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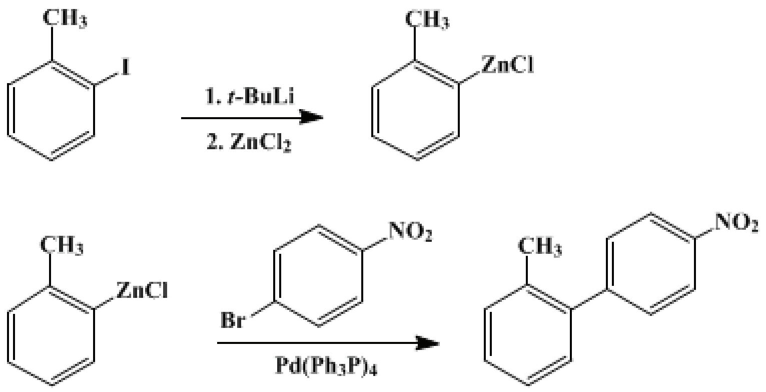
SYNTHESIS OF BIARYLS VIA PALLADIUM-CATALYZED CROSS-COUPLING: 2-METHYL-4'-NITROBIPHENYL

[1,1'-Biphenyl, 2-methyl-4'-nitro-]



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1. Procedure

Caution! tert-Butylithium is extremely pyrophoric and must not be allowed to come into contact with the atmosphere. This reagent should only be handled by individuals trained in its proper and safe use. It is recommended that transfers be carried out by using a 20-mL or smaller glass syringe filled to no more than 2/3 capacity, or by cannula. For a discussion of procedures for handling air-sensitive reagents, see Aldrich Technical Bulletin AL-134. [Note added August 2009].

A. *o-Tolylzinc chloride.* An oven-dried, 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, a dropping funnel, a rubber septum inlet, and an outlet connected to a mercury bubbler is flushed with nitrogen, immersed in a dry-ice bath kept at −78°C, and charged with 26.2 g (120 mmol) of *o*-iodotoluene (Note 1) and 60 mL of ether (Note 2). To this solution is added dropwise, with stirring, 154 mL (1.56 *M*, 240 mmol) of a hexane solution of *tert*-butyllithium (Note 3). After the reaction mixture is stirred for 1 hr at −78°C, it is warmed to room temperature, stirred for 1 hr, and concentrated under diminished pressure using a water aspirator (ca. 15 mm) until most of the volatile solvents are evaporated. To this concentrate is added 80 mL of tetrahydrofuran (THF) (Note 4) and (Note 5). The mixture is, in turn, added to 16.3 g (120 mmol) of dry zinc chloride (Note 6) and 60 mL of tetrahydrofuran placed in a similarly equipped, 500-mL flask using a 16-gauge double-ended needle under a slight positive pressure of nitrogen; the resulting mixture is stirred for 1 hr at room temperature.

B. *2-Methyl-4'-nitrobiphenyl.* To a mixture of 1.16 g (1 mmol) of tetrakis(triphenylphosphine)palladium (Note 7), 100 mL of tetrahydrofuran and 20.2 g (100 mmol) of 1-bromo-4-nitrobenzene (Note 8) in a 500-mL flask, set up as described above and immersed in a water bath, is added the *o*-tolylzinc chloride solution prepared above. The reaction mixture is stirred for 6 hr at room temperature and poured onto a mixture of 100 mL of ether and 300 mL of ice-cold 3 *N* hydrochloric acid. The organic layer is separated, and the aqueous layer is extracted with two 100-mL portions of ether. The combined organic layer is washed with saturated aqueous sodium bicarbonate and dried over anhydrous magnesium sulfate. After filtration, the solvent is removed using a rotary evaporator to give a light-brown solid. The solid is recrystallized from 300 mL of hexane to yield 16.0 g of yellow crystals. The second crop from 50 mL of hexane is 2.4 g. The combined product is recrystallized from 100 mL of ethanol to afford 16.0 g of light-yellow needles. Crystallization of the mother liquor from 25 mL of ethanol gives a second crop of 0.5 g. The total yield of 2-methyl-4'-nitrobiphenyl is 16.5 g (78% based on 1-bromo-4-nitrobenzene) (Note 9).

2. Notes

1. The submitters used *o*-iodotoluene from Aldrich Chemical Company, Inc. The checkers purchased it from Wako Chemical Industries, Ltd.

2. Ether available from Fisher Scientific Company or Sanraku Company was distilled from sodium and benzophenone.

3. The submitters used *tert*-butyllithium from Aldrich Chemical Company, Inc. after titration by the method of Watson and Eastham.[2] The checkers titrated it by the method of Lipton.[3]

4. Tetrahydrofuran from Fisher Scientific Company or Kishida Chemical Company was distilled from sodium and benzophenone.

5. Although somewhat more cumbersome, the following more economical procedure using lithium metal may also be used to generate *o*-tolyllithium. To 1.7 g (240 mg-atom) of freshly cut lithium in 35 mL of ether at 0°C is added dropwise 20.5 g (120 mmol) of *o*-bromotoluene in 25 mL of ether. After formation of *o*-tolyllithium, it is diluted with 60 mL of tetrahydrofuran before use.

6. Zinc chloride, available from Mallinckrodt, Inc., was flame-dried under a slow stream of nitrogen in the reaction flask. The checkers used zinc chloride from Wako Pure Chemical Industries, Inc. after fusion by flame-drying under reduced pressure for 20 min.

7. Tetrakis(triphenylphosphine)palladium was prepared according to the procedure of Coulson.[4]

8. The submitters used 1-bromo-4-nitrobenzene from Aldrich Chemical Company, Inc. without further purification. The checkers purchased it from Tokyo Kasei Kogyo Company.

9. Gas-chromatographic examination of another reaction mixture run on a 10-mmol scale with undecane as an internal standard indicates that 2-methyl-4'-nitrobiphenyl is formed in 90% yield based on 1-bromo-4-nitrobenzene. The product obtained by this procedure shows the following properties: mp 99–101°C (lit.,[5] mp 103–105°C); IR (neat) cm^{-1}: 1600 (s), 1510 (s), 1480 (s), 1340 (s), 858 (s), 778 (s), 756 (s), 730 (s), 702 (s); ^{1}H NMR (90 MHz, $CDCl_3$) δ: 2.26 (s, 3 H), 7.15–7.40 (m, 4 H), 7.48 (d, 2 H, J = 8.5), 8.27 (d, 2 H, J = 8.5); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ: 20.30, 123.42, 126.16, 128.50, 129.42, 130.11, 130.75, 135.09, 139.67, 147.00, 148.85.

3. Discussion

The procedure described above is based on a paper reporting the Ni- or Pd-catalyzed reaction of arylzinc derivatives with aryl halides.[6] The Ni- or Pd-catalyzed cross-coupling reaction[7] represents one of the most general and satisfactory routes to unsymmetric biaryls.

The currently available data, such as those summarized in Table I, indicate the following. First, Ni-Phosphine and Pd-phosphine complexes may be used interchangeably in many cases (Entries 1 and 2). In cases where sterically hindered aryl reagents, such as mesitylzinc chloride, are used, Ni catalysts tend to lead to higher product yields than the corresponding Pd catalysts (Entries 11 and 12). The scope with respect to the halogen leaving group of aryl halides is broader with Ni catalysts than with Pd catalysts. As a general rule, Ni-catalyzed aryl–aryl cross-coupling proceeds smoothly with both aryl iodides and aryl bromides, whereas aryl bromides must be activated by an electron-withdrawing group in Pd-catalyzed cross-coupling. Palladium-catalyzed cross-coupling, however, is considerably more chemoselective than Ni-catalyzed cross-coupling. Thus, for example, the nitro group appears to be totally incompatible with Ni-phosphine catalysts (Entry 9), and the presence of an alkynyl group tends to lower significantly the yield of product.

TABLE I

PREPARATION OF BIARYLS BY THE Ni- OR Pd-CATALYZED REACTION OF ARYL METALS WITH ARYL HALIDES[a]

Entry	Ar^1M[b]	ArX	Catalyst[c]	Amount (%)	Yield[d] (%)
1	PhZnCl	*p*-Iodoanisole	Ni	5	85
2	PhZnCl	*p*-Iodoanisole	Pd[e]	5	87
3	PhMgBr	*p*-Iodoanisole	Pd[e]	5	71
4	PhAl (*i*-Bu)$_2$	*p*-Iodoanisole	Pd[e]	5	72
5	PhZnCl	*p*-BrC_6H_4CN	Ni	5	90
6	PhZnCl	*p*-BrC_6H_4COOMe	Ni	5	70
7	PhZnCl	*p*-$IC_6H_4NO_2$	Pd[e]	5	90 (74)
8	*o*-TolZnCl	*p*-$BrC_6H_4NO_2$	Pd[e]	1	90 (70)
9	*o*-TolZnCl	*p*-$BrC_6H_4NO_2$	Ni	1	0
10	*m*-TolZnCl	*m*-$IC_6H_4CH_3$	Ni	5	95
11	MesZnCl[f]	*o*-$IC_6H_4CH_3$	Ni	5	93
12	MesZnCl	*o*-$IC_6H_4CH_3$	Pd	5	88
13	MesMgBr[g]	*o*-$IC_6H_4CH_3$	Ni	5	38
14	MesMgBr	*o*-$IC_6H_4CH_3$	Ni	5	92
15	PhZnCl	2-Furyl iodide	Pd	5	91
16	2-FurylZnCl	PhI	Pd	5	94 (89)
17	3-FurylZnCl	PhI	Pd	5	89 (85)
18	PhZnCl	2-Furyl bromide	Pd	5	0
19	2-ThienylZnCl	PhI	Pd	5	81 (75)
20	PhZnCl	2-Pyridyl bromide	Pd	5	99 (89)
21	PhZnCl	3-Pyridyl bromide	Pd	5	0

Entry	Ar^1M[b]	ArX	Catalyst[c]	Amount (%)	Yield[d] (%)

[a] The reactions are carried out in THF at room temperature. The time required for completion is usually less than several hours.

[b] Unless otherwise mentioned, arylzinc chlorides and arylalanes are prepared via in situ transmetalation of aryllithiums, while arylmagnesium halides are prepared by treating aryl halides with Mg. The molar ratio of an aryl metal to an aryl halide is 1–1.5.

[c] Ni = $Ni(PPh_3)_4$ prepared in situ by the reaction of $Ni(acac)_2$, PPh_3, and $(i\text{-}Bu)_2AlH$ (1:4:1). Unless otherwise indicated, Pd = $Pd(PPh_3)_4$.

[d] By GLC. The numbers in parentheses are isolated yields.

[e] The Pd catalyst is prepared by treating $Cl_2Pd(PPh_3)_2$ with $(i\text{-}Bu)_2AlH$ (2 equiv).

[f] Mes = mesityl.

[g] Generated in situ by treating MesLi with $MgBr_2$ generated from 1,2-dibromoethane and Mg.

Second, the choice of metal counterion is of critical importance. Except in some special cases, alkali metals such as Li, Na, and K are unsatisfactory, partly because arylmetals that contain these metals readily participate in halogen–metal exchange leading to cross–homo scrambling,[6] and also because these organometals are among the least chemoselective. Zinc appears to be among the most satisfactory metals from the standpoint of (a) product yield, (b) cross/homo ratio, (c) chemoselectivity, and (d) ease of preparation of arylmetal reagents, although Mg has also been used successfully in many cases.[8,9] Results shown in Entries 11 and 13 indicate that the mesitylmagnesium reagent, generated in situ by treatment of mesityllithium with magnesium bromide, appears to be considerably inferior to mesitylzinc chloride generated in a similar manner. On the other hand, mesitylmagnesium bromide generated by treatment of mesityl bromide with Mg is as effective as mesitylzinc chloride (Entry 14). However, the yield of mesitylmagnesium bromide itself is in the range 50–60% and is substantially lower than that of mesitylzinc chloride (ca. 90%). Recent results obtained with arylboron derivatives[10] appear highly promising, although the preparation of arylboronic acids is, at present, more elaborate than that of Grignard reagents or in situ generation of arylzinc reagents. Various other metals, such as Cd,[11] Hg,[12] Al,[6] Sn,[12] Zr,[11] and Cu,[12] have been shown to participate in aryl–aryl cross-coupling. Their advantages over Zn or Mg are, however, largely unknown.

Third, the procedure described above has been applied to the preparation of various biaryls containing heteroaromatic rings (Entries 15–17, 19, 20). Although the number of papers reporting the use of the Ni- or Pd-catalyzed procedure for aryl–aryl coupling is still small, the synthesis of steganone by Raphael and his co-workers[13] is demonstrative of its synthetic potential.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 10, 102

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

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium bicarbonate (144-55-8)

nitrogen (7727-37-9)

Benzophenone (119-61-9)

zinc (7440-66-6)

sodium (13966-32-0)

1,2-dibromoethane (106-93-4)

zinc chloride (7646-85-7)

magnesium bromide (7789-48-2)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

mesityl bromide (576-83-0)

o-Bromotoluene (95-46-5)

Tetrahydrofuran (109-99-9)

2-Pyridyl bromide (109-04-6)

o-iodotoluene (615-37-2)

hexane (110-54-3)

mesitylmagnesium bromide (2633-66-1)

3-Pyridyl bromide (626-55-1)

mesityl

undecane (1120-21-4)

Tetrakis(triphenylphosphine)palladium (14221-01-3)

tert-Butyllithium (594-19-4)

1-bromo-4-nitrobenzene (586-78-7)

2-Methyl-4'-nitrobiphenyl,
1,1'-Biphenyl, 2-methyl-4'-nitro- (33350-73-1)

mesitylzinc chloride

2-Furyl iodide

2-Furyl bromide

mesitylmagnesium

mesityllithium

p-Iodoanisole (696-62-8)

o-Tolyllithium

o-Tolylzinc chloride