The Aminopalladation/Reductive Elimination Domino Reaction in the Construction of Functionalized Indole Rings

Gianfranco Battistuzzi,[a] Sandro Cacchi,*[a] and Giancarlo Fabrizi[a]

Dedicated to Professor B. S. Thyagarajan on the occasion of the Symposium honoring his career

Keywords: Alkynes / Catalysis / Cyclization / Domino reaction / Palladium

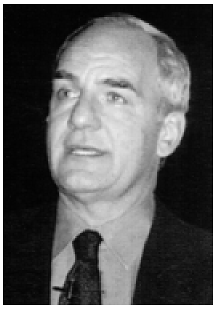
The palladium-catalyzed reaction between *o*-alkynyltrifluoroacetanilides and aryl and vinyl iodides, bromides or triflates, alkyl halides and allyl esters has been developed into an efficient and versatile procedure for the construction of substituted pyrrole nuclei incorporated into indole systems. The reaction can be performed in the presence of carbon monoxide, producing indoles incorporating a molecule of carbon monoxide. In this Microreview, we discuss the concept of this useful approach to the preparation of a variety of indole derivatives and comment on the parameters influencing the reaction outcome.

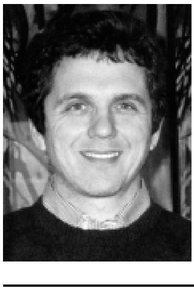
Introduction

The aminopalladation/reductive elimination domino reaction of internal and terminal alkynes containing proximate nitrogen nucleophiles has proven to be a powerful and useful tool for the construction of substituted pyrrole nuclei incorporated into indole systems. The fact that the reaction can be carried out with a wide assortment of organopalladium precursors and readily available starting alkynes, its ease of execution, and its tolerance of a wide range of functional groups highlight its importance and flexibility, and may contribute toward its utilization in the synthesis of

---

[a] Dipartimento di Studi di Chimica e Tecnologia delle Sostanze Biologicamente Attive, Università degli Studi "La Sapienza", P.le A. Moro 5, 00185 Roma, Italy





Gianfranco Battistuzzi (top, left) was born in Rome in 1973. He graduated in Chemistry at "La Sapienza" University, Rome in 2000. He is now in the second year of his Ph.D. studies at the "Dipartimento di Studi di Chimica e Tecnologia delle Sostanze Biologicamente Attive" under the supervision of Professor Sandro Cacchi. He is interested in organic synthesis and the organometallic chemistry of palladium.

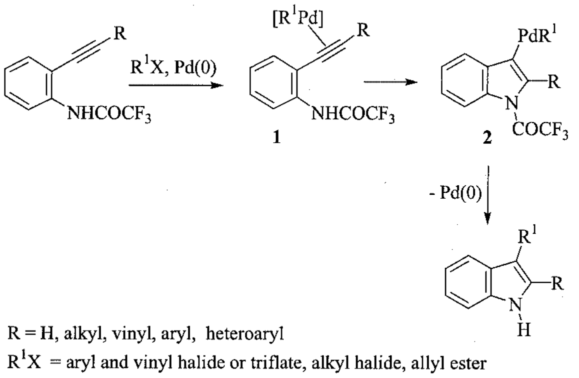
Sandro Cacchi (top, right) was born in Macerata (Marche) in 1943. He began his university training at the University of Camerino, where he graduated in Chemistry in 1967. He moved directly to the University of Bologna, where he worked under the direction of Professor Luciano Caglioti. After his national service (October 1968 to December 1969), he returned to the University of Bologna and was promoted to Assistant Professor in 1970. In 1972 he joined "La Sapienza" University, Rome, where he became Associate Professor of Organic Chemistry (in 1983), and subsequently (1986), full Professor of Organic Chemistry. Professor Cacchi made a contribution early in his career with the development of new, selective synthetic procedures directed toward the functionalization or preparation of complex molecules. More recently, the utilization of palladium catalysis in organic synthesis has been a major goal that he has pursued in many ways, with the search for new and selective methodologies being a major thrust even in this area.

Giancarlo Fabrizi (bottom, left) was born in Rome, in 1963. He graduated in Medicinal Chemistry and Technology at "La Sapienza" University, Rome in 1987. He spent four years (1990−1994) at the Science Department of the University of L'Aquila as an Inorganic Chemistry Researcher. In 1994 he became an Organic Chemistry Researcher at the Dipartimento di Studi Chimica e Tecnologia delle Sostanze Biologicamente Attive in Rome, working under the supervision of Professor Sandro Cacchi and since 2001 he has been Assistant Professor at the same department. He is interested in organic synthesis, the organometallic chemistry of palladium, asymmetric synthesis, and NMR techniques.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

complex indole derivatives. The method may provide a versatile complement to 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*-haloanilines, the Madelung cyclization of *N*-acyl-*o*-toluidines, and the reductive cyclization of *o*-nitrobenzyl ketones,[1] to name a few, and an effective alternative to other palladium-based approaches to the construction of pyrrole nuclei incorporated into indole systems, such as the cyclization of *N*-allyl-*o*-haloanilines,[2] *o*-halo-*N*-propargylanilides,[3] *o*-vinylanilines and *o*-vinylnitroarenes,[4] *o*-allylanilines,[5] *o*-haloanilino enamines,[6] the coupling/cyclization methodology,[7] and the annulation of internal alkynes.[8]

The reaction most probably proceeds through the intermediacy of the (η^2-alkyne)organopalladium complex **1** − formed by coordination of the alkyne to an organopalladium complex generated in situ − that undergoes an intramolecular nucleophilic attack by the nitrogen atom across the carbon−carbon triple bond. Subsequently, the resultant σ-indolylpalladium intermediate **2** affords the desired indole product by a reductive elimination step that regenerates the palladium catalyst (Scheme 1).



Scheme 1

The course of the reaction 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 carbon atoms, the absence, presence, and nature of phosphane ligands, and the strength of the nucleophilic center. This article reviews some of our results in this area.

2-Substituted 3-Aryl(vinyl)indoles

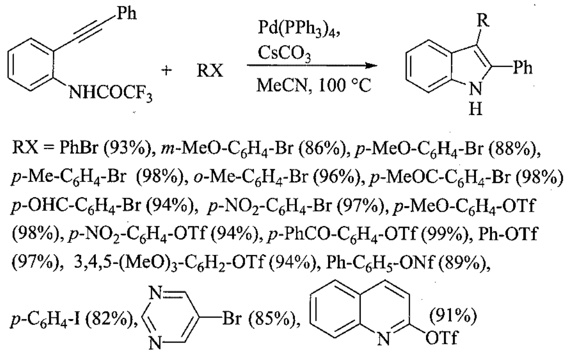
In 1992, as an extension of our oxypalladation/reductive elimination domino reaction of pentynoic acids,[9,10] we started our studies on the use of the aminopalladation/reductive elimination domino reaction to prepare 2,3-disubstituted indole products.[11] We believed that such a procedure should provide a fundamentally new, straightforward approach to the construction of functionalized pyrrole rings incorporated into indole systems, from arylalkynes containing nitrogen nucleophiles in the *ortho* position and aryl iodides or vinyl triflates.

Our early studies showed that the reaction outcome could be influenced by the base and the nature of the nitrogen nucleophile. Best results were obtained by use of K_2CO_3, whereas the employment of triethylamine gave lower yields. As for the nitrogen nucleophile, the starting alkyne was recovered in 88 and 79% yield, respectively, when *o*-(phenylethynyl)aniline was treated with *p*-chlorophenyl iodide and cyclooct-1-en-1-yl triflate. The use of *o*-(phenylethynyl)acetanilide produced similar results; the starting alkyne was recovered in 98 and 97% yield, respectively. A change to *o*-(phenylethynyl)trifluoroacetanilide, however, resulted in the isolation of the desired indole products in 80 and 74% yield, respectively.

The dramatic change observed with the trifluoroacetamido 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, in order to perform an intramolecular attack across the carbon−carbon triple bond of the (η^2-alkyne)organopalladium intermediate. Alternatively, proton removal from the amido group in the transition state, giving rise to the *trans* addition aminopalladation intermediate, might also be involved. Whatever the real mechanism may be, it remains the case that the organopalladium complexes used by us appear to be less effective than palladium dichloride in activating the carbon−carbon triple bond toward intramolecular nucleophilic attack. A number of palladium dichloride catalyzed cyclizations of alkynes containing amino[12] and amido[12d,13] groups close to the carbon−carbon triple bond support this view.

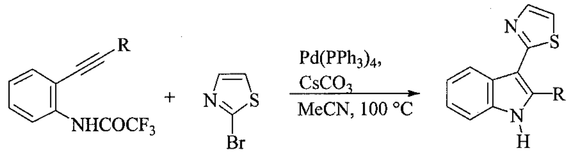
The trifluoroacetamido group provides the additional advantage of being readily cleaved, so as to allow the formation of the indole product containing the free amino functionality.

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 and at 80 °C with aryl iodides. Subsequently, the reaction was extended to a wide variety of aryl and heteroaryl bromides, triflates, and nonaflates. The best results were obtained by the use of $Pd(PPh_3)_4$ as the precursor of the catalytic species, Cs_2CO_3 as the base, and acetonitrile as the solvent (Scheme 2).[14]



Scheme 2

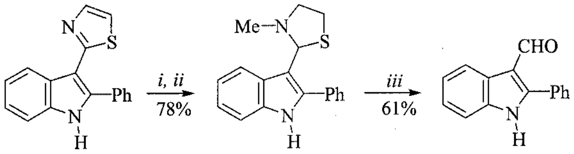
Electron-withdrawing and electron-donating groups are tolerated well in the substituent bound to the *ortho*-ethynyl fragment (Scheme 3).



R = *p*-MeOC-C_6H_4- (74%), *p*-MeO-C_6H_4- (80%), *p*-NO_2-C_6H_4- (40%), Ph (70%)

Scheme 3

The successful preparation of 3-thiazolylindoles may offer a route to indole-3-carbaldehydes from *o*-alkynyltrifluoroacetanilides. As an example, 2-phenylindole-3-carbaldehyde has been prepared from *o*-(phenylethynyl)trifluoroacetanilide in about 35% overall yield by the procedure described in the literature for the conversion of the thiazolyl group into the formyl group[15] (Scheme 4).



i: MeI, MeCN, 90 °C, 12 h; *ii*: $NaBH_4$, MeOH, -10 °C;
iii: CuO, $CuCl_2 \cdot H_2O$, MeCN/H_2O 10/1 (*ii* + *iii* 2 h)

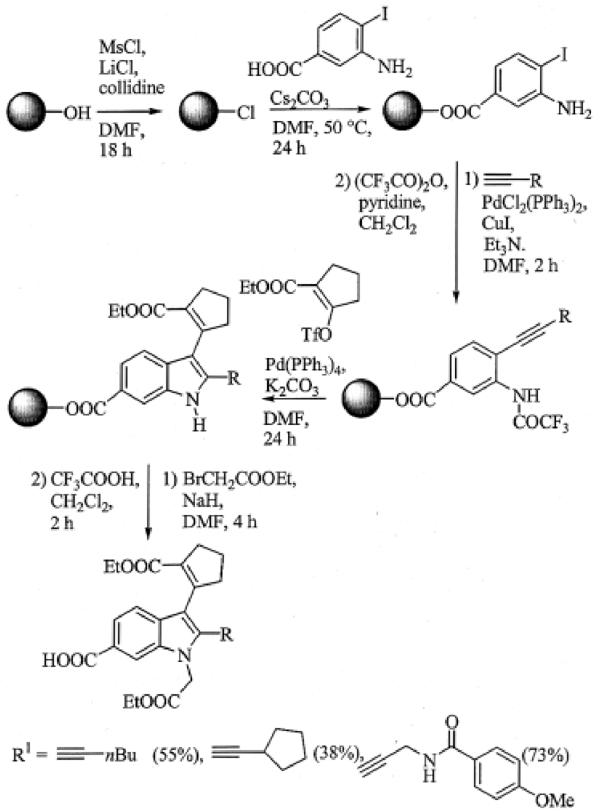
Scheme 4

This domino chemistry has been adapted to a solid-supported synthesis for the preparation of combinatorial libraries of indoles with three variable components[16] (Scheme 5). Interestingly, K_2CO_3 was found to be the optimal base even though it might have been expected that a soluble base would be needed for a solid-phase synthesis. Another solid base, NaH, proved to be optimal even for the *N*-alkylation step.

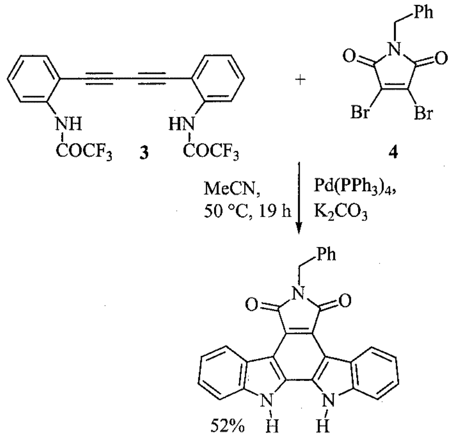
This methodology was successfully applied to an elegant, straightforward assembly of the parent indolo[2,3-*a*]carbazole ring,[17] common to several biologically active molecules such as arcyriaflavin A and the potent antitumor agent rebeccamycin. The process involved a polyannulation reaction in which four bonds were formed in a single step from the simple 1,3-diacetylene precursor **3** (prepared from *o*-ethynylaniline by a two-step process in approximately 60% overall yield) and *N*-benzyl-3,4-dibromomaleimide (Scheme 6).

2-Unsubstituted 3-Arylindoles

Since many biologically active 3-substituted indoles contain no substituents at C-2,[18] we decided to extend the methodology to the synthesis of this indole nucleus by cyclization of *o*-ethynyltrifluoroacetanilide.[19] A model study was undertaken to determine the facility with which this



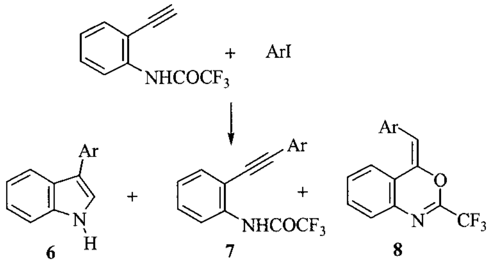
Scheme 5



Scheme 6

class of indole derivatives would be generated by use of our domino chemistry.

Use of the same conditions as employed in the synthesis of 2,3-disubstituted indoles[11] produced the desired derivatives only in low yields, along with the expected coupling byproducts. With *p*-iodoacetophenone, for example, the corresponding 3-arylindole **6** and the coupling product **7** were isolated in 23 and 37% yields, respectively (Scheme 7). The influence of ligands, temperature, and solvents on the outcome of the reaction was investigated. Use of $Pd_2(dba)_3$ as Pd^0 donor in the presence of a variety of phosphane ligands afforded **6** as the minor product, with compound **7** being obtained in variable amounts [in the presence of tris(*p*-chlorophenyl)phosphane (tcpp), with a Pd/ligand = 1:6 ratio, it was isolated in 83% yield] and the *O*-cyclization derivative **8** resulting as the main reaction product. The formation of the latter – very probably generated through a competitive oxypalladation/reductive elimination domino reaction[20] – underlines the behavior of the trifluoroacetamido group as a bidentate (pro)nucleophile in this cyclization reaction.

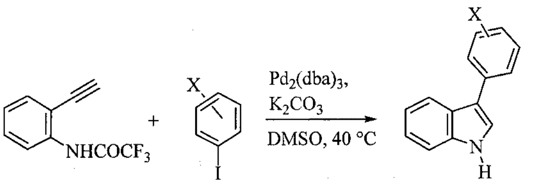


ArI = p-MeCO-C_6H_4-I

Reaction conditions	**6**	**7**	**8**
a) $Pd(PPh_3)_4$, K_2CO_3, MeCN, 80 °C, 1 h	23%	37%	–
b) $Pd_2(dba)_3$, ttmpp, K_2CO_3, THF, 60 °C, 7 h	18%	5%	61%
c) $Pd_2(dba)_3$, $Pd(PPh_3)_4$, K_2CO_3, THF, 60 °C, 7 h	25%	23%	36%
d) $Pd_2(dba)_3$, tcpp, K_2CO_3, THF, 60 °C, 7 h	28%	13%	46%
e) $Pd_2(dba)_3$, K_2CO_3, DMSO, 40 °C, 1.25 h	64%	8%	17%
f) $Pd_2(dba)_3$, Cs_2CO_3, DMSO, 40 °C, 1 h	62%	–	3%

Scheme 7

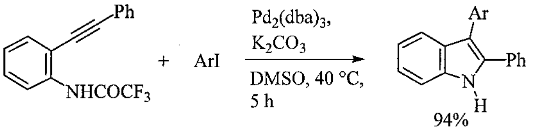
The best results with regard to yields and reaction times were obtained in DMSO as solvent, with K_2CO_3 as base, at 40 °C, and with the phosphane ligand omitted. Under these conditions, compound **6** was isolated in 64% yield. Another reaction parameter that was found to influence the *N*-cyclization/*O*-cyclization ratio remarkably was the cation of the carbonate base. For example, an approximately 4:1 ratio was obtained with our model system with K_2CO_3, but this increased to 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, the less expensive K_2CO_3 was usually employed as the base when this cyclization procedure was extended to include other aryl iodides (Scheme 8).



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

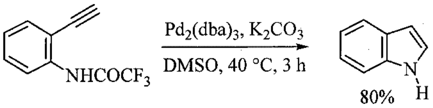
Interestingly, while the formation of 3-arylindoles from *o*-ethynyltrifluoroacetanilide has been found to compete with the formation of the *O*-cyclization product, no products derived from the *O*-cyclization process are usually observed when 2,3-disubstituted indoles are prepared from *o*-alkynyltrifluoroacetanilides under the same conditions. For example, whereas the reaction between *p*-iodoacetophenone and *o*-ethynyltrifluoroacetanilide afforded the *O*-cyclization by-product in 17% yield (Scheme 7e), no evidence of the same derivative was found in the reaction between *p*-iodoacetophenone and *o*-(phenylethynyl)trifluoroacetanilide (Scheme 9). A tentative rationale accounting for such behavior considers the electron density of the acetylenic carbon atoms as the main factor controlling the *N*-cyclization/*O*-cyclization ratio.[19]



ArI = p-MeOC-C_6H_4-I

Scheme 9

Under the same conditions that had worked 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 but with omission of the aryl iodide and the palladium catalyst. However, the 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 10).

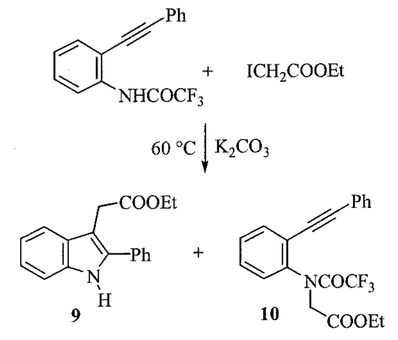


Scheme 10

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

2-Substituted 3-Alkylindoles

Current interest in the synthesis and reactivity[21] as well as the biological activity[22] of indole-3-acetic acid derivatives prompted us to explore the extension of our domino methodology to the construction of indole rings containing the 3-(ethoxycarbonyl)methyl group.[23] Use of conditions similar to those reported for the preparation of 2,3-disubstituted indoles[11] (Scheme 11a) and 2-unsubstituted 3-arylin-

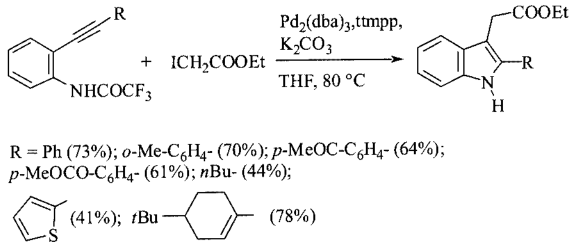


Reaction conditions	**9**	**10**
a) $Pd(PPh_3)_4$, MeCN, 60 °C, 2 h	7%	75%
b) $Pd_2(dba)_3$, DMSO, 60 °C, 2 h	–	56%
c) $Pd_2(dba)_3$, ttmpp, MeCN, 60 °C, 4 h	16%	66%
d) $Pd(PPh_3)_4$, THF, 80 °C, 2 h	5%	28%
e) $Pd_2(dba)_3$, PPh_3, THF, 80 °C, 3.5 h	23%	58%
f) $Pd_2(dba)_3$, P(*o*-tol)$_3$, THF, 80 °C, 4 h	69%	9%
g) $Pd_2(dba)_3$, ttmpp, THF, 80 °C, 2 h	73%	traces

Scheme 11

doles[19] (Scheme 11b) met with failure, at least with our model system. The *N*-alkyl derivative **10** – generated by a competitive base-catalyzed nucleophilic substitution process – was isolated as the main or the sole reaction product.

Ligands and solvents were found to play major roles in controlling the cyclization/*N*-alkylation ratio. Satisfactory results were obtained with $Pd_2(dba)_3$ and P(*o*-tol)$_3$ in THF (Scheme 11f). Use of $Pd_2(dba)_3$ in conjunction with the strongly basic and sterically demanding tris(2,4,6-trimethoxyphenyl)phosphane (ttmpp)[24] in THF provided the highest reaction rate and cyclization to *N*-alkylation ratio (Scheme 11g). By the use of these ligands, several indolylcarboxylate esters bearing vinyl, aryl, and alkyl substituents at C-2 (Scheme 12) were prepared in satisfactory yields, with only minor or trace amounts of the *N*-alkyl by-product. Depending on the nature of the alkyne, non-alkylated 2-substituted indoles were also isolated, sometimes in considerable amount.

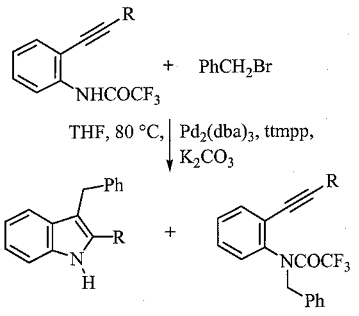


R = Ph (73%); *o*-Me-C_6H_4- (70%); *p*-MeOC-C_6H_4- (64%);
p-MeOCO-C_6H_4- (61%); *n*Bu- (44%);

Scheme 12

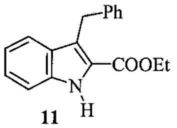
Likewise, treatment of *o*-alkynyltrifluoroacetanilides with benzyl bromide furnished the corresponding 2-substituted 3-benzylindoles (Scheme 13).

Interestingly, during the course of our investigation of the influence of solvents on the palladium-catalyzed reaction between ethyl iodoacetate and *o*-alkynyltrifluoroacetanilides, we found out that the use of DMSO as solvent had a remarkable effect on the reaction outcome. When the reaction was carried out in DMSO, ethyl 3-alkylindole-2-carboxylates were isolated as the main products instead of indole-3-acetic acid esters and/or *N*-alkyl derivatives. For example, treatment 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 resulted in the formation of the indole derivative **9** in 12% yield, whereas the indole-2-carboxylate **11** was isolated in 64% yield.



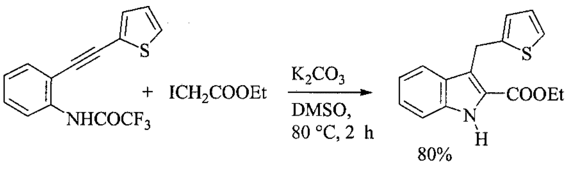
R = Ph-	70	22
R = *p*-MeCO-C_6H_4-	65	12
R = *p*-MeOCO-C_6H_4-	62	16
R = 2-thienyl	50	22

Scheme 13

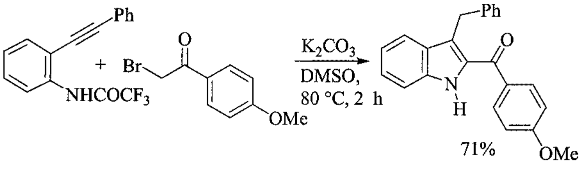


11

This cyclization reaction proved to be independent of the palladium catalyst, and could be successfully employed for the preparation of a variety of indole-2-carboxylates (Scheme 14) and 2-acylindoles (Scheme 15).[25]



Scheme 14

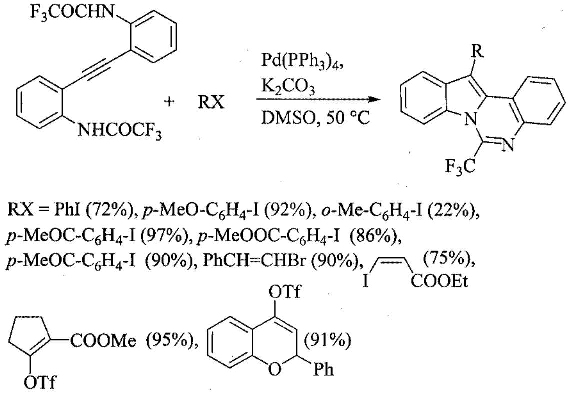


Scheme 15

The reaction most probably proceeds through an *N*-alkylation step that is followed by a cyclization step, the mechanism of which should be similar to that proposed for related base-catalyzed cyclization reactions of alkynes that we have recently investigated.[26,27]

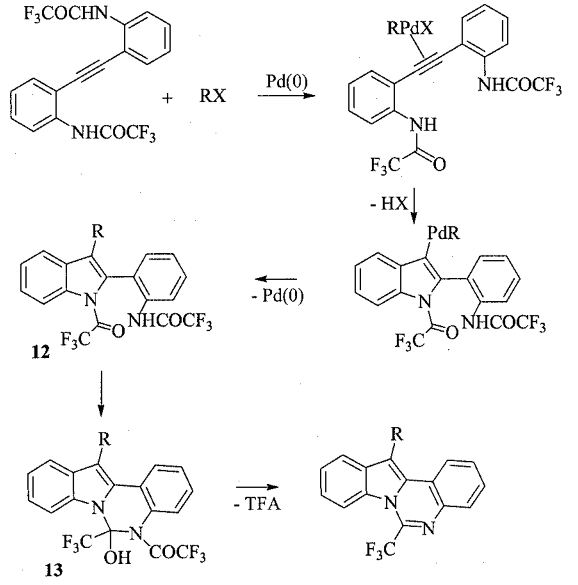
12-Aryl(vinyl)indolo[1,2-*c*]quinazolines

The palladium-catalyzed reaction between bis(*o*-trifluoroacetamidophenyl)acetylene and a variety of aryl or vinyl halides and triflates provides a straightforward approach to 12-aryl(vinyl)indolo[1,2-*c*]quinazolines[28] (Scheme 16), the skeleton of which is present in substances such as Hinckdentine A,[29] an unusual marine alkaloid that has been isolated from the bryozoan *Hincksinoflustra denticulate.* Certain derivatives of indolo[1,2-*c*]quinazoline have been shown to exhibit biological activity.[30,31] The best conditions developed employ $Pd(PPh_3)_4$ and K_2CO_3 in DMSO at 50 °C. The reaction gives good results with neutral, electron-rich, and electron-poor aryl halides, as well as with various vinyl bromides and triflates. *p*-Bromoacetophenone requires a higher reaction temperature (100 °C). Steric hindrance close to the carbon atom involved in the oxidative addition step appears to hamper the reaction to some extent.



Scheme 16

A possible explanation for the formation of the indoloquinazoline nucleus involves the intermediacy of the indole **12**, generated by an aminopalladation/reductive elimination domino pathway, its subsequent conversion into the tetracyclic derivative **13**, and the elimination of trifluoroacetic acid (Scheme 17). Formation of indoloquinazolines by the alternative reaction pathway involving (1) carbopalladation of the carbon−carbon triple bond, (2) isomerization of the resultant *cis*-σ-vinylpalladium adduct to the *trans*-σ-vinylpalladium adduct,[32] (3) formation of a six-membered nitrogen-containing palladacycle intermediate by nucleophilic attack on the palladium atom by the nitrogen atom, and (4) subsequent regeneration of the palladium(0) catalyst through reductive elimination cannot be ruled out a priori.



Scheme 17

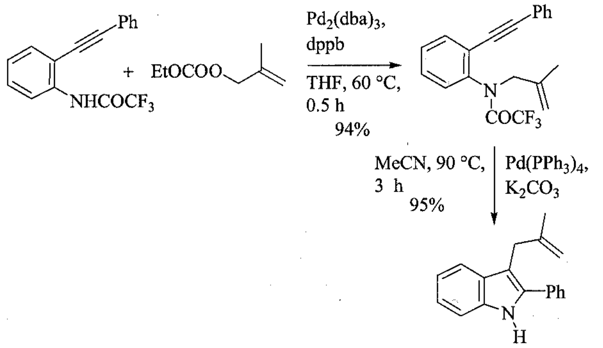
2-Substituted 3-Allylindoles

As an extension of our studies on this alkyne chemistry, we developed a new approach to the construction of indole rings containing 3-allyl substituents, involving the use of allyl esters as carbon donors.[33] This method allows for the preparation of 3-allylindoles unavailable by means of the $PdCl_2(MeCN)_2$-catalyzed reaction between allyl chlorides and *o*-alkynyl-*N*-(methoxycarbonyl)anilines, a process presumed to proceed by trapping of σ-indolylpalladium intermediates with allyl chlorides (which have to be used in large excess) and generates the new C−C bond regioselectively at the γ-position in an S_N2' fashion.[12d]

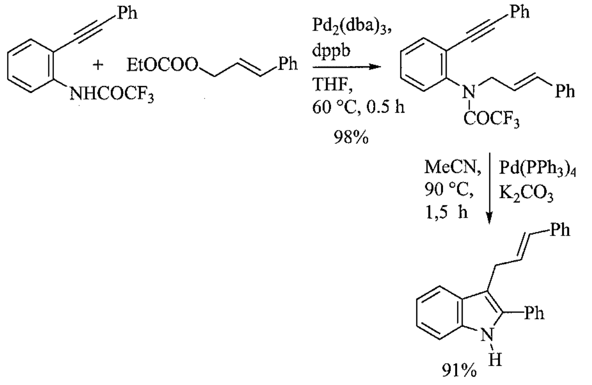
We have developed three basic procedures allowing for the preparation of a variety of 2-substituted- and 2-unsubstituted-3-allylindoles (the latter, however, were obtained only in moderate yield). Allyl carbonates were usually employed as allyl donors (with substituted allyl components they gave better results then allyl acetates).

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

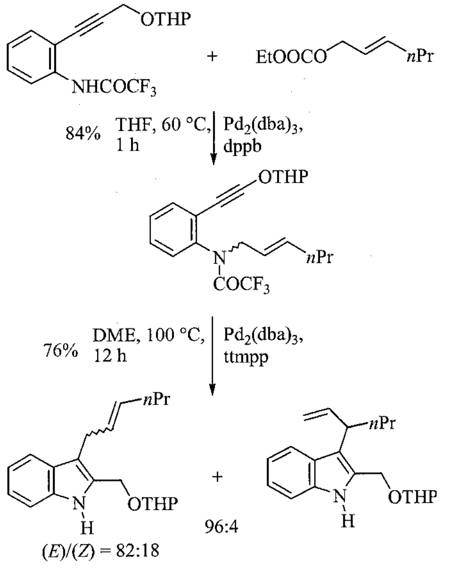
If the *N*-allyl derivatives are isolated (*stepwise procedure*), they can be converted into the corresponding 3-allylindoles by use of $Pd(PPh_3)_4$ and K_2CO_3 in MeCN at 90 °C or $Pd_2(dba)_3$ and ttmpp in DME at 100 °C. Use of $Pd(PPh_3)_4$ gives good results with allylic carbonates generating symmetric η^3-allylpalladium complexes (Scheme 18) and when the two allylic termini are markedly different from a steric point of view (Scheme 19). The $Pd_2(dba)_3$/ttmpp [tris(2,4,6-trimethoxyphenyl)phosphane)][24] combination is the catalyst system of choice when the steric differences between the two allylic termini are small (Scheme 20). In these cases, in the presence of ttmpp, the reaction exhibits remarkable regioselectivity, and almost exclusive formation of the 3-allylindoles with the indolyl moiety bound to the less substituted allyl terminus is usually observed.



Scheme 18

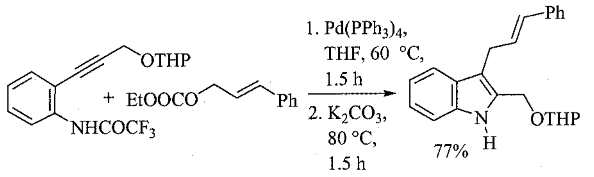


Scheme 19



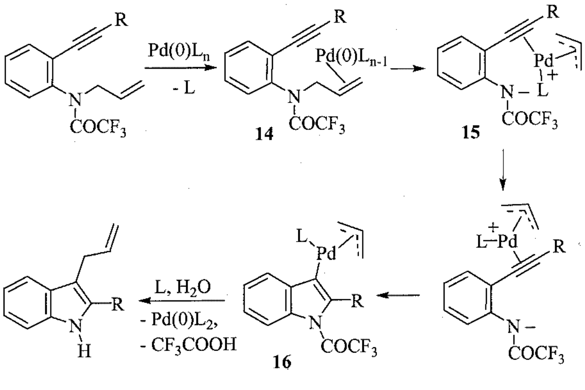
Scheme 20

Alternatively, N-allyl derivatives can be converted into the corresponding indole products without isolation (*one-pot procedure*): the starting alkyne and the allyl ester are treated with $Pd(PPh_3)_4$ in THF at 60 °C until the disappearance of the former, K_2CO_3 is added, and the temperature is raised to 80 °C (Scheme 21).



Scheme 21

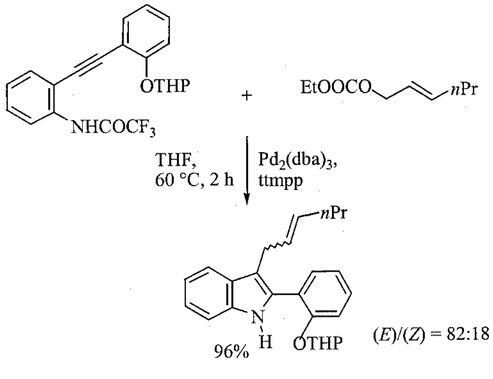
The formation of 3-allylindoles from N-allyl intermediates is believed to follow the mechanism outlined in Scheme 22 for the N-allyl intermediate derived from allyl carbonate. The initially formed (η^2-olefin)palladium complex **14** [(η^2-olefin)palladium complexes are usually believed to be the first intermediates in the palladium-catalyzed allylations[34]] is converted into the (η^2-alkynyl)(η^3-allyl)palladium complex **15** by ionization of the $N-C_{allyl}$ bond and displacement of one palladium ligand by the C−C triple bond (this may be favored by the proximity of the acetylenic moiety to the metal center and may also take place before ionization). Subsequent nucleophilic attack of the nitrogen atom across the activated acetylenic fragment affords the (η^3-allyl)(σ-indolyl)palladium complex **16**, from which the indole product is generated through a reductive elimination step.



Scheme 22

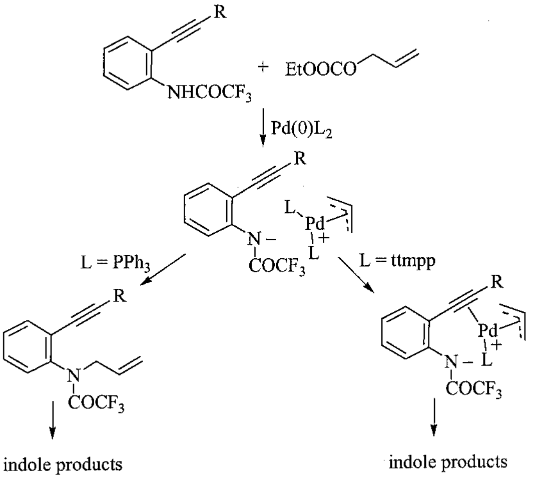
According to this scheme, the nitrogen atom intervenes in the process as a nucleophile in the N-allylation step and as a leaving group[35,36] in the cyclization step. Such ambivalent behavior of amino groups has been observed in other reactions.[37] However, known applications of this chemistry use free amino groups in the N-allylation step and allylammonium salts in the ionization of the $N-C_{allyl}$ bond. In this reaction, the reversible formation of the C−N bond does not involve any change in the nature of the amino group.

The third procedure we developed for the preparation of 3-allylindoles was based on the reaction between o-alkynyltrifluoroacetanilides and allyl carbonates in the presence of $Pd_2(dba)_3$ and ttmpp (Scheme 23).



Scheme 23

Under these conditions, no *N*-allyl intermediate is discernible in the reaction mixture. Apparently, in the presence of ttmpp [or even tris(2,6-dimethoxyphenyl)phosphane (tdmpp) or $P(o\text{-tol})_3$], coordination of the alkyne to the η^3-allylpalladium complex derived from the allyl carbonate is faster than the *N*-allylation and an (η^2-alkyne)(η^3-allyl)palladium intermediate is formed in preference to the *N*-allyl derivative (Scheme 24).

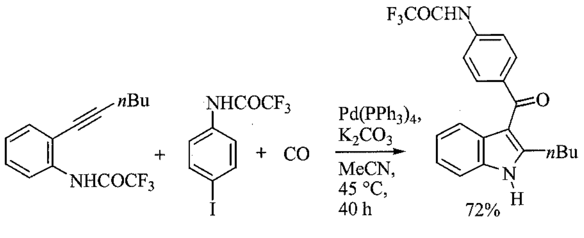


Scheme 24

2-Substituted 3-Acylindoles

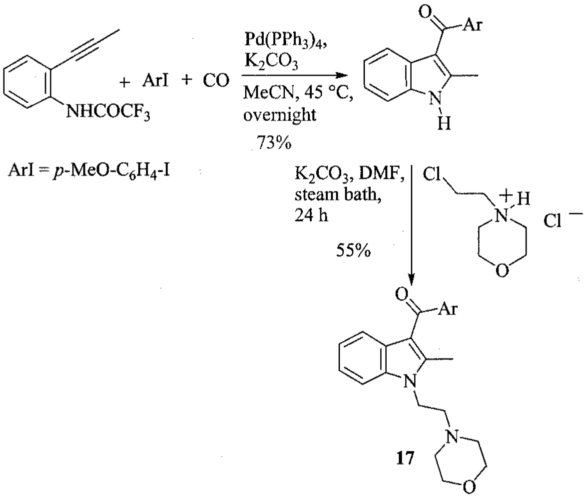
The chemistry used in the preceding sections for the construction of the indole skeleton is based on the assembly of two components. We thought that the addition of carbon monoxide as a third component might provide an opportunity for generating indole molecules possessing higher degrees of complexity,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

After some experimentation, it was found that the use 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[38] (Scheme 25). The use of anhydrous acetonitrile and a higher carbon monoxide pressure or, alternatively, $Pd_2(dba)_3$ and $P(o\text{-tol})_3$ under standard conditions was found necessary with aryl iodides containing electron-withdrawing substituents. With vinyl triflates, use of anhydrous acetonitrile gave the best results.



Scheme 25

The methodology was applied to the synthesis of pravadoline **17**, an indole derivative designed as a nonacidic analogue of nonsteroidal antiinflammatory drugs (NSAIDs)[39] (Scheme 26)

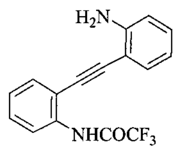


17

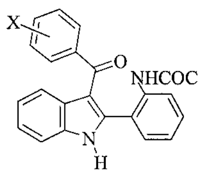
Scheme 26

12-Aryl-11*H*-indolo[3,2-c]quinolines and 12-Acylindolo[1,2-c]quinazolines

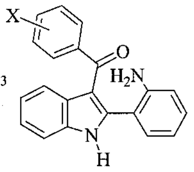
Having established conditions allowing for the conversion of *o*-alkynyltrifluoroacetanilides into 3-acylindoles, we next focused our attention on the possible utilization of 3-acylindoles bearing suitable functionality in a subsequent cyclization step. Since we were particularly interested in the preparation of indoloquinolines,[40] the reaction of *o*-(*o*′-aminophenylethynyl)trifluoroacetanilide (**18**) was explored. Interestingly, first attempts showed that the reaction produced the 2-(*o*-trifluoroacetamidophenyl)-3-acylindoles **19** instead of the expected 2-(*o*-aminophenyl)-3-acylindoles **20**.



18

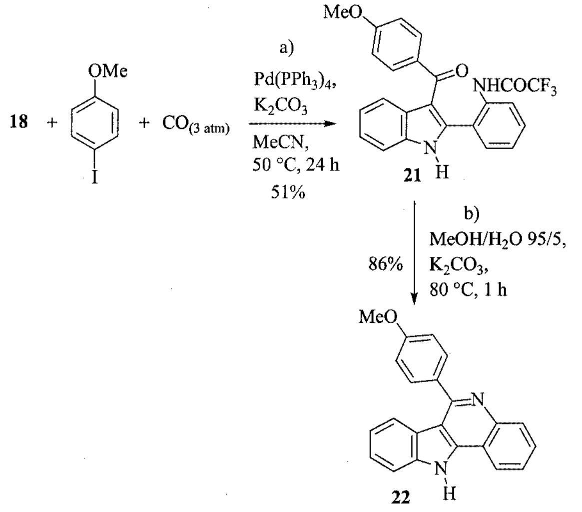


19



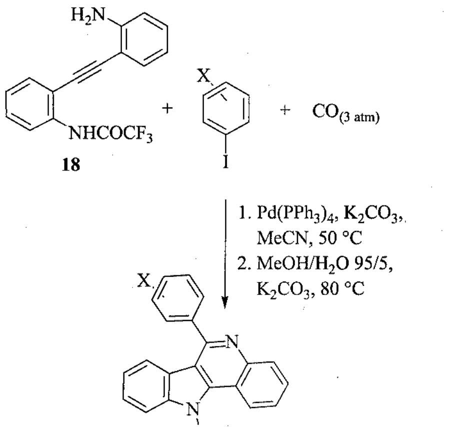
20

For example, exposure of **18** to *p*-iodoanisole in the presence of Pd(PPh$_3$)$_4$ under 3 atm of carbon monoxide produced the trifluoroacetamido derivative **21** (Scheme 27a). However, we were pleased to find that compound **21** could readily be converted into the corresponding derivative **22** in high yield by treatment with MeOH/H$_2$O (95:5) and K$_2$CO$_3$ (Scheme 27b).



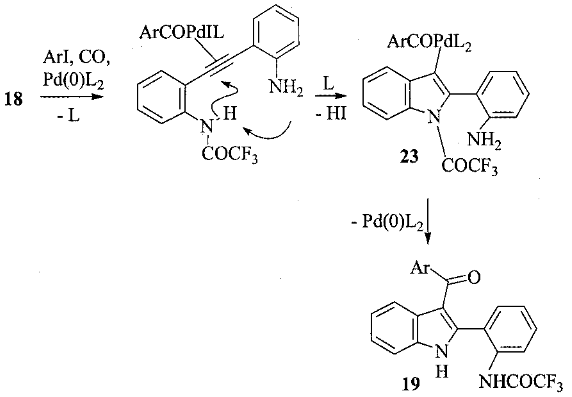
Scheme 27

It is possible to perform the preparation of 6-aryl-11*H*-indolo[3,2-*c*]quinolines by such a stepwise approach. The process can, however, also be carried out more conveniently as a one-pot procedure, omitting the isolation of acylindole intermediates. Use of the one-pot procedure allowed for the preparation of several substituted indoloquinolines from aryl iodides containing electron-donating and electron-withdrawing substituents (Scheme 28).



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%)

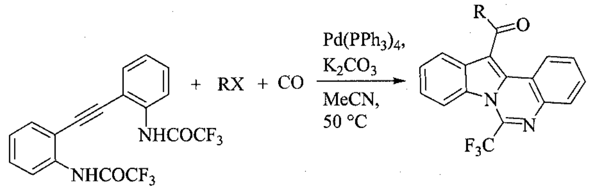
Scheme 28



Scheme 29

A reasonable explanation for the formation of 3-acyl-2-(*o*-trifluoroacetamidophenyl)indoles is outlined in Scheme 29; nucleophilic attack of the nitrogen atom of the trifluoroacetamido group across the C−C triple bond, activated by coordination to an acylpalladium complex, generates **23**, which subsequently undergoes the reductive elimination of a Pd^0 species and a transamidation reaction, not necessarily in that order. The possibility that formation of the indole derivative **19** may involve the free amino group in the cyclization step is ruled out by our early studies,[11] which showed that the free amino group was unable to participate in the aminopalladation/reductive elimination domino 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

Subjection of bis(*o*-trifluoroacetamidophenyl)acetylene instead of *o*-(*o*′-aminophenylethynyl)trifluoroacetanilide (**18**) to aryl or vinyl halides and triflates in the presence of carbon monoxide and a palladium catalyst provides a straightforward approach to 12-acylindolo[1,2-*c*]quinazolines[41] (Scheme 30). The best standard reaction conditions developed employ Pd(PPh$_3$)$_4$ and anhydrous K$_2$CO$_3$ in anhydrous MeCN at 50 °C under 5 bar of carbon monoxide.



Scheme 30

Concluding Remarks

Over the past few years we have shown that many diverse indole derivatives can readily be prepared by the *aminopalladation/reductive elimination domino reaction*. The key step of the process is the intramolecular nucleophilic attack of a proximate nitrogen nucleophile across the C−C triple bond, activated through 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.

Acknowledgments

We thank the Ministero dell'Università e della Ricerca Scientifica (MURST; National Project "Stereoselezione in Sintesi Organica. Metodologie e Applicazioni"), the Consiglio Nazionale delle Ricerche (CNR) and the Università degli Studi "La Sapienza" for their continuing financial support of the work done in our laboratories.

---

[1] R. J. Sundberg, "Pyrroles and their Benzo Derivatives: Synthesis and Applications" in *Comprehensive Heterocyclic Chemistry*, vol. 4 (Eds.: A. R. Katritzky, C. W. Rees), Pergamon, Oxford **1984**, pp. 313−376.

[2] For some examples, see: [2a] M. Mori, K. Chiba, Y. Ban, *Tetrahedron Lett.* **1977**, 1037−1040. [2b] R. Odle, B. Blevins, M. Ratcliff, L. S. Hegedus, *J. Org. Chem.* **1980**, *45*, 2709−2710. [2c] R. C. Larock, S. Babu, *Tetrahedron Lett.* **1987**, *28*, 5291−5294. [2d] J. P. Genet, E. Blart, M. Savignac, *Synlett* **1992**, 715−717. [2e] M. A. Carroll, A. B. Holmes, *Chem. Commun.* **1998**, 1395−1396. [2f] R. J. Sundberg, W. J. Pitts, *J. Org. Chem.* **1991**, *56*, 3048−3054. [2g] J. E. Macor, R. J. Ogilvie, M. J. Wythes, *Tetrahedron Lett.* **1996**, *37*, 4289−4292. [2h] W. Yun, R. Mohan, *Tetrahedron Lett.* **1996**, *37*, 7189−7192. [2i] D. Wensbo, S. Gronowitz, *Tetrahedron* **1996**, *52*, 14975−14988. [2j] H.-C. Zhang, B. E. Maryanoff, *J. Org. Chem.* **1997**, *62*, 1804−1809.

[3] [3a] R. Grigg, A. Teasdale, V. Sridharan, *Tetrahedron Lett.* **1991**, *32*, 3859−3862. [3b] D. Brown, R. Grigg, V. Sridharan, V. Tambyrajah, M. Thorntorn-Pett, *Tetrahedron* **1998**, *54*, 2595−2606.

[4] For some examples, see: [4a] P. J. Harrington, L. S. Hegedus, *J. Org. Chem.* **1984**, *49*, 2657−2662. [4b] M. E. Krolski, A. F. Renaldo, D. E. Rudisill, J. K. Stille, *J. Org. Chem.* **1988**, *53*, 1170−1176. [4c] A. Kasahara, T. Izumi, S. Murakami, K. Miyamoto, T. Hino, *J. Heterocycl. Chem.* **1989**, *26*, 1405−1413. [4d] M. Akazome, T. Kondo, Y. Watanabe, *J. Org. Chem.* **1994**, *59*, 3375−3380. [4e] B. C. Söderberg, J. A. Shriver, *J. Org. Chem.* **1997**, *62*, 5838−5845. [4f] B. C. Söderberg, S. R. Rector, S. N. O'Neil, *Tetrahedron Lett.* **1999**, *40*, 3657−3660. [4g] B. C. Söderberg, A. C. Chisnell, S. N. O'Neil, J. A. Shriver, *J. Org. Chem.* **1999**, *64*, 9731−9734.

[5] [5a] L. S. Hegedus, G. F. Allen, D. J. Olsen, *J. Am. Chem. Soc.* **1980**, *102*, 3583−3587. [5b] M. Gowan, A. S. Caillé, C. K. Lau, *Synlett* **1997**, 1312−1314.

[6] For some examples, see: [6a] A. Kasahara, T. Izumi, S. Murakami, H. Yanai, M. Takatori, *Bull. Chem. Soc. Jpn.* **1986**, *59*, 927−928. [6b] T. Sakamoto, T. Nagano, Y. Kondo, H. Yamanaka, *Synthesis* **1990**, 215−218. [6c] C. Chen, D. R. Lieberman, R. D. Larsen, T. R. Verhoeven, P. J. Reider, *J. Org. Chem.* **1997**, *62*, 2676−2677.

[7] For some examples, see: [7a] E. C. Taylor, A. H. Katz, H. Salgado-Zamora, *Tetrahedron Lett.* **1985**, *26*, 5963−5966. [7b] K. Iritani, S. Matsubara, K. Utimoto, *Tetrahedron Lett.* **1988**, *29*, 1799−1802. [7c] D. E. Rudisill, J. K. Stille, *J. Org. Chem.* **1989**, *54*, 5856−5866. [7d] A. Arcadi, S. Cacchi, F. Marinelli, *Tetrahedron Lett.* **1989**, *30*, 2581−2584. [7e] Y. Kondo, T. Sakamoto, H. Yamanaka, *Heterocycles* **1989**, *29*, 1013−1016. [7f] S. Cacchi, V. Carnicelli, F. Marinelli, *J. Organomet. Chem.* **1994**, *475*, 289−296. [7g] M. Botta, V. Summa, F. Corelli, G. Di Pietro, P. Lombardi, *Tetrahedron: Asymmetry* **1996**, *7*, 1263−1266. [7h] M. C. Fagnola, I. Candiani, G. Visentin, W. Cabri, F. Zarini, N. Mongelli, A. Bedeschi, *Tetrahedron Lett.* **1997**, *38*, 2307−2310. [7i] A. Yasuhara, M. Kaneko, T. Sakamoto, *Heterocycles* **1998**, *48*, 1793−1799. [7j] M. S. Yu, L. Lopez de Leon, M. A. McGuire, G. Botha, *Tetrahedron Lett.* **1998**, *39*, 9347−9350. [7k] H.-C. Zhang, K. K. Brumfield, L. Jaroskova, B. E. Maryanoff, *Tetrahedron Lett.* **1998**, *39*, 4449−4452. [7l] H.-C. Zhang, H. Ye, A. F. Moretto, K. K. Brumfield, B. E. Maryanoff, *Org. Lett.* **2000**, *2*, 89−92.

[8] [8a] R. C. Larock, E. K. Yum, *J. Am. Chem. Soc.* **1991**, *113*, 6689−6690. [8b] D. Wensbo, A. Eriksson, T. Jeschke, U. Annby, S. Gronowitz, L. A. Cohen, *Tetrahedron Lett.* **1993**, *34*, 2823−2826. [8c] T. Jeschke, D. Wensbo, U. Annby, S. Gronowitz, L. A. Cohen, *Tetrahedron Lett.* **1993**, *34*, 6471−6474. [8d] F. Maassarani, M. Pfeffer, J. Pencer, E. Wehman, *J. Organomet. Chem.* **1994**, *466*, 265−271. [8e] C. Chen, D. R. Lieberman, R. D. Larsen, R. A. Reamer, T. R. Verhoeven, P. J. Reider, I. F. Cottrell, P. G. Houghton, *Tetrahedron Lett.* **1994**, *35*, 6981−6984. [8f] R. C. Larock, E. K. Yum, M. J. Doty, K. K. Sham, *J. Org. Chem.* **1995**, *60*, 3270−3271. [8g] C. Chen, D. R. Lieberman, L. J. Street, A. R. Guiblin, R. D. Larsen, T. R. Verhoeven, *Synth. Commun.* **1996**, *26*, 1977−1984. [8h] G. V. W. Rosso, D. A. Lust, P. J. Bernot, J. A. Grosso, S. P. Modi, A. Rusowicz, T. C. Sedergran, J. H. Simpson, S. K. Srivastava, M. J. Humora, N. G. Anderson, *Org. Proc. Res. Dev.* **1997**, *1*, 311−314. [8i] H.-C. Zhang, K. K. Brumfield, B. E. Maryanoff, *Tetrahedron Lett.* **1997**, *38*, 2439−2442. [8j] P. Blurton, A. Brickwood, D. Dhanak, *Heterocycles* **1997**, *45*, 2395−2405. [8k] R. C. Larock, M. J. Doty, X. Han, *Tetrahedron Lett.* **1998**, *39*, 5143−5146. [8l] A. L. Smith, G. I. Stevenson, C. J. Swain, J. L. Castro, *Tetrahedron Lett.* **1998**, *39*, 8317−8320. [8m] R. C. Larock, E. K. Yum, M. D. Refvik, *J. Org. Chem.* **1998**, *63*, 7652−7662. [8n] F. Ujjainwalla, D. Warner, *Tetrahedron Lett.* **1998**, *39*, 5355−5358. [8o] K. R. Roesch, R. C. Larock, *J. Org. Chem.* **1998**, *63*, 5306−5307. [8p] S. S. Park, J.-K. Choi, E. K. Yum, D.-C. Ha, *Tetrahedron Lett.* **1998**, *39*, 627−630. [8q] K. R. Roesch, R. C. Larock, *Org. Lett.* **1999**, *1*, 1551−1553. [8r] K. R. Roesch, R. C. Larock, *J. Org. Chem.* **2001**, *66*, 412−420. [8s] H. Zhang, R. C. Larock, *Org. Lett.* **2001**, *3*, 3083−3086.

[9] A. Arcadi, A. Burini, S. Cacchi, M. Delmastro, F. Marinelli, B. R. Pietroni, *J. Org. Chem.* **1992**, *57*, 976−982.

[10] For pioneering work in the area of activation of the carbon−carbon triple bond by organopalladium complexes towards nucleophilic attack of proximate nucleophiles, see: Oxygen nucleophiles: [10a] J. Tsuda, Y. Ohashi, N. Nagahama, R. Sumiya, J. Saegusa, *J. Org. Chem.* **1988**, *53*, 2650−2653. [10b] Y. Inoue, Y. Itoh, J. F. Yen, S. Imaizumi, *J. Mol. Catal.* **1990**, *60*, L1−L3. Carbon nucleophiles: [10c] G. Fournet, G. Balme, B. Van Hemelryck, J. Gore, *Tetrahedron Lett.* **1990**, *31*, 5147−5150.

[11] A. Arcadi, S. Cacchi, F. Marinelli, *Tetrahedron Lett.* **1992**, *33*, 3915−3918.

[12] [12a] A. Arcadi, S. Cacchi, F. Marinelli, *Tetrahedron Lett.* **1989**, *30*, 2581−2584. [12b] K. Utimoto, H. Miwa, H. Nozaki, *Tetrahedron Lett.* **1981**, *22*, 4277−4278. [12c] K. Utimoto, *Pure Appl. Chem.* **1983**, *55*, 1845−1852. [12d] K. Iritani, S. Matsubara, K. Utimoto, *Tetrahedron Lett.* **1988**, *29*, 1799−1802. [12e] Y. K. Kondo, T. Sakamoto, H. Yamanaka, *Heterocycles* **1989**, *29*, 1013−1016. [12f] Y. Fukuda, S. Matsubara K. Utimoto, *J. Org. Chem.* **1991**, *56*, 5812−5816. [12g] S. Cacchi, V. Carnicelli, F. Marinelli, *J. Organomet. Chem.* **1994**, *475*, 289−296.

[13] [13a] E. C. Taylor, A. H. Katz, H. Salgado-Zamora, *Tetrahedron Lett.* **1985**, *26*, 5963−5966. [13b] D. E. Rudisill, J. K. Stille, *J. Org. Chem.* **1989**, *54*, 5856−5866.

[14] S. Cacchi, G. Fabrizi, L. M. Parisi, in preparation.

[15] A. Dondoni, A. Marra, D. Perrone, *J. Org. Chem.* **1993**, *58*, 275−277.

[16] M. D. Collini, J. W. Ellingboe, *Tetrahedron Lett.* **1997**, *38*, 7963−7966.

[17] M. G. Saulnier, D. B. Frennesson, M. S. Deshpande, D. M. Vyas, *Tetrahedron Lett.* **1995**, *36*, 7841−7844.

[18] For recent references, see for example: [18a] J.-L. Malleron, C. Gueremy, S. Mignani, J.-F. Peyronel, A. Truchon, J.-C. Blanchard, A. Doble, P. Laduron, O. Piot, J.-L. Zundel, J. Betschart, H. Canard, P. Chaillou, O. Ferris, C. Huon, B. Just, R. Kerphirique, B. Martin, P. Mouton, A. Renaudon, *J. Med. Chem.* **1993**, *36*, 1194−1202. [18b] J.-H. Sheu, Y.-K. Chen, H.-F. Chung, P.-J. Sung, S.-F. Lin, *Heterocycles* **1996**, *43*, 1751−1758.

[19] S. Cacchi, G. Fabrizi, F. Marinelli, L. Moro, P. Pace, *Synlett* **1997**, 1363−1370.

[20] S. Cacchi, G. Fabrizi, A. Goggiamani, *Heterocycles* **2002**, *56*, 613−632, and references cited therein.

[21] For recent references, see, for example: [21a] J. D. Chisholm, D. L. Van Vranken, *J. Org. Chem.* **1995**, *60*, 6672−6673. [21b] J. Bergman, E. Koch, B. Pelcman, *Tetrahedon Lett.* **1995**, *36*, 3945−3948. [21c] J. Bergman, E. Koch, B. Pelcman, *Tetrahedron* **1995**, *51*, 5631−5642. [21d] D. Chen, L. Yu, P. G. Wang, *Tetrahedron Lett.* **1996**, *37*, 4467−4470. [21e] K. M. Depew, S. J. Danishefsky, N. Rosen, L. Sepp-Lorenzino, *J. Am. Chem. Soc.* **1996**, *118*, 12463−12464. [21f] M. Hasegawa, M. Tabata, K. Satoh, F. Yamada, M. Somei, *Heterocycles* **1996**, *43*, 2333−2336. [21g] D. S. Carter, D. L. Van Vranken, *Tetrahedron Lett.* **1996**, *37*, 5629−5632. [21h] K. Miyashita, K. Kondoh, K. Tsuchiya, H. Miyabe, T. Imanishi, *Chem. Pharm. Bull.* **1997**, *45*, 932−935.

[22] [22a] N. M. Gray, M. S. Dappen, B. K. Cheng, A. A. Cordi, J. P. Biesterfeldt, W. F. Hood, J. B. Monahan, *J. Med. Chem.* **1991**, *34*, 1283−1292. [22b] A. P. Kozikowski, D. Ma, J. Brewer, S. Sun, E. Costa, E. Romeo, A. Guidotti, *J. Med. Chem.* **1993**, *36*, 2908−2920.

[23] A. Arcadi, S. Cacchi, G. Fabrizi, F. Marinelli, *Synlett* **2000**, 394−396.

[24] M. Wada, S. Higashizaki, *J. Chem. Soc., Chem. Commun.* **1984**, 482−483.

[25] A. Arcadi, S. Cacchi, G. Fabrizi, F. Marinelli, *Synlett* **2000**, 647−649.

[26] Arcadi, S. Cacchi, G. Fabrizi, F. Manna, P. Pace;, *Synlett* **1998**, 446−448.

[27] [27a] A. Arcadi, S. Cacchi, F. Marinelli, *Tetrahedron Lett.* **1989**, *30*, 2581−2584. [27b] A. Arcadi, S. Cacchi, G. Fabrizi, F. Marinelli, *Synlett* **1993**, 65−68. [27c] A. Arcadi, S. Cacchi, F. Marinelli, *Tetrahedron* **1993**, *49*, 4955−4964. [27d] S. Cacchi, V. Carnicelli, F. Marinelli, *J. Organomet. Chem.* **1994**, *475*, 289−296. [27e] S. Cacchi, G. Fabrizi, A. Carangio, *Synlett* **1997**, 959−961.

[28] A. Arcadi, S. Cacchi, A. Cassetta, G. Fabrizi, L. M. Parisi, *Synlett* **2001**, 1605−1607.

[29] A. J. Blackman, T. W. Hamley, R. Picker, W. C. Taylor, N. Thirasana, *Tetrahedron. Lett.* **1987**, *28*, 5561−5562.

[30] R. L. Duncan, *Ger. Offen.* 2,051,961, April 29, **1971**.

[31] A. N. Grinev, G. N. Kurilo, A. A. Cherkasova, M. D. Mashkovskii, N. I. Andreeva, I. K. Sokolov, *Khim.-Farm. Zh.* **1978**, *12*, 97−101.

[32] For a reference on palladium-catalyzed overall *trans* additions to acetylenic compounds, see: [32a] A. Arcadi, S. Cacchi, G. Fabrizi, F. Marinelli, P. Pace, *Eur. J. Org. Chem.* **1999**, 3305−3313. [32b] S. Cacchi, G. Fabrizi, F. Marinelli, L. Moro, P. Pace, *Tetrahedron* **1996**, *52*, 10225−10240. [32c] J. Ji, Z. Wang, X. Lu, *Organometallics* **1996**, *15*, 2821−2828. [32d] R. A. Gibbs, U. Krishnan, J. M. Dolence, C. D. Poulter, *J. Org. Chem.* **1995**, *60*, 7821−7829. [32e] P. de Vaal, A. Dedieu, *J. Organomet. Chem.* **1994**, *478*, 121−129. [32f] G. Dyker, A. Kellner, *Tetrahedron Lett.* **1994**, *35*, 7633−7636. [32g] D. Zargarian, H. Alper, *Organometallics* **1991**, *10*, 2914−2921.

[33] S. Cacchi, G. Fabrizi, P. Pace, *J. Org. Chem.* **1998**, *63*, 1001−1011.

[34] See, for example: [34a] B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395−422. [34b] J. M. J. Williams, *Synlett* **1996**, 705−710.

[35] For the utilization of trialkylallylammonium salts as precursors of η^3-allylpalladium complexes, see: [35a] T. T. Doi, A. Yanagisawa, M. Miyazawa, K. Yamamoto, *Tetrahedron: Asymmetry* **1995**, *6*, 389−392. [35b] R. Hunter, C. D. Simon, *Tetrahedron Lett.* **1988**, *29*, 2257−2260.

[36] For the utilization of 3-vinylaziridines as precursors of η^3-allylpalladium complexes, see: G. Spears, W. F. Nakanishi, Y. Ohfune, *Synlett* **1991**, 91−92.

[37] [37a] S. Lemaire-Audoire, M. Savignac, C. Dupuis, J. P. Genet, *Bull. Soc. Chim. Fr.* **1995**, *132*, 1157−1166. [37b] F. Garro-Helio, A. Merzouk, F. Guibé, *J. Org. Chem.* **1993**, *58*, 6109−6113.

[38] A. Arcadi, S. Cacchi, V. Carnicelli, F. Marinelli, *Tetrahedron* **1994**, *50*, 437−452.

[39] D. R. Haubrich, S. J. Ward, E. Baizman, M. R. Bell, J. Bradford, R. Ferrari, M. Miller, M. Perrone, A. K. Pierson, J. K. Saelens, D. Luttinger, *J. Pharmacol. Exp. Ther.* **1990**, *255*, 511−522.

[40] S. Cacchi, G. Fabrizi, P. Pace, F. Marinelli, *Synlett* **1999**, 620−622.

[41] G. Battistuzzi, S. Cacchi, G. Fabrizi, F. Marinelli, L. M. Parisi, *Org. Lett.* **2002**, *4*, 1355−1358.

Received February 7, 2002
[O02076]