Pergamon

Tetrahedron Letters 39 (1998) 3001–3004

TETRAHEDRON LETTERS

o-Bromophenylzinc Compound: A Readily Available and Efficient Synthetic Equivalent of *o*-Phenylene 1-Anion 2-Cation

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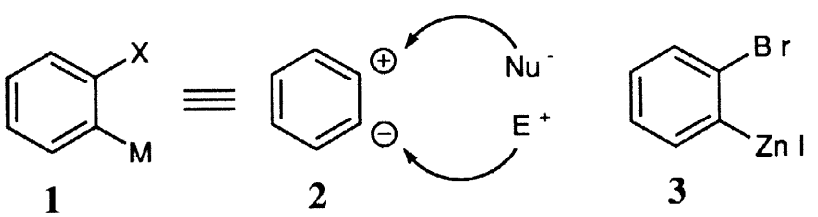
Received 22 December 1997; revised 14 February 1998; accepted 20 February 1998

Abstract: An *o*-bromophenylzinc compound, first prepared in an excellent yield by the reaction of *o*-bromoiodobenzene with zinc powder in THF, was found to be an efficient synthetic equivalent of *o*-phenylene 1-anion 2-cation in Pd(0)-catalyzed stepwise cross-coupling reactions, affording unsymmetrically 1,2-disubstituted benzenes with diverse substitution patterns and with a variety of functional groups.

o-Halophenylmetal compounds **1** formally possess two ionic carbons, whose signs are opposite to each other, at adjacent positions on the benzene ring **2**. The inherent zwitterionic character appears to make the compounds particularly attractive building blocks of the *o*-phenylene group during the convergent synthesis of unsymmetrically 1,2-disubstituted benzenes, since the incoming reagents can only react with either of the two carbons depending on the electronic property of the reagents.[1,2,3] Although such structural types of arenes are ubiquitously observed in many natural and chemical products, evaluation of a synthetic strategy based on **1** has been limited, presumably due to the lack of a suitable **1**. For example, **1** containing a conventional metal and halogen like M=Li or MgX and X=Br or I is not practically useful as a synthetic reagent because of the difficulty in its preparation and/or its sensitivity to heat.[4] We then directed our attention to utilizing easily handled Zn derivatives of Li or Mg in the light of the relatively high stability of arylzinc compounds.[5] In this communication, we report the first successful synthesis of *o*-bromophenylzinc iodide **3** and its application to Pd(0)-catalyzed cross-coupling.

Scheme 1



1 **2** **3**

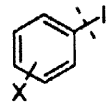
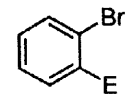
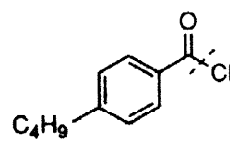
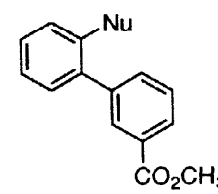
Presently, several methods are known for the preparation of arylzinc compounds.[5] Among them, we chose the straightforward method of the oxidative addition between aryl iodides and zinc powder, featuring the use of polar solvents such as HMPA, TMU, DMF, or NMP, for the attempted synthesis of **3**.[6] The reaction smoothly took place in TMU at 70 °C and reached completion in 24 h. Subsequent treatment of the resultant mixture with I_2 showed that *o*-bromoiodobenzene from **3** and *o*-diiodobenzene from the *o*-phenylenedizinc compound were

0040-4039/98/$19.00
PII: S0040-4039(98)00443-2

produced in yields of 80% and 17%, respectively, indicating that the oxidative addition of zinc powder took place not only at the bond between C-I but also at C-Br under the examined conditions.[7] To our surprise, the reaction smoothly took place in THF at 70 °C to form the desired product, **3**, in an excellent yield (95%), and uncontaminated with *o*-phenylenedizinc compound.[8] The THF solution of **3** is stable enough at room temperature to be safely stored for months.

The efficiency of **3** as a reagent producing the *o*-phenylene group **2** was examined for the Pd(0)-catalyzed cross-coupling.[9] Although the Pd(0) catalyst is known to activate both nucleophilic carbons in arylzinc compounds and electrophilic carbons in aryl bromide, and **3** contains both groups in the molecule, we were able to control the reaction sites in **3** by means of adjusting the reaction temperatures. That is, at room temperature, only the nucleophilic carbon was incorporated into the reaction with such external electrophilic reagents as aryl iodides, alkenyl iodides, alkynyl iodides or acyl chlorides. The internal electrophile was left unchanged during each run. These results are summarized in Table 1 (entries 1~7). However, at elevated temperatures of 70~85 °C, the previously remaining group took part in the Pd(0)-catalyzed cross-coupling with such external nucleophillic reagents as alkynes[10] or KCN[11] (entries 8 and 9). Thus, two different substituents are introduced onto the adjacent positions of the benzene ring with perfect regioselectivity. The stepwise cross-coupling is even attained in one flask, when arylzinc compounds are used as an external nucleophile; treatment of **3** with electrophilic reagents in the presence of Pd(0) catalyst at room temperature for 1 h and then with ArZnX at 70 °C

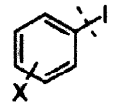
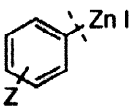
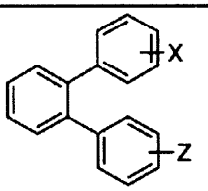
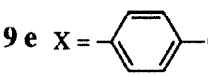
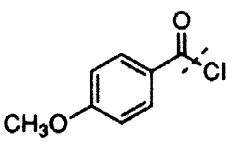
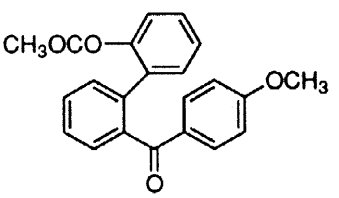
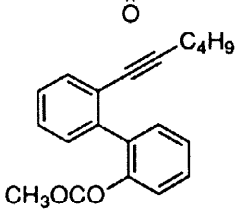
Table 1. Pd(0)-Catalyzed Cross-Coupling of **3** with E^+ and Nu^- : Step by Step Method [a]

Entry	Starting Material	E^+ or Nu^-	Product	Yield / % [b]
1	**3**	 **4 a** X = 3-NO_2	 **5 a** X = 3-NO_2	98
2		**4 b** X = 2-CO_2CH_3, 4-CH_3	**5b** X = 2-CO_2CH_3, 4-CH_3	85
3		**4 c** X = 3-CO_2CH_3	**5 c** X = 3-CO_2CH_3	94
4				95
5		C_6H_5—≡—I		84
6		 **6 a** Y = CO_2CH_3	**7 a** Y = CO_2CH_3	91
7		**6 b** Y = C_6H_{13}	**7 b** Y = C_6H_{13}	89
8	**5 c**	C_6H_5—≡—H		79
9		K^+ $^-$CN		98

[a] Reaction Conditions: $Pd(PPh_3)_4$ 2 mol%, room temperature, 1 h (entry 1~7); $Pd(PPh_3)_4$ 5 mol%, NEt_3, 70 °C, 18 h (entry 8); $Pd(dppf)_2$ 2 mol%, $Zn(CN)_2$ 5 mol%, DMF, 85 °C, 18 h (entry 9).

[b] Isolated yield.

Table 2. Pd(0)-Catalyzed Cross-Coupling of **3** with E^+ and Nu^- : One-Pot Method [a]

Entry	E^+	Nu^-	Product	Yield / % [b]
10				
	4 c X = 3-CO_2CH_3	**8 a** Z = 2-Cl	**9 a** X = 3-CO_2CH_3, Z = 2-Cl	88
11		**8 b** Z = 4-$CO_2C_2H_5$	**9 b** X = 3-CO_2CH_3, Z = 4-$CO_2C_2H_5$	93
12		**8 c** Z = 2-CO_2CH_3	**9 c** X = 3-CO_2CH_3, Z = 2-CO_2CH_3	90
13	**4 d** X = 4-OCH_3		**9 d** X = 4-OCH_3, Z = 2-CO_2CH_3	80
14	**4 e** X = 4-Br	**8 c** Z = 2-CO_2CH_3 [c]	**9 e** X =  , Z = 4-$CO_2C_2H_5$	86
15		**8 c** Z = 2-CO_2CH_3		84
16		**8 c** Z = 2-CO_2CH_3		88

[a] Reaction of **3** with E^+ was carried out at room temperature for 1 h in the presence of 2 mol% of $Pd(PPh_3)_4$. The TMU solution of Nu^- was then added to the resulting solution and the entire solution was stirred for 18 h at 70 °C. [b] Isolated yield. [c] Four equivalents of Nu^- was used.

for 18 h accomplished the selective synthesis of 2-substituted biaryls in high yields as shown in Table 2.

In conclusion, by virtue of the Zn property, the stable but potentially active *o*-halophenylmetal compound **2** has been prepared, which serves as a novel synthetic equivalent of *o*-phenylene 1-anion 2-cation as exemplified by the Pd(0)-catalyzed cross-coupling reactions.[12]

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2. **For a stepwise introduction of two different E^+** onto a synthetic equivalent of the *o*-phenylene dianion, see for example: **Kim, S-H.; Rieke, R. D.** *Tetrahedron Lett.* **1997**, 38, 993.
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7. Takagi, K.; Shimoishi, Y.; Sasaki, K. *Chem. Lett.* **1994**, 2055. We observed the formation of **3** (58%) accompanied with *o*-phenylenedizinc (12%) when a similar reaction was carried out at 30 °C for 12 h under the irradiation of ultrasound.[6]
8. THF was found to be a suitable solvent for the reaction of aryl iodides like methyl 2-iodobenzoate with zinc powder at 70 °C.
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12. Typical Procedure: Preparation of THF solution of **3**; A mixture of *o*-bromoiodobenzene (4.0 ml, 31 mmol), Zn powder (3.0 g, 45 mmol), and THF (10 ml) was stirred for 24 h at 70 °C under nitrogen to yield a 2.1 M THF solution of **3**. Sometimes, a small amount of the aryl iodide remained at this point (by GLC analysis) and, in such a case, trimethylchlorosilane (0.1 ml, 0.8 mmol) was added to the mixture and the whole mixture was stirred for an additional 24 h at the same temperature to reach completion. Using GLC analysis with heptylbenzene as the internal standard, the yield of *o*-bromoiodobenzene derived from **3** was determined to be 95% after the treatment of the resultant mixture with I_2.

    Preparation of 4"-ethyl 3-methyl 1,1':2',1"-terphenyl-3,4"-dicarboxylate (**9b**); A solution of methyl *m*-iodobenzoate (138 mg, 0.5 mmol), $Pd(PPh_3)_4$ (11.6 mg, 0.01 mmol), and the THF solution of **3** (0.25 ml, 0.5 mmol) was stirred for 1 h at room temperature under nitrogen. To the resulting solution, a 0.8 M TMU solution of *p*-ethoxycarbonylphenylzinc iodide (1.2 ml, 1 mmol)[6] was added and the entire solution was stirred for 18 h at 70 °C under nitrogen. After the conventional work-up using silica-gel column chromatography, 176 mg of 4"-ethyl 3-methyl 1.1':2',1"-terphenyl-3,4"-dicarboxylate was obtained (93 %). Mp 97-98 °C; IR (nujor) 1710, 1717 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ=1.37 (t, 3H), 3.88 (s, 3H), 4.35 (q, 2H), 7.1-8.0 (m, 12H). Found: C, 76.49; H, 5.58%. Calcd for $C_{23}H_{20}O_4$; C, 76.65; H, 5.59%.