PhD Thesis

THE APPLICATION OF PALLADIUM-CATALYSED REACTIONS IN SYNTHESES

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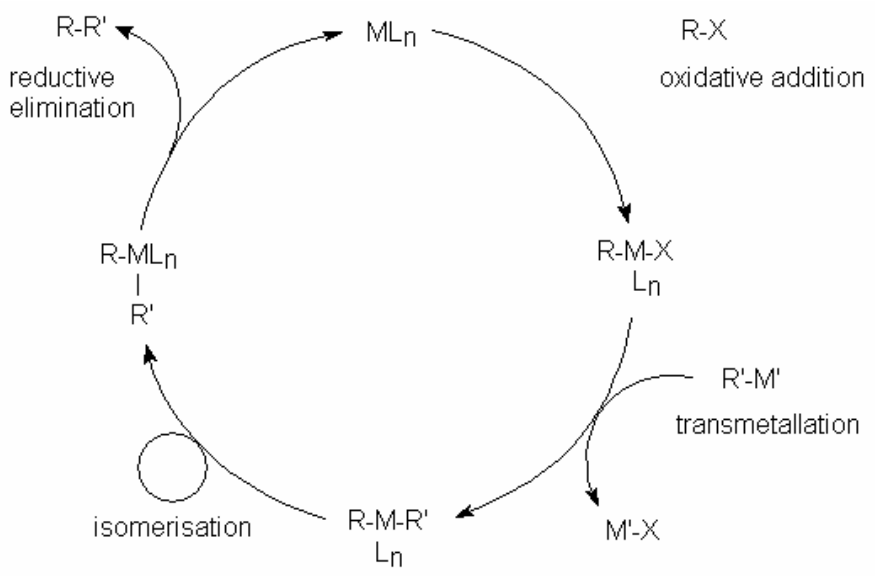
1. Introduction

The organo-transition metal chemistry, following a remarkable progress over the past decades, has now reached the stage of general application in synthetic organic chemistry. The recognition of carbon-metal bonding properties, as well as the definition of the scope and limitations have rendered many of the transition metal catalysed reactions among them carbonylation reactions involving the use and the mechanistic understanding of the basic catalytic reactions Solving practical problems in this field has been greatly promoted by understanding the structure of transitional-metal carbon binding and the elementary steps during the catalytic reactions, as well as the mechanisms of reactions taking place in the coordination sphere of transitional metals. Due to their favorable yield and exceptional chemo-, regio- and enantioselectivity, nowadays only rarely can we encounter with modern synthetic reactions of importance without some forms of organometallic homogenous catalysis. Transitional metal-complexes are regularly used in homogenous catalytic carbonylations for generating various skeletons or introducing C=O functionalities of practical importance.

Many reactions employing organometallic reagents have been named after their inventors. In the cross-coupling reactions catalysts containing low oxidation state transition metals are used. In the most frequently used catalysts the 0 oxidation stage is generated either *in situ* from appropriate metal compounds (*e.g.* $PdCl_2(PPh_3)_2$, $Pd(OAc)_2$ precursors) or the initial complex itself contains 0 oxidation state metal. Most frequently phosphine or triethylamine is used as reducing agent for the generation of catalytically active low oxidation state catalyst intermediates, which also acts as a ligand for the catalyst. The first step of the reaction is the oxidative addition of organic halide onto the transition metal, in which the oxidation number of the transition metal increases by two. Carbon-metal σ-bonding is formed, while the transition metal becomes +2 oxidation state. The other organic compound to be coupled (R'M') is positioned upon the transition metal by transmetallation, thus a metal complex with organic ligands in *trans*-position is formed. During isomerisation the complex with *trans* structure is transformed into *cis*-derivate. The steric rearrangement permits the reductive elimination yielding the final product, and the active catalyst is also recovered. The speed of a catalytic reaction is determined by the slowest elementary reaction, usually by the oxidative addition.

The majority of catalysts and ligands used in the coupling reactions are now commercially available. Ligands that bind to the metals stabilize the catalyst, and also permit the reaction to occur in homogeneous (overwhelmingly liquid) phase.

The above catalytic reactions are also preferred for the industrial production of fine chemicals. The selectivity of the reaction can be directed within a broad spectrum by choosing the appropriate ligand and central metal.



ML_n: Pd(0), Ni(0)
M': B - Suzuki-Miyaura coupling; Mg - Kharasch coupling; Cu - Sonogashira coupling
X: I, Br, Cl, OTf, OSO_2R, SOR, SR
Sn - Stille coupling; Zn - Negishi coupling; Si - Hiyama coupling

Figure 1. General mechanism of cross-coupling reactions

2. Aims

The major aim of my experimental work was to establish novel and efficient methods by using palladium-catalysed carbonylation reactions for producing compounds that contain biologically active steroid moiety with 17-formyl-16-ene functionality. These compounds can be applied either as active compounds or their precursors, or as prodrugs. In our experiments 'iodo-vinyl' steroids (17-iodo-16-ene) compounds were functionalized. Simple iodo-alkene (1-iodo-cyclohexene) was also used as starting model compound.

My target subfields were as follows:

- Optimization of Suzuki-Miyaura cross-coupling reaction between 1-iodo-cyclohexene and arylboronic acids, the characterization of its products. As well as description of the elementary steps of the reaction.
- Synthesis of unsaturated ketones under carbonylative Suzuki conditions, a better understanding of formylation and the identification of reaction products.
- Synthesis of 17-formyl-steroids via palladium-catalysed carbonylation reaction.
- Synthesis of 17-carboxamido-androstanes containing crown ether structural subunit.

3. Methods

Inert Schlenk-technique and high-pressure autoclave method was used. The experiments involving high pressure (12 or 42 bar) were performed in an stainless steel autoclave of 100 cm^3.

The conversions and the product distributions were determined by using GC/MS. The products were identified by GC-MS, IR, ^{1}H- and ^{13}C-NMR measurements and element (C, H, N) analyses.

4. Results

In my PhD work three types of the homogenous catalytic reactions catalysed by palladium complexes were investigated: the Suzuki-Miyaura-reaction, the formylation and carbonylation reactions of steroids containing iodo-alkene functionality. The investigations were directed to reveal novel reaction mechanisms, and also to establish procedures for the functionalization of several steroids via carbonylation and aminocarbonylation reactions, thus generating novel steroid compounds. The conditions for the reactions were optimized, and the problems of application and the difficulties arising during synthesis were defined. An important feature of the reactions studied in my work is their exceptional selectivity.

My results and observations are summarized as follows:

1. Most publications reporting on the application of the Suzuki-Miyaura reaction focus on the production of a desired compound, while overlooking the „unwanted” side-products, despite the fact that the latter entities being essential for the understanding

the details of a catalytic reaction. In my experimental work a series of experiments were set up, in which both the catalysts and the reaction conditions were systhematically altered. *We have established that the carbonylative Suzuki reaction applied for iodo-vinyl substrates can, be used for producing aril-alkenyl ketones by reacting arilboronic acid and iodo-alkenes at a high degree of chemoselectivity under suitable circumstances*. The catalytic mixtures of Suzuki-Miyaura reaction of 1-iodo-cyclohexene and phenylboronic acid (or 3-trifluoromethoxy-phenylboronic acid) used as model compound were analysed, and the side products of both carbonylative and direct coupling reactions were identified. We have demonstrated that the amount of expected carbonylative products was greatly influenced by the reaction conditions (catalysts, type of boronic acid, reaction period, temperature, CO-pressure, type of solvent, presence of water in solvent).

2. We have established if using the parent phenylboronic acid in carbonylative Suzuki reactions, with catalyst containing 1,1'-bis(diphenylphosphano)-ferrocene with conformational rigidity, complete chemoselectivity can be achieved, whereas the use of trifluoromethoxy-phenylboronic acid results in a lower chemoselectivity.

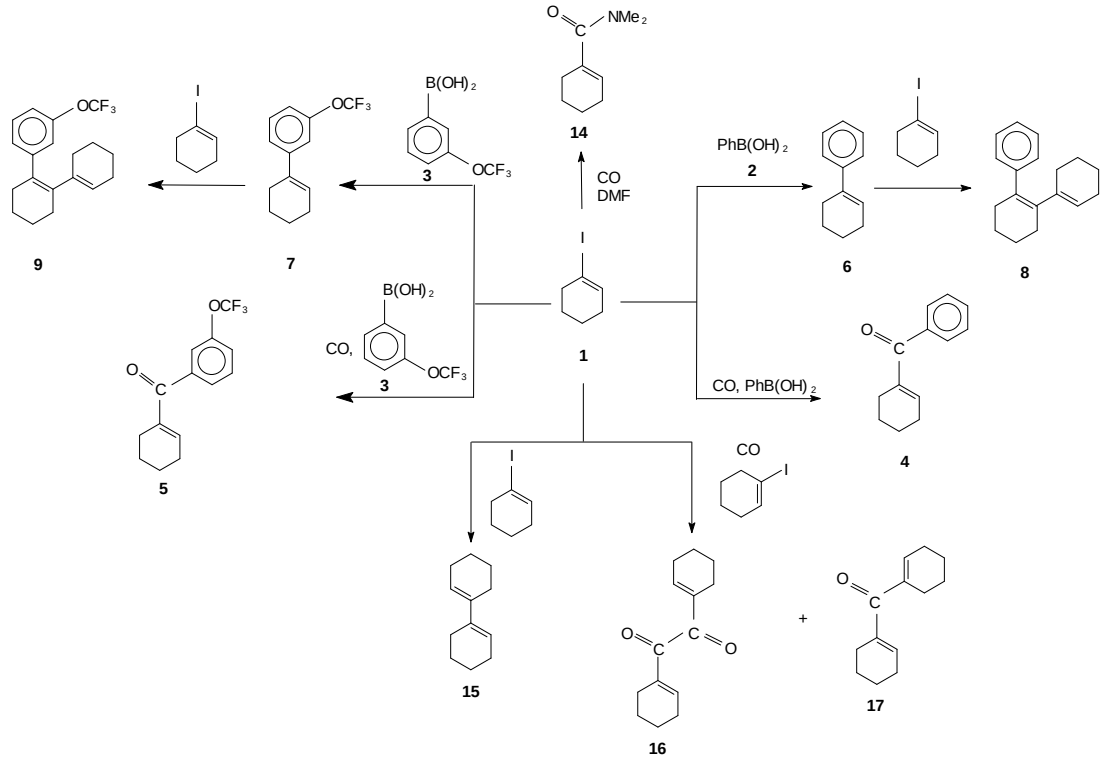


Figure 2. Products of the carbonylation reaction of 1-iodo-cyclohexene and arylboronic acids (including the side-products)

3. High solvent-dependence of the reaction was observed. Using DMF as solvent a complete ketone selectivity can be achieved in palladium-acetate-dppf catalyst

system. In the presence of DMSO a large amount of byproducts were formed in consecutive Suzuki coupling and Heck reactions.

4. The increasing of the CO pressure also influences the selectivity of the reaction. At a higher CO-pressure the carbonylated products were produced at lower chemoselectivity. A possible explanation is that at higher pressure palladium carbonyls are formed, which in such form can not activate the substrate in the coordination sphere, thus the catalyst will be partially deactivated.
5. We have established that as long as the carbonyl insertion is not preferred, in the presence of solvents containing water traces a large amount of cyclohexen-1-yl-formiate is formed. The explanation for this reaction is that in the presence of catalysts formic acid is generated *in situ* which, upon reacting with the substrate, yields alkenil-formiates.
6. In normal Suzuki reactions the highest rate of conversion was observed when phenylboronic acid was used as aryl source in the presence of 1,4-bis(diphenylphosphano)butane forming a seven-membered chelate ring. Upon increasing the reaction time enhanced conversions were obtained, but the chemoselectivity of the reaction decreased.
7. When 3-trifluoromethoxy-phenylboronic acid was used in the Suzuki reaction, the highest activity was observed in the presence of PPh_3 and 1,2-bis(diphenylphosphano)ethane forming five-membered chelate ring.
8. The highest chemoselectivity of direct coupling Suzuki reactions was observed in those cases when 1,1'-bis(diphenylphosphano)ferrocene, 1,3-bis(diphenylphosphano)-propane or 1,4-bis(diphenylphosphano)butane ligand was used. The application of rigid phosphane (1,1'-bis(diphenylphosphano)-ferrocene) together with phenylboronic acid, as well as the conformationally more flexible chelate forming phosphane (1,4-bis(diphenylphosphano)butane) with 3-trifluoromethoxy-phenylboronic acid resulted in higher chemoselectivity.
9. In the absence of phosphane ligand, the side-products and their isomers were formed at an unexpectedly high proportion during Heck-reactions, irrespectively of the type of arilboronic acid. Their production was facilitated by the use of palladium-acetate containing no phosphine ligand.
10. Our detailed analysis of the reaction products was the first report on the products generated by the Heck-products and homo-coupling of substrates during the direct

and carbonylative Suzuki-Miyaura coupling reaction, including cyclohexen-1-yl-cyclohexene, bis(1-cyclohexenyl)glyoxal and the di-(cyclohexen-1-yl)-ketone.

11. The formyl group, particularly at the position-17 of the androstane-skeleton is suitable for further functionalization of the androstane-skeleton. Formylation reactions that are easy to perform at low pressure were developed, in which aryl-, benzyl- and vinyl-halides are reacted with tributylstannane as a hydrogen donor in the presence of $Pd(PPh_3)_4$ catalyst. *We have established that, under appropriate circumstances readily accessible iodo-vinyl steroids as substrates can be used for producing unsaturated androstane-skeletal aldehydes in palladium-catalysed carbonylation reactions.* The 17-formil-16-ene derivatives may serve as versatile intermediates for compounds of pharmacological importance.
12. We have explored the structure of androst-16-ene and its isomers formed by hydrostannolysis during the above reaction and the conditions of their formation. We have described the elemental steps of formylation and hydrostannolysis. In our experiments we have determined the reaction conditions influencing its chemoselectivity (the rate of adding tributyl-stannane-hydride and the characteristics of bidentate phosphine ligand).
13. We have established that reducing the rate of adding tributylstannane increases the chemoselectivity towards the target product, due to the insertion of CO into palladium-alkenyl bond being the slowest elementary reaction of the catalytic cycle. In this way the longer period allowed for the reaction facilitates the formation of the palladium-acyl intermediate.

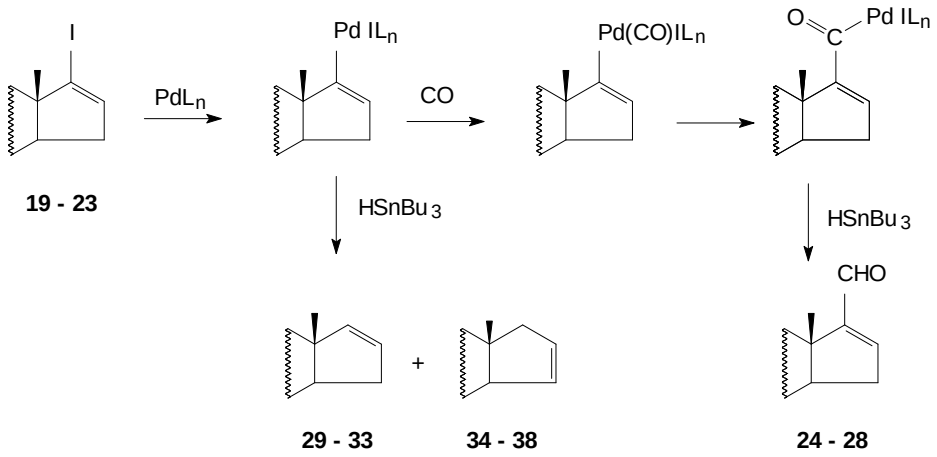


Figure 3. Elementary steps of formylation and hydrostannolysis

14. In case of 17-formyl-steroids as expected products the best conversion and chemoselectivity could be achieved by palladium-1,4-bis(diphenylphosphano)-butane *in situ* system. The target compounds were isolated in 70-75% yield.
15. We have established that the formylation reaction tolerates the presence of various functional groups on the A and B rings of steroids, and also observed that, due to the presence of lactame NH-functional group and the 6β-hydroxy functional group, the tributylstannan-hydrid causes mainly hydrodehalogenation. The known conformationally flexible chelate-forming diphosphanes, such as the 1,4-bis(diphenylphosphano)butane and 1,3-bis(diphenylphosphano)propane proved much more effective that either the rigid bidentate diphosphanes (*e.g.* ferrocene-based 1,1'-bis(diphenylphosphano)-ferrocene)) or the monodentate PPh_3.
16. The parent 17-iodo-androsta-16-ene basic skeletal steroids were reacted with crown ethers, containing amino functional groups, in palladium-catalysed homogeneous aminocarbonylation reaction. The expected steroidal crown ether were obtained in excellent yields (up to 93%). Subsequent analysis by thin-layer chromatography indicated that the reactions were practically completed within a few hours period under mild reaction conditions.

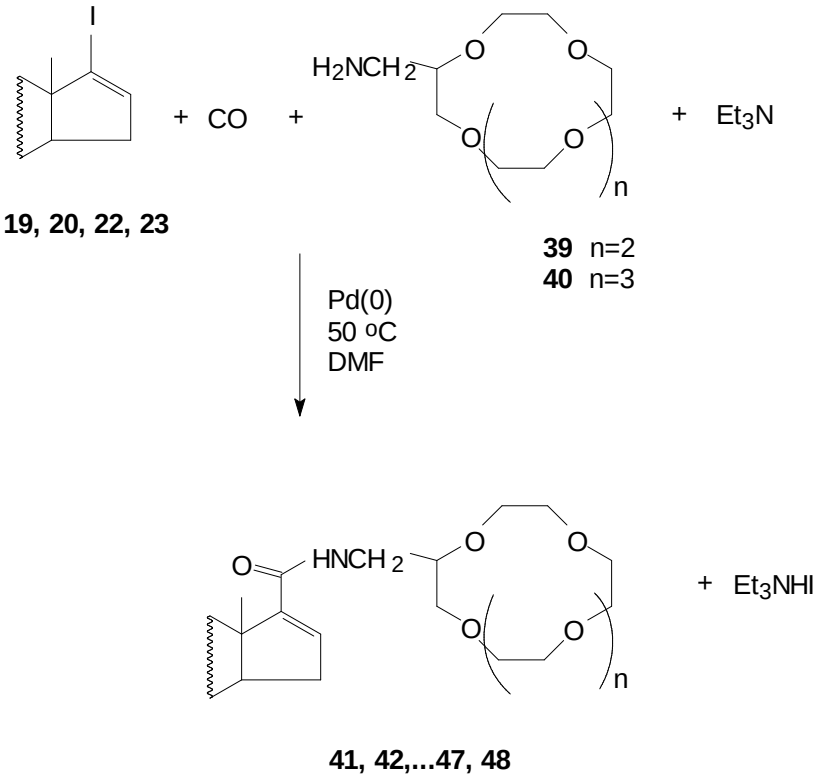


Figure 4. The aminocarbonylation of 17-iodo-16-ene steroids with crown ethers

17. According to our observations only the amino-group of the crown ether became acylated. We also described the palladium-acyl intermedier and the mechanism of the aminocarbonylation reaction.
18. The palladium-catalysed reactions tolerated the presence of various functional groups on the A and B ring of steroidal skeleton. It can be stated that this methodology can be successfully applied for the synthesis of these compounds of practical importance.

5. Publications, presentations

I. Publications forming the basis of PhD dissertation

1. **A. Petz,** Gy. Gálik, J. Horváth, Z. Tuba, Z. Berente, Z. Pintér, L. Kollár: Facile, High-yielding Synthesis of Steroidal Crown Ethers via Palladium-catalyzed Carbonylation Reaction. *Synth. Commun.* 31 (3), (2001) 335-341. **IF: 0,912**

2. **A. Petz,** J. Horváth, Z. Tuba, Z. Pintér, L. Kollár: Facile synthesis of 17-formyl steroids via palladium-catalyzed homogeneous carbonylation reaction. *Steroids* 67 (2002) 777-781. **IF: 2,524**

3. **A. Petz**, Z. Pintér, L. Kollár: Mass spectrometric studies on the coupling model reaction towards alkenyl-aryl-ketones. *J. Biochem. Biophys. Meth.* 61 (2004) 241-245. **IF: 1,302**

4. **A. Petz,** G. Péczely, Z. Pintér, L. Kollár: Carbonylative and direct Suzuki-Miayaura cross-coupling reactions with 1-iodo-cyclohexene *J. Mol. Catal.* 255 (2006) 97-102. **IF: 2,511**

II. Other publications

1. Y. Qu, A. Harris, A. Hegmans, **A. Petz**, P. Kabolizadeh, H. Penazova, N. Farrell: Synthesis and DNA conformational changes of non-covalent polynuclear platinum complexes. *J. Inorg. Biochem.* 98 (2004) 1591-1598. **IF: 2,225**

2. P Balogh, **A Petz**: Selective binding of biotinylated albumin to the lymphoid microvasculature. *Histochem. Cell Biology* 123 (4-5) (2005) 357-363. **IF: 2,239**

3. A. Takács, B. Jakab, **A. Petz**, L. Kollár: Homogeneous catalytic aminocarbonylation of nitrogen-containing iodo-heteroaromatics. Synthesis of N-substituted nicotinamide related compounds. *Tetrahedron*, 63 (2007) 10372-10378. **IF: 2,817**

4. A. Takács, **A. Petz**, B. Jakab, L. Kollár: Aminocarbonylation of 2-iodothiophene: High-yielding synthesis of thiophen-2-yl-glyoxylamides. *Lett. Org. Chem.* 4 (8) (2007) 590-594. **IF: 1,004**

5. A. Takács, **A. Petz**, L. Kollár.: Palladium-catalysed aminocarbonylation of iodoarenes and iodoalkenes with aminophosphonate as N-nucleophile. *Tetrahedron* 64 (37) (2008) 8726-8730. **IF: 2,817**

6. A. Takács, R. Farkas, **A. Petz,** L. Kollár: High-yielding Synthesis of 2-Aryl-acrylamides via Homogeneous Catalytic Aminocarbonylation of a-Iodo-styrene and a,a'-Diiodo-1,4-divinylbenzene. T*etrahedron* 64 (2008) 61-66. **IF:2,817**

7. R. Farkas, A. Szilágyi, **A. Petz,** L. Kollár: High-yielding Palladium-catalysed Aminocarbonylation of 1',4-Diiodostyrene. *Tetrahedron* (accepted) **IF:2,817**

8. Kovács B., **Petz A.**: Fluoreszcencia kioltáson alapuló új eljárás uranil-ionok meghatározására.- *A lumineszcencia kutatások aktuális kérdései XVIII*/ MTA-JPTE Pécs (1995) 21-29.

9. **Petz A.**, Kovács B., Szabó K.: Extrakciós eljárás optimalizálása uranil-ionok fluoreszcenciás meghatározásához.- *A lumineszcencia kutatások aktuális kérdései* XVIII/ MTA-JPTE Pécs (1995) 60-67.

10. Kovács B., **Petz A.:** Novel method for Determination of Uranyl Ion Based on Fluorescence Quenching.- *The 3rd Symposium on Analytical and Environmental Problems* /ed. Z Galbács/ (1998) p. 48-56

11. **Petz A.**, Kollár L.: Királis homogén katalizátorok. *Magyar Kémikusok Lapja* 59 (2004) 376-381.

III. Presentations and posters forming the basis of PhD dissertation

1. Skodáné Földes R., Horváth J., Tuba Z., **Petz A**., Kollár L.:Szteroidok funkciós csoportjainak kiépítése homogénkatalitikus reakciókban. (p. 42) XXXIV. Komplexkémiai Kollokvium, Tata, 1999. 05. 19-21.

2. **A. Petz**, Z. Tuba, Z. Pintér, Z. Berente, L. Kollár: Synthesis and characterization of steroidal crown ethers. (P-10) 5th Symposium on Instrumental Analysis. Pécs, 24-27. 10. 1999.

3. **A. Petz**, R. Skoda-Földes, L. Kollár: Homogeneous catalytic carbonylation of steroids (p.69). 13th Eur. Symp. on Org. Chem.; Dubrovnik-Cavtat, 10-15. 09. 2003.

4. **A. Petz**, Z. Pintér, L. Kollár: Mass spectrometric studies on the complex reaction mixtures obtained under carbonylative Suzuki-coupling. (P-52) 7th Int. Symp. on Instrumental Analysis. Pécs, 21-24. 09. 2003.

5. **A. Petz**, Z. Tuba, Z. Berente, Z. Pintér, L. Kollár: Synthesis and characterization of steroidal crown ethers. (p.111) 7th Int. Symp. on Applied and Bioinorganic Chemistry (ISABC-7). Guanajuato (Mexico), 01-05. 04. 2003.

IV. Other presentations

1. K. Szabó, **A. Petz**: Fluorimetric determination of critical micelle concentration of tensides. (p31) 3rd Symposium on Instrumental Analysis Pécs, (1995.)