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Consecutive cross-coupling of *o*-phenylenedizinc compound with acyl and/or aryl halides in the presence of Pd(0)-tris(2,4,6-trimethoxyphenyl)phosphine

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Abstract

Consecutive cross-coupling of an *o*-phenylenedizinc compound **1** with two different acyl or aryl halides or acyl and aryl halides was accomplished in one pot by the catalysis of Pd(0)-tris(2,4,6-trimethoxyphenyl)phosphine to yield a variety of functionalized unsymmetrical 1,2-disubstituted benzenes in good yields. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: coupling reactions; palladium and compounds; polyaryls; zinc and compounds.

Transition metal-catalyzed cross-coupling reactions of *o*-dihalobenzenes with two different organometallic compounds in a step by step manner allow the introduction of discrete substituents onto the *o*-phenylene segment, which provides one of the most important synthetic methods for 1,2-disubstituted benzenes (Fig. 1).[1] In contrast, an electronically counter process, the stepwise reactions of *o*-phenylenedimetal compounds with two electrophilic reagents, has been little studied so far, presumably because of the difficulties both in obtaining these dimetallic compounds[2] and in running the reactions regioselectively (vide infra). In the course of our study on the synthesis and the synthetic application of arylzinc compounds, we discovered that the *o*-phenylenedizinc compound **1** is readily available in a good yield through the reaction of *o*-diiodobenzene with zinc powder.[3–5] For the first time, we then examined the successive reaction of **1** with two discrete electrophilic reagents to explore for the novel access to 1,2-disubstituted benzenes.[6,7]

At the beginning, the reaction of **1** with 1 equiv. of benzoyl chloride **2a** was tried in the presence of Pd(PPh_3)$_4$ at 40°C for 3 h. I_2-Quenching of the resulting solution afforded **3a** in 70% yield along with **4a** and **5** (Scheme 1).[8] While the yields of **3a** were changed to a great extent, depending on the Pd(0) complexes used,[9] the Pd(0) complex containing tris(2,4,6-trimethoxyphenyl)-phosphine ligand (Pd(0)-TTMOP) dramatically increased the yield of **3** (98%). A similar high

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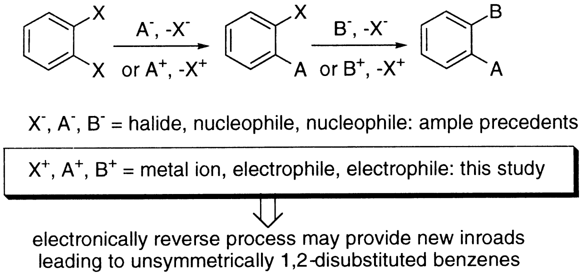
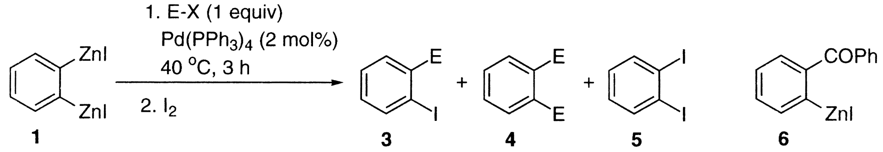


Figure 1. Stepwise reaction of 1,2-disubstituted benzenes

degree of regioselectivity was realized by this Pd(0) catalyst in the reaction of **1** with iodobenzene **2b** as the electrophilic reagents: **3b** was obtained in 86% yield along with a 4% yield of **4b**. On the other hand, the $Pd(PPh_3)_4$ catalyst afforded the two products in 60 and 12% yield, respectively (Scheme 1). Significantly, the catalytic activity of the Pd(0) complex remained after the first step reaction was completed. Hence, whenever an additional portion of electrophilic reagent was added to the resulting mixture, catalytic reactions smoothly took place, enabling the introduction of an electrophile onto the intermediary compounds like **6** as the second side chain. The results using various acyl halides and/or aryl halides as the electrophilic reagents are summarized in Table 1. It is noted that both aryl iodides and acyl chlorides, including ones containing functional groups such as cyano, alkoxycarbonyl, chloro, or alkoxy, are arbitrarily available as the first and/or the second electrophilic reagents. As the first reagent, a divalent one like **7** or **8** was also available. Therefore, novel polyaryl compounds **9** or **10** were readily obtained by the Pd(0)-TTMOP catalyzed reaction of **1** with **7** or **8** (molar ratio of **7** or **8**/**1** = 0.5), followed by the subsequent treatment of the resulting mixture with the second electrophilic reagent (molar ratio of **2a**/**1** = 2), respectively (Scheme 2).



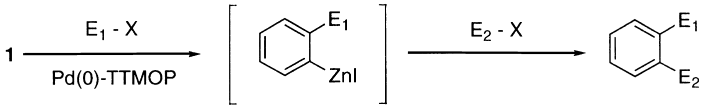
E−X		3 (yield / %)	4 (yield / %)	5 (yield / %)
PhCO—Cl	**2a**	**3a** (70)	**4a** (14)	(14)
Ph—I	**2b**	**3b** (60)	**4b** (12)	(7)

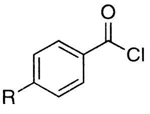
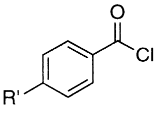
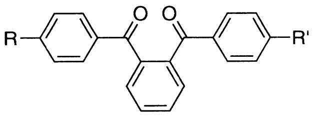
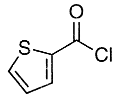
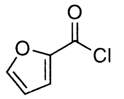
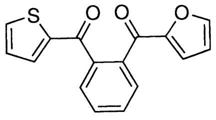
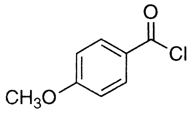
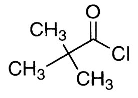
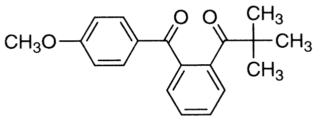
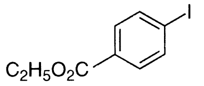
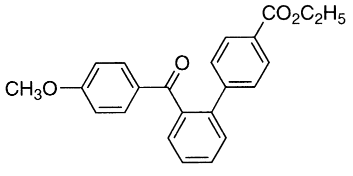
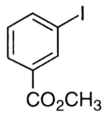
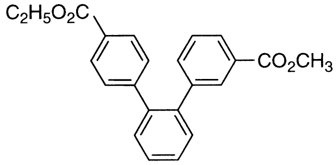
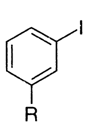
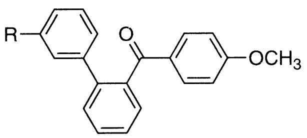
Scheme 1.

In summary, an efficient and facile method for the introduction of aryl and/or acyl side chains onto the *o*-phenylene segment has been established, which provides new methods to functionalized arenes, characterized by the novelty in the electronic properties of the coupling partners.

Representative experimental procedure: to the mixture prepared by the reaction of $PdCl_2(CH_3CN)_2$ (0.0033 mmol), TTMOP (0.13 mmol), and Zn powder (0.13 mmol), in *N*,*N*,*N*′,*N*′-tetramethylurea (TMU) (0.75 mL) at ambient temperature for 30 min and then for 30 min at 40°C under nitrogen, 2-thienoyl chloride (1.65 mmol) and the 1.8 mL-TMU solution of **1** (1.5 mmol)[3] were successively

Table 1
Pd(0)-TTMOP-catalyzed consecutive cross-coupling of **1** with two discrete acyl and/or aryl halides[a]



Entry	E_1 - X	E_2 - X	Product		Yield / %[b]
1 2 3				R, R' = CN, H C_4H_9, CH_3O OCH_3, H	73 70 90
4					77
5	 **2b**				50
6	**2b**	 **2c**			84
7	**2c**				92
8 9		**2b**		R = CF_3 Cl	82 69

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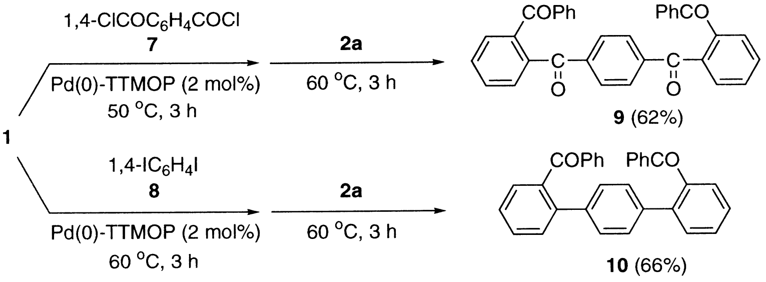
[a] Molar ratio: **1** / E_1-X / E_2-X / Pd(0)-TTMOP = 1 / 1.1 / 2 / 0.02, 40 °C, 3h (for 1st step of entries 1-9 and 2nd step of entries 1-3, 5, 8, and 9), 50 °C, 3h (for 2nd step of entry 4), 60 °C, 3h (for 2nd step of entry 6), or 80 °C, 3h (for 2nd step of entry 7).

[b] Isolated yield.



Scheme 2.

added and stirred for 3 h at 40°C. To the resulting mixture, furoyl chloride (3.0 mmol) was added and stirred at 50°C for 3 h. After the treatment of the resulting mixture with aqueous HCl, the ether extract was chromatographed on a silica-gel column, affording 325 mg of 2-furyl 2-(2-thienylmethanoyl)phenyl ketone (77%). Mp 158–160°C; IR 1652 cm^{-1}; ^{1}H NMR: δ 6.50 (dd, $J=3.6$ and 1.7 Hz, 1H), 7.0–7.1 (m, 2H), 7.4–7.8 (m, 7H). Anal. calcd for $C_{16}H_{10}O_3S$: C, 68.07; H, 3.57. Found: C, 68.0; H, 3.6.

References

1. For recent examples, see: (a) Ernst, A.; Gobbi, L.; Vasella, A. *Tetrahedron Lett.* **1996**, *37*, 7959. (b) Rottlander, M.; Palmer, N.; Knochel, P. *Synlett* **1996**, 573. (c) Powell, N. A.; Rychnovsky, S. D. *Tetrahedron Lett.* **1996**, *37*, 7901. (d) Haley, M. H.; Bell, M. L.; English, J. J.; Johnson, C. A.; Weakley, T. J. R. *J. Am. Chem. Soc.* **1997**, *119*, 2956. (e) Kojima, A.; Honzawa, S.; Boden, C. D. J.; Shibasaki, M. *Tetrahedron Lett.* **1997**, *38*, 3455. (f) Balavoine, F.; Madec, D.; Mioskowski, C. *Tetrahedron Lett.* **1999**, *40*, 8351. (g) Bowles, D. M.; Anthony, J. E. *Organic Lett.* **2000**, *2*, 85.
2. Okano, M.; Amano, M.; Takagi, K. *Tetrahedron Lett.* **1998**, *39*, 3001 and references cited therein.
3. Takagi, K.; Shimoishi, Y.; Sasaki, K. *Chem. Lett.* **1994**, 2055 and references cited therein.
4. Goedheijt, M. S.; Nijbacker, T.; Akkerman, O. S.; Bickelhaupt, F.; Veldman, N.; Spek, A. L. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1550.
5. Amano, M.; Saiga, A.; Ikegami, R.; Ogata, T.; Takagi, K. *Tetrahedron Lett.* **1998**, *39*, 8667.
6. For the introduction of two different electrophiles onto the adjacent carbons of the benzene, pyridine, thiophene, or pyrolle ring via the stepwise generation of organometallic compounds followed by the treatment with electrophilic reagents at one reaction center and then at another reaction center, see: (a) Takahashi, M.; Hatano, K.; Kawada, Y.; Koga, G.; Tokitoh, N.; Okazaki, R. *Chem. Commun.* **1993**, 1850. (b) Takahashi, M.; Hatano, K.; Kimura, M.; Watanabe, T.; Oriyama, T.; Koga, G. *Tetrahedron Lett.* **1994**, *35*, 579. (c) Gu, Y. G.; Bayburt, E. K. *Tetrahedron Lett.* **1996**, *37*, 2565. (d) Kim, S.-H.; Rieke, R. D. *Tetrahedron Lett.* **1997**, *38*, 993. (e) Banwell, M. G.; Flynn, B. L.; Hamel, E.; Hockless, D. C. R. *Chem. Commun.* **1997**, 207.
7. Frid, M.; Perez, D.; Peat, A. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9469.
8. The present results are far from satisfactory because the purification of the intermediary compound **6**, prior to the treatment with the second electrophiles, is not possible from a practical point of view.
9. Yields of **3a** and **4a** (utilized ligand): 35, 26 (tris(perfluorophenyl)phosphine); 75, 6 (tris(2-trifluoromethylphenyl)-phosphine); 48, 15 (tri-2-furylphosphine); 62, 15 (triphenylarsine) 91, 2 (tri(*o*-tolyl)phosphine). A very different effect of ligands was observed in the Pd(0)-catalyzed stepwise reaction of bis(iodozincio)methane with two different electrophiles. See: Utimoto, K.; Toda, N.; Mizuno, T.; Kobata, M.; Matsubara, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2804.