# MICROWAVE-ASSISTED Pd-CATALYZED C-P OR C-C CROSS COUPLINGS ON 13α-ESTRANE CORE

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## Abstract

Novel 2- or 4-substituted 13α-estrone derivatives were synthesized via Hirao or Suzuki reaction. Transformations of 2- and/or 4-halogenated derivatives of 13α-estrone and its 3-benzyl or -methyl ether were carried out in a microwave (MW) reactor. Facile and efficient C-C or C-P coupling procedures were established using Pd or Ni catalysts. The newly synthesized compounds might have promising antitumoral properties.

## Introduction

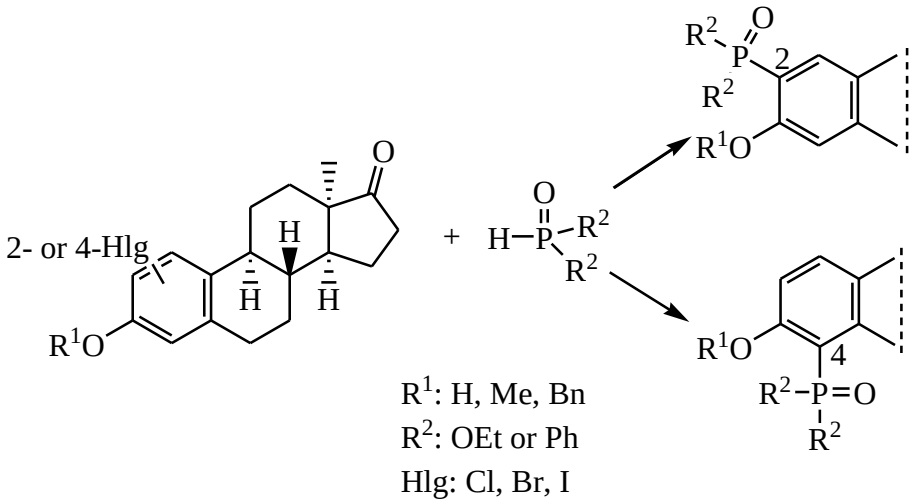
Introduction of large apolar substituents onto C-2 of estrane core may lead to compounds possessing substantial antitumoral activity. The functionalization of the aromatic ring A of estrone might be achieved via Pd-catalyzed cross coupling reactions. Hirao reaction is a powerful tool for the synthesis of aryl phosphonates from aryl bromides or iodides using dialkyl phosphites (H-phosphonates) as the reagents, $Pd(PPh_3)_4$ as the catalyst and $Et_3N$ as the base.[1,2,3] Suzuki reaction is a cross coupling reaction between aryl/alkyl halides with organoboronic acids and $Pd(PPh_3)_4$ as the catalyst.[4] Our aim was to develop facile and effective C-C and C-P cross coupling methods for the preparation of 2- or 4-substituted 13α-estrone derivatives by MW irradiation. We planned to use "green" methodologies by replacing the Pd catalyst with Ni under P-ligand- and solvent-free conditions.

## Experimental

The optimization of the Hirao reaction conditions was carried out using 2-bromo- or 2-iodo-13α-estrone 3-methyl ether as starting compounds and diethyl phosphite as a reagent. $Pd(OAc)_2$ or $Pd(PPh_3)_4$ catalysts were used without addition of any P-ligand. The Suzuki couplings were optimized using 2-bromo- or 2-iodo- 13α-estrone 3-methyl ether as starting compounds, phenylboronic acid as a reagent and $Pd(PPh_3)_4$ catalyst. The structures of the new compounds were confirmed by $^1H$ and $^{13}C$ NMR measurements.

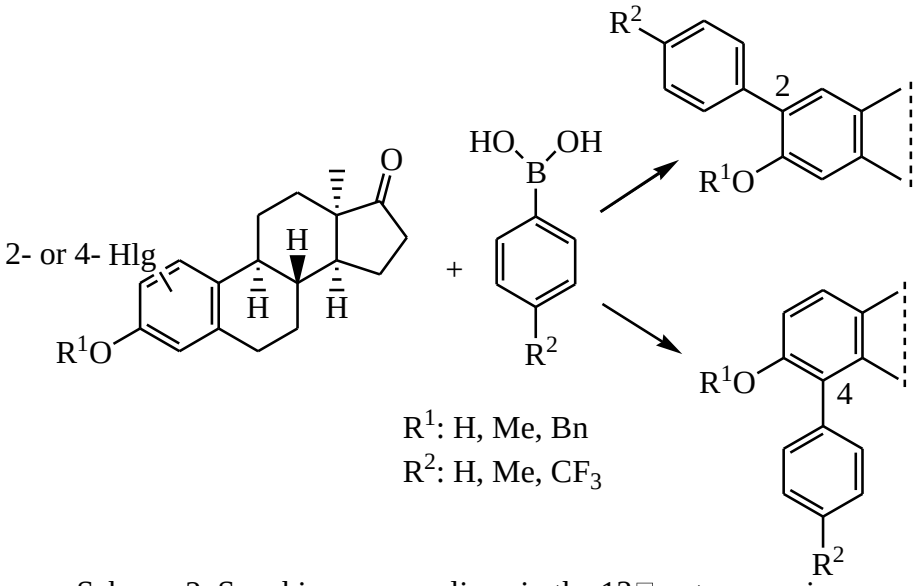
## Results and discussion

The optimal conditions were selected for extension of C-P couplings to other steroidal scaffolds, which differ in position and nature of the halogen and/or nature of the C-3 substituent (Scheme 1). All the couplings resulted in the desired product with high yields. Couplings with $NiCl_2$ as the catalyst required higher reaction temperatures and longer reaction times.




Scheme 1. C-P couplings at C-2 or C-4 in the 13□-estrone series

Suzuki reactions were efficiently performed with different para-substituted phenylboronic acids (Scheme 2). The couplings of C-2 or C-4 regioisomers could be achieved under different conditions. It can be stated that transformations at more hindered C-4 required harsher reaction conditions.




Scheme 2. Suzuki cross couplings in the 13□-estrone series

## Conclusion

We have developed efficient microwave-assisted, P-ligand-free, Pd- or Ni-catalyzed cross coupling procedures. Certain reactions proved to be effective under solvent solvent-free conditions too.

## Acknowledgements

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