Efficient One-Pot Synthesis of a Densely Functionalized Tetrahydropyridine in the Presence of [1,1′-Binaphthalene]-2,2′-diol/Indium(III) Chloride (binol/$InCl_3$) or Simple *Brønsted* Acids as Catalysts

by **Anna A. Kończyk**[a]), **Joanna Szawkało**[a]), **Jan K. Maurin**[b])[c]), and **Zbigniew Czarnocki***[a])

[a]) University of Warsaw, Faculty of Chemistry, Pasteura 1, PL-Warsaw (phone: +48 22 822 02 11; fax: +48 22 822 59 96; e-mail: czarnoz@chem.uw.edu.pl)
[b]) National Medicines Institute, Chełmska 30/34, PL-Warsaw
[c]) National Centre for Nuclear Research, Sołtana 7, PL-Otwock-Świerk

The highly functionalized tetrahydropyridine **4** was obtained in an indium(III) chloride catalyzed multi-component reaction from benzaldehyde, 4-methoxyaniline, and ethyl acetoacetate (=ethyl 3-oxobutanoate) in the presence of [1,1′-binaphthalene]-2,2′-diol (binol). It was found that binol played a beneficial role in this reaction, allowing a substantial decrease of the amount of indium salt. Also, simple organic *Brønsted* acids may serve as effective organocatalysts in this process.

Introduction. – The multicomponent coupling of aromatic aldehydes, anilines, and β-keto esters gained recently a special attention due to the ability to apply it in combinatorial chemistry and solid phase or flow syntheses [1]. This useful reaction was found to be substantially accelerated by various catalysts. Recently, the use of tetrabutylammonium tribromide ($(Bu_4N)Br_3$) [2], $InCl_3$ [3], L-proline/CF_3COOH [4], thiourea dioxide [5], PEG-embedded KBr_3 [6], hydrated $ZrOCl_2$ [7], and cerric ammonium nitrate (CAS) [7], and even elemental iodine [8] have been reported.

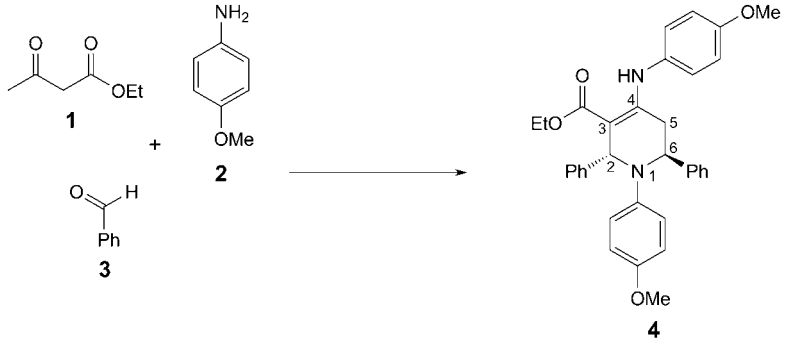
We turned our attention to the use of indium(III) chloride as the catalyst due to its ability to form complexes in which the structure of ligands may regulate properties of the catalyst.

Results and Discussion. – Initially, we concentrated on the reaction of ethyl acetoacetate (=ethyl 3-oxobutanoate; **1**) with 4-methoxyaniline (=4-methoxybenzenamine; **2**) and benzaldehyde (**3**) in the presence of $InCl_3$ (33 mol-%) [3]. Tetrahydropiperidine **4** was obtained in 69% yield (*Scheme 1*).

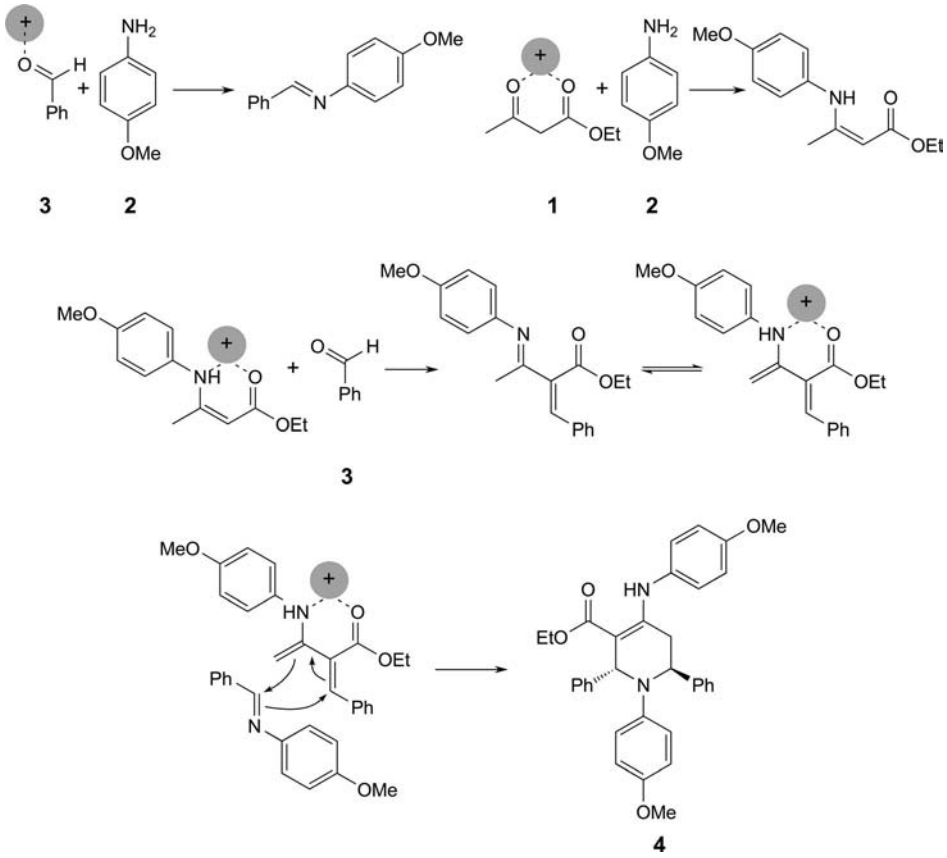
The possible mechanism for the formation of compound **4** is presented in *Scheme 2*.

The structure of **4** was confirmed by an X-ray crystal-structure analysis (*Fig.*). The molecule is composed of the central tetrahydropyridine ring which adopts a boat conformation. Five substituents are attached to the ring. Ph–C(2) and Ph–C(6) are in *trans*-relation to each other. The conformation and geometry of the central boat-ring is defined by geometrical parameters shown in *Table 1*. The pyridine N-atom (N(1)) has almost flat sp^2 configuration, which is shown by the sum of the adjacent bond angles of 359.74°. The slightly longer C(3)=C(4) bond length 1.371(2) Å and a bit shorter C(3)–C(7) single C_{sp^2}–C_{sp^2} bond length 1.437(2) Å confirm the partial conjugation between the C=C bond and the ester CO group. An additional confirmation of the

Scheme 1. *Synthesis of Tetrahydropyridine* **4** *in the Presence of* $InCl_3$ *in MeCN*



Scheme 2. *Mechanism for the Formation of Tetrahydropyridine* **4**



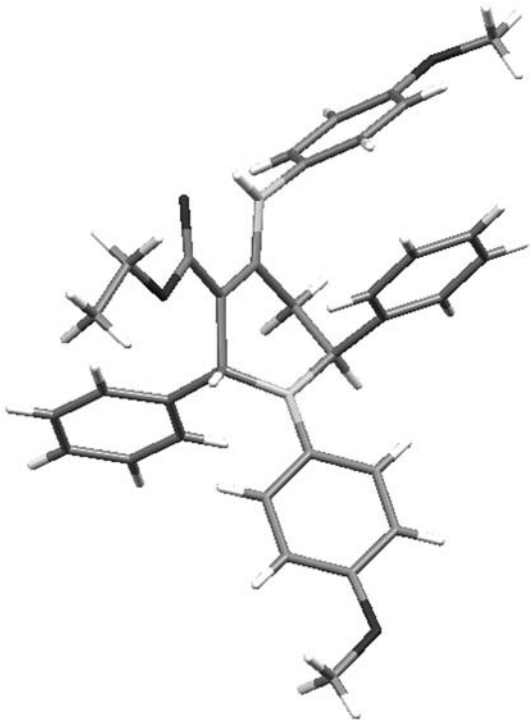


Figure. *X-Ray crystal structure of tetrahydropyridine* **4**

Table 1. *Selected Bond Lengths, Angles, and Torsion Angles of Tetrahydropyridine* **4**

Bond lengths [Å]		Angles [°]		Torsion angles [°]	
N(4)–C(4)	1.3452(17)	C(6)–N(1)–C(2)	119.72(10)	C(6)–N(1)–C(2)–C(3)	–24.16(16)
N(1)–C(11)[a])	1.3952(16)	N(1)–C(2)–C(3)	111.35(10)	N(1)–C(2)–C(3)–C(4)	39.65(16)
N(1)–C(6)	1.4513(15)	C(4)–C(3)–C(2)	118.25(11)	C(2)–C(3)–C(4)–C(5)	–2.06(17)
N(1)–C(2)	1.4674(17)	C(3)–C(4)–C(5)	116.31(11)	C(3)–C(4)–C(5)–C(6)	–48.24(15)
C(2)–C(3)	1.5204(18)	C(4)–C(5)–C(6)	107.73(11)	C(2)–N(1)–C(6)–C(5)	–24.29(16)
C(2)–C(21)[a])	1.5333(18)	N(1)–C(6)–C(5)	109.29(11)	C(4)–C(5)–C(6)–N(1)	60.73(14)
C(3)–C(4)	1.3708(17)			C(4)–C(3)–C(7)–O(2)[b])[c])	7.5(2)
C(3)–C(7)[b])	1.4373(19)			C(2)–C(3)–C(7)–O(3)[b])[c])	1.10(1)
C(4)–C(5)	1.4916(19)				
C(5)–C(6)	1.537(2)				
C(6)–C(61)[a])	1.5246(17)				

[b]) C(11), C(21), and C(61) = C_{ipso} *Ph*–C(1), *Ph*–C(2), and *Ph*–C(6), respectively. [b]) C(7)=*C*=O. [c]) O(2)–C(7)=O(3).

above assumption is the coplanarity of the C(4)–C(3)–C(2) and O(2)–C(7)–O(3) part – see appropriate torsion angles in *Table 1*.

We were interested in a decrease of the concentration of the toxic metal catalyst, and we chose [1,1′-binaphthalene]-2,2′-diol (binol) as an additive, which may serve as an environmentally more benign cocatalyst. Indeed, we found that binol played a beneficial role in the reaction both in terms of the yield and the reaction time. The reaction was carried out in CH_2Cl_2 as a solvent, and the results are summarized in *Table 2*. The optimal yield of product **4** (81%) was obtained with 3.3 mol-% of $InCl_3$ in the presence of 30 mol-% of binol. The reaction still proceeded even when the amount of the metal catalyst was decreased to $6.7 \cdot 10^{-6}$ mmol but the yield was only 26%. The absence of $InCl_3$ stopped the reaction completely.

Table 2. *Synthesis of Tetrahydropyridine* **4** *in the Presence of Indium(III) Chloride Modified by binol as Catalyst in* CH_2Cl_2

Reaction time [d]	$InCl_3$ [mmol]	binol [mol-%]	Yield[a]) [%]
1	0	20	0
1	0.67	0	15
1	0.67	10	23
1	0.67	20	35
1	0.67	30	69
2	0.067	30	81
2	0.0067	30	65
2	0.00067	30	58
2	$6.7 \cdot 10^{-5}$	30	37
2	$6.7 \cdot 10^{-6}$	30	26

[a]) Yield of isolated pure **4**.

An increased yield of product **4** was observed when MeCN was used as a solvent, reaching almost 70% with 0.33 mol-% of $InCl_3$ and 20 mol-% of binol. The reaction proceeded quantitatively with 33 mol-% of $InCl_3$ and 30 mol-% of binol (*Table 3*).

Table 3. *Synthesis of Tetrahydropyridine* **4** *in the Presence of Indium (III) Chloride Modified by binol as Catalyst in MeCN*

Reaction time [d]	$InCl_3$ [mmol]	binol [mol-%]	Yield[a]) [%]
1	0	20	0
1	0.67	0	69
1	0.67	20	88
1	0.67	30	98
1	0.067	20	77
1	0.0067	20	69

[a]) Yield of isolated pure **4**.

The above results indicate that the addition of binol allows a substantial decrease of the amount of the metal catalyst needed for the reaction, but some minute amount of $InCl_3$ is still required.

Exploring the possibility of stereoselectivity during the process, we performed some experiments with (*R*)-binol with the hope to obtain an enantiomerically enriched product. Unfortunately, we found that tetrahydropyridine **4** was formed as a racemate. Also, the use of other chiral catalysts or cocatalysts like the combination of $InCl_3$/L-prolinol or $Sc(OTf)_3$/(*R*)-binol did not show any stereoselectivity although the yield of racemic **4** was acceptable (61–80%, *Table 4*).

Table 4. *Synthesis of Tetrahydropyridine* **4** *with Modified* Lewis *Acids as a Catalyst in MeCN*

Reaction time [d]	Catalyst/amount [mmol]	Organic catalyst/amount [mol-%]	Yield[a]) [%]
2	$InCl_3$/0.67	L-prolinol/20	80
2	$Sc(OTf)_3$/0.67	(*R*)-binol/20	61

[a]) Yield of isolated pure **4**.

It is interesting to note that the use of the metal catalyst may be completely avoided. We found that **4** formed in a good yield when (+)-camphorsulfonic acid or di-*O*-*p*-toluoyl-L-tartaric acid (=(2*R*,3*R*)-2,3-bis-[(4-methylbenzoyl)oxy]butanedioic acid) were applied (*Table 5*). Unfortunately, also in those cases the reaction did not bring about the formation of a nonracemic product.

Table 5. *Synthesis of Tetrahydropyridine* **4** *with* Brønsted *Acid as a Catalyst in* CH_2Cl_2

Reaction time [d]	*Brønsted* acid/amount [mol-%]	Yield[a]) [%]
2	(+)-Camphorsulfonic acid/20	66
2	Di-*O*-toluoyl-L-tartaric acid/20	64

[a]) Yield of isolated pure **4**.

Nevertheless, the above results indicate that the multicomponent reactions giving highly substituted pyridine derivatives like **4** can be effectively realized with a moderate amount of organocatalysts (like simple organic *Brønsted* acids) or with a small amount of transition-metal catalysts accompanied by an organic additive (binol), allowing an environmentally more friendly procedure.

Experimental Part

General. All reactions were carried out under air atmosphere without any special precautions. Chemicals were purchased from *Merck* and *Aldrich* and used for the synthesis as obtained. TLC: silica gel plates (*60* F_{256}; *Merck*). Column chromatography (CC): *Merck silica gel 60* (0.075–0.15 mm, 100–200 mesh). M.p.: *Kofler* apparatus, type *Boetius*. ^{1}H- and ^{13}C-NMR Spectra: *Varian Unity Plus*; at 200 (^{1}H) and 50 MHz (^{13}C); in $CDCl_3$; δ in ppm, *J* in Hz. MS: *Micromass-LCT* (TOF); positive-ion mode ESI; in *m/z*.

*Ethyl (2*RS,*6*SR*)-1,2,5,6-Tetrahydro-1-(4-methoxyphenyl)-4-[(4-methoxyphenyl)amino]-2,6-diphenylpyridine-3-carboxylate* (**4**) *in the Presence of* Brønsted *or* Lewis *Acid as a Catalyst. General Procedure. Brønsted* acid (see *Table 5*, 20 mol-%) or Indium(III) chloride (148 mg, 0.67 mmol) was dissolved in MeCN or CH_2Cl_2 (4 ml) followed by the addition of 4-methoxyaniline (**2**; 492 mg, 4.0 mmol). The mixture was stirred until a clear soln. was formed. Next, **3** (389 µl, 4.0 mmol) and **1** (252 µl, 2.0 mmol) were introduced, and the mixture was stirred for 24 h at r.t. The crystalline product formed was filtered

off, washed with MeCN (1 ml) and recrystallized from MeCN. The results are summarized in *Tables 2*, *3*, and *5*.

X-Ray Crystal-Structure Analysis of **4** (*Fig.* and *Table 1*). A colorless monocrystal of **4** of dimensions $0.27 \times 0.20 \times 0.15$ mm was mounted on the goniometer of an *Xcalibur-R* κ-axis single-crystal diffractometer from *Oxford Diffraction*. Monochromatic CuK_α radiation was used to collect the data up to $2\theta < 142°$. Of the 27267 intensity data collected, 5492 were independent data. The data were corrected with *Lorenz*-polarization effects, extinction and, after solving the structure, also for absorption. The crystal structure was solved with SHELXS-98 [9] and then refined by a least-squares method with the SHELXL-98 program [9]. The experimental parameters are shown in *Table 6*. CCDC 861542 contains the supplementary crystallographic data for this article. These data can be obtained free of charge *via* http:/www.ccdc.cam.ac.uk/data_request/cif.

Table 6. *Crystal Data and Structure Refinement of Tetrahydropyridine* **4**

CCDC Deposition No.	861542
Empirical formula	$C_{34}H_{34}N_2O_4$
M_r	534.63
Temperature	293(2) K
Wavelength	1.54178 Å
Crystal system	monoclinic
Space group	$P2_1/n$
Unit cell dimensions	$a = 10.00420(10)$ Å, $\alpha = 90°$ $b = 27.1937(2)$ Å, $\beta = 100.1460(10)°$ $c = 10.76230(10)$ Å, $\gamma = 90°$
Volume	2882.11(4) Å^3
Z	4
Density (calculated)	1.232 Mg/m^3
Absorption coefficient	0.644 mm^{-1}
$F(000)$	1136
Crystal size	$0.2691 \times 0.1966 \times 0.1459$ mm
θ Range for data collection	3.25 – 70.99°
Index ranges	$-12 \le h \le 12$, $-33 \le k \le 33$, $-12 \le l \le 9$
Reflections collected	27267
Independent reflections	5492 (R(int) = 0.0335)
Completeness to $\theta = 70.99°$	98.5%
Absorption correction	analytical
Max. and min. transmission	0.927 and 0.884
Refinement method	full-matrix least-squares on F^2
Data, restraints, parameters	5492, 0, 353
Goodness-of-fit on F^2	1.012
Final R indices ($I > 2\sigma(I)$)	$R_1 = 0.0376$, w$R_2 = 0.1040$
R indices (all data)	$R_1 = 0.0511$, $wR_2 = 0.1090$
Extinction coefficient	0.0050(3)
Largest diff. peak and hole	0.165 and -0.187 e Å^{-3}

*Ethyl (2*RS,*6*SR*)-1,2,5,6-Tetrahydro-1-(4-methoxyphenyl)-4-[(4-methoxyphenyl)amino]-2,6-diphenylpyridine-3-carboxylate* (**4**), *in the Presence of* Lewis *Acid Modified with [1,1′-Binaphthalene]-2,2′-diol* (binol) *or* L-*Prolinol as Catalyst. General Procedure.* Indium(III) chloride 148 mg (0.67 mmol) was dissolved in MeCN or CH_2Cl_2 (4 ml) followed by the addition of binol (114.4 mg, 20 mol-%, 0.4 mmol). The mixture was stirred for 2 h. Next, **2** (492 mg, 4.0 mmol), **3** (389 µl, 4.0 mmol), and **1** (252 µl, 2.0 mmol) were introduced, and the mixture was stirred for 24 h at r.t. The crystalline product formed was filtered off, washed with MeCN (1 ml), and recrystallized from MeCN. After reaction with the chiral

reagents (*R*)-binol or L-prolinol, the soln. in CH_2Cl_2 was purified by CC (CH_2Cl_2). The results are summarized in *Tables 2–4*.

Data of **4**: M.p. 168–169°. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.44 (*t*, *J* = 7.1, 3 H); 2.56–2.85 (*m*, 2 H); 3.65 (*s*, 3 H); 3.74 (*s*, 3 H); 4.21–4.53 (*m*, 2 H); 5.05 (*d*, *J* = 6.0, 2 H); 6.19 (*d*, *J* = 8.8, 2 H); 6.44 (*d*, *J* = 9.2, 2 H); 6.60 (*d*, *J* = 8.8, 2 H); 6.66 (*d*, *J* = 9.0, 2 H); 7.12–7.34 (*m*, 10 H); 10.14 (*s*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 15.0; 33.8; 55.6 (2 C); 55.8 (2 C); 58.5; 59.7; 97.4; 114.1 (2 C); 114.2 (2 C); 114.7 (2 C); 126.4; 126.7 (2 C); 127.0 (2 C); 127.2; 128.0 (2 C); 128.3 (2 C); 128.8 (2 C); 130.9; 141.8; 143.5; 144.5; 157.0; 157.9; 168.5. ESI-MS (pos.): 557.21 ($[M+Na]^+$), 1091.57 ($[2\,M+Na]^+$).

REFERENCES

[1] T. J. J. Müller, *Beilstein J. Org. Chem.* **2011**, *7*, 960.
[2] A. T. Khan, M. Lan, M. M. Khan, *Tetrahedron Lett.* **2010**, *51*, 4419.
[3] P. A. Clarke, A. V. Zaytzev, A. C. Whitwood, *Tetrahedron Lett.* **2007**, *48*, 5209.
[4] M. Misra, S. K. Pandey, V. P. Pandey, J. Pandey, R. Tripathi, R. P. Tripathi, *Bioorg. Med. Chem.* **2009**, *17*, 625.
[5] S. Verma, S. Kumar, S. L. Jain, B. Sain, *Org. Biomol. Chem.* **2011**, *9*, 6943.
[6] S. Verma, S. L. Jain, B. Sain, *Beilstein J. Org. Chem.* **2011**, *7*, 1334.
[7] S. Mishra, R. Ghosh, *Tetrahedron Lett*. **2011**, *52*, 2857.
[8] H.-J. Wang, L.-P. Mo, Z.-H. Zhang, *ACS Comb. Sci.* **2011**, *13*, 181.
[9] G. M. Sheldrick, *Acta Crystallogr., Sect A* **2008**, *64*, 112.

Received September 11, 2012