NICKEL-CATALYZED CROSS-COUPLING OF UNACTIVATED NEOPENTYL IODIDES WITH GRIGNARD REAGENTS

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Summary: Primary neopentyl iodides react with anyl Grignard reagents in the presence of 10 mol\$ (dppf)NiCl₂ to give the cross-coupled product.

Palladium- and nickel-catalyzed cross-coupling reactions have become increasingly popular for mediating the reactions of electrophiles which have sp or sp² carbons at or immediately adjacent to the electrophilic center. During a program directed toward the development of Group 10 metal complexes which catalyze carbon-carbon bond formation using primary neopentyl electrophiles, we discovered that dichloro-1,1'-bis(diphenylphosphino)-ferrocenepalladium(II),¹ ((dppf)PdCl₂) will effectively catalyze the Grignard-mediated reduction of both primary neopentyl iodides and <u>n</u>-alkyl iodides in diethyl ether.^{2,3}

Because the pailadium-catalyzed reduction appeared to circumvent the problems of slow oxidative-addition and rapid β -hydride elimination inherent to Group 10 metal-catalyzed reactions of unactivated alkyl electrophiles, we investigated the mechanism of both the pailadium-catalyzed reduction and the uncatalyzed reduction.³ These studies indicated a number of factors which must be considered for successful cross-coupling of unactivated electrophiles with nucleophiles. The nucleophile must be sufficiently stable under the reaction conditions to avoid direct reduction of the electrophile and to resist hydride delivery to the catalyst. At the same time, the nucleophile must be sufficiently reactive to allow for transmetallation within the catalytic cycle. The solvent must be optimized to minimize uncatalyzed interactions between the electrophile and the nucleophile. In this study and others, ⁴ Et₂O appeared to be preferable to THF for that reason. Finally, the catalyst must be sufficiently nucleophilic to allow the oxidative addition reaction to occur. We chose to study the effect of varying this last criterion on the course of the coupling reaction.

Herein we report on the use of $(dppf)NiCl_2^5$ to catalyze the cross-coupling of primary unactivated neopentyl electrophiles with Grignard reagents. The nickel catalyst was chosen in order to increase the nucleophilicity of the catalyst while retaining the steric effects and electron donating effects of the dppf ligand. Though $(dppf)NiCl_2$ has been used to catalyze the reactions of 5-alkyl-2,3-dihydrofurans,⁶ allylic esters and sulfones,⁷ silyl enol etters,⁸ β-bromostyrene,⁹ and 2-methylthic-4,4-dimethyl-2-oxazoline,¹⁰ there have been no reports of its use to catalyze the reactions of unactivated electrophiles.

As shown in Table 1, $(dppf)NiCl_2$ effectively catalyzes the cross-coupling of neopentyl lodides with anyl Grignard reagents in good to moderate yields.¹¹ Use of either Et₂0 or DME leads to the highest yields of cross-coupled products. The yield of product increases as the amount of catalyst is increased from 1 molf to 10 molf. No coupling occurs in the absence of catalyst. The coupling reaction is general for anyl Grignard reagents, including heteroaryl and naphthalenyl systems. This represents the first general case of the Group 10 metal-catalyzed cross-coupling of primary unactivated electrophiles.¹²

Entry	<u>Halide (R-1)</u>	Grignard <u>Reagent (R'MgX)</u>	Product_(R-R ^c)	Isclated <u>Yield (3)</u>
ł		PhMgBr <u>2</u>		71 ^b
2	1	CH ₃ MgBr 4		71 ^C
3	1	н ₃ со — — Мавг <u>6</u>	С досна	94 ^b
4	1	∭ ^S MgBr 8 MgBr		59 ^d
5	1			57
6		2		77 ^C
7	12	<u>6</u>		58
8	× <u>15</u>	2		86
9	15	6		80

Table 1. (dppf)NiCl₂-catalyzed cross-coupling of anyl Grignard reagents with primary neopentyl lodides.^a

- (a) Reaction of iodide (1.0 mmoi) and $(dppf)NiCl_2$ (0.1 mmol, 10 mol\$) with Grignard reagent (4.0 mmol) in Et₂O (10 mL) at the reflux temperature for 12-20 h. Isolated yields based on starting iodide.
- (b) The product mixture also contained 5% of homocoupled electrophile based on starting lodide. The by-product was not separated.
- (c) The product mixture also contained 10% of homocoupled electrophile based on starting iodide. The by-product was not separated.
- (d) The product mixture also included 2,21-bithiophene which was readily removed by chromatography (SiO₂, hex).

<u>Entr</u> ¥	Halide (R-1)	Grignard <u>Reagent (R'MgX)</u>	Product Ratio ^a <u>R-R' : R-R : R-H</u>	isclated <u>Yield (\$)</u>
1		CH ₃ MgC1	79:16:9	98
2	1	Ph(CH ₂) ₃ MgBr	71 : 16 : 12	80
3	1	CH ₃ CH ₂ MgBr	42 : 0 : 58	72
4	1	CH2=CHMgBr	0:0:12	b,c
5	1	CH ₂ =CH-CH ₂ MgBr	17 : 0 : 83	b

Table 2. (dppfNiCl2-catalyzed coupling of Grignard reagents.

(a) Product ratios determined by GC assuming equal response factors for R-R*, R-R and R-H.

(b) Product mixture not isolated. Yields refer to GC yields.

(c) Starting iodide (R-1) was also observed in 88%.



It is noteworthy that, unlike the (dppf)PdCl₂-catalyzed reaction,^{2,3} no reduction of the alkyl lodide was observed. In some cases, the product mixture contained small amounts of homocoupled electrophile, plausibly formed through a competitive radical pathway. In general this by-product was not separated from the cross-coupled product. The amounts of cross-coupled and homocoupled compounds in the product mixture were determined by GC and NMR analyses. Use of thienyImagnesium bromide also generated a large quantity of 2,21-bithiophene. This was readily removed from the cross-coupled product by column chromatography.

In general, the ability of Grignard reagents to cross-couple with primary neopentyl locides in the presence of substolchiometric amounts of (dppf)NiCl₂ follows the common pattern of anyl > methyl > alkyl (Table 2). Use of alkyl Grignard reagents leads to increased reduction of the lodice. With methylmagnesium chloride and 3-phenylpropyl-magnesium bromide the yield of cross-coupled product remained moderately high. However use of ethylmagnesium chloride led to reduction and cross-coupled product in a 3:2 ratio. The mechanism of this reduction is not clear at this time.³ Surprisingly, vinyl and allyl Grignard reagents failed to couple under the reaction conditions.

To date, the cross-coupling cannot be extended to other sixyl iodides. For example, attempted cross-coupling of 1-iododecane with methylmagnesium chloride in the presence of (dopf)NiCl₂ afforded 1-decene (54% GC yield) and decane (42%) with only 4% of the cross-coupled product.

In conclusion, we have demonstrated the first case of Group 10 metal-catalyzed crosscoupling of unactivated alkyl electrophiles. Primary neopentyl iodides couple with aryl Grignard reagents to give the substituted arenes in good to very good yield. Homocoupling of the electrophile remains a minor problem. Alkyl Grignard reagents couple in variable yields and vinyl and allyl Grignard reagents do not afford cross-coupled products. We feel that this methodology will prove generally useful to the synthetic chemist and will also open the use of alkyl electrophiles to the scope of reactions catalyzed by Group 10 metals.

General Experimental Procedure: To a mixture of neopentyl lodide 12 (0.24 g, 1.0 mmol) and (dppf)NiCl₂ (0.065 g, 9.0 mol⁴) in Et₂O (15 mL) at the reflux temperature was rapidly added <u>p</u>-methoxyphenyimagnesium bromide (4.0 mL, 1.26 M/Et₂O, 5.5 mmol). The resulting solution was kept at the reflux temperature overnight, cooled to room temp, diluted with Et₂O(20 mL), washed with a 1% HCl solution (5x30 mL), water (2x50 mL), a sat NaCl solution (2x50 mL), and water (2x10 mL), dried (MgSO₄), and filtered through a pad of silica. Concentration under reduced pressure followed by radial chromatography (SiO₂, hex) afforded 14 (0.13 g, 58%) as a clear oil: TLC (hex) R_f 0.32; IR (neat) 3030, 3000, 1240, 820, 800 cm⁻¹; ¹H NMR (300 MHz) 8 0.80 (s, 6H); 1.22-1.26 (m, 4H), 1.42-1.49 (m, 6H), 2.45 (s, 2H), 3.74 (s, 3H), 6.78 (d, μ =8.5 Hz, 2H), 7.20 (d, μ =8.5 Hz, 2H); ¹³C NMR (75 MHz) 8 22.2 (2C), 24.5, 26.5, 34.0, 37.5 (2C), 47.9, 55.0, 112.9 (2C), 131.1, 131.5 (2C), 157.7; LRMS m/z (rel intensity) 218 (12). Acknowledgments: The authors gratefully acknowledge support for this research by the Office of the Vice President for Research at The University of Iowa. Mass spectra were obtained in the University of Iowa High Resolution Mass Spectrometry Facility.

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