Summary of PhD thesis

Structural diversity-driven synthesis of cycloalkane-based heterocycles and 1,3-bifunctional compounds

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Introduction and aims

Alicyclic β-amino acids and their derivatives, such as 1,3-amino alcohols, 1,3-diamines and β-amino esters, play important roles in both fundamental and applied research. Apart from their proven pharmacological effects (*e.g.* icofungipen and tramadol), they are also interesting from a chemical viewpoint. They can serve as excellent starting materials for the synthesis of diverse *N*-containing heterocycles or, in an enantiomerically pure form, they can be applied as asymmetric auxiliaries or catalysts in enantioselective transformations. The primary aim of the work reported in this thesis therefore, was to develop new procedures for their synthesis and to explore their chemical reactivities.

Since monoterpenes are excellent starting materials for the synthesis of enantiomeric alicyclic compounds, our aim was to synthetize new α-pinane-based optically active 1,3-amino alcohols and 1,3-diamines and to apply them as catalysts in the enantioselective addition of diethylzinc to various aldehydes. The major advantage of the chosen α-pinene over other monoterpenes is that both enantiomeric forms are commercially available in bulk. Moreover, due to the highly constrained bicyclic pinane skeleton, a high degree of chiral information transfer can be expected in asymmetric transformations. Besides the synthesis of optically pure 1,3-amino alcohols, an additional aim was to develop a simple and short procedure for the synthesis of alicyclic *N*-substituted 1,3-amino alcohols, since the preparation of such compounds with increased diversity usually requires a time-consuming multistep process.

The synthesis and properties of cycloalkane-based six-membered heterocycles are well established, whereas only limited or no procedures have been reported for the synthesis of seven- and especially eight-membered ones, although the synthesis of such compounds would greatly increase the structural diversity of the family of *N*-containing heterocycles. Accordingly, our aim was to investigate novel reactions of β-amino acid derivatives to prepare such compounds via the utilization of microwave irradiation techniques, for example, and previously little-used methods such as Pd(II)-catalysed transformations.

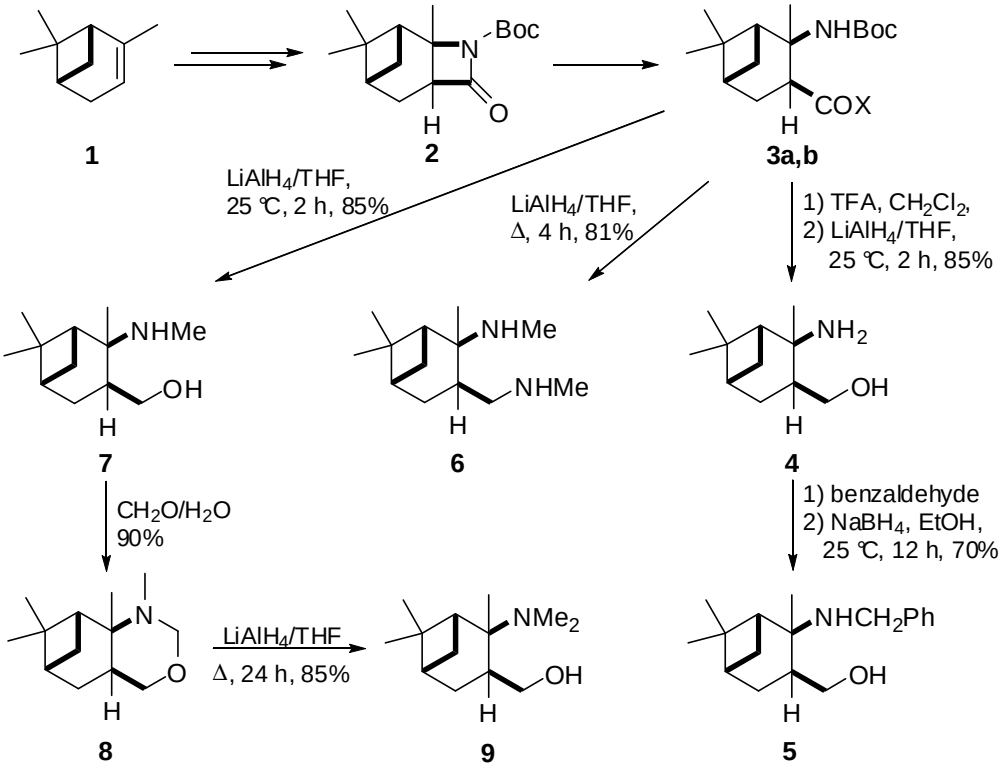
Applied investigation methods

Reactions were performed on a mmol scale, and products were separated and purified by silica gel column chromatography or by fractional recrystallization. All new compounds were characterized by their melting points, IR, NMR and mass spectra and elemental analysis. Enantiomers were separated by chiral stationary-phase GC. Complex structures were

identified by means of two-dimensional NMR techniques (COSY, HSQC, HMBC and NOESY) and X-ray crystallography.

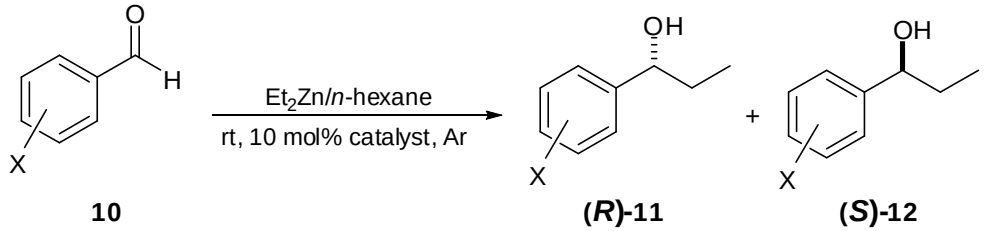
Results and discussion*

1. Novel enantiopure γ-amino alcohols **4, 5, 7, 9** and diamine **6** were synthetized from (+)- and (-)-α-pinene, respectively, according to Scheme 1. The cycloaddition of chlorosulfonyl isocyanate to α-pinene (**1**) is highly regio- and stereoselective and establishes the configuration of all the products derived from the obtained β-lactam (**2**).



Scheme 1

2. The synthetized 1,3-amino alcohols (**4, 5, 7, 9**) and 1,3-diamine (**6**) were used as chiral catalysts in the enantioselective addition of diethylzinc to aromatic aldehydes, as a test reaction resulting in optically active secondary alcohols (Scheme 2).

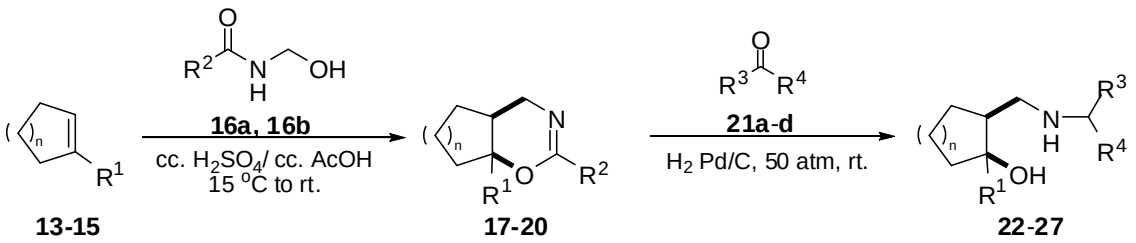


Scheme 2

* Compound numbering is identical to that applied in the thesis.

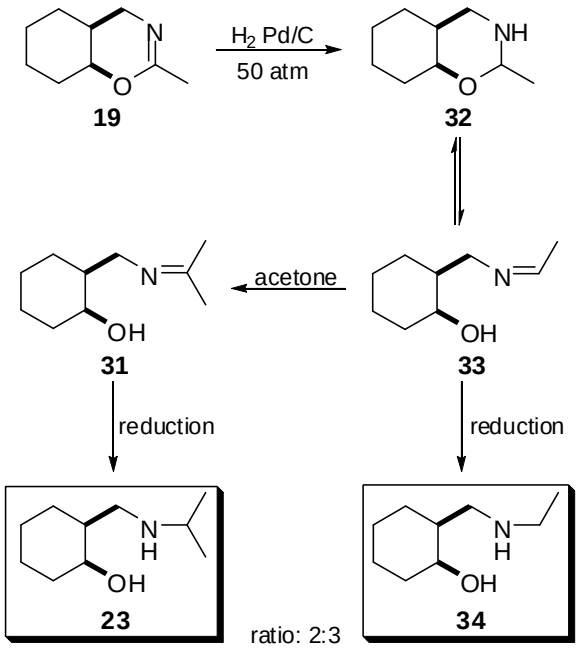
Diamine **6** showed no enantioinduction while amino alcohol **7** provided the product 1-aryl-1-propanols with moderate enantioselectivities and with *R* selectivity. Catalyst **9** gave both the highest yields and enantioselectivities up to 72% ee with *S* selectivity. To the best of our knowledge, this is the first report on an *N*-substituent-dependent enantioswitch in the field of 1,3-amino alcohol-catalysed asymmetric reactions. The results of the molecular modelling studies performed were in good accordance with our experimental findings.

3. Alicyclic condensed 1,3-oxazines **17-20** were transformed into the corresponding *N*-substituted 1,3-amino alcohols **22-27** in the presence of a ketone **21a-d** in a simple one-pot reductive process (Scheme 3).



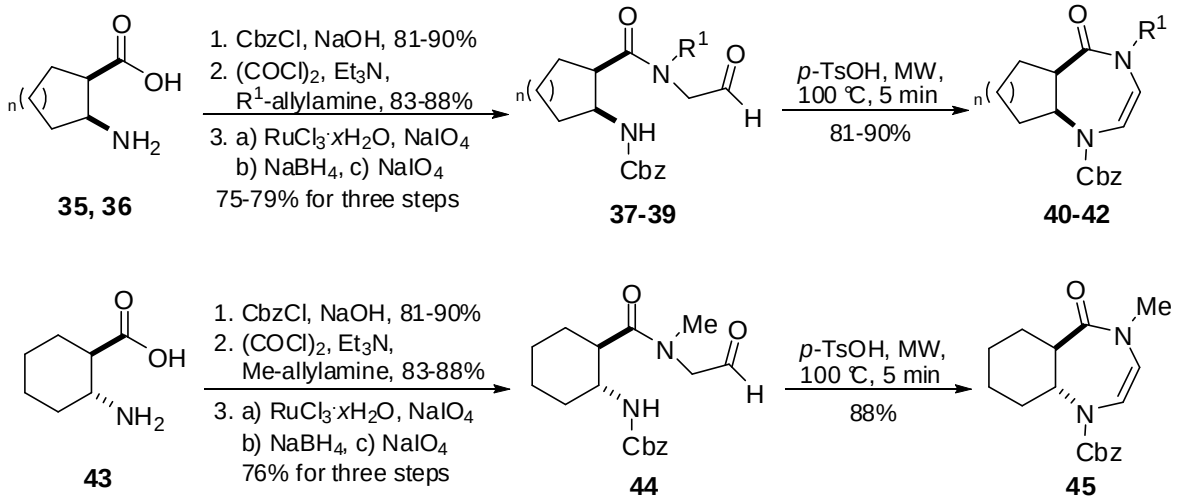
Scheme 3

4. We found that the reaction can proceed via two different pathways: classical reductive debenzylation followed by Schiff base formation, or transimination of the chain form of the ring-chain tautomeric mixture obtained by partial reduction of the starting oxazine. We successfully provided experimental evidence for the alternative transimination pathway by the application of 2-methyl-substituted oxazine, where debenzylation cannot occur (Scheme 4)



Scheme 4

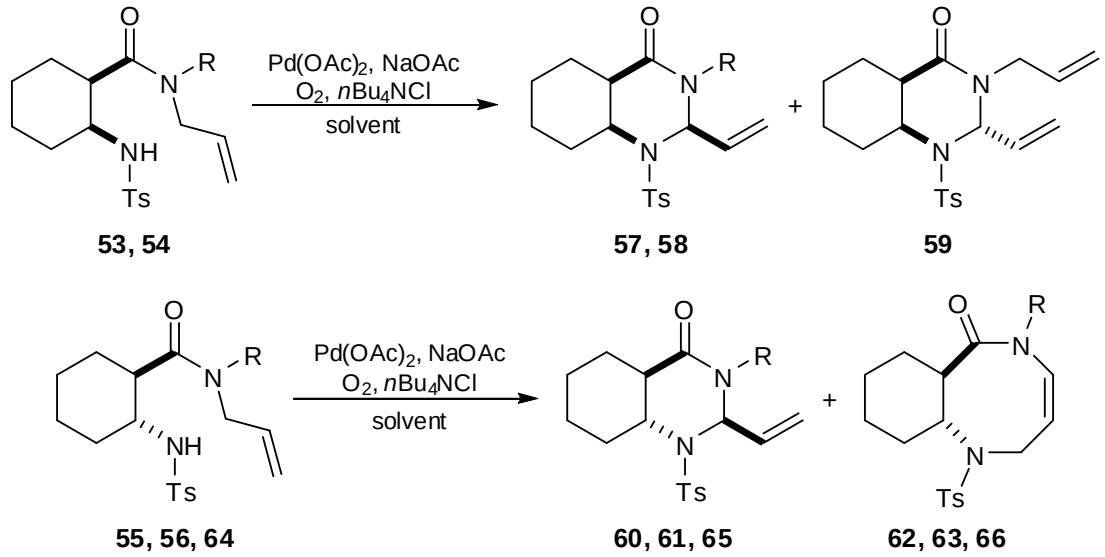
5. An efficient, microwave(MW)-assisted method was developed for the cyclization of benzyloxycarbonyl(Cbz)-protected *cis*- and *trans*-cyclohexane- and *cis*-cyclopentane-formylmethyl carboxamides to furnish the corresponding 5*H*-1,4,6,7-tetrahydro-1,4-diazepin-5-one derivatives **40-42** and **45** (Scheme 5). Starting formylmethyl carboxamides **37-39** and **44** were obtained from the corresponding allyl carboxamides by RuO_4-catalysed dihydroxylation and subsequent oxidative cleavage.



Scheme 5

The developed method gives a high yield in general and was also applied for non-alicyclic β-amino acid derivatives.

6. Efficient cyclizations of tosyl-protected *cis*- and *trans*-*N*-allyl-2-aminocyclohexane-carboxamides (**53-56** and **64**) were carried out in the Pd(II)-catalysed oxidative amination reaction, resulting in cyclohexane-fused 2-vinylpyrimidin-4-ones **57-61** and **65** and 1,5-diazocin-6-ones **62, 63** and **66** (Scheme 6). The reaction conditions were optimized, and the application of 10 mol% of Pd(II) acetate, 1 equivalent of tetra-*n*-butylammonium chloride at 100 °C under an oxygen atmosphere was found to give the best yields.



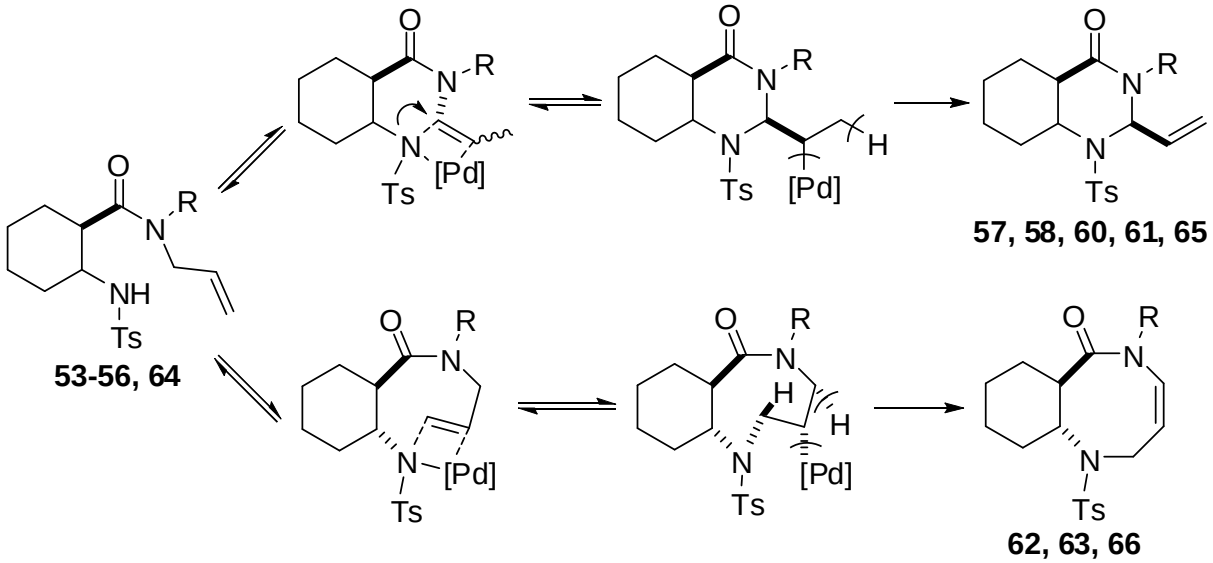
55, **60**, **62**: R = allyl; **56**, **61, 63**: R = methyl; **64-66**: R = *p*-methoxybenzyl

Scheme 6

7. We found that *cis* starting materials cyclize into 2-vinylpyrimidin-4-ones diastereoselectively, whereas *trans* compounds cyclise regioselectively into a mixture of 1,5-diazocin-6-ones as major and 2-vinylpyrimidin-4-ones as minor products.

8. A marked solvent effect on the regioselectivity was observed, and acetonitrile was identified as the best solvent for the selective preparation of 1,5-diazocin-6-ones.

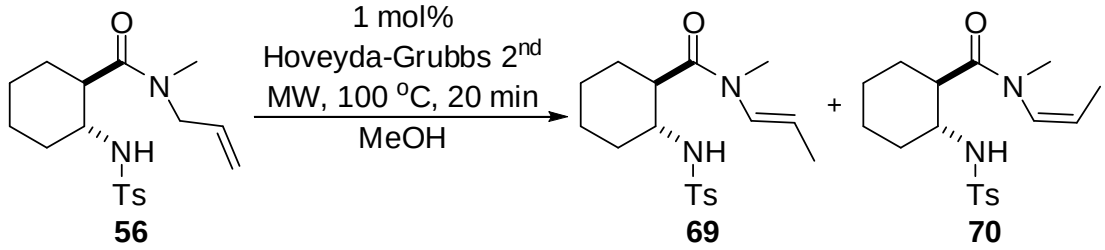
9. The mechanistic studies performed clearly indicated that an aminopalladation/β-hydride elimination pathway is feasible in these transformations (Scheme 7).



R = allyl, methyl, *p*-methoxybenzyl

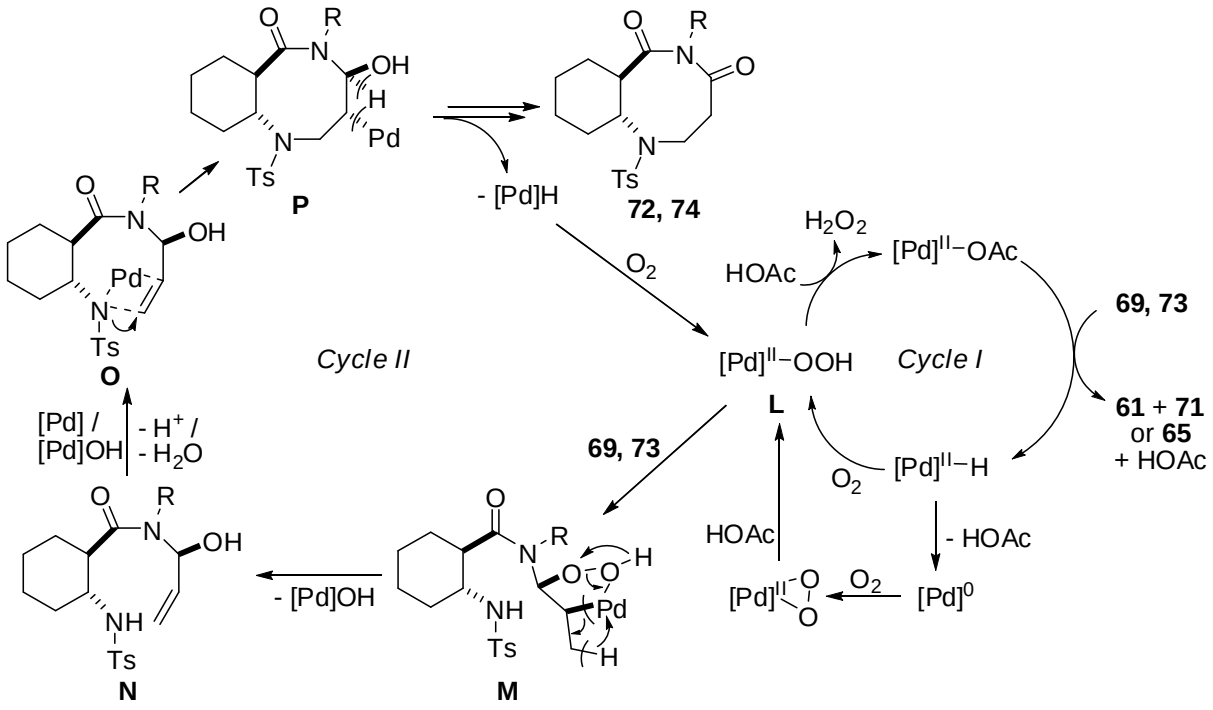
Scheme 7

10. A novel MW-assisted allyl to propenyl isomerization was developed in order to obtain a model compound to provide experimental support for our mechanistic theory (Scheme 8).



Scheme 8

11. As a result of this experimental study, a new 1,5-diazocine-4,6-dione-type compound was obtained, formation of which was explained by a novel Pd(II)-catalysed domino oxidation/oxidative amination cascade reaction (Scheme 9).



65, 73, 74: R = *p*-methoxybenzyl; **61, 69, 71, 72**: R = methyl

Scheme 9

12. In the course of the experimental work, 50 novel, structurally diverse alicyclic compounds were synthetized and characterized.

Publications related to the thesis:

1. Zsolt Szakonyi, **Árpád Balázs**, Tamás A. Martinek, Ferenc Fülöp:
   Enantioselective addition of diethylzinc to aldehydes catalyzed by γ-amino alcohols derived from (+)- and (-)-α-pinene
   Tetrahedron: Asymmetry **17**, 199-204 (2006)

   If: 2.796

2. **Árpád Balázs**, Zsolt Szakonyi, Ferenc Fülöp:
   Synthesis of alicyclic *N*-substituted 1,3-amino alcohols via 1,3-oxazines
   J. Heterocyclic Chem. **44**, 403-406 (2007)

   If: 0.899

3. **Árpád Balázs**, Erik Van der Eycken, Ferenc Fülöp:
   A novel, microwave-assisted method for the synthesis of alicyclic condensed 5*H*-1,4,6,7-tetrahydro-1,4-diazepin-5-ones
   Tetrahedron Lett. **49**, 4333-4335 (2008)

   If: 2.538

4. **Árpád Balázs**, Anasztázia Hetényi, Zsolt Szakonyi, Reijo Sillanpää, Ferenc Fülöp:
   Solvent-enhanced diastereo- and regioselectivity in the Pd(II)-catalyzed synthesis of six- and eight-membered heterocycles via *cis*-aminopalladation
   Chem. Eur. J. **15**, 7376-7381 (2009)

   If: 5.454

Total impact factor: 11.687

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1. Martinek Tamás, Szakonyi Zsolt, **Balázs Árpád**, Fülöp Ferenc: Ab initio modeling of enantioselective catalysis in the application of 1,3-amino alcohols with a monoterpene skeleton
   MTA, Elméleti kémiai munkabizottság ülése
   Budapest, január 27, 2005.
2. Szakonyi Zsolt, **Balázs Árpád**, Martinek Tamás, Fülöp Ferenc: Synthesis and application of chiral 1,3-difunctional compounds with a monoterpene skeleton; Vegyészkonferencia
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3. **Árpád Balázs**, Zsolt Szakonyi, Tamás Martinek, Ferenc Fülöp: Synthesis of Monoterpene skeleton 1,3-difunctional compounds and their application in enantioselective transformations; Semi-centennial conference of Semmelweis University, Faculty of Pharmacy; Hungarian Academy of Sciences;
   Budapest, October 12-14, 2005, P-5.
4. **Balázs Árpád**: Preparation of secondary 1,3-amino alcohols via the reductive transimination of 1,3-oxazines
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   Szeged, január 17, 2006. Különdíj
5. **Balázs Árpád**: Regioselective ring closing reactions of 2-tosylaminocyclohexane-1-carboxylic acid derivatives via palladium(II)-catalyzed oxidative amination;
   XXIX. Kémiai Előadói Napok
   Szeged, október 30-31, 2006.
6. **Balázs Árpád**: Ciklohexánnal kondenzált heterociklusok szintézise, Pd(II)-katalizált oxidatív aminálással
   VIII. Clauder Ottó Emlékverseny
   Budapest, Április 12-13, 2007. Különdíj
7. **Balázs Árpád**, Szakonyi Zsolt, Hetényi Anasztázia, Fülöp Ferenc: Ciklohexánnal kondenzált heterociklusok szintézise, Pd(II)-katalizált oxidatív aminálással
   Centenáriumi Vegyészkonferencia

Sopron, május 29-június 1, 2007, SZ-P-2.

8. **Árpád Balázs**, Zsolt Szakonyi, Anasztázia Hetényi, Ferenc Fülöp: Synthesis of cyclohexane-fused six- and eight-member heterocycles via Pd(II)-catalyzed intramolecular oxidative amination;
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   Dublin, Ireland, July 8-13, 2007, P18.

9. **Balázs Árpád**: Ciklohexánnal kondenzált heterociklusok szintézise, Pd(II)-katalizált oxidatív aminálással
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   Balatonszemes, szeptember 12-14, 2007.

10. **Árpád Balázs**, Erik Van der Eycken, Ferenc Fülöp: Synthesis of Cyclohexane-fused Six- and Eight-Membered Heterocycles via Pd(II)-Catalyzed Intramolecular Oxidative Amination
    11th Sigma-Aldrich Organic Synthesis Meeting
    Spa, Belgium, December 6-7, 2007, P2.

11. **Balázs Árpád**, Erik Van der Eycken, Fülöp Ferenc: Egy új, mikrohullámmal segített módszer aliciklusokkal kondenzált 1,4,6,7-tetrahidro-1,4-diazepin-5-onok előállítására
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12. **Balázs Árpád**, Hetényi Anasztázia, Szakonyi Zsolt, Fülöp Ferenc: Ciklohexánnal kondenzált hat- és nyolctagú heterociklusok szintézise Pd(II)-katalizált oxidatív aminálással. Egy új Pd(II)-katalizált dominó reakció
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