

# Organic Synthesis Reaction Involved by Aryl-Triazene As an Arylation Reagent

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The aryl-triazene, as an extremely useful and versatile organic synthesis midbody, can be extracted from the aromatic amines in a simple way. This paper mainly describes the arylation reaction between palladium catalysis aryl-triazene and indole andazole compounds; the cyclization reaction between rhodium catalysis aryl-triazene and N-methoxybenzamide; while we also design a cross-coupling reaction of palladium catalysis aryl-triazene with indole, and filter catalysts, solvents and additives to contribute the best experiment conditions and a good harvest in the end. The results deduced in the paper show that aryl-triazene attributes to a useful organic synthesis midbody which actively involves in coupled reaction with indole-2.

## 1. Introduction

The formation of the aryl-aryl bond in the molecule is one of the important means of organic synthesis in modern time. United aromatic ring structure unit is contained in many natural products, a large mass of drugs, agricultural chemicals with biological activity, as well as in commercialized dyes; the polyaromatic hydrocarbon has yet been used as materials for semiconductors, organic conductors and liquid crystals due to its special physical and electronic properties (Jeyaraj et al., 2015); The chiral united aromatic ring compounds with counter-isomerism can be used in the study of asymmetric catalytic reactions, which are in the enantioselective reaction one of the most important chiral ligands in the transition metal catalyzed asymmetric reaction (Nuyken and Dahn, 2015). The sp<sup>2</sup> carbon in the C(sp<sup>2</sup>)-C(sp<sup>2</sup>) coupling reaction can be derived from aromatic ring and olefin, for example, the aryl-triazene just belongs to coupling reagent able to provide an aromatic ring (Lei et al., 2016). The aryl-triazene is an organic reagent which is simply prepared and widely used in the combinatorial chemistry, the protecting group in the composition of natural products, the formation of coordination complexes with the triazene as ligand, the polymer and heterocycles syntheses, the coupling reaction, etc. This chapter focuses on the organic synthesis reaction the aryl-triazene involves as an arylation reagent.

## 2. Literature review

The catalytic process of Stille-type reaction has been proposed in a long time, but the detailed reaction mechanism is still under study. The catalytic cycle has three parts: oxidative addition, reductive elimination, metal transfer (Al-Saadawy and Faraj, 2016). Active species is considered to be zero valent palladium, it is through the reduction of stable two valent palladium in situ production. Pd(OAc)<sub>2</sub>, Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>, Pd(MeCN)<sub>2</sub>Cl<sub>2</sub> two valent palladium can be used as catalyst, organotin reagents or adding phosphine ligands to restore them can have zero valent palladium species with catalytic activity. In the catalytic cycle, the rate determining step is the transfer of metal. Organotin reagents with different palladium occurrence rate of sequential turn metallization is: alkynyl aryl vinyl >>> allyl alkyl.

Reseachers reported Lewis acid induced aryl three azene Stille-type coupling reaction substrate, the reaction was carried out at room temperature and under the protection of argon, optimization of solvent, two substrate molar ratio, catalyst dosage and other factors influencing the yield, and to obtain the best reaction conditions to obtain good yield (Melinte et al., 2015). The mechanism of the reaction is similar to that of Suzuki-type and

Hiyama-type reactions involving aryl three ene, and aryl three nitrogen is transferred to palladium compounds by cocatalyst Lewis acid, and the coupling reaction is catalyzed by PD catalyst.

A team reported an efficient method for the synthesis of substituted indoles and NH- indoles in the presence of three alkenyl nitrogen (Vila et al., 2015). This method can be controlled by different metal salts to the preparation of indazole and indole compounds, if copper salt is added to the system (copper acetate), generating indazole compounds; if the system is added to the silver (silver acetate), is generated by the indole compounds.

### 3. Experiment

#### 3.1 Preparation of aryl-triazene

Here we take phenyl triazene as a sample, add 2 mL of concentrated hydrochloric acid to a 100mL round bottom flask, stir it with a magnetic stirrer at a low temperature (constant temperature); the temperature was controlled at 0°C, slowly add aniline (466.5mg, 5.0 mmol); put the sodium nitrite (366mg, 5.3mmol) into 10mL ice water, mix them fully to prepare the sodium nitrite solution. The prepared sodium nitrite solution is slowly added to a round bottom flask with a constant pressure funnel and stirred them at 0°C for 30 min. Sodium carbonate (12.51g, 90.5 mmol) and diethylamine (2.647g, 36.2 mmol) are placed in 50 mL Erlenmeyer flask where 8.4 mL acetonitrile and 16.8 mL water are added, mix them evenly to prepare a mixture solution of diethylamine and carbonic acid sodium, and then slowly add it into a round bottom flask with constant pressure funnel and stir it at 0°C for 6h. After the reaction ends up, 20mL water and 3x10mL dichloromethane are added to the system mixture, extract and combine the organic phases. The organic phases are then dried over anhydrous magnesium sulfate for 30 min, and the solvent is removed after the pressure drops. The elution reagent is petroleum ether and vinyl acetate available by V/V-30: 1-50: 1 column chromatography separation and purification.

#### 3.2 Preparation of N-substituted indol

Add potassium hydroxide (448 mg, 8 mmol) to 15 mL dimethyl sulfoxide (DMSO), and then 4 mmol NH-indole to it after stirring evenly; lastly add 8 mmol aryl iodohydrocarbon to it slowly dropwise. After the reaction ends up, 15 mL water and 3X8 mL dichloromethane are mixed into the solution, and the organic phase are combined after liquid separation and extraction. The organic phases are then dried over anhydrous magnesium sulfate for 30 min, and the solvent is removed after the pressure drops. The target product is separated by the column chromatography purification.

#### 3.3 Catalytic aryl-triazene and N-substituted indole reaction

N-methyl indole and 1-(p-benzyl) triazene reaction is taken as an example, respectively add palladium acetate (2.8 mg, 0.0125 mmol), N-methylindole (65.5 mg, 0.5 mmol), 1-benzal triazene (114.6 mg, 0.6 mmol) to the dry pressure tube, and then orderly put 2.0 mL N, N-Dimethylacetamide (DMAC) newly distilled and boron trifluoride diethyl etherate (71.0 mg, 0.5 mmol) into it; let this solution react at 80°C for 12 hours. TLC detects whether it has fully reacted, if this is the case, add 20 mL water and 3X 10mL dichloromethane. It is treated with liquid separation and extraction. The organic phases are combined and dried over anhydrous magnesium sulfate for 30 min, and the solvent is removed after the pressure drops. The elution reagents are petroleum ether and ethyl acetate by V/V=15: 1-50: 1. The pure white solid is separated by the column chromatography purification. The yield of the target product reaches 92%.

#### 3.4 Coupling reaction between palladium catalyzed aryl triazene and azole compounds

Benzoxazole and 1-(p-benzyl) triazene reaction are taken as an example, palladium acetate (11.2mg, 0.05 mmol), benzoxazole (59.5mg, 0.50mmol), 1-(p-benzyl) triazene (114.6mg, 0.60mmol), cuprous iodide (142.8 mg, 0.50mmol) and DMF (2.0mL) are added to the drying pressure tube respectively. The system is reacted at 100°C for 12 h, and the reaction is detected by TLC. After the reaction, 20mL water, 3X10mL methylene chloride are added into the mixture of the system. The liquid extraction is carried out and organic phase is merged. The organic phases are combined and dried over anhydrous magnesium sulfate for 30 min, and the solvent is removed after the pressure drops. The target product is purified by column chromatography. The elution reagent is: petroleum ether: ethyl acetate=5:1-20:1. Finally, the pure white solid can be obtained, and the target product yield is 81%.

#### 3.5 Preparation of N- methoxy benzoyl amine compounds

Taking preparing N- methoxy benzoyl diamine as an example, 5.52g potassium carbonate (40mmol) is added into a round bottle (150mL) with 60 mL water and ethyl acetate mixed liquid (V: V-1:2). The mixture solution is

iced to 0°C. Then, 1.67g hydroxylamine hydrochloride (20mmol) is added into the solution, and then 2.8 g benzoyl diamine (20mmol) is added to the mixture after being stirred evenly. Finally, the solution is stirred for 6 hours at room temperature. After the reaction is finished, the organic layer is separated and the water layer is extracted with ethyl acetate. The organic layer is combined and dried with magnesium sulfate anhydrous. When the solvent is removed and dried, a higher purity of benzoyl diamine is obtained without the need for re-purification.

### 3.6 Reaction of rhodium catalyzed aryl triazene and N- methoxy benzoyl amine compounds

N- methoxy benzoyl diamine and 1-(p-benzyl) triazene reaction are taken as an example,  $[\{\text{RhCp}^*\text{C12}\}_2]$  (4.3 mg, 0.006mmol, 2.0mol%), N-methoxy benzoyl diamine (45.3mg, 0.30mmol) and silver oxide (139.0 mg, 0.6 mmol) are added to the drying pressure tube respectively. The tube is sealed and nitrogen is exchanged for three times. Then, trifluoroethanol (2.0mL), 1-(p-benzyl) triazene (86mg, 0.45mmol) and boron trifluoride diethyl etherate (42.6 mg, 0.3 mmol) are injected into the mixture by syringe respectively. Finally, the system is stirred for 12 h at room temperature, and the reaction is detected by TLC. At the end of the reaction, water (18mL) and methylene chloride (3X8mL) are added to the mixture. The liquid extraction is carried out and organic phase is merged. The solvent is removed after the pressure drops. The target product is purified by column chromatography. The elution reagent is: petroleum ether: ethyl acetate=3:1-10:1. Finally, the pure white solid can be obtained, and the target product yield is 87%.

## 4. Reaction between palladium catalysis aryl-triazene and N-substituted indole C2-arylation

Indole and its derivatives are a class of critical nitrogen heterocyclic ring compound, widely distributed in nature. As they have a huge contribution to dye industry, spices, pharmaceuticals, pesticide synthesis and other fine chemical products in terms of the synthesis of midbodies (Shafiekhani et al., 2016), it is of great significance to study the synthesis and the reaction of heterocyclic compound containing indole (Reheim and Tolba, 2016). Chemists have succeeded in direct arylation of the indole CH with activated aromatics in the presence of transition metal catalyst, which provides an effective way to synthesize aryl indole directly without prior indole functionalization (i.e. halogenation or metallization of chemical equivalent (Brodmann et al., 2015).

### 4.1 Indole 2-arylation reaction

In the early 1980s, the Itahara panel reported for the first time that the C2-arylation reaction occurred directly in the indole compound with oxidative coupling, where N-ethylphthalimide-substituted indole and stoichiometric palladium acetate are required, reflux in AcOH / ArH solvent, but with low yield. The reaction was shown in Figure 1.

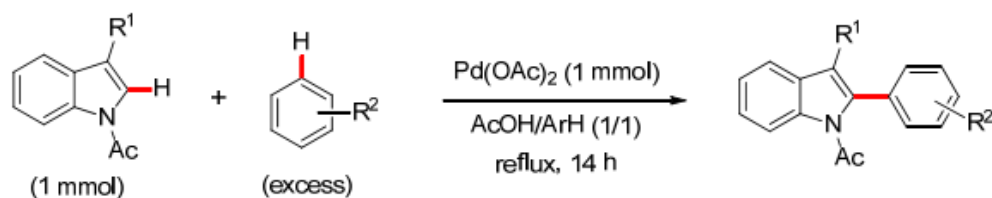


Figure 1: C2- arylation

In 2004, a selective C2-arylation reaction was attempted between N-substituted indole and aryl halohydrocarbon so that a high-yield indole compound of 2-arylation was synthesized (Rao and Dhanorkar, 2015). In the reaction conditions, the doses of the alkali and the catalyst are two key factors in the reaction. The reduction of the dose of the catalyst can suppress the formation of the biphenyl and increase the yield of the target product. There is a better function group tolerance in this reaction (Liu et al. 2015). The reaction was shown in Figure 2.

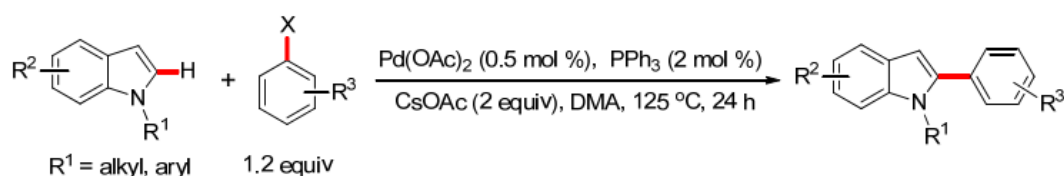


Figure 2: 2-aryl indole compounds

Rough removal of N-substituted protecting groups restrains the synthesis of NH-aryl indole compounds. In 2006, it was proposed that Pd/NHCs /ligands as a catalyst made up SEM-protected indole C-H activation and arylation reaction (Li et al., 2016). Although SEMC1 (2-(trimethylsilyl) ethoxy methyl chloride) is expensive, it facilitates the further synthesis of NH-indole compounds. The catalyst can also be better applied to the reactions of pyrrole, N-Azaindole and the like (Gagnon et al., 2017).

#### 4.2 Indole 3-arylation reaction

In 1988, the copper was first used as a catalyst for indole-3 arylation reaction, where 1xPh3Bi (TFA) 2, dichloromethane was chosen as the solvents to react at room temperature for 1-24 hours under mild conditions. The catalyst varies according to substrates (Indole: 1 mol% Cu (0); 2-methylindole: 10 mol% Cu (OAc) 2; N-methyl-2-methylindole: 10 mol% Cu (TFA) 2). In particular, N-substituted indole can generate the product of C3-arylation with an excellent yield (Rérat et al., 2016). The reaction was shown in Figure 3.

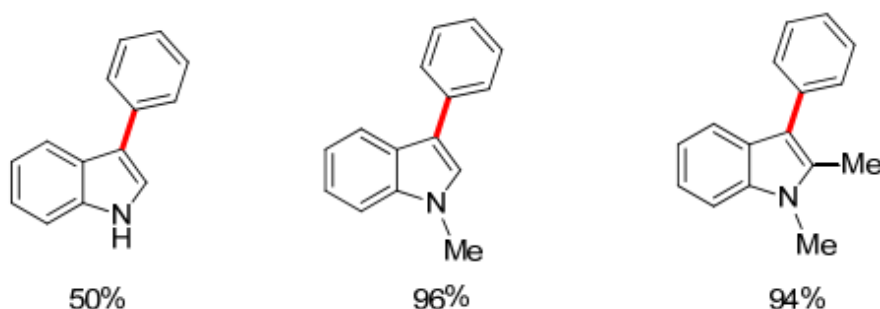


Figure 3: C3- arylation product

In 2007, the catalytic indole reacted with brominated aromatic hydrocarbons in C3-arylation. In this reaction, a palladium salt (POPd [O-Bu] 2P (OH) 2PdCl<sub>2</sub>) that stably presents in the air is used as a catalyst, potassium carbonate as a base, to get appropriate C3-aryl indole compounds with high selectivity (C3/C2>100/1) and high yield in the 1,4-dioxane (Atkinson, et al., 2015). It is regrettable that, in the catalytic system, the reaction is unworkable due to the indole with a strong electron-withdrawing groups (e.g.: 2-Ac, 5-CN and 5-NO<sub>2</sub>), so that the C3-arylation product can not be available.

In 2007, the copper-catalyzed indole compound and the aryl iodide synthesized C2 or C3-arylationindole in a high selectivity and in good broad spectrum, where various substituted indoles and aryl iodides can react well. If the reaction temperature is controlled at 35 °C, the major product is C3-arylation; If controlled at 70 °C, it is C2-arylation. The reaction was shown in Figure 4.

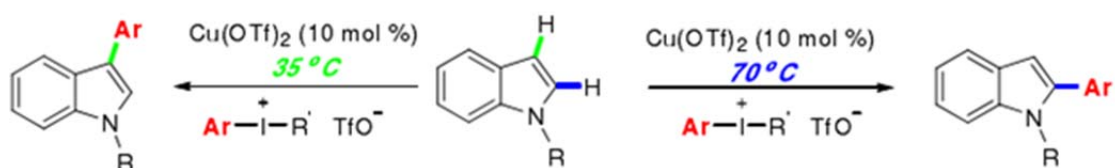


Figure 4: Selective synthesis of indole derivatives with aryl iodide salts

These efficient syntheses provide a sound basis for the formation of aryl indole compounds and are capable of selectively coupling reaction at indole-2 or -3, making great contribution to both science and practice.

#### 4.3 Optimization of reaction conditions

The aryl-triazene reagent is mainly used as an electrophile to be involved in the reaction. Under the transition metal catalysis, the cracking of carbon and nitrogen bonds release the nitrogen to facilitate the formation of metal arylide reagents for carbon-hydrogen bond activation, which is rare in the organic synthesis. This imposes an opportunity and challenge for the transition-metal catalyze de-triazene reaction. In this context, we design the cross-coupling reaction between palladium catalysis aryl-triazene and indole (Betancourt-mendiola, et al., 2015). The reaction was shown in Figure 5.



Figure 5: Pd-catalyzed C-2 arylation of indoles with 1-aryltriazenes.

At inception, we chose benzoxazole (1a) and 1-(p-tolyl) triazene (2a) as template substrates to investigate the effect of the reaction. In 5mol% Pd (PPh<sub>3</sub>)<sub>4</sub>, 2x Cul, N, N-dimethyl benzamide solvents (DMF), 2-(p-toluene) benzoxazole 3a (Table 3.1, entry 1), the oxazole-2 arylation product is available in 38% yield at 130°C. But the fact we deserve to note is that only 13% target product 3a can be derived from the tetrafluoroborate p-methylphenyl nitrogen salt instead of 1-(p-tolyl) triazene (2a). This preliminary result inspires us to optimize the reaction conditions for palladium catalysis, additives and solvents. These results are given in the following table.

Table 1: Optimization of reaction conditions for the Pd-catalyzed direct C2-arylation of benzoxazole with 3,3-diethyl-1-(p-tolyl) triazene.<sup>a</sup>

Entry	Pd catalyst	additive	solvent	Yield (%) <sup>b</sup>
1	Pd (PPh) <sub>4</sub> (5%)	Cul (2.0) eq.	DMF	38
2	Pd <sub>2</sub> (dba) <sub>3</sub> (5%)	Cul (2.0) eq.	DMF	35
3	PdCl <sub>2</sub> (5%)	Cul (2.0) eq.	DMF	53
4	Pd (CH <sub>3</sub> CN) <sub>2</sub> Cl <sub>2</sub> (5%)	Cul (2.0) eq.	DMF	50
5	Pd (PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub> (5%)	Cul (2.0) eq.	DMF	48
6	Pd (OAc) <sub>2</sub> (5%)	Cul (2.0) eq.	DMF	63
7	Pd (OAc) <sub>2</sub> (10%)	Cul (2.0) eq.	DMF	83 <sup>b</sup> , 81 <sup>c</sup> , 64 <sup>b</sup>
1	Pd (PPh) <sub>4</sub> (5%)	Cul (2.0) eq.	DMF	38

<sup>a</sup>Reaction conditions: 1a (0.50 mmol), 2a (0.75 mmol), Pd catalyst (5-10 mol%), additive (1.5-2.0 eq.), solvent (3.0 mL), 130°C for 12 h.

<sup>b</sup>Isolated yield.

<sup>c</sup>1.5 equiv of Cul was used.

## 5. Conclusions

This paper proposes a new experimental method to generate the coupling reaction immediately between N-substituted and aryl-triazene compounds where the palladium acetate is taken as catalysis, N,N-Dimethylacetamide as solvent, in presence of boron trifluoride diethyl etherate, in order to capture 2-arylationindole compound in a high yield. In this paper, we filter out the catalysts, solvents and additives to obtain the best experimental conditions and a good yield.

We have probed into the substrates under the above reaction conditions, whether it is the electron withdrawing group or the electron donating group, we have achieved a moderate or high yield. The strong electron donating groups therein have also been quantitative harvest. The aryl-triazene is a very useful organic synthesis midbody that can form an efficient coupling reaction with indole-2.

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