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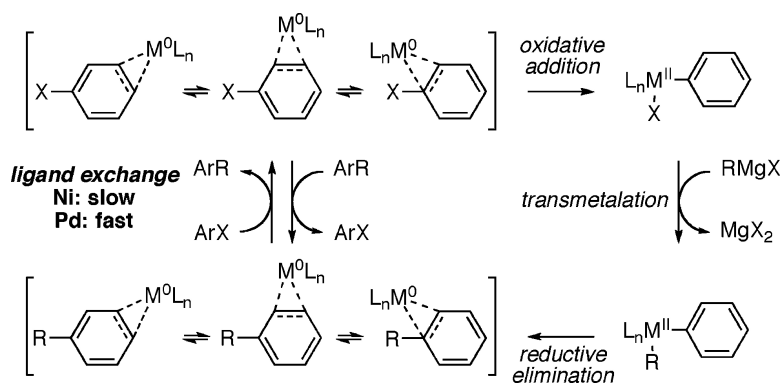
Ligand Exchange as the First Irreversible Step in the Nickel-Catalyzed Cross-Coupling Reaction of Grignard Reagents

Naohiko Yoshikai, Hirokazu Matsuda, and Eiichi Nakamura

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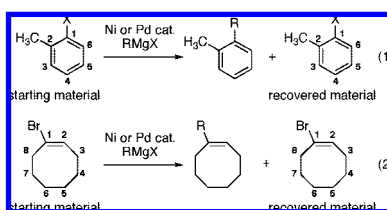
Naohiko Yoshikai, Hirokazu Matsuda, and Eiichi Nakamura*

Department of Chemistry, The University of Tokyo, Bunkyo-ku, Tokyo 113-0033, Japan
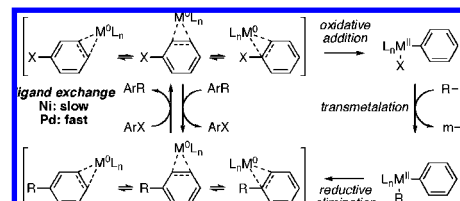
Received September 4, 2008; E-mail: nakamura@chem.s.u-tokyo.ac.jp

Ni-catalyzed cross-coupling of an aryl or alkenyl halide with a Grignard reagent, known as the Kumada–Tamao–Corriu (KTC) reaction,[1] paved the way for later development of the currently more popular and selective Pd catalysis.[2] Oxidative addition, transmetalation, and reductive elimination have been studied widely as important elementary steps of such reactions, as outlined in Scheme 1.[3] We propose herein that the ligand exchange step preceding the whole catalytic cycle needs more careful attention to understand these reactions. Studies of the Ni-catalyzed KTC reaction by analysis of kinetic isotope effects (KIEs) and theoretical calculations indicated that the ligand exchange process is the first irreversible step (FIS) and may affect the turnover efficiency and the selectivity of the reaction. On the other hand, the oxidative addition step is the FIS in Pd catalysis. This finding not only has useful implications about group 10 metal catalysis but also illustrates the importance of the catalyst turnover step, which has so far received less attention than the subsequent catalytic steps.

First, we measured the $^{12}C/^{13}C$ KIE[4] in the cross-coupling reaction of 1-halo-2-methylbenzene (*o*-halotoluene, X = Cl, Br, or I, eq 1) or 1-bromocyclooctene (eq 2) with phenyl- or alkylmagnesium bromide catalyzed by a Ni- or Pd-bisphosphine complex. The KIE data provide information on the FIS of the catalytic cycle.[5] If there are any elements of π-complexation involved in the FIS, we shall observe a dissymmetric distribution of KIE over the aromatic carbon atoms.

The KIE data for Ni(dppp) catalysis[6] of *o*-chloro- or bromotoluene with C_6H_5MgBr (Figure 1, data a and b) or $n\text{-}C_4H_9MgBr$ (data c) exhibit small KIE values (1.003−1.009) distributed only on the less hindered side of the benzene ring.[7] The data strongly suggest that the FIS of the reaction is the π-complexation of the Ni catalyst on the (less hindered) π-face of the haloarene. This interpretation is supported by the calculated equilibrium isotope effect (EIE).[8] In other words, once a Ni/haloarene π-complex forms through ligand exchange, it does not dissociate and proceeds quickly to the oxidative addition step in an intramolecular manner. We can ascribe this observation to the d-electron donative property of the Ni(0) catalytic species.[9]

Similarly, the KIE data for the Ni(dppe)-catalyzed coupling[6] of $n\text{-}C_4H_9MgBr$ with 1-bromocyclooctene (data d) exhibited a KIE of equal magnitude at two olefinic carbon atoms (1.015 at C1, 1.014 at C2). Thus, the π-complexation is also the FIS in the alkenylation reaction.
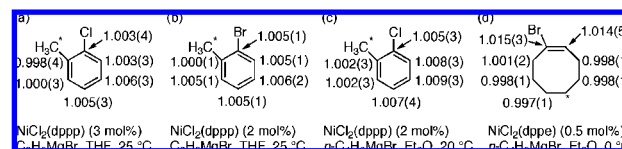
Scheme 1

The KIE experiments tell us little about the nature of the C–X bond cleavage that occurs in the Ni(dppp) (or dppe) catalysis after the FIS. We addressed this issue through experimental analysis of Pd catalysis and theoretical studies. Pd(0) is a weaker d-electron donor,[9] and the haloarene-Pd(0) complex may become less stable than the Ni(0) complexes; that is, the oxidative addition step that follows the ligand exchange step may become the FIS.

The Pd(dppf)-catalyzed coupling[10] of *o*-bromotoluene with C_6H_5MgBr or $n\text{-}C_8H_{17}MgBr$ (Figure 2, data a and b) exhibited large KIE values at C1 (1.031, 1.024) and small values at C6 (1.007, 1.009).[11] The reaction of 1-bromocyclooctene (data c) also showed unequal KIEs at C1 (1.023) and C2 (1.014). Similar results were obtained previously for the oxidative addition reaction of $(CH_3)_2$-CuLi·LiI (data d).[12] With Pd(0) being moderately donative of d-electrons, similar to Cu(I),[13] we can therefore conclude that the FIS in the Pd catalysis is the C–X bond cleavage step.

The information given by the experiments being rather limited, we performed DFT calculations on the interactions of model Ni- and Pd-bisphosphine complexes with *o*-chloro- and *o*-bromotoluene, respectively (Scheme 2),[14] and we found, not unexpectedly, that both reactions share the same pathway, i.e., formation of a series

Figure 1. $^{12}C/^{13}C$ KIE values for Ni-catalyzed KTC reactions. Standard deviations in the last digit are shown in parentheses. The asterisked carbon atoms were taken as references for each measurement (KIE = 1 was assumed). dppp = 1,3-bis(diphenylphosphino)propane. dppe = 1,2-bis(diphenylphosphino)ethane.
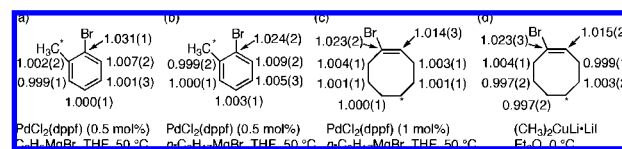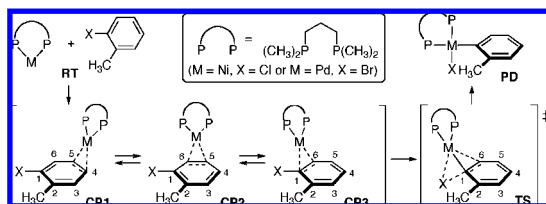

Figure 2. $^{12}C/^{13}C$ KIE values for Pd-catalyzed KTC reactions and organocopper-mediated substitution reaction. See Figure 1 caption for standard deviations and the asterisked carbon atoms. dppf = 1,1′-bis(diphenylphosphino)ferrocene. Data d were taken from ref 12.
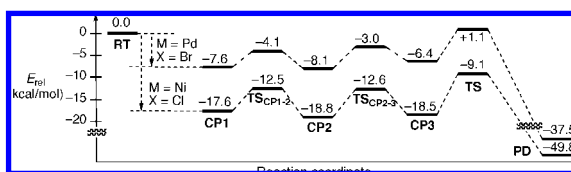
Scheme 2

of η^2-complexes (**CP1**–**3**; as well three others illustrated in Scheme S1), isomerization between these η^2-complexes, and C−X bond cleavage (**CP3** to **PD** via **TS**).[15,16] However, the Ni and Pd catalyses have different energetics (Figure 3). For the π-complexation between the Ni(0) complex and *o*-chloro- or bromotoluene, formation of **CP1**–**3** was highly exothermic (17−19 kcal/mol), but much less so for the interaction between Pd(0) and *o*-bromotoluene (6−8 kcal/mol). This result predicts that the Ni(0) species in solution would form stable π-complexes with haloarenes, but the Pd(0) species would not. This is supported by the fact that some Ni(0)/arene η^2-complexes, including a fluoroarene complex, are isolable.[17]

The activation energy from **CP3** to the oxidative addition product is very small for Ni catalysis ($\Delta E^{\ddagger} = 9.4$ and 5.1 kcal/mol for chloro- and bromotoluene, respectively; 7.5 kcal/mol for bromotoluene in Pd catalysis[18]). For both the Ni and Pd reactions, the oxidative addition transition state (**TS**) retains the character of the π-complex **CP3**. This structural property agrees with the unequal distribution of KIE values for the Pd(dppf) catalysis (Figure 2, data a and b).[19] We draw the same conclusion for the model reactions of the Ni and Pd complexes with 1-bromocyclooctene (see Supporting Information, SI).

We also discuss briefly the thermodynamics and kinetics of the migration of Ni(0) from the product to the substrate (Figure 4.). The least sterically hindered product π-complex (**CP1′**) was calculated to be less stable than **CP1** by 1.3 kcal/mol and other more hindered isomers less stable by 1−4 kcal/mol than the respective haloarene complexes. We also consider that the ligand exchange that likely accompanies a high entropy-cost process would take place with a sizable activation barrier (Figure 4.).

In summary, the KIE data and theoretical study showed that the early stages of the Ni- and Pd-catalyzed KTC reactions share the same pathway but show different kinetic profiles. With Ni(0) being a strong electron donor, the FIS of Ni catalysis is the complexation of the Ni atom on the π-face of the haloarene; i.e., the Ni catalyst undergoes oxidative addition immediately after ligand exchange from the product to the haloarene. We can surmise that the pro-

Figure 3. Potential energy diagram (kcal/mol, B3LYP/6-311+G(d,p)-SDD-TZVP//B3LYP/6-31G(d)-LANL2DZ-SVP) for the reaction shown in Scheme 2. See Supporting Information for details of the basis sets.
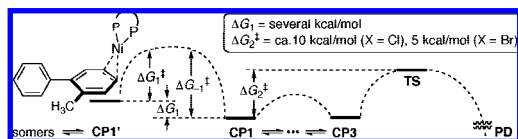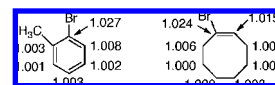

Figure 4.

pensity of the Ni catalyst to retain π-complexation with the haloarene substrate is beneficial for some reactions, such as the synthesis of oligoarenes via polycondensation,[20] but not for others, such as the chemoselective cross-coupling of polyhaloarenes.[6] It is possible that accelerated π-complexation/decomplexation is a reason for the high activity of the Ni/hydroxyphosphine catalyst that we reported recently.[21] We suspect that sluggish catalyst turnover may be ubiquitous in catalysis,[22] but its significance is underappreciated.

Supporting Information Available: Details of experiments and computation. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) The KIE data for *o*-iodotoluene were similar yet may be uninformative because the reaction gave the desired product in only 42% yield and toluene in 36% yield at 88% conversion.
(8) The experimental data are of similar magnitude to the calculated EIE for the π-complexation.

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