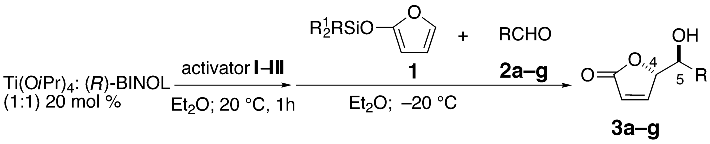
Highly Enantioselective Aldol Reaction with 2-Trimethylsilyloxyfuran: The First Catalytic Asymmetric Autoinductive Aldol Reaction**

Magali Szlosek and Bruno Figadère*

We report herein the first quantitative and highly enantioselective autoinductive aldol reaction (up to 96% *ee*) between 2-trimethylsilyloxyfuran (TMSOF) **1a** and an achiral aldehyde **2**. The origin of homochirality of biomolecules (such as α-amino acids and sugars) remains a puzzling question.[1] It is now well accepted that physical factors like circulary polarized light can induce chirality in molecules through photosynthetic procedures.[2, 3] However the *ee* values so obtained are very low and cannot be directly correlated with the enantiomeric purity of the known biomolecules. Thus, Soai et al. have shown that amplification of a slight enantiomeric imbalance in molecules could be due to an asymmetric autocatalytic system, and this was proved to be the case for the 1,2-addition of organozinc reagents to 2-methylpyrimidine-5-carbaldehyde.[4] Since then, only catalytic asymmetric 1,2-addition of nucleophiles on aldehydes has been shown to be either autocatalyzed[4–6] or autoinduced[7–9] by the chiral product of the reaction, apart from several Diels–Alder reactions which were reported to be autoinduced by the cyclic adduct.[10]

We recently disclosed that **1a** adds to aldehyde **2a** to afford the corresponding butenolides **3a** with good selectivity (76 to 90% *ee*) when the (*R*)-(1,1′-bi-2-naphthol)$_2$Ti complex ((*R*)-BINOL$_2$Ti) was used (Scheme 1).[11] In order to improve both the chemical yield and the *ee* value of this reaction, we studied the use of a second chiral ligand, as an activator, based on the chiral ligand acceleration concept.[12–15] The catalysts were prepared in situ at 20°C in Et$_2$O by mixing 20 mol% of Ti(O*i*Pr)$_4$, (*R*)-BINOL, and the activator **I**–**III** in a 1:1:1 ratio for 1 hour. Then 1 equivalent of **2a** (0.5 mmol) followed by 1.5 equivalents of **1a** were added. Butenolides **3a** so obtained were analyzed by ^{1}H NMR spectroscopy in the presence of chiral europium salt (Eu(hfc)$_3$). It should be noted that, in the presence of only Ti(O*i*Pr)$_4$, **1a** does not add to **2a**.[11] The first experiment shows that **1a** added to **2a**, with (*R*)-BINOL$_2$Ti as the catalyst gave, after 2 hours, **3a** with low d.r. (53:47), a good *ee* value (87%) for the major *syn* product, and moderate 50% yield (this is quite often encountered in such reactions[13–15]). Under the same reaction conditions, but at lower temperature (−78°C), the *ee* value of the *syn* butenolide **3a** was significantly increased (96%) but to the detriment of the chemical yield (10%). When (−)-TADDOL was added to the Ti(O*i*Pr)$_4$ and (*R*)-BINOL (1:1:1 ratio), a similar yield and only a slight decrease in the *ee* value (70 relative to 87%) were observed. We thought that these conditions may correspond to a mismatch case and so performed the same reaction with (+)-TADDOL and observed a quantitative reaction with formation of the same major diastereomer (*syn*) **3a** (d.r. = 70:30) with 82% *ee*. In all cases the absolute configuration of the major isomer **3a** was *S*,*S* as determined by comparison with related products.[11] The last two experiments gave good evidence that the (*R*)-BINOLTi(−)-TADDOL is less active than the (*R*)-BINOLTi(+)-TADDOL complex which is probably formed,[13] and that the chiral induction is controlled by (*R*)-BINOL. Again a temperature effect was observed and, in the presence of a 1:1:1 mixture of Ti(O*i*Pr)$_4$, (*R*)-BINOL, and (+)-TADDOL at −78°C, **1a** added to **2a** to afford the major *syn* butenolide **3a** with a better *ee* value (90 relative to 82%) but lower chemical yield (40 relative to 99%).



Scheme 1. Activators: **I** = (R)-BINOL, **II** = (−)-TADDOL, **III** = (+)-TADDOL; **1a**: R^1 = R = Me; **1b**: R^1 = Me and R = *t*Bu; **1c**: R^1 = Ph and R = *t*Bu; **2a**–**g**: see Table 2.

It was now possible to perform the aldol reaction with a "reluctant" aldehyde, heptadecanal **2b**, in 55% yield with a 75:25 d.r. and with an *ee* value of 75% for the major *syn* isomer **3b** (see supporting information). So far, it is clear that BINOL is necessary for the aldol reaction to occur, and that addition of a second aliphatic alcohol (TADDOL for instance) could form an even more reactive complex with both titanium(IV) and BINOL. It was therefore important to check if the product of the reaction could interact with the catalytic species. This investigation led us to describe the first autoinductive aldol reaction (Scheme 1 and Table 1).

The first experiment shows that, in the presence of 20 mol% of the catalyst (*R*)-BINOL$_2$Ti and 5 mol% of

Table 1. 2-TMSOF (**1a**) addition to octanal (**2a**) in the presence of the BINOL$_2$Ti complex at −20°C in Et$_2$O.

Entry	activator[a]	yield of **3a** [%]	*syn*:*anti* ratio	*ee* of *syn* (abs. conf.)
1	(*S*,*S*)-**3a**[b]	99	70:30	> 96 (*S*,*S*)[b]
2	(*R*,*R*)-**3a**[c]	99	70:30	40 (*S*,*S*)
3	(*RS*,*SR*)-**3a**[d]	57	60:40	92 (*S*,*S*)
4	none[e]	99	70:30	70 (*S*,*S*)
5	none[f]	90	60:40[g]	> 96 (*S*,*S*)

[a] 5 mol% solution; [b] (*S*,*S*)-**3a** with 82% *ee*, and thus, the *ee* value for the butenolide **3a** is 96.88%, as calculated in ref. [8]; [c] (*R*,*R*)-**3a** with >96% *ee*; [d] racemic *anti* butenolide **3a**; [e] after 24 hours; [f] with addition of a mixture of 2-TMSOF (**1a**) and octanal (**2a**) in four portions (ratios of **2a** to **1a** = 0.032:0.049, 0.093:0.139, 0.125:0.188, and 0.250:0.375 mmol with 15, 15, 30, and 60 min. of delay, respectively); [g] the *anti* product (4*R*,5*S*)-**3a** with an *ee* value of 90%.

---

[*] Priv.-Doz. Dr. B. Figadère, Dr. M. Szlosek
Laboratoire de Pharmacognosie, associé au CNRS (BIOCIS)
Université Paris-Sud, Faculté de Pharmacie
rue Jean-Baptiste Clément, 92296 Châtenay-Malabry (France)
Fax: (+33) 1-46-83-53-99
E-mail: Bruno.Figadere@cep.u-psud.fr

[**] The authors wish to thank J. C. Jullian for his help in NMR experiments, Dr. X. Franck for stimulating discussions, and Prof. R. Hocquemiller for his continuous interest in this study. Thanks are due to M.J. Vega Capela for the experiments with heptadecanal. L. Tache and B. Mbeninack are acknowledged for the preparation of the (*R*,*R*)-**2** isomer.

Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.

(*S*,*S*)-**3a** (82% *ee*), the reaction was quantitative with an *ee* value of 96% determined for all *syn* butenolide **3a** (which corresponds to 96.9% *ee* for the newly formed butenolide, see reference [8] for calculations). In the presence of the minor enantiomer (*R*,*R*)-**3a**, a much lower *ee* value was observed for **3a**, as expected (40% *ee*, entry 2, Table 1). These results suggested that the major chiral products formed in this reaction are incorporated into the active chiral catalyst to form new catalysts which are more active due to a ligand accelerating effect (leading to higher chemical yields) and which have a better asymmetric inductive effect (higher *ee* values observed). However, when 5 mol% of racemic *anti* isomer **3a** was introduced into a 20 mol% (*R*)-BINOL$_2$Ti catalyst solution followed by **2a** and then **1a**, the expected butenolides **3a** were obtained in 57% yield as a 60:40 *syn*:*anti* mixture, with an *ee* value of 92% for the major *syn* product. This important result shows that there is not a significant increase in the chemical yield (57 relative to 50%) or the *ee* value (92 in comparison with 87%). This is, furthermore, in accordance with the result obtained in the absence of added aldol, therefore, we assume that the *anti* isomer has a negligible influence on the course of the reaction.

We then examined the amplification of the *ee* values when the reaction is performed in a stepwise manner. Indeed, by adding the mixture of reagents **1a** and **2a** in four portions (ratios of **2a**:**1a** were 0.032:0.049, 0.093:0.139, 0.125:0.188, and 0.250:0.375 mmol with 15, 15, 30, and 60 minutes of delay, respectively) to the reaction medium containing 20 mol% of the (*R*)-BINOL$_2$Ti catalyst, we observed the formation of **3a** with excellent yield (90 relative to 50%) with an *ee* value of 96% after only 2 hours at −20°C! This result may be rationalized as follows: After the first addition of 6.5 mol% of the mixed **1a** and **2a**, the major *syn* butenolide **3a** so formed can be incorporated into the new catalyst and gives identical results to those observed when *syn* **3a** is first added to the reaction mixture. The amplification can be shown by comparing the *ee* value obtained in the one addition protocol (87%) with the value of 96% obtained after the "stepwise" experiment. Indeed, these results are consistent with an autoinduced process with amplification[16] of the *ee* value of the product. In this last experiment, the *ee* value of the *anti* aldol **3a** was measured (90% *ee*), and its absolute configuration was assumed to be (4*R*,5*S*) by comparison with the sign of the specific rotation of the dihydrogenated compound with epimuricatacin.[17] Thus, epimerization at the allylic position of the *anti* aldol **3a** (for example, through Et$_3$N treatment[18]) would eventually lead to the formation of the major *syn* aldol compound **3a**.

Several other aldehydes (**2c**–**g**) were added with **1a** in four portions as above (Scheme 1 and Table 2). It is noteworthy that aldehydes possessing either isolated double bonds, such as **2c**, or a long saturated aliphatic chain, like **2f**, gave the corresponding aldols with excellent yields and high *ee* values (**3c** and **3f**, 94 and 96% *ee*, respectively). In the case of α,β-unsaturated aldehyde **2e** (Entry 3), we were delighted to observe that the aldols **3e**, which resulted from 1,2-addition, were the major compounds formed (ratio of 1,2- to 1,4-addition[19] = 70:30). However, in this latter case the major product is now the *anti* isomer, and the *syn* isomer only had an *ee* value of 52%; the absolute configuration of the major enantiomer was determined as (4*S*,5*S*). In the case of the aromatic aldehyde **2d**, the reaction was again quantitative (Entry 2) and the major *anti* aldol **3d** had an *ee* value of 90%, whereas the *syn* product only had a 60% *ee* value (absolute configurations have not yet been determined). The reverse diastereoselectivity, as well as a lower enantioselectivity in these two cases may be rationalized by including electronic factors. Finally, when a bulky aldehyde, such as cyclohexylcarbaldehyde **2g**, is involved (Entry 5) a 70:30 mixture of the *syn*:*anti* aldols **3g** was obtained in 70% yield. The major *syn* product had an *ee* value of 71%, whereas the *anti* isomer showed a 79% *ee* value. Thus, as far as chemical yields and *ee* values are concerned, the reaction seems sensitive to steric hindrance, which is often the case with aldol reactions.[20]

In an attempt to improve the d.r., we turned our attention to the use of different silyloxyfurans, 2-*tert*-butyldimethylsilyloxyfuran (TBDMSOF) **1b**[21] and 2-*tert*-butyldiphenylsilyloxyfuran (TBDPSOF) **1c**. When these silyloxyfurans were separately mixed with **2a** in the presence of a (*R*)-BINOL$_2$Ti complex solution (20 mol%) in Et$_2$O cooled to −20°C, no reaction occurred (after 12 hours). However, when the reaction was performed with either **1b** or **1c** in a stepwise fashion at −20°C (ratios of **2a** to **1b** or **1c** = 0.032:0.049, 0.093:0.139, 0.125:0.188, and 0.250:0.375 mmol with 30, 60, 90, and 180 min delay, respectively), the aldols **3a** were obtained in 60% yield as a 70:30 *syn*:*anti* mixture with *ee* values of 97% for the (4*S*,5*S*) isomer and 86% for the (4*R*,5*S*) isomer for the reaction involving **1b**, and 45% yield as a 86:14 *syn*:*anti* mixture with a value of 82% *ee* for the (4*S*,5*S*) isomer, for the reaction with **1c** (results not optimized). It is worth noting that the d.r. was improved from 60:40 to 70:30 and finally 86:14 by using the more bulky reagents.

In conclusion, the reaction of **1a** with achiral aldehydes in the presence of BINOL/titanium(IV) complexes is the first catalytic asymmetric autoinductive aldol reaction reported.[22] Both yields and enantiomeric excess values are good to

Table 2. Additions of various couples of 2-TMSOF (**1a**) and aldehyde (**2c**–**g**) in the presence of the BINOL$_2$Ti complex at −20°C in Et$_2$O.

Entry	aldehyde	time [h]	yield [%] **3c**–**g**	*syn*:*anti* ratio	*ee* of *syn* (abs. conf.)	*ee* of *anti* (abs. conf.)
1	*E*-decen-4-al (**2c**)	2	99	53:47	94 (*S*,*S*)	90 (*R*,*S*)
2	benzaldehyde (**2d**)	6	99	24:76	60 (ND)[a]	90 (ND)[a]
3	*E*-nonen-2-al (**2e**)	2	70[b]	30:70	52 (*S*,*S*)	24 (*R*,*S*)[c]
4	tridecanal (**2f**)	6	80[d]	60:40	>96 (*S*,*S*)	90 (*R*,*S*)
5	cyclohexylcarbaldehyde (**2g**)	2	70	65:35	71 (*S*,*S*)	79 (*R*,*S*)

[a] ND = not determined; [b] 1,4-addition = 30%; [c] measured on the hydrogenated product by comparison with the specific rotation of an authentic compound; [d] when addition is performed in one portion: yield = 20%, d.r. = 60:40, *ee* = 90% (*syn S*,*S*).

excellent, which is unusual for such reactions. The stepwise procedure allows the highest *ee* values to be obtained together with high chemical yields.[23] These results show the wide scope of such aldol reactions, with certain limitations for bulky and/or conjugated aldehydes (results not optimized). The use of bulkier trialkylsilyloxyfurans slightly improved the d.r.; further optimization studies are in progress. Furthermore these findings may provide some evidence for amplification of *ee* values of biomolecules (by chemical reactions) in the chemical origins of life. Indeed, conditions for aldol reactions may have been found in prebiotic systems. More experiments are nevertheless needed to set a mathematical model for such a mechanism.[24] Such a process could also be involved in other asymmetric reactions.[23, 25, 26]

Received: November 12, 1999 [Z14266]

---

[1] K. Soai, T. Shibata, H. Morioka, K. Choji, *Nature* **1995**, *378*, 767.

[2] a) N. P. M. Huck, W. F. Jager, B. de Lange, B. L. Feringa, *Science* **1996**, *273*, 1686; b) Y. Zhang, G. B. Schuster, *J. Org. Chem.* **1995**, *60*, 7192.

[3] O. Buchardt, *Angew. Chem.* **1974**, *86*, 222; *Angew. Chem. Int. Ed. Engl.* **1974**, *136*, 179.

[4] T. Shibata, J. Yamamoto, N. Matsumoto, S. Yonekubo, S. Osanai, K. Soai, *J. Am. Chem. Soc.* **1998**, *120*, 12157.

[5] T. Shibata, H. Morioka, T. Hayase, K. Choji, K. Soai, *J. Am. Chem. Soc.* **1996**, *118*, 471.

[6] T. Shibata, T. Hayase, J. Yamamoto, K. Soai, *Tetrahedron: Asymmetry* **1997**, *8*, 1717.

[7] A. H. Alberts, H. Wynberg, *J. Am. Chem. Soc.* **1989**, *111*, 7265.

[8] L. Shengjian, J. Yaozhong, M. Aiqiao, Y. Guishu, *J. Chem. Soc. Perkin Trans 1* **1993**, 885.

[9] H. Danda, H. Nishikawa, K. Otaka, *J. Org. Chem.* **1991**, *56*, 6740.

[10] a) F. Rebiere, O. Riant, H. B. Kagan, *Tetrahedron: Asymmetry* **1990**, *1*, 199; b) D. P. Heller, D. R. Goldberg, W. D. Wulff, *J. Am. Chem. Soc.* **1997**, *119*, 10551.

[11] M. Szlosek, X. Franck, B. Figadère, A. Cavé, *J. Org. Chem.* **1998**, *63*, 5169.

[12] D. J. Berrisford, C. Bolm, K. B. Sharpless, *Angew. Chem.* **1995**, *107*, 1159; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1059.

[13] K. Mikami, S. Matsukawa, T. Volk, M. Terada, *Angew. Chem.* **1997**, *109*, 2936; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2768.

[14] K. Mikami, S. Matsukawa, *Nature* **1997**, *385*, 613.

[15] M. Chavarot, J. J. Byrne, P. Y. Chavant, J. Pardillos-Guindet, Y. Vallée, *Tetrahedron: Asymmetry* **1998**, *9*, 3889.

[16] a) C. Puchot, O. Samuel, E. Dunach, S. Zhao, C. Agami, H. B. Kagan, *J. Am. Chem. Soc.* **1986**, *108*, 2353; b) N. Oguni, Y. Matsuda, T. Kaneko, *J. Am. Chem. Soc.* **1988**, *110*, 7877; c) M. Kitamura, S. Okada, S. Suga, R. Noyori, *J. Am. Chem. Soc.* **1989**, *111*, 4028; d) C. Girard, H. B. Kagan, *Angew. Chem.* **1998**, *110*, 3088; *Angew. Chem. Int. Ed.* **1998**, *37*, 2922; e) B. L. Feringa, R. A. van Delden, *Angew. Chem.* **1999**, *111*, 3624; *Angew. Chem. Int. Ed.* **1999**, *38*, 3418.

[17] B. Figadère, J.-C. Harmange, A. Laurens, A. Cavé, *Tetrahedron Lett.* **1991**, *32*, 7539.

[18] B. Figadère, C. Chaboche, J. F. Peyrat, A. Cavé, *Tetrahedron Lett.* **1993**, *34*, 8093.

[19] H. Nishikori, K. Ito, T. Katsuki, *Tetrahedron: Asymmetry* **1998**, *9*, 1165.

[20] S.-I. Kiyooka, H. Maeda, M. Abu Hena, M. Uchida, C.-S. Kim, M. Horiike, *Tetrahedron Lett.* **1998**, *39*, 8287.

[21] G. Rassu, F. Zanardi, L. Battistini, E. Gaetani, G. Casiraghi, *J. Med. Chem.* **1997**, *40*, 168.

[22] A. H. Alberts, H. Wynberg, *J. Chem. Soc. Chem. Commun.* **1990**, 453.

[23] S. Kobayashi, Y. Fujishita, T. Mukaiyama, *Chem. Lett.* **1990**, 1455.

[24] E. F. Kogut, J. C. Thoen, M. A. Lipton, *J. Org. Chem.* **1998**, *63*, 4604.

[25] M. Pichon, J. C. Jullian, B. Figadère, A. Cavé, *Tetrahedron Lett.* **1998**, *39*, 1755.

[26] D. A. Evans, M. C. Kozlowski, J. A. Murry, C. S. Burgey, K. R. Campos, B. T. Connell, R. J. Staples, *J. Am. Chem. Soc.* **1999**, *121*, 669.

Interconversion between μ-η^2,η^2-C_{60} and μ_3-η^2,η^2,η^2-C_{60} on a Carbido Pentaosmium Cluster Framework**

Kwangyeol Lee, Chang Hoon Lee, Hyunjoon Song, Joon T. Park,* Hong Young Chang, and Moon-Gun Choi

Exohedral metallofullerenes have recently attracted much attention concerning the effects of metal coordination on the chemical and physical properties of C_{60}.[1] Most approaches to forming metal complexes have been based on metal–C_{60} π-complex chemistry, which has resulted in η^2-C_{60}, μ-η^2,η^2-C_{60}, and μ_3-η^2,η^2,η^2-C_{60} ligands in monometallic (for most metals),[2] bimetallic (Re_2, Ru_2, Ir_2),[3] and metal cluster complexes (Ru_3, Os_3, Ru_5C, Ru_6C, $PtRu_5C$),[4, 5] respectively. Metal clusters can potentially accommodate all these C_{60} bonding modes, but the interaction of C_{60} with cluster frameworks has been, thus far, dominated by the face-capping cyclohexatriene-like bonding mode, μ_3-η^2,η^2,η^2-C_{60}. The μ-η^2,η^2-C_{60} bonding mode has never been observed on a cluster framework, although it has been postulated as an intermediate for the transformation of $[Os_3(CO)_{11}(\eta^2\text{-}C_{60})]$ to $[Os_3(CO)_9(\mu_3\text{-}\eta^2,\eta^2,\eta^2\text{-}C_{60})]$ by loss of carbonyl ligands.[5c] The interconversion among the three kinds of the C_{60} ligands remains to be established in the area of C_{60}–metal cluster chemistry. We have recently observed the elusive μ-η^2,η^2-C_{60} bonding mode on an Os_5C cluster framework, and furthermore demonstrated that the two C_{60} bonding modes μ-η^2,η^2 and μ_3-η^2,η^2,η^2 are interconvertible.

Reaction of $[Os_5C(CO)_{12}(PPh_3)(NCMe)_2]$ with C_{60} in refluxing ClC_6H_5 produced a mixture of **1** and **2** (see the Experimental Section). The conversion of **1** into **2** could be effected by heating a solution of **1** in ClC_6H_5 at 80 °C under 1 atm of carbon monoxide. Upon thermolysis at 132 °C, **2** was cleanly reconverted into **1** by loss of a carbonyl ligand (Scheme 1).

$[Os_5C(CO)_{11}(PPh_3)(\mu_3\text{-}\eta^2,\eta^2,\eta^2\text{-}C_{60})]$ **1**

$[Os_5C(CO)_{12}(PPh_3)(\mu\text{-}\eta^2,\eta^2\text{-}C_{60})]$ **2**

The solid-state structure of **1** is isomorphous to that of the ruthenium analogue $[Ru_5C(CO)_{11}(PPh_3)(\mu_3\text{-}\eta^2,\eta^2,\eta^2\text{-}C_{60})]$.[4b] The structure of **2** (Figure 1) reveals a very intriguing feature

---

[*] Prof. J. T. Park, Dr. K. Lee, C. H. Lee, H. Song
Department of Chemistry & Center for Molecular Science
Korea Advanced Institute of Science and Technonogy
Taejon, 305-701 (Korea)
Fax: (+82) 42-869-2810
E-mail: jtpark@kaist.sorak.ac.kr
H. Y. Chang, Prof. M.-G. Choi
Department of Chemistry, Yonsei University
Seoul, 120-749 (Korea)

[**] We are grateful to the Korea Science Engineering Foundation (KOSEF) for financial support (project no. 1999-1-122-001-5) of this research and a postdoctoral fellowship to K.L. The X-ray diffraction studies were carried out at the X-ray Crystallographic Laboratory of Yonsei University, which was supported in part by KOSEF.

Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.