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Asymmetric heterocyclocondensation of polyfluorinated aldehydes catalysed by a chiral titanium(IV) complex

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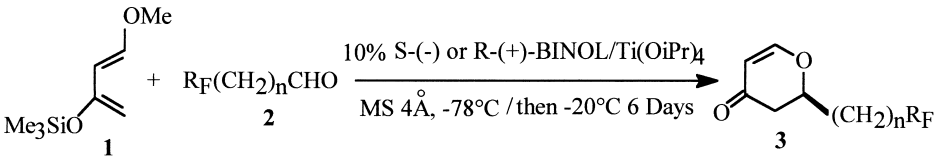
Abstract

The Binol/Ti(O*i*Pr)$_4$ chiral titanium complex catalyses the asymmetric cyclocondensation of polyfluoroalkylaldehydes with the Danishefsky's diene leading to chiral polyfluoroalkyl dihydropyrenones with high enantiomeric excesses. © 2000 Published by Elsevier Science Ltd.

Since its description by Danishefsky,[1] the Lewis acid catalysed diene aldehyde cyclocondensation (LACDAC) has proven to be one of the most reliable reactions for preparing pyranosic synthons. The reaction of 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's diene) **1** and an appropriate aldehyde in the presence of a Lewis acid provides a general route to the 6-substituted pyr-2-en-4-ones (Scheme 1).



Scheme 1.

In a previous paper,[2] we reported the heterocyclocondensation of **1** with polyfluoroalkylaldehydes such as $R_F(CH_2)_nCHO$ **2**,[3] leading to the 6-polyfluoroalkylpyr-2-en-4-ones in good yields. The present one deals with the asymmetric synthesis of such pyrenones.

Asymmetric hetero cyclocondensations from achiral aldehydes and achiral dienes catalysed by chiral Lewis acids have been frequently reported in the literature: the most efficient were vanadium

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β-diketonates,[4] acyloxyborane[5] or oxazaborolidine[6] derivatives, copper-bisoxazoline complexes,[7] lanthanide derivatives[8] a naphtol or binaphtol complexes of aluminium[9] or titanium.[10,11] With linear aldehydes such as octanal, the best results were obtained by using a chiral complex prepared from 1,1′-bi-2-naphthol (BINOL) and titanium halides or alkoxides.[11a]

According to the procedure used for asymmetric aldol condensation and glyoxylate-ene reaction,[12] one equiv. of the freshly distilled polyfluoroalkylaldehyde **2** and 1.2 equiv. of the Danishefsky's diene **1** in dichloromethane were successively added at –78°C to 0.1 equiv. of the chiral titanium(IV) complex prepared beforehand in situ by heating *R*(+) or *S*(–)-1,1′-bi-2-naphthol and $Ti(OiPr)_4$ in 2:1 ratio in the presence of 4 Å molecular sieves in dichloromethane. Chiral chromatographic monitoring (column Lipodex-E, permethyled β-cyclodextrin)[13] showed that the polyfluoroaldehydes were completely consumed after six days at –20°C (i.e. more slowly than with their hydrocarbon analogues) and also testified to the high enantioselectivity in the synthesis of the 6-*F*-alkylpyr-2-en-4-ones **3**. Oven-drying activation of the molecular sieves neither improve the yields nor the enantiomeric excess, thus all reactions were run without activating the molecular sieves. The results are summarized in Table 1.

Table 1
Asymmetric cycloaddition of diene **1** and *F*-alkylaldehydes **2**

	R_F	n	Catalyst [a]	Yields % [b]	ee % [c]	[α] [d]	Mp-Cp °C [e]
3a	C_6F_{13}	2	(+)	35	95	-45	29-35
3b	C_6F_{13}	3	(+)	48	92	-40	30-38 (39)
3c	C_6F_{13}	3	(-)	46	95	+39.5	32-39
3d	C_6F_{13}	4	(+)	60	95	-29	32-45 (49)
3e	C_6F_{13}	4	(-)	58	90	+30	31-43
3f	C_8F_{17}	4	(+)	50	98,5	-25	42-57 (54)
3g	C_8F_{17}	4	(-)	53	95	+25.5	41-56
3h	CF_3	0	(+)	0			
3i	C_3F_7	0	(+)	0			

a) **(+):** prepared from R(+)-BINOL and Ti(O-iPr)4 - **(-) :** prepared from S(-)-BINOL and Ti(O-iPr)4
b) yields in isolated products.
c) enantiomeric excess of isolated products determined by chiral GC.
d) At 25°C in CH_2Cl_2 with λ=589.3 nm.
e) Mp melting point, Cp clearing point, in brackets the melting point of racemic **3**.

The reaction yield decreases when decreasing the methylene chain length in **2** and for $n=0$ no cycloaddition product was observed, as previously shown with an achiral catalyst.[2]

All (+) 6-poly-fluoroalkylpyr-2-en-4-ones **3** were obtained from *R*(+)-BINOL/$Ti(OiPr)_4$ complexes, and their enantiomers from the enantiomeric *S*(–)-BINOL/$Ti(OiPr)_4$ complexes.[14] The higher the absolute rotatory power [α], the shorter the *F*-alkyl chain (**3d**–**g**) and the closer to the chiral centre (**3a**–**c**).

Enantiomerically pure **3** did not exhibit sharp melting points: they melted in a 7 to 15°C temperature range with a mesophase evidenced by a polarized light microscopy study.[15] This unexpected behaviour was found reversible and was not observed with racemic **3**: they melted sharply at slightly higher temperatures.

In conclusion, this paper reports the first asymmetric heterocyclocondensation of the Danishefsky's diene and per(poly)fluoro aldehyde catalysed by a chiral Lewis acid prepared from binaphthol and titanium isopropoxide. A particularly attractive feature of this approach is that a large variety of asymmetric dihydropyrones is directly accessible in unprecedentedly high level of enantiomeric excess giving synthetic access to *F*-alkyl pyranosic compounds with potential liquid crystal properties.[16]

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References

1. (a) Danishefsky, S. J. *Acc. Chem. Res.* **1981**, *14*, 400–406. (b) Danishefsky, S. J.; De Ninno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 15–23. (c) Danishefsky, S. J. *Aldrichimica Acta* **1986**, *19*, 59–68. (d) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380–1419.
2. Lévêque, L.; Le Blanc, M.; Pastor, R. *Tetrahedron Lett.* **1997**, *38*, 6001–6002.
3. Lévêque, L.; Le Blanc, M.; Pastor, R. *Tetrahedron Lett.* **1998**, *39*, 8857–8860.
4. Togni, A. *Organometallics* **1990**, *9*, 3106–3113.
5. (a) Gao, Q.; Maruyama, T.; Mouri, M.; Yamamoto, M. *J. Org. Chem.* **1992**, *57*, 1951–1952. (b) Gao, Q. Z.; Ishihara, K.; Maruyama, T.; Mouri, M.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 979–988. (c) Gao, Q. Z.; Ishihara, K.; Maruyama, T.; Mouri, M.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 4555.
6. (a) Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, *33*, 6907–6910. (b) Motoyama, Y.; Mikami, K. *Chem. Commun.* **1994**, 1563–1564.
7. Ghosh, A. K.; Mathivanan, P.; Cappiello, J.; Krishnan, K. *Tetrahedron: Asymmetry* **1996**, *7*, 2165–2168.
8. (a) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1–30. (b) Mikami, K.; Kotera, O.; Motoyama, Y.; Sakaguchi, H. *Synlett* **1995**, 975–977. (c) Arai, Y.; Masuda, T.; Masaki, Y.; Shiro, M. *Tetrahedron: Asymmetry* **1996**, *7*, 1199–1204.
9. (a) Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310–312. (b) Graven, A.; Johannsen, M.; Jorgensen, K. A. *Chem. Commun.* **1996**, 2373–2374.
10. Hanamoto, T.; Furuno, H.; Sugimoto, Y.; Inanaga, J. *Synlett* **1997**, 79–80.
11. (a) Keck, G. E.; Li, X. Y.; Krishnamurthy, D. *J. Org. Chem.* **1995**, *60*, 5998–5999. (b) Motoyama, Y.; Terada, M.; Mikami, K. *Synlett* **1995**, 967–968. (c) Matsukawa, S.; Mikami, K. *Tetrahedron: Asymmetry* **1997**, *8*, 815–816. (d) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357–389.
12. (a) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949. Mikami, K.; Yajima, T.; Terada, M.; Uchimaru, T. *Tetrahedron Lett.* **1993**, *34*, 7591–7594. (b) Mikami, K.; Yajima, T.; Terada, M.; Kato, E.; Maruta, M. *Tetrahedron: Asymmetry* **1994**, *5*, 1087–1090. (c) Motoyama, Y.; Terada, M.; Mikami, K. *Synlett* **1995**, 967–968. (d) Mikami, K.; Yajima, T.; Takasaki, T.; Matsukawa, S.; Terada, M.; Uchimaru, T.; Maruta, M. *Tetrahedron* **1996**, *52*, 85–98.
13. All chiral GC analyses were performed on a HP-5890 A chromatograph, equipped with a 25 m×0.25 mm Lipodex® E column and with a FID detector. As an example, at a fixed temperature of 140°C, and with a 100 kPa inlet pressure of nitrogen, the retention times t_R were 23 min for (+)**3f** and 24.15 min for (–)**3g**.
14. General procedure: a mixture of (*R*)-(+)-BINOL or (*S*)-(–)-BINOL (28.6 mg, 0.1 mmol), 1 M Ti(*O*-*i*Pr)$_4$ in CH_2Cl_2 (50 μL, 0.05 mmol), CF_3CO_2H (3 μl, 0.5 M in CH_2Cl_2) and powdered (or oven-dried) 4 Å molecular sieves (200 mg) in ether (2.0 ml) was heated at reflux for 1 h. The red–brown mixture was cooled to room temperature, and the *F*-alkyl aldehyde **2** (75.0 mg, 0.5 mmol) was added. The mixture was stirred for 5 min and cooled to –78°C, Danishefsky's diene (103 mg, 0.59 mmol) was added, and the contents were stirred for 10 min and placed in a freezer at –20°C for six days. Then, saturated $NaHCO_3$ (0.5 ml) was added; the mixture was stirred for 1 h and filtered through a plug of Celite®. The organic layer was separated and the aqueous layer was extracted with ether (6 ml). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The crude product

was redissolved in CH_2Cl_2 (6 ml) and cooled to 0°C. Trifluoroacetic acid (0.025 ml) was added to this solution. The mixture was then stirred for 1 h and saturated aqueous $NaHCO_3$ (3 ml) was added. After stirring for 10 min the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (15 ml), and the combined organic layers were dried over Na_2SO_4 and concentrated. The crude material was purified by liquid chromatography on silica gel, with pentane:acetone (4:1) as an eluent. Spectrometric data are the same as for racemic **3** (see Ref. 2). For example, for compound **3d**: IR (cm^{-1}, KBr film) 1770 (νC=O), 1600 (νC=C), 1300–1100 (νCF). ^{1}H NMR: (200 MHz, $CDCl_3$): 1.6 (m, 8H), 2.4 (m, 2H), 4.4 (m, 1H), 5.35 (d, J = 8.7 Hz, 1H), 7.3 (d, J = 8.7 Hz, 1H). ^{13}C NMR: 188.4, 163.2, 107.3, 79.2, 41.9, 34.2, 31.0 (t, $^3J_{CF} = 23.3$ Hz), 24.5, 20.0. ^{19}F NMR: -81.2, -114.8, -122.4, -123.4, -124.0, -126.6.

15. For example, the microscopic observation of the repeated heating and cooling of a sample of compounds **3f** or **3g** shows the reversible appearance and disappearance of a mesophase (not yet characterized) around 50°C, the liquid phase occurring at 56–57°C (the melting point of the racemic analogue was found at 54°C). D.S.C. and polarized microscopy studies are in progress.
16. (a) Zur, C.; Miller, A. O.; Miethchen, R. *Liq. Cryst.* **1998**, *24*, 695–699. (b) Zur, C.; Miller, A. O.; Miethchen, R. *J. Fluorine Chem.* **1998**, *90*, 67–76. (c) Hein, M.; Miethchen, R. *Tetrahedron Lett.* **1998**, *39*, 6679–6682.