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Kinetic Studies of the Ni-catalyzed Cross-coupling of Alkyl Halides and a Tosylate with Butyl Grignard Reagent in the Presence of 1,3-Butadiene

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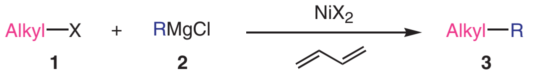
Kinetic studies of the nickel-catalyzed cross-coupling reaction of alkyl bromides, iodides, and tosylates with butyl Grignard reagents in the presence of butadiene were performed. The reaction rate was first order with respect to the halides and the nickel catalyst. The butyl Grignard reagent, at concentrations of ca. 0.4 M or higher, had little effect on the reaction rate. The relative reactivities and activation parameters were determined for these alkyl halides and a tosylate.

Cross-coupling reactions are useful and powerful tools for connecting two different organic moieties via a single bond and have been widely employed in organic synthesis.[1] During the past decade, the scope of this cross-coupling has been expanded to the use of alkyl halides as a coupling partner.[2] In a previous study, we reported that nickel as well as palladium and copper showed unique catalytic activities for cross-coupling reactions in which alkyl halides were used in the presence of a π-carbon ligand such as 1,3-butadiene or an alkyne.[3] The Ni/butadiene system (eq 1) showed particularly high performance, allowing the selective alkyl–alkyl cross-coupling of alkyl halides with a Grignard reagent[4] in the presence of various functional groups.[5] Furthermore, the turn-over number can reach the order of 10^7.[6] In order to probe this reaction in more detail, we performed kinetic studies and report on the results obtained.



(1)

We first examined the time course for the reaction of nonyl bromide (**1a**) with excess butyl Grignard reagent using various Ni salts and 1,3-butadiene in THF at 0 °C. As shown in Figure 1, all of the Ni salts afforded tridecane (**3a**) exclusively in quantitative yield based on the bromide within 15 min, but an induction period was observed for several salts probably due to their low solubilities in THF. $NiBr_2$/dme (dme: dimethoxyethane) and $[Ni(acac)_2]$ did not show any apparent induction period. Therefore, we used $NiBr_2$/dme as the source of the Ni catalyst throughout this kinetic study.

We then examined order of the rate for each reagent. A reaction using $NiBr_2$/dme, similar to that of Figure 1 was performed using different concentrations of nonyl bromide (**1a**) at −35 °C and the reaction was quenched with 1 M HCl(aq) after stirring for 90 s. These results were plotted in Figure 2 and a good straight line was obtained, indicating that this reaction obeys first-order kinetics with respect to nonyl bromide with a pseudo-first-order rate constant $k_{obs} = 1.76 \times 10^{-3}\ s^{-1}$ for $r = k_{obs}[n\text{-}C_9H_{19}Br]$.

The effect of the catalyst and Grignard reagent on the reaction rate was examined using heptyl tosylate (**1b**) at 1 °C for 150 s. In a similar manner, the yield of undecane (**3b**) was plotted against the concentration of the Ni catalyst employed, and the results are shown in Figure 3. These data clearly indicate that the reaction rate is first order with respect to the catalyst concentration.

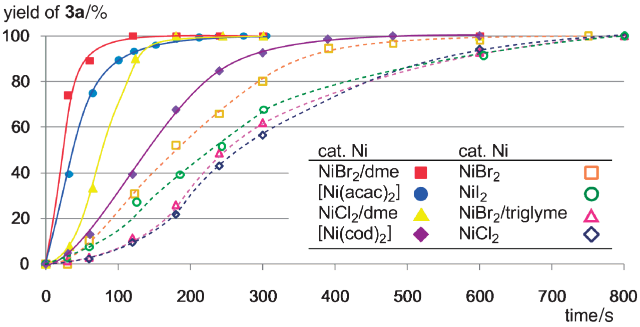


Figure 1. Time course of the reaction of n-$C_9H_{19}Br$ (**1a**, 0.2 M) with n-BuMgCl (0.6 M) using 2.5 mol % of a Ni salt (0.005 M) and 1,3-butadiene (0.2 M) in THF at 0 °C.

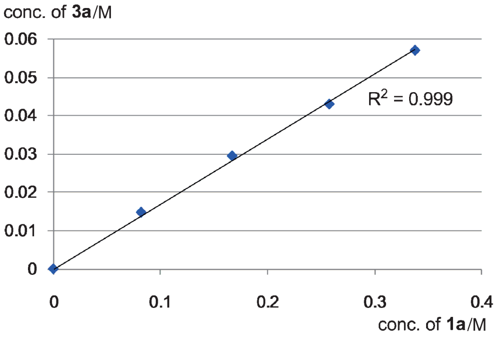


Figure 2. n-$C_9H_{19}Br$ (**1a**, 0.082–0.38 M), n-BuMgCl (0.6 M), $NiBr_2$/dme (2.5 mol %, 0.005 M), 1,3-butadiene (0.2 M), at −35 °C for 90 s.

When we ran the same reaction using different concentrations of n-BuMgCl, an interesting result was obtained (Figure 4). The reaction was accelerated with increasing concentrations of n-BuMgCl up to ca. 0.4 M, while the rate became constant in the region of higher concentrations.

This result can be explained by assuming an equilibrium process I between the bis(π-allyl) complex (**A**)[7] and ate complex (**B**)[8] and the subsequent rate-determining process II (Scheme 1). When the concentration of RMgX is sufficiently high, the equilibrium is shifted toward the ate complex (**B**), and its concentration is not substantially increased at higher concentration of RMgX. However, at lower concentrations of RMgX, the equilibrium is biased toward the bis(π-allyl) complex (**A**) and the

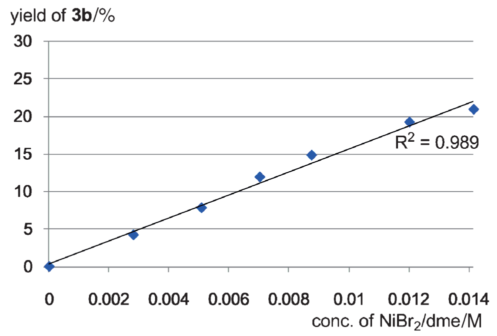


Figure 3. n-$C_7H_{15}OTs$ (**1b**, 0.2 M), n-BuMgCl (0.6 M), $NiBr_2$/dme (0–0.014 M), 1,3-butadiene (0.2 M), at 1 °C for 2.5 min.

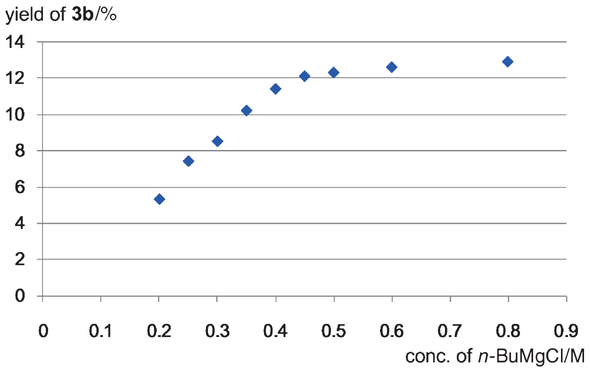
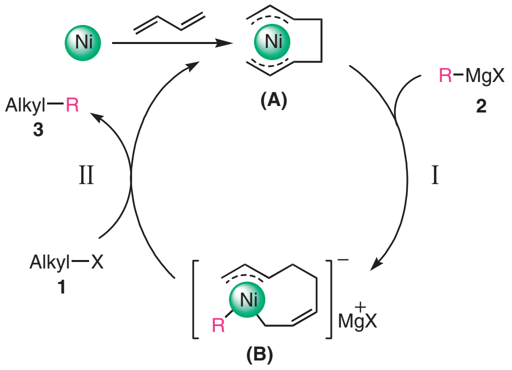


Figure 4. n-$C_7H_{15}OTs$ (**1b**, 0.2 M), n-BuMgCl (0.2–0.8 M), $NiBr_2$/dme (0.005 M), 1,3-butadiene (0.2 M), at 1 °C for 2.5 min.



Scheme 1. Ni-Catalyzed cross-coupling reaction.

concentration of the ate complex (**B**) increases with increasing concentration of RMgX, thus resulting in an acceleration of the reaction rate. However, another possibility that process I could become the rate-determining step when the concentration of RMgX is low and/or the effect of the aggregation of RMgX cannot be ruled out.

With these results, under conditions using excess amounts of Grignard reagents and a constant amount of the Ni salt, the reaction rate obeys pseudo-first-order kinetics for RX with

$$r = k_X[RX][Ni] = k_{obs(X)}[RX] \qquad (2)$$

We then ran the reaction at different temperatures and the rate constants were determined by fitting the data to the pseudo-first-order rate equation. The results obtained using nonyl bromide (**1a**) are shown in Figures 5a and 5b. All reactions reached completion on stirring to give **3a** quantitatively (Figure 5a). From the slopes of the lines in a plot of ln([**1a**]/[**1a**]$_0$) against reaction time (Figure 5b), rate constants $k_{obs(Br)}$ of eq 2 at each temperature were obtained using several sets of data for the early stage of reactions, and these results are listed in Table 1. These values are in accord with that obtained from Figure 2 (vide supra). Similar treatment of heptyl tosylate (**1b**) and hexyl iodide (**1c**) afforded corresponding rate constants $k_{obs(OTs)}$ and $k_{obs(I)}$, and these data are also summarized in Table 1.

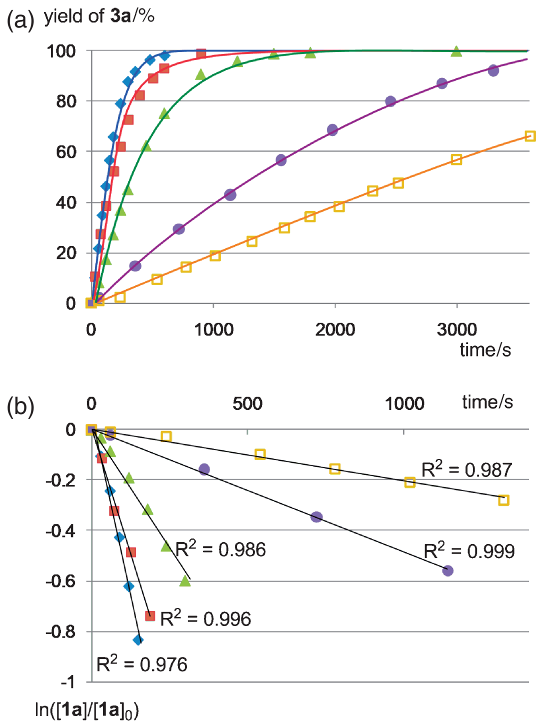


Figure 5. (a) Time course of the cross-coupling of n-$C_9H_{19}Br$ (0.2 M) with n-BuMgCl (0.6 M) using $NiBr_2$/dme (0.005 M) and 1,3-butadiene (0.2 M) at −18 °C (blue iozenge), −24 °C (red square), −29 °C (green triangle), −40 °C (purple circle), and −45 °C (orange box) in THF. (b) Fitting the data in Figure 5a to the pseudo-first-order line.

With the slope and intercept of the Eyring plot using the data from Table 1 (Figure 6), the activation parameters for the cross-coupling were calculated and these findings are shown in Table 2. The data indicate that the activation entropies are relatively small and that the reaction rates are mainly controlled by enthalpy factors (vide infra).

From these data, the relative reactivities of primary alkyl iodides, bromides, and tosylates were estimated to be,

$$\begin{aligned} n\text{-}C_7H_{15}OTs{:}n\text{-}C_9H_{19}Br{:}n\text{-}C_6H_{13}I &= 0.015{:}1{:}15 \text{ (at 25 °C)} \\ &= 0.018{:}1{:}19 \text{ (at 0 °C)} \\ &= 0.022{:}1{:}25 \text{ (at −25 °C)} \end{aligned} \qquad (3)$$

suggesting that primary alkyl bromides react ca. 50 times faster than the corresponding tosylates and iodides react ca. 20 times faster than bromides.

A detailed mechanism that explains the rate-determining step (process II) is not clear at this time, but a stepwise pathway involving the oxidative addition of alkyl halides to solvent separated ate complexes (**B**) leading to the formation of Ni(IV)

Table 1. Rate constans $k_{\mathrm{obs(X)}}$ ($\mathrm{s^{-1}}$) of cross-coupling of RX with *n*-BuMgCl[a]

X = OTs					
Temp/°C	22	21	9	4	−3
$k_{\mathrm{obs(X)}}/\mathrm{s^{-1}}$	4.58×10^{-3}	3.77×10^{-3}	1.81×10^{-3}	1.20×10^{-3}	5.00×10^{-4}
Temp/°C	−8	−15	−20	−25	
$k_{\mathrm{obs(X)}}/\mathrm{s^{-1}}$	2.26×10^{-4}	1.82×10^{-4}	5.76×10^{-6}	1.19×10^{-5}	
X = Br					
Temp/°C	−18	−24	−29	−40	−45
$k_{\mathrm{obs(X)}}/\mathrm{s^{-1}}$	5.16×10^{-3}	3.94×10^{-3}	1.89×10^{-3}	4.86×10^{-4}	2.05×10^{-4}
X = I					
Temp/°C	−52	−56	−60	−65	
$k_{\mathrm{obs(X)}}/\mathrm{s^{-1}}$	3.21×10^{-3}	1.66×10^{-3}	1.04×10^{-3}	5.12×10^{-4}	

[a] Reaction conditions: RX (0.2 M), *n*-BuMgCl (0.6 M), $\mathrm{NiBr_2/dme}$ (0.005 M), 1,3-butadiene (0.2 M).

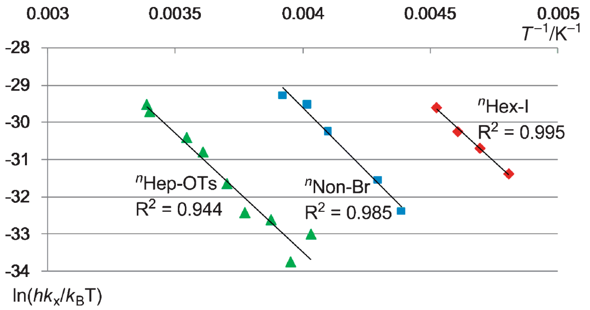
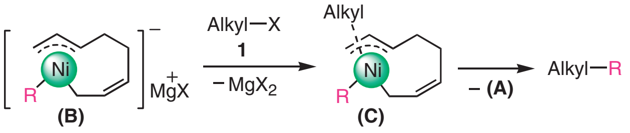


Figure 6. Eyring plot of data of Table 1.

Table 2. Activation free energies (0 °C) and activation parameters of Ni-catalyzed cross-coupling

R–X	$\Delta G^{\ddagger}_{273}/\mathrm{kJ\,mol^{-1}}$	$\Delta H^{\ddagger}/$ $\mathrm{kJ\,mol^{-1}}$	$\Delta S^{\ddagger}/$ $\mathrm{J\,K^{-1}\,mol^{-1}}$
n-Heptyl–OTs (**1b**)	71.1 ± 9.8	52.7 ± 4.9	-67.6 ± 18.0
n-Nonyl–Br (**1a**)	61.9 ± 8.6	57.3 ± 4.0	-16.9 ± 16.7
n-Hexyl–I (**1c**)	55.3 ± 6.0	51.2 ± 2.6	-14.8 ± 12.3



Scheme 2. Reaction of Alkyl–X with an ate complex intermediate.

intermediates (**C**) and a subsequent reductive elimination seems likely (Scheme 2).[9] Theoretical calculations regarding this pathway suggest the possibility of Ni(IV) intermediates (**C**).[10,11] If the reaction proceeds via **C**, although counter Mg cations may play important roles in the real system, the activation parameters shown in Table 2 correspond to this oxidative addition step, because the calculations suggest that the successive reductive elimination step is highly exergonic with a low energy barrier and so should be rapid, even at low temperatures.[10] Fu performed a kinetic study of the oxidative addition of alkyl halides to Pd(0) as a key step in Pd-catalyzed cross-coupling and revealed that activation parameters of the oxidative addition of nonyl bromide with $\mathrm{Pd[P(\mathit{t}\text{-}Bu)_2Me]_2}$ leading to $n\text{-}\mathrm{C_9H_{19}PdBr[P(\mathit{t}\text{-}Bu)_2Me]_2}$ were $\Delta G^{\ddagger} = 87.1\,\mathrm{kJ\,mol^{-1}}$ at 20 °C, $\Delta H^{\ddagger} = 10\,\mathrm{kJ\,mol^{-1}}$, and $\Delta S^{\ddagger} = -2.6 \times 10^2\,\mathrm{J\,K^{-1}\,mol^{-1}}$.[12] It is interesting that reaction of a Pd complex with alkyl halides has a small activation enthalpy and is controlled by an entropy factor, while the reaction of the Ni complex (**B**) with alkyl halides is enthalpy-controlled.

In conclusion, it was revealed that Ni-catalyzed alkyl–alkyl cross-coupling using 1,3-butadiene obeys first-order kinetics for the alkyl halide and the Ni catalyst but the concentration of the Grignard reagents exerts little effect on the rate at concentrations higher than ca. 0.4 M. The reaction rates of an alkyl tosylate, bromide, and iodide at different temperatures were measured and activation parameters for these compounds were obtained.

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