

Asymmetric Michael-addition Catalyzed by a Cinchona Alkaloid Derivative Non-covalently Immobilized over Layered Materials



György Szöllősi¹, Lenke Kovács², Viktória Kozma³, Vanessza Judit Kolcsár³

¹ MTA-SZTE Stereochemistry Research Group, University of Szeged, 6720 Szeged, Dóm tér 8, Hungary. E-mail: szollosi@chem.u-szeged.hu

² Institute of Pharmaceutical Chemistry, University of Szeged, Hungary.

³ Department of Organic Chemistry, University of Szeged, Hungary.



Development of novel **asymmetric catalytic methods** for the synthesis of chiral fine chemicals is of paramount importance. These processes should be **environmentally friendly, economic** and should allow a **sustainable** production. To fulfil these requirements heterogeneous stereoselective catalysts are designed, which may be recovered, reused or applied in continuous-flow systems.

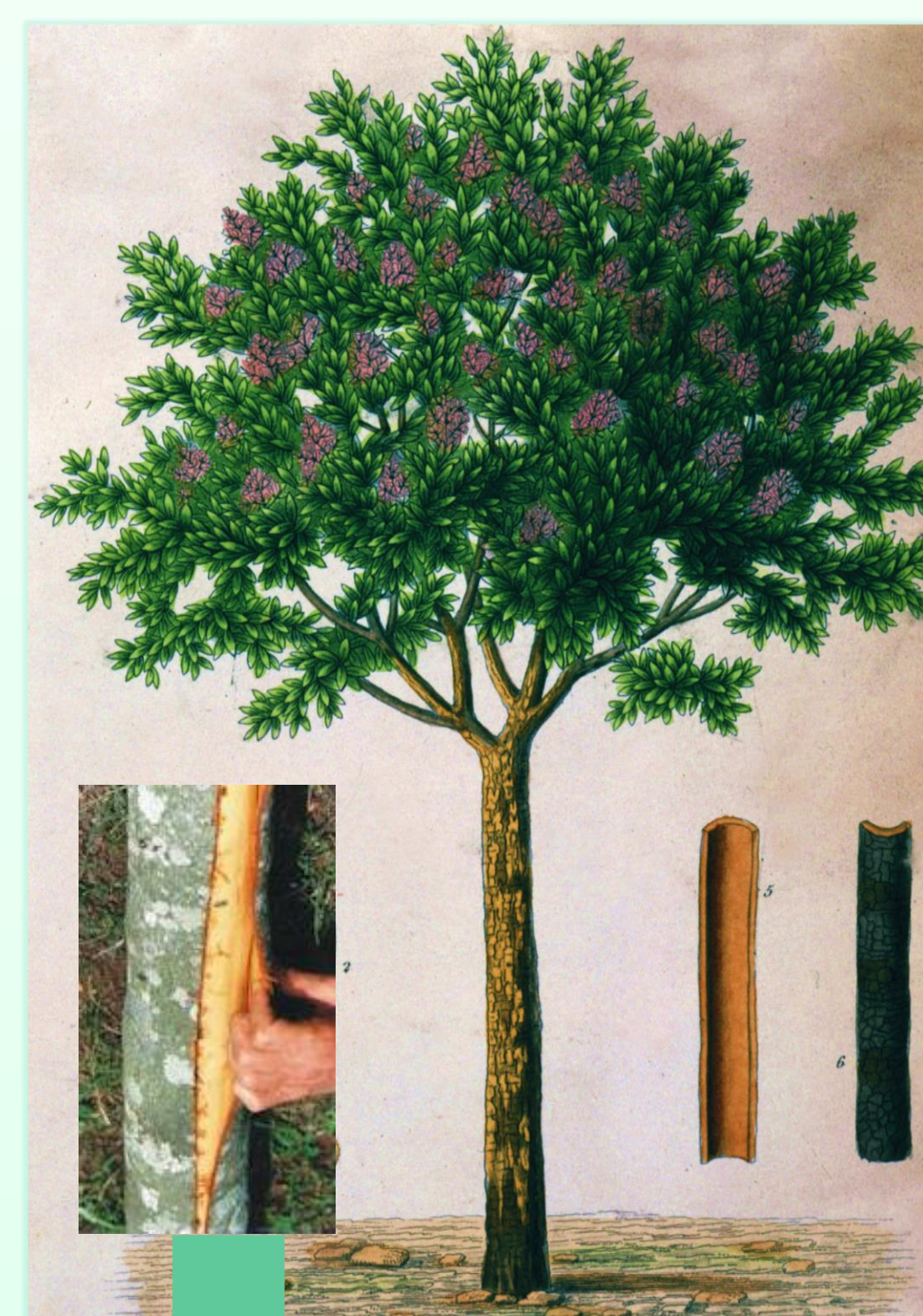
Asymmetric Michael additions are among the convenient C-C bond-forming reactions often used for preparing optically pure chiral intermediates. Natural chiral amines are preferentially used as base catalysts in these reactions, among which cinchona alkaloid derivatives were found highly efficient.¹ However, the preparation of the most efficient derivatives is laborious. These derivatives could be recovered and recycled by immobilization over solid supports.

Aims

Development of a cinchona alkaloid derivative easily prepared from natural alkaloid, which is highly efficient in the chosen asymmetric Michael-addition.

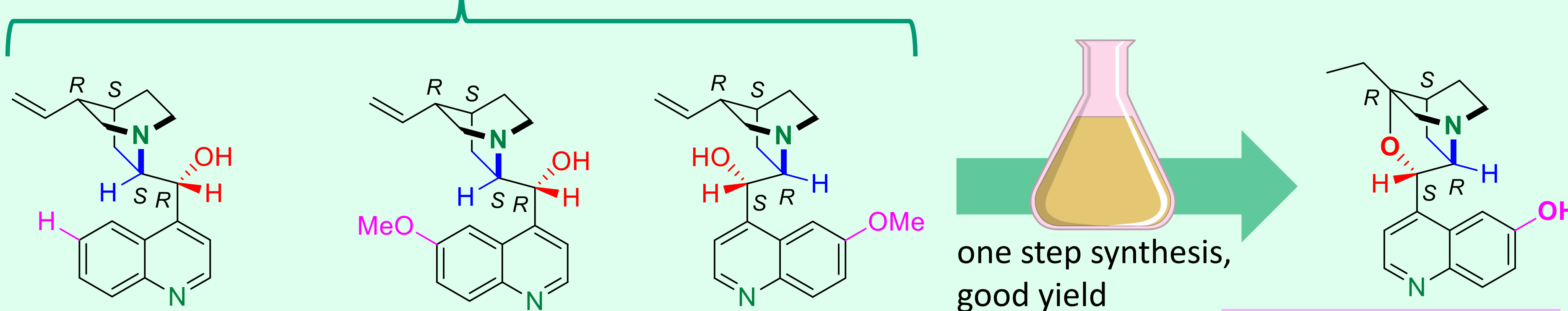
Immobilization by easy procedures of this cinchona alkaloid derivative over solid supports. Characterization of the obtained materials.

Examination of the efficiency of the immobilized cinchona alkaloid in the test reaction. Recovery and reuse of the materials which are proved to be catalytically active. Application of the most effective catalysts in a continuous-flow system.



"Cinchona tree"
i.e. *Cinchona officinalis*

natural cinchonas



cinchonidine

conversion 98%;
dr 57/43;
ee 36% (R,R);
28% (S,R)

quinine

conversion 93%;
dr 39/61;
ee 42% (R,R);
40% (S,R)

quinidine

conversion 99%;
dr 38/62;
ee 26% (S,S);
42% (R,S)

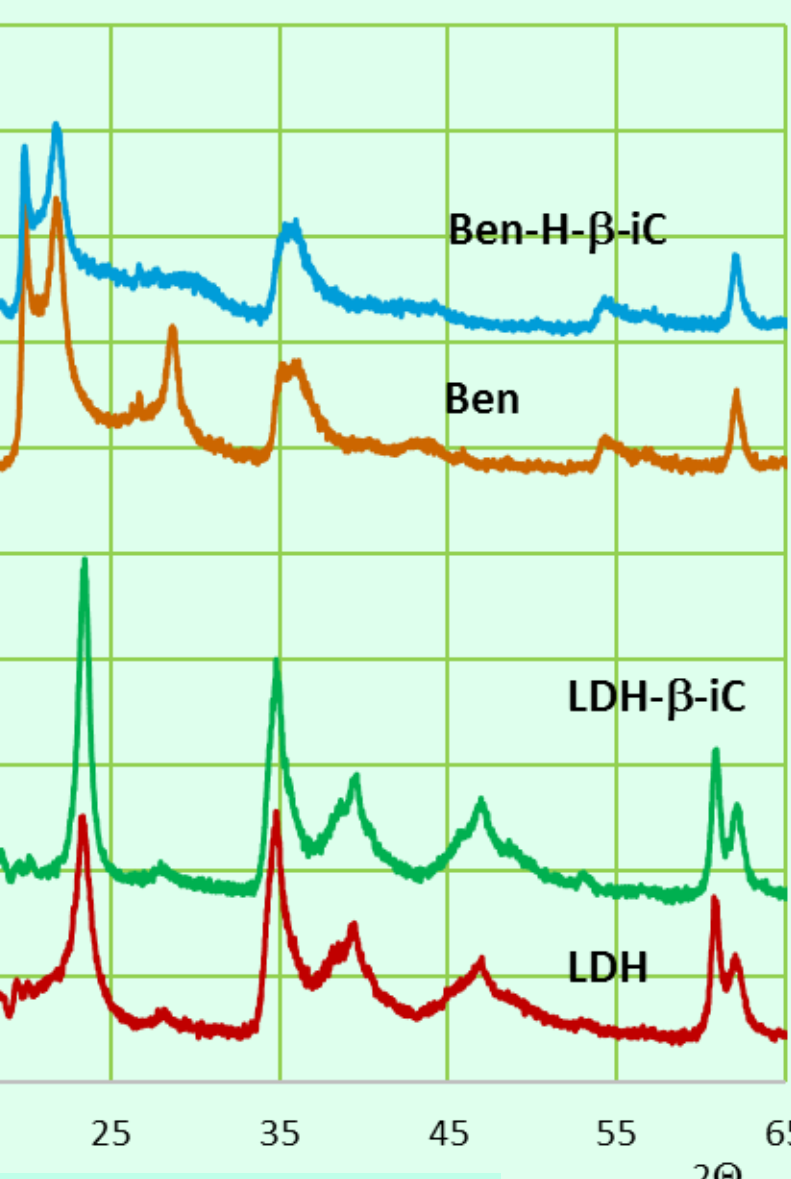
β -isocupreidine (β -iC)

conversion 99.8%;
dr 85/15;
ee 98% (R,R);
96% (S,R)

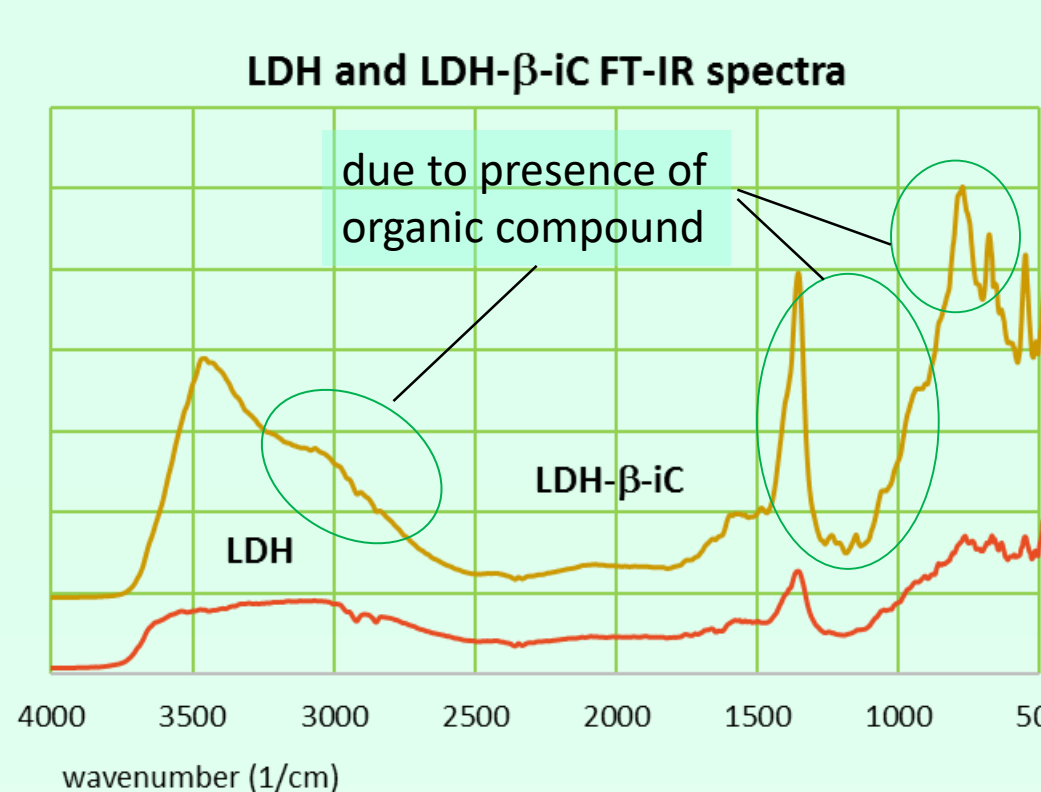
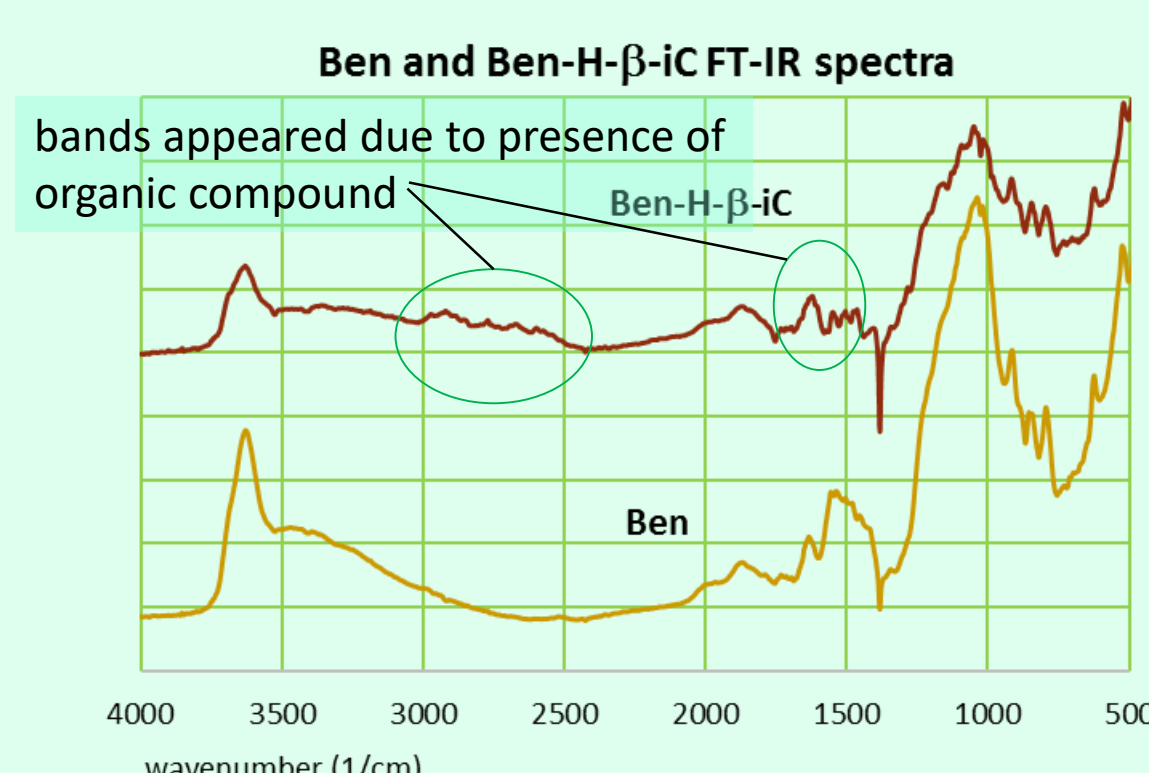
similar results as in ref 3

shift of the (001) reflexion shows inclusion of the cinchona derivative between the lamellae

XRD characterization

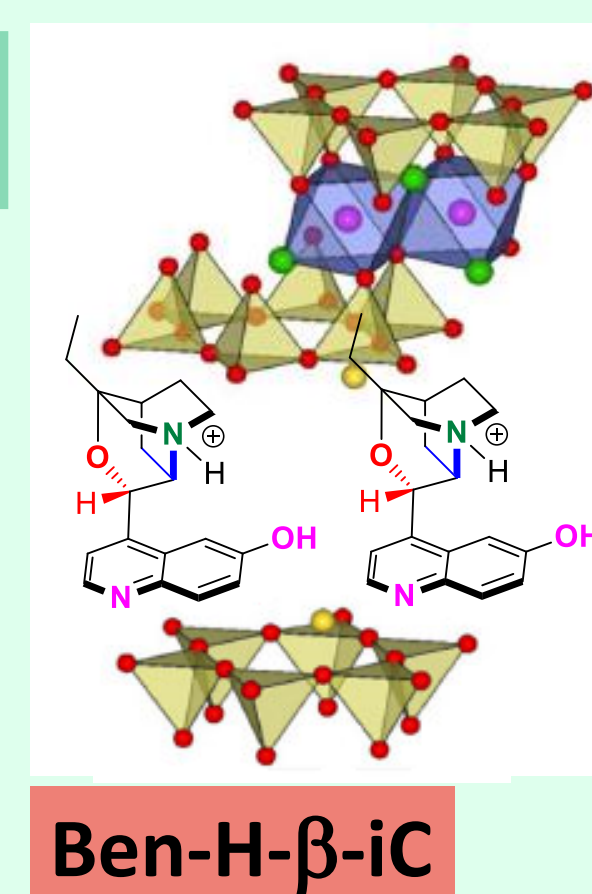


no shift in the position of peaks shows adsorption of the cinchona derivative on the solid surface



Characterization: XRD, FT-IR

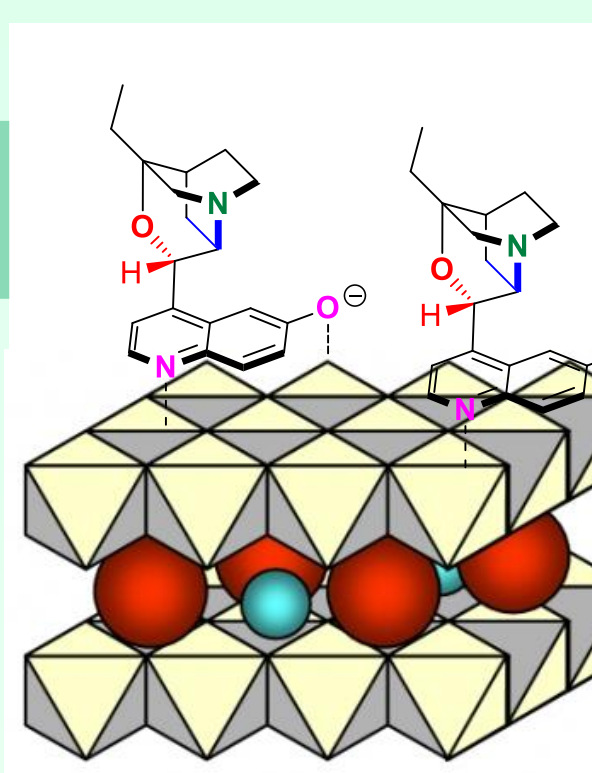
50 mg catalyst Ben-H- β -iC,
conversion 26% (18 h);
dr 87/13;
ee 0%; 0%



Ben-H- β -iC

Characterization: XRD, FT-IR

10 mg catalyst LDH- β -iC,
conversion 99.6% (18 h);
dr 81/19;
ee 95% (R,R);
80% (S,R)



LDH- β -iC

Smectite type aluminosilicate (Bentonite H, Na-form)

50 mg Bentonite H, 18 h: conversion 24%,
dr 71/29; ee 0%; 0%

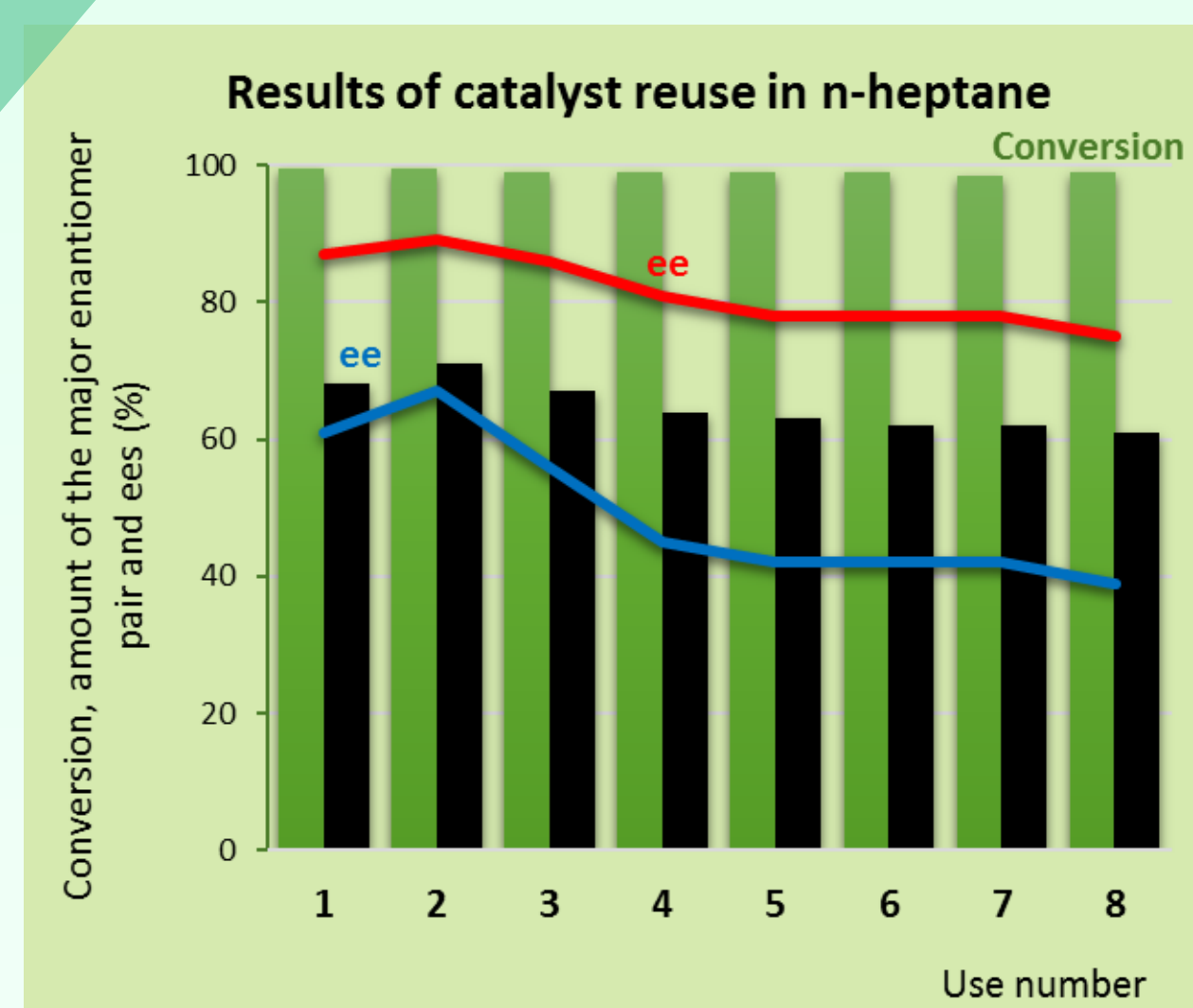
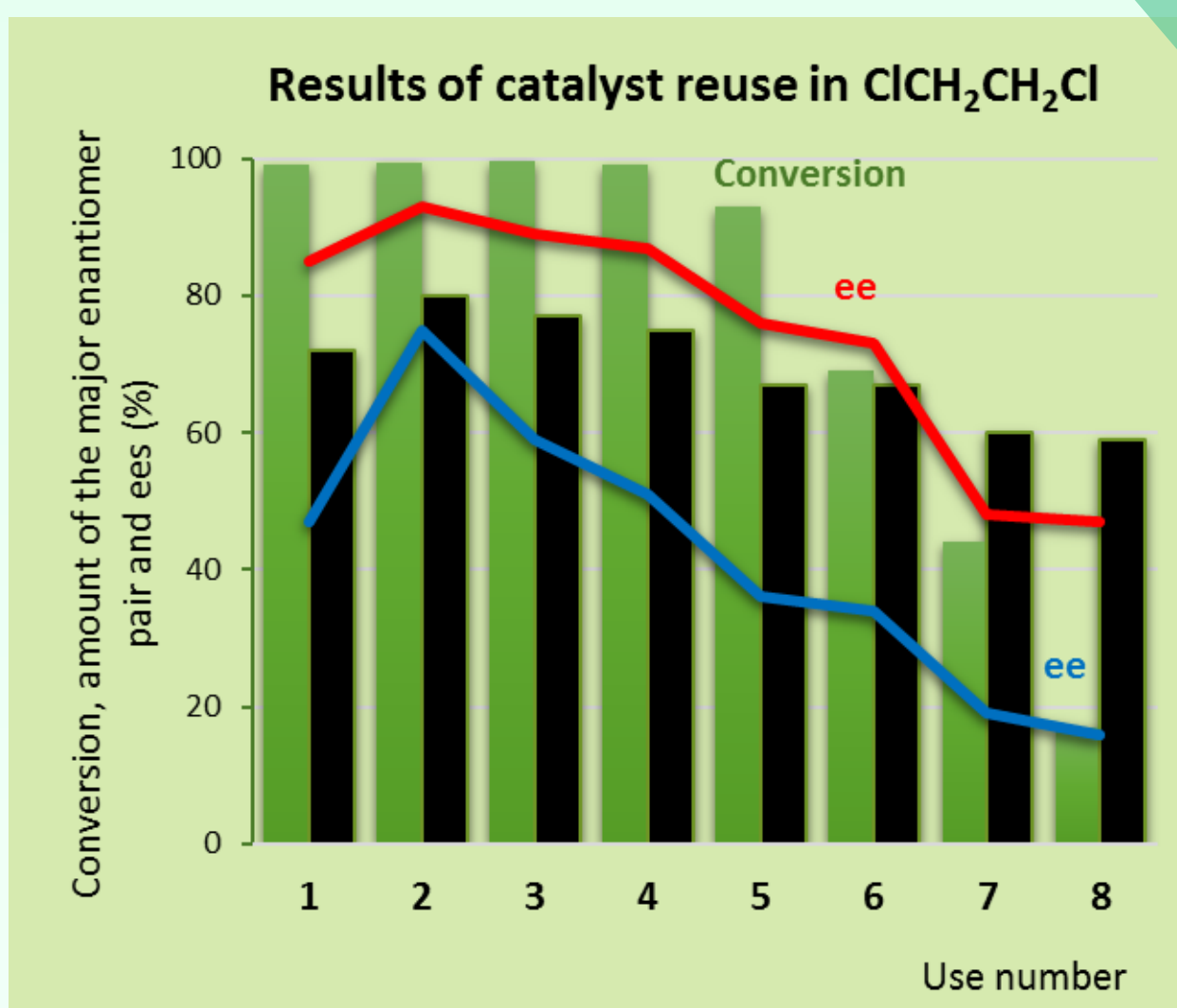
protonated H- β -iC⁺

Layered double hydroxide (LDH: Plural MG50, MgO:Al₂O₃ 50:50, CO₃²⁻, as received)

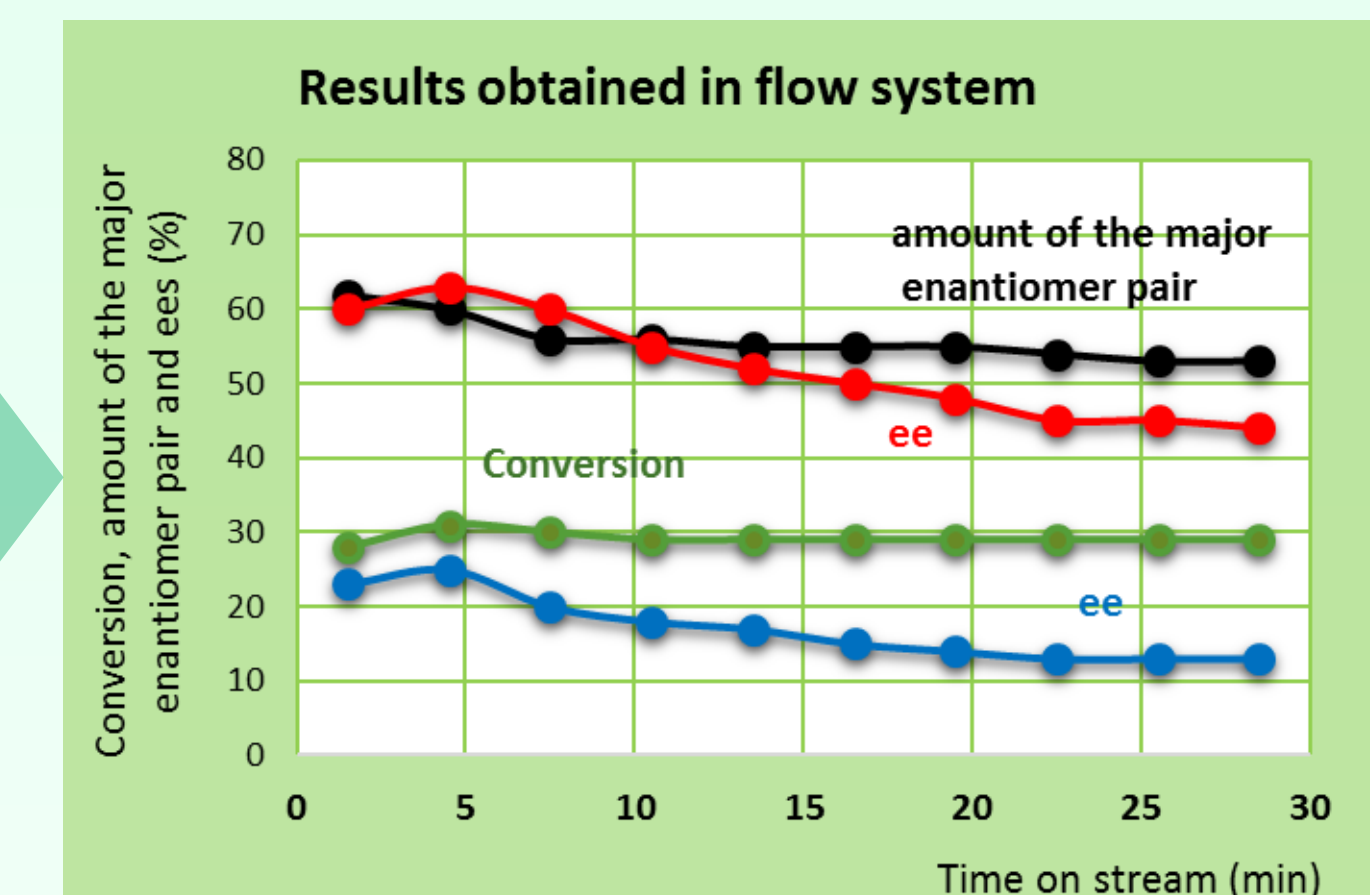
50 mg LDH, 18 h: conversion 99%,
dr 53/47; ee 0%; 0%

deprotonated β -iC⁻

Reuse of the LDH- β -iC catalyst



LDH- β -iC in continuous-flow system



In flow system in 1,2-dichloroethane lower selectivity values were obtained, as in batch experiments. The conversion value was kept at constant value, throughout the measurement, however, decrease in the selectivities (dr and ees) could be detected.

Conclusions

We found that β -isocupreidine (β -iC), which may be prepared in good yield in a one step synthesis procedure from the natural cinchona alkaloid quinidine, is similarly efficient in the enantioselective Michael-addition of an α -fluoro- β -ketoester to β -nitrostyrene, as the derivatives described in the literature (prepared more laboriously).

β -iC may be immobilized over both cation- and anion-exchanger supports. The protonated alkaloid could be inserted between the lamellae of a cation-exchanger smectite type clay, however, by this immobilization loses its catalytic activity. The anion-exchanger layered double hydroxide having carbonate anion as counterion bonded the deprotonated cinchona derivative on its surface by means of hydrogen bonding (surface adsorption). The catalytic performance of this material approached that of the homogeneous catalysts, moreover, from an appropriate solvent could be recovered and reused, with only small loss in the selectivity values and could be filled in fixed-bed reactor and used in continuous-flow system, though under flow conditions lower selectivities were obtained as compared with the batch system.

References:

- ¹ *Cinchona Alkaloids in Synthesis and Catalysis, Ligands, Immobilization and Organocatalysis*; C. E. Song, Ed.; Wiley-VCH, Weinheim, **2009**.
- ² Y. Oh, S. M. Kim, D. Y. Kim, *Tetrahedron Lett.*, **2009**, 50, 4674.
- ³ H. Li, S. Zhang, C. Yu, X. Song, W. Wang, *Chem. Commun.*, **2009**, 2136.

Acknowledgements

Financial support by OTKA K109278 grant is acknowledged.