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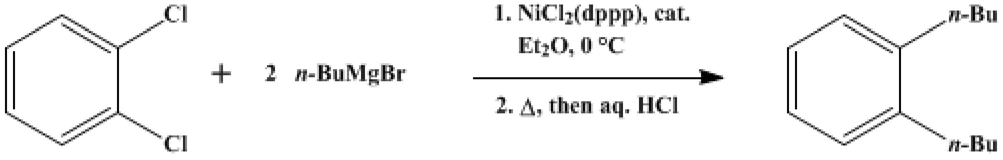
PHOSPHINE–NICKEL COMPLEX CATALYZED CROSS-COUPLING OF GRIGNARD REAGENTS WITH ARYL AND ALKENYL HALIDES: 1,2-DIBUTYLBENZENE

[Benzene, 1,2-di-*n*-butyl-]

$$CH_3(CH_2)_3Br + Mg \xrightarrow{\text{ethyl ether}} CH_3(CH_2)_3MgBr$$



(dppp) = $Ph_2P(CH_2)_3PPh_2$

Submitted by Makoto Kumada, Kohei Tamao, and Koji Sumitani[1].
Checked by Teresa Y. L. Chan and S. Masamune.

1. Procedure

A 500-ml., three-necked flask equipped with a mechanical stirrer, a pressure-equalizing dropping funnel, and a reflux condenser attached to a nitrogen inlet is charged with 12.2 g. (0.502 g.-atom) of magnesium turnings. The magnesium is dried under a rapid stream of nitrogen with a heat gun. After the flask has cooled to room temperature, the rate of nitrogen flow is reduced, and 200 ml. of anhydrous diethyl ether (Note 1) and approximately 5 ml. of a solution of 68.5 g. (0.500 mole) of 1-bromobutane (Note 2) in 50 ml. of anhydrous ether are added. The mixture is stirred at room temperature, and within a few minutes an exothermic reaction begins. The flask is immersed in an ice bath, and the remaining ether solution is added dropwise over *ca.* 1 hour. After addition is complete, the mixture is refluxed with stirring for 30 minutes and then cooled to room temperature.

A 1-l., three-necked flask, equipped in the same manner, is charged with *ca.* 0.25 g. (*ca.* 0.5 mmole) of dichloro[1,3-bis(diphenylphosphino)propane]nickel(II) (Note 3), 29.5 g. (0.201 mole) of 1,2-dichlorobenzene (Note 4), and 150 ml. of anhydrous ether (Note 5). The Grignard reagent prepared above is transferred to the dropping funnel and added over 10 minutes, with stirring, to the mixture cooled in an ice bath. The nickel complex reacts immediately with the Grignard reagent, and the resulting clear-tan reaction mixture is allowed to warm to room temperature, with stirring. An exothermic reaction starts within 30 minutes, and the ether begins to reflux gently. After stirring for 2 hours at room temperature, most of the magnesium bromochloride salt has deposited (Note 6). The mixture is refluxed with stirring for 6 hours, cooled in an ice bath, and cautiously hydrolyzed with 2 *N* hydrochloric acid (*ca.* 250 ml.) (Note 7). The nearly colorless organic layer is separated and the aqueous layer extracted with two 70-ml. portions of ether. The combined organic layer and extracts are washed successively with water, aqueous saturated sodium hydrogen carbonate, and again with water, dried over anhydrous calcium chloride, and filtered. After evaporation of the solvent the residue is distilled under reduced pressure through a 25-cm. column packed with glass helices, giving a forerun (*ca.* 4 g.) of 1-butyl-2-chlorobenzene, b.p. 52–54° (3.5 mm.), n_D^{20} 1.5110, followed by 30.0–31.5 g. (79–83%) of 1,2-dibutylbenzene, b.p. 76–81° (3.5 mm.), n_D^{20} 1.4920, as a colorless liquid (Note 8).

2. Notes

1. Ether was dried over sodium wire and freshly distilled before use.
2. Commercial 1-bromobutane was dried over anhydrous calcium chloride and distilled before use.
3. Dichloro[1,3-bis(diphenylphosphino)propane]nickel(II) can be easily prepared in an open reaction

vessel.[2] To a hot solution of 9.5 g. (0.040 mole) of nickel(II) chloride hexahydrate in 175 ml. of a 5:2 (v/v) mixture of 2-propanol and methanol, is added, with stirring, a hot solution of 14.5 g. (0.0352 mole) of 1,3-bis(diphenylphosphino)propane in 200 ml. of 2-propanol. A reddish brown precipitate deposits immediately. The mixture is heated for 30 minutes and allowed to cool to room temperature. Filtration, washing with methanol, and drying under reduced pressure provide the red complex in almost quantitative yield. 1,3-Bis(diphenylphosphino)propane may be purchased from Strem Chemicals Inc., and nickel(II) chloride hexahydrate from Fisher Scientific Company.

4. Commercial G.R.-grade 1,2-dichlorobenzene can be used without further purification. At least a 20% excess of the Grignard reagent should be used to compensate for some loss through undesirable side reactions (see Discussion section).

5. The nickel complex is insoluble in the mixture.

6. If stirring becomes difficult, approximately 100 ml. of anhydrous ether may be added.

7. This hydrolysis is exothermic, and the acid should be added slowly, maintaining gentle refluxing of the ether.

8. GC analysis on a 3.5-m. column packed with Silicone DC 550 and operated at 200° showed that the product was at least 99.5% pure. The product has the following spectral properties: IR (neat): 750 cm^{-1} (1,2-disubstituted benzene); ^1H NMR (CCl_4), δ (multiplicity, number of protons, assignment): 0.7–1.7 (m, 14H, 2 $CH_2CH_2CH_3$), 2.60 (t, 4H, 2 benzylic CH_2), 7.0 (s, 4H, C_6H_4).

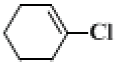
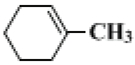
3. Discussion

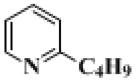
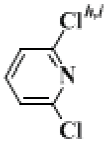
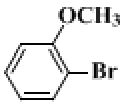
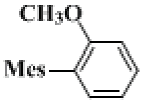
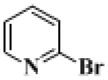
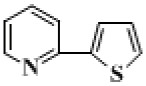
1,2-Dibutylbenzene has been prepared from cyclohexanone by tedious, multistep procedures.[3,4] The present one-step method is based on the selective cross-coupling of a Grignard reagent with an organic halide in the presence of a phosphine–nickel catalyst.[5]

The phosphine–nickel complex catalyzes the cross-coupling of alkyl, alkenyl, aryl, and heteroaryl Grignard reagents with aryl, heteroaryl, and alkenyl halides. The method, thus, has wide application. Alkyl halides also exhibit considerable reactivity, but give a complex mixture of products. Some representative examples are listed in Table I. A labile diorganonickel complex involving the two organic groups originating from the Grignard reagent and from the organic halide, respectively, has been proposed as a reaction intermediate. The fact that simple alkyl Grignard reagents with hydrogen-bearing β-carbon atoms react with equal efficiency is one of the most remarkable features of the present method, considering the great tendency with which transition metal alkyls undergo a β-elimination reaction, forming alkenes and metal hydrides.[6] Although the β-elimination may be responsible for the side products formed during the coupling, an appropriate choice of phosphine ligand for the nickel catalyst minimizes this side reaction. The catalytic activity of the phosphine–nickel complex depends not only on the nature of the phosphine ligand but also on the combination of the Grignard reagent and organic halide. Of several catalysts, including $[NiCl_2(dppp)]$, $[NiCl_2(dppe)]$, $[NiCl_2(dmpe)]$, and $[NiCl_2\{P(C_6H_5)_3\}_2]$, where dppe = $(C_6H_5)_2PCH_2CH_2P(C_6H_5)_2$ and dmpe = $(CH_3)_2PCH_2CH_2P(CH_3)_2$, the first has been found most effective in almost all cases, except for alkenyl Grignard reagents. The halide may be chloride, bromide, or iodide, although chlorides usually give the most satisfactory results. Even fluorides react with comparable facility in some cases.[7] Vinyl chloride is one of the most reactive halocompounds, and the coupling (Table I, entry 10) can be conveniently conducted in an open system, similar to that described here, by the gradual addition of the Grignard reagent at 0° to a mixture of vinyl chloride, $[NiCl_2(dppp)]$, and ether, followed by stirring at room temperature for 2 hours.

TABLE I

CROSS-COUPLING OF GRIGNARD REAGENTS WITH VARIOUS ARYL AND ALKENYL HALIDES IN THE PRESENCE OF $[NiCl_2(dppp)]$ AS A CATALYST[a]

Entry	RMgX	Halides	Product (% yield)[b]
1	CH_3MgBr		 (98)

2	$CH_3(CH_2)_3MgBr$	C_6H_5Cl	$C_6H_5C_4H_9$ (96)
3	$CH_3(CH_2)_3MgBr$		 (71)[c]
4	$(CH_3)_3SiCH_2MgCl$	1,3-$Cl_2C_6H_4$	1,3-$[(CH_3)_3SiCH_2]_2C_6H_4$ (83)[c]
5	$(CH_3)_2CHMgCl$	C_6H_5Cl	$(CH_3)_2CH$- and $CH_3(CH_2)_2C_6H_5$ (96:4) (89) (10:90) (84)[d]
6	$C_6H_5CH(CH_3)MgCl$	CH_2=CHBr[e,f]	(*S*)-(+)-$C_6H_5CH(CH_3)CH=CH_2$[g] (96)
7	$BrMg(CH_2)_{10}MgBr$	[h,i]	 (33)
8	C_6H_5MgBr	(*Z*)-$C_6H_5CH=CHBr$	(*Z*)-$C_6H_5CH=CHC_6H_5$ (100)
9	C_6H_5MgBr	ClCH=CHCl[d,j]	(*Z*)-$C_6H_5CH=CHC_6H_5$[k] (95–100)
10	4-ClC_6H_4MgBr	CH_2=CHCl[l]	4-$ClC_6H_4CH=CH_2$ (79)[c]
11	2,4,6-$(CH_3)_3C_6H_2MgBr$		 (74)
12	$CH_2=C(CH_3)MgBr$	α-$C_{10}H_7Br$[d,h]	α-$C_{10}H_7C(CH_3)=CH_2$ (78)
13			 (78)

[a] The reaction was carried out on a 0.01–0.02 mole scale in refluxing ethyl ether for 3–20 hours, unless otherwise noted.

[b] Determined by GC, unless otherwise noted.

[c] Isolated Yield.

[d] The catalyst is $[NiCl_2(dmpe)]$, dmpe = $(CH_3)_2PCH_2CH_2P(CH_3)_2$.

[e] The catalyst is a mixture of $NiCl_2$ and (*S*)-Valphos. (*S*)-Valphos = (*S*)-(+)-(2-Dimethylamino-3-methylbutyl)diphenylphosphine (see ref. [8]).

[f] At 0° for 2 days.

[g] Configuration of the predominant enantiomer; 13.0% enantiomeric excess.

[h] Solvent is tetrahydrofuran.

[i] At 40° for 9 hours.

[j] At room temperature for 2 hours.

[k] (*Z*)-Stilbene is formed stereoselectively regardless of whether (*Z*)- or (*E*)-dichloroethene is used (see text).

[l] Carried out on a 0.2 mole scale at 0° to room temperature over 2 hours.

Several other features deserve comment. The coupling of secondary alkyl Grignard reagents is accompanied by alkyl group isomerization from secondary to primary, the extent of which is strongly dependent on the electronic nature of the phosphine ligand in the catalyst (entry 5).[7] Asymmetric cross-coupling can be achieved by using optically active phosphine–nickel complexes as catalysts (entry 6).[9,10,11,12,13,8,14] Cyclocoupling of di-Grignard reagents with dihalides offers a new, one-step route to cyclophanes (entry 7).[15] Though the cross-coupling of monohaloalkenes proceeds stereospecifically (entry 8),[16] that of 1,2-dihaloethylenes proceeds nonstereospecifically, yielding a (*Z*)-alkene, the stereoselectivity being dependent on the nature of the phosphine ligand in the catalyst (entry 9).[16] Sterically hindered aryl Grignard reagents also react with ease (entry 11).[14]

The couplings are usually exothermic, and care must be taken *not* to add the phosphine–nickel catalyst to a mixture of a Grignard reagent and an organic halide, particularly in a large-scale preparation. For example the addition of a small amount of [$NiCl_2$(dppp)] to a mixture of vinyl chloride and 4-chlorophenylmagnesium bromide in ether at 0° led, after a few minutes' induction period, to an uncontrollable, violent reaction.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 172
- Org. Syn. Coll. Vol. 8, 441

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

magnesium bromochloride

$(C_6H_5)_2PCH_2CH_2P(C_6H_5)_2$

$(CH_3)_2PCH_2CH_2P(CH_3)_2$

$[NiCl_2(dppp)]$

$[NiCl_2(dmpe)]$

(Z)- or (E)-dichloroethene

$NiCl_2(dppp)$

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether,
ethyl ether,
diethyl ether (60-29-7)

sodium hydrogen carbonate (144-55-8)

magnesium (7439-95-4)

Cyclohexanone (108-94-1)

1-bromobutane (109-65-9)

nitrogen (7727-37-9)

nickel (7440-02-0)

sodium wire (13966-32-0)

2-propanol (67-63-0)

nickel(II) chloride hexahydrate (7791-20-0)

Tetrahydrofuran (109-99-9)

phosphine (7723-14-0)

vinyl chloride (9002-86-2)

1,2-Dibutylbenzene,
Benzene, 1,2-di-n-butyl- (17171-73-2)

dichloro[1,3-bis(diphenylphosphino)propane]nickel(II) (15629-92-2)

1,2-dichlorobenzene (95-50-1)

1-butyl-2-chlorobenzene

1,3-bis(diphenylphosphino)propane (6737-42-4)

4-chlorophenylmagnesium bromide

(Z)-Stilbene (645-49-8)