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Desulfinylative Pd-catalyzed coupling reaction of arenediazonium salt with aryl sulfinates to give unsymmetrical biaryls

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ABSTRACT

An efficient route for the synthesis of unsymmetrical biaryls was developed via palladium catalyzed reaction of arenediazonium salts and aryl sulfinates under inert atmosphere. This synthesis involves cascade processes. Tetrabutylammonium iodide was used as an iodide source for in situ formation of aryl iodide, followed by desulfinylative cross-coupling reaction between aryl sulfinates and aryl iodides. A wide range of biaryls were selectively prepared in one pot from simple substrates in good to excellent yields.

Introduction

A palladium-catalyzed cross-coupling reaction is one of the most applied synthetic methods for the construction of carbon-carbon (C—C) bonds.[1] The importance of biaryls, especially for their applications in the synthesis of natural products, organic semiconductors, nonlinear optics, synthesis of herbicides, medicinal chemistry and conducting polymers[2] is well known. The most common approaches to prepare biaryls include traditional cross-coupling reactions such as Suzuki,[3] Stille[4] and Hiyama.[5] The examples of few top selling drug molecules, highlighting the biaryl core present in these molecules are given below[6] (Fig. 1).

Some of the previous reported methods for the synthesis of biaryls by using transition metal-catalyzed homocoupling reactions are presented below (Fig. 2).

Palladium-catalyzed desulfitative cross-coupling of arylsulfinates with arylboronic acids[7a] (Fig. 2, route a), palladium catalyzed desulfinylative couplings between aryl sulfinates and aryl iodide for the synthesis of biaryls[7b] (Fig. 2, route b), catalytic desulfitative homocoupling of sodium arylsulfinates in water using $PdCl_2$ as the recyclable catalyst and O_2[7c] (Fig. 2, route c), palladium-catalyzed Hiyama type cross coupling reactions of arenesulfinates with organosilanes[7d] (Fig. 2, route d), Ni- or Co-catalyzed cross-coupling of arylsulfonic acid salts with RMgX[7e] (Fig. 2, route e) and Pd/C catalyzed coupling of arenediazonium salts with potassium aryltrifluoroborates[7f] (Fig. 2, route f) are previous reported methods for the synthesis of biaryls. Aromatic diazonium salts are highly attractive synthetic alternatives to the corresponding aromatic halides, which exhibit higher reactivity. They are also good arylating agents. They are easy to handle, stable and can be conveniently prepared from anilines.[8] Several groups have reported the synthesis of organic compounds by using arenediazonium salts in various coupling reactions,[9] such as Suzuki-Miyaura,[10] Stille,[11] Sonogashira[12] and Mizoroki-Heck reactions.[13]

In the past few decades, aryl sulfinates have been shown to be more reactive substrates for the synthesis of various aromatic compounds.[14] Cu- or Pd-catalyzed cross-coupling reactions of sulfinate salts with disulfides,[15] phenylacetylene,[16] aryl halide,[17] aryl boronic acid,[18] azoles,[19] phenylethylene[20] and arenediazonium salts[21] are also reported. Therefore, in this work, we describe the alternative path for the synthesis of biaryls using arenediazonium salts and sodium arylsulfinates as starting materials, $Pd(dppf)Cl_2$ as catalyst, $P(OPh)_3$ as ligand and TBAI as iodine source. The reaction proceeds in DMF at 150 °C under inert atmosphere (Scheme 1).

Results and discussion

The reaction conditions were optimized by carrying out the coupling reaction of 4-Methoxybenzenediazonium tetrafluoroborate with sodium arylsulfinates.

Initially we screened various palladium sources as a catalyst for model reaction by employing $PdCl_2$, $Pd(OAc)_2$, $Pd(PPh_3)_4$ and Pd

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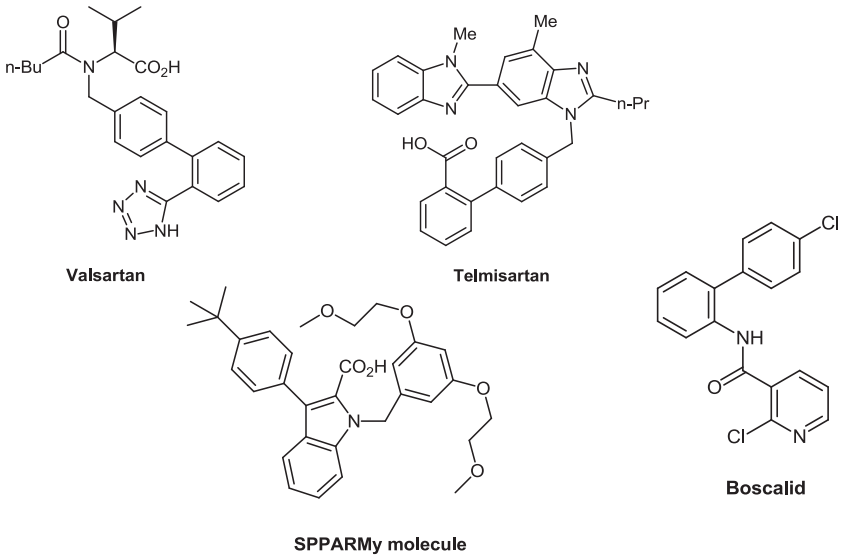


Fig. 1. Drug molecules containing the biaryl core.

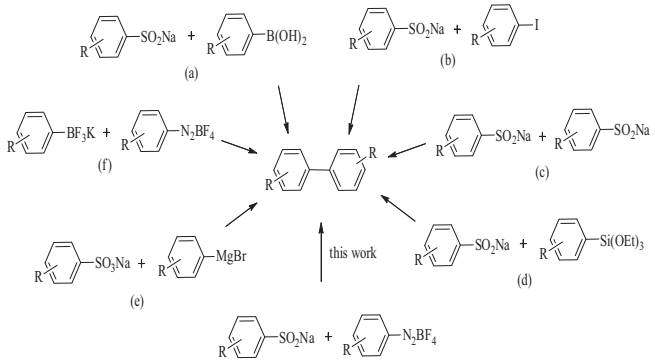
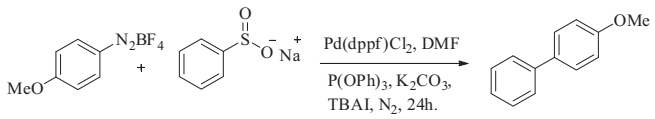


Fig. 2. Synthesis of biaryls by using metal catalyzed coupling methods.



Scheme 1. Reaction between 4-Methoxybenzenediazonium tetrafluoroborate and sodium aryl sulfinate.

$(dppf)Cl_2$ as catalyst (Table 1, entries 1–4). In the course of this study, it was found that $Pd(dppf)Cl_2$ is the best catalyst as it afforded maximum yield (81%) of the desired product. Phosphine ligand plays a very crucial role in homogeneous palladium catalysis. Here we screened various ligands such as triphenyl phosphite [$P(OPh)_3$], Tri(o-tolyl)phosphine and triphenyl phosphine [$P(Ph)_3$] (Table 1, entries 4–6) and the best results were obtained when the reaction was carried out with $Pd(dppf)Cl_2$ as a catalyst and triphenyl phosphite as the ligand. We also examined the effect of various bases by employing K_2CO_3, Na_2CO_3, CS_2CO_3 and $NaHCO_3$ (Table 1, entries 4, 8, 9 & 10). Potassium carbonate was found to be the most effective base in the model reaction.

We also performed model reaction with various halogen sources (to form the aryl halide in situ) such as TBAI (Tetrabutylammonium iodide), KI (Potassium iodide) and TBAB (Tetrabutylammonium bromide) (Table 1, entries 4, 11 & 12). The results clearly show that TBAI is the most suitable halogen source giving maximum product yield. The optimum temperature was found to be 150 °C for the model reaction. Increase in temperature to 160 °C, did not improve the product yield, whereas significant decrease in the product yield was observed when the temperature was decreased to 140 °C (Table 1, entries 4, 13 & 14). All above experiments reveal that the optimized reaction conditions are 4-Methoxybenzenediazonium tetrafluoroborate (0.8 mmol), sodium arylsulfinates (0.5 mmol), $Pd(dppf)Cl_2$ (2.5 mol%), $P(OPh)_3$ (5 mol%), TBAI (0.8 mmol), K_2CO_3 (1.0 mmol), DMF (2 mL), 150 °C temperature and 24 h reaction time under inert atmosphere.

After optimizing all parameters such as catalyst, ligand, base, additive and reaction temperature, we further investigated the catalytic activity for the coupling of structurally different arenediazonium salts and aryl sulfinates as substrates under the optimized reaction conditions. The results are shown in Table 2.

Arenediazonium salts with many valuable functional groups present on aromatic ring such as $-OCH_3$, $-CH_3$, -Cl and -F groups were screened to give the desired unsymmetrical biaryl (Table 2, entries 1–14). Aryl sulfinates coupled smoothly with arenediazonium salts bearing both electron-deficient and electron-rich substituents, to afford the corresponding products in good to excellent yields. It was observed that substrates containing electron donating group deliver excellent products as compared to substrates containing withdrawing groups. It was also observed that the substituent at *para*-position exhibits greater reactivity than *ortho*- or *meta*-position, which might be due to steric factors.

The proposed reaction mechanism for synthesis of biaryls is illustrated in Fig. 3

The reaction proceeds in three sequential steps as oxidative addition, transmetalation and reductive elimination.

The palladium(0) compound required in this cycle is generally prepared in situ from a $Pd(dppf)Cl_2$(II) precursor, which is reduced by triphenylphosphite to Pd(0). Further, arenediazonium salt in presence of TBAI form aryl iodide, which immediately undergoes oxidative addition with the Pd(0) species to give the aryl–Pd complex.

A weakly coordinated halide ion, is replaced by sulfinate to produce sulfinato-complex. Then the reaction proceeds via the direct extrusion of SO_2 to yield bis-arylated species. Finally, reductive