Cross-coupling of alkyl halides with Grignard reagents using nickel and palladium complexes bearing η^3-allyl ligand as catalysts†

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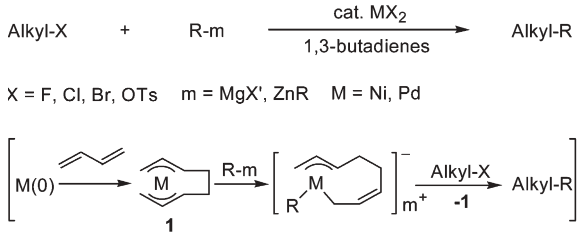
The cross-coupling of Grignard reagents with alkyl bromides and tosylates has been achieved by the use of η^3-allylnickel and η^3-allylpalladium complexes as catalysts.

Transition metal-catalyzed cross-coupling reactions of organic halides with organometallic reagents are among the most important transformations in organic synthesis, especially for building complex structures of compounds from readily available components.[1] As for the substrates, a variety of organometallic reagents have been employed, whereas the scope of the coupling partner had long been limited to aryl and alkenyl halides. The use of alkyl halides usually gave unsatisfactory results due mainly to the slow oxidative addition to transition metal catalysts and the fast β-elimination from the alkylmetal intermediates. During the past several years,[2,3] cross-coupling reaction of alkyl halides with organometallic reagents has been studied extensively, however, and alkyl halides as well as sulfonates have now become promising candidates as reagents in transition metal catalyzed cross-coupling reaction. As a practical method for such transformations, we developed a unique catalytic system where Ni and Pd catalyzes cross-coupling of alkyl fluorides, chlorides, bromides and tosylates with Grignard reagents in the presence of conjugated dienes such as 1,3-butadiene, isoprene, or bisdienes (Scheme 1).[4]

In this catalytic system, bis(η^3-allyl)nickel or bis(η^3-allyl)palladium complexes (**1**) formed by the reaction of M(0) [M = Ni, Pd] with 2 molecules of 1,3-butadienes were proposed to be involved as key intermediates.



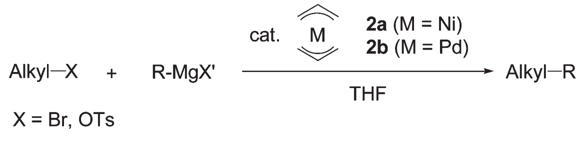
Scheme 1

To prove the intermediary of bis(η^3-allyl)metal complexes and to reveal, if so, whether the ethylene tether (CH_2CH_2) between two allyl ligand is essential or not, we examined the reaction using the simplest bis(η^3-allyl)metal complexes **2** as catalysts. As a result, here we disclose that cross-coupling of alkyl bromides and tosylates with Grignard reagents proceeded efficiently without using conjugated diene additives in the presence of Pd and Ni complexes having η^3-allyl ligands (Scheme 2).

Table 1 summarizes the results obtained by the reaction of *n*-decyl bromide with *n*-butylmagnesium chloride or methylmagnesium bromide (1.3 equiv.) for 3 h using various catalysts in THF. When $PdCl_2$ (0.1 equiv.) was employed only a trace amount of the cross-coupling product was obtained, and significant amounts of decane (54%) and decenes (26%) were formed (entry 1).

No reaction took place with $PdCl_2(PPh_3)_2$ (entry 2). Although (η^3-allyl)palladium chloride gave only 10% yield of tetradecane, bis(η^3-allyl)palladium[5] complex afforded a moderate yield of cross-coupling product (entries 3 and 4). When a methyl Grignard reagent was employed, both mono- and bis(η^3-allyl)palladium complexes gave satisfactory yields of product, whereas Pd complexes having no η^3-allyl ligands again failed to catalyze this reaction (entries 5–8).[6] Nickel complexes having no η^3-allyl ligands were also ineffective (entries 9 and 10). Bis(η^3-allyl)nickel catalyst shows by far the highest activity for both butyl and methyl Grignard reagents (entries 12 and 16). Mono(η^3-allyl)nickel complex afforded a successful result when MeMgBr was employed but not in the case of ^{n}Bu-MgCl (entries 11 and 15).

Results of some other representative combinations of substrates using bis(η^3-allyl)nickel are shown in Table 2. This cross-coupling reaction also proceeds efficiently by using alkyl tosylates (entries 1, 2 and 5). Aryl Grignard reagents afforded the corresponding coupling product in good yield (entry 2). When the reaction of 5-hexenyl bromide with *n*-butylmagnesium chloride were carried out, 1-decene was obtained as the sole coupling product in 91% yield without the formation of pentylcyclopentane, suggesting that the 5-hexenyl radical, which may undergo ring-closing, was not formed (entry 3).[7] Cyclopropylmethyl bromide gave only nonylcyclopropane as a coupling product (entry 4).[8] These results rule out a radical mechanism. It should be noted that a bromo substituent on the aryl ring remained intact in this reaction system



Scheme 2

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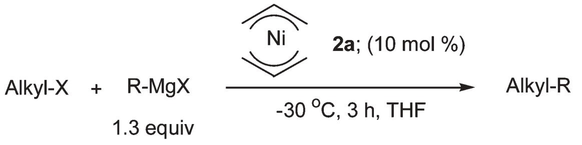
Table 1 Pd- or Ni-catalyzed cross-coupling reactions of decyl bromide with Grignard reagents

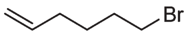
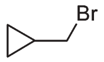
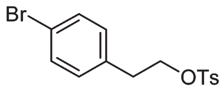
$$^n\text{Dec–Br} + \underset{1.3\ \text{equiv}}{\text{R–MgX}} \xrightarrow[\text{THF}]{\text{cat. (10 mol\%)}}$$

Entry	R	Cat.	T/°C	^{n}Dec-R	decane	decenes
				Yield[a] (%)		
1	Bu	$PdCl_2$	0	3	54	26
2	Bu	$(PPh_3)_2PdCl_2$	0	2	1	1
3[b]	Bu	$(C_3H_5PdCl)_2$	0	10	26	23
4	Bu	$(C_3H_5)_2Pd$	0	58	13	12
5	Me	$PdCl_2$	0	9	26	26
6	Me	$(PPh_3)_2PdCl_2$	0	9	1	1
7[b]	Me	$(C_3H_5PdCl)_2$	0	83	6	6
8	Me	$(C_3H_5)_2Pd$	0	90	3	1
9	Bu	$NiCl_2$	−30	5	33	18
10	Bu	$(PPh_3)_2NiCl_2$	−30	1	3	1
11[b]	Bu	$(C_3H_5NiCl)_2$	−30	7	33	24
12	Bu	$(C_3H_5)_2Ni$	−30	94	4	2
13	Me	$NiCl_2$	−30	1	8	14
14	Me	$(PPh_3)_2NiCl_2$	−30	3	4	4
15[b]	Me	$(C_3H_5NiCl)_2$	−30	92	2	3
16	Me	$(C_3H_5)_2Ni$	−30	98	0	2

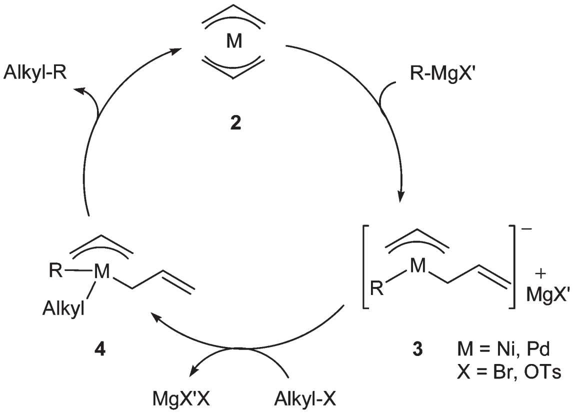
[a] Determined by GC. [b] 5 mol% of catalyst was used.

Table 2 Cross-coupling reactions using bis(η^3-allyl)nickel complex as a catalyst

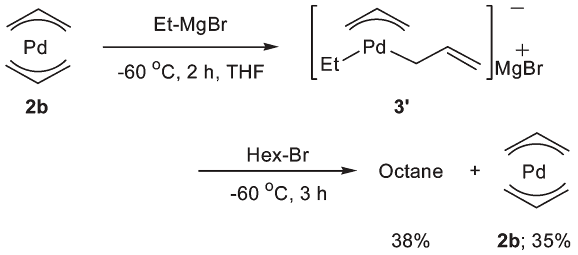


entry	Alkyl–X	R–MgX	Yield[a] (%)
1	^{n}Oct–OTs	Et–MgBr	78
2	^{n}Oct–OTs	Ph–MgBr	87
3		^{n}Bu–MgCl	91
4		^{n}Oct–MgCl	86 (81)
5		Et–MgBr	76 (71)
6[b]	^{n}Dec–Br	Me_3SiCH_2–MgCl	70 (65)

[a] Determined by GC. Isolated yield is in parentheses. [b] Reaction was carried out at −20 °C for 20 h.



Scheme 3 A plausible reaction pathway.



Scheme 4

(entry 5). A sterically hindered Grignard reagent also gave a moderate yield of the corresponding coupling product (entry 6).

A plausible reaction pathway is depicted in Scheme 3. Bis(η^3-allyl)metal complex **2** reacts with Grignard reagents to form a bis(η^1,η^3-allyl)metal complex **3**. This anionic complex would possess enhanced nucleophilicity at the metal centre toward alkyl halides. Coupling products were formed by nucleophilic attack of **3** to alkyl halides yielding dialkylmetal complexes **4** followed by reductive elimination.

To confirm the validity of this proposed pathway, we examined the stoichiometric reaction of alkyl halides with the anionic bis(η^1,η^3-allyl) complex **3**. As might be expected, bis(η^1,η^3-allyl)palladate complex (**3′**),[9,10] formed by the reaction of bis(π-allyl)palladium with EtMgBr, reacted with *n*-hexyl bromide at −60 °C for 3 h, giving rise to nearly equal amounts of octane (38% GC yield) and bis(η^3-allyl)palladium (35% NMR yield) (Scheme 4). This result suggests that anionic complex (**3′**) undergoes substitution reaction with alkyl bromides to give the corresponding coupling products along with generation of bis(η^3-allyl)palladium. It should be noted that possible products, 1-pentene or 1-nonene by the reductive elimination of an allyl group of intermediate **4** in Scheme 3 were not formed from GC and NMR analysis. This fact is in accord with the evidence that reductive elimination proceeds preferentially with alkyl group than allyl group.[11] When the reaction was conducted using *n*-decyl bromide at −30 °C for 20 h, dodecane was formed in 66% yield but **2b** could not be detected in the resulting mixture.

In conclusion, Ni and Pd catalysts bearing simple allyl ligands were found to catalyze cross-coupling reaction of Grignard reagents with alkyl bromides and tosylates. This reaction proceeds efficiently by the use of alkyl- or arylmagnesium halides. It was revealed that two allyl ligands are essential to attain high yields of the cross-coupling products.

Notes and references

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6 Typical procedure (entry 8 in Table 1): A 50 mL Pyrex glass vessel containing a magnetic stirring bar, decyl bromide (442.4 mg, 2.0 mmol), a catalytic amount of bis(η^3-allyl)palladium (37.8 mg, 0.2 mmol), and nonane (internal standard, 128.3 mg, 1.0 mmol) was cooled to −78 °C under nitrogen. Then MeMgBr (0.9 M in THF, 3.2 mL, 2.9 mmol) was added slowly to the solution at −78 °C, and the mixture was warmed to 0 °C. After stirring for 3 h, 3 M HCl (aq) (2 mL) was added to the solution at 0 °C. The product was extracted with diethyl ether (10 mL) and analyzed by GC (dodecane, 90% GC yield).

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8 Typical procedure (entry 4 in Table 2): A mixture of cyclopropylmethyl bromide (270.0 mg, 2.0 mmol) and a catalytic amount of bis(η^3-allyl)nickel (28.2 mg, 0.2 mmol) was cooled to −78 °C. Then nonylmagnesium chloride (1 M in THF, 2.6 mL, 2.6 mmol) was added slowly to the solution and the mixture was warmed to −30 °C. After stirring for 3 h, 3 M HCl (aq) (2 mL) was added to the solution. The product was extracted with diethyl ether (10 mL), dried over MgSO$_4$, and evaporated to give a clear crude product (86% GC yield). Purification by HPLC with CHCl$_3$ as the eluent afforded 272.7 mg (81%) of 1-cyclopropylnonane. IR (neat): 3076, 3000, 2957, 2923, 2864, 2360, 1464, 1378, 1014, 911, 820, 721 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ −0.02–0.01 (m, 2H), 0.34–0.43 (m, 2H), 0.60–0.78 (m, 1H), 0.89 (t, J = 6.8 Hz, 3H), 1.15–1.38 (m, 16H), ^{13}C NMR (100 MHz, CDCl$_3$): δ_u 11.1, 14.3, δ_d 4.6, 22.9, 29.5, 29.7, 29.8, 29.9, 32.1, 34.9; MS (EI) *m/z* (relative intensity, %) 168 (M$^+$, 1.48), 125 (4), 111 (19), 97 (49), 83 (74), 69 (91), 55 (100), 41 (59); HR-MS: calc. for C$_{12}$H$_{24}$ (M$^+$): 168.1878; found: 168.1879; elemental analysis: calc. for C$_{12}$H$_{24}$: C, 85.63; H, 14.37; found: C, 85.32; H, 14.02%.

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10 Formation of **3′** was confirmed by NMR at −60 °C (^{1}H NMR (400 MHz, THF-d_8, −60 °C): δ 0.6–0.9 (m, 2H) 1.26 (t, J = 7.7 Hz, 3H), 1.51 (d, J = 14.9 Hz, 1H), 1.55 (d, J = 14.4 Hz, 1H), 1.71 (d, J = 8.8 Hz, 2H), 2.01 (d, J = 6.9 Hz, 1H), 2.15 (d, J = 6.6 Hz, 1H), 3.41 (d, J = 9.3 Hz, 1H), 3.91 (d, J = 16.4 Hz, 1H), 4.3–4.6 (m, 1H), 6.1–6.4 (m, 1H); ^{13}C NMR (100 MHz, THF-d_8, −60 °C): δ 8.3, 22.8, 23.4, 45.9, 50.0, 91.1, 113.3, 152.7). A similar complex was identified by NMR, see ref. 9.

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