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Synthesis of Polyfused Heteroaromatics by Palladium-Catalyzed Cross-Coupling Reaction

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Abstract

The palladium-catalyzed coupling of unsaturated halides or triflates with organostannanes (the Stille reaction) or with organo-boronic acids (the Suzuki reaction) has involved as a powerful means of carbon-carbon bond formation. As an extension of our work on the synthesis and reactivity of positively charged bridge-head nitrogen containing fused azinium salts, we have been studying the formation of polyfused heteroaromatics with angular annellation pattern.

The reaction of such positively charged salts with nucleophiles has proven to be a suitable tool for the preparation of heteroaryl dienes, which have been shown to be excellent intermediates for several ring closure reaction. A selection of results will be presented, including applications to natural product synthesis.

Keywords: cross-coupling reaction, furoquinolone, thienoisoquinoline, azinium salt, review

Introduction

In organic chemistry the formation of carbon-carbon bonds - especially between sp^2 -atoms - has always been a great challenge. In the last decades the introduction of organometallic reagents and catalysts into organic synthesis opened up new routes to establish such connections. These

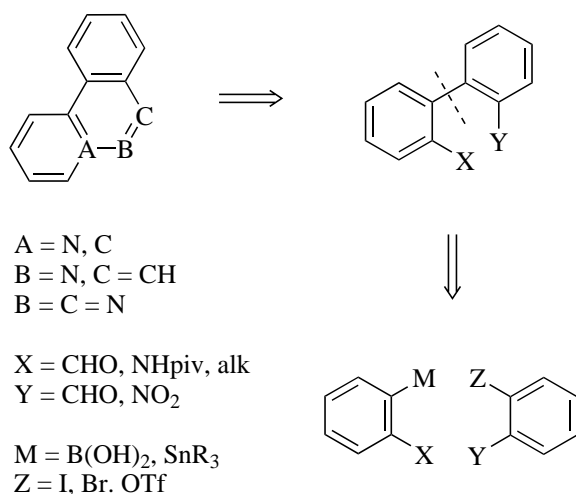
cross-coupling reactions are now accessible via a variety of organometallic reagents and are considered as a fundamental synthetic methodology (Eq. (1)).



In these reactions organometallic reagents containing metals such as magnesium, zinc, zirconium, aluminium, mercury, boron or tin and organic halides or triflates produce a carbon-carbon σ -bond. Of this rich selection of organometallic cross-coupling partners organostannanes [1] and organoboranes [2] are employed the most frequently due to their stability, general availability and their tolerance towards a wide variety of functional groups.

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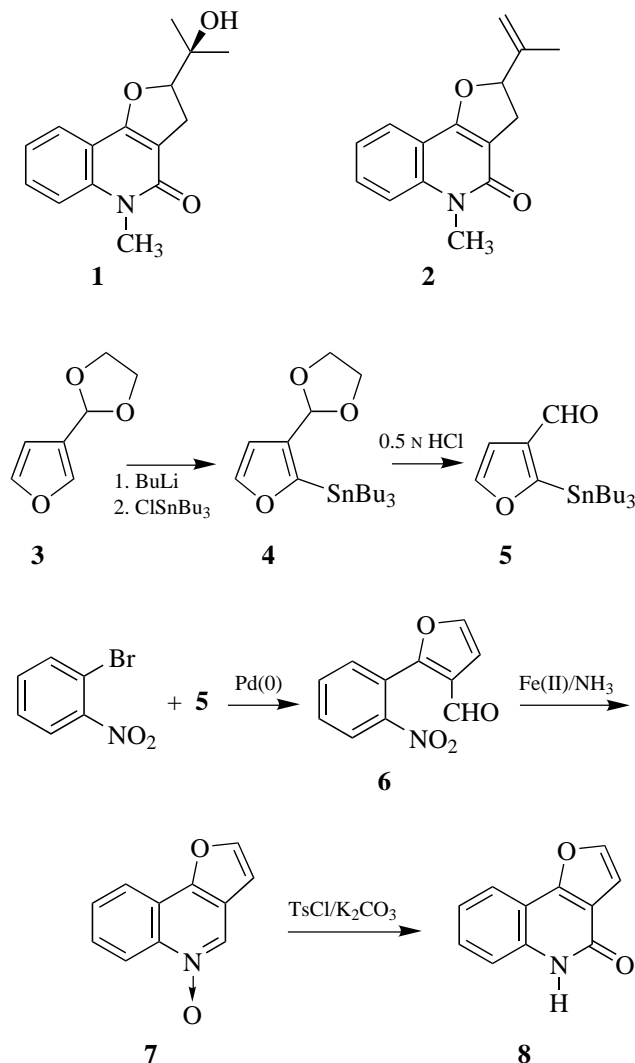
Scheme 1.

Our aim was the synthesis of various pyridine-, pyridazine- and v-triazine-containing angularly fused heteroaromatic systems implaying the strategy shown in Scheme 1, which is based on the ring-closure of the suitably substituted asymmetric biaryl compounds prepared from the corresponding organometallics and aryl halides by Pd(0)-catalysed cross-coupling reaction.

Synthesis of neutral angularly fused tricyclic systems.

Recently, furoquinoline derivatives with the phenantrene annelation pattern, such as araliopsine (**1**) and almein (**2**) have been found in *Rutaceae*. There are several procedures for the synthesis of this type of compounds but most of them consist of tedious multistep procedures and the overall yields are generally poor. In order to overcome these difficulties, a five step synthetic route was elaborated [3] for the preparation of furo[3,2-c]quinolone (**8**) (Scheme 2).

Metallation of furan-3-carboxaldehyde ethylene acetal (**3**) with BuLi, followed by reaction with tributyltin chloride, gave 2(2-tributylstannyl-3-furyl)-1,3-dioxolane (**4**) in 98% yield, which upon hydrolysis with 0.5 N hydrochloric acid in THF gave the deprotected aldehyde **5** in 67% yield. Pd(0)-catalysed coupling of **5** with *o*-bromonitrobenzene in DMF at 100 °C afforded the biaryl compound (**6**) in 62% yield. Ferrous sulphate in aqueous ammonia was chosen as the reducing agent, for its ability to reduce the nitro group to an amino function selectively in the presence of formyl moiety. However, somewhat to our surprise we isolated the corresponding *N*-oxide derivative (**7**) of the expected ring-closed product in 76% yield. Presumably the intermediate hydroxylamine derivative was being trapped by the aldehyde. Treatment of **7** with tosyl chloride and potassium carbonate in solution gave the desired compound **8** in 85% yield. This route also offers a

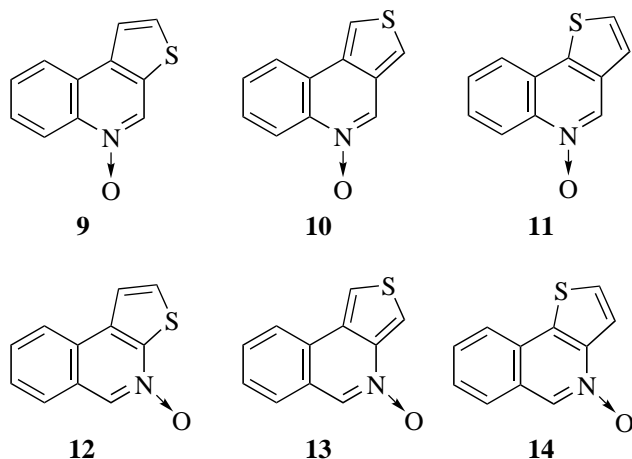


Scheme 2.

general method for the preparation of the variously substituted derivatives of **8** by starting from the appropriately substituted furan-tin derivatives and bromonitrobenzenes.

Upon the above successful approach to furoquinolone system (**8**) we aimed at the preparation of its thieno-fused analogues. In principle there are three isomeric thienoquinoline-*N*-oxides (**9**, **10**, **11**). Furthermore, because of our interest in biological activity and spectroscopic properties, preparation of the three possible isoquinoline derivatives (**12**, **13**, **14**) seemed also of interest (Scheme 3).

Synthesis of two such quinoline-*N*-oxides [4] (**9** and **10**) was accomplished by employing the strategy devised for the preparation of the furo-quinoline-*N*-oxide (**7**). The third isomer, thieno[3, 2-c]quinoline-*N*-oxide (**11**) could not be obtained from 3-formyl-2-thiopheneboronic acid due to deboronation, and was later prepared [5] by using 2-tributylstannyl-3-thiophenecarboxaldehyde (**15**) as the organometallic reagent, which gave 2-(2-nitrophenyl)-3-thiophenecarboxaldehyde (**16**) in 52% yield. The reduc-



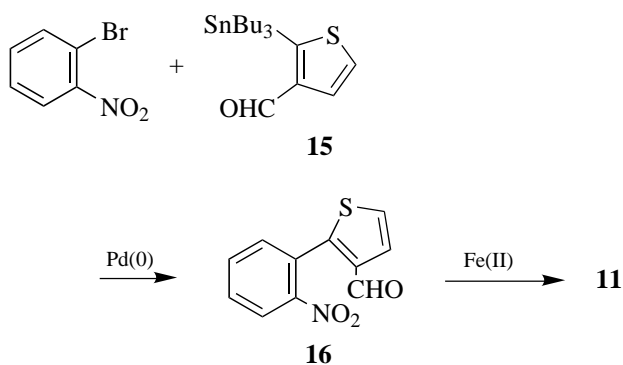
Scheme 3.

tion of the nitro-aldehyde then yielded **11** in 77% yield (Scheme 4).

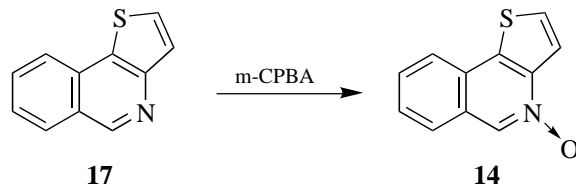
Coupling of *o*-formylbenzeneboronic acid with 2- and 4-nitro-3-bromothiophene led to the formation of nitro-formyl-phenylthiophenes which then were subjected to reductive ring closure to **12** and **13**, respectively. Attempts to couple *o*-formylbenzeneboronic acid or *o*-tributylstannylbenzaldehyde with 2-bromo-3-nitrothiophene to **14** failed due to the high unstability of the latter compound. The missing thieno[3,2-*c*]isoquinoline-*N*-oxide (**14**) was therefore prepared in 85% yield through the oxidation of thieno[3,2-*c*]isoquinoline (**17**) with *m*-chloroperbenzoic acid (Scheme 5).

Synthesis of positively charged angularly-fused systems.

As a continuation of these studies, a similar strategy for the synthesis of bridgehead nitrogen containing fused azinium compounds has also been applied. The reaction of such positively charged salts with nucleophiles has been proven to be a suitable tool for the preparation of heteroaryl



Scheme 4.



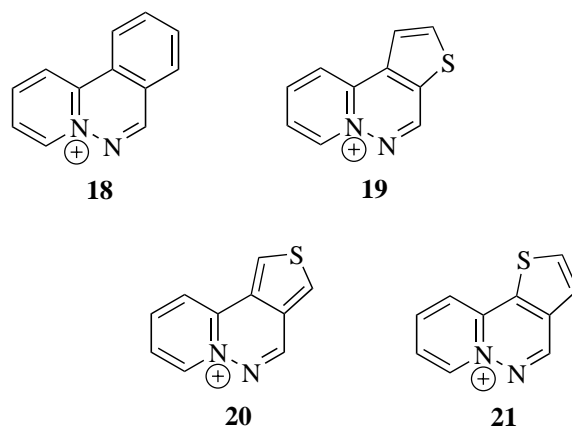
Scheme 5.

dienes [6,7] which have been shown to be excellent intermediates for several ring closure reactions [8,9,10].

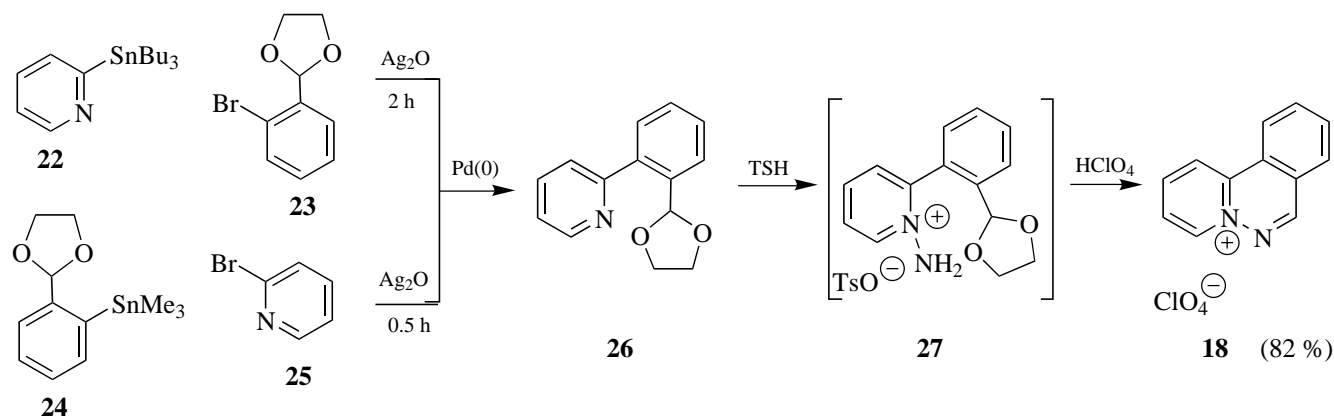
We decided to prepare [**11**] the pyrido[2, 1-*a*]phthalazin-5-ium perchlorate (**18**) and its three thieno-fused analogues (**19–21**) (Scheme 6). Compound **18** is a benzo[*c*] derivative of the fully aromatic bicyclic pyrido[1, 2-*b*]pyridinium salt which has been prepared for the first time recently by the condensation of 2-alkyl-1-amino-pyridinium salts with 1,2-dicarbonyl compounds [12].

We considered *o*-(2-pyridyl)benzaldehyde to be the key compound for the preparation of **18**. Somewhat surprisingly, however, our attempts to couple *o*-formylbenzeneboronic acid with 2-bromopyridine according to modified Suzuki condition failed, as did the Stille coupling of *o*-tributylstannylbenzaldehyde with 2-bromopyridine. It has been recently found [13] that the use of one equivalent of silver oxide in the Stille reaction increased the both rate and the yield of the process. Using this co-catalyst in the above mentioned reactions no positive effect was observed. Coupling of protected benzaldehyde derivatives (**23**, **24**), however, with **22** and **25** in the presence of silver oxide proved to be successful and the desired biaryl compound **26** was obtained in satisfactory yield. When **26** was *N*-aminated by *O*-tosylhydroxylamine (TSH) [14], a spontaneous ring closure of the *N*-amino derivative **27** took place, and the new tricyclic diazonium salt **18** was isolated in 82% yield (Scheme 7).

For the synthesis of the thieno fused systems we followed the same strategy (Scheme 8). The cross-coupling



Scheme 6.



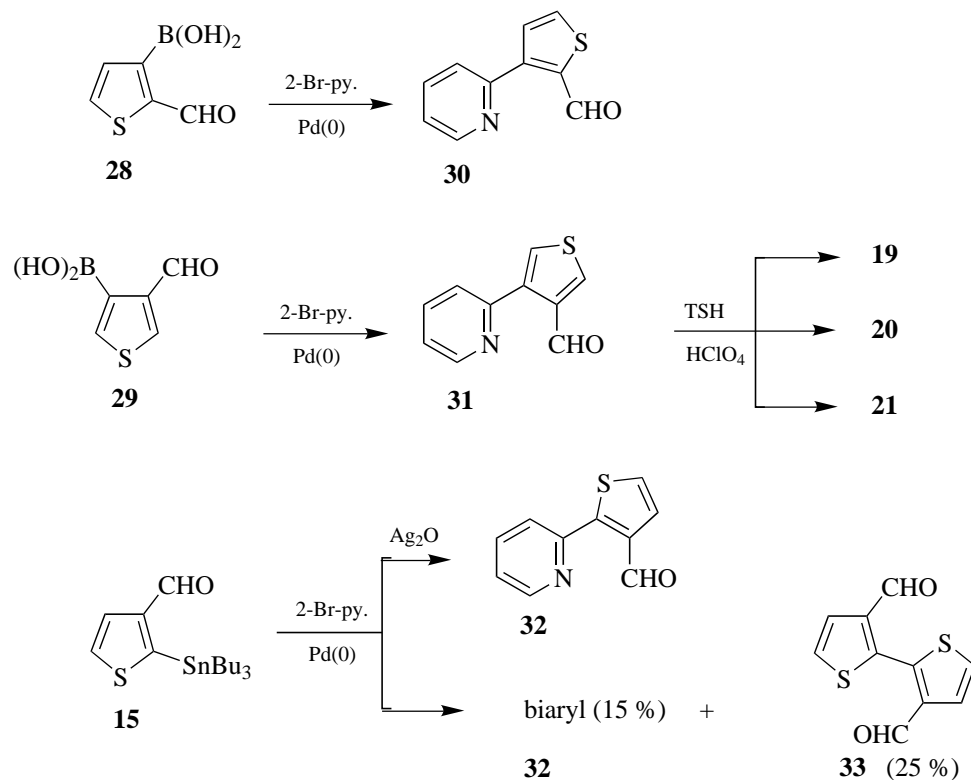
Scheme 7.

reaction of 2-bromopyridine (**25**) and *o*-formyl thiopheneboronic acids (**28,29**) under modified Suzuki conditions [15] were, in contrast to the corresponding attempts with *o*-formylbenzeneboronic acid, successful and afforded the desired biaryls (**30,31**) in good yield. Due to the easy deboronation of 3-formyl-2-thiopheneboronic acid in the third case we used the corresponding tin derivative **15**. Without silver oxide, however, the biaryl compound **32** was obtained only in 15% yield accompanied by a large amount of the homo-coupled product (**33**). The addition of silver oxide had a marked effect on the reaction and the biaryl (**32**) was isolated in 60% yield. *N*-amination and a subsequent ring closure of these biaryls (**30-32**) afforded the

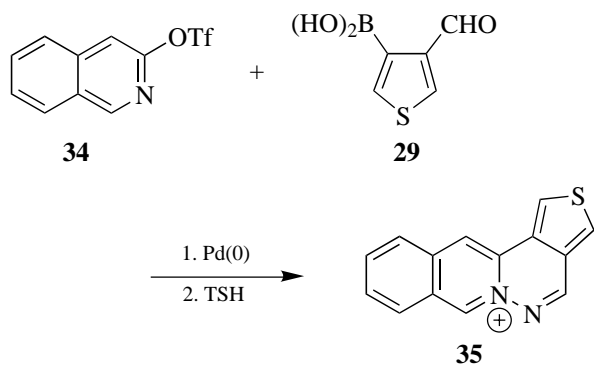
three thieno-fused pyrido[1, 2-b]pyridinium salts **19-21** in excellent yield.

This ring closure methodology was also found to be suitable for the synthesis of the benzologues, starting from the corresponding quinoline or isoquinoline derivatives. For example, 3-trifluoromethanesulphonyl-isoquinoline (**34**) was successfully coupled with 3-formyl-4-thiopheneboronic acid (**29**) and the resulting biaryl compound was ring closed as above to give the tetracyclic system (**35**) (Scheme 9).

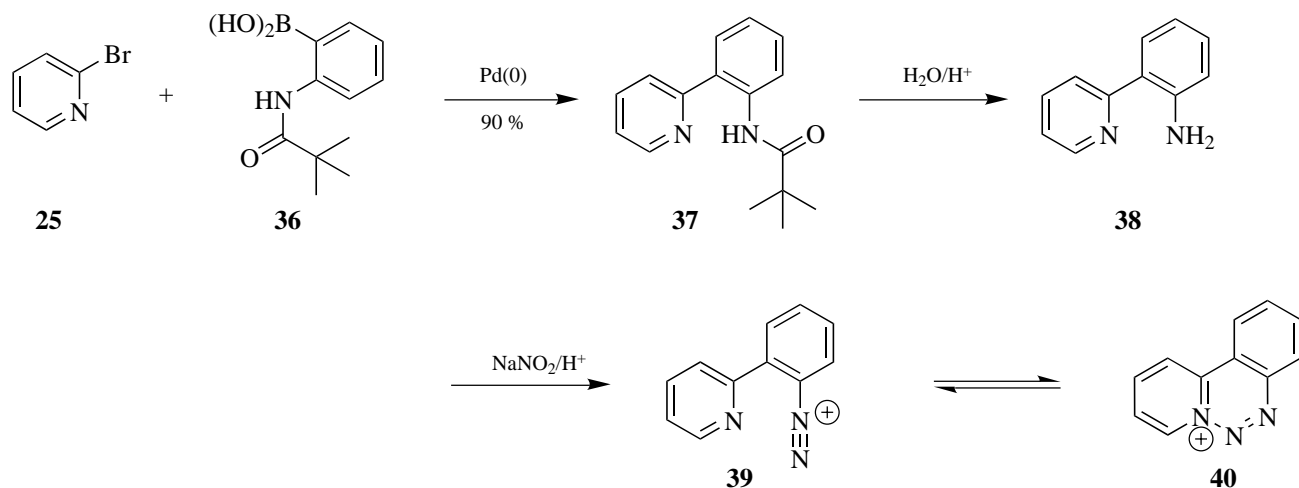
This procedure proved to be extensible for the preparation of the three adjacent nitrogen containing ν -triazinium salts (Scheme 10). In this case the key intermediate 2(2-aminophenyl)pyridine (**38**) was prepared by the cross-coupling reaction of 2-bromopyridine (**25**) and 2-(*N*-pivaloyl)-aminophenyl boronic acid [16] followed by



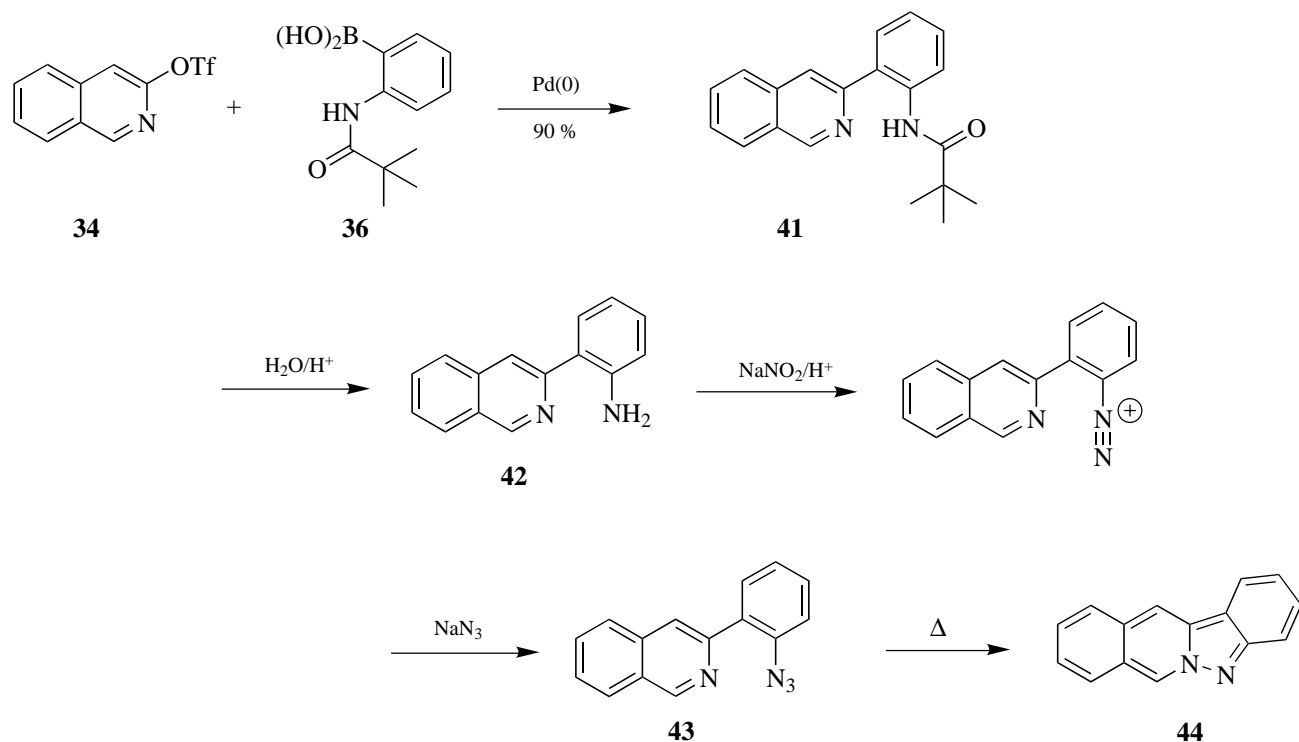
Scheme 8.



Scheme 9.



Scheme 10.



Scheme 11.

deprotection of the coupling product (**37**). The recognition that a-pyridylphenyldiazonium salts could undergo valence bond isomerization [17] prompted us to study the use of this process for the formation of fused v-triazinium salts.

When the free amine **38** was treated with nitrous acid in the presence of aqueous fluoroboric acid the isolated product - in accordance with our expectations- showed that isomers **39** and **40** form an equilibrium - based on IR and NMR studies - both in the solid state and in solution.

Most recently we were interested in the synthesis of bridgehead-nitrogen containing polycyclic heteroaromat-

ics because of their biological interest. These type of compounds like **44** have been believed to be a new family of DNA intercalating agents [18].

Now we have developed a simple methodology to synthesize indazolo[2, 3-b]isoquinoline (**44**) - the ring system of which differs from that of the well known and potent antitumor compound ellipticine only in the position of one nitrogen atom - by means of the orthometallation-cross coupling strategy (Scheme 11).

Hydrolysis of the asymmetric heterobiaryl compound (**41**), obtained from **34** and **36** in normal Suzuki reaction, led to the free amine **42**. The amine functional group was transferred to an azide in a one-pot procedure through diazotation followed by treatment with sodium azide to give **43** which was ring closed to the desired tetracyclic compound **44** by heating, presumably through nitrogen elimination and formation of an intermediate nitrene [19].

Broder application of these tactics to the synthesis of polyfused aromatics and heteroaromatics, including alkaloids is in progress.

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