

Selective Dehalogenative Homocoupling of Haloarylsulfonates by the Use of Palladium Catalyst

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The palladium catalyzed dehalogenative homocoupling of haloarylsulfonates under reductive conditions has proceeded selectively depending on the type of the halogen. Thus, an iodo or a bromo leaving group of haloarylsulfonates was homocoupled to give symmetrical biaryls in good yields with the sulfonate group intact, whereas a chloro leaving group gave no reaction under the conditions used. When the more reactive nickel catalyst was employed instead of the palladium catalyst in the reaction, both dehalogenative and desulfonative homocouplings of haloarylsulfonates occurred regardless of the type of the halogen used.

Keywords : Palladium catalyst, Nickel catalyst, Haloarylsulfonate, Homocoupling.

Introduction

The use of transition-metal complexes as catalysts for aromatic carbon-carbon bond forming reactions has attracted the interest of synthetic organic chemists, since a variety of organic and organometallic substrates can be used.¹ Among the Group 10 triad (Ni, Pd and Pt) of transition metals, palladium has been used extensively to promote the various cross-coupling reactions for preparing unsymmetrical biaryls.¹ Nickel catalyzed Ullmann-type homocoupling reactions have been employed to give symmetrical biaryls.² The use of palladium catalysts to run the homocoupling reaction of aryl halides also has been reported in the literature.³ However, the relatively low yield and the requirement of drastic reaction conditions for palladium catalyzed homocoupling reactions greatly limit its practical applications in organic synthesis.

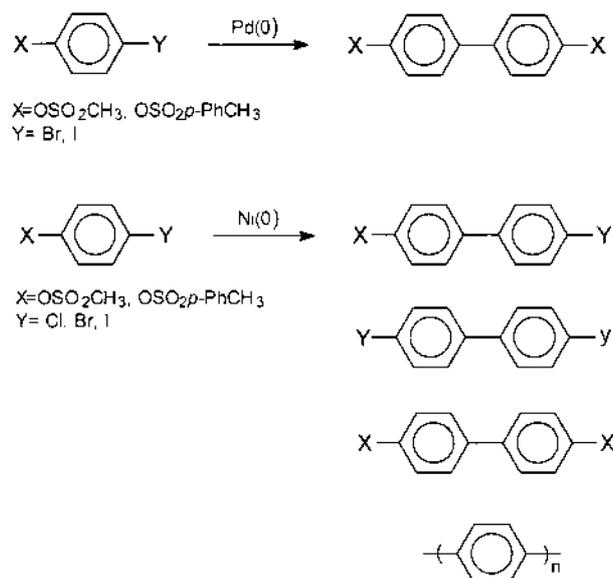
Aryl halides and sulfonates are important substrates in transition metal (particularly palladium) catalyzed coupling reactions.¹ Most palladium catalyzed reactions with aryl halides employ aryl bromides and iodides. Aryl chlorides usually do not undergo palladium catalyzed coupling reactions even under drastic conditions, because oxidative addition of nonactivated aryl chlorides to the Pd(0) species is slow, and premature decomposition of the catalyst is frequently encountered. Therefore, most coupling reactions of nonactivated aryl chlorides require nickel catalyst, because zero-valent nickel can activate the carbon-chlorine bond.² Similarly, most palladium catalyzed reactions with aryl sulfonates use rather expensive aryl triflates. The less reactive aryl mesylates and arenesulfonates usually require nickel instead of palladium in most coupling reactions.⁵

In the present study, efforts have been made to expand the scope of palladium catalyzed homocoupling reactions by seeking an efficient catalyst system to selectively homocouple the substrates which have two different leaving groups (*i.e.*, halogen and sulfonate), as well as a suitable starting material. We report in the present study that the use of

$\text{PdCl}_2(\text{PPh}_3)_2$ among various palladium catalysts in combination with zinc as a reducing agent could selectively homocouple the halo leaving group of haloarylsulfonates with the sulfonate group intact; only dehalogenative homocoupling of haloarylsulfonates containing an iodo or a bromo leaving group occurred, with the unreacted starting substrate fully recovered, whereas a chloro leaving group gave no reaction under the conditions used (Scheme 1). However, when nickel was used as a catalyst, a major side reaction, producing insoluble poly(*p*-phenylene) was observed.

Experimental Section

Techniques. Melting points are uncorrected and were determined with a Thomas Hoover Uni-Melt capillary melting point apparatus. ¹H NMR (500-MHz) spectra were



Scheme 1. Synthetic Scheme of Palladium and Nickel Catalyzed Homocoupling Reaction of Haloarylsulfonates.

recorded on a Varian Unity Inova Spectrometer in CDCl_3 and with tetramethylsilane (TMS) as an internal standard. Thin layer chromatograph (TLC) analyses were performed on polyester sheets precoated with 0.25 mm-thick silica gel containing a 254 nm indicator (Kodak 13181). Elemental analyses were obtained with a Yanaco MT-3 CHN-Analyzer.

Materials. All reagents were purchased from commercial sources (Aldrich or TCI) and used without further purification unless otherwise noted. Dimethylformamide (DMF) was dried over CaH_2 and vacuum distilled. Tetrahydrofuran (THF) was distilled over sodium/benzophenone. $\text{NiCl}_2(\text{PPh}_3)_2$ was prepared according to the literature procedure.⁴ Zinc dust was stirred in acetic acid, washed with water and dried *in vacuo* at 120 °C. Triphenylphosphine was recrystallized from EtOH.

Haloarylsulfonates. All haloarylsulfonates were prepared by the reaction of *p*-toluene sulfonyl chloride or methane sulfonyl chloride with the corresponding halophenols in pyridine (Scheme 2).⁵ Only representative examples are given here.

4-Iodophenyl *p*-toluene sulfonate: *p*-Toluene sulfonyl chloride (17.7 mmol) was added slowly to a solution of 4-iodophenol (13.6 mmol) in pyridine (20 mL) at 25 °C. The solution was stirred for 30 h. Then, the reaction mixture was poured into aqueous HCl and the resulting precipitate was collected, washed with H_2O , and recrystallized from a mixture of CHCl_3 and *n*-hexane, yielding white crystals: yield 72%; mp 90–92 °C; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 2.45 (s, 3H, $-\text{CH}_3$), 6.73 (d, $J = 8.50$ Hz, 2H, ortho to iodo), 7.35 (d, $J = 8.50$ Hz, 2H, ortho to $-\text{CH}_3$), 7.59 (d, $J = 8.50$ Hz, 2H, meta to iodo), 7.69 (d, $J = 8.50$ Hz, 2H, meta to $-\text{CH}_3$). Anal. Calcd for $\text{C}_{13}\text{H}_{11}\text{O}_3\text{SI}$: C, 41.73; H, 2.96. Found: C, 42.02; H, 2.90.

4-Bromophenyl *p*-toluene sulfonate: yield 80%; white crystals (CHCl_3/n -hexane); mp 74–76 °C; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 2.45 (s, 3H, $-\text{CH}_3$), 6.86 (d, $J = 9.07$ Hz, 2H, ortho to bromo), 7.32 (d, $J = 8.22$ Hz, 2H, ortho to $-\text{CH}_3$), 7.40 (d, $J = 9.07$ Hz, 2H, meta to bromo), 7.69 (d, $J = 8.22$ Hz, 2H, meta to $-\text{CH}_3$). Anal. Calcd for $\text{C}_{13}\text{H}_{11}\text{O}_3\text{SBr}$: C, 47.72; H, 3.39. Found: C, 48.22; H, 3.31.

4-Iodophenyl methane sulfonate: yield 74%; white crystals (CHCl_3/n -hexane); mp 66–68 °C; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 3.15 (s, 3H, $-\text{CH}_3$), 7.05 (d, $J = 9.07$ Hz, 2H, meta to mesylate), 7.43 (d, $J = 9.07$ Hz, 2H, ortho to mesylate). Anal. Calcd for $\text{C}_7\text{H}_7\text{O}_3\text{SI}$: C, 28.20; H, 2.37. Found: C, 29.20; H, 2.80.

4-Bromophenyl methane sulfonate: yield 87%; white crystals (CHCl_3/n -hexane); mp 78–80 °C (lit.⁶ mp 78–80 °C); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 3.15 (s, 3H, $-\text{CH}_3$), 7.17 (d, $J = 9.07$ Hz, 2H, meta to mesylate), 7.54 (d, $J = 9.07$ Hz, 2H, ortho to mesylate). Anal. Calcd for $\text{C}_7\text{H}_7\text{O}_3\text{SBr}$: C, 33.48; H, 2.80. Found: C, 32.32; H, 2.96.

General procedure for Pd(0) catalyzed homocoupling.

As a typical procedure, a 125 mL schlenk tube was charged with 4-iodophenyl *p*-toluene sulfonate (0.534 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (0.080 mmol), PPh_3 (0.160 mmol), Zn powder (1.602 mmol) and a magnetic stirring bar. After the tube was

sealed with a rubber septum, the contents were dried at 25 °C under reduced pressure (1×10^{-3} mmHg) for 24 h. Then the tube was filled with N_2 . Freshly distilled DMF (1.0 mL) was added via a syringe through the rubber septum. The reaction mixture was stirred at 95 °C for 24 h. The mixture was then cooled to 25 °C, poured into aqueous HCl solution. The resulting precipitate was collected and recrystallized from a mixture of acetone and *n*-hexane to give white crystals (67%).

General procedure for Ni(0) catalyzed homocoupling.

As a typical procedure, a 125 mL schlenk tube was charged with 4-iodophenyl *p*-toluene sulfonate (0.534 mmol), $\text{NiCl}_2(\text{PPh}_3)_2$ (0.080 mmol), PPh_3 (0.160 mmol), Zn powder (1.602 mmol), Et_3NI (0.80 mmol) and a magnetic stirring bar. After the tube was sealed with a rubber septum, the contents were dried at 25 °C under reduced pressure (1×10^{-3} mmHg) for 24 h. Then the tube was filled with N_2 . Freshly distilled THF (1.0 mL) was added *via* a syringe through the rubber septum. The reaction mixture was stirred at 67 °C for 24 h. The mixture was then cooled to 25 °C, poured into aqueous HCl solution. The resulting precipitate was collected and recrystallized from a mixture of acetone and *n*-hexane to give white crystals (64%).

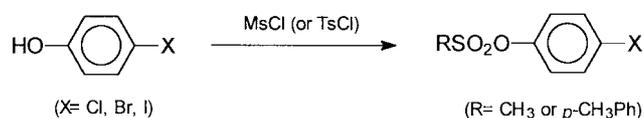
Biaryls.

4,4'-Bis[*p*-toluene sulfonyloxy]biphenyl: yield 67%; white crystals (acetone/*n*-hexane); mp 184–188 °C (lit.⁷ mp 186 °C); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 2.46 (s, 6H, $-\text{CH}_3$), 7.04 (d, $J = 8.79$ Hz, 4H, meta to tosylate), 7.32 (d, $J = 8.50$ Hz, 4H, ortho to $-\text{CH}_3$), 7.42 (d, $J = 8.79$ Hz, 4H, ortho to tosylate), 7.74 (d, $J = 8.50$ Hz, 4H, meta to $-\text{CH}_3$). Anal. Calcd for $\text{C}_{26}\text{H}_{22}\text{O}_6\text{S}_2$: C, 63.14; H, 4.48. Found: C, 63.00; H, 4.90.

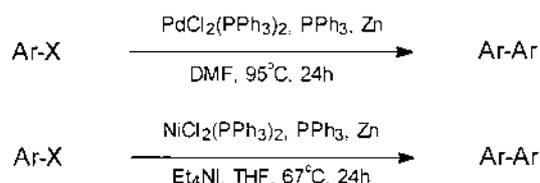
4,4'-Bis[(methyl sulfonyloxy)biphenyl: yield 70%; white crystals (acetone/*n*-hexane); mp 186 °C (lit.⁸ mp 186 °C); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 3.19 (s, 6H, $-\text{CH}_3$), 7.38 (d, $J = 8.79$ Hz, 4H, meta to mesylate), 7.58 (d, $J = 8.79$ Hz, 4H, ortho to mesylate). Anal. Calcd for $\text{C}_{14}\text{H}_{14}\text{O}_6\text{S}_2$: C, 49.11; H, 4.12. Found: C, 48.72; H, 3.98.

Results and Discussion

Sulfonates of various halophenols were prepared by the reaction of *p*-toluene sulfonyl chloride or methane sulfonyl chloride with the corresponding halophenols (Scheme 2). The homocoupling reactions of haloarylsulfonates were mediated by Pd(0) or Ni(0) catalyst in the presence of triphenylphosphine, excess zinc (and/ or Et_3NI) in DMF (or THF) (Scheme 3). As reported previously, palladium catalyzed homocoupling reactions usually employ palladium acetate^{10a} (or palladacycle^{10b}) in conjunction with tertiary amine as a base. In our study, however, a new catalytic sys-



Scheme 2. Synthesis of Haloarylsulfonates.


Scheme 3. Homocoupling Reactions of Aryl Halides Using Pd(0) or Ni(0) Catalyst.

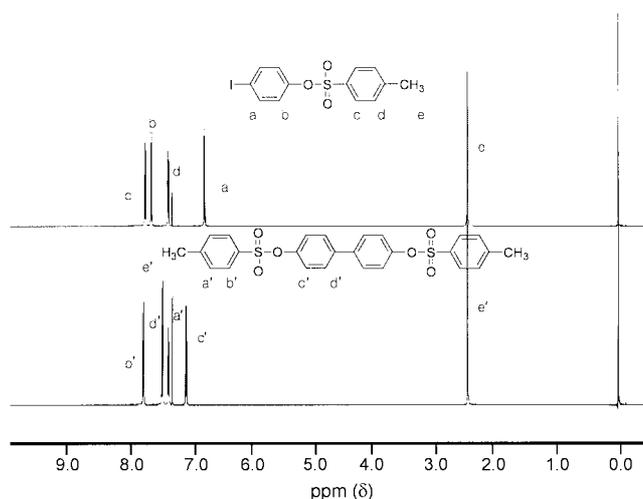
tem using PdCl₂(PPh₃)₂ and zinc was developed to promote the homocoupling reactions of haloarylsulfonates. The nickel catalyzed homocoupling method used in this study is reported in the literature.⁵

An initial series of homocoupling experiments of haloarylsulfonates employing various reaction conditions was attempted to evaluate the effect of Ni(0) and Pd(0) catalysts in homocoupling. Since Ni(0) catalyst can be decomposed easily even by a trace of water, the addition of excess amounts of ligand and co-catalyst (0.3 equiv of PPh₃ and 1.5 equiv. of Et₄NI) was essential to obtain high yields of the coupling product. In particular, the use of Et₄NI as the promoter to run the homocoupling of aryl halides was required to achieve good yields. In the absence of this promoter, the early precipitation of black nickel during the reaction was observed. In the Pd(0) catalytic system, however, the addition of extra phosphine ligand diminished the reactivity of active zerovalent palladium by forming the stable metal-ligand complex to give the reduced yields. The results from Table 1 show that the choice of catalytic system is important in the homocoupling reaction with haloarylsulfonates containing two reaction sites (*i.e.*, one is halogen and the other is sulfonate group). Pd(0) catalyst is assumed to activate the carbon-halogen bond (especially, C-I and C-Br bonds) but not the carbon-oxygen bond, whereas the more reactive Ni(0) catalyst can activate both.¹ As expected, the reaction at the phenolic site did not occur at all when palladium was used as a catalyst. The use of PdCl₂(PPh₃)₂ in the reaction of

Table 1. Pd(0) or Ni(0) Catalyzed Homocoupling of Various Aryl Halides Containing Sulfonate Groups

| Entry | X | Y | Catalyst | Solvent | Temp. (°C) | Yield (%) ^a |
|-------|-----|----|---|---------|------------|------------------------|
| 1 | OTs | I | PdCl ₂ (PPh ₃) ₂ | DMF | 95 | 67 |
| 2 | OTs | Br | PdCl ₂ (PPh ₃) ₂ | DMF | 95 | 38 |
| 3 | OTs | Cl | PdCl ₂ (PPh ₃) ₂ | DMF | 95 | trace |
| 4 | OMs | I | PdCl ₂ (PPh ₃) ₂ | DMF | 95 | 49 |
| 5 | OMs | Br | PdCl ₂ (PPh ₃) ₂ | DMF | 95 | 35 |
| 6 | OMs | Cl | PdCl ₂ (PPh ₃) ₂ | DMF | 95 | trace |
| 7 | OTs | I | NiCl ₂ (PPh ₃) ₂ ^b | THF | 67 | 64 |
| 8 | OTs | Br | NiCl ₂ (PPh ₃) ₂ ^b | THF | 67 | 44 |
| 9 | OTs | Cl | NiCl ₂ (PPh ₃) ₂ ^b | THF | 67 | trace |
| 10 | OMs | I | NiCl ₂ (PPh ₃) ₂ ^b | THF | 67 | 50 |
| 11 | OMs | Br | NiCl ₂ (PPh ₃) ₂ ^b | THF | 67 | 33 |
| 12 | OMs | Cl | NiCl ₂ (PPh ₃) ₂ ^b | THF | 67 | trace |

^aIsolated Yield. ^b1.5 equiv. of Et₄NI was added.


Figure 1. ¹H NMR Spectra of 4-Iodophenyl *p*-Toluene Sulfonate and 4,4'-Bis[(*p*-toluenesulfonyl)oxy]biphenyl.

iodo- and bromophenyl *p*-toluenesulfonates produced the biaryls in 67% and 38% isolated yields, respectively (entries 1-2). Actually, the tosylate group was found to remain intact under this reaction condition, as determined by GC and ¹H-NMR analysis. The ¹H NMR spectrum of the resulting biaryls shows the sulfonate group unreacted (Figure 1). However, we did not have any success when chlorophenyl *p*-toluene sulfonate was used in the reaction (entry 3) as reported in the literature.^{10a} In the case of the homocoupling of iodophenylsulfonates with Pd(0) in DMF (entries 1 and 4), the reaction did not go to completion under the given experimental conditions (67% with tosylate and 49% with mesylate). However, the resulting reaction mixture contained the homocoupled products and the unreacted starting materials with a trace amount of side reaction products, such as sulfonate homocoupled products, which implies that the reaction proceeded smoothly with the sulfonate group intact. To increase the yield, the more reactive Ni(0) catalyst was used in the reaction instead of Pd(0) (entries 7 and 10). Although this did not enhance the yield, a substantial change in the product distribution was observed: the Ni(0) activates not only the C-I bond but also the C-O bond, resulting in the formation of insoluble oligomeric poly(*p*-phenylene). The polymer obtained was not soluble in common solvents such as chloroform, THF and DMSO. Employing other substrates such as bromophenyltosylate and bromophenylmesylate also resulted in the same trends (entries 2, 5, 8, and 11). However, using the Pd(0) catalyst substantially suppressed the side reaction giving only the homocoupled product.

In general, the order of reactivity of aryl halides with Pd(0) is ArI > ArBr >> ArCl,⁹ and the reactivity of zerovalent d¹⁰ transition metal complexes toward oxidative addition of aryl halides is known to decrease significantly in the order of Ni > Pd > Pt.¹⁰ This trend was also found in our studies. Table 1 shows the effect of various halogens and sulfonates as leaving groups, from which it can be found that the yield increases as the more reactive halogen was intro-

duced in the substrate (entries 1-3). Although we observed much difference in yields with variation of the halo leaving groups, both tosylate and mesylate groups gave similar coupling results (entries 1 and 4).

Conclusions

In summary, iodoarylsulfonates and bromoarylsulfonates undergo reductive homocoupling of carbon-halogen bond to produce biaryls in relatively high yields in the presence of a catalytic amount of PdCl₂(PPh₃)₂ and zinc in DMF at 95 °C. Under similar reaction conditions, chloroarylsulfonates give no reaction. When the more reactive nickel catalyst instead of palladium catalyst was employed in the reaction, both dehalogenative and desulfonative homocouplings of haloarylsulfonates occurred regardless of the type of the halogen used. In Ni(0) catalyzed homocoupling reactions, the mesylate or tosylate leaving group can participate in the coupling reaction. Thus, the product contains the insoluble by-products (*i.e.*, desulfonatively homocoupled products).

It was of obvious interest to extend the synthetic tool developed in the present study to other applications, such as the Pd-catalyzed synthesis of poly(phenylene)s, with tosylate or mesylate functional groups in their backbone, based on AB₂ type phenolic monomers containing two halo groups (especially, bromo groups) and one tosylate (or mesylate) group.¹¹ In this case, the tosylate or mesylate group can be used as a solubilizing substituent, not a leaving group, toward the palladium catalyzed couplings, resulting in the reaction of only halo groups.

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