Nickel-Catalyzed Cross-Coupling Reaction of Grignard Reagents with Alkyl Halides and Tosylates: Remarkable Effect of 1,3-Butadienes

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In 1972, Kumada’s group and Corriu’s group independently reported cross-coupling reaction of Grignard reagents with aryl and alkenyl halides catalyzed by nickel(II) halides. The catalytic cycle, which involves oxidative addition, transmetalation, and reductive elimination steps, has become a prototype of a more practical Pd-catalyzed cross-coupling reaction. These reactions proceed smoothly using a variety of organometallic reagents containing B, Mg, Li, Sn, Al, and Zn as the metal connecting to alkyl, alkenyl, aryl, alkynyl, allyl, and benzyl groups as the organic part. As for the coupling partner, however, the scope is generally limited to aryl and alkenyl moieties. The use of alkyl halides, triflates, or tosylates usually gives unsatisfactory results due mainly to the slow oxidative addition to transition metal catalysts and the facile β-elimination from the alkylmetal intermediates. Thus, the alkyl–alkyl cross-coupling reaction catalyzed by transition metal complexes has remained as an interesting and challenging theme to be solved in this field. Recently, we have developed regioselective mono- and dialkylation of alkenes or dienes with alkyl halides or tosylates using titanocene8 or zirconocene9 catalysts. During the course of our study on transition metal catalyzed alkylation reactions, we have found that Ni catalyzes the cross-coupling reaction of alkyl chlorides, bromides, and tosylates with Grignard reagents in the presence of a 1,3-butadiene as an additive (eq 1).

$$\text{R} - \text{X} + \text{R'} - \text{MgX} \xrightarrow{\text{cat. NCl}_2, 1,3\text{-butadiene}} \text{R} - \text{R'}$$  (1)

For example, a reaction of n-decyl bromide with n-butylmagnesium chloride (1.3 equiv) in the presence of isoprene (1.0 equiv) and NiCl₂ (0.03 equiv) at 25 °C for 3 h gave tetradecane in 92% yield along with trace amounts of decane (<1%) and decenes (2%) (Table 1, entry 1). In the absence of isoprene, tetradecane was obtained in only 2% yield and significant amounts of decane and decenes were formed (entry 2). The use of Ni(acac)₂ and Ni(COD)₂ also afforded tetradecane in high yields (entries 3 and 4). When nickel complexes bearing phosphine ligands, such as NiCl₂(dppp) and NiCl₂(dppe), were used, tetradecane was obtained only in 45% and 22% yields, respectively. Under similar conditions, FeCl₃ and CoCl₂(dppe) were ineffective, and PdCl₂ gave a moderate yield of tetradecane (entry 5). Next, we examined the effect of additives which are essential to promote the present coupling reaction. Unsubstituted 1,3-butadiene shows by far the highest activity for this cross-coupling reaction (entry 6). 2,3-Dimethyl-1,3-butadiene, COD, alkenes, and alkynes are far less effective under the same conditions (entries 7–10).

Optimization of the reaction conditions using 1,3-butadiene revealed that use of only 1 mol % of NiCl₂ and 10 mol % of 1,3-butadiene (0.07 M in THF, 10 equiv to Ni catalyst) based on the halides at 0 °C afforded coupling products quantitatively in the reaction of primary bromides with primary alkyl Grignard reagents (Table 2, entries 1 and 2). Interestingly, the bromo substituent on the aryl ring remained intact in this reaction system (entry 2). This cross-coupling reaction also proceeds efficiently by using alkyl tosylates (entries 3–5). It should be noted that alkyl chlorides can also undergo this cross-coupling reaction, giving rise to the desired products in good yields (entry 8). This is the first example of cross-coupling of inactivated alkyl chlorides. Aryl and secondary alkyl Grignard reagents also afforded the corresponding products in moderate to good yields (entries 5–7), but no reaction took place with CH₂=CHMgBr and PhC≡CMgCl under similar conditions and most of the alkyl bromides were recovered.

To elucidate the reaction pathway, we first performed a reaction of NiBr₂ with 2 equiv of n-octylmagnesium chloride in the presence of isoprene (0.7 M in THF) at 25 °C for 15 min. This reaction gave octane and 1-octene in 43% and 45% yields, respectively; however, homocoupling product, n-hexadecane, was not formed. Assuming that NiBr₂ reacts with n-octylmagnesium chloride to form n-Oct-Ni-Br, this result implies that the present coupling reaction does not involve a process of oxidative addition of alkyl halides to Ni(0) since this process also affords n-Oct-Ni-Br. It was also confirmed that n-decyl bromide does not undergo oxidative addition toward Ni(COD)₂ in THF containing 1,3-butadiene (0.7 M) at 0 °C resulting in the recovery of n-decyl bromide.

To examine the intermediary of alkyl radicals, we then carried out the coupling reaction of (bromomethyl)cyclopropane with n-Oct-
In conclusion, a novel method for the cross-coupling reaction of Grignard reagents with alkyl halides has been developed with the aid of Ni catalysts. This reaction proceeds efficiently by the use of primary and secondary alkyl- or arylmagnesium halides under mild conditions. The use of Grignard reagents with alkyl chlorides, bromides, and tosylates has been reported, see: (a) Li, G. Y.; Marshall, W. J. Organometallics 2000, 19, 2070 and references sited therein. (b) Lipshutz, B. H.; Parker, V. L.; Saito, K.; Sonoda, N.; Suzuki, A. J. Am. Chem. Soc. 1998, 120, 11822—11823.

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Supporting Information Available: Experimental procedures and compound characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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