Pd-Catalyzed Cross-Coupling Reaction of Alkyl Tosylates and Bromides with Grignard Reagents in the Presence of 1,3-Butadiene

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A new method for cross-coupling reaction of alkyl tosylates and bromides with Grignard reagents has been developed by the use of Pd(acac)$_2$ or PdCl$_2$ as the catalyst. Addition of 1,3-butadiene is essential to afford good yields of coupling products. This reaction proceeds efficiently at room temperature using primary and secondary alkyl and aryl Grignard reagents.

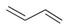
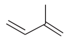
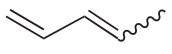
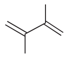
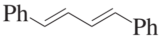
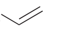
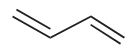
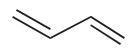
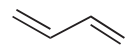
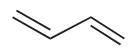
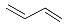
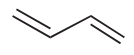
Palladium catalyzes cross-coupling reaction of aryl and alkenyl halides with a variety of organometallic reagents providing extremely useful and straightforward methods for C–C bond formation in organic synthesis.[1] These reactions proceed via oxidative addition of organic halides to Pd(0) followed by transmetallation and reductive elimination. Until quite recently, it was considered that alkyl halides are difficult to adapt to this cross-coupling reaction due to the slow oxidative addition of alkyl halides to Pd(0) and the facile β-elimination from the alkylpalladium intermediates.[2] Fu et al. recently established Pd-catalyzed cross-coupling reaction of alkyl halides with various organometallic reagents, such as organoboranes,[3] alkenyltins,[4] and arylsilanes[5] by the use of bulky trialkylphosphines as additives. We have developed independently a unique Ni-catalyzed cross-coupling reaction between alkyl electrophiles (Alkyl–X; X = F, Cl, Br, and OTs) and Grignard reagents (R–MgX′; R = alkyl and aryl) in the presence of 1,3-butadienes (Eq 1)[6] demonstrating that this reaction proceeds by a new mechanism involving bis-allylnickelate complexes[7] as the key intermediates.

$$\text{Alkyl–X} \quad + \quad \text{R–MgX}' \xrightarrow[\text{1,3-butadienes}]{\text{cat. NiCl}_2} \text{Alkyl–R} \qquad (1)$$

X = F, Cl, Br, OTs   R = alkyl, aryl

We intended to apply this methodology to Pd chemistry since Pd can promote more superior and convenient reactions than the corresponding Ni-catalyzed system in many instances.[8] We disclose herein Pd-catalyzed cross-coupling reaction of alkyl tosylates and bromides with Grignard reagents using 1,3-butadiene as an additive.

Table 1. Pd-catalyzed cross-coupling of n-$C_7H_{15}OTs$ with PhMgBr[a]

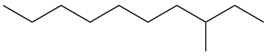
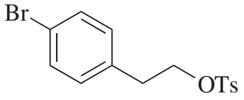
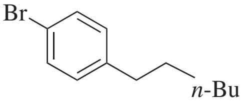
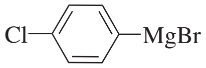
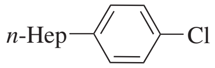
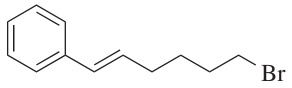
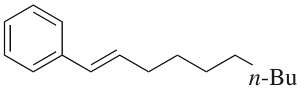
Entry	Catalyst	Additive	GC yield/% Ph-n-Hep	Heptane	Heptenes[b]
1	Pd(acac)$_2$		85	3	0
2	Pd(acac)$_2$	none	9	14	17
3	Pd(acac)$_2$		43	5	20
4	Pd(acac)$_2$		25	4	10
5	Pd(acac)$_2$		10	12	27
6	Pd(acac)$_2$		5	8	22
7	Pd(acac)$_2$	1,5-cyclooctadiene	16	14	26
8	Pd(acac)$_2$	p-F-C_6H_4	2	14	18
9	Pd(acac)$_2$	Ph—≡—Et	<1	3	7
10	PdCl$_2$		60	<1	<1
11	PdCl$_2$(PPh$_3$)$_2$		5	5	14
12	PdCl$_2$(dppe)		3	<1	<1
13	Ni(acac)$_2$		70	0	4
14	NiCl$_2$		68	<1	4
15	PtCl$_2$		2	0	0

[a] Conditions: n-$C_7H_{15}OTs$ (2 mmol), PhMgBr (1.5 equiv, 0.9 M in THF, 3.3 mL), 3 mol% catalyst, additive (0.5 equiv, 1 mmol, 0.3 M), 25 °C, 3 h. [b] A mixture of 1-heptene and 2-heptenes.

For example, a reaction of n-heptyl tosylate (2 mmol) with phenylmagnesium bromide (1.5 equiv.) in the presence of 1,3-butadiene (0.5 equiv.) and Pd(acac)$_2$ (0.03 equiv., 0.06 mmol) at 25 °C for 3 h gave n-heptylbenzene in 85% yield along with 3% yield of heptane (Table 1, Entry 1). In the absence of 1,3-butadiene, the coupling product was obtained in only 9% yield and heptane and heptenes were formed as major products in 14% and 17% yields, respectively (Entry 2). Isoprene and 1,3-pentadiene are less effective under the same conditions (Entries 3 and 4). 2,3-Dimethyl-1,3-butadiene, 1,4-diphenyl-1,3-butadiene, 1,5-cyclooctadiene, 4-fluorostyrene, and phenylethylacetylene did not promote this coupling reaction (Entries 5–9). PdCl$_2$ also afforded coupling product in good yield (Entry 10), whereas palladium complexes bearing phosphine ligands, such as PdCl$_2$(PPh$_3$)$_2$ and PdCl$_2$(dppe) did not show catalytic activity (Entries 11 and 12). Under the same conditions, Ni(acac)$_2$ and NiCl$_2$ also catalyzed this reaction but slightly less effectively than Pd(acac)$_2$ (Entry 1 vs Entries 13 and 14). PtCl$_2$ was ineffective (Entry 15).

Results of Pd-catalyzed cross-coupling reaction using some other reagents are shown in Table 2. Alkyl–alkyl cross-coupling has been achieved efficiently using n-BuMgCl (Entry 1). Use of alkyl bromides and secondary alkyl Grignard reagent also afforded corresponding coupling products in good yields (Entries 2 and 3). When NiCl$_2$ was used under identical conditions as Entries 1–3, excellent results were obtained in the case of primary alkyl Grignard reagents, whereas less activity was observed for secondary alkyl Grignard reagent than in the case of Pd. Cl and Br substituents on aromatic rings tolerate in these reactions (Entries 4 and 5). When 6-bromo-1-phenyl-1-hexene was employed, 1-phenyl-1-decene was obtained as the sole coupling product in 77% yield (Entry 6). No formation of the cy-

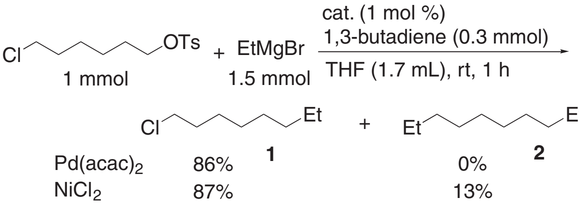
Table 2. Pd-catalyzed cross-coupling of alkyl tosylates and bromides with Grignard reagents

Entr	R–X	R'-MgX'	Pd(acac)$_2$ /mol %	1,3-Butadiene /mol %	Product	Yield/%[a]
1	*n*-Hex-OTs	*n*-Bu-MgCl	1	30 (0.19 M)	*n*-$C_{10}H_{22}$	93 (>99)[c]
2	*n*-Oct-Br	*n*-Pr-MgCl	1	30 (0.19 M)	*n*-$C_{11}H_{24}$	86 (>99)[c]
3	*n*-Hep-OTs	*s*-Bu-MgCl	1	30 (0.20 M)		71 (45)[c]
4		*n*-Bu-MgCl	3	100 (0.62 M)		71[b]
5	*n*-Hep-OTs		3	50 (0.30 M)		96
6		*n*-Bu-MgCl	1	30 (0.19 M)		77[b]

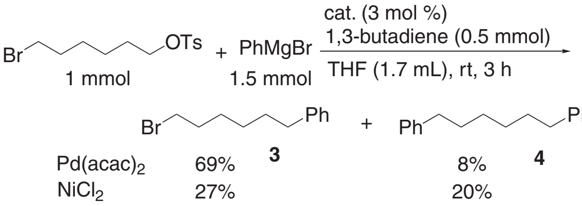
[a]GC yield unless otherwise stated. [b]Isolated yield. [c]NiCl$_2$ was used instead of Pd(acac)$_2$.

clized product in this reaction suggests that carbon radicals are not involved as intermediates.[9]

Under the same conditions, 1-chlorooctane was sluggish. This result prompted us to examine the reaction of 6-chlorohexyl tosylate and site selective cross-coupling was achieved to give **1** in 86% yield (Eq 2). This is in large contrast to the reaction using NiCl$_2$, where dialkylated product **2** was obtained in 13% yield. When 6-bromo-hexyl tosylate was employed, Pd catalyst also showed high chemoselectivity in favor of cross-coupling at the tosylate site whereas Ni was non-selective (Eq 3).



(2)



(3)

As for the reaction mechanisms of this Pd-catalyzed cross-coupling, we would like to propose a possible pathway where bis-allylpalladium complexes[10] play important roles as active catalytic species as the case of our Ni-catalyzed reaction. However no experimental information is available at the moment about the mechanism and alternative pathways might not be ruled out.

In conclusion, we revealed Pd-catalyzed alkyl–alkyl and alkyl–aryl cross-coupling reaction of alkyl tosylates and bromides with primary and secondary alkyl and aryl Grignard reagents by the use of 1,3-butadiene as an additive. Pd catalyst shows higher chemoselectivities in favor of tosylates against bromides and chlorides. For the reaction of aryl and *sec*-alkyl Grignard reagents, better yields were attained by the use of Pd than Ni catalyst. A detailed study of the mechanism of this reaction is currently under investigation.

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References and Notes

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