An enantioselective approach to the Biginelli dihydropyrimidinone condensation reaction using $CeCl_3$ and $InCl_3$ in the presence of chiral ligands

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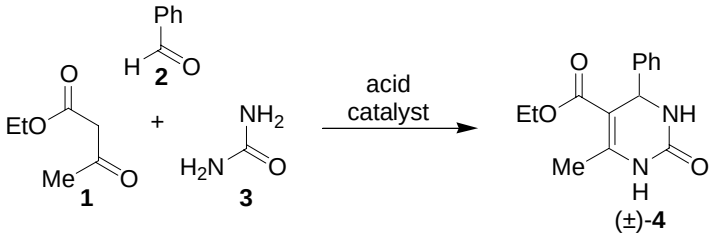
Abstract

A search for suitable reaction conditions for the preparation of 4-phenyldihydropyrimidinone derivative **6**, activated by $CeCl_3$ and $InCl_3$ [equimolar or catalytic amount (20%)] revealed that the reaction proceeds in good yields (65-92% yield) in THF or toluene as a solvent. The preparation of enantiomerically enriched compound **6** was achieved in moderate enantioselectivity (8-40% ee) by a modified one-pot Biginelli condensation procedure in the presence of the chiral ligands (*R*,*R*)-**13** or (*S*,*S*)-**14**.

Keywords: Biginelli reaction, multicomponent reactions, enantioselective, chiral ligands, asymmetric catalysis, indium chloride, cerium chloride

Introduction

In recent times, dihydropyrimidinone derivatives have attracted considerable attention owing to their high activity as antihypertensive, antiviral, antitumor and anti-inflammatory agents, and as calcium channel blockers.[1] The original procedure for the preparation of this type of compounds was reported by Biginelli in 1893, involving one-pot condensation of ethyl acetoacetate (**1**), benzaldehyde (**2**), and urea (**3**) under strongly acidic conditions (Scheme 1).[2]

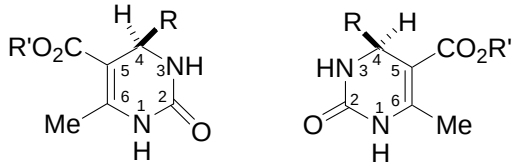


Scheme 1. The classical Biginelli dihydropyrimidinone one-pot synthesis.

A serious limitation of this protocol is that it produces low yields of the desired heterocycle when substituted aromatic and aliphatic aldehydes are used. Of course, the original Biginelli methodology does not have any enantiocontrol during formation of the new stereocenter.[3] Although in the last years the development of alternative multi-step strategies to produce higher overall yields of the dihydropyrimidonone heterocycle has been met with success,[4] the art of performing efficient enantioselective coupling of three or more components in a single operation still represents a fundamental target in modern organic synthesis.[5]

Pharmacological studies concerning the structure-activity relationship for various dihydropyrimidinones have established that calcium channel modulation (*antagonist vs agonist* activity) depends on the absolute configuration in C(4) (Scheme 2). For this reason, the control of the stereochemistry of the substituent at C(4) has essential importance since it acts like a molecular gear of chiral regulation during drug-receptor recognition.[6] Nevertheless, the absence of any general asymmetric synthesis of this heterocyclic system, chemical resolution and enzymatic strategies have been the most practical methods to obtain enantiomerically pure dihydropyrimidinone derivatives.[7]

Recently, cerium(III) chloride and indium(III) chloride have emerged as powerful catalysts imparting high regio- and chemoselectivity in various chemical transformations.[8] Here we wish to report in full detail the development of conditions for performing enantioselective Biginelli condensation reactions catalyzed with $InCl_3$ or $CeCl_3$ in the presence of chiral ligands.



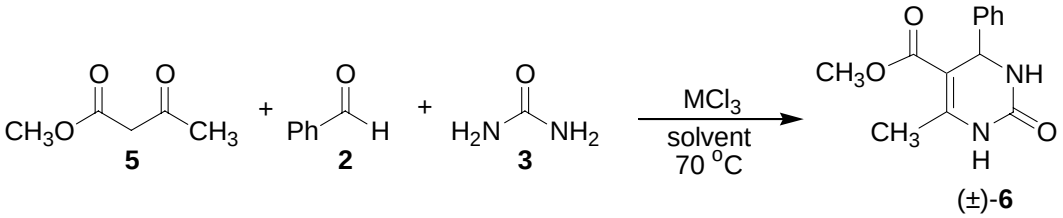
Scheme 2. Contrasting biological activity between opposite enantiomers in several dihydropyrimidinones with calcium channel modulator activity.

Results and Discussion

Our initial attempts focused on the use of Lewis acids such as Ce(III) and In(III) as activators of the Biginelli reaction for the preparation of dihydropyrimidinones such as compound **6** in racemic form. For this goal, we explored the effect of both equimolar and catalytic amounts of the Lewis acid. Furthermore, two different solvents were tested in order to find the best Lewis

acid/solvent combination in terms of efficiency of the reaction. The results obtained in these preliminary experiments are shown in Table 1.

Table 1. Solvent and Lewis acid effect on the yield of the racemic dihydropyrimidinone **6**

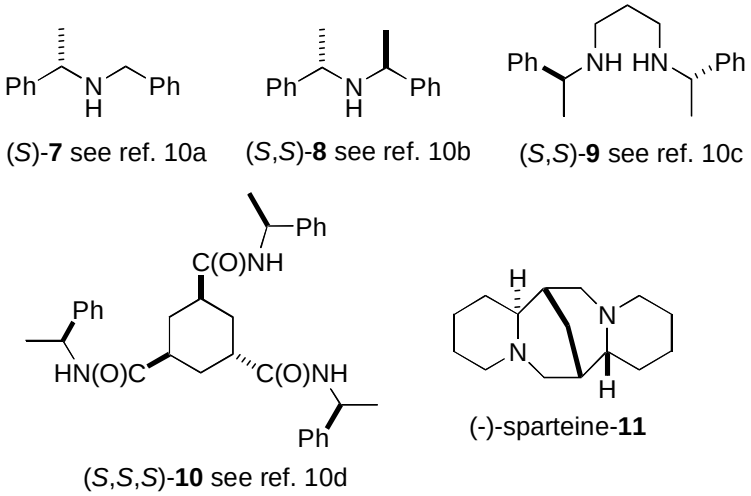


Entry	M	Catalyst (%)	Solvent	Time (h)	Yield (%)
1	Ce	100	THF	6	89
2	Ce	20	THF	12	85
3	Ce	100	Toluene	18	72
4	Ce	20	Toluene	24	70
5	In	100	THF	6	92
6	In	20	THF	12	79
7	In	100	Toluene	18	75
8	In	20	Toluene	24	65

Salient observations from Table 1 are the following: (1) In THF, both Lewis acids are efficient promotors of the Biginelli reaction when used either in equimolar amounts or catalytic (20 mol %) amounts. (Compare for example, entries 1 and 2 in Table 1). (2) In toluene, the Biginelli condensation proceeds in slightly lower yields relative to THF solvent. Also, increased reaction times are required to achieve complete consumption of the starting materials. (Compare for example, entries 5 and 6 in Table 1). In toluene, the lower yields attained with both Lewis acids are presumably due to lower solubility of the chloride salts. (3) Comparison of entries 1 and 2, 3 and 4, 5 and 6, and 7 and 8 (diminution of the amount of Lewis acid to 20 %) confirmed that the process could be performed under catalytic conditions. Of course, this proved to be an advantage when chiral ligands were used. (See below).

Once we had established suitable conditions for the Biginelli reaction promoted by $CeCl_3$ and $InCl_3$, and taking into account that one of the useful methodologies in asymmetric synthesis is based on the use of chiral ligands, we decided to use chiral amines **7-9** and amide **10** incorporating the (*S*)-α-phenylethylamino group[9,10] in order to explore the potential stereoinduction in this reaction. (–)-Sparteine was also included as chiral test ligand in this reaction since this chiral diamine has received considerable attention in the area of

enantioselective synthesis (Scheme 3).[11] Based on the results obtained in our initial studies (see Table 1), we decided to use THF as solvent and 20% of the Lewis acid as activator, as well as 20% of the chiral ligands. The results obtained in this reactions are shown in Table 2.



Scheme 3. Chiral ligands used in this work.

Table 2. Enantioselectivity in the asymmetric Biginelli reactions promoted by $CeCl_3$ or $InCl_3$ and chiral ligands **7**-**11**

Entry	Chiral Ligand (20 mol %)	M	Yield (%)	e. r.[a]	Configuration on major product[b]
1	(*S*)-**7**	Ce	20	52:48	*R*
2	(*S*)-**8**	Ce	26	52:48	*R*
3	(*S*,*S*)-**9**	Ce	32	53:47	*R*
4	(*S*,*S*,*S*)-**10**	Ce	88	41:59	*S*
5	(-)-**11**	Ce	66	58:42	*R*
6	(*S*)-**7**	In	12	51:49	*R*
7	(*S*)-**8**	In	17	53:47	*R*
8	(*S*,*S*)-**9**	In	28	52:48	*R*
9	(*S*,*S*,*S*)-**10**	In	75	42:58	*S*
10	(-)-**11**	In	72	57:43	*R*

[a] Quantified by HPLC. [b)] The assignment of the absolute configuration was carried out by comparison with the retention times reported in ref. 12.

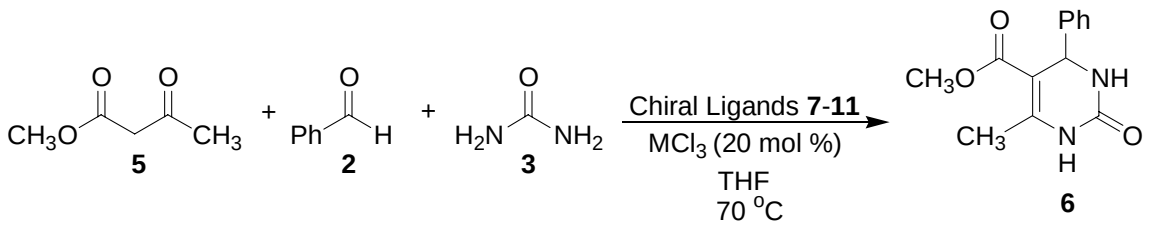
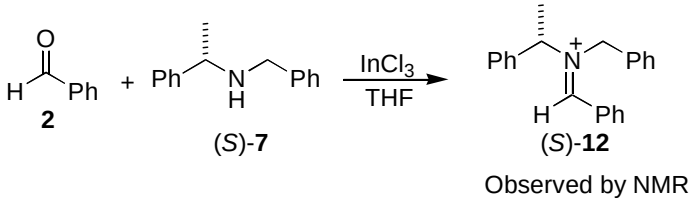


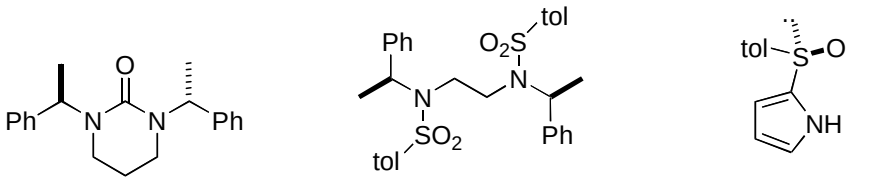
Table 2 collects the results of the Biginelli condensation in the presence of chiral ligands **7-11**. The enantioselectivities were generally poor, presumably because of the high temperature required for the reaction (70 ^{o}C). In some cases (see, entries 1-3 and 6-8 in Table 2), the reaction yields were low, probably because a side reaction between benzaldehyde and the amino-containing chiral ligands affords the corresponding iminium ion, that inhibits the mechanism operative for the desired reaction. Support for this lateral reaction (Scheme 4) was gained from ^{13}C NMR examination of a mixture of benzaldehyde and chiral ligand (*S*)-**7** in THF with $InCl_3$ as activator. The formation of compound **12** seems to be confirmed by the appearance of a signal at δ = 163.8 ppm, which is reasonable for the iminium carbon.[13]



Scheme 4. Formation of iminium ion (*S*)-**12** in the reaction of benzaldehyde with chiral amine (*S*)-**7** in the presence of $InCl_3$ Lewis acid.

On the other hand, the enantioselectivities and yields improved slightly when the condensation reaction was carried out in the presence of triamide (*S*,*S*,*S*)-**10** and (–)-sparteine **11** (entries 4-5 and 9-10 in Table 2. Interestingly, triamide (*S*,*S*,*S*)-**10** provided the best yields and enantioselectivities in comparison with other amine ligands, including (–)-sparteine.

We then decided to explore the use of other chiral ligands that would not be prone to iminium ion formation (Scheme 5). The results obtained with these ligands are shown in Table 3.

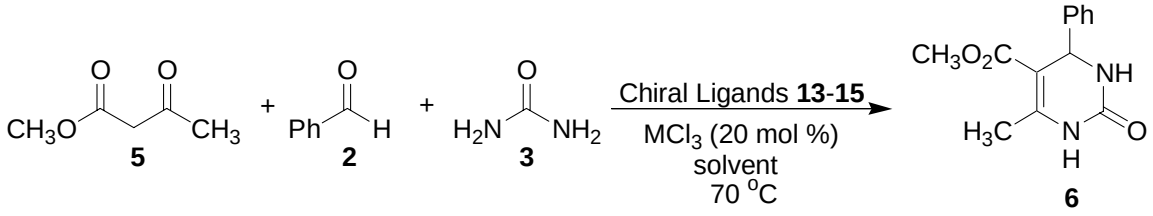


(*R*,*R*)-**13** see ref. 14. (*S*,*S*)-**14** see ref. 15 (*R*)-**15** see ref. 16

Scheme 5. Additional chiral ligands used in this work.

The experiments performed with chiral ligands, **13**-**15** afforded good efficiencies both with regard the yield of **6**, as well as a moderate increase in the enantioselectivity of the reaction. (In particular, entries 4, 6, 10 and 12 in Table 3 compare favorably with most enantiomeric relations presented in Table 2). Interestingly, the enantioselectivities observed in both THF and toluene solvents were quite similar.

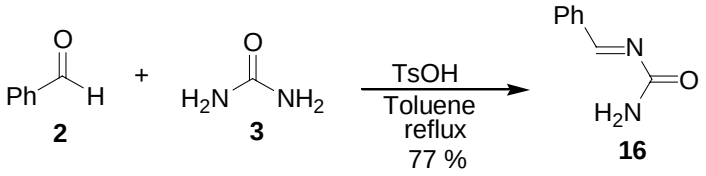
Table 3. Asymmetric Biginelli reaction in the presence of chiral ligands **13**-**15**



Entry	Chiral Ligand (20 mol %)	M	Solvent	Yield (%)	e. r.[a]	Configuration of major product[b]
1	(*R*,*R*)-**13**	Ce	THF	93	62:38	*R*
2	(*S*,*S*)-**14**	Ce	THF	57	50:50	---
3	(*R*)-**15**	Ce	THF	90	41:59	*S*
4	(*R*,*R*)-**13**	Ce	Toluene	88	64:36	*R*
5	(*S*,*S*)-**14**	Ce	Toluene	55	50:50	---
6	(*R*)-**15**	Ce	Toluene	87	40:60	*S*
7	(*R*,*R*)-**13**	In	THF	90	58:42	*R*
8	(*S*,*S*)-**14**	In	THF	59	46:54	*S*
9	(*R*)-**15**	In	THF	85	44:56	*S*
10	(*R*,*R*)-**13**	In	Toluene	84	60:40	*R*
11	(*S*,*S*)-**14**	In	Toluene	51	44:56	*S*
12	(*R*)-**15**	In	Toluene	86	41:59	*S*

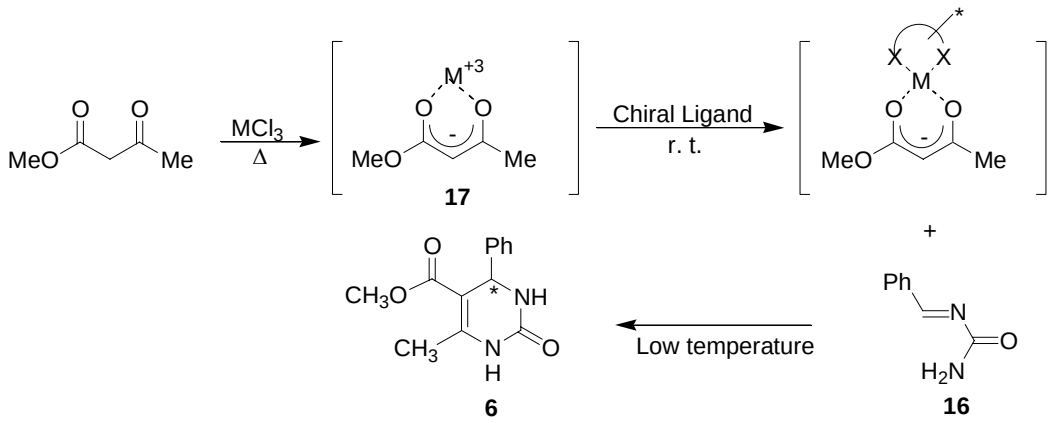
[a] Quantified by HPLC. [b] The assignment of the absolute configuration was carried out by comparison with the retention times reported in ref. 12.

Looking for another alternative to increase the enantiomeric excess of the reaction, benzylidene urea **16**, presumably one of key intermediates in the mechanism,[17] was synthesized according to the reaction shown in Scheme 6.



Scheme 6. Preparation of the benzylidene urea **16**.

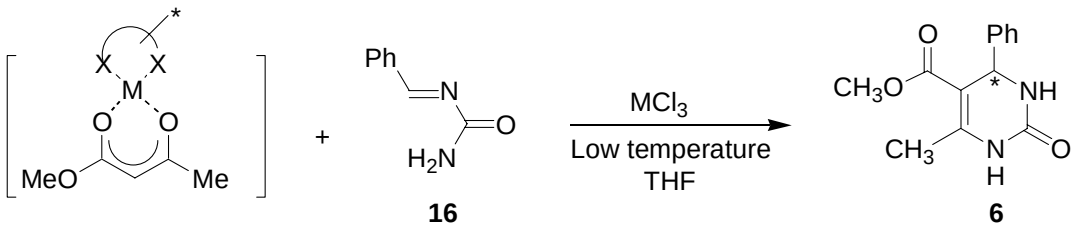
Furthermore, in order to carry out the condensation reaction at low temperature, preformation of the enolate derived from methyl acetoacetate was accomplished by use of Lewis acids. The subsequent reaction between freshly prepared enolate **17** with the chiral ligands **13** and **14** at low temperature was anticipated to facilitate the transfer of the chiral information, necessary to make the process enantioselective. It was expected that the addition of benzyldene urea **16** to the preformed enolate **17** could, under kinetic control, increase the enantioselectivity of the overall process (Scheme 7). The results of this modification are collected in Table 4.



Scheme 7. Modified Biginelli reaction protocol.

The enantiomeric ratios obtained by this experimental modification (Table 4) reveal that stereoselectivity is indeed higher when the temperature of the reaction is lower (compare entries 1, 3, 5 and 7 with entries 2, 4, 6 and 8 in Table 4). Although this experimental modification to the normal Biginelli conditions presents some disadvantages such as longer reaction times, the encouraging enantiomeric excesses (up to 40 % *ee* in entry 1, Table 4), pave the road for further improvements in this important reaction.

Table 4. Enantioselectivity and yields of modified Biginelli reaction in the presence of chiral ligands **13** and **14**



Entry	Chiral Ligand (20 mol %)	M	Temp (^oC)	Time (h)	Yield (%)	e. r.[a]	Configuration of major product[b]
1	(*R*,*R*)-**13**	Ce	-78 → 0	36	25	70:30	*R*
2	(*R*,*R*)-**13**	Ce	25	24	86	65:35	*R*
3	(*S*,*S*)-**14**	Ce	-78 → 0	36	21	37:63	*S*
4	(*S*,*S*)-**14**	Ce	25	24	79	40:60	*S*
5	(*R*,*R*)-**13**	In	-78 → 0	36	12	67:33	*R*
6	(*R*,*R*)-**13**	In	25	24	61	62:38	*R*
7	(*S*,*S*)-**14**	In	-78 → 0	36	18	40:60	*S*
8	(*S*,*S*)-**14**	In	25	24	84	43:57	*S*

[a] Quantified by HPLC. [b] The assignment of the absolute configuration in product **6** was carried out by comparison with retention time data reported in ref. 12.

Conclusions

$CeCl_3$ and $InCl_3$ Lewis acid activators can efficiently catalyze the Biginelli condensation reaction, both in THF and toluene as solvent. The use of chiral ligands **7**-**9**, incorporating active amino groups, did not induce good enantioselectivities in the product, and actually proceeded in low yield owing to undesired condensation of the ligand with benzaldehyde. When the reaction was performed with chiral ligands **10**-**15**, it was possible to improve the enantiomeric excesses to values in the 18 to 28 % ee range. An experimental modification based in the preformation of the key precursors and subsequent reaction under kinetic control (low temperature) gave enantiomeric excesses as high as 40 %. This modification of the Biginelli condensation reaction offers a promising alternative for the preparation of enantiomerically enriched dihydropyrimidinones.

Experimental Section

General Procedures. All reactions were carried out with reagent grade solvents. Commercially available reagents were used without further purification. $CeCl_3$ and $InCl_3$ were dried at 130 ^oC at 25 mmHg for 3 h. Melting points were obtained on a melting point apparatus with capillary tubes and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on 400 MHz for ^1H, 100 MHz for ^{13}C) NMR spectrometers in DMSO-d_6 solutions. Chemical shifts are given as δ values (ppm) and coupling constants (*J*) in Hz. HPLC: instrument fitted with UV-Vis detector and a chiral stationary phase of chirobiotic T for the determination of the enantiomeric ratios.

General procedure for the synthesis of dihydropyrimidinone (6). A solution of methyl acetoacetate (260 mg, 2 mmol), benzaldehyde (212 mg, 2 mmol) and urea (156 mg, 2,6 mmol) in 10 mL of THF or toluene was heated at 70 °C in the presence of 20 mol % of the Lewis acid under nitrogen atmosphere until consumption of the methyl acetoacetate and benzaldehyde reagents (between 12-24 h). Following this, the reaction was left standing at room temperature and then at 0 ^oC until formation of a precipitate that was filtered and recrystallized from hot ethanol and washed with 20 mL of cold water to give the pure product **6** (494 mg, 92% yield), mp. 211-212 °C (lit.[1a] mp. 209-212 °C). ^1H NMR (DMSO-d_6, 400 MHz): δ 8.08 (s, 1H), 7.30 (m, 5H), 5.70 (s, 1H), 5.39 (d, *J* = 2.7 Hz, 1H), 3.62 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 165.7, 152.0, 148.5, 144.6, 128.3, 127.2, 126.0, 98.9, 53.7, 50.7, 17.7.

Synthesis of benzylidene urea (16). In a 100 mL round flask provided with magnetic stirrer and Dean-Stark trap were placed benzaldehyde (1 g, 9,44 mmol), urea (0.68 g, 11.33 mmol) and a catalytic amount of *p*-toluensulfonic acid in 40 mL of toluene. The reaction mixture was heated for 4 h until no additional water formation was observed. The reaction mixture was concentrated and the resulting solid was filtered to give 1,04 g (77 % yield) of the desired product **16**, with mp. 202-205 ^oC. (lit.[18] mp. 204-205 ^oC). This product was dried in the oven with vacuum during 4 h (50 ^oC at 20 mmHg) before its use. IR (KBr) 3440, 3300, 1677, 1450, 1381, 1315, 1145, 1052, 866 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 7.8 (s, 5H), 6.8 (d, *J* = 8 Hz, 2H), 3.4 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 160.3, 158.3, 143.1, 128.7, 127.6, 126.5.

General procedure for the synthesis of dihydropyrimidinone 6 by the modified Biginelli protocol. A solution of methyl acetoacetate (260 mg, 2 mmol) in 15 mL of anhydrous THF was placed in a round bottom flask, treated with 2 mmol of $InCl_3$ and was stirred at 70 ^oC for 1 h. Following this, the chiral ligand (2 mmol) dissolved in 2 mL of the same solvent was added dropwise. The reaction mixture was stirred for 30 minutes at room temperature and then left standing at -78 ^oC for 30 min. At this point, benzylidene urea **16** (0.3 g, 2 mmol) suspended in 10 mL of the same solvent was slowly added to the indium enolate. The reaction is allowed to 12

Determination of the absolute configuration and measurement the enantiomeric purity of dihydropyrimidinone 6. The determination of the enantiomeric excess was performed by means of HPLC, which was standardized and validated with the data reported by Kappe et al.[7c] The separation of the corresponding enantiomers was obtained with a chiral column Chirobiotic T and using a mixture of acetonitrile:water (70:30) as mobile phase with 1.0 flow of ml/min. The retention time of the (*R*) enantiomer was 3.20 min and the retention time of for the (*S*) enantiomer was 5.35 min.

Acknowledgements

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References

1. For a recent review, see: (a) Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879. See also: (b) Atwal, K. S.; Swanson, B. N.; Unger, S. E.; Floyd, D. M.; Moreland, S.; Hedberg, A.; O'Reilly, B. C. *J. Med. Chem.* **1991**, *34*, 806. (c) Rovnyak, G. C.; Atwal, K. S.; Hedberg, A; Kimball, S. D.; Moreland, S.; Gougoutas, J. Z.; O'Reilly, B. C.; Schwartz, J.; Malley, M. F. *J. Med. Chem.* **1992**, *35*, 3254. (d) Barrow, J. C.; Nantermet, P. G.; Selnick, H. G.; Glass, K. L.; Rittle, K. E.; Gilbert, K. F.; Steele, T. G.; Homnick, C. F.; Freindeger, R. M.; Ransom, R. L.; O'Malley, S. S.; Olah, T. V.; Ellis, J. D.; Barrish, A.; Kassahun, K.; Leppert, P.; Nagarathnam, D.; Forray, C. *J. Med. Chem.* **2000**, *43*, 2703. (e) Kappe, C. O.; Shishkin, O. V.; Uray, G.; Verdino, P. *Tetrahedron* **2000**, *56*, 1859.
2. Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360.
3. (a) Atwal, K. S.; Rovnyak, G. C.; O'Relly, B. C.; Schwartz, J. *J. Org. Chem.* **1989**, *54*, 5898. (b) Barluenga, J.; Tomas, M.; Ballesteros, A.; Lopez, L. A. *Tetrahedron Letters* **1989**, *30*, 4573. (c) See also, Juaristi, E. *Introduction to Stereochemistry and Conformational Analysis*, Wiley: New York, 1991.
4. O'Relly, B. C.; Atwal, K. S. *Heterocycles* **1987**, *26*, 1185.
5. Mizuno, N.; Misuno, M. *Chem. Rev.* **1998**, *98*, 199.
6. (a) Grover, G. J.; Dzwonczyk, S.; McMullen, D. M.; Normandin, D. E.; Parham, C. S.; Sleph, P. G.; Moreland, S. *J. Cardiovasc. Pharmacol.* **1995**, *26*, 289. (b) Rovnyak, G. C.; Kimball, S. D.; Beyer, B.; Cucinotta, G.; DiMarco, J. D.; Gougoutas, J.; Hedberg, A.; Malley, M.; McCarthy, J. P.; Zhang, R.; Moreland, S. *J. Med. Chem.* **1995**, *38*, 119. (c) Kappe, C. O.; Fabian, W. M. F. *Tetrahedron* **1997**, *53*, 2803.

7. (a) Kappe, C. O.; Uray, G.; Roschger, P.; Lindner, W.; Kratky, C.; Keller, W. *Tetrahedron* **1992**, *48*, 5473. (b) Kleidernigg, O. P.; Kappe, O. *Tetrahedron: Asymmetry* **1997**, *8*, 2057. (c) Wang, F.; Loughlin, T.; Dowling, T.; Bicker, G.; Wyvratt, J. *J. Chromatogr. A* **2000**, *872*, 279. (d) Schnell, B.; Strauss, U. T.; Verdino, P.; Faber, K.; Kappe, C. O. *Tetrahedron: Asymmetry* **2000**, *11*, 1449.
8. (a) Mukaiyama, T.; Ohno, T. Han, J. S.; Kobayashi, S. *Chem. Lett.* **1991**, 949. (b) Loh, T.-P.; Chua, G-L.; Vittal, J. J.; Wong, M-W. *Chem. Commun.* **1998**, 861. (c) Li. X-R.; Loh, T.-P. *Tetrahedron* **1999**, *55*, 10789. (d) Muñoz-Muñiz, O.; Quintanar-Audelo, M.; Juaristi, E. *J. Org. Chem.* **2003**, *68*, 1622-1625. (e) Ranu, B. C.; Hajra, A.; Jana, U. *Org. Lett.* **1999**, *1*, 1141. (f) Ranu, B. C.; Hajra, A.; Jana, U. *J. Org. Chem.* **2000**, *65*, 6270.
9. (a) Juaristi, E.; Escalante, J.; León-Romo, J. L.; Reyes, A. *Tetrahedron: Asymmetry* **1998**, *9*, 715. (b) Juaristi, E.; León-Romo, J. L.; Reyes, A.; Escalante, J. *Tetrahedron: Asymmetry* **1999**, *10*, 2441.
10. (a) Juaristi, E.; Murer, P.; Seebach, D. *Synthesis* **1993**, 1243. (b) Overberger, G. C.; Marullo, N. P.; Hiskey, R. G. *J. Am. Chem. Soc.* **1961**, *83*, 1374. (c) Hulst, R.; de Vries, K.; Feringa, B. L. *Tetrahedron: Asymmetry* **1994**, *5*, 699. (d) Hirose, T.; Naito, K.; Shitara, H.; Nohira, H.; Baldwin, B. W. *Tetrahedron: Asymmetry* **2001**, *12*, 375.
11. (a) Nozaki, H.; Aratani, T.; Noyori, R. *Tetrahedron Lett.* **1968**, *26*, 2087. (b) Nozaki, H.; Aratani, T.; Noyori, R. *Tetrahedron* **1971**, *27*, 901. (c) Gallagher, D. J.; Wu, S.; Nikolic, N. A.; Beak, P. *J. Org. Chem.* **1995**, *60*, 8148. (d) Weisenburger, G. A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 12218. (e) Park, Y. S.; Beak, P. *J. Org. Chem.* **1997**, *64*, 1574. (f) Weisenburger, G. A.; Faibish, N. C.; Pippel, D. J.; Beak, P. *J. Am. Chem. Soc.* **1999**, *121*, 9522. (g) Barberis, C.; Voyer, N. *Synlett* **1999**, 1106. (h) Hoppe, D.; Woltering, M. J.; Oestreich, M.; Fröhlich, R. *Helvetica Chimica Acta* **1999**, *82*, 1860. (i) Wiberg, K. B.; Bailey, W. F. *J. Mol. Struct.* **2000**, *556*, 239. (j) Wiberg, K. B.; Bailey, W. F. *Tetrahedron Lett.* **2000**, *41*, 9365.
12. Kleidernigg, O. P.; Kappe, C. O. *Tetrahedron: Asymmetry* **1997**, *8*, 2057.
13. Cf. Arend, M.; Risch, N. *Synlett* **1997**, *8*, 974.
14. Juaristi, E.; Hernández-Rodríguez, M.; López-Ruiz, H.; Aviña, J.; Muñoz-Muñiz, O.; Hayakawa, M.; Seebach, D. *Helv. Chim. Acta* **2002**, *85*, 1999.
15. (a) Sowinsky, A. F.; Whitesides, G. M. *J. Org. Chem.* **1979**, *44*, 2369. (b) Kiyoshi, M.; Hirokazu, L.; William, L. J. *Heterocycles* **2000**, *52*, 1015.
16. Arai, Y.; Masuda, T.; Masaki, Y. *J. Chem. Soc., Perkin Trans 1* **1999**, 2165.
17. Kappe, C. O. *J. Org. Chem.* **1997**, *62*, 7201.
18. Dalton, D. R. ; Foley, H. G. *J. Org. Chem.* **1973**, *38*, 4200.