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PALLADIUM-CATALYZED CROSS-COUPLING REACTION OF 4-METHYLTHIAZOLE AND 2-TRIMETHYLSILYLTHIAZOLES WITH BIARYL TRIFLATES

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Abstract – 2-Trimethylsilylthiazoles serve as an efficient counterpart for direct palladium-catalyzed cross-coupling reaction with aromatic triflates without any fluoride anion source to afford 2-arylthiazoles.

Thiazoles are among the most important heteroaromatics with pharmaceutical importance and as starting material of thiazolium salts, which attract attention for their utility as organocatalysts.[1,2] Direct coupling of thiazoles with aromatic halides or triflates is a preferable method for preparation of derivatized thiazoles in terms of its synthetic simplicity. In the course of our synthetic study on chiral thiazolium salts, we encountered direct palladium-catalyzed cross-coupling reaction of 2-trimethylsilylthiazoles with biaryl triflates leading to 2-arylthiazoles. Prior to our investigation, three groups have examined a similar approach to 2- and/or 5-arylthiazoles using copper-mediated cross-coupling of 2-trimethylsilylthiazole with aromatic iodides,[3] the Negishi coupling with thiazolylzinc reagents,[4] and direct coupling of thiazole itself.[5] However, to date there is no report on direct palladium-catalyzed cross-coupling reaction of 2-trimethylsilylthiazole with aryl triflates.

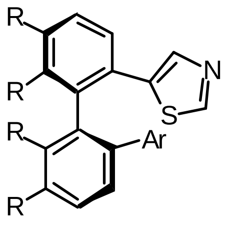

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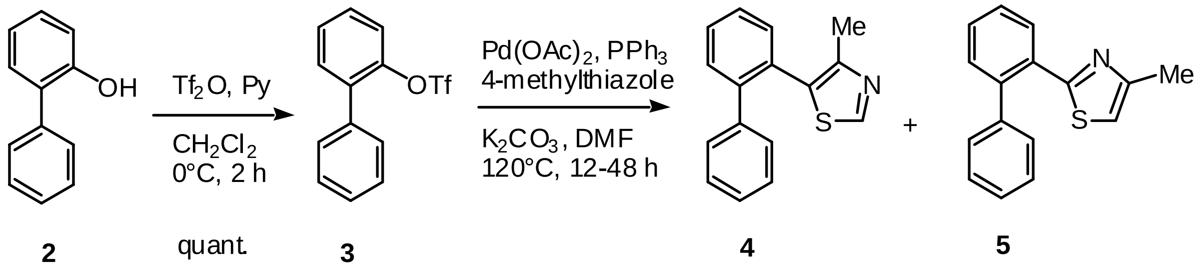
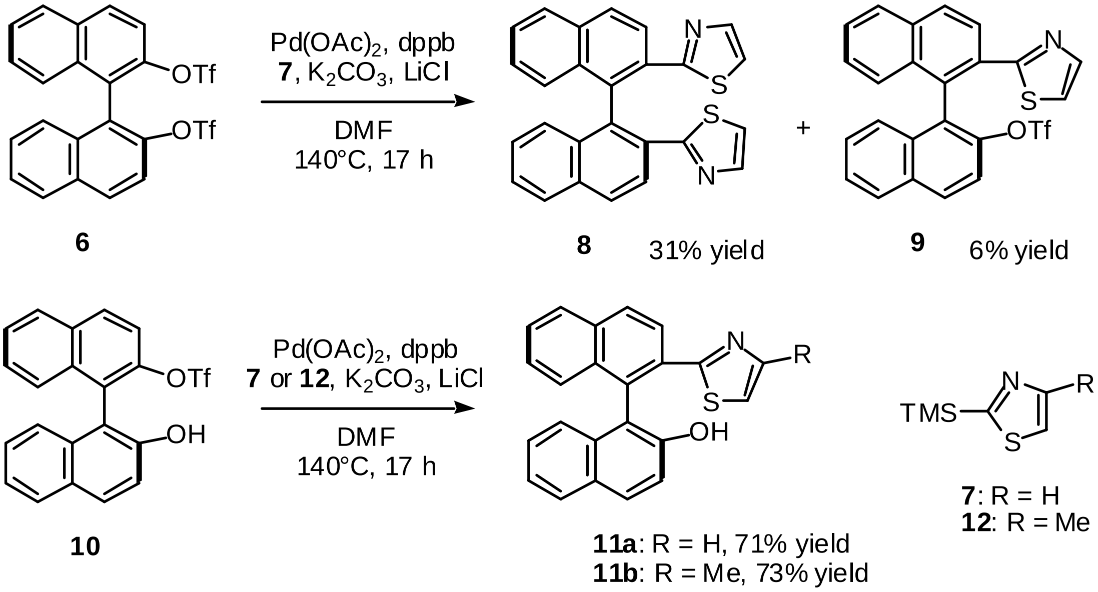
Figure 1

Our study was first directed towards synthesis of the thiazole (**1**) from BINOL for preparation of the corresponding chiral thiazolium salts as shown in Figure 1. As a model reaction, we started investigating cross-coupling reaction of 4-methylthiazole with 2-phenylphenyl triflate as shown in Scheme 1. The triflate (**3**) was obtained by treatment of commercially available 2-phenylphenol (**2**) with triflic anhydride



Scheme 1

in the presence of pyridine in methylene chloride at 0°C for 2 h. in quantitative yield. The coupling reaction of **3** was first carried out according to the literature procedure[4] using 4-methylthiazole (5 equiv.), palladium acetate ($Pd(OAc)_2$, 10 mol%), and triphenylphosphine (PPh_3, 20 mol%) in the presence of cesium carbonate in dimethylformamide (DMF) at 120°C for 48 h. Unsurprisingly, two regioisomers (**4**) and (**5**) were obtained in a ratio of 1:1.6. Interestingly, use of potassium carbonate instead of cesium carbonate was found to dramatically change the ratio to 3.5:1 giving the C5-coupling thiazole (**4**) as the major product. The desired thiazole (**4**) for thiazolium salts chemistry could be obtained in laboratory scale in 72% yield. With the optimized conditions in hand, we next examined cross-coupling reaction with BINOL bis(triflate) and BINOL monotriflate[6] for obtaining chiral thiazolium salts. Unfortunately, the reaction, however, failed to afford any coupling product. Therefore, we had to turn our attention to development of an alternative method for the coupling of BINOL bis(triflate) (**6**) and BINOL monotriflate (**10**) with thiazole derivatives. We chose 2-trimethylsilylthiazole (**7**) as a counterpart for the coupling as shown in Scheme 2. The cross-coupling reaction of **6** with an excess amount of **7** (10 equiv.) was performed using $Pd(OAc)_2$ (30 mol%) and 1,4-bis(diphenylphosphino)butane (dppb, 30 mol%) in the presence of potassium carbonate (2 equiv.) and lithium chloride (2.5 equiv.) in DMF at 140°C for 17 h. Although no desired reaction proceeded, the alternative coupling at the C2 position of **7** was found to take place to provide bis-thiazole (**8**) in 31% yield along with 6% yield of mono-thiazole (**9**). The reaction of **10** more efficiently proceeded to afford the mono-thiazole (**11a**) (R = H) in 71% yield. 4-Methyl-2-trimethylsilylthiazole (**12**) also reacted under the same reaction conditions to produce the product (**11b**) (R = Me) in 73% yield. Generally, palladium-catalyzed cross-coupling of organosilanes with aromatic halides is called the Hiyama coupling,[7,8] which has been known to require addition of some fluoride anion source for activation of the weakly reactive organosilanes. It should be noted that this direct palladium-catalyzed cross-coupling of the 2-trimethylsilylthiazoles with aromatic triflates is the first example without any fluoride anion source.



Scheme 2

In conclusion 2-trimethylsilylthiazoles have first proved to serve as an efficient counterpart for palladium-catalyzed cross-coupling reaction with aromatic triflates without any fluoride anion source to afford 2-arylthiazoles. The method described here will be useful for synthesis of new 2-arylthiazoles.

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