Synthetic Methods

Nickel-Catalyzed Cross-Coupling Reaction of Alkyl Halides with Organozinc and Grignard Reagents with 1,3,8,10-Tetraenes as Additives**

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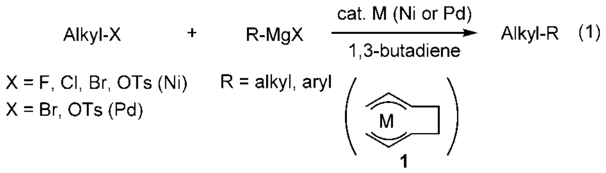
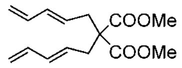
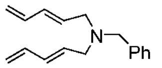
Transition-metal-catalyzed cross-coupling reactions between organic halides and organometallic reagents is a powerful tool for constructing carbon skeletons.[1] Significant advances have been achieved in this field over the last decade that have enabled cross-coupling reactions to be effected between alkyl groups by using either a nickel or palladium catalyst.[2] We have contributed to this progress by developing a unique catalytic system that proceeds efficiently under mild conditions by using 1,3-butadiene as an additive in the absence of phosphane ligands, where bis-π-allylnickel or -palladium intermediates (**1**) are proposed to be involved [Eq. (1)].[3] This system facilitates the cross-coupling of a wide variety of alkyl tosylates and halides, such as fluorides, chlorides, and bromides, with Grignard reagents. However, a drawback of this methodology is the range of functional groups that are tolerant to this system because of the high reactivity of the Grignard reagents. Herein, we reveal a solution to this problem by employing 1,3,8,10-tetraenes (**2**) that serve as extremely efficient ligands to promote the nickel-catalyzed cross-coupling reaction of alkyl halides with organozinc reagents[4–6] in a THF/*N*-methylpyrrolidone (NMP) mixed solvent containing magnesium bromide. It was also found that these tetraenes (**2**) were effective also for the nickel-catalyzed cross-coupling of alkyl fluorides with Grignard reagents.



(1)



2a



2b

First we examined a cross-coupling reaction of alkyl halides with organozinc reagents that used 1,3-butadiene as the additive. For example, *n*-decyl bromide (1 mmol), diethylzinc (2 equivalents, 1M in hexane), NiCl$_2$ (0.03 equiv), and 1,3-butadiene (1 equivalent) were added sequentially to a solution of THF (8 mL) and NMP (4 mL) at −78 °C and the mixture stirred at 25 °C for 48 hours. However, this reaction gave only a trace amount of the cross-coupling product, *n*-dodecane (< 1 %), as shown in Table 1 (entry 1). Addition of magnesium bromide increased the yield of *n*-dodecane to 45 %, but side reactions (reduction and HBr elimination) could not be suppressed (entry 2). Only a trace amount of dodecane was obtained without 1,3-butadiene even in the presence of magnesium bromide (entries 3 and 4). The salts Bu$_4$NBr, Bu$_4$NI,[5] and LiBr were also shown to be not effective as additives (entries 5–7). The yield of dodecane was increased up to 73 % by adding four equivalents of 1,3-butadiene; however, formation of by-products, *n*-decane and decenes, could not completely be suppressed (entries 8 and 9). Under similar conditions, [Ni(acac)$_2$] (acac = acetylacetanoate) afforded a slightly better yield of the product (entry 10), while nickel catalysts bearing phosphane ligands were less efficient (entries 11 and 12). PdCl$_2$ did not show a high catalytic activity (entry 13). The coupling products were obtained in yields of only 37 and 7 %, respectively (entries 14 and 15), when isoprene and *p*-fluorostyrene[5] were employed as additives under the same conditions as entry 10.

It is noteworthy that this cross-coupling reaction proceeded very rapidly and quantitatively when 2,2-bis(penta-2,4-dienyl)malonic acid dimethyl ester (**2a**) was employed as an additive in place of 1,3-butadiene, with complete suppression of the formation of decane and decenes (entry 16). The NiCl$_2$ catalyst also gave a satisfactory result under identical conditions (entry 17). The excellent performance of tetraene **2a** is demonstrated readily as the reaction was completed within 1 h at 25 °C with only 9 mol % of **2a** and 1.3 equivalents of diethylzinc (entry 18). *N*,*N*-Bis(penta-2,4-dienyl)benzylamine (**2b**) also showed high activity (entry 19). The yield of dodecane decreased when the amount of magnesium bromide was decreased (entry 18).

Reactions of various alkyl halides and a tosylate with organozinc reagents were examined with **2a** as an additive

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Table 1: Nickel-catalyzed cross-coupling reaction of $nC_{10}H_{21}$-Br with diethylzinc.[a]

Entry	Catalyst	Additive (equiv)	*t* [h]	Product yield [%][b]		
				Dodecane	Decane	Decenes[c]
1	$NiCl_2$	C_4H_6 (1)	48	< 1	23	< 1
2	$NiCl_2$	C_4H_6 (1), $MgBr_2$ (3)	48	45	20	11
3	$NiCl_2$	none	48	0	5	< 1
4	$NiCl_2$	$MgBr_2$ (3)	48	2	49	46
5	$NiCl_2$	C_4H_6 (1), Bu_4NBr (3)	48	< 1	45	3
6	$NiCl_2$	C_4H_6 (1), Bu_4NI (3)	48	3	69	23
7	$NiCl_2$	C_4H_6 (1), LiBr (3)	48	16	7	0
8	$NiCl_2$	C_4H_6 (2), $MgBr_2$ (3)	48	69	14	9
9	$NiCl_2$	C_4H_6 (4), $MgBr_2$ (3)	48	73	2	2
10	$[Ni(acac)_2]$	C_4H_6 (4), $MgBr_2$ (3)	48	84	3	3
11	$[NiCl_2(PPh_3)_2]$	C_4H_6 (4), $MgBr_2$ (3)	48	40	2	< 1
12	$[NiCl_2(dppp)]$	C_4H_6 (4), $MgBr_2$ (3)	48	31	3	0
13	$PdCl_2$	C_4H_6 (4), $MgBr_2$ (3)	48	5	55	3
14	$[Ni(acac)_2]$	isoprene (4), $MgBr_2$ (3)	48	37	5	3
15	$[Ni(acac)_2]$	*p*-fluorostyrene (4), $MgBr_2$ (3)	48	7	< 1	23
16	$[Ni(acac)_2]$	**2a** (2), $MgBr_2$ (3)	48	> 99	0	0
17	$NiCl_2$	**2a** (2), $MgBr_2$ (3)	48	> 99	0	0
18[d,e]	$[Ni(acac)_2]$	**2a** (0.09), $MgBr_2$ (3)	1	> 99	0	0
19[d]	$[Ni(acac)_2]$	**2b** (0.09), $MgBr_2$ (3)	1	> 99	0	0

[a] Conditions unless otherwise stated: *n*-Decyl bromide (1 mmol), catalyst (3 mol%), additive (equivalents based on the substrate), diethylzinc (2 equiv, 1 M in hexane), mixed solution of THF (8 mL) and NMP (4 mL), 25 °C, 48 h. [b] Determined by GC analysis. [c] A mixture of 1-decene and 2-decenes. [d] *n*-Decyl bromide (1 mmol), diethylzinc (1.3 equiv, 1 M in hexane), mixed solution of THF (8.4 mL) and NMP (4.2 mL), 25 °C, 1 h. [e] The yields were decreased to 41 and 11% when the amount of $MgBr_2$ was decreased to 1.3 and 0.65 equivalents, respectively.

(Table 2). This catalytic system tolerates unsaturated heteroatom functional groups, such as nitriles, ketones, amides, and esters (entries 1–4). The use of the secondary alkyl zinc reagent iPr_2Zn (entry 5) or an aryl zinc reagent (entry 6) also afforded the corresponding products in good yields. An alkyl tosylate was also shown to undergo this cross-coupling reaction under the same conditions (entry 7). Secondary alkyl halides and tosylates were found to react sluggishly. For example, treatment of 2-octyl bromide with diethylzinc afforded decane in a yield of only 3%, along with octane (6%) and octenes (3%), and 82% of 2-octyl bromide was recovered. Cyclohexyl tosylate also gave butylcyclohexane in a yield of only 5% after treatment with dibutylzinc.

We have shown that nickel catalyzes cross-coupling reactions of alkyl fluorides with Grignard reagents in the presence of 1,3-butadiene. However, this reaction is less efficient than those of the alkyl bromides, as they afford only moderate yields of the coupling products.[3b] For example, treatment of *n*-nonyl fluoride with 1.5 equivalents of *n*PrMgBr in the presence of 3 mol% of $[Ni(acac)_2]$ and 30 mol% of 1,3-butadiene gave dodecane in a yield of only 11% (Table 3, entry 1). Increasing the amount of 1,3-butadiene improved the yield moderately; however, satisfactory yields could not be attained (Table 3, entries 2–4). These poor yields were probably because the Ni^0 center will react with more than two equivalents of 1,3-butadiene in the presence of a high concentration of 1,3-butadiene and will form complexes composed of C_{12}-butadiene-oligomer units. The formation of these units will then predominantly result in a low concentration of **1**.[7] To prepare the bis-π-allylnickel complex structure exclusively, we applied tetraene **2b** as an additive and found that the yield was dramatically improved by the use of only 0.6 mol% of nickel catalyst and 15 mol% of **2b** (entry 5).

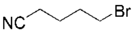
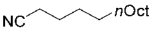
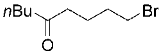
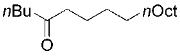
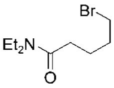
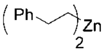
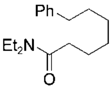
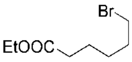
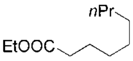
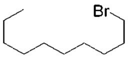
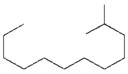
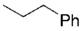
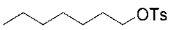
A plausible reaction pathway is shown in Scheme 1. A bis-π-allylnickel structure **3** is constructed by the oxidative cycloaddition of Ni^0 with two butadiene moieties of a

Table 3: Affect of the additive on the cross-coupling of alkyl fluorides.

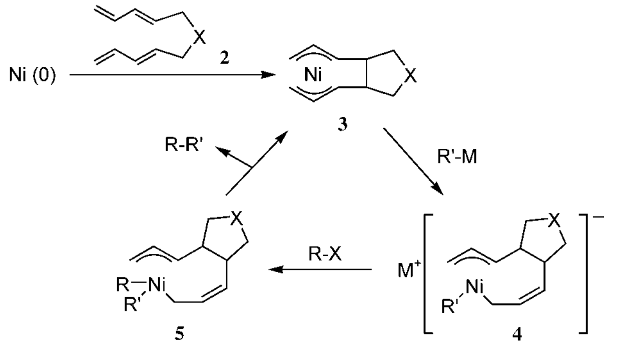
$$\underset{2\ \text{mmol}}{nC_9H_{19}\text{-F}} + \underset{3\ \text{mmol}}{nC_3H_7\text{-MgBr}} \xrightarrow[\text{THF (1.5 mL), RT, 6 h}]{3\ \text{mol}\ \%\ [Ni(acac)_2]} \text{Dodecane}$$

Entry	$[Ni(acac)_2]$ [mol%]	Additive (mol%)	Yield [%]
1	3	1,3-butadiene (30)	11
2	3	1,3-butadiene (100)	58
3	3	1,3-butadiene (200)	65
4	3	1,3-butadiene (30)	67
5	0.6	**2b** (15)	94

Table 2: Nickel-catalyzed cross-coupling reaction of alkyl halides and a tosylate with organozinc reagents using tetraene **2a**.[a]

Entry	RX	R'_2Zn	Product	Yield [%][b]
1		$nOct_2Zn$		96
2		$nOct_2Zn$		87
3				91
4		nPr_2Zn		87
5		iPr_2Zn		79[c]
6	*n*PrBr	Ph_2Zn		86[c]
7		Et_2Zn		83[c]

[a] Conditions: RX (1 mmol), R'_2Zn (1.3 equiv), $NiCl_2$ (3 mol%), **2a** (9 mol%), $MgBr_2$ (3 mmol), mixed solution of THF (8.4 mL) and NMP (4.2 mL), 25 °C, 1 h. [b] Yield of isolated product. [c] GC yield.



Scheme 1. A plausible reaction pathway.

1,3,8,10-tetraene.[8] An organomagnesium or -zinc reagent attacks the bis-π-allyl complex **3** to generate the η^1,η^3-octadienediylnickelate complex **4**, which then reacts with alkyl halides to give a complex **5**. Subsequent reductive elimination affords the coupling product along with **3** to complete the catalytic cycle. Selective and efficient formation of **3** from Ni^0 and **2** would, in comparison to 1,3-butadiene,[7] facilitate the generation of complex **4** and so accelerate the subsequent oxidative addition process that leads to **5**.

In conclusion, it was found that tetraenes **2** exerted dramatic effects that improved the cross-coupling reactions of organozinc reagents with alkyl halides catalyzed by nickel. This reaction proceeds efficiently by the use of primary and secondary alkyl or aryl zinc reagents under mild conditions. The use of tetraene **2b** as an additive also resulted in high yields of products in the cross-coupling of an alkyl fluoride with a Grignard reagent.

Experimental Section

Heptadecan-5-one: A solution of $n\mathrm{Oct_2Zn}$ (0.33 M in THF, 3.9 mL, 1.3 mmol) was added to a solution of 1-bromononan-5-one (221 mg, 1.0 mmol), $MgBr_2$ (552 mg, 3.0 mmol), $NiCl_2$ (4 mg, 0.03 mmol), **2a** (24 mg, 0.09 mmol), and NMP (4.2 mL) in THF (4.6 mL) at 25 °C under nitrogen. After stirring the mixture for 1 h, 1 M HCl (ca. 2 mL) was added to the solution at 0 °C and the mixture was warmed to 25 °C. Saturated aqueous $NaHCO_3$ solution (20 mL) was then added, and the product was extracted with diethyl ether (20 mL), dried over $MgSO_4$, and evaporated to give the crude product. Purification by silica gel column chromatography with hexane/diethyl ether (15:1) as an eluent afforded 233 mg (87 %) of octadecan-5-one. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.39$ (t, $J = 7.6$ Hz, 2 H), 2.38 (t, $J = 7.4$ Hz, 2 H), 1.59–1.51 (m, 4 H), 1.34–1.21 (m, 22 H), 0.90 (t, $J = 8.4$ Hz, 3 H), 0.88 ppm (t, $J = 8.8$ Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 211.1$, 42.7, 42.4, 31.8, 29.60, 29.57, 29.56, 29.54, 29.40, 29.35, 29.28, 29.20, 25.9, 23.8, 22.6, 22.3, 14.1, 13.8 ppm; MS (EI) m/z (relative intensity, %) 268 (M^+, 0.4), 211 (25), 113 (20), 101 (33), 85 (74), 71 (39), 58 (100); HR-MS: calcd for $C_{18}H_{36}O$: 268.2766, found 268.2758; elemental analysis (%): calcd for $C_{18}H_{36}O$: C 80.53, H 13.52; found: C 80.46, H 13.40.

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Keywords: alkyl halides · cross-coupling · Grignard reagents · nickel · organozinc reagents

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