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The Aminopalladation-Reductive Elimination Tandem Reaction in the Construction of the Functionalized Indole Ring

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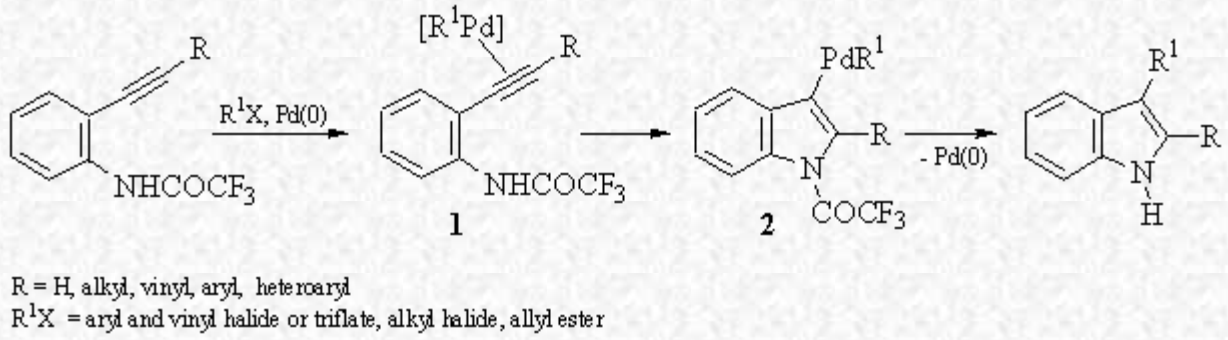
Introduction

The aminopalladation-reductive elimination tandem reaction of internal and terminal alkynes containing proximate nitrogen nucleophiles has been proved to be a powerful and useful tool for the construction of the substituted pyrrole nucleus of the indole system. The fact that the reaction can be carried out with a wide assortment of organopalladium precursors and readily available starting alkynes, the ease of execution and the tolerance of a wide range of functional groups highlights its importance and flexibility and may contribute toward its utilization in the synthesis of complex indole derivatives. The method may provide a versatile complement of well established classical methods such as the Batcho-Limgruber synthesis of indoles from *o*-nitrotoluenes and dimethylformamide acetals, the Fisher indole synthesis, the Gassman synthesis of indoles from *N*-halo anilines, the Madelung cyclization of *N*-acyl-*o*-toluidines, and the reductive cyclization of *o*-nitrobenzyl ketones.[1]

The reaction most probably proceeds through the intermediacy of the h^2-alkyne-organopalladium complex **1** - formed via the coordination of the alkyne to an organopalladium complex generated in situ - that undergoes an intramolecular nucleophilic attack by the nitrogen atom across the C-C triple bond. Subsequently, the resultant s-indolylpalladium intermediate **2** affords the desired indole product via reductive elimination of Pd(0) species (Scheme 1).



Scheme 1.

The reaction course is influenced by a variety of reaction parameters such as temperature, solvents, additives and bases, the nature of the alkyne (internal or external), the electronic density on the acetylenic carbons, the absence or the presence as well as the nature of phosphine ligands, and the strength of the nucleophilic center. This article overviews some of our results in this area.

2-Substituted-3-aryl(vinyl)indoles

As an extension of our oxypalladation-reductive elimination tandem reaction of pentynoic acids,[2] in 1992 we started our studies on the aminopalladation-reductive elimination tandem reaction to prepare 2,3-disubstituted indole products.[3] We believed that such a protocol would provide a fundamentally new, straightforward approach to the construction of the functionalized pyrrole ring of the indole system from aryl alkynes containing nitrogen nucleophiles in the ortho position and aryl iodides or vinyl triflates.

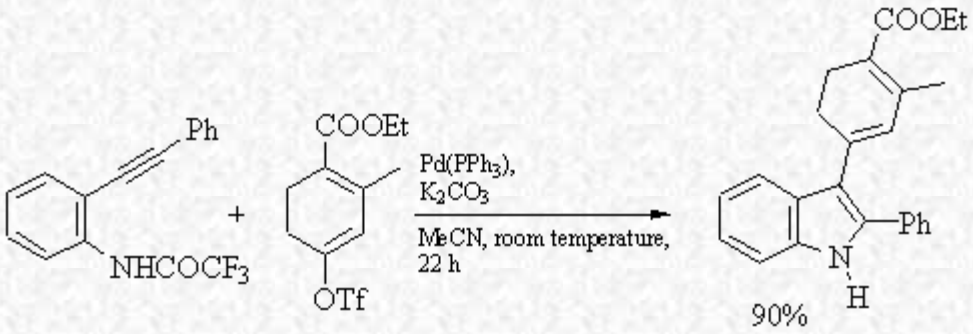
Our early studies showed that the base and the nature of the nitrogen nucleophile can influence the reaction outcome. Best results were obtained by using K_2CO_3 whereas the employment of triethylamine gave lower yields. As to the nitrogen nucleophile, the starting alkyne was recovered in 88 and 79% yield, respectively, when *o*-(phenylethynyl)aniline was subjected to *p*-chlorophenyl iodide and cyclooct-1-en-1-yl triflate. The utilization of *o*-(phenylethynyl)acetanilide produced similar results: the starting alkyne was recovered in 98 and 97% yield, respectively. Switching to *o*-(phenylethynyl)trifluoroacetanilide led to the isolation of the desired indole products in 80 and 74% yield, respectively.

The dramatic change observed with the trifluoracetamido group supports the notion that the acidity of the nitrogen-hydrogen bond plays a major role in this cyclization reaction. Most probably, a strong, anionic nucleophile is required to attack the h^2-alkyne-organopalladium intermediate. Alternatively, proton removal from the amido group in the transition state leading to the *trans* addition aminopalladation intermediate might also be involved. Whatever the real mechanism may be, it remains that organopalladium complexes appear to be less effective than palladium dichloride in activating the C-C triple bond toward intramolecular nucleophilic attack. A number of cyclizations of alkynes containing close amino[4] and amido[4d,5] groups catalyzed by palladium dichoride supports this view.

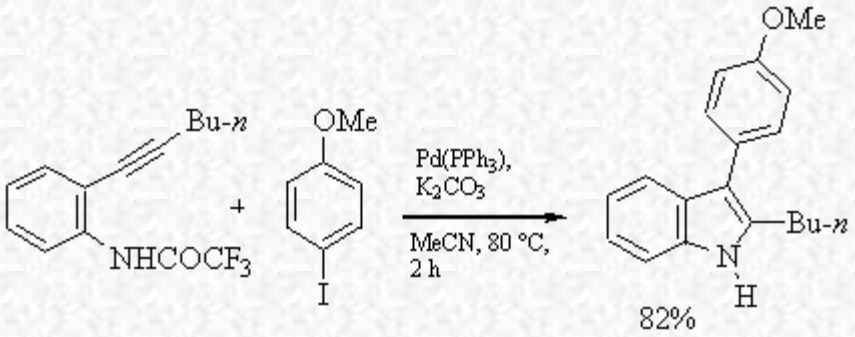
The trifluoroacetamido group provides the additional advantage of being readily cleaved so as to allow for the formation of the indole product containing the free amino functionality.

Several *o*-trifluoroacetanilides were successfully converted into the corresponding 2,3-disubstituted indoles in the presence of $Pd(PPh_3)_4$ and K_2CO_3, at room temperature with vinyl triflates (Scheme 2) and at 80 °C with aryl halides (Scheme 3).

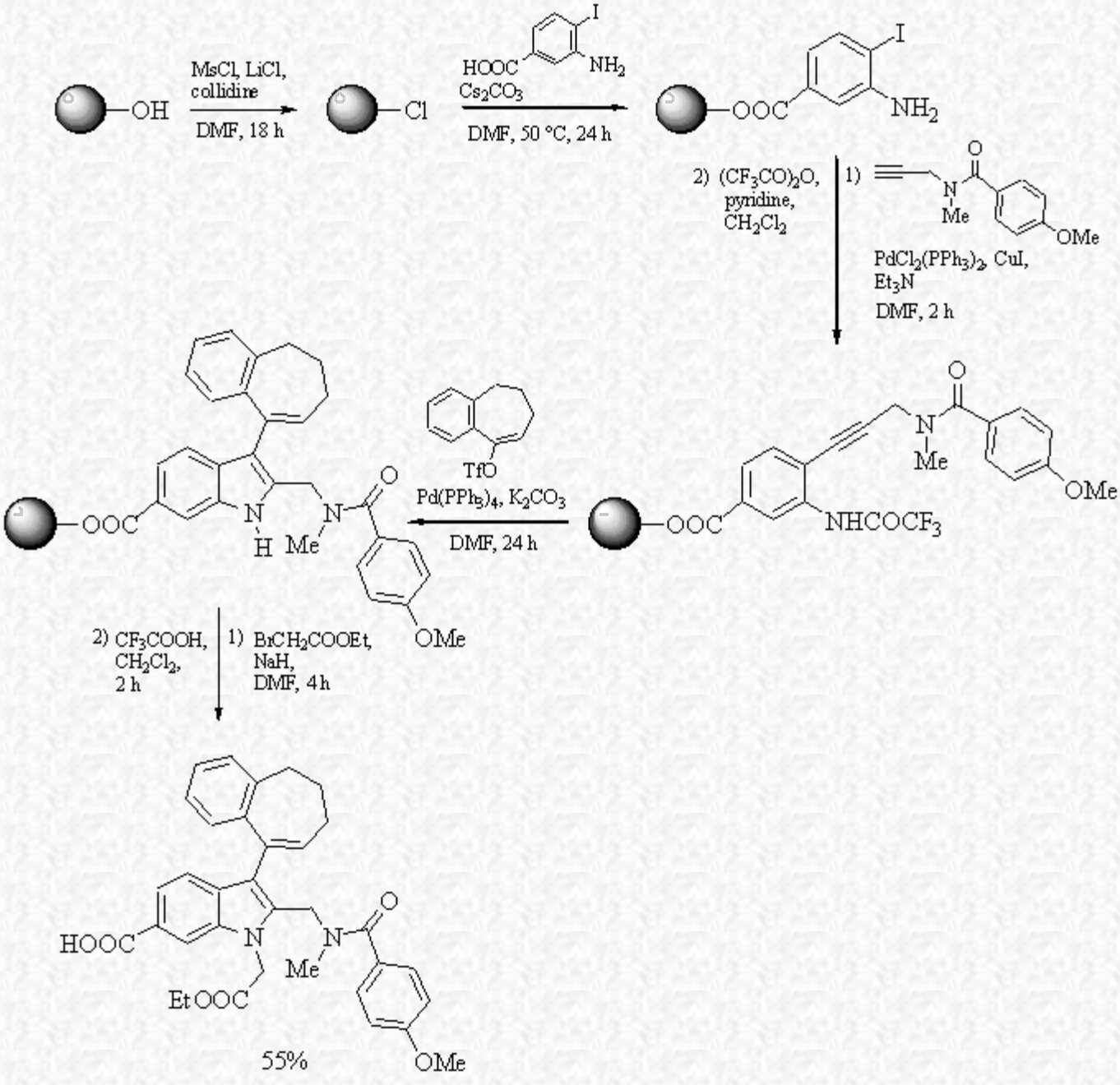
This tandem chemistry was adapted to a solid-supported synthesis for the preparation of combinatorial libraries of indoles with three variable components[6] (Scheme 4). Interestingly, K_2CO_3 was found to be the optimal base even though it could be expected that a soluble base would be needed for a solid phase synthesis. A solid base, NaH, resulted optimal even for the *N*-alkylation step.



Scheme 2.



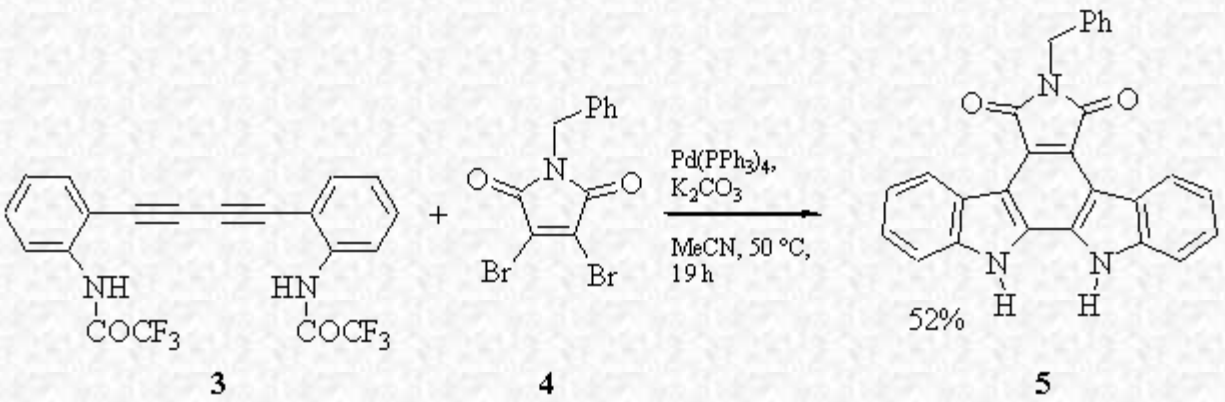
Scheme 3.



Scheme 4.

The methodology was successfully applied to an elegant, straightforward assembly of the parent indolo[2,3-a]carbazole ring,[7] common to several biologically active molecules such as arcyriaflavin A and the potent antitumor

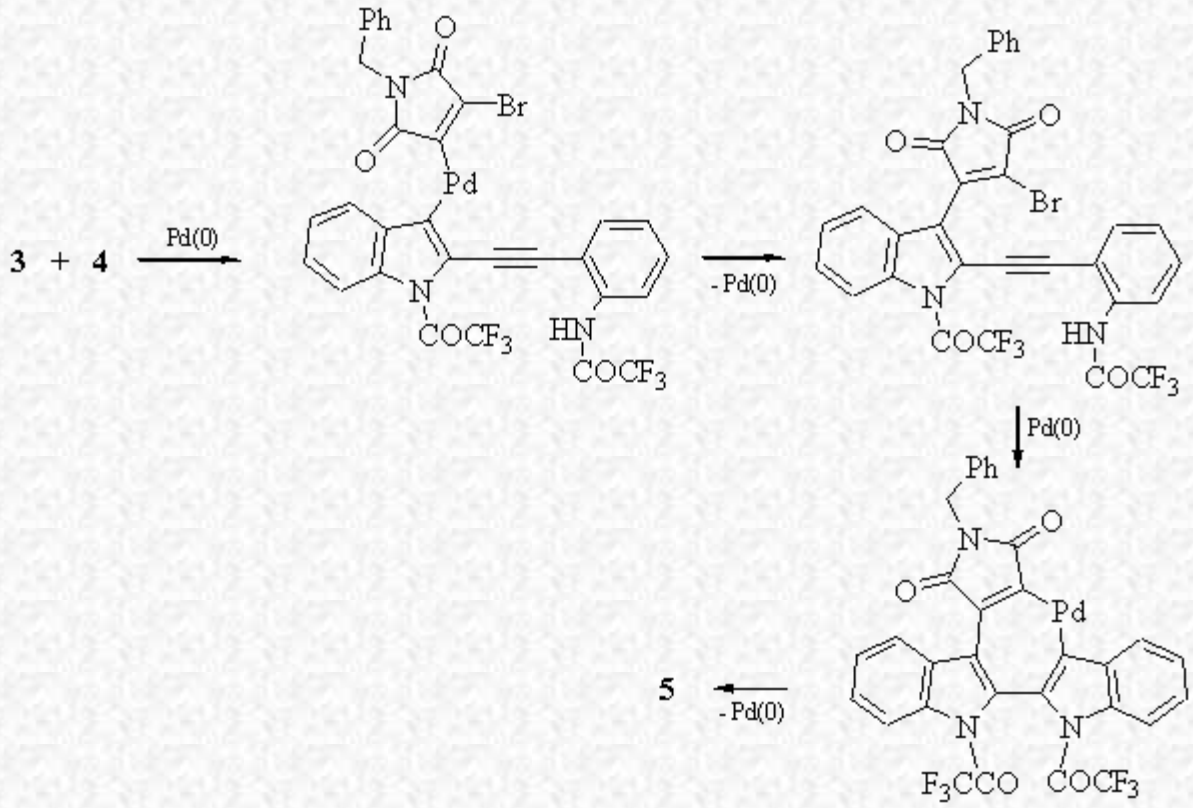
agent rebeccamycin. The process involves a polyannulation reaction wherein four bonds are formed in a single step from the simple 1,3-diacetylene precursor **3** - prepared from *o*-ethynylaniline through a two step process in an approximately overall 60% yield - and *N*-benzyl-3,4-dibromomaleimide (Scheme 5).



3 **4** **5**

Scheme 5.

The reaction is assumed to proceed according to the mechanism outlined in Scheme 6:



Scheme 6.

2-Unsubstituted-3-arylindoles

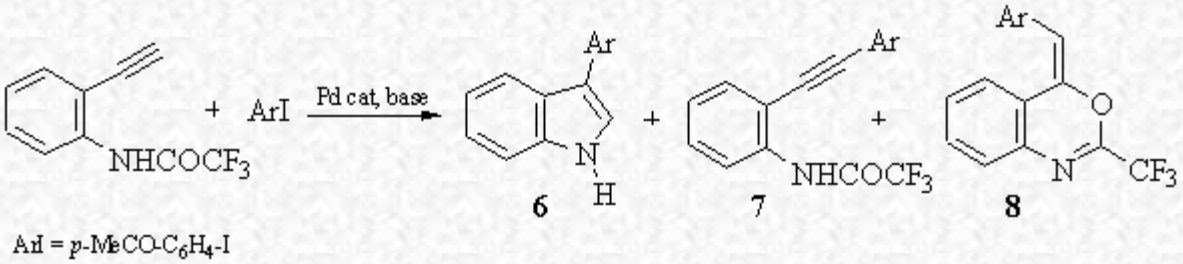
Since many biologically active 3-substituted indoles contain no substituents at the C-2,[8] we decided to extend the methodology to the synthesis of this indole nucleus via cyclization of *o*-ethynyltrifluoroacetanilide.[9] A model study was undertaken to determine the facility with which this class of indole derivatives would be generated by using our tandem chemistry.

Utilization of the same conditions employed in the synthesis of 2,3-disubstituted indoles[3] produced the desired derivatives in low yield along with the expected coupling byproducts. For example, with *p*-iodoacetophenone the

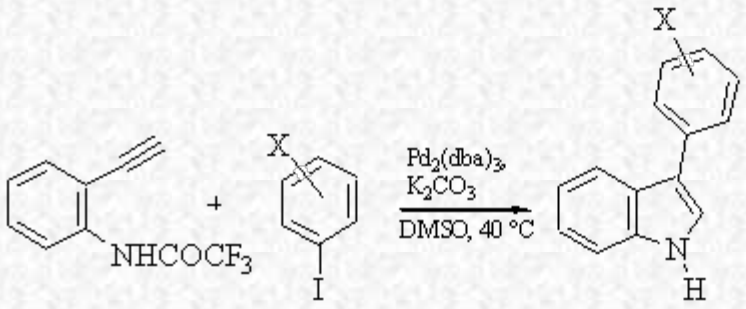
corresponding 3-arylindole **6** and the coupling product **7** were isolated in 23 and 37% yield, respectively (Scheme 7). The influence of ligands, temperature and solvents on the reaction outcome was investigated. Employment of $Pd_2(dba)_3$ as Pd(0) donor in the presence of a variety of phosphine ligands afforded **6** as the minor product, compound **7** was obtained in variable amounts [in the presence of tris(*p*-chlorophenyl)phosphine it was isolated in 83% yield] and the O-cyclization derivative **8** - very likely generated through the competitive oxypalladation-reductive elimination tandem reaction - resulted to be the main reaction product. The formation of the latter outlines the possible behavior of the trifluoroacetamido group as a bidentate (pro)nucleophile in this cyclization reaction.

The best results with regard to yields and reaction time were obtained in DMSO as solvent with K_2CO_3 as base, omitting the phosphine ligand at 40 °C. Under these conditions, compound **6** was isolated in 64% yield after 1.25 h (**8** was obtained in 17% yield). Interestingly, the O-cylization product is not formed when *p*-iodoacetophenone is reacted with an internal alkyne such as *o*-(phenylethynyl)trifluoroacetanilide under the same conditions: the corresponding 2,3-disubstituted indole was isolated in 94% yield. Since steric effects do not appear to account for such a different behavior, a tentative rationale considers the electron density of the acetylenic carbons as the main factor controlling the N-cyclization to O-cyclization ratio.[9]

Another reaction parameter that was found to influence remarkably the N-cyclization to O-cyclization ratio was found to be the cation of the carbonate base. For example, an approximately 4:1 ratio was obtained with K_2CO_3 that increased up to an approximately 21:1 in the presence of the more expensive Cs_2CO_3. The indole product **6**, however, was isolated in similar yield (62%). Therefore, K_2CO_3 was selected as the base when this cyclization procedure was extended to include other aryl iodides (Scheme 8).



Scheme 7.

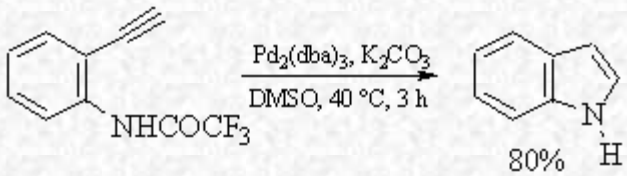


X = *p*-MeO- (56%); *p*-Me (63%); *p*-MeCONH (62%); H (67%); *p*-F (71%); *m*-F (57%); *p*-Cl (86%); *m*-CF (82%); *p*-EtOOC (69%); *m*-EtOOC (78%); *m*-NO_2 (85%); *m*-NO_2-*p*-Me (69%)

Scheme 8.

Under the same conditions that work well with aryl iodides, aryl bromides failed to give the desired 3-arylindoles. For example, *p*-bromoacetophenone was recovered essentially unchanged and the parent indole nucleus - most probably generated through a palladium-catalyzed cyclization - was isolated in 74% yield. That the formation of indole is based on a palladium-catalyzed reaction seems to be supported by the observation that *o*-ethynyltrifluoroacetanilide was recovered in 88% yield when it was treated under standard conditions omitting the aryl iodide and the palladium catalyst. However, indole was isolated in high yield when the same reaction was carried out in the presence of catalytic

amounts of $Pd_2(dba)_3$ (Scheme 9).

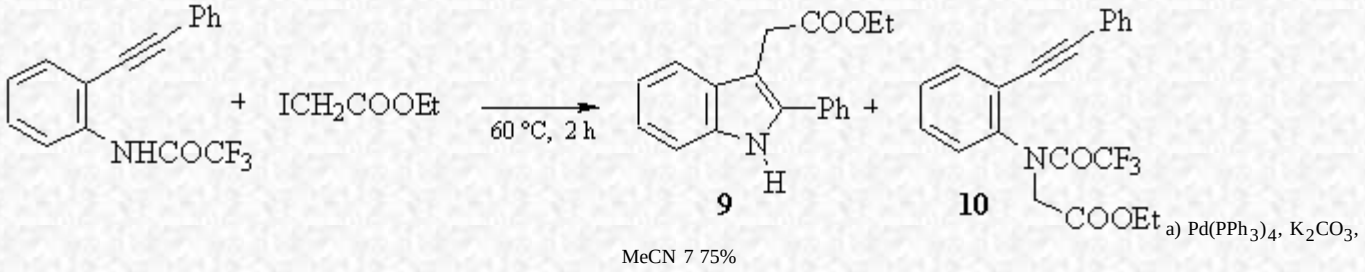


Scheme 9.

The methodology was next (*vide infra*) extended to the preparation of 2-unsubstituted indoles containing an allyl group at the C-3. 3-Unsubstituted-3-allylindoles, however, were isolated in moderate yield.

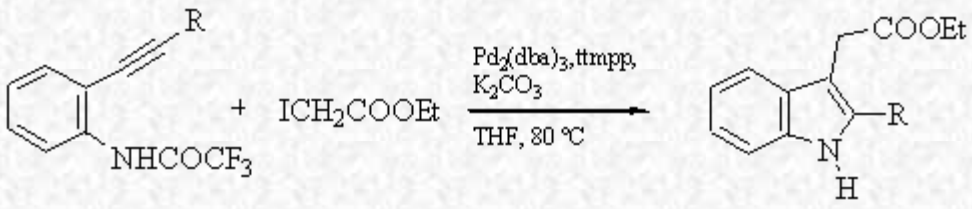
2-Substituted-3-alkylindoles

Current interest in the synthesis and reactivity[10] as well as biological activity[11] of indole-3-acetic acid derivatives, prompted us to explore the extension of our tandem methodology to the construction of indole rings containing the 3-(ethoxycarbonyl)methyl group.[12] Employment of the same conditions reported for the preparation of 2,3-disubstituted-indoles[3] (Schemes 10a) and 2-unsubstituted-3-arylindoles[9] (Scheme 10b) met with failure, at least with our model system. The *N*-alkyl derivative **10** - most likely generated via a competitive base-catalyzed nucleophilic substitution process - was isolated as the main or sole reaction product.



Scheme 10.

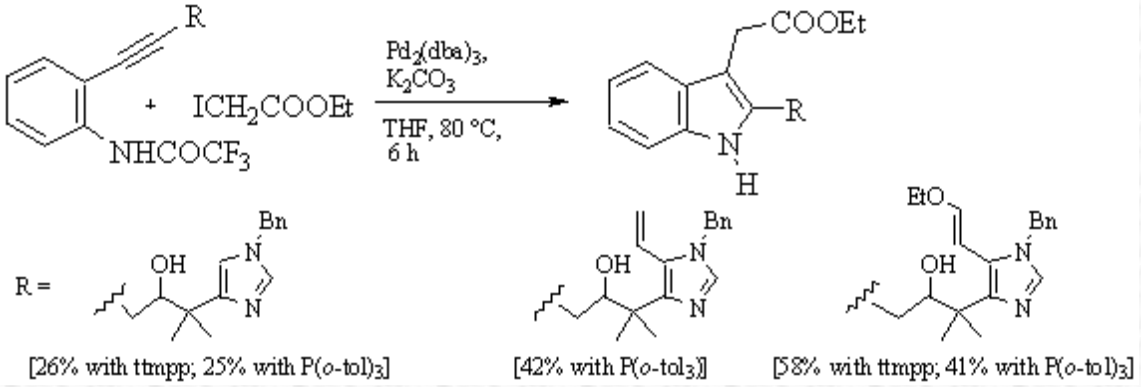
Ligands and solvents were found to play a major role in controlling the cyclization to *N*-alkylation ratio. Satisfactory results were obtained with $Pd_2(dba)_3$ and P(*o*-tol)$_3$ in THF. Employment of $Pd_2(dba)_3$ in conjunction with the strongly basic sterically demanding tris(2,4,6-trimethoxyphenyl)phosphine (ttmpp)[13] in THF provided the highest reaction rate and cyclization to *N*-alkylation ratio with our model system. By using these ligands, several indole derivatives bearing vinyl, aryl, simple alkyl (Scheme 11) as well as highly functionalized[14] (Scheme 12) substituents were prepared in satisfactory yield with only minor or trace amounts of the *N*-alkyl byproduct. Depending on the nature of the alkyne, unalkylated indoles were also isolated, sometimes in considerable amount.



R = Ph (73%); *o*-Me-C_6H_4- (70%); *p*-MeOC-C_6H_4- (64%); *o*-MeOCO-C_6H_4- (61%);

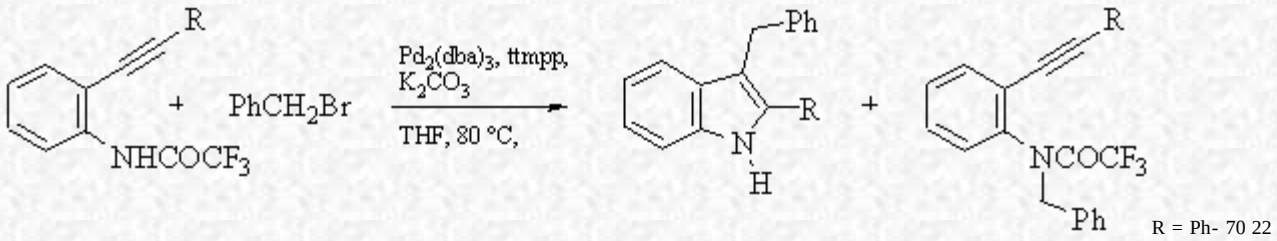
n-Bu- (44%);  (41%); *t*-Bu-  (78%)

Scheme 11.



Scheme 12.

Likewise, the reaction of *o*-alkynyltrifluoroacetanilides with benzyl bromide furnished 3-benzylindoles (Scheme 13).



R = Ph- 70 22

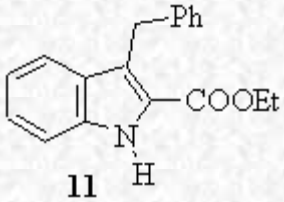
R = *p*-MeCO-C_6H_4- 65 12

R = *p*-MeOCO-C_6H_4- 62 16

R = 2-thienyl 50 22

Scheme 13.

Interestingly, during the course of our investigation of the influence of solvents on the palladium-catalyzed reaction of ethyl iodoacetate with *o*-alkynyltrifluoroacetanilides, we found out that employment of DMSO as solvent had a remarkable effect on the reaction outcome. Instead of indole-2-carboxylates and/or *N*-alkyl products, the reaction produced a 2-ethoxycarbonyl-3-alkylindoles in good yield. For example, the reaction of *o*-(phenylethynyl)trifluoroacetanilide with ethyl iodoacetate in the presence of $Pd_2(dba)_3$ and ttmpp in DMSO at 80 °C for 2 h led to the formation of the indole derivative **9** in 12% yield whereas the indole-2-carboxylate **11** was isolated in 64% yield.



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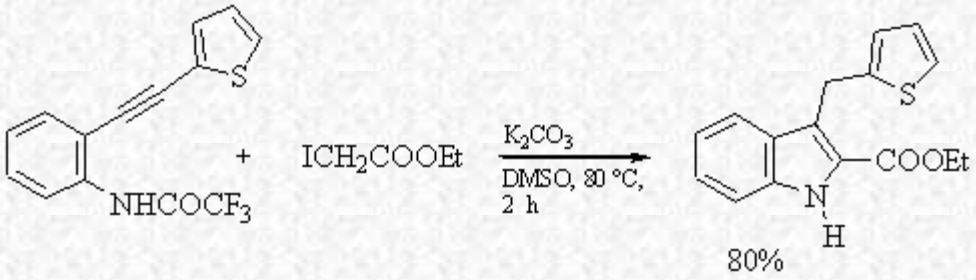
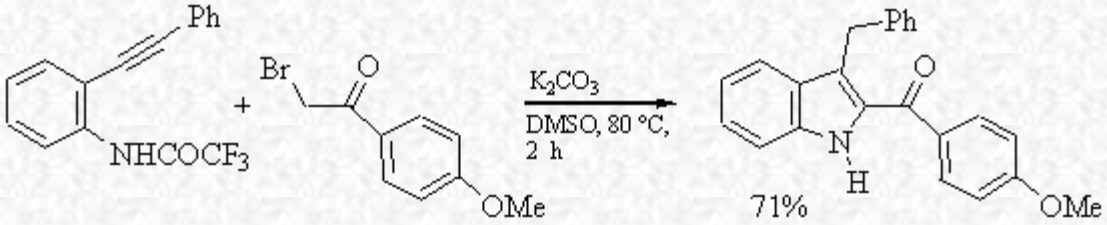
This cyclization reaction resulted to be independent of the palladium catalyst. A brief investigation of its scope was undertaken and we found that the reaction can be successfully employed for the preparation of a variety of indole-2-carboxylates (Scheme 14) and 2-acylindoles (Scheme15).[15]

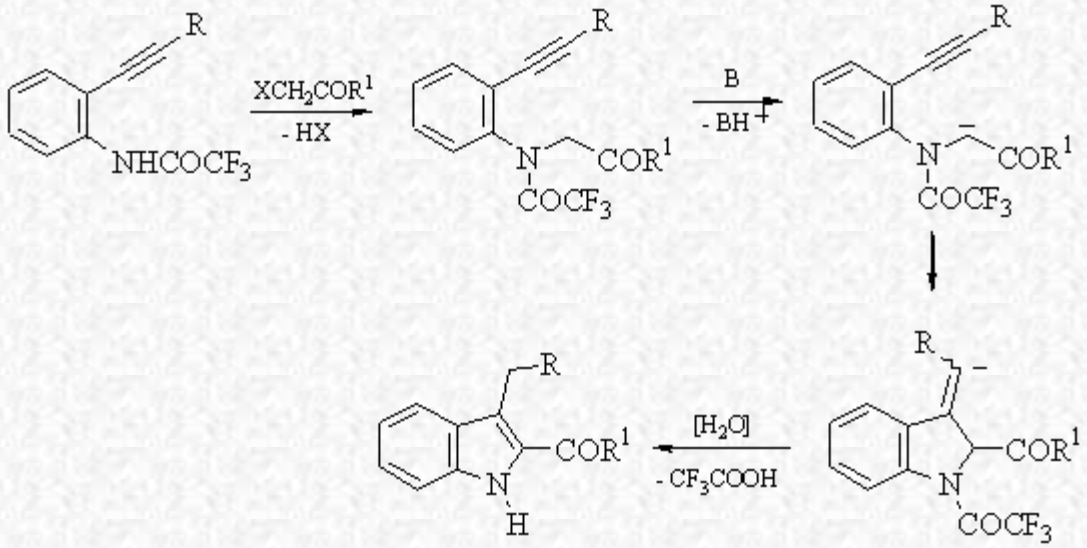


Scheme 14.



Scheme 15.

As to the mechanism, most probably the reaction proceeds through an *N*-alkylation step that is followed by a cyclization step, whose mechanism should be similar to that proposed for related base-catalyzed cyclization reactions of alkynes that we have recently investigated[16,17] (Scheme 16).



Scheme 16.

2-Substituted-3-allylindoles

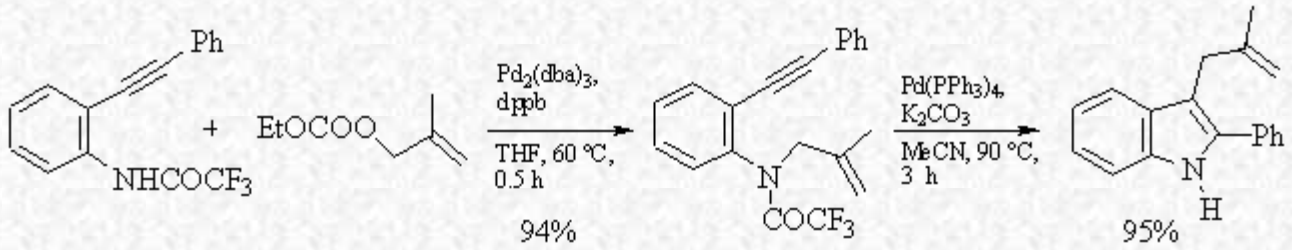
As an extension of our studies on this alkyne chemistry, we developed a new approach to the construction of the indole ring containing 3-allyl substituents which involves the utilization of allyl esters as carbon donors.[18] This method allows for the preparation of 3-allylindoles not available by means of the $PdCl_2(MeCN)_2$-catalyzed reaction of allyl chlorides with *N*-methoxycarbonyl-*o*-alkynylanilines, a process which is presumed to proceed via trapping of s-indolylpalladium intermediates with allyl chlorides and generates the new C-C bond regioselectively at the g-position in an S_N2' fashion.[4d]

We developed three basic procedures that allowed for the preparation of a variety of 2-substituted- and 2-unsubstituted-3-allylindoles (the latter, however, were obtained in moderate yield). Allyl carbonates were usually

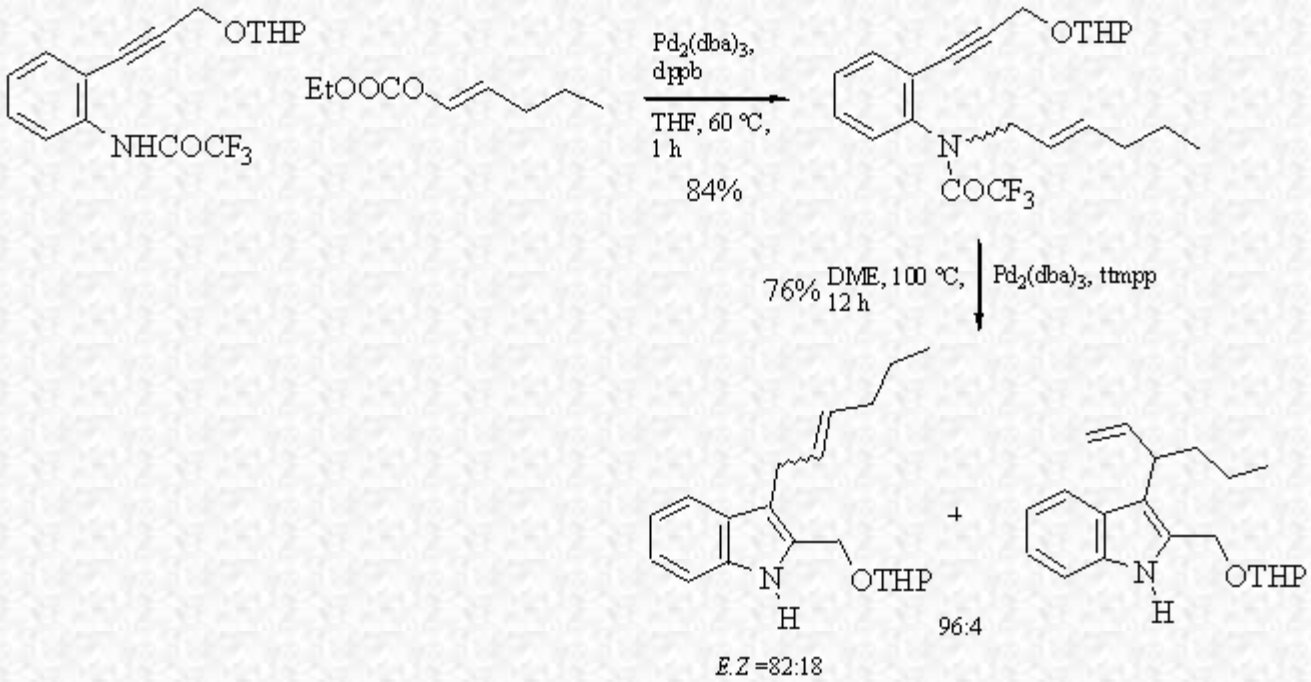
employed as allyl donors (with substituted allyl fragments, they gave better results then allyl acetates).

Two of these procedures are based on the initial formation of *N*-allyl derivatives generated through the nucleophilic attack of the nitrogen atom of the trifluoroacetamido group on the h^3-allylpalladium complex formed in situ from the allyl carbonate and the palladium catalyst. Satisfactory conditions for the *N*-allylation of *o*-alkynyltrifluoroacetanilides are as follows: $Pd_2(dba)_3$, 1,4-bis(diphenylphosphino)butane (dppb), THF, 60 °C. Only *N*-allyl derivatives bearing the nitrogen fragment on the less substituted allyl terminus were isolated.

When *N*-allyl derivatives are isolated (stepwise protocol), they can be converted into the corresponding 3-allylindoles by using $Pd(PPh_3)_4$ and K_2CO_3 in MeCN at 90 °C (Scheme 17) or $Pd_2(dba)_3$ and ttmpp in DME at 100 °C (Scheme 18). Employment of $Pd(PPh_3)_4$ gives good results with allylic carbonates generating symmetric h^3-allylpalladium complexes and when the two allylic termini are markedly different from a steric point of view. The $Pd_2(dba)_3$/ttmpp combination is the catalyst system of choice when the steric differences between the two allylic termini are small. In these cases, in the presence of ttmpp, the reaction exhibits remarkable regioselectivity and almost exclusive formation of 3-allylindoles with the indolyl moiety bound to the less substituted allyl terminus is usually observed.

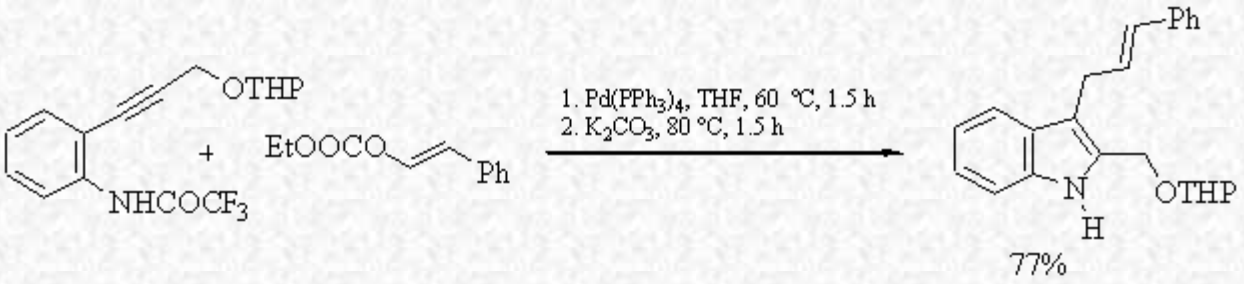


Scheme 17.



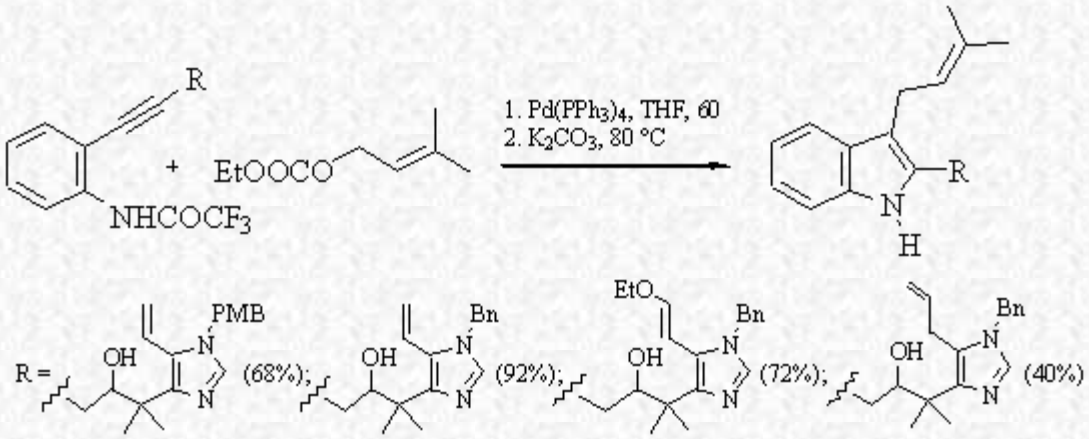
Scheme 18.

Alternatively, *N*-allyl derivatives can be converted into the corresponding indole products omitting their isolation (one-pot protocol): the starting alkyne and the allyl ester is treated with $Pd(PPh_3)_4$ in THF at 60 °C till the disappearance of the former, K_2CO_3 is added, and the temperature is raised up to 80 °C (Scheme 19).



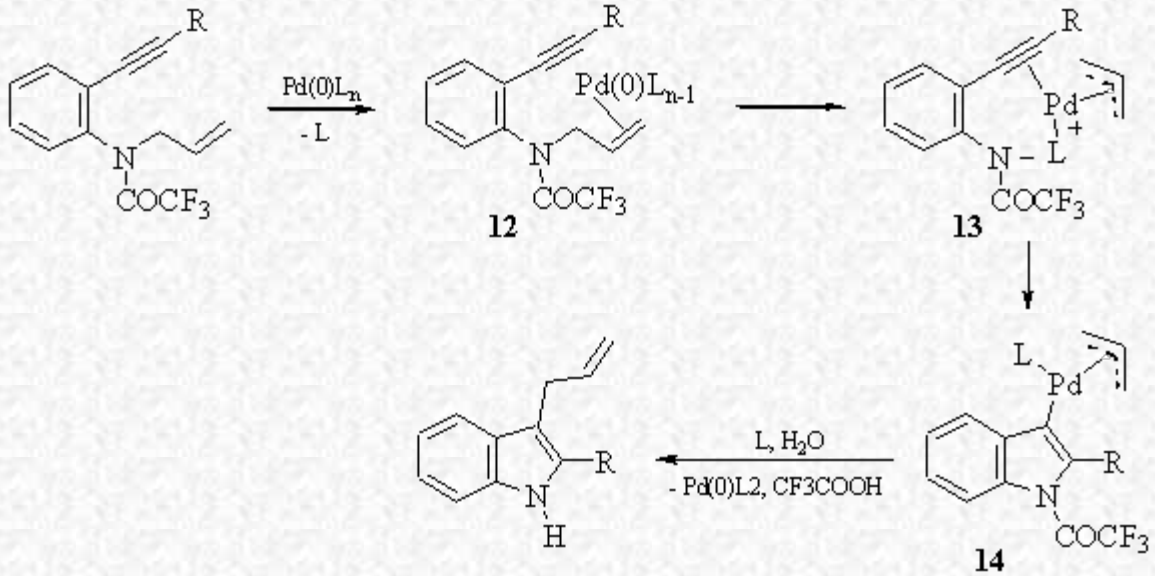
Scheme 19.

The procedure can tolerate a high degree of complexity in the alkyne fragment, as shown in the following synthesis of 3-prenylindoles (Scheme 20).[14]



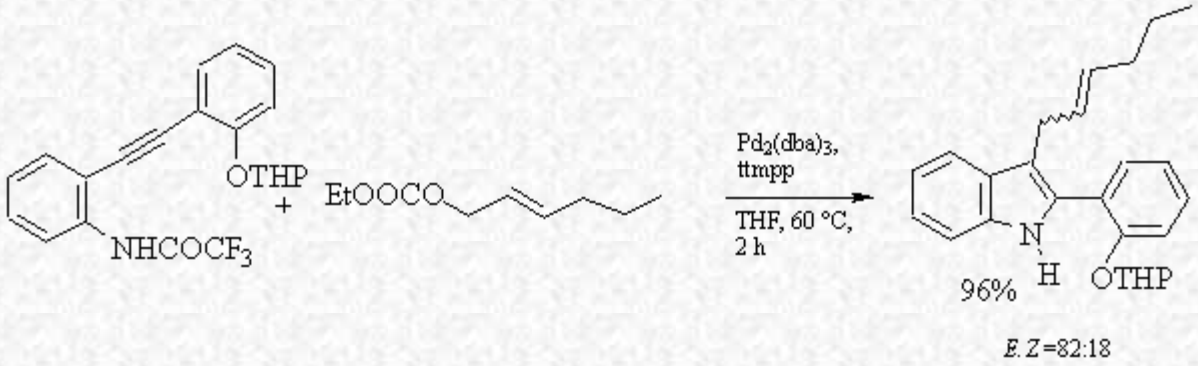
Scheme 20.

The formation of 3-allylindoles from *N*-allyl intermediates is envisioned to follow the mechanism outlined in Scheme 21 using the *N*-allyl intermediate derived from allyl carbonate: the h^2-olefinpalladium complex **12** formed initially is converted into the h^3-alkynepalladium complex **13** via ionization of the N-C_{allyl} bond and displacement of one ligand to palladium by the C-C triple bond; subsequent nucleophilic attack of the nitrogen atom across the activated acetylenic fragment affords the s-indolyl-h^3-allylpalladium complex **14** from which the indole product is generated through reductive elimination of Pd(0) species.



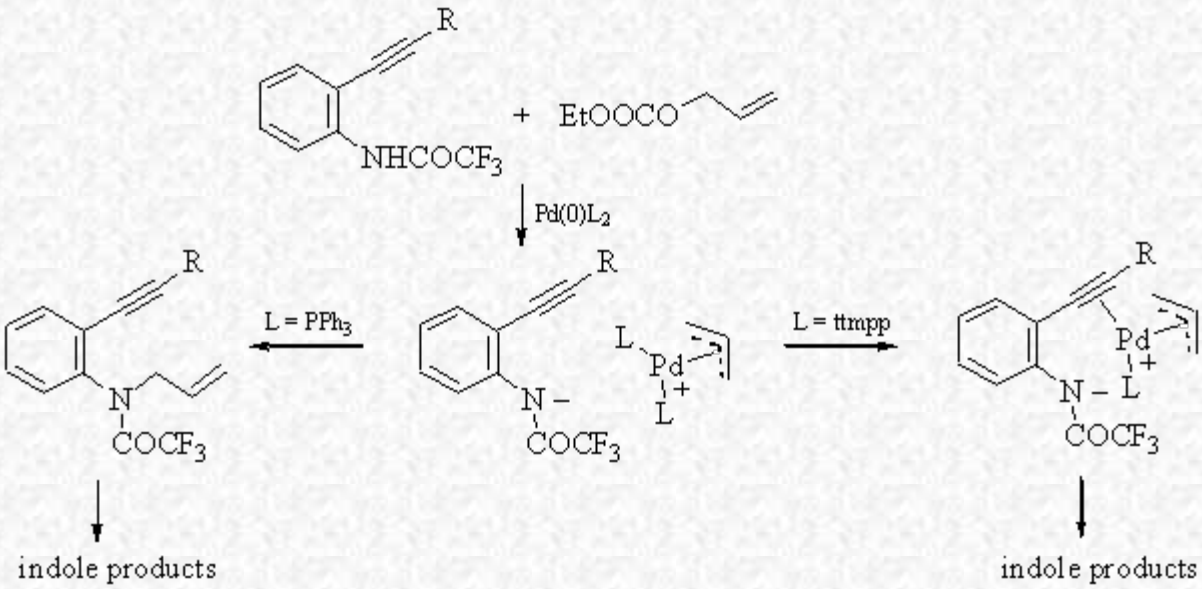
Scheme 21.

The third procedure we developed for the preparation of 3-allylindoles is based on the reaction of *o*-alkynyltrifluoroacetanilides with allyl carbonates in the presence of $Pd_2(dba)_3$ and ttmpp (Scheme 22).



Scheme 22.

Under these conditions no *N*-allyl intermediate is discernible in the reaction mixture. Apparently, coordination of the alkyne to the h^3-allylpalladium complex derived from the allyl carbonate is faster than *N*-allylation and an h^2-alkyne-h^3-allylpalladium intermediate is formed preferentially over the *N*-allyl derivative (Scheme 23).



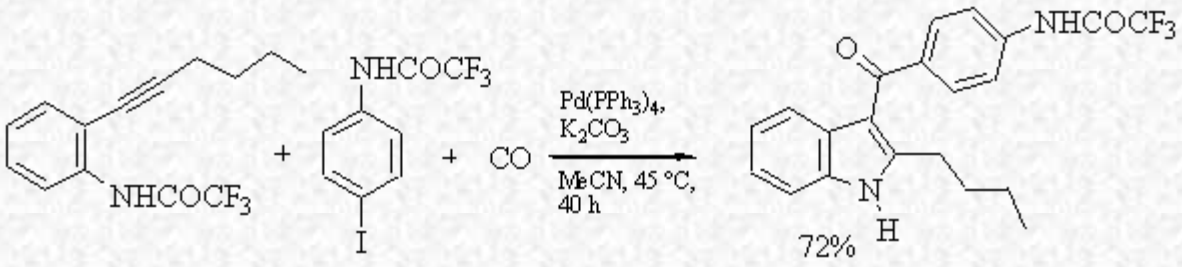
Scheme 23.

2-Substituted-3-acylindoles

The chemistry utilized in the preceding sections for the construction of the indole skeleton is based on the assembly of two components. We thought that the addition of carbon monoxide as a third component would provide an opportunity for generating indole molecules possessing a higher degree of complexity which would otherwise require technically demanding multi-step synthesis. Specifically, we surmised that the procedure might provide a ready approach to indole derivatives containing an acyl group at the C-3.

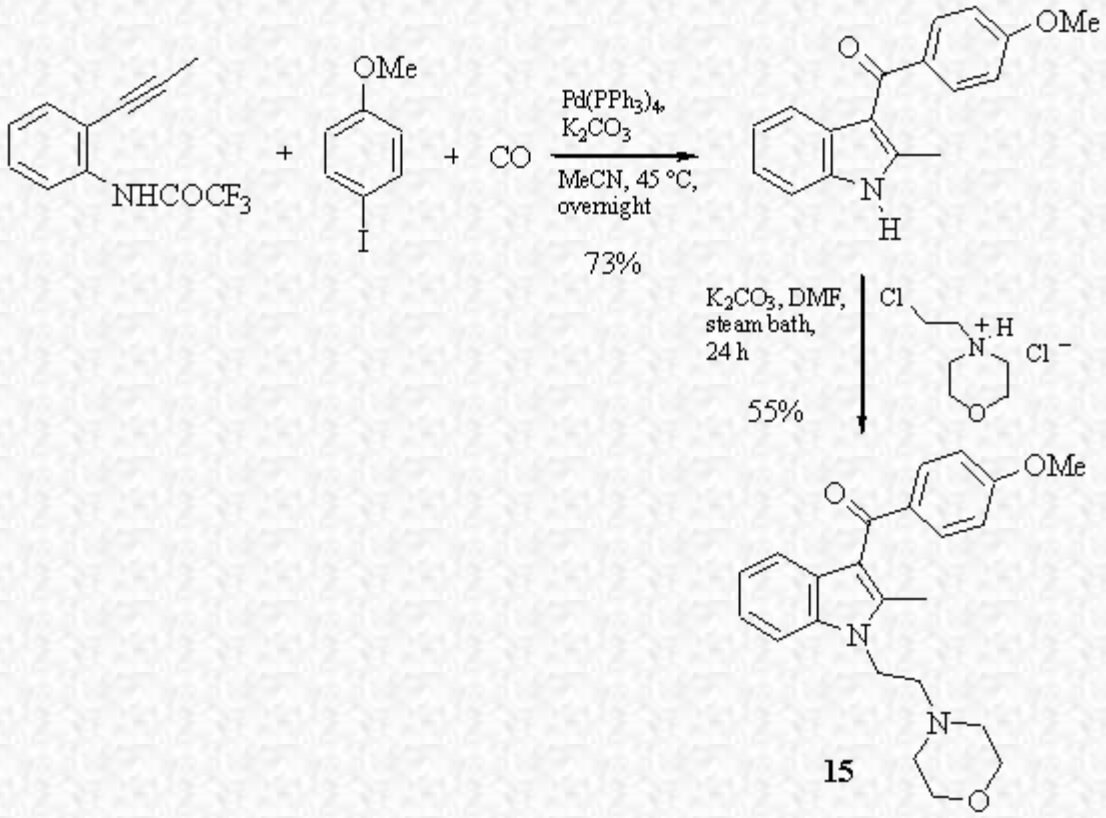
After some experimentation, it was found that the employment of $Pd(PPh_3)_4$ or $Pd(OAc)_2(PPh_3)_2$ in acetonitrile under a balloon of carbon monoxide could give good results with many aryl iodides[19] (Scheme 24). The use of anhydrous acetonitrile and a higher pressure of carbon monoxide or, alternatively, $Pd_2(dba)_3$ and P(*o*-tol)$_3$ under standard conditions was found necessary with aryl iodides containing electron-withdrawing substituents. With vinyl triflates the

employment of anhydrous acetonitrile gave the best results.



Scheme 24.

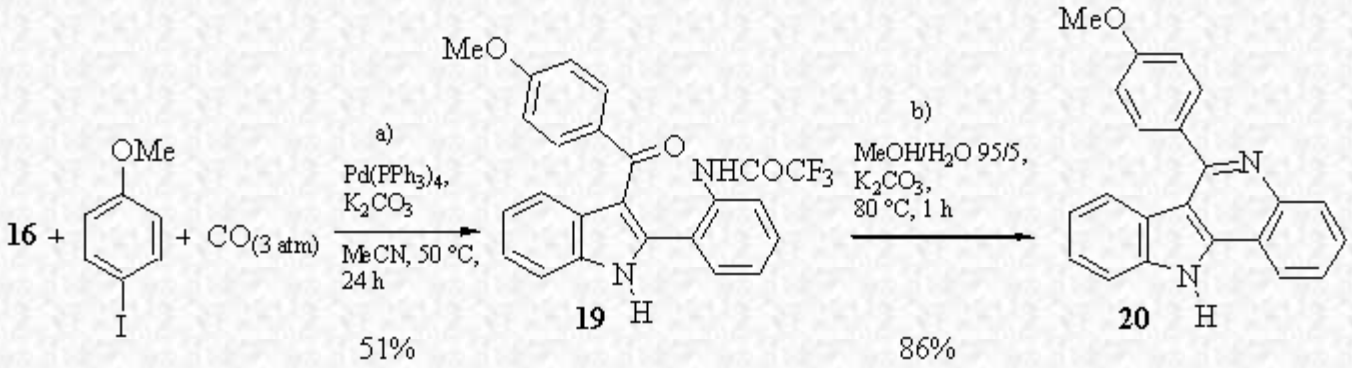
The methodology was applied to the synthesis of pravadoline **15**, an indole derivative designed as a nonacidic analogue of non-steroidal anti-inflammatory drugs (NSAIDs)[20] (Scheme 25)



Scheme 25.

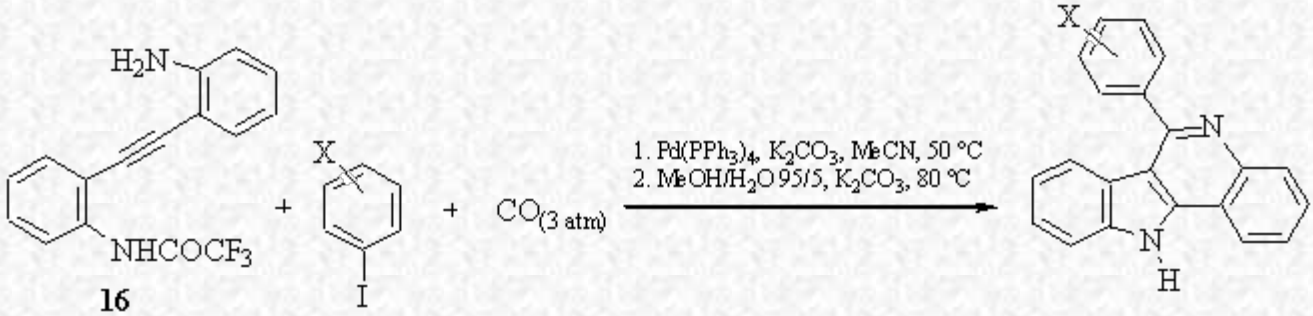
Having established the conditions that allow for the conversion of *o*-alkynyltrifluoroacetanilides into 3-acylindoles, we next focused our attention on the possible utilization of 3-acylindoles bearing suitable functionality in a subsequent cyclization step. Since we were particularly interested in the preparation of indoloquinolines,[21] the reaction of *o*-(*o'*-aminophenylethynyl)trifluoroacetanilide **16** was explored. Interestingly, first attempts showed that the reaction produced the 2-(*o*-trifluoroacetamidophenyl)-3-acylindoles **17** instead of the expected 2-(*o*-aminophenyl)-3-acylindoles **18**.

For example, exposure of **16** to *p*-iodoanisole in the presence of $Pd(PPh_3)_4$ under 3 atm of carbon monoxide formed the trifluoroacetamido derivative **19** (Scheme 26a). This result, however, did not invalidate our approach to indoloquinolines. Compound **19**, in fact, was readily converted into the corresponding derivative **20** in high yield by treatment with $MeOH/H_2O$ 95/5 and K_2CO_3 (Scheme 26b).



Scheme 26.

Using such a stepwise protocol can perform the preparation of indoloquinolines. The process, however, can be more conveniently carried out as a one-pot procedure omitting the isolation of acylindole intermediates. Employment of the one-pot procedure allowed for the preparation of several substituted indoloquinolines from aryl iodides containing electron-donating and electron-withdrawing substituents (Scheme 27).

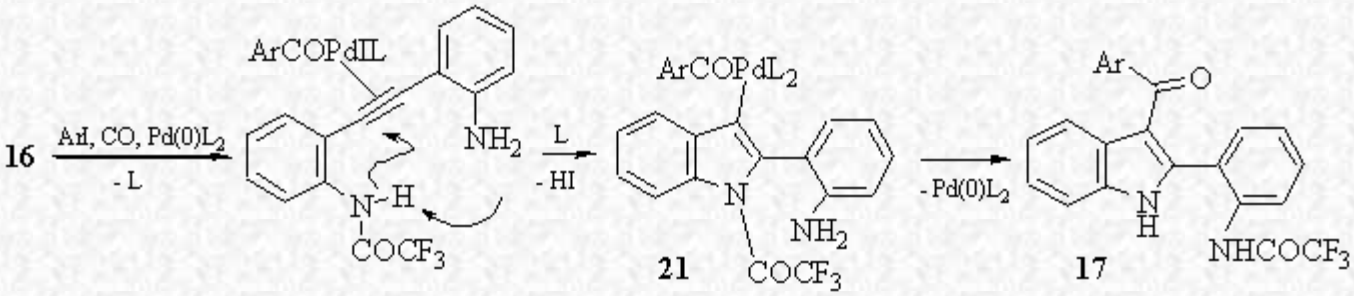


X = H (80%); *p*-MeCO (48%); *m*-Me (86%); *p*-F (79%); *m*-CF_3 (40%); *p*-Me,*m*-NO_2 (40%); *p*-HO,*m*-Me (35%); *o*,*p*-Me_2 (70%); *p*-MeCONH (51%);

Scheme 27.

A reasonable rationale for the formation of 2-(*o*-trifluoroacetamidophenyl)-3-acylindoles is outlined in Scheme 28: nucleophilic attack of the nitrogen atom of the trifluoroacetamido group across the C-C triple bond activated by coordination to an acylpalladium complex generates **21**, which subsequently undergoes the reductive elimination of Pd(0) species and a transamidation reaction, not necessarily in this order. The possibility that formation of the indole derivative **17** may involve the free amino group in the cyclization step is ruled out by our early studies[3] showing that the free amino group is unable to participate in the aminopalladation-reductive elimination tandem process and by the observation that none of the indole product was formed when bis(*o*-aminophenyl)acetylene, containing two free amino

groups, was subjected to cyclization conditions.



Scheme 28.

Concluding Remarks

Over the past few years we have shown that many diverse indole derivatives can be readily accessed via the *aminopalladation-reductive elimination tandem reaction*. The key step of the process is the intramolecular nucleophilic attack of a proximate nitrogen nucleophile across the C-C triple bond activated via coordination to the palladium atom of an organopalladium complex generated in situ. The reaction can tolerate a variety of internal and external alkynes and a number of precursors of organopalladium intermediates (aryl and vinyl halides or triflates, alkyl halides, allyl esters). In the presence of carbon monoxide it allows for the synthesis of indole products that incorporate a molecule of carbon monoxide. New applications and further evolution of the methodology will undoubtedly widen its scope in the future.

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