# Comparative study for 3, 3´-[(4-X-phenyl)-methanediyl] *bis*(1*H*-indoles) synthesis catalyzed by Ce(III) cations

Eva Havránková[1], Jozef Csöllei[2], Pavel Pazdera[3]

[1,3]Centre for Syntheses at Sustainable Conditions and Their Management, Department of Chemistry, Faculty of Science, Masaryk University, University Campus, Kamenice 753/5, CZ-625 00 Brno, Czech Republic
[1,2]Department of Chemical Drugs, Faculty of Pharmacy VFU Brno, Palackého 1-3, 612 42 Brno, Czech Republic

***Abstract***— *Results of comparative study for 3,3´-[(4-X-phenyl)methanediyl]bis(1H-indoles) synthesis starting from 4-X-benzaldehyde (X = H,* $OCH_3$*,* $N(CH_3)_2$*,* $NO_2$*, OH) and 1H-indole in dichloromethane solution at room temperature and catalyzed by cerium trichloride heptahydrate or by new resin supported Ce(III) catalyst are described. It was found that Ce(III) cations supported on weakly acidic macroporous low-cost industrial resin have at least the same or better catalytic activity as* $CeCl_3.7H_2O$ *(or other mentioned catalytic systems) advantageously its easy separation for a recycling.*

***Keywords***— ***Green chemistry, Heterocycles, One-pot synthesis, Supported catalysts.***

## I. INTRODUCTION

Solid support metal catalysis is a way for a combination of both positive properties connected with heterogeneous and homogeneous metal catalysis, i.e. a simple separation of catalyst by sedimentation, filtration or by similar processes (heterogeneous catalysis) and on other hand an utilization of auxiliary ligands for an optimal catalytic action of a metal in the case of the homogeneous metal catalysis. [1, 2] Auxiliary ligands are in the optimal cases a part of supporting matter. Solid supported catalysts are, thanks to these properties, suitable as catalysts for the synthesis carried out according to the principles of Green Chemistry. [3]

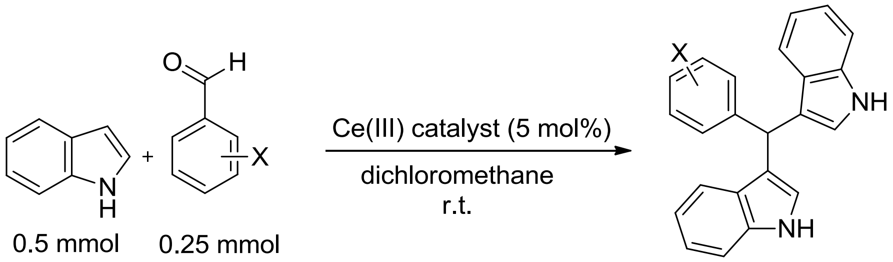
Recently, we found and described a possibility for support of some metal cations by an application of weakly acidic macroporous low-cost industrial acrylate resins. [4] Also cerium(III) cations can be immobilized/supported in this manner. Cerium(III) in many different forms (i.e. chloride, nitrate, supported on silica gel and other), as a Lewis acid, attracted the attention especially due to its high reactivity, low toxicity, ease of handling, stability, air tolerance and finally low cost. [5, 6]

The catalytic efficiency of Ce(III) cations in synthesis of 3,3´-[(4-X-phenyl)methanediyl]bis(1H-indole) derivatives was studied in this paper. Alkylated indole derivatives are frequently present in many pharmaceutical and natural products and also in wide range of functional synthetics. [7, 8] Furthermore, 3,3´-[(4-X-phenyl)-methanediyl]bis--(1H-indole) derivatives show a broad range of biological activities such as anti-fungal, anti-inflammatory, anti-pyretic, cardiovascular, anti-convulsant, COX2 inhibitory and selective β-glucuronidase activity. [9, 10, 11] This is one of the reasons, why is in recent years paid more attention to the methods of their syntheses.

Derivatives of 3,3´-[(4-X-phenyl)methanediyl]bis(1H-indoles) are usually prepared from carbonyl compounds and indole in the presence of Lewis acids or protic acids. [9, 12, 13, 14] The catalysts used for their synthesis may be even zirconium or palladium complexes [15] or CeCl3.7H2O [16].

## II. RESULTS AND DISCUSSION

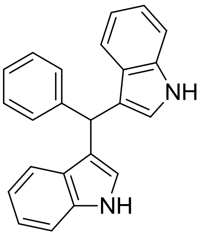
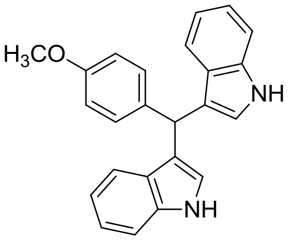
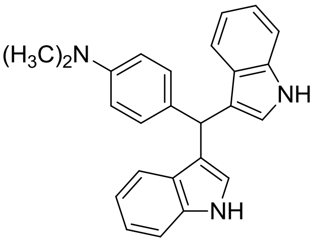
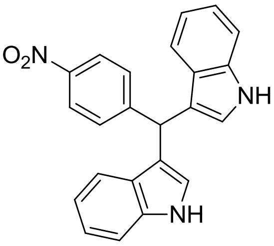
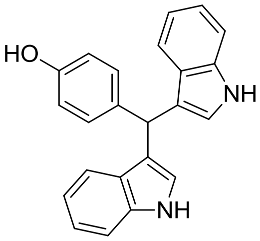
The catalytic efficiency of cerium(III) cations (in form of $CeCl_3.7H_2O$, or supported on macroporous weakly acidic cation exchanger) in regioselective C3 alkylation of indoles was studied in this paper. The reactions proceeded as is written in Experimental part (according to the method of synthesis of 3,3´-[(4-X-phenyl)methanediyl] *bis* (1*H*--indoles) published in [15]). General scheme of reaction is given in Scheme 1. Catalyst was used in amount of 5 mol% in this set of reactions and all reactions were monitored by TLC (see Experimental part). Uncatalyzed reactions were performed as well. The obtained results were compared in terms of yield and reaction time (see Table 1).



SCHEME 1 GENERAL SCHEME FOR SYNTHESES OF 3,3´-[(4-X-PHENYL)METHANEDIYL]BIS(1H-INDOLES)

TABLE 1

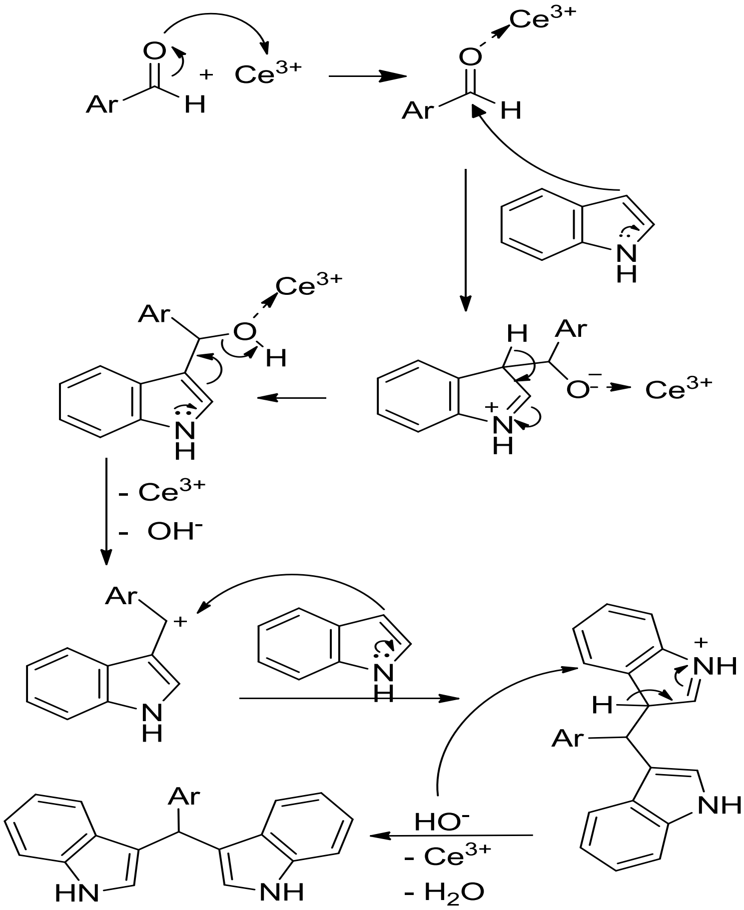
SYNTHESES OF 3,3´-[(4-X-PHENYL)METHANEDIYL]BIS(1H-INDOLES)

| Entry | 4-X-benzaldehyde | Product | Catalyst | Yield (%) | Time(h) |
|---|---|---|---|---|---|
| 1 | H- |  | - | NR | 72 |
| | | | Ce(III)supp. | 84 | 10 |
| | | | $CeCl_3.7H_2O$ | 82 | 12 |
| 2 | $CH_3O$- |  | - | NR | 72 |
| | | | Ce(III)supp. | 91 | 8 |
| | | | $CeCl_3.7H_2O$ | 92 | 18 |
| 3 | $(CH_3)_2N$- |  | - | NR | 72 |
| | | | Ce(III)supp. | 96 | 6 |
| | | | $CeCl_3.7H_2O$ | 94 | 17 |
| 4 | $O_2N$- |  | - | NR | 72 |
| | | | Ce(III)supp. | 83 | 14 |
| | | | $CeCl_3.7H_2O$ | 83 | 21 |
| 5 | HO- |  | - | NR | 72 |
| | | | Ce(III)supp. | 89 | 10 |
| | | | $CeCl_3.7H_2O$ | 87 | 19 |

***NR means no reaction – no conversion was observed and after 72 hours, the reaction was forcibly terminated***

No conversion of starting indole was observed, in the case of uncatalyzed reactions, even after 72 hours (after this time the reaction was forcibly terminated). The Table 1 reveals, that catalytic system with supported Ce(III) cations has at least the same catalytic activity as used $CeCl_3.7H_2O$ in the term of the yield and slightly better results in the term of reaction time.

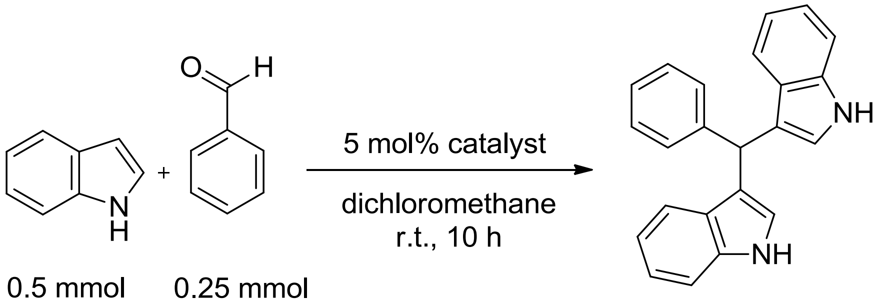
The catalytic role of Ce(III) cations in the reaction can be explained by the probable pathway of this reaction (Scheme 2). Coordination of Ce(III) cation to the oxygen of carbonyl group in aldehyde, because high oxophilicity of Ce(III), increases electron withdrawing character of this group. That causes bigger partial positive charge on the carbon of this group. This facilitates the formation of bond between the carbon of carbonyl group and C3 carbon of indole (negative partial charge). Than the Ce(III), which is still coordinated to oxygen, withdraws together with the hydroxy group (this induces a positive charge on the carbon at the point where the hydroxy group leaved the molecule) and this allows the formation of bond between intermediate and the C3 carbon of another molecule of indole.



SCHEME 2 PROBABLE REACTION PATHWAY FOR THE SYNTHESES OF 3,3´-[(4-X-PHENYL)METHANEDIYL]BIS(1H-INDOLES)

This probable reaction pathway also explains, why catalytic efficiency of Ce(III) cations depends on the character of the functional group (EWG *vs.* EDG) present in aldehyde. The catalytic effect of Ce(III) cations are the biggest in the case of reaction of indole with 4-methoxybenzaldehyde (strong π-EDG). This is caused by stronger interaction between Ce(III) cation and the oxygen of carbonyl group due to the influence of methoxy group compensates the increased electron withdrawing character of the carbonyl group. This leads to decrease of LUMO energy of carbonyl and thereby facilitates the interaction with other nucleophilic reagent.

We also compared our results obtained from reaction of benzaldehyde with indole catalyzed by supported Ce(III) cations with reaction times and yields of this reaction catalyzed by other catalytic systems from literature [15] (see the Table 2). This reaction was proceeded according to the literature at room temperature, dichloromethane was used as an eluent, the amount of catalyst was 5 mol% and the reaction time was 10 hours. This comparison showed that in this reaction the catalytic system of Ce(III) cations supported on weakly acidic exchanger has at least the same effectiveness as catalysts chosen from literature, at most of cases even better (for example $Cu(NO_3)_2$, $Sc(OTf)_3$, $SnCl_2.2H_2O$, $InBr_3$, *ect.*), advantageously its easy separation for a recycling. Finally, we studied and calculated turnover number (TON) [21] for the reaction of indole with benzaldehyde catalyzed by supported Cu(III) catalyst as well as by cerium trichloride heptahydrate. TON was calculated as a ratio of mole of indole converted to product and mole of Ce(III) present in catalyst. We found TON (supported Ce(III)) 49.7, for applied non-supported cerium(III) salt TON value only 3.7.



**SCHEME 3 GENERAL SCHEME OF REACTION OF INDOLE WITH BENZALDEHYDE**

**TABLE 2**
**RESULTS FOR REACTION OF INDOLE WITH BENZALDEHYDE CATALYZED BY VARIOUS CATALYSTS**

| Catalyst | Conversion (%) | Time (h) | Yield (%) | References |
|---|---|---|---|---|
| $PdCl_2(MeCN)_2$ | >95 | 10 | 80 | [15] |
| $PdCl_2(MeCN)$ in complex with indole | >95 | 10 | 83 | [15] |
| $Cu(NO_3)_2.3H_2O$ | ~80 | 10 | 70 | [15] |
| $SnCl_2.2H_2O$ | ~55 | 10 | 50 | [15] |
| $Sc(OTf)_3$ | ~80 | 10 | 70 | [15] |
| $InBr_3$ | ~75 | 10 | 62 | [15] |
| Ce(III) supported on resin | >95 | 10 | 84 | - |
| $CeCl_3.7H_2O$ | >95 | 10 | 76 | - |

## III. EXPERIMENTAL

All reagents and starting materials were purchased from commercial suppliers and used without any further purification.

Purolite C104 Plus (Purolite®Worldwide) was used as a solid support. Purolite C104 Plus is a weakly acidic macroporous cation exchanger of polyacrylate type in $H^+$ ionic form. Total volume capacity of this resin is 4.5 eq/L and specific gravity is 1.19 g/mL.

The syntheses were monitored by TLC: Performed on precoated Silica gel 60 $F^{254}$ plates (Merck), dichloromethane was used as eluent, detection with UV light (254 nm). Indole limit of detection was between 1 $10^{-4}$ mmol/l and 1 $10^{-5}$ mmol/L.

Structures of all synthetized 3,3´-[(4-X-phenyl)methanediyl]*bis*(1*H*-indoles) were confirmed by $^1$H, $^{13}$C NMR and FTIR. All spectral data were in agreement with published one [17].

### 3.1 Catalyst Preparation

The catalytic system of Ce(III) cations supported on weakly acidic macroporous polyacrylate cation exchanger resin was prepared according to the patent [4]. This preparation method was also previously published in [18, 19, 20]

Purolite C104 Plus (75g) was suspended in 200 mL of water and saturated aqueous potassium carbonate solution was added under stirring until pH of the solution remained at value of 12 for 10 min after the last addition. Then the aqueous solution was decanted and the resin beads were washed 4 times by 200 mL of water. Cerium(III) chloride heptahydrate (122.7 g, 33 mmol) was dissolved in 500 mL of water and modified resin beads were dropped into the solution which was then stirred overnight. After that was the aqueous solution again decanted and the resin beads were washed 2 times by 200 mL of water and 2 times by 200 mL of methanol and finally dried in vacuum to constant weight. The prepared catalyst contains about 2.3 mmol of Ce(III) per 1 g of modified resin beads. [4]

### 3.2 General Synthetic Method for Preparation of 3,3´-[(4-X-phenyl)methanediyl]bis(1H-indoles): [15]

Indole (0.5 mmol), aldehyde (0,25 mmol) and 5 mol% of appropriate catalytic system was stirred in 2 mL of dichloromethane at room temperature until disappearance of starting indole (monitored by TLC: dichloromethane was used as eluent, detection with UV light (254 nm), indole limit of detection was between 1 $10^{-4}$ mmol/L and 1 $10^{-5}$ mmol/L). After the completion of reaction, the catalyst was removed by filtration, washed by dichloromethane, dried and re-used eventually. Filtrate was purified with silica gel. The crystalline product was obtained by evaporation of the solvent on a rotary vacuum evaporator. The identity of all synthetized 3,3´-[(4-X-phenyl)methanediyl]*bis*(1*H*-indoles) was confirmed by $^{1}$H, $^{13}$C NMR and FTIR spectra. All spectral data were in agreement with published one in Ref. [17].

## IV. CONCLUSION

In this comparative study we proved, that catalytic system of Ce(III) supported on weakly acidic macroporous resin of polyacrylate type has in the regioselective C3 alkylation of indoles at least the same efficiency as $CeCl_3.7H_2O$ and some other catalysts chosen from literature (containing for example palladium, copper or scandium). Furthermore, this catalytic system has all advantages of supported catalysts and as solid support was used low-cost stable industrial resin.

## ACKNOWLEDGEMENTS

This study was funded by internal grant agency of University of Veterinary and Pharmaceutical Sciences Brno (grant number IGA363151) and also by Ministry of Industry and Trade of the Czech Republic (project number 2A-1TP1/090, grant recipient - doc. Pavel Pazdera) performed in an effort to find an efficient catalyst for derivatization of the side chain, such as piperazine or chalcone structural motives, in substituted s-triazines.

## REFERENCES

[1] A. Choplin, F. Quignard, M. Bosco, G. Foglia, A. Giuliani, E. Marcantoni, et al., “From Supported Homogeneous Catalysts to Heterogeneous Molecular Catalysts,” Coordination Chemistry Reviews, vol. 178-180, pp. 1679-1702, 1998.

[2] V.K. Ahluwalia, and R. Aggarwal, Organic Synthesis: Special Techniques, 2nd Ed. Oxford: Alpha Science International, 2006.

[3] P. Pazdera “Chapter 1.” in Handbook on Applications of Ultrasound-Sonochemistry for Sustainability, Boca Raton FL USA: CRC Press/ Taylor&Francis Group, 2011.

[4] P. Pazdera, B. Zberovská, D. Herová, and V. Datinská, “Catalyst for chemical syntheses based on metal complexes and method for its preparation” (Czech Republic, Masaryk University) Patent number CZ 305277, 2015.

[5] G.A. Molander, “Application of lanthanide reagents in organic synthesis,” Chemical Reviews, vol. 92, pp. 29, 1992.

[6] T. Imamoto, Lanthanides in Organic Synthesis, San Diego: Academic Press, 1994.

[7] M. Bandini, and A. Eichholzer, “Catalytic functionalization of indoles in a new dimension,” Angew Chem, Int Ed, vol. 48, pp. 9608-9644, 2009.

[8] D. Das, S. Pratihar, and S. Roy, “Heterobimetallic Pd–Sn catalysis: highly selective intermolecular hydroarylation of α-methyl substituted aryl alkenes,” Tetrahedron Lett., vol. 54, pp. 335-338, 2013. and references therein

[9] M. Shiri, M.A. Zolfigol, H.G. Kruger, and Z. Tanbakouchian, “Bis- and trisindolylmethanes (BIMs and TIMs)” Chem. Rev., vol. 110, pp. 2250-2293, 2010. and references therein

[10] K.M., Khan, F. Rahim, A. Wadood, *et al*., “Evaluation of bisindole as potent β-glucuronidase inhibitors: synthesis and in silico based studies,” Bioorg. Med. Chem. Lett., vol. 24, pp. 1825-1829, 2014.

[11] K. Sujatha, P.T. Perumal, D. Muralidharan, and M. Rajendran, “Synthesis, analgesic and anti-inflammatory activities of bis(indolyl)methanes,” Indian J. Chem, vol. 48, pp. 267–272, 2009.

[12] S.S. Ekbote, K.M. Deshmukh, Z.S. Qureshi, and B.M. Bhanage, “Polyvinylsulfonic acid as a novel Brønsted acid catalyst for the synthesis of bis (indolyl) methanes,” Green Chem. Lett. Rev., vol. 4, pp. 177-183, 2011.

[13] H. Qu, C. Xiao, N. Wang, K. Yu, Q. Hu, and L. Liu, “$RuCl_3·3H_2O$ Catalyzed Reactions: Facile Synthesis of Bis(indolyl)methanes under Mild Conditions,“ Molecules, vol. 16, pp. 3855-3868, 2011.

[14] F. Shirini, N.G. Khaligh, and O.G. Jolodar, “Preparation, characterization and use of 1,3-disulfonic acid imidazolium hydrogen sulfate as an efficient, halogen-free and reusable ionic liquid catalyst for the trimethylsilyl protection of hydroxyl groups and deprotection of the obtained trimethylsilanes,“ Dyes. Pigm., vol. 98, pp. 290-296, 2013.

[15] S.S. Mohapatra, P. Mukhi, A. Mohanty, S. Pal, A.O. Sahoo, D. Das, and S. Roy,”Palladium(II) in electrophilic activation of aldehydes and enones: efficient C-3 functionalization of indoles,” Tetrahedron Lett., vol. 56, pp. 5709-5713, 2015.

[16] B. Das, R.A. Kumar, D. Aruna, and J. Kashanna, “CeCl~37H~2O-Catalysed rapid synthesis of bis (indolyl) methanes under solvent-free conditions,” Indian Journal of Heterocyclic Chemistry, vol. 19, pp. 295, 2010.

[17] B.Y. Giri, P.D. Bla, K. Vijayalakshmi, R.B.N. Prasad, N. Lingaiah, and P.S. Sai Prasad, “A mild and efficient synthesis of bis(indolyl)methane derivatives catalyzed by ammonium salt of 12-tungstophosphoric acid,” Indian Journal of Chemistry, vol. 51B, pp. 1731-1737, 2012.

[18] E. Havránková, and P. Pazdera, “Kabachnik-Fields and PrinsRitter Synthesis: Application of Ce(III) Supported on a Weakly Acidic Cation-exchanger Resin in Comparative Study” J. Chem. Applications, vol. 2, pp. 1-8, 2015.

[19] E. Havránková, and P. Pazdera, “Comparative studies of catalytic application of cerium(iii) chloride and resin supported cerium(iii) in domino syntheses of 1,5-benzodiazepines and 1,3-diazine skeletons,” Journal of Chemical Engineering and Chemistry Research, vol. 2014, pp. 229-237, 2014.

[20] E. Havránková, P. Pospíšil, and P. Pazdera, “Synergism of metal and organocatalysis in condensation reactions of aromatic aldehydes with anilines affording imines: effect of catalysts on the base of a supported cerium(iii) and proline,” Science Journal of Chemistry, vol. 2, pp.1-8, 2014.

[21] K.V. Raghavan, B.M. Reddy, Industrial Catalysis and Separations: Innovations for Process Intensification Toronto New Jersey: CRC Press/ Taylor&Francis Group/ Apple Academic Press, p. 332, 2014.