Catalytic Asymmetric Vinylogous Mukaiyama-Aldol (CAVM) Reactions: The Enolate Activation

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The Catalytic Asymmetric Vinylogous Mukaiyama (CAVM) reactions of various aldehydes with dienolate **1** using different enolate activations (CuF·(*S*)-TolBinap, *t*-BuOCu·(*S*)-Tol-Binap, and various chiral nonracemic ammonium fluorides derived from cinchona alkaloids) are described. These reactions proved to be highly regioselective leading exclusively to the α-aldol products in good yields and poor to good enantioselectivities.

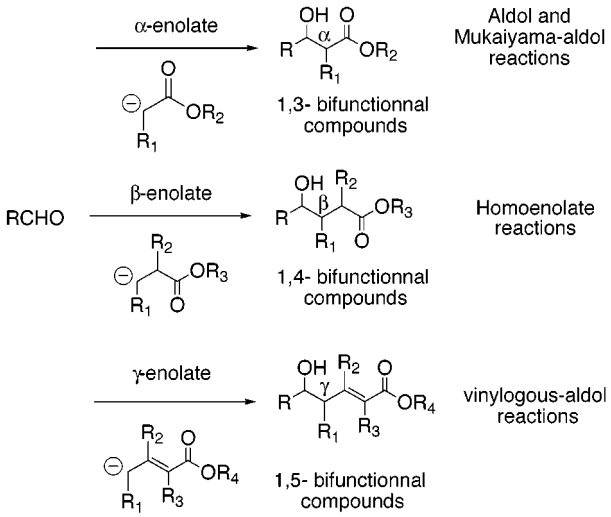
Introduction

The vinylogous aldol reaction,[1] the reaction of an aldehyde with a γ-dienolate, allows the direct formation of 1,5 difunctional compounds (Scheme 1). However, the development of this reaction was longer hampered by the formation of a mixture of both α (kinetic) and γ (thermodynamic) products (Scheme 2).[2]

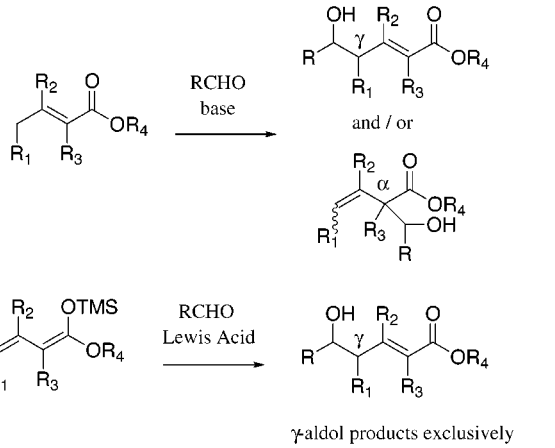
These problems of regioselectivity in direct vinylogous aldol reactions were, only very recently, overcome by using the bulky Lewis acid ATPH.[3] Another solution has previously appeared, in the early seventies, using silyl dienolates as nucleophiles. In the presence of a suitable Lewis acid, these nondirect vinylogous Mukaiyama-aldol reactions allowed for the exclusive formation of the γ-aldol products (Scheme 2).[4]

Although the vinylogous Mukaiyama-aldol reactions have found wide interest in the total synthesis of natural products,[5−10] to the best of our knowledge, no asymmetric version of this reaction was described when this work was initiated. However, related, but mechanistically quite different, asymmetric and catalytic asymmetric vinylogous aldol reactions using aceto-acetate derivatives,[1,11] or cyclic dienolates,[1,12] and asymmetric vinylogous Mannich reactions[1,13] have been previously reported.

Scheme 1



Scheme 2



In the aim of constructing the side-chain of Octalactin A,[14] we embarked on the catalytic asymmetric vinylogous Mukaiyama-aldol (CAVM) using silyl-dienolate **1**.[15] In a previous communication,[16] we have reported our preliminary results on catalytic asymmetric vinylogous reactions using either an aldehyde or enolate activation (Scheme 3).

(1) For a comprehensive review, see: Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929.
(2) (a) Dugger, R. W.; Heathcock, C. H. *J. Org. Chem.* **1980**, *45*, 1181. (b) Lei, B.; Fallis, A. *Can. J. Chem.* **1991**, *69*, 1450.
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(4) (a) Mukaiyama, T.; Ishida, A. *Chem. Lett.* **1975**, 319. (b) Fleming, I.; Goldhill, J.; Paterson, I. *Tetrahedron Lett.* **1979**, *34*, 3205.
(5) Evans, D. A.; Cameron, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497.
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(7) Paterson, I.; Smith, J. D. *J. Org. Chem.* **1992**, *57*, 3261.
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(9) Mouné, S.; Niel, G.; Busquet, M.; Eggleston, I.; Jouin, P. *J. Org. Chem.* **1997**, *62*, 3332.
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(11) (a) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669. (b) Singer, A. R.; Carreira, E. M. *J. Am. Chem. Soc.* **1995**, *117*, 12360. (c) Krüger, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837. (d) Pagenkopf, B. L.; Krüger, J.; Stojanovic, A.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 3124. (e) Kim, Y.; Singer, A. R.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1261. (f) Krüger, J.; Carreira, E. M. *Tetrahedron Lett.* **1998**, *39*, 7013.

10.1021/jo015567s CCC: $20.00
Published on Web 05/12/2001

Scheme 3

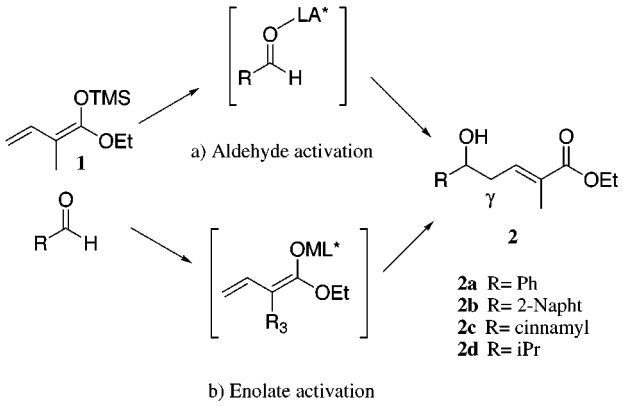


Table 1. CAVM Reactions of Aldehydes with 1 Using 10% of CuF·(*S*)-Tol-Binap at Room Temperature

aldehyde	product	yield (%)	ee (%)	γ/α ratio
benzaldehyde	**2a**	80	70	100:0
2-naphthaldehyde	**2b**	70	48	100:0
cinnamaldehyde	**2c**	35	56	100:0
isobutyraldehyde	**2d**	68	77	100:0

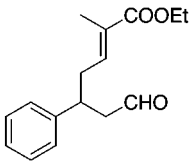
In this paper, we would like to report our efforts and results in developing asymmetric catalytic systems for the enolate activation.

Results and Discussion

When this project was initiated, our major concerns were (1) the possibility of α-alkylation when generating a metal-dienolate (vide supra) and (2) the asymmetric induction from the dienolate to the prochiral aldehyde.

To our delight, using Carreira's catalyst CuF·(*S*)-Tol-Binap,[11c] the γ-aldol products were obtained exclusively[17] at room temperature in good yields and enantioselectivities with both aromatic and aliphatic aldehydes (Table 1).

With cinnamaldehyde, the yield proved to be rather low (35%) due to the presence in the crude material of a 1:1 ratio (^{1}H NMR) of **2c** and the unstable aldehyde **3** which results from the 1,4 addition of the silyl-dienolate on cinnamaldehyde.



3 (e. e. non determined)

Attempts to optimize the reaction either by changing the ligand (in the model reaction with benzaldehyde,

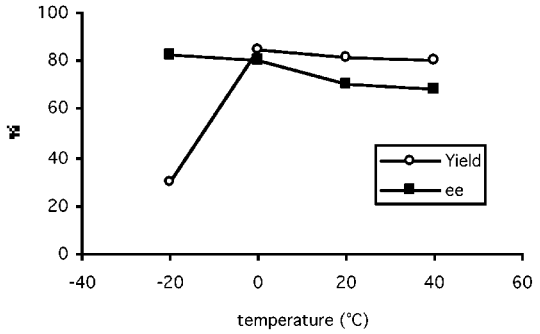
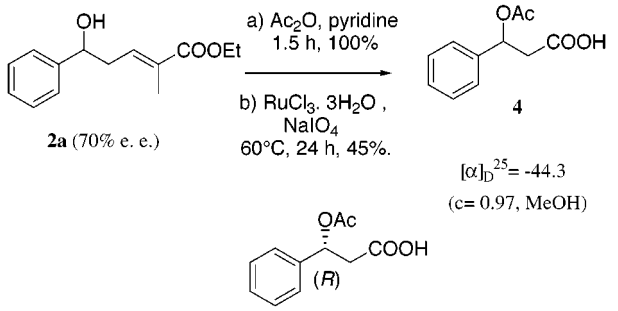


Figure 1. Influence of the temperature on yield (○) and enantioselectivity (■) in the model reaction of **1** with benzaldehyde in the presence of 10% of CuF·(*S*)-TolBinap.

Scheme 4



Lit[18]: $[\alpha]_D^{25}$= +63.8 (c= 5, MeOH)

Binap gave 75% ee but in 42% yield, and among different bis-oxazolines, the best results were obtained with bis-(isopropyloxazolinyl)pyridine but with bad efficiency: 35% yield and 15% ee) or conditions (solvents, concentration, ligand amount, etc.) proved to be unsuccessful.

As shown in Figure 1, temperature has a small effect on the enantioselectivities, but yields decreased rapidly at temperature below −30 °C. The optimum temperature between enantioselectivities and chemical efficiency was found to be approximately 0 °C.

To determine the absolute configuration of adducts **2**, compound **2a** (R=Ph) was converted in two steps into the previously described compound **4**.[18] A rotation of −44.3 (for 70% ee) compares favorably with the rotation of +63.8 for the enantiomerically pure (*R*) compound. Consequently, adducts **2a**−**c** obtained with CuF·(*S*)-Tol-Binap were tentatively assigned to the (*S*) configuration (Scheme 4).

Examining the relationship[19] between ee (ligand) and ee (product), a small negative nonlinear effect (−)-NLE was observed for low ee (ligand) and a very slight positive

(12) (a) Pichon, M.; Jullian, J.-C.; Figadère, B.; Cavé, A. *Tetrahedron Lett.* **1998**, *39*, 1755. (b) Dudot, B.; Micouin, L.; Baussane, I.; Royer, J. *Synthesis* **1999**, 688. (c) Szlosek, M.; Figadère, B. *Angew. Chem., Int. Ed.* **2000**, *39*, 1799−1801. (d) Casiraghi, G.; Rassu, G.; Zanardi, F.; Battistini, L. *Adv. Asymmetric Synth.* **1998**, *3*, 113−189.

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(16) Bluet, G.; Campagne, J.-M. *Tetrahedron Lett.* **1999**, *40*, 221−222.

(17) The absence of α-alkylation products was checked by NMR on the crude material by synthesising[25a] the corresponding α-aldol products.

(18) (a) Stühmer, W.; Frey, H.-H. *Arch. Pharm. Ber. dtsch. Pharm. Ges.* **1953**, *286*, 26. (b) Santaniello, E.; Ferraboschi, P.; Grisenti, P.; Manzocchi, A.; Trave, S. *Gazz. Chim. Ita.* **1989**, *119*, 581. (c) Reed, P. E.; Katzenellenbogen, J. A. *J. Med. Chem.* **1991**, *34*, 1162.

(19) (a) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2923. (b) Heller, D.; Drexler, H.-J.; Fischer, C.; Buschmann, H.; Baumann, W.; Heller, B. *Angew. Chem., Int. Ed.* **2000**, *39*, 495. (c) Girard, C.; Kagan, H. B. *Can. J. Chem.* **2000**, *78*, 816. (d) Mikami, K.; Terada, M.; Korenaga, T.; Matsumoto, Y.; Ueki, M.; Angelaud, R. *Angew. Chem., Int. Ed.* **2000**, *39*, 3532 and references cited therein.

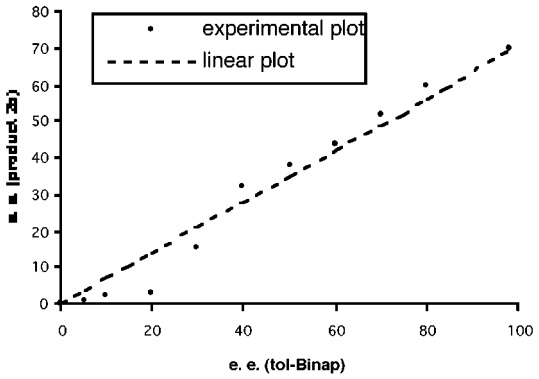


Figure 2. Relationship between ee (Tol-Binap) and ee (**2a**) in the CAVM reaction between benzaldehyde and 1 in the presence of 10% of CuF·(*S*)-Tol-Binap.

nonlinear effect (+)-NLE was observed for the higher (>40%) ee (ligand) (Figure 2).

Such an intriguing shape has been previously observed,[20] and is supported by a mathematical calculation described by Kagan and co-workers,[19a] which suggests a nonlinear curve for ML_4 complexes. Such behavior implies a rather complicated mechanism whereby some aggregation is believed to take place.

Nevertheless, according to the mechanism described by Carreira for the asymmetric aldol reactions of acetoacetate derivatives,[11d] a catalytic cycle can be postulated for the CAVM reactions.

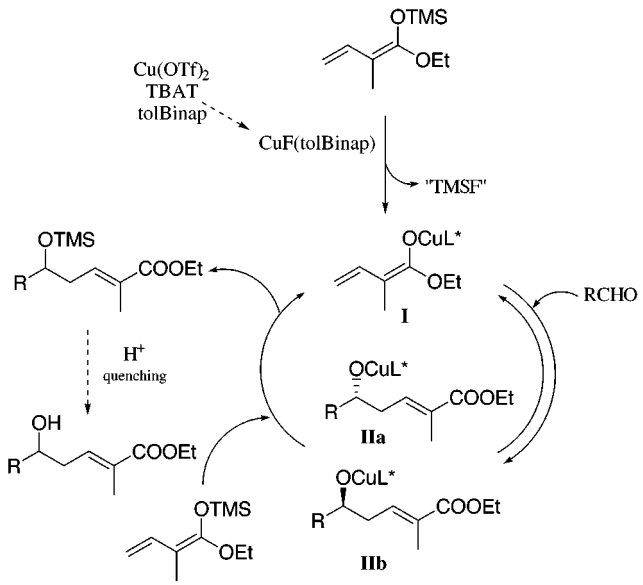
In the catalytic cycle, CuF·(*S*)-Tol-Binap (generated in situ from TBAT,[21] $Cu(OTf)_2$, and (*S*)-Tol-Binap) acts as a precatalyst and generates the copper dienolate **I** which is the real catalytic species. This species, or further species generated thereof, can then react with the aldehyde to create the vinylogous copper alcoholate **II** as a mixture of two diastereomers **IIa** and **IIb**. This alcoholate further reacts with the silyl dienolate to regenerate the catalytic species **I** and the vinylogous aldol product is formed protected as the TMS ether (Scheme 5).

However, compared to Carreira's reactions,[11d] two major changes should be pointed out. First, the reactions are run at room temperature, under thermodynamic conditions: consequently the influence of the retro-aldol in the enantiodiscrimination can be questioned.[22] Second, contrary to Carreira's dienolate,[11c–f] there is no oxygen atom present in our dienolate that could participate in transmitting the chiral information from the copper dienolate to the prochiral aldehyde.

To gain an insight into the reaction mechanism and understand the factors that govern the enantiodiscrimination, we tried to play around the catalytic cycle.

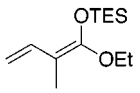
First, since the synthesis of TBAT[21] was reported to be quite unreliable,[21b] we tried to develop a more convenient precatalyst for these reactions. It was found that tBuO·Cu (S)-tol-Binap[23] (generated in situ from NaOtBu, CuCl and (S)-tol-Binap) proved to be an efficient pre-

Scheme 5



catalyst but surprisingly the enantioselectivity was much lower (50% ee) than that observed using CuF·(S)-Tol-Binap) (70% ee). This result highlights the fact that CuF·(S)-Tol-Binap (or salts generated during its formation) does not only play the role of precatalyst but seems to interfere in the catalytic cycle.

We attempted to modify the structure of the dienolate by increasing the size of the silyl group hoping to change the course of the reaction. The synthesis of higher derivatives of **1** proved to be difficult, and only the triethylsilyl derivative **1b** could be isolated in reasonable yield. Catalytic asymmetric vinylogous Mukaiyama-aldol reactions using this dienolate were somewhat slower (with benzaldehyde, the vinylogous aldol product was isolated, after 24 h, in 40% yield) and a small enantioselectivity decrease (60% ee) could be observed.



1b

The influence of the retro-aldol reaction in the enantiodiscrimination was then questioned. According to the isoinversion principle,[22] when two transient diastereomeric species are in a dynamic equilibrium, the stereoselectivity can be controlled at two levels (Scheme 6). At the "first selection level" the two diastereomeric intermediates [Dia1] and [Dia2] (in our case, **IIa** and **IIb**) are formed from the reaction between the prochiral starting material B and the chiral substrate A* (in our case, the prochiral aldehyde and the copper dienolate **I**). At the "second selection level" competition between conversion of the intermediates to the products Ent1 and Ent2 and then reversion to the starting materials (A* and B) can modify the initial selection.

Usually the iso-inversion principle can be observed by plotting an Eyring diagram (ln(Ent1/Ent2) vs 1/*T*). However in our case, the temperature domain (−30 °C

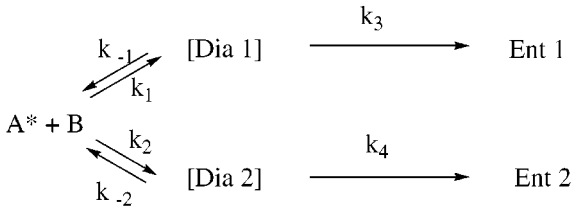
(20) (a) Puchot, C.; Samuel, O.; Duñach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc.* **1986**, *108*, 2353. (b) Tanaka, K.; Matsui, J.; Suzuki, H. *J. Chem. Soc., Perkin Trans. 1* **1993**, 153.

(21) TBAT= tetrabutylammonium triphenyldifluorosilicate. (a) Pilcher S. A.; Ammon, H. L.; Deshong P. *J. Am. Chem. Soc.* **1995**, *117*, 5166. (b) Handy, C. J.; Lam, Y.-F.; Deshond, P. *J. Org. Chem.* **2000**, *65*, 3542.

(22) (a) Buschman, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 477. (b) Hale, K. J.; Ridd, J. H. *J. Chem. Soc., Perkin Trans. 2* **1995**, 357. (c) Hale, K. J.; Ridd, J. H. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1601. (d) Gypser, A.; Norrby, P. *J. Chem. Soc., Perkin Trans. 2* **1997**, 939.

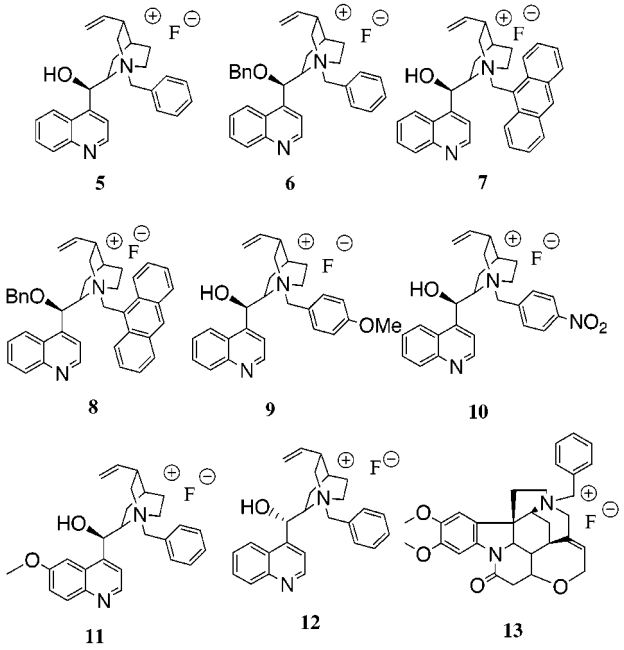
(23) Appella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9473.

Scheme 6



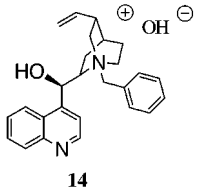
to 40 °C) is too small to get any clear conclusion.[24] Nevertheless, the possibility that the enantiodiscrimination could be controlled during the "second selection level" led us to investigate the case where chiral nonracemic "naked"[25] dienolates are involved. To test this hypothesis, we turned our attention to chiral nonracemic ammonium fluorides derived from cinchona alkaloids.[26] Ammonium fluoride **5** derived from cinchonidine was first synthesized. The CAVM reaction of isobutyraldehyde with dienolate **1** in the presence of 10% of catalyst **5** led to the formation of the vinylogous aldol product **2d** in 70% yield and 20% ee thus confirming our initial hypothesis (Scheme 7).

This somewhat encouraging result led us to tune the electronic and steric properties of the catalyst. Consequently catalysts **6**−**10** derived from cinchonidine, **11** derived from quinine, **12** derived from cinchonine and **13** derived from brucine were synthesized.



However, by using these catalysts with different structural, steric, and electronic properties, enantioselectivity could not be raised to useful levels (Table 2). The best result, with isobutyraldehyde, was obtained with catalyst **5** in 30% ee, performing the reaction at 0 °C.[27] The ammonium fluoride **12** derived from cinchonine, pseudo-enantiomer of **5**, indeed gave the opposite enantiomer.

Quite surprisingly, the corresponding ammonium hydroxide **14** was also found to be an excellent catalyst (quantitative yields in the reaction of **1** with isobutyraldehyde) for these reactions but again with low levels of enantioselectivity (<30% ee).



Scheme 7

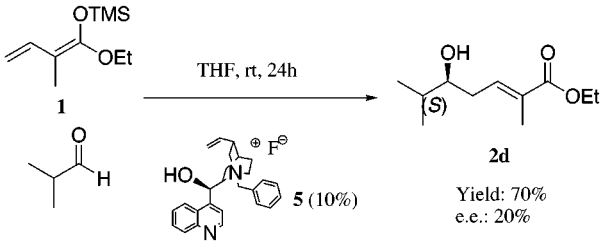


Table 2. CAVM Reactions of Isobutyraldehyde with 1 Using 10% of Various Chiral Nonracemic Ammonium Fluorides at Room Temperature

ammonium fluoride	yield (%)	γ/α ratio	ee (%)	configuration of the major enantiomer
5	70	100: 0	20 (30)[a]	(*S*)
6	25	100: 0	26	(*S*)
7	15	100: 0	18	(*S*)
8	<10%	100: 0	n. d.	(*S*)
9	54	100: 0	17	(*S*)
10	61	100: 0	14	(*S*)
11	42	100: 0	11	(*S*)
12	35	100: 0	18	(*R*)
13	30	100: 0	11	(*R*)

[a] Reaction carried out at 0 °C.

Conclusion

In conclusion, among the different catalytic asymmetric enolate activations (CuF·(*S*)-TolBinap, *t*-BuOCu·(*S*)-TolBinap, and various chiral nonracemic ammonium fluorides derived from cinchona alkaloids) tested, the Carreira's catalyst CuF·(*S*)-Tol-Binap proved to be the more efficient in terms of enantioselectivity and led us to propose an efficient synthesis of the Octalactin side-chain constructed in five steps starting from isobutyraldehyde (Scheme 8).[28] The key step was a CAVM reaction, using 10% Carreira's catalyst at 0 °C, to introduce the C13 chirality in 80% ee and 90% yield.

(24) To suppress the second step (copper alcoholate quenching with the silyldienolate) and see the influence on the enantioselectivity, the reaction was run with a stoichiometric amount of precatalyst tBuOCu·(*S*)-Tol-Binap, and, indeed, a small influence on the enantioselectivity could be observed (60% ee to be compared to the 50% ee obtained with 10% of the precatalyst) showing the negative influence of this second step on the global enantioselectivity.

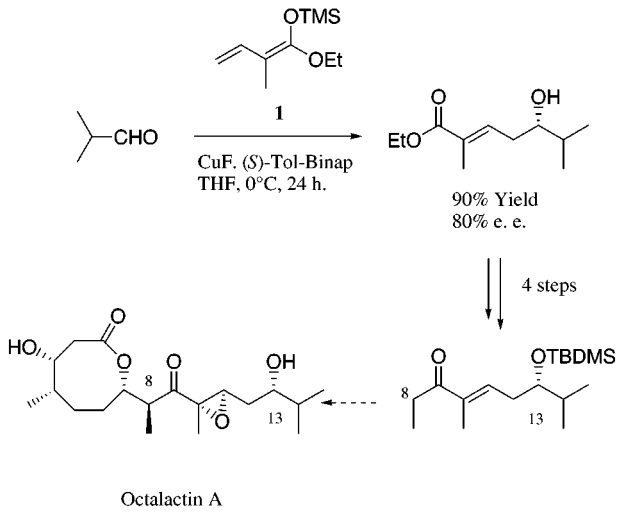
(25) (a) Hertler, W. R.; Reddy, G. S.; Sogah, D. Y. *J. Org. Chem.* **1988**, *53*, 3532. (b) Noyori, R.; Nishida, I.; Sakata, J. *J. Am. Chem. Soc.* **1981**, *103*, 2106. (c) Noyori, R.; Nishida, I.; Sakata, J. *J. Am. Chem. Soc.* **1983**, *105*, 1598.

(26) Ando, A.; Miura, T.; Tatematsu, T.; Shioiri, T. *Tetrahedron Lett.* **1993**, *34*, 1507 and references cited herein.

(27) During the course of this work, a highly enantioselective Mukaiyama-aldol reaction using chiral ammonium fluoride **8** was described: Horikawa, M.; Busch-Petersen J.; Corey, E. J. *Tetrahedron Lett.* **1999**, *40*, 3843.

(28) Bluet, G.; Campagne, J.-M. *Synlett* **2000**, 221.

Scheme 8



Octalactin A

The study of CAVM reactions involving other substituted and nonsubstituted silyldienolates is currently under investigation.

Experimental Section

General. Unless otherwise specified, the reactions were carried out in oven-dried glassware under an argon atmosphere. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, or at 250 MHz, in $CDCl_3$ as solvent: chemical shifts are given in ppm. Column chromatography was performed on silica gel 230−400 mesh. THF was distilled from sodium/benzophenone. Diisopropylamine and Chlorotrimethylsilane were freshly distilled over CaH_2 prior to use. Copper-(II) trifluoromethanesulfonate, purchased from ACROS was dried over P_2O_5 under vacuum prior to use. (*S*)-Tol-Binap was purchased from STREM. TBAT was synthesized according to the procedure described by Deshong[21](also commercialy available from Aldrich). Elemental analyses were carried out by "laboratoire de micro-analyse ICSN - Gif/Yvette". IR Spectra were recorded with an FTIR spectrometer. Mass spectra were recorded by chemical ionization (CI) on a AEI MS-9 mass spectrometer with isobutane and otherwise as indicated. Optical rotations were determined operating at the sodium D line. HPLC analyses were conducted using CHIRALCEL OD or OJ column with solvent mixtures of hexane/2-propanol and flow rates as indicated.

1-Ethoxy-1-(trimethylsilyloxy)-2-methyl-1,3 Butadiene (1). To a solution of diisopropylamine (22 mmol, 3 mL) in THF (50 mL) at −20 °C was added ^{n}BuLi (22 mmol, 14 mL, 1.6 M in hexane). After 30 min at −20 °C, the solution was cooled to −78 °C and HMPA (22 mmol, 3.8 mL) was added slowly. After 30 min, ethyl *trans*-but-2-enoate (20 mmol, 2.5 mL) was added dropwise. The mixture was stirred for a further 15 min and quenched with methyl iodide (22 mmol, 1.4 mL). The solution was allowed to warm to 0 °C over 1h and then recooled to −78 °C. A solution of LDA prepared as above at 0 °C was added dropwise over 20 min at −78 °C via a syringe pump. After 15 min, the mixture was quenched with chlorotrimethylsilane (30 mmol, 4 mL) in THF (4 mL) added over 15 min via a syringe pump. The solution was allowed to warm to room temperature and stirred for 1.5 h and the solvent was evaporated in vacuo in a cold bath. Then pentane (100 mL) was added to the residue, and the resulting mixture was filtered on Celite to remove the precipitated HMPA−lithium chloride complex and evaporated in *vacuo*. The residue was distilled under reduced pressure using a Kugelrhor apparatus (40−45 °C/1.5 mmHg) to give **1** as an inseparable mixture of isomers *Z* and *E* (70:30) (2.5 g, 63%, clear yellow oil). The spectroscopic data of the compound **1** were in accordance with the litterature. [15]

Typical Reaction Procedure for the Preparation of Vinylogous Aldol Products 2a−d Using Carreira's Catalyst. A mixture of copper (II) trifluoromethanesulfonate (0.05 mmol, 18.4 mg, 10%) and (*S*)-Tol-Binap (0.055 mmol, 38 mg, 11%) in 10 mL of THF was strirred for 15 min (a clear yellow solution was obtained). A solution of TBAT[21a] (0.1 mmol, 55.6 mg, 20%) in 0.5 mL of THF was added dropwise and after 15 min a bright yellow solution was obtained. Then, 1-ethoxy-1-(trimethylsilyloxy)-2-methyl-1,3 butadiene **1** (0.75 mmol, 150 mg, 1.5 equiv) was added dropwise (the resulting solution turned to red-brown) followed by the aldehyde (0.5 mmol, 1 equiv) slowly added and the reaction mixture was stirred for 24 h at room temperature. After quenching (MeOH/HCl 9:1 20 min), the reaction mixture was diluted with a satured aqueous solution of NH_4Cl and extracted with ether. The organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was then purified by flash chromatography on silicagel (pentane/EtOAc, 80/20).

(*S*)-Ethyl-2-methyl-5-hydroxy-5-phenyl-2-pentenoate (2a). 80% yield, clear yellow oil; $[\alpha]_D^{25} = -26.2$ ($c = 0.56$, $CHCl_3$); 70% ee (HPLC: chiralcel OJ, hexane/2-propanol 95: 05, flow rate 1 mL/min, major enantiomer 19.7 min, minor enantiomer 23.9 min). The ^{1}H, ^{13}C NMR data were in accordance with the literature.[25a]

(*S*)-Ethyl-2-methyl-5-hydroxy-5-naphthalen-2-yl-2-pentenoate (2b). 70% yield, yellow oil; $[\alpha]_D^{25} = -16.0$ ($c = 1$, $CHCl_3$); 48% e.e. (HPLC: chiralcel OD, hexane: 2-propanol 90:10, flow rate 1 mL/min, major enantiomer 18.8 min, minor enantiomer 21.6 min); IR (KCl) 3445, 2980, 1703, 1698, 1651, 1279, 1080, 748 cm^{-1}; ^{1}H NMR δ (200 MHz) 1.28 (t, $J = 7.0$ Hz, 3H), 1.82 (s, 3H), 2.17 (bs, OH), 2.73 (m, 2H), 4.18 (q, $J = 7.0$ Hz, 2H), 4.98 (m, 1H), 6.86 (m, 1H), 7.49 (m, 3H), 7.82 (m, 4H); ^{13}C NMR δ (75 MHz) 12.5, 14.0, 38.2, 60.3, 73.4, 123.5, 124.3, 125.8, 126.1, 127.5, 127.8, 128.2, 131.0, 134.1 (2C), 137.1, 140.9, 167. 7; MS (CI) *m/e* 302 (M + NH_4^+, 92%), 268 (38%), 267 (100%). Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.88; H, 7.25;

(*S*)-Ethyl-2-methyl-5-hydroxy-5-cinnamyl-2-pentenoate (2c). 35% yield, yellow oil; $[\alpha]_D^{25} = -37.0$ ($c = 1.62$, $CHCl_3$); 56% ee (HPLC: chiralcel OD hexane/2-propanol 80: 20, flow rate 1 mL/min, major enantiomer 12.0 min, minor enantiomer 8.1 min); IR (KCl) 3446, 2982, 1706, 1649, 1369, 1277, 1097 cm^{-1}; ^{1}H NMR δ (250 MHz) 1.22 (t, $J = 7.1$ Hz, 3H), 1.66 (bs, OH), 1.82 (s, 3H), 2.48 (m, 2H), 4.13 (q, $J = 7.1$ Hz, 2H), 4.40 (q, $J = 6.4$ Hz, 1H), 6.19 (dd, $J = 6.52$ and 15.9 Hz, 1H), 6.57 (d, $J = 15.8$ Hz, 1H), 6.78 (m, 1H), 7.15−7.35 (m, 5H); ^{13}C NMR δ (75 MHz) 12.8, 14.3, 36.8, 60.6, 72.0, 126.6, 127.9, 128.6 (2C), 130.4 (2C), 130.9, 131.3, 136.4, 137.0, 168.0; MS (CI) *m/e* 261 (M + H^+, 25%), 243 (100%), 157 (23%). Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.65; H, 7.96.

(*S*)-Ethyl-2-methyl-5 hydroxy-5-isopropyl-2-pentenoate (2d). 68% yield, yellow oil; $[\alpha]_D^{25} = -16.1$ ($c = 0.97$, $CHCl_3$); 77% ee (HPLC: chiralcel OD, hexane/2-propanol 98:2, flow rate 1 mL/min, major enantiomer 10.7 min, minor enantiomer 12.6 min); IR (KCl): 3451, 1709, 1648, 1279 cm^{-1}; ^{1}H NMR δ (200 MHz) 0.92 (~d, $J = 6.8$ Hz, 6H), 1.26 (t, $J = 7$ Hz, 3H), 1.68 (m, 1H), 1.82 (s, 3H), 1.98 (s, OH), 2.31 (m, 2H), 3.53 (m, 1H), 4.16 (q, $J = 7$ Hz, 2H), 6.82 (m, 1H). ^{13}C NMR δ (75 MHz) 12.5, 14.1, 17.1, 18.6, 33.2, 33.5, 60.4, 71.1, 129.2, 138.4, 168.1; MS (CI) *m/e* 201 (M + H^+, 100%), 183 (41%), 155 (24%), 146 (12%), 73 (45%), 59 (85%), 43 (40%). Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07; O, 23.97. Found: C, 65.71; H, 10.10; O, 23.74.

Preparation of (*S*)-3-(Acetyloxy)-3-phenylpropanoic Acid (4). To a solution of compound **2a** (0.34 mmol, 80 mg, 70% ee) in acetic anhydride (0.5 mL) was added pyridine (0.5 mL) dropwise. The reaction was monitored by TLC on silica gel (pentane/ethyl acetate, 80/20). After 1.5 h, the mixture was diluted in toluene and evaporated in vacuo (three times). The corresponding product, (*S*)-ethyl-2-methyl-5-(acetyloxy)-5-phenyl-2-pentenoate, was obtained in quantitative yield and used without further purification. This product (0.115 mmol, 31.7 mg) was diluted in CCl_4 (0.4 mL) and CH_3CN (0.4 mL), then distilled water (0.6 mL) was added. To this mixture was added $RuCl_3 \cdot 3H_2O$ (6% molar in water, 70 μL) and $NaIO_4$ (4.2 equiv). The mixture was then heated at 60 °C for 24 h. After

cooling, distilled water was added and the solution was extracted with CH_2Cl_2 (three times). The aqueous layer was acidified with 1 M HCl and extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and evaporated in vacuo. Compound **4** was obtained as a cream-colored solid in 45% yield (10.7 mg). The ^{1}H NMR, IR, and mass spectroscopy data were identical with those reported in the literature.[18c] $[\alpha]_D^{25} = -44.3$ ($c = 0.97$, MeOH), lit. [18a,b] $[\alpha]_D^{25} = +63.8$ ($c = 5$, MeOH) for the (R)-(+) pure enantiomer. ^{13}C NMR δ (75 MHz) 21.3, 41.2, 72.0, 126.7 (2C), 128.7 (2C), 128.9, 139.2, 170.1, 175.2.

General Procedure for the Preparation of the Chiral Nonracemic Amonium Fluorides (5−13). According to Shiori,[26] Amberlyst A-26 (Cl^- form, 1 g, 10 mol equiv) was transformed into the OH^- form by passing 1 N NaOH until complete exchange of the chloride anion was achieved. The column was washed carefully with water until neutral and then with methanol. A solution of the *cinchona* ammonium bromide or chloride (0.4 mmol) in methanol (10 mL) was slowly passed through the column and the column then washed with methanol. The eluent was neutralized until pH = 7 with HF and the solvents were removed in vacuo. The residue was coevaporated with toluene three times and dried over P_2O_5 under vaccum overnight and the chiral nonracemic ammonium fluorides were used without further purification.

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