

# New palladium-catalyzed reactions of unsaturated triflates with alkenes and alkynes

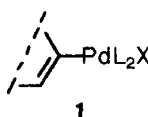
Sandro Cacchi

Dip. di Studi di Chimica e Tecnologia delle Sostanze Biologicamente Attive,  
Università degli Studi "La Sapienza", P.le A. Moro 5, I-00185 Roma, Italy

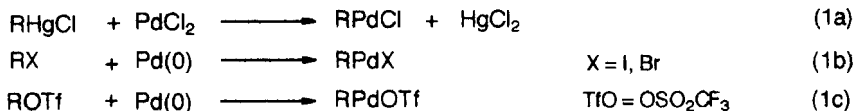
**Abstract** - The palladium-catalyzed reaction of vinyl triflates with  $\beta$ -substituted- $\alpha,\beta$ -unsaturated carbonyl compounds affords regio- and stereoselectively the corresponding vinylic substitution derivatives. The application of this reaction to the synthesis of quinolines, coumarins, and cardenolides is described. The palladium-catalyzed reaction of unsaturated triflates with functionalized internal and terminal alkynes produces a variety of heterocyclic compounds such as furans, benzo[*b*]furans, indoles, butenolides,  $\gamma$ -alkylidene- $\gamma$ -butyrolactones, and precocenes.

## INTRODUCTION

Palladium catalysis represents a well established and very useful methodology in organic synthesis and in the last decades many papers dealing with reaction mechanisms and synthetic applications appeared in the literature. A large number of reactions involve the generation and transformation *in situ* of  $\sigma$ -vinyl or  $\sigma$ -arylpalladium complexes **1**.



The increased use of these complexes as reaction intermediates paralleled the utilization of more convenient and versatile precursors for their preparation. Switching from vinyl- and arylmercury compounds (eq. 1a) to vinyl and aryl halides (eq. 1b) widened considerably the scope and utility of this methodology. More recently, our discovery that vinyl triflates (trifluoromethanesulfonates) can be used as precursors of  $\sigma$ -vinylpalladium complexes (eq. 1c) in the reaction with olefinic systems (**1**) and the development by Stille and co-workers of a procedure to allow the cross-coupling of vinyl triflates with organostannanes (**2**) marked a further, significant step forward in homogeneous catalysis.



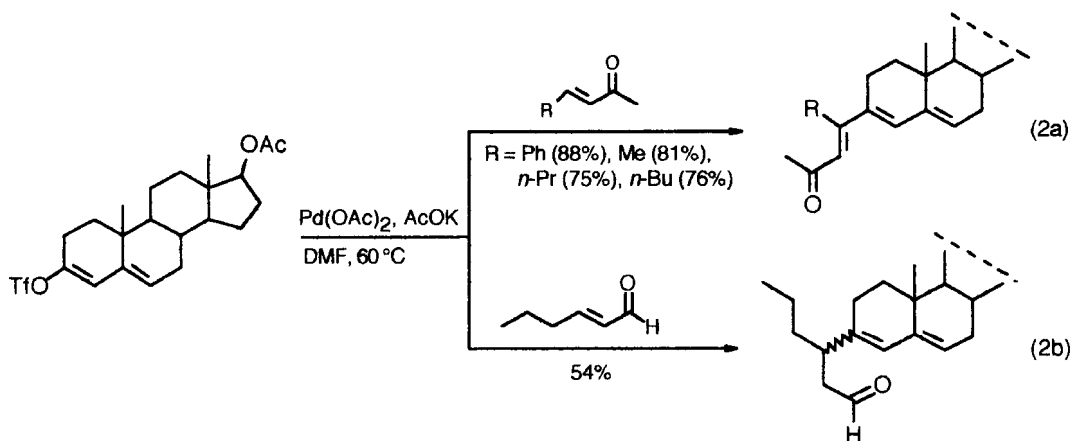
R = vinyl, aryl

Considering unsaturated triflates as pseudohalogens provided in fact the chemist with the new and extraordinary possibility of looking at a wide variety of ketones and phenols as potential vinyl and aryl donors in palladium-catalyzed reactions. In addition, the presence of the poorly coordinating triflate counterion in the coordination sphere of palladium in organopalladium complexes made it possible to take advantage of their peculiar properties in unusual synthetic applications. In little more than ten years, the triflate-based palladium chemistry has grown tremendously and now this methodology represents a valuable tool in organic synthesis.

Our own recent work in this area focused mainly on the reaction of unsaturated triflates with alkenes and alkynes, particularly on (a) vinylic substitution of  $\beta$ -substituted- $\alpha,\beta$ -unsaturated carbonyl compounds, (b) vinylic substitution/cyclization of  $\beta$ -substituted- $\alpha,\beta$ -unsaturated carbonyl compounds, (c) coupling/cyclization of alkynes, (d) cyclization of alkynes promoted by  $\sigma$ -vinyl- or  $\sigma$ -arylpalladium complexes, (e) hydrovinylation/cyclization of alkynes. These are the themes of the present paper.

VINYLIC SUBSTITUTION OF  $\beta$ -SUBSTITUTED- $\alpha,\beta$ -UNSATURATED CARBONYL COMPOUNDS

Since our first report on the utilization of vinyl triflates in the Heck reaction (1), a variety of alkenes containing carbon-carbon double bonds conjugated to electron-withdrawing substituents have been reacted with vinyl and aryl triflates in the presence of palladium catalysts. In the great majority of these studies, however, the substitution pattern of  $\alpha,\beta$ -unsaturated carbonyl compounds has been quite simple and very little has been done with  $\beta$ -substituted- $\alpha,\beta$ -unsaturated carbonyl compounds (3,4). Recently we have developed a general methodology for the preparation of vinylic substitution derivatives from  $\beta$ -substituted- $\alpha,\beta$ -unsaturated carbonyl compounds and vinyl triflates (5) (eq. 2a).

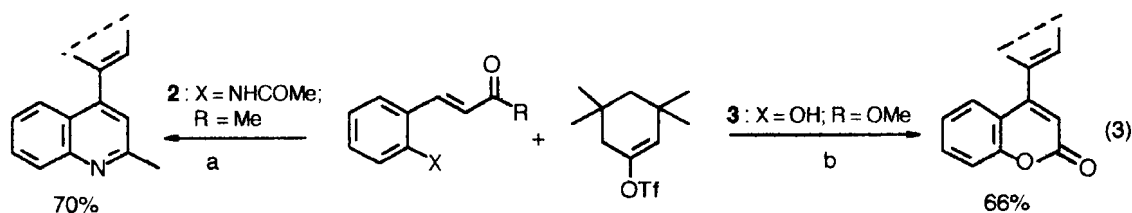


Best results have been obtained in the presence of KOAc and Pd(OAc)<sub>2</sub>. The utilization of a variety of other bases (Et<sub>3</sub>N, NaHCO<sub>3</sub>/*n*-Bu<sub>4</sub>NCl, K<sub>2</sub>CO<sub>3</sub>/*n*-Bu<sub>4</sub>NCl, NaOAc) and phosphine ligands resulted in lower yields. The reaction is regioselective and preferential  $\beta$ -attack of vinyl units is invariably observed supporting the notion that electronic effects play a dominant role in controlling the direction of the carbopalladation step in the vinylic substitution of olefins bearing electron-withdrawing substituents. Only small amounts of regioisomeric vinylic substitution derivatives have been isolated in some cases, most probably as the result of competing steric effects. As far as the stereochemistry is concerned, essentially one stereoisomer has been obtained in the reactions we run and vinylic substitution derivatives contain the added vinylic unit *trans* to the carbonyl group.

Depending on the nature of unsaturated triflates and  $\beta$ -substituted- $\alpha,\beta$ -unsaturated carbonyl compounds, the formation of hydrovinylation products (formal conjugate addition) (6) has been also observed (eq. 2b).

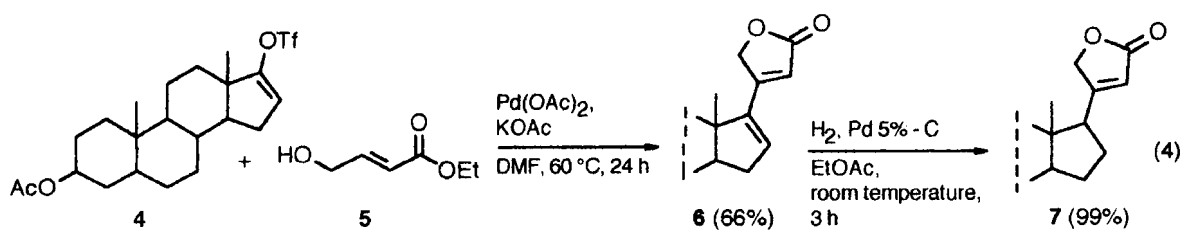
VINYLIC SUBSTITUTION/CYCLIZATION OF  $\beta$ -SUBSTITUTED- $\alpha,\beta$ -UNSATURATED CARBONYL COMPOUNDS

This reaction appears especially promising for the design of annulation processes. In fact, as the stereochemical course of the Heck reaction puts the  $\beta$ -substituent and the carbonyl group of the starting  $\alpha,\beta$ -unsaturated carbonyl compound on the same side, in the presence of nucleophilic centers on the  $\beta$ -substituent the initially formed vinylic substitution derivative could undergo an intramolecular cyclization reaction. Accordingly, 4-(*o*-acetamidophenyl)-3-buten-2-one **2** and methyl 4-(*o*-hydroxyphenyl)-3-butenolate **3** have been reacted with vinyl triflates and aryl halides to provide new access to a variety of substituted quinolines (5) (eq. 3a) and coumarins (5) (eq. 3b).



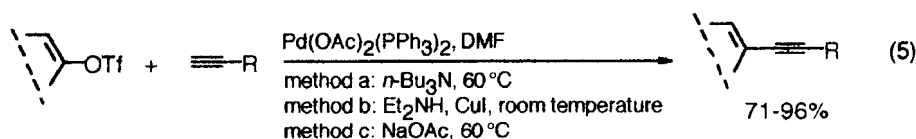
The reaction has been applied to the synthesis of the cardenolide **7** starting from the steroidal triflate **4** and ethyl 4-hydroxy-2-pentenoate **5** (7) (eq. 4). No reaction was reported to occur when **4** was reacted with **5** in the presence of Pd(OAc)<sub>2</sub>, PPh<sub>3</sub>, and triethylamine (3). Furthermore, when we carried out the reaction

employing the  $\text{NaHCO}_3/n\text{-Bu}_4\text{NCl}$  or  $\text{K}_2\text{CO}_3/n\text{-Bu}_4\text{NCl}$  combinations, the butenolide derivative **6** was isolated only in trace amounts.



#### COUPLING/CYCLIZATION OF ALKYNES

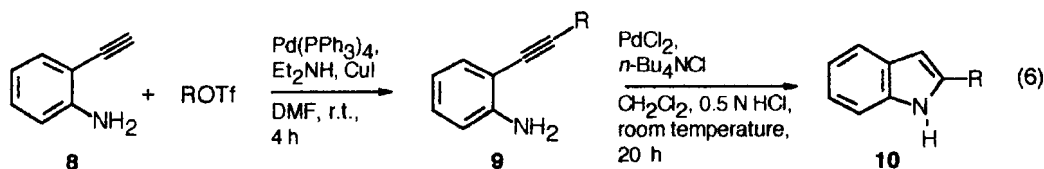
The palladium-catalyzed reaction of vinyl triflates with 1-alkynes (**8**) provides a useful entry into the interesting class of conjugated enynes (eq. 5).



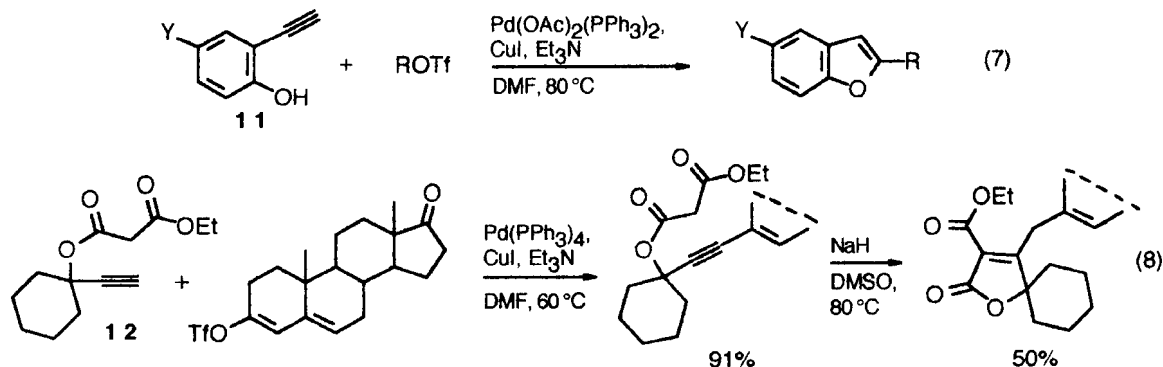
The reaction occurs with a wide variety of alkyl- and arylacetylenes and can tolerate numerous functionalities both on the vinyl triflate and on the alkyne moiety. Dienes related to vitamin D (**9**), propargylglycine derivatives (**10**), dienediynes related to neocarzinostatin (**11**), a potent antitumor agent, and 5-alkynyluracils (**12**) have been prepared in this manner.

In the presence of nucleophilic centers near the carbon-carbon triple bond, enynes resulting from the coupling step can be reacted to give cyclization products.

This chemistry has been employed in an efficient synthesis of 2-vinyl-indoles **10** from *o*-ethynylaniline **8** (**13**) (eq. 6).

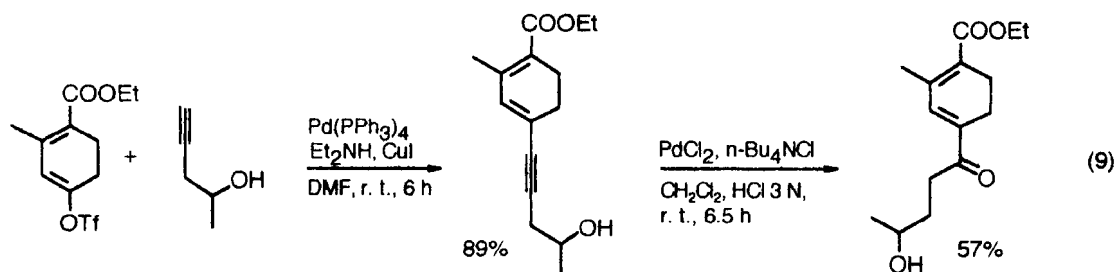


The cyclization step has been carried out in an acidic  $\text{CH}_2\text{Cl}_2/3 \text{ N HCl}$  two-phase system in the presence of the  $n\text{-Bu}_4\text{NCl}/\text{PdCl}_2$  combination. The procedure proved to be especially convenient for the *one-flask* conversion of **8** into **10**, without the isolation of the intermediate **9**. Under these conditions compounds **10** have been isolated in 62-98% yield. Related reactions have been carried out starting from *o*-ethynylphenols **11** and propargyl ethylmalonates **12** to afford 2-substituted-benzo[*b*]furans (**14**) (eq. 7) and functionalized butenolides (**15**) (eq. 8).



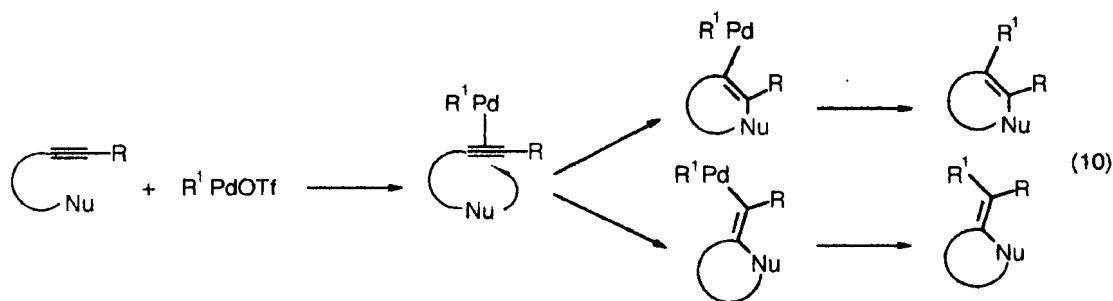
As to the coupling of propargyl malonates **12** with vinyl triflates and aryl halides (eq. 8), it is worth noting that good to high yields of coupling products can be obtained although propargyl esters (acetates,

trifluoroacetates, carbonates, sulfinates and sulfonates) have been reported to undergo a variety of palladium-catalyzed transformations through the supposed intermediacy of  $\sigma$ -allenylpalladium complexes (16). The palladium-catalyzed coupling of vinyl triflates with 1-butyne-4-ols, followed by the reaction of the obtained 1-hydroxy-3-yn-5-enes in an acidic two-phase system, in the presence of the  $n$ -Bu<sub>4</sub>NCl/PdCl<sub>2</sub> combination, led to the formation of  $\gamma$ '-hydroxy- $\alpha,\beta$ -enones (eq. 9), most probably through the intermediacy of an unstable oxygen-containing five-membered ring system (17). Both the coupling step and the conversion of the carbon-carbon triple bond into the ketonic group have been performed at room temperature. The whole process can be carried out through a *one-flask* process, without the isolation of 1-hydroxy-3-yn-5-enes.

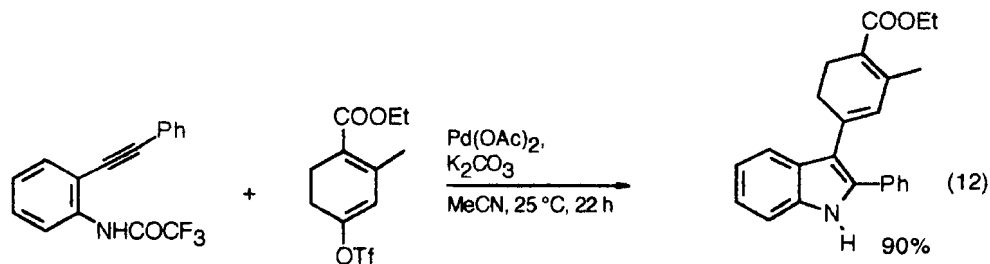
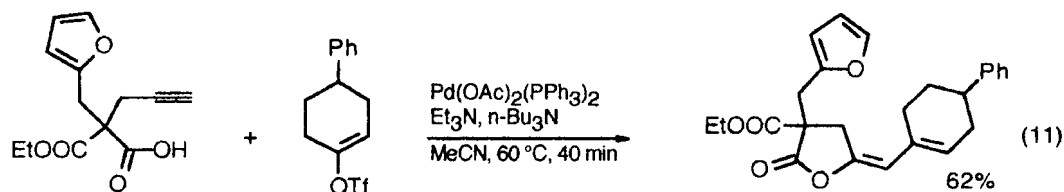


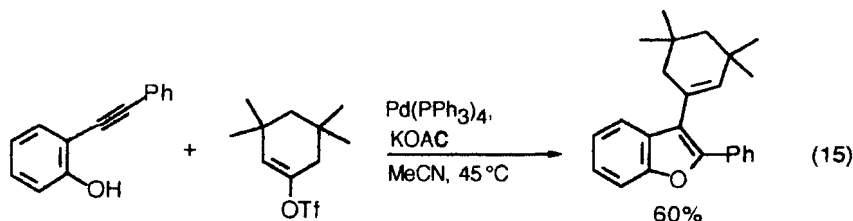
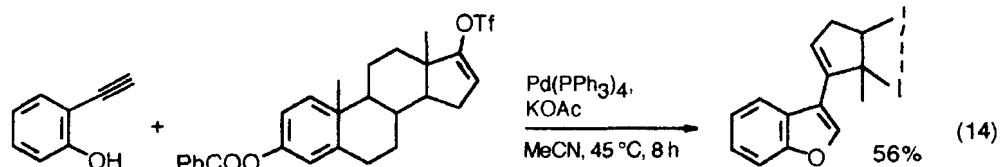
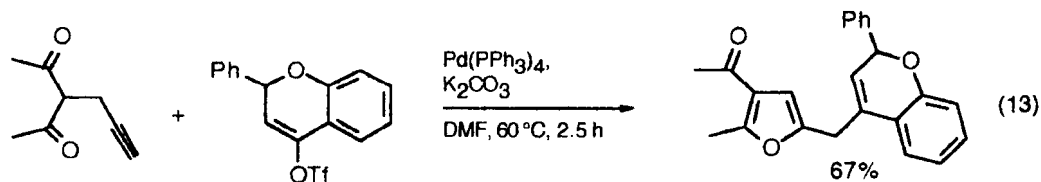
### CYCLIZATION OF ALKYNES PROMOTED BY $\sigma$ -VINYL- OR $\sigma$ -ARYLPALLADIUM COMPLEXES

The scope of the palladium chemistry of unsaturated triflates and alkynes is considerably widened by the observation that nucleophiles near the carbon-carbon triple bond can participate in the reaction through intramolecular attack on the multiple bond activated by the coordination to  $\sigma$ -vinyl- and  $\sigma$ -arylpalladium complexes generated *in situ* (eq. 10).



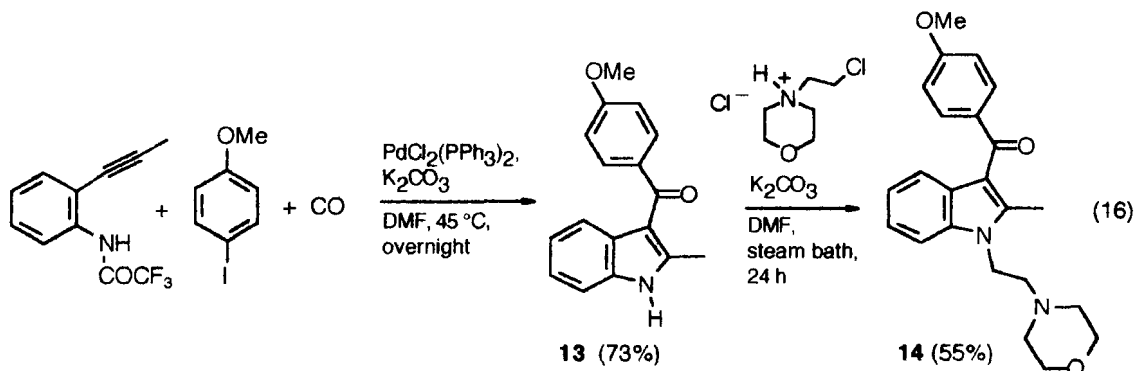
Heteroannulations promoted by  $\sigma$ -vinyl- and  $\sigma$ -arylpalladium complexes appear to be extremely valuable since the generation of cyclic compounds combines with the ability of accommodating functionalities amenable to further functional-group manipulation and with a rapid increase in molecular complexity. (*E*)- $\delta$ -vinyl- $\gamma$ -methylene- $\gamma$ -butyrolactones (18) (eq. 11), 2,3-disubstituted indoles (19) (eq. 12), 2,3,5-trisubstituted furans (20) (eq. 13), 3-substituted benzo[*b*]furans (14) (eq. 14), and 2,3-disubstituted benzo[*b*]furans (14) (eq. 15) have been prepared by reacting vinyl triflates and aryl halides with suitable functionalized alkynes.



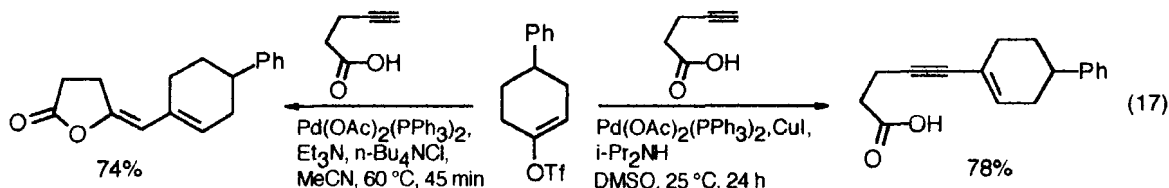


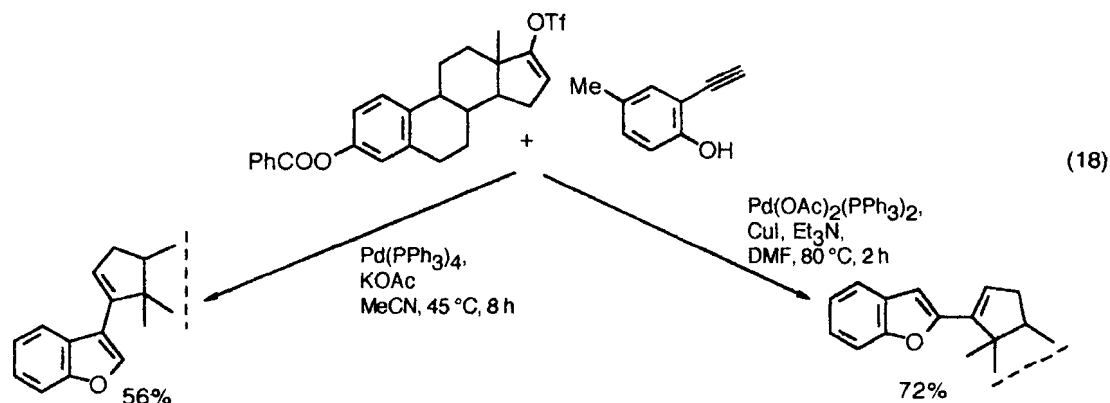
Interestingly, while the reaction of palladium dichloride with functionalized alkynes generates  $\pi$ -palladium complexes able to react with nucleophiles such as the hydroxy (21, 22) the amino (22-25), and the amido groups (25, 26),  $\pi$ -palladium complexes generated from the coordination of the carbon-carbon triple bond to  $\sigma$ -vinyl- and  $\sigma$ -arylpalladium intermediates (27) apparently need anionic nucleophiles to allow the intramolecular nucleophilic attack. For example, in our palladium-catalyzed synthesis of 2,3-disubstituted indoles (19) (eq. 12), no indole derivatives were formed by reacting vinyl triflates and aryl halides with *o*-alkynylanilines or *o*-alkynylacetanilides and using  $K_2CO_3$  as the base. Good results were instead obtained with *o*-alkynyltrifluoroacetanilides, which are more prone to generate anionic nucleophiles.

When such reactions are carried out under an atmosphere of carbon monoxide the formation of the carbon-heteroatom bond can combine with the formation of two carbon-carbon bonds as shown in the preparation of **13**, an intermediate on the way to pravadoline **14**, an indole derivative designed as a nonacidic analogue of non-steroidal anti-inflammatory drugs (NSAIDs) (28) (eq. 16).



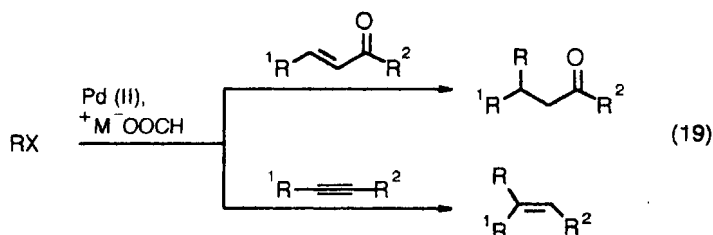
As it has been shown, the reaction of 1-alkynes with  $\sigma$ -organopalladium intermediates can produce coupling products and cyclic derivatives. In some cases, products derived from both coupling and cyclization can be prepared by introducing apparently minor changes in the reaction mixture composition. The palladium-catalyzed reactions of vinyl triflates with 4-pentynoic acid (29) (eq. 17) and *o*-ethynylphenols (14) (eq. 18) represent impressive examples of this.





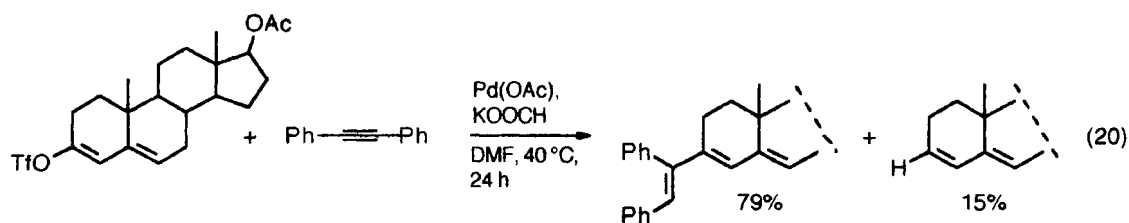
### HYDROVINYLTION/CYCLIZATION OF ALKYNES

The reaction of alkenes and alkynes with  $\sigma$ -vinyl- and  $\sigma$ -arylpalladium complexes in the presence of reducing agents, typically formate anions, is known to afford hydroarylation and hydrovinylation derivatives (30) (eq. 19).

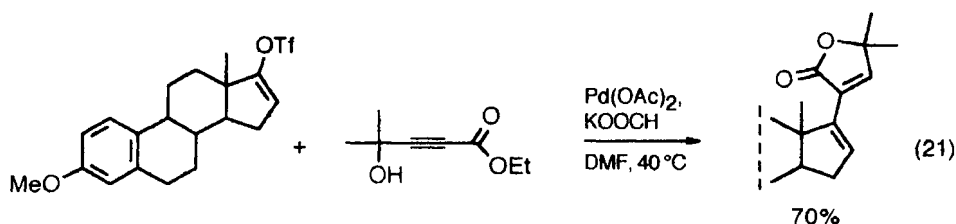


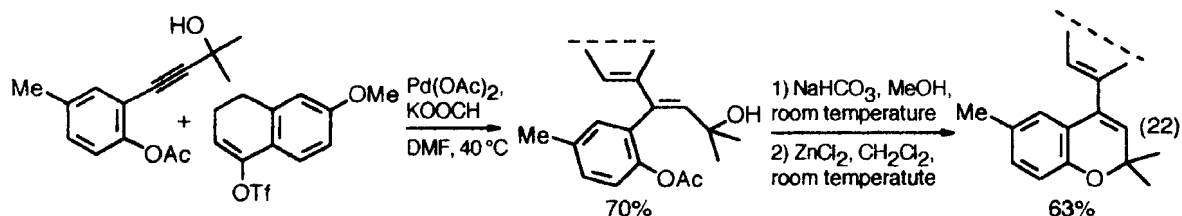
The extension of this methodology to unsaturated triflates may provide an interesting entry into new functionalizations of ketones and phenols. The reaction of vinyl triflates with  $\beta$ -substituted- $\alpha,\beta$ -unsaturated carbonyl compounds (eq. 2b) showed that hydrovinylation can occur even in the presence of potassium acetate, most probably as the result of the proton assisted heterolytic cleavage of the carbon-palladium bond of  $\sigma$ -alkylpalladium intermediates derived from the addition of  $\sigma$ -vinyl- and  $\sigma$ -arylpalladium complexes to the carbon-carbon double bond.

Our attention, however, has mainly been focused on the hydrovinylation of alkynes. Treatment of vinyl triflates with alkynes in the presence of potassium formate has been found to produce hydrovinylation products in good yield. Best results have been obtained in the absence of phosphine ligands (31) (eq. 20). The addition of phosphines to the reaction mixture tends to favor the competitive reduction to alkenes (32).



The reaction has been utilised to develop new syntheses of functionalized butenolides (31) (eq. 21) and precocenes (33) (eq. 22)





## CONCLUSIONS

A variety of new, and in many cases unique, palladium-catalyzed carbon-heteroatom and carbon-carbon bond forming reactions have been developed starting from unsaturated triflates (and halides) and alkenes or alkynes. These reactions can tolerate a wide range of functional groups, occur under mild conditions, and appear particularly promising for their application to the area of natural product synthesis.

## Acknowledgements

I wish to express my sincere appreciation to co-workers, whose names appear in the references, for their contribution and application. Continuing financial support from the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST) and the Consiglio Nazionale delle Ricerche (CNR) is gratefully acknowledged.

## REFERENCES

1. S. Cacchi, E. Morera and G. Ortar *Tetrahedron Lett.* **25**, 2271 (1984).
2. W.J. Scott, G.T. Crisp and J.K. Stille *J. Am. Chem. Soc.* **106**, 4630 (1984).
3. W. Harnisch, E. Morera and G. Ortar *J. Org. Chem.* **50**, 1990 (1985).
4. S. Liang and L.A. Paquette *Acta Chem. Scand.* **46**, 597 (1992).
5. A. Arcadi, S. Cacchi, G. Fabrizi, F. Marinelli and P. Pace, work in progress.
6. S. Cacchi and A. Arcadi *J. Org. Chem.* **48**, 4236 (1983); A. Amorese, A. Arcadi, E. Bernocchi, S. Cacchi, S. Cerrini, W. Fedeli and G. Ortar *Tetrahedron* **45**, 813 (1989).
7. S. Cacchi and P. Pace, work in progress.
8. S. Cacchi, E. Morera and G. Ortar *Synthesis* 320 (1986).
9. J.R. Granja, L. Castedo and A. Mourino *J. Org. Chem.* **58**, 124 (1993); L.A. Sarandeses, M.J. Vallés, L. Castedo and A. Mourino *Tetrahedron* **49**, 731 (1993).
10. G.T. Crisp and T.A. Robertson *Tetrahedron* **48**, 3239 (1992).
11. R. Brückner, S.W. Scheuplein and J. Suffert *Tetrahedron Lett.* **32**, 1449 (1991); J. Suffert and R. Brückner *Tetrahedron Lett.* **32**, 1453 (1991); K. Nakatani, K. Arai, N. Hirayama, F. Matsuda and S. Terashima *Tetrahedron Lett.* **31**, 2323 (1990); K. Nakatani, K. Arai, N. Hirayama, F. Matsuda and S. Terashima *Tetrahedron* **48**, 633 (1992).
12. K. Hirota, Y. Kitade, Y. Isobe and Y. Maki *Heterocycles* **26**, 355 (1987).
13. S. Cacchi, V. Carnicelli and F. Marinelli. *J. Organomet. Chem.* **475**, 289 (1994).
14. A. Arcadi, S. Cacchi, M. Del Rosario and F. Marinelli, work in progress.
15. A. Arcadi, S. Cacchi, G. Fabrizi and F. Marinelli *Synlett* 65 (1993)
16. J. Tsuji, T. Sugiura and I. Minami *Synthesis* 603 (1987); C.J. Elsevier, P.M. Stehouwer, H. Westmijze and P. Vermeer *J. Org. Chem.* **48**, 1103 (1983); K. Ruitenbergh, H. Keijn, C.J. Elsevier, J. Meijer and P. Vermeer *Tetrahedron Lett.* **22**, 1451 (1981); T. Mandai, K. Ryoden, M. Kawada and J. Tsuji *Tetrahedron Lett.* **32**, 7683 (1991); T. Mandai, S. Suzuki, A. Ikawa, T. Murakami, M. Kawada and J. Tsuji *Tetrahedron Lett.* **32**, 7687 (1991); T. Mandai, M. Ogawa, H. Yamaoki, T. Nakata, H. Murayama, M. Kawada and J. Tsuji *Tetrahedron Lett.* **32**, 3397 (1991); T. Mandai, T. Nakata, H. Murayama, H. Yamaoki, M. Ogawa, M. Kawada and J. Tsuji *Tetrahedron Lett.* **31**, 7179

- (1990); L. Geng and X. Lu *J. Chem. Soc., Perkin Trans. 1* **17** (1992); H. Kataoka, K. Watanabe and K. Goto *Tetrahedron Lett.* **31**, 4181 (1990).
17. A. Arcadi, S. Cacchi and F. Marinelli *Tetrahedron* **49**, 4955 (1993).
  18. A. Arcadi, A. Burini, S. Cacchi, M. Delmastro, F. Marinelli and B.R. Pietroni *J. Org. Chem.* **57**, 976 (1992).
  19. A. Arcadi, S. Cacchi and F. Marinelli *Tetrahedron Lett.* **33**, 3915 (1992).
  20. A. Arcadi, S. Cacchi, R.C. Larock and F. Marinelli *Tetrahedron Lett.* **34**, 2813 (1993).
  21. Y. Fukuda, H. Shiragami, K. Utimoto and H. Nozaki *J. Org. Chem.* **56**, 5816 (1991); Y. Wakabayashi, Y. Fukuda, H. Shiragami, K. Utimoto and H. Nozaki *Tetrahedron* **41**, 3655 (1985); C. Lambert, K. Utimoto and H. Nozaki *Tetrahedron Lett.* **25**, 5323 (1984).
  22. K. Utimoto *Pure & Appl. Chem.* **55**, 1845 (1983).
  23. A. Arcadi, S. Cacchi and F. Marinelli *Tetrahedron Lett.* **30**, 2581 (1989).
  24. Y. Fukuda, S. Matsubara and K. Utimoto *J. Org. Chem.* **56**, 5812 (1991); Y.K. Kondo, T. Sakamoto and H. Yamanaka *Heterocycles* **29**, 1013 (1989); K. Utimoto, H. Miwa and H. Nozaki *Tetrahedron Lett.* **22**, 4277 (1981).
  25. K. Iritani, S. Matsubara and K. Utimoto *Tetrahedron Lett.* **29**, 1799 (1988).
  26. D.E. Rudisill and J.K. Stille *J. Org. Chem.* **54**, 5856, (1989); E.C. Taylor, A.H. Katz and H. Salgado-Zamora *Tetrahedron Lett.* **26**, 5963 (1985)
  27. For cyclizations involving carbon nucleophiles, see: G. Fournet, G. Balme, B. Van Hemelryck and J. Gore *Tetrahedron Lett.* **31**, 5147 (1990); G. Fournet, G. Balme and J. Gore *Tetrahedron* **47**, 6293 (1991); N. Monteiro, G. Balme and J. Gore *Tetrahedron Lett.* **32**, 1645 (1991).  
For cyclizations involving oxygen nucleophiles, see: ref. 18 and 20; D. Bouyssi, J. Gore and G. Balme *Tetrahedron Lett.* **33**, 2811 (1992); F.-T. Luo, I. Schreuder and R.-T. Wang *J. Org. Chem.* **57**, 2213 (1992).  
For cyclizations involving nitrogen nucleophiles, see: ref. 19; F.-T. Luo and R.-T. Wang *Tetrahedron Lett.* **33**, 6835 (1992).
  28. A. Arcadi, S. Cacchi, V. Carnicelli and F. Marinelli *Tetrahedron* **50**, 437 (1994).
  29. A. Arcadi, S. Cacchi, M. Delmastro and F. Marinelli *Synlett* 409 (1991).
  30. S. Cacchi *Pure & Appl. Chem.* **62**, 713 (1990).
  31. A. Arcadi, S. Cacchi, G. Fabrizi, F. Marinelli and P. Pace, work in progress.
  32. S. Cacchi, E. Morera and G. Ortar *Tetrahedron Lett.* **25**, 4821 (1984); S. Cacchi, E. Morera and G. Ortar *Org. Synth.* **68**, 138 (1990).