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Communications

Direct Observation of Noninnocent Reactivity of $ZnBr_2$ with Alkyl Halide Complexes of Nickel

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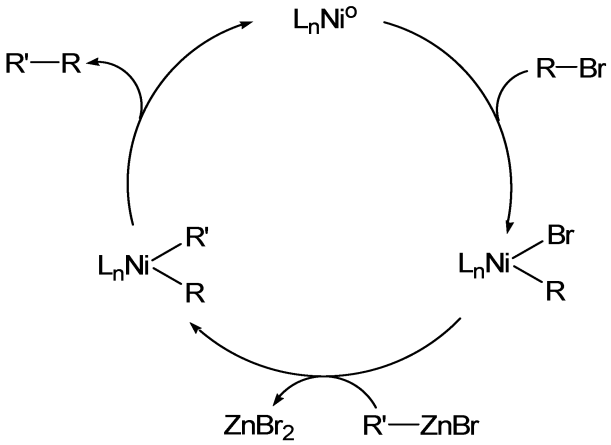
Summary: Nickel-catalyzed cross-coupling reactions of alkylzinc reagents with alkyl halides (Negishi couplings) are powerful tools in synthetic organic chemistry. These reactions typically provide the coupled alkane with $ZnBr_2$ as the final products. We report here that generated $ZnBr_2$ does not always act innocently but can mediate a halogen abstraction from the nickel alkyl halide complex. Such reactivity warrants consideration in developing mechanisms and catalyst design for these versatile reactions.

Nickel-catalyzed cross-coupling reactions to make new carbon−carbon bonds have become very powerful tools in synthetic organic chemistry.[1−4] Of particular note, recent advances of the Negishi cross-coupling reaction have enabled chemists to catalytically couple two sp^3 carbon centers.[5−9] Fu has even described catalytic methods to prepare tertiary sp^3 carbon centers with nickel.[9] Palladium is also known to effectively catalyze $C(sp^3)-C(sp^3)$ bond formations involving zinc transmetalation events.[10] The generally accepted mechanism of the Negishi reaction is outlined in Scheme 1. Among the important steps of this mechanism is the activation of an alkyl halide by low-valent nickel to form a nickel(II) alkyl halide complex. Alkyl iodides and alkyl bromides are the usual substrates for this oxidative addition process. When alkyl bromides are used, the resulting $L_nNi(alkyl)Br$ complex subsequently undergoes transmetalation with an alkylzinc bromide reagent,

Scheme 1. General Mechanism for Negishi Cross-Coupling of Alkanes



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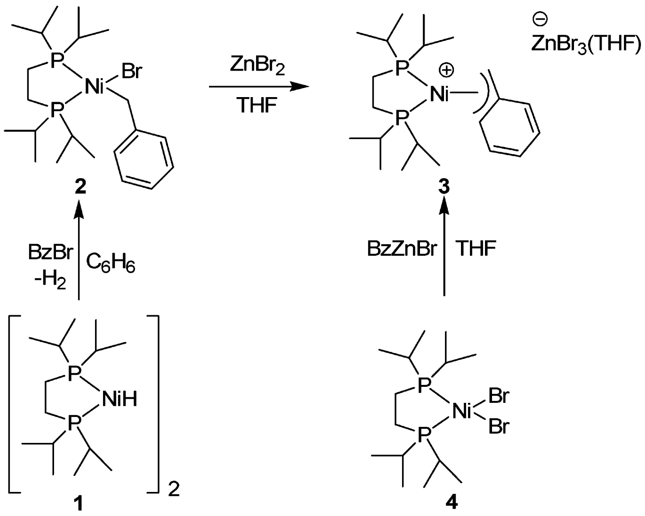
Scheme 2. Formation of Nickel Benzyl Cation 3 from Independent Routes



affording a nickel(II) dialkyl complex, which reductively eliminates the cross-coupled product and regenerates low-valent nickel. Mass balance leaves $ZnBr_2$ as a coproduct.

It seemed feasible to us that $ZnBr_2$ could also participate in this reaction by interacting with the organonickel intermediates. As future catalyst development would need to account for any type of noninnocent behavior of the coproducts, we set out to prepare well-defined alkyl halide complexes of nickel so that their interactions with $ZnBr_2$ could be studied in detail. Considering that halogen-atom abstraction of the organonickel halides by $ZnBr_2$ was one possible reaction that could occur, a challenge was to develop a system where the resulting alkyl cation could be stabilized so that spectroscopic support for its structure could be obtained. Simple *n*-alkyl bromide complexes of nickel were not targeted as model systems, as the resulting alkyl cation complexes are known to be highly reactive and short-lived, generally affording β-hydride elimination products if left without a reaction partner.[11,12] Therefore, benzylic bromides were studied as viable intermediates of the Negishi cross-coupling reaction, as nickel benzyl cations are known to be longer lived and even isolable[13,14] species. Importantly, the benzyl architecture can be used both as an electrophile and as a nucleophile in cross-coupling reactions, and benzyl sulfonium salts[15] and benzyl zinc bromides[16] have each been used successfully in Negishi couplings with nickel.

The benzyl bromide complex **2** was prepared under mild conditions by reacting the convenient Ni^0 source $[(dippe)NiH]_2$ (**1**; dippe = $(i\text{-}Pr_2PCH_2)_2$) with benzyl bromide in benzene solution at room temperature (Scheme 2). This reaction affords an η^1-benzyl bromide complex, whose structure was confirmed by X-ray crystallography. The ORTEP diagram of **2** is provided in Figure 1 and shows the square-planar arrangements of the ligands around nickel. The clean synthesis of **2** allowed for its reactivity with $ZnBr_2$ to be studied by NMR spectroscopy.

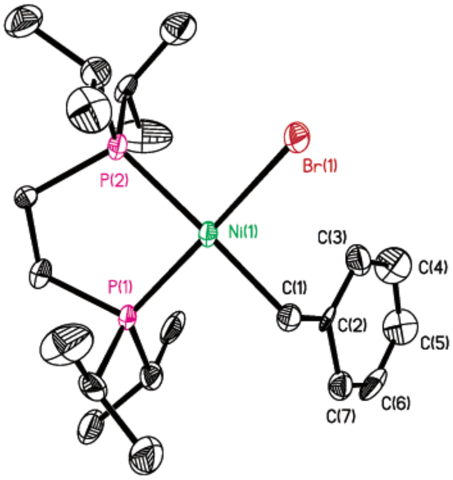


Figure 1. ORTEP diagram of **2**. Ellipsoids are shown at the 50% level. Hydrogen atoms are omitted for clarity.

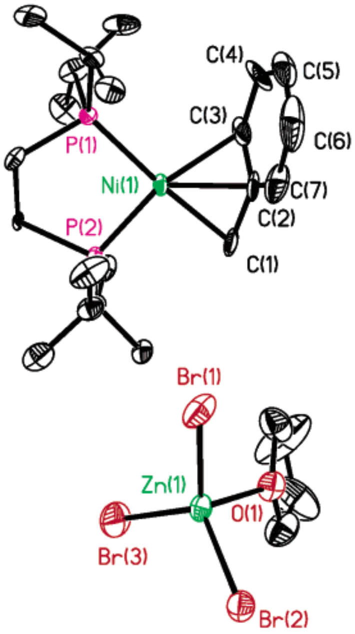


Figure 2. ORTEP diagram of **3**. Ellipsoids are shown at the 50% level. Hydrogen atoms are omitted for clarity.

Addition of 1 equiv of $ZnBr_2$ to a THF-d_8 solution of **2** led to an instant and dramatic change in the ^1H NMR spectrum (see the Supporting Information). The proton on the carbon atom *ortho* to the *ipso* carbon undergoes a large upfield shift of about 1.1 ppm, indicative of metal interactions with the *ortho* carbons. Such a change in NMR resonances can be explained by formation of an η^3-benzyl species such as **3**, in which the η^3-bound metal shields the *ortho* hydrogens. The structure of **3** was eventually confirmed by X-ray crystallography, and the ORTEP diagram is provided in Figure 2.

Figure 2 clearly shows the fate of the $ZnBr_2$ after participation in the halogen abstraction event. Upon halide abstraction, a nickel benzyl cation is formed along with a stable four-coordinate $ZnBr_3$(THF) counterion.[17]

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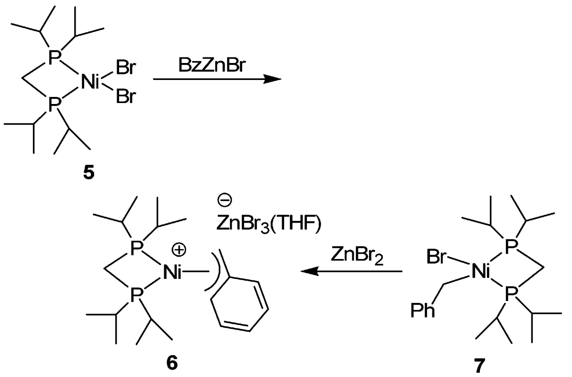
Complex **3** can also be made directly from reaction of (dippe)NiBr$_2$ (**4**) with BzZnBr in THF solution (Scheme 2). Thus, it appears that even when ZnBr$_2$ is produced *in situ* from a transmetalation reaction, halogen atom abstractions from nickel benzyl bromides can readily occur.

We have also found that the halogen atom abstraction event is not limited to dippe ligands. It was important to establish that phosphines containing different bite angles undergo similar reactivity, as oftentimes changes in bite angles can lead to dramatic effects in the catalytic activity of coupling reactions.[18] (dippm)NiBr$_2$ (**5**; dippm = bis(diisopropylphosphino)methane) was found to react similarly with BzZnBr, directly affording the η^3-benzyl cation complex **6** (eq 1). The η^1-benzyl bromide complex **7** has also been prepared by the reaction of Ni(COD)$_2$ and BzBr in the presence of dippm and was found to react instantly with ZnBr$_2$ in THF-d_8 solution to afford **6** in quantitative yield by NMR spectroscopy. Both **6** and **7** have been structurally characterized, and the ORTEP diagram for **7** is shown in Figure 3.



(1)

The results presented here suggest that the ability of ZnBr$_2$ to abstract a halogen atom from nickel alkyl halides should be considered in the developing mechanisms of Negishi-like couplings and may also be relevant to future catalyst design. It may also help rationalize some intriguing results in which additives[6,17] or excess ligands[9] were found to increase the efficiency of Negishi couplings. Moreover, Negishi noted that many of the Pd- or Ni-catalyzed reactions of alkenyl-aluminum or -zirconium species with alkenyl, aryl, and alkynyl halides *could only be achieved* when performed in the presence of additional ZnCl$_2$,[19] although the exact role of ZnCl$_2$ was not established. Further investigations of the mechanism of the Negishi couplings are underway.

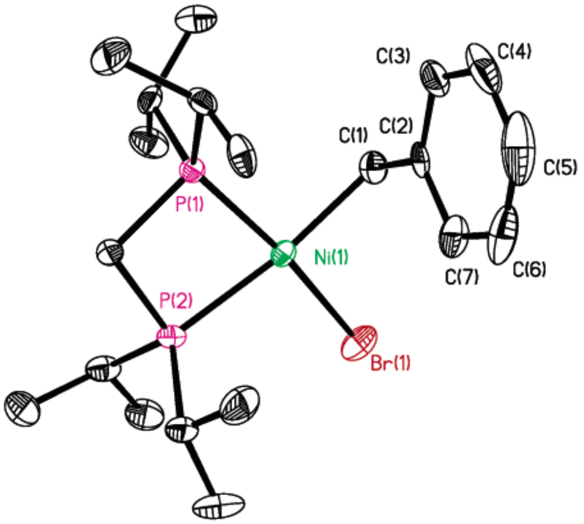


Figure 3. ORTEP diagram of **7**. Ellipsoids are shown at the 50% level. Hydrogen atoms are omitted for clarity.

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Supporting Information Available: Text, tables, and figures giving general methods and procedures, NMR spectra, and X-ray data for all relevant compounds; crystallographic data are also given as CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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