde with Ni^0 slowly decomposed to furnish an α,β-enone and no decarbonylated product.[7b] This result indicated that the oxanickelacycle can act as a potential intermediate in Ni^0-catalyzed alkyne hydroacylation (Scheme 1, path b). We also reported the Ni^0-catalyzed crossed- and homodimerization of aldehydes to give esters. Although it can be regarded as the hydroacylation of an aldehyde, the undesired decarbonylation was not observed.[7c,d] The results of kinetic experiments are consistent with the participation of a dioxanickelacycle intermediate in the reaction path.

The formation of dimeric oxanickelacycles in the stoichiometric reaction of *o*-allylbenzaldehyde (**1a**), $[Ni(cod)_2]$ (cod = 1,5-cyclooctadiene), and tertiary phosphines has been reported as well.[7a] Thus, the construction of a catalytic alkene hydroacylation through an oxanickelacycle seems quite effective for the generation of a benzocyclic ketone without decarbonylation (Scheme 2). Given the importance of benzocyclic ketones, the structural motifs of which have been found in the synthetic intermediates of numerous biologically active natural products and medicinal agents,[8,9] this new approach is an attractive method. Herein, we report an intramolecular alkene hydroacylation catalyzed by a Ni^0/N-heterocyclic carbene (NHC) complex that yields a variety of five- and six-membered benzocyclic ketones. Mechanistic studies that include stoichiometric reactions and the isolation of the oxanickelacycle intermediate are also discussed.



Scheme 2. Catalytic generation of a benzocyclic ketone without decarbonylation.

An optimization of the reaction conditions for the intramolecular hydroacylation of **1a** was conducted.[10] NHCs with an *N*-alkyl-substituent, such as I*t*Bu and IAd, gave 2-methylindanone (**2a**) in excellent yields, whereas PPh_3,

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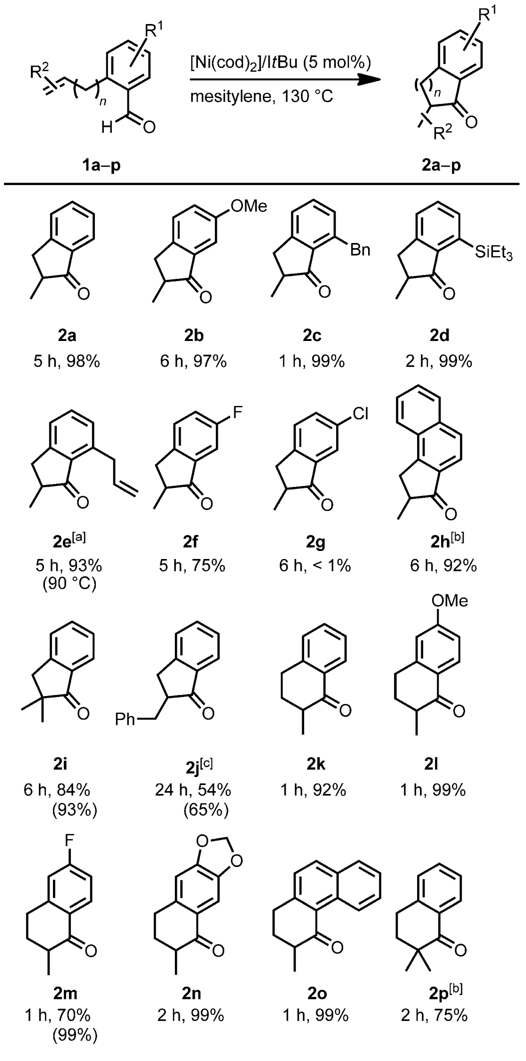
PCy_3, and *N*-aryl-substituted NHCs were not effective. We found that the treatment of **1a** at 130 °C for 5 h in the presence of $[Ni(cod)_2]$/I*t*Bu (5 mol %) in mesitylene resulted in the formation of **2a**, which was isolated in 98 % yield.

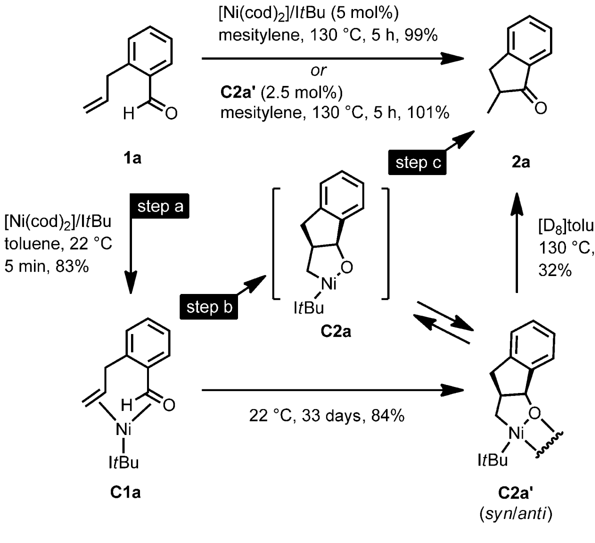
The scope of the reaction was investigated with respect to *o*-allylbenzaldehyde derivatives **1a–j** (Scheme 3). When an electron-donating group was bonded to the benzene ring (**1b–e**), the hydroacylation proceeded to give the corresponding indanones, which were isolated in > 93 % yield.[11] Fluorine-substituted product **2f** was obtained in moderate yield. Chlorine-substituted **1g** did not afford the corresponding ketone **2g** and was recovered in 95 % yield after isolation. In this case, *o*-allylbenzaldehyde was detected by GC-MS, thus the oxidative addition of an Ar–Cl bond to Ni^0 might deactivate the catalyst. Although $[Ni(cod)_2]$/I*t*Bu (10 mol %) was required, **1h** was successfully converted into **2h** in 92 % yield. This method can also be applied to substituted allyl groups (**1i** and **1j**) to give the corresponding ketones (**2i** and **2j**) in moderate to good yields. Furthermore, we applied the method to the hydroacylation of *o*-homoallylbenzaldehyde derivatives **1k–p**. For reported transition-metal-catalyzed alkene hydroacylations, the formation of six-membered (or larger) ring systems is difficult,[3,12–14] as the rate of the ring-closing step is much slower than that of the decarbonylation from an acyl metal intermediate.[1a] Thus, the introduction of suitable chelation assistance by heteroatoms has been essential for stabilizing the acyl metal intermediate.[3] By contrast, in the Ni^0/I*t*Bu-catalyst system, the formation of 1-tetralone derivatives was successfully achieved in excellent yields (**2k–o**, up to 99 % yield) without the need for chelation assistance. A decrease in yield was observed in the case of **2p**, and the decarbonylated olefinic product, 2-methyl-4-phenylbutene, was also detected in 2 % yield by GC analysis (see below).



Scheme 3. Ni^0-catalyzed intramolecular alkene hydroacylation. Reaction conditions: Enal **1a–p** (0.80 mmol), $[Ni(cod)_2]$/I*t*Bu (5 mol %, 0.040 mmol) and mesitylene (2 mL) were reacted at 130 °C. Yields presented are of isolated product; yields determined by GC analysis using *n*-pentadecane as an internal standard are given in parentheses. [a] $[Ni(cod)_2]$ (7 mol %) and I*t*Bu (5 mol %) in toluene were used. [b] $[Ni(cod)_2]$/I*t*Bu (10 mol %) was used. [c] $[Ni(cod)_2]$/IMes (10 mol %) was used. cod = 1,5-cyclooctadiene (For the structures of I*t*Bu and IMes, see the Supporting Information).

The presented Ni^0-catalyzed hydroacylation is 100 % atom-efficient and generates no waste. Thus, it is a highly environmentally favorable route to 1-indanone and 1-tetralone derivatives.[7,8,15] The most common approach to these compounds has been the intramolecular Friedel–Crafts acylation with conventional conditions that require excess amounts of acid promoters and high temperatures, particularly for the formation of 1-indanone.[16] Thus, the approach for the preparation of five- and six-membered benzocyclic ketones demonstrated here has synthetic utility.

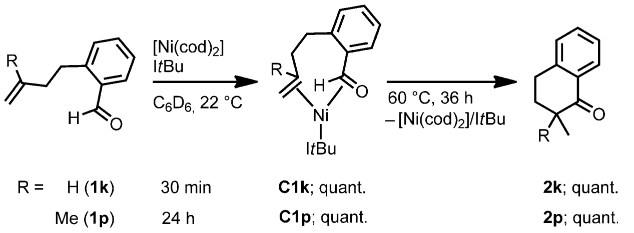
To gain insight into the reaction mechanism, some stoichiometric reactions were conducted (Scheme 4). The treatment of **1a** with $[Ni(cod)_2]$ and I*t*Bu in C_6D_6 (or toluene) at 22 °C resulted in the quantitative formation of (η^2:η^2-CH_2=$CHCH_2C_6H_4CHO$)Ni(I*t*Bu) (**C1a**) within 5 min, which was isolated in 83 % yield. Complex **C1a** was converted into dimeric oxanickelacycle **C2a′**, which was isolated in 84 % yield (22 °C, 33 days). The monomeric complex **C2a** was not observed by NMR spectroscopy; however, it is logical that **C2a′** was formed through the dimerization of **C2a**. The



Scheme 4. Stoichiometric reactions with **1a** and proposed reaction pathways. See text for details on the structure of **C2a′**.

structure of **C2a′** in solution was identified by NMR as a mixture of two isomers, *syn*-**C2a′** and *anti*-**C2a′**. Moreover, the molecular structure of *anti*-**C2a′** was confirmed by X-ray crystallography (Figure 1 a). We also observed the conversion of **C2a′** into the hydroacylated ketone **2a** in 32 % yield when **C2a′** was heated at 130 °C for 24 h (32 % conv.).[17] Compared with the catalytic reaction, the generation of **2a** from **C2a′** at 130 °C was significantly slower. However, in the presence of 2.5 mol % **C2a′**, **2a** was obtained in 101 % from both **1a** and **C2a′** (maximal yield of **2a** is 105 %) within 5 h. These results indicate that the formation of **C2a′** has no significant influence on catalytic efficiency under the catalytic reaction conditions.

The stoichiometric reaction of **1k** or **1p** with [Ni(cod)$_2$]/I*t*Bu was also examined to confirm whether the decarbonylation occurs through (η^2:η^2-enal)Ni(I*t*Bu) complex **C1** or not (Scheme 5). Both **1k** and **1p** quantitatively reacted with [Ni(cod)$_2$]/I*t*Bu to give **C1k** and **C1p**, respectively. The structure of **C1k** was confirmed by X-ray analysis (Figure 1 b). Thermolysis of **C1k** or **C1p** in C_6D_6 at 60 °C for 36 h resulted in the quantitative formation of the corresponding tetralone derivatives (**2k** or **2p**) with the regeneration of [Ni(cod)$_2$]/I*t*Bu.[18] Although a small amount of the decarbonylated olefinic product was observed in the catalytic reaction of **1p**, no decarbonylated product was observed by ^{1}H NMR or GC-MS analysis during the formation of **2p** from **C1p**. Based on these results, **C1p** afforded **2p** exclusively, and the lower yield of **2p** vs. **2k** in the catalytic reaction could be rationalized by the slower formation of **C1p** (24 h) vs. **C1k** (30 min).



Scheme 5. Stoichiometric reactions with **1k** and **1p**.

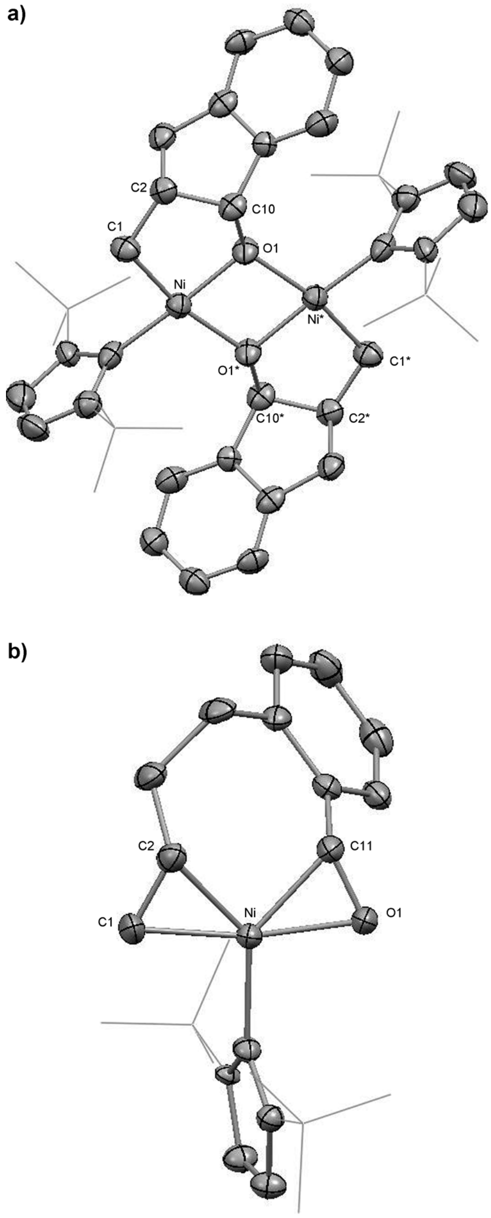


Figure 1. Molecular structure of a) *anti*-**C2a′** and b) **C1k** with thermal ellipsoids set at 50% probability. Calculated hydrogen atoms are omitted for clarity.

This intramolecular hydroacylation might proceed through the steps shown in Scheme 4. The coordination of **1** to Ni^0/L gives rise to **C1** (step a) and the oxidative cyclization then takes place to give the monomeric nickelacycle intermediate **C2** (step b). Finally, β-hydride elimination and reductive elimination occur to give **2**, along with regeneration of the catalyst (step c).[19]

In conclusion, we have developed the first Ni^0/NHC-catalyzed intramolecular hydroacylation. A variety of indanone derivatives were prepared in good to excellent yields. Notably, the synthesis of tetralone derivatives, which were difficult to prepare by the reported hydroacylation systems without chelation assistance, was also achieved. The enal-coordinated complex **C1** and the dimeric oxanickelacycle **C2′** were isolated. The transformation of **C2′** into the corresponding ketone under both stoichiometric and catalytic conditions was also observed, which indicated the participation of the oxanickelacycle complex (as a monomeric and/or dimeric structure) in the presented hydroacylation. This work provides a novel design for alkene hydroacylation that proceeds without the decarbonylation, that is, the simultaneous coordination of both olefin and formyl moieties to Ni^0 followed by oxidative cyclization to give the oxanickelacycle. Further studies on the reaction mechanism (kinetics and computational chemistry) are ongoing in our laboratory.

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[10] See the Supporting Information for details on the optimization of reaction conditions (Table S1) and the structures of NHCs employed in this manuscript. CCDC 892817 (*anti*-**C2a′**) and 892816 (**C1k**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[11] When the reaction of **1e** was conducted at 130 °C for 3 h, (*E*)-7-propenyl-2-methyl-1-indanone was isolated in 79 % yield. This species is presumably formed by an I*t*Bu-catalyzed 1,3-hydride shift of **2e**.

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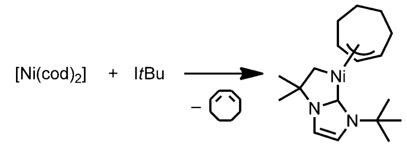

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