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4-Hydroxyproline containing podands as new chiral catalysts for the asymmetric Biginelli reaction

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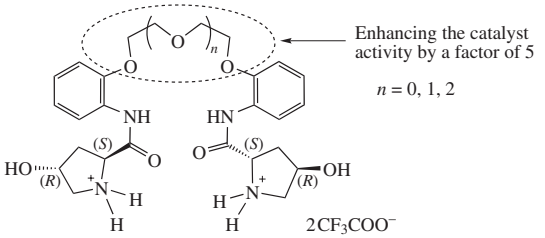
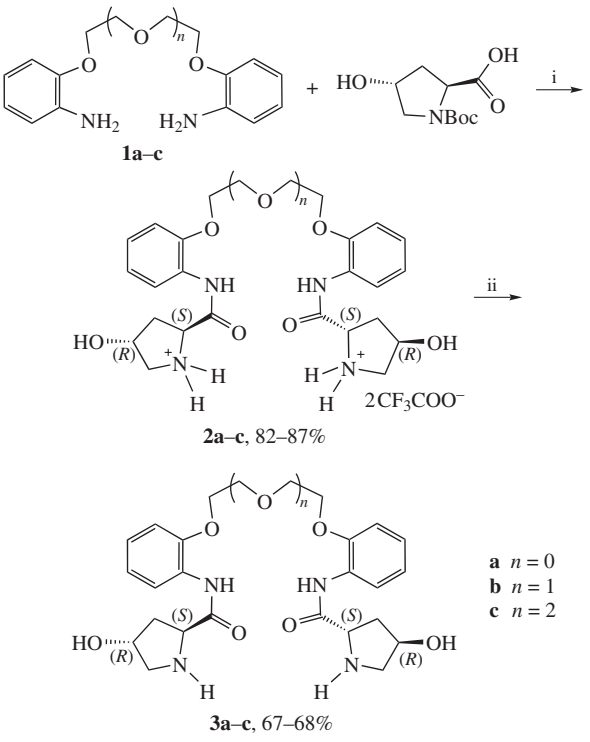
The novel C_2-symmetric chiral organocatalysts of (2*S*,4*R*)-hydroxyproline containing podand type have been synthesized and evaluated in the asymmetric Biginelli reaction. Combination of polyether spacer with (2*S*,4*R*)-hydroxyproline allowed one to enhance the effect of the latter on enantioselectivity of the Biginelli reaction by a factor of 5. The best results have been achieved for salts of (2*S*,4*R*)-hydroxyproline containing podands with trifluoroacetic acid.



The use of C_2-symmetric chiral diols[1,2] and diamines[3] as chiral organocatalysts in asymmetric synthesis is a new interesting trend of the last decade. The presence in such catalysts of several binding sites capable of reversibly forming covalent and non-covalent (ionic, hydrogen, *etc.*) bonds provides optimal location of reactants in transition states responsible for high enantioselectivity of the reactions.[3] As a rule, C_2-symmetric catalysts described in the literature[1–3] have a short spacer of ethylene type or its cyclic derivatives. Assuming that the ability of cyclic and acyclic polyethers to coordinate cations and/or organic molecules[4,5] can also increase the effectiveness of the chiral catalyst, we synthesized herein the podands containing conformationally flexible oligo ether spacer and (2*S*,4*R*)-hydroxyproline moieties (Scheme 1). The latter is frequently used as a structural fragment of chiral organocatalysts of the Biginelli reactions,[6] 1,4-addition,[7] Mannich[8,9] and aldol[9–11] reactions.



Scheme 1 *Reagents and conditions*: i, $ClCO_2Et$, then CF_3CO_2H; ii, NaOH (aq.).

Only two types of C_2-symmetric bishydroxyprolinamide catalysts have been reported to date and used in an aldol reaction: complicated hybrid systems modified with fragments of ionic liquids[3] and polyhedral oligomeric silsesquioxane supported catalyst with chiral diphenylethane spacer.[12]

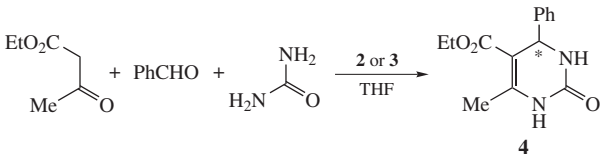
In continuation of our interest in the asymmetric multicomponent Biginelli reaction,[13–15] we decided to investigate synthesized structures as chiral catalysts for the reaction between benzaldehyde, urea and ethyl acetoacetate. A variety of organic compounds, such as BINOL and quinine derivatives, proline-derived chiral amines, and metal complexes of chiral ligands have been reported to act as chiral catalysts in the Biginelli reaction,[16,17] however 4-hydroxyproline containing podands were not tested for promotion of this reaction.

The target podands **2** and **3** were synthesized according to Scheme 1. At the first stage, *N*-Boc-hydroxyproline containing podands were obtained in THF at room temperature by amidation of podands **1a–c**[18] with *N*-Boc-hydroxyproline ethyl formate (generated using ethyl chloroformate). Further removal of the Boc group with trifluoroacetic acid (TFA) led to target salts **2a–c** in 82–87% yields.† The podands **3a–c** were obtained by heterophase

† *Podands* **2a–c** *(typical procedure)*. To a solution of *N*-Boc protected *trans*-4-hydroxy-L-proline (0.45 g, 2 mmol) in $CHCl_3$ (20 ml) Et_3N (0.25 ml, 2.5 mmol) and ethyl chloroformate (0.25 ml, 2.5 mmol) were added at 0 °C under stirring. After 30 min, amino podand **1** (0.7 mmol) in $CHCl_3$ (10 ml) was added. The mixture was stirred at 25 °C for 7 h. The chloroform solution was washed with 1 M $NaHCO_3$ (30 ml) and H_2O (3×30 ml). After removal of the solvent, the crude product was stirred in TFA (10 ml) until the deprotection finished. After evaporating TFA, product **2** was extracted with ethyl acetate and recrystallized from *n*-butanol (for **2a**) or EtOH (for **2b**,**c**) with ice cooling as a white solid.

neutralization of salts **2a–c** in chloroform with aqueous sodium hydroxide.‡ All synthesized compounds were characterized and identified with ^{1}H and ^{13}C NMR, IR spectroscopy, HRMS and elemental analysis (see Online Supplementary Materials).

Podands **2**, **3** were investigated as chiral catalysts in the Biginelli asymmetric synthesis of pyrimidine derivative **4** (Scheme 2).§



Scheme 2

In the presence of podands **3a–c**, the reaction proceeded to give dihydropyrimidinone **4** in critically low yield (up to 2%) and with low enantioselectivity (8–24%) (Table 1). However, in the presence of TFA salts **2a–c**, the yield was reasonably improved and enantioselectivity was significantly increased (up to 62–68% *ee*).

Incorporating of a polyether spacer into a molecule of a known chiral catalyst **5**[6] considerably changes its catalytic activity. The stereochemical outcome of the Biginelli reaction is fivefold improved on moving to podands **2a–c**. This clearly demonstrates the influence of a polyether spacer on the coordination of the reactants in the transition states and the preferential formation of

Table 1 Screening of chiral catalysts **2a–c**, **3a–c** or **5** (THF, 10 mol% of chiral catalyst, room temperature, 45 h) in the synthesis of compound **4**.

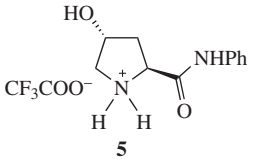
Catalyst	Yield (%)	*ee* (*R*)[a] (%)	Catalyst	Yield (%)	*ee* (*R*)[a] (%)
2a	11	62	**3b**	1	14
2b	15	64	**3c**	2	8
2c	23	68	**5**[6]	37	13
3a	1	24			

[a] Chiral HPLC data (YMC-Pack Chiral-NEA-R). The absolute configuration was determined by comparison with the reported[6] optical rotation.

*(2S,2′S,4R,4′R)-*N,N′*-{2,2′-[Ethane-1,2-diylbis(oxy)]bis(2,1-phenylene)}-bis(4-hydroxypyrrolidine-2-carboxamide)·2CF$_3$COOH* **2a**: $[\alpha]_D^{20}$ = –31.20 (*c* 0.5, H_2O). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.86 (m, 2H, C^{3}H), 2.30 (dd, 2H, C^{3}H), 3.12 (d, 2H, C^{5}H), 3.29 (dd, 2H, C^{5}H), 4.29 (m, 2H, C^{4}H), 4.42 (m, 4H, OCH_2), 4.60 (dd, 2H, C^{2}H), 5.54 (br. s, 2H, OH), 6.99 (t, 2H, Ph), 7.17–7.22 (m, 4H, Ph), 7.73 (d, 2H, Ph), 8.66 (br. s, 2H, N^{1}H), 9.75 (br. s, 2H, N^{1}H), 9.81 (s, 2H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 39.60 (2C), 53.89 (2C), 58.73 (2C), 62.27 (2C), 67.55 (2C), 69.57 (2C), 112.94 (2C), 116.09, 118.49, 120.80 (2C), 122.81 (2C), 125.66 (2C), 126.32 (2C), 149.69 (2C), 157.68, 157.92, 168.29 (2C). IR (film, ν/cm^{-1}): 3322, 3092, 2954, 2730, 1667, 1610, 1598, 1554, 1496, 1479, 1459, 1433, 1333, 1288, 1267, 1187, 1131, 1054, 1036, 1024, 967, 837, 800, 758, 724, 657.

‡ *Podands* **3a–c** *(typical procedure)*. Salt **2** was dissolved in H_2O and basified up to the pH 11 by the addition of 1 M NaOH. Product **3** was extracted with $CHCl_3$ (5×25 ml). The extract was washed with water (30 ml) and dried over anhydrous Na_2SO_4. The solvent was evaporated and product **3** was purified by recrystallization from MeCN (for **3a**) or THF (for **3b**,**c**) with ice cooling as a white solid.

§ *Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate* **4** (*the Biginelli reaction, typical procedure*). A solution of benzaldehyde (0.050 g, 0.47 mmol), urea (0.084 g, 1.41 mmol) and chiral catalyst **2** or **3** (0.047 mmol) in THF (2 ml) was stirred for 30 min, then ethyl acetoacetate (0.074 g, 0.70 mmol) was added. The mixture was stirred at 23 °C for 45 h and evaporated to dryness under reduced pressure. The residue was dissolved in DMF and the resulting solution was analyzed by chiral HPLC to determine the enantiomeric excess of compound **4** and then evaporated to dryness under reduced pressure. The residue was treated with diethyl ether (2×20 ml), then stirred in water (10 ml) for 3 h, filtered off and dried to yield compound **4**. The ^{1}H NMR and IR spectra were in good agreement with the published data.[19] For sample with *ee* 68% $[\alpha]_D^{20}$ = –38 (*c* 0.2, MeOH) {lit.,[4] *ee* 80%; $[\alpha]_D^{20}$ = 30.5 (*c* 0.2, MeOH)}.



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one of the enantiomers **4**. Note that the *ee* value depends on polyether spacer length for podands **2** and **3**. For podands **3a–c**, enantioselectivity decreases with elongation of polyether spacer, while for their salts **2a–c** the inverse trend is observed.

In conclusion, we have synthesized a series of novel C_2-symmetric (2*S*,4*R*)-hydroxyproline containing podands with different lengths of polyether spacer for application in the enantioselective Biginelli reaction. It has been shown that the polyether fragment and its length, as well as a protonation of the nitrogen atom of the pyrrolidine ring by acid in the catalyst molecule significantly affect their catalytic activity. These compounds are of interest for further optimization of synthesis conditions to increase chemo-, enantioselectivity and investigation of the mechanism of their action.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.07.004.

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