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Palladium-catalyzed cross-coupling of bromobenzenes, containing an acetyl or a formyl group, with organozinc reagents

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Abstract

The reaction of organozinc halides $RZnX$ ($R = Bu, Ph$; $X = Cl, Br$) with *m*- and *p*-bromoacetophenones in the presence of $PdCl_2(PPh_3)_2$ in THF/HMPA (THF = tetrahydrofuran; HMPA = *N,N,N',N',N'',N''*-hexamethylphosphoric triamide) takes place chemoselectively to give the corresponding *m*- and *p*-*R*-substituted acetophenones in high yields. Similarly reaction of $RZnX$ with *p*-bromobenzaldehyde also proceeds chemoselectively to give the *p*-*R*-substituted benzaldehyde in good yields.

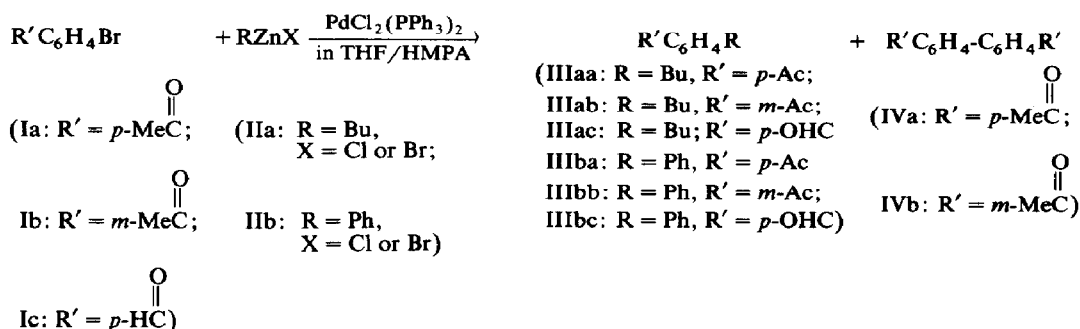
Introduction

It is fairly well known that organozinc reagents, in particular dialkylzincs, react with ketones containing an α -H atom to give aldol condensation products [1]. Acetophenone reacts with diethylzinc to give a dehydrated aldol, β -methylchalcone [2]. On the other hand, the reaction of organozinc reagents with aldehydes gives secondary alcohols [3]. Up to now the cross-coupling of halobenzenes containing a carbonyl group with non-Reformatsky organozinc reagents has not been studied. In this paper we report on the unprecedented chemoselective cross-coupling of bromoacetophenones and bromobenzaldehyde with organozinc halides.

Results and discussion

All reactions were carried out in a mixed solvent of THF and HMPA (THF = tetrahydrofuran; HMPA = *N,N,N',N',N'',N''*-hexamethylphosphoric triamide) after the observations by Fauvarque et al. that HMPA is an excellent co-solvent in the Ni- or Pd-catalyzed Reformatsky reactions in dimethoxymethane [4].

The reaction of *p*-bromoacetophenone (Ia) with butylzinc (IIa) or phenylzinc halide (IIb) in the presence of a palladium (II) complex as catalyst gives *p*-butyl-



Scheme 1

acetophenone (IIIaa) or 4-acetylbiphenyl (IIIba), respectively, as the major product (Scheme 1).

As shown in Table 1, of the palladium (II) complexes examined, $\text{PdCl}_2(\text{PPh}_3)_2$ exhibits the highest catalytic activity in the reactions of Ia with II (Entries 1, 8). The analogous Ni complex, $\text{NiCl}_2(\text{PPh}_3)_2$, however, showed poor activity (Entries 6, 13).

Similarly, reactions of *m*-bromoacetophenone (Ib) and *p*-bromobenzaldehyde (Ic) with RZnX (IIa or IIb) in the presence of $\text{PdCl}_2(\text{PPh}_3)_2$ gave the corresponding R-substituted acetophenones and benzaldehydes, respectively. GC-MS analyses revealed that no dehydrated aldols of Ia and Ib, (4,4'- and 3,3'-dibromo- β -methylchalcones, respectively), or addition products of II to the formyl group of Ic

Table 1

Catalytic activities of Pd or Ni complexes in the chemoselective cross-coupling of *p*-bromoacetophenone (Ia) with organozinc halides (II) in THF/HMPA^a

Entry	Catalyst ^b	RZnX (II) ^c (R =)	Yield of product (III) (%) ^d
1	$\text{PdCl}_2(\text{PPh}_3)_2$	a (Bu)	aa: 90
2	$\text{PdCl}_2(\text{dppb})$	a (Bu)	aa: 49
3	$\text{PdCl}_2(\text{dppf})$	a (Bu)	aa: 50
4	$\text{PdCl}_2(\text{dppp})$	a (Bu)	aa: 45
5	PdCl_2	a (Bu)	aa: 46
6	$\text{NiCl}_2(\text{PPh}_3)_2$	a (Bu)	aa: 46
7	$\text{NiCl}_2(\text{dppp})$	a (Bu)	aa: 45
8	$\text{PdCl}_2(\text{PPh}_3)_2$	b (Ph)	ba: 98 ^e
9	$\text{PdCl}_2(\text{dppb})$	b (Ph)	ba: 70 ^e
10	$\text{PdCl}_2(\text{dppf})$	b (Ph)	ba: 75 ^e
11	$\text{PdCl}_2(\text{dppp})$	b (Ph)	ba: 60 ^e
12	PdCl_2	b (Ph)	ba: 61 ^f
13	$\text{NiCl}_2(\text{PPh}_3)_2$	b (Ph)	ba: 84 ^e
14	$\text{NiCl}_2(\text{dppp})$	b (Ph)	ba: 75 ^e

^a The molar ratio Ia:II:catalyst = 1.0:1.2:0.02; the volume-to-volume ratio THF/HMPA = 1/2; at reflux (100 °C); for 15 min. ^b Abbreviations for ligands: dppb = 1,4-bis(diphenylphosphino)butane; dppf = 1,1'-bis(diphenylphosphino)ferrocene; dppp = 1,3-bis(diphenylphosphino)propane. ^c X = Cl or Br. ^d III = *p*-CH₃COC₆H₄R; determined by GLC. ^e Trace amounts of 4,4'-diacetylbiphenyl (IVa) were also detected. ^f IVa = 11%.

Table 2

Chemoselective cross-coupling of *p*- and *m*-bromoacetophenones (Ia and Ib) and *p*-bromobenzaldehyde (Ic) with RZnX (II) in the presence of PdCl₂(PPh₃)₂ in THF/HMPA^a

Entry	I (R')	II (R)	Reaction temp	THF/HMPA (ratio)	Yield of III (%) ^b
1	a (<i>p</i> -CH ₃ CO)	a (Bu)	reflux	1/2	aa: 90
15	a (<i>p</i> -CH ₃ CO)	a (Bu)	50 °C	1/2	aa: 80
16	a (<i>p</i> -CH ₃ CO)	a (Bu)	reflux	1/1	aa: 80
17	a (<i>p</i> -CH ₃ CO)	a (Bu)	reflux	1/3	aa: 84
8	a (<i>p</i> -CH ₃ CO)	b (Ph)	reflux	1/2	ba: 98 ^c
18	a (<i>p</i> -CH ₃ CO)	b (Ph)	50 °C	1/2	ba: 76 ^c
19	a (<i>p</i> -CH ₃ CO)	b (Ph)	reflux	1/1	ba: 96 ^c
20	a (<i>p</i> -CH ₃ CO)	b (Ph)	reflux	1/3	ba: 90 ^c
21	b (<i>m</i> -CH ₃ CO)	a (Bu)	reflux	1/2 ^d	ab: 69 ^e
22	b (<i>m</i> -CH ₃ CO)	a (Bu)	50 °C	1/2 ^d	ab: 52 ^f
23	b (<i>m</i> -CH ₃ CO)	b (Ph)	reflux	1/2 ^g	bb: 79 ^h
24	c (<i>p</i> -OHC)	a (Bu)	reflux	1/2	ac: 87
25	c (<i>p</i> -OHC)	a (Bu)	50 °C	1/2	ac: 61
26	c (<i>p</i> -OHC)	b (Ph)	reflux	1/2	bc: 92

^a The molar ratio I:II: PdCl₂(PPh₃)₂ = 1.0:1.2:0.02; for 15 min. ^b III = R'C₆H₄R; determined by GLC. ^c Trace amounts of IVa were also detected. ^d For 30 min. ^e 3,3'-Diacylbiphenyl (IVb) was also detected in 21% yield. ^f IVb = 33%. ^g For 45 min. ^h IVb = trace amounts.

(1-(*p*-bromophenyl)-1-pentanol and *p*-bromophenylphenylmethanol) were produced.

As shown in Table 2, the reactions of I with II resulted in the highest yields of chemoselectively cross-coupled products (III), in a mixed solvent of THF/HMPA (volume ratio = 1/2) under reflux (Entries 1, 8). A larger amount of HMPA in the mixed solvent did not give better yields of III (Entries 17, 20).

As a control experiment, we carried out the reaction of acetophenone with PhZnX (IIb) in the presence of PdCl₂(PPh₃)₂ in refluxing THF/HMPA (1/2) for 60 min and found that (*E*)- β -methylchalcone was produced in 58% yield. Under similar conditions benzaldehyde reacts with IIb to give diphenylmethanol in 63% yield.

The reactions of benzaldehyde and bromobenzene, when both are present in the mixture, with IIb in the PdCl₂(PPh₃)₂ at reflux for 30 min, are competitive and give biphenyl in 76% yield; 95% of the benzaldehyde is recovered unchanged. In the absence of PdCl₂(PPh₃)₂, the same reaction of benzaldehyde and bromobenzene with IIb at reflux for 60 min gives diphenylmethanol in 61% yield and about 91% of bromobenzene remains unchanged. Moreover, the reaction of a mixture of Ic and bromobenzene with IIb in the presence of PdCl₂(PPh₃)₂ at reflux for 15 min gives 80% of 4-biphenylcarbaldehyde (IIIbc) and trace amounts of biphenyl. These results suggest that the reactivity toward PhZnX in the presence of PdCl₂(PPh₃)₂ falls in the order: *p*-OHCC₆H₄Br (Ic) > C₆H₅Br > C₆H₅CHO. The high reactivity of Ic is because of the electron-attracting effect of the *p*-formyl group, which probably facilitates the oxidative addition by the phenyl-Br bond to the palladium of the catalyst [5], the key step of the cross-coupling reaction. Cross-coupling of I with II is thus much faster than the aldol condensation of acetyl group and addition of II to formyl group in the presence of PdCl₂(PPh₃)₂.

In a reaction of Ia with IIb in the presence of PdCl_2 , 4,4'-diacetylbiphenyl (IVa) is also obtained in 11% yield (Entry 12). Similarly, from a reaction of Ib with IIa, 3,3'-diacetylbiphenyl (IVb) is produced in 21–33% yields (Entries 21, 22). The by-product IVb was scarcely formed in homo-coupling of Ib with $\text{PdCl}_2(\text{PPh}_3)_2$ and zinc dust in THF/HMPA, in contrast to the observation that the reaction of *p*-chloroacetophenone with a red-brown mixture, prepared from NiCl_2 , Ph_3P , and zinc dust in DMAC (N,N-dimethylacetamide) or DMF (N,N-dimethylformamide), gave IVa quantitatively [6].

Thus, IVa and IVb should be produced by the cross-coupling of Ia and Ib with *p*- and *m*-acetylphenylzinc halide, respectively, that are formed by halogen-metal exchange of Ia and Ib with II. Similar reasoning has been presented by Beletskaya et al. [7] for the formation of small amounts of 4,4'-dimethoxybiphenyl from *p*-iodoanisole with PhZnCl in the presence of $\text{PdCl}_2(\text{PPh}_3)_2$ in THF/ Et_2O .

Experimental

General

All reactions were carried out under nitrogen. Organozinc halides (II) were freshly prepared from equimolecular amounts of the corresponding Grignard reagents and ZnCl_2 at room temperature in THF under nitrogen. GLC was performed (i) with a Silicone OV-17 column (2 m), with triphenylmethane was the internal standard for the reaction of I with IIa, and (ii) with a Silicone GE SE-54 column (2 m); with acenaphthene as the internal standard for the reaction of I with IIb. All the reactions products described were found to be spectrally identical with authentic samples (^1H NMR (270 MHz), ^{13}C NMR (67.9 MHz), GC-MS (60–600 m/z) and/or IR (4000–400 cm^{-1})). ^1H NMR and ^{13}C NMR spectra were recorded with a JEOL JNM-GX270 NMR spectrometer, GC-MS spectra with a Shimadzu GCMS-QP1000 gas chromatograph-mass spectrometer, and IR spectra on a Hitachi 270-30 infrared spectrophotometer.

Reaction of I with II in the presence of $\text{PdCl}_2(\text{PPh}_3)_2$

A typical procedure (Entry 8) was as follows. To a suspension of Ia (0.60 g, 3.0 mmol) and $\text{PdCl}_2(\text{PPh}_3)_2$ (0.043 g, 0.06 mmol) in HMPA (18 ml) was added freshly prepared IIb (3.6 mmol) in THF (9 ml). After having been refluxed at 100°C for 15 min, the reaction mixture was quenched with dilute aqueous HCl. The reaction products were isolated by preparative LC on silica gel with hexane/AcOEt = 5/1 as eluent. IIIba [8], m.p. 120.5–121°C (from EtOH) (lit. m.p. 119–121.5°C); R_f 0.34 (on silica gel TLC with hexane/AcOEt = 5/1). IVa (in 1% yield) [9], m.p. 189–190°C (from C_6H_6) (lit. m.p. 190–191°C); R_f 0.62 (hexane/AcOEt = 10/1).

Other reactions of I with II were carried out in the same way IIIaa [10], b.p. 95–95.5°C/0.1 Torr (lit. 167°C/33 Torr); R_f 0.56 (hexane/AcOEt = 5/1). *m*-Butylacetophenone (IIIab), b.p. 103–105°C/6 Torr; R_f 0.41 (hexane/AcOEt = 5/1); ^1H NMR (CDCl_3): δ 0.93 (t, 3H), 2.58 (s, 3H); ^{13}C NMR (CDCl_3): δ 137.2 (C-1 in Ar), 143.4 (C-3 in Ar); m/z : 176 (20%, M^+), 161 (100%, $M^+ - \text{CH}_3$), 133 (25%, $M^+ - \text{CH}_3\text{CO}$); IR (neat): 1686 cm^{-1} ($\nu(\text{C}=\text{O})$), 794 and 693 cm^{-1} ($\delta(\text{CH})$); Anal. Found: C, 81.67; H, 9.30. $\text{C}_{12}\text{H}_{16}\text{O}$ calcd.: C, 81.77; H, 9.15%. *p*-Butylbenzaldehyde (IIIac) [11], b.p. 96–98°C/5 Torr (lit. b.p. 160–165°C/44 Torr); R_f 0.56 (hexane/AcOEt = 10/1). 3-Acetylbiphenyl (IIIbb) [12], b.p. 160–164°C/3

Torr (lit. b.. 148–151°C/1 Torr); R_f 0.39 (hexane/AcOEt = 5/1). IIIbc [13], m.p. 59–60°C (from hexane) (lit. m.p. 60–61°C); R_f 0.41 (hexane/AcOEt = 5/1). IVb [14]: m.p. 123–124°C (from EtOH) (lit. m.p. 122–123°C); R_f 0.67 (hexane/AcOEt = 3/1).

Reaction of acetophenone with IIb

The reaction of acetophenone (0.37 g, 3 mmol) with freshly prepared IIb (3.6 mmol) in the presence of $\text{PdCl}_2(\text{PPh}_3)_2$ (0.043 g, 0.06 mmol) in a mixture of THF (9 ml) and HMPA (18 ml) was carried out at reflux for 60 min. (*E*)- β -Methylchalcone [15] was obtained in 58% yield; b.p. 157–162°C/1 Torr (lit. b.p. 150–155°C/1 Torr); R_f 0.64 (hexane/AcOEt = 3/1).

A reaction of benzaldehyde (0.32 g, 3 mmol) with IIb (3.6 mmol) was carried out under similar conditions, diphenylmethanol [16] was obtained in 63% yield; m.p. 67–68°C (from EtOH/H₂O) (lit. m.p. 68°C); R_f : 0.40 (hexane/AcOEt = 3/1).

The competition between benzaldehyde and bromobenzene for reaction with IIb

To a mixture of benzaldehyde (0.32 g, 3 mmol), bromobenzene (0.47 g, 3 mmol), and $\text{PdCl}_2(\text{PPh}_3)_2$ (0.043 g, 0.06 mmol) in HMPA (18 ml) was added freshly prepared IIb (3.6 mmol) in THF (9 ml) and the mixture was refluxed for 30 min. Biphenyl [17] was obtained in 76% yield; m.p. 69.5–70.5°C (from EtOH) (lit. m.p. 70.5°C); R_f 0.60 (hexane/AcOEt = 50/1). Benzaldehyde was recovered unchanged (95%).

The competition between bromobenzene (0.47 g, 3 mmol) and Ic (0.56 g, 3 mmol) for reaction with IIb (3.6 mmol) was left to take place during 15 min under similar conditions. IIIbc was obtained in 80% yield and biphenyl was formed in trace amounts. About 92% of bromobenzene remained unchanged.

The competition between benzaldehyde and bromobenzene for reaction with IIb in the absence of $\text{PdCl}_2(\text{PPh}_3)_2$

To a mixture of benzaldehyde (0.32 g, 3 mmol) and bromobenzene (0.47 g, 3 mmol) in HMPA (18 ml) was added freshly prepared IIb (3.6 mmol) in THF (9 ml) and the mixture was refluxed for 60 min. Diphenylmethanol was obtained in 61% yield and about 91% of bromobenzene was recovered unchanged.

Homo-coupling of Ib with $\text{PdCl}_2(\text{PPh}_3)_2$ and zinc dust

This reaction was attempted by way of the procedure used to make IVa from *p*-chloroacetophenone and $\text{NiCl}_2/\text{Ph}_3\text{P}/\text{Zn}$ in DMAC or DMF [6]. A suspension of Ib (0.60 g, 3 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (43 mg, 0.06 mmol), and zinc dust (0.30 g, 4.6 mmol) in a mixed solvent of THF (9 ml) and HMPA (18 ml) was refluxed for 3 h. IVb was obtained in only 0.2% yield and 93% Ib was recovered unchanged.

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References

- 1 A.T. Nielson and W.J. Houlihan, in R. Adams, A.H. Blatt, V. Boekelheide, T.L. Cairns, A.C. Cope, D.J. Cram, and H.O. House (Eds.), *Organic Reactions*, Vol. 16, John Wiley & Sons, Inc., New York, 1968, p. 1.
- 2 M. Delacre, *Bull. Acad. Roy. Belg.* (3), 20 (1898) 466; von B. Prager, P. Jacobsen, P. Schmidt, und D. Stern (Bearbeitet), *Beilsteins Handbuch der Organischen Chemie*, 4 Aufl., Bd. 7, Verlag von J. Springer, Berlin, 1943, S. 485.
- 3 For example, N. Oguni, T. Omi, Y. Yamamoto, and A. Nakamura, *Chem. Lett.*, (1983) 841; M. Kitamura, S. Suga, K. Kawai, and R. Noyori, *J. Am. Chem. Soc.*, 108 (1986) 6071; K. Soai, A. Ookawa, K. Ogawa, and T. Kaba, *J. Chem. Soc., Chem. Commun.*, (1987) 467; *J. Am. Chem. Soc.*, 109 (1987) 7111; N. Oguni, Y. Matsuda, and T. Kaneko, *J. Am. Chem. Soc.*, 110 (1988) 7877.
- 4 J.F. Fauvarque and A. Justand, *J. Organomet. Chem.*, 177 (1979) 273.
- 5 J.F. Fauvarque, F. Pflüger, and M. Troupel, *J. Organomet. Chem.*, 208 (1981) 419.
- 6 I. Colon and D.R. Kelsey, *J. Org. Chem.*, 51 (1986) 2627.
- 7 N.A. Bumagin, A.B. Ponomaryov, and I.P. Beletskaya, *J. Organomet. Chem.*, 291 (1985) 129.
- 8 H. Suzuki, *Bull. Chem. Soc. Jpn.*, 33 (1960) 613.
- 9 C.V. Ferris and E.E. Turner, *J. Chem. Soc.*, 117 (1920) 1147.
- 10 M. Sulzbacher and E. Bergman, *J. Org. Chem.*, 13 (1948) 303.
- 11 G. Tsatsas, A. Psarrea-Sandris, and C. Sandris, *Bull. Soc. Chim. Fr.*, (1964) 2615.
- 12 E. Campaigne and Wm. B. Reid, Jr., *J. Am. Chem. Soc.*, 68 (1946) 1663.
- 13 L. Gattermann, *Justus Liebigs Ann. Chem.*, 347 (1906) 381.
- 14 E. Iwata, S. Yoshikawa, S. Tsutsumi, *Kogyo Kagaku Zasshi*, 64 (1961) 463.
- 15 W. Wayne and H. Adkins, in E.C. Horning (Ed. in Chief), *Organic Syntheses*, Coll. Vol. 3, John Wiley & Sons, Inc., New York, 1955, p. 367.
- 16 F.Y. Wiselodle and H. Sonneborn, III., in H. Gilman (Ed. in Chief), *Organic Syntheses*, Coll. Vol. 1, John Wiley & Sons, Inc., New York, 1941, p. 90.
- 17 R. Fittig, *Justus Liebigs Ann. Chem.*, 121 (1862) 363.