Diastereoselective Monoalkylation of Lithium and Potassium Enolates of a Chiral Imine of Ethyl Glycinate: The Role of Added Salts

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The dimer **2C** which was designed using the X-ray literature information and which could be folded (**2Cf**) or unfolded (**2Cu$_1$**/**2Cu$_2$**) according to the nature of the alkylating agent and/or of the added salts, has been able to rationalize the following results: S or R diastereoselectivity according to the nature of the alkylating agent, increase of diastereoselectivity upon addition of a more chelating metal, decrease in diastereoselectivity on disruption of aggregates with introduction of TBAF, and decrease in diastereoselectivity with an increase of the temperature. Therefore, one could reasonably postulate that dimeric aggregates of the type of the model used could well be involved as reacting species in these reactions; the main origin of the diastereoselectivity would then be the self-clustering of the polyfunctionalized three-dimensional anion enolate.

Introduction

During work on the asymmetric synthesis of (*R*)-(−)- and (*S*)-(+)-DABA[1] we were confronted with the difficulty of obtaining a satisfactory diastereoselectivity upon monoalkylation of the Li enolate of the imine of ethyl glycinate **2** with bromoacetonitrile (Scheme I).

Thinking of the glycinate enolate in terms of aggregates (instead of a monomer as was usually done[2]) and using recent X-ray literature results, we designed as a model the dimer **2C**, which could be *f*olded (**2C*f***) or *u*nfolded (**2C*u***) according to the reagent and the metal used (Schemes II, IV, and V). Even if this was an oversimplified model, it allowed us to solve our problem and to increase the diastereoselectivity up to >98%.[1]

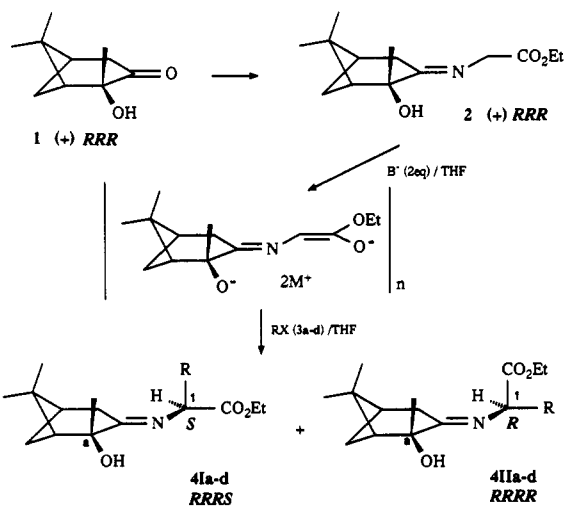
We report here new results which support this model and show that it could also be used to rationalize the results obtained with the K enolate, as well as the changes in diastereoselectivity with the nature of the alkylating agents.

Results and Discussion

Methyl iodide, benzyl bromide, bromoacetonitrile, and ethyl iodoacetate were reacted with Li and K enolates of imino ester **2** with and without $MgBr_2$ and TABF. The crude products of the reactions were analyzed (using 200-MHz ^{1}H NMR) in order to determine the diastereomer ratios with a minimum chance of enrichment. The results are gathered in Tables I and II.

Alkylation with Alkyl Halides. The high diastereoselectivity and the ***S*** absolute configuration[3a] of the preferred diastereomer obtained with MeI and $PhCH_2Br$ in the presence of LDA as base (entries 1 and 5, Table I) were consistent with Yamada's first results,[2a,b,3b] but neither of these features could be straightforwardly explained through chelated-enforced chirality transfer.[4]

Scheme I



$M^+ = Li^+, K^+$

RX : 3a = MeI ; 3b = $PhCH_2Br$; 3c = $BrCH_2CN$; 3d = ICH_2CO_2Et

In fact, neither of the two possible chelated monomeric forms **2A** and/or **2B** (Scheme III) could account for the high diastereoselectivity and the *S* configuration observed. As far as steric effects are concerned, such chelations (A type and B type) have no effect on the three-bond distance between the prochiral C1 carbon undergoing the addition and the first chiral center Ca, which, in any event, is a quaternary carbon leading to difficult-to-evaluate and small (if any) face differentiation. The only diastereo-

(1) Solladié-Cavallo, A.; Simon, M. C. *Tetrahedron Lett.* **1989**, *30*, 6011.

(2) (a) Yamada, S.; Oguri, T.; Shioiri, T. *J. Chem. Soc., Chem. Commun.* **1976**, 136. (b) Oguri, T.; Kaway, N.; Yamada, S. *Chem. Pharm. Bull.* **1978**, *26*, 803. (c) McIntoch, J. M.; Mishra, P. *Can. J. Chem.* **1986**, *64*, 726. (d) Bajgrowicz, J. A.; Cossec, B.; Pigière, Ch.; Jacquier, R.; Viallefont, Ph. *Tetrahedron Lett.* **1983**, *24*, 3721.

(3) (a) When R = Me, CH_2Ph, and CH_2CN, the configuration at C1 of the major diastereomer was determined from the sign of the rotation of the corresponding amino acids. When R = CH_2CO_2Et, it was postulated that the major diastereomer obtained with LDA/$MgBr_2$ had the same configuration as in the other cases, on the basis of the chemical shift of one of the bridge's Me groups. (b) The differences observed between Yamada's values (91/9 (MeI), 86/14 ($PhCH_2Br$)) and ours (97/3 (MeI), 96/4 ($PhCH_2Br$)) are probably due to the way these ratios have been determined (respectively rotation of isolated and derivatized amino acids or 200-MHz ^{1}H NMR of crude products).

(4) *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, 1–100.

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Table I. Alkylation of Imino Ester 2 with MeI and $PhCH_2Br$

entry no.	base	t, °C	alkylating agent	4a,b yield, %	4a,b I/II	4a,b config[a]
1	LDA	−78	MeI[b]	68	97/3	*S*
2	LDA	−50	MeI	80	65/35	*S*
3	LDA + $MgBr_2$ (0.5 equiv)	−50	MeI	65	90/10	*S*
4	LDA + TBAF	−78	MeI	80	66/34	*S*
5	LDA	−78	$PhCH_2Br$[b]	90	96/4	*S*
6	LDA	−50	$PhCH_2Br$	90	92/8	*S*
7	LDA + $MgBr_2$ (0.5 equiv)	−50	$PhCH_2Br$	80	99/1	*S*
8	LDA + TBAF	−78	$PhCH_2Br$	90	32/68	*R*
9	tBuOLi	−50	$PhCH_2Br$	80	84/16	*S*
10	tBuOLi + $MgBr_2$ (0.5 equiv)	−50	$PhCH_2Br$	95	95/5	*S*
11	tBuOK	−78	MeI	85	85/15	*S*
12	tBuOK + $MgBr_2$ (0.5 equiv)	−50	MeI	50	93/7	*S*
13	tBuOK	−78	$PhCH_2Br$	50	91/9	*S*
14	tBuOK	−50	$PhCH_2Br$	95	80/20	*S*
15	tBuOK + $MgBr_2$ (0.5 equiv)	−50	$PhCH_2Br$	50	93/7	*S*

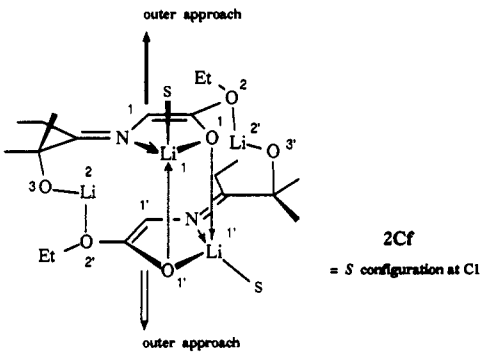
[a] Configuration at C1. [b] Yamada and co-workers[2] obtained 52%, 91/9 with MeI and 79%, 86/14 with $PhCH_2Br$. From the *SSS* hydroxypinanone the *R* configuration was preferred, but in this work the *RRR* hydroxypinanone has been used and the *S* configuration is preferred.

Table II. Alkylation of Imino Ester 2 with $BrCH_2CN$ and ICH_2CO_2Et

entry no.	base	t, °C	alkylating agent	4c,d yield, %	4c,d I/II	4c,d config[a]
1	LDA	−78	$BrCH_2CN$	90	65/35	*S*
2	LDA + $MgBr_2$ (1 equiv)	−50	$BrCH_2CN$	65	99/1	*S*
3	LDA + $MgBr_2$ (0.5 equiv)	−50	$BrCH_2CN$	85	99/1	*S*
4	LDA + TBAF	−78	$BrCH_2CN$	90	45/55	
5	LDA	−78	ICH_2CO_2Et	80	35/65	*R*
6	LDA + $MgBr_2$ (0.5 equiv)	−78	ICH_2CO_2Et	80	92/8	*S*
7	LDA + TBAF	−78	ICH_2CO_2Et	80	50/50	
8	tBuLi	−78	$BrCH_2CN$	60	60/40	*S*
9	tBuOK	−78	$BrCH_2CN$	95	22/78	*R*
10	tBuOK + $MgBr_2$ (1 equiv)	−78	$BrCH_2CN$	35	98/2	*S*
11	tBuOK	−78	ICH_2CO_2Et	85	34/66	*R*
12	tBuOK + $MgBr_2$ (1 equiv)	−78	ICH_2CO_2Et	40	82/18	*S*

[a] Configuration at C1.

Scheme II



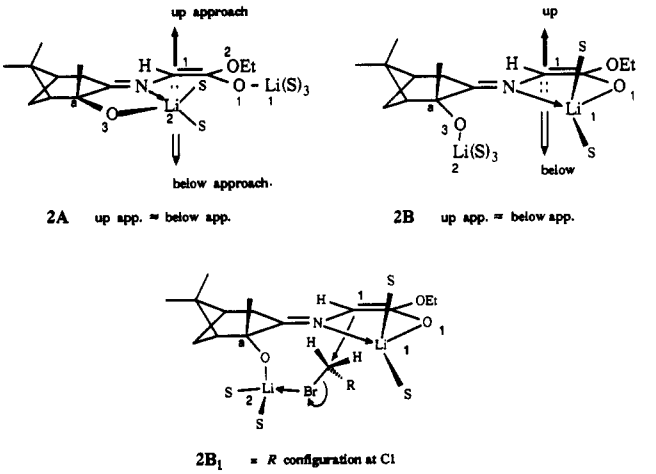
2Cf = *S* configuration at C1

selective mechanism one could think of, which could lead to high diastereoselectivity through face differentiation, would be a Li2-directed approach of the alkylating agent, as shown in $\mathbf{2B_1}$, but the absolute configuration at C1 would be *R*, which is not the case.

We thus turned toward aggregates. That Li or Na enolates are solvated aggregates was proposed about 30 years ago,[5] and a great amount of work has been devoted to studying the role of these aggregates on the reactivity of the enol moiety (rate of reaction or C- *vs* O-alkylation),[6] but it was not until 1981 that Jackman and co-workers[7] correlated the degree of aggregation (determined by NMR)

(5) Zook, H. D.; Russo, T. J. *J. Am. Chem. Soc.* **1960**, *82*, 1258.

Scheme III



2A up app. ≈ below app. **2B** up app. ≈ below app.

$2B_1$ = *R* configuration at C1

and the C- *vs* O-alkylation and postulated the aggregates to be the "the true reactants" in these reactions. Simultaneously, Seebach and co-workers[8] obtained the first crystal structures of Li enolate aggregates, thus providing definite information about the geometry of these species, and proposed, in consistency with Zimmerman's model,[9a] that the aldol reaction may proceed through aggregate intermediates.[9b]

Since these first crystal structures, numerous other aggregates of Li, Na, K, and Mg enolates have been crystallized and studied by X-ray diffraction.[10-15] They provide geometrical information which, extrapolated to similar, not yet crystallized substrates, can be extremely useful for predictive purposes (as have been bond lengths and/or bond angles gathered from X-ray diffraction analysis of nonionic molecules).

In spite of the great variety of structurally different enolate aggregates, it appears that (a) in dimeric ester enolates with THF as ligand the two enolate units are cis to each other (that is, on the same side of the OLiOLi quadrangle),[8b,12] (b) even prepared from LDA, dimeric ketone enolates are THF-solvated when THF is used as solvent,[8] and (c) when a heteroatom is present, chelation on the lithium occurs and may serve to stabilize the aggregate.[15-17] The dimeric enolate **2Cf** (Scheme II) was thus built up (as a model) from the above geometric structural information.[8,10-15] Then it was obvious (from molecular models) that Li2 of one of the enolate units was

(6) (a) Zook, H. D.; Russo, T. J.; Fernand, E. F.; Stotz, D. S. *J. Org. Chem.* **1968**, *33*, 2222. (b) House, H. O.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1971**, *36*, 2361.

(7) Jackman, L. M.; Lange, B. C. *J. Am. Chem. Soc.* **1981**, *103*, 4494.

(8) (a) Amstutz, R.; Schweizer, W. B.; Seebach, D.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2617. (b) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624.

(9) (a) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920. (b) Seebach, D.; Amstutz, R.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2622.

(10) Seebach, D.; Bauer, W.; Hansen, J.; Laube, T.; Schweizer, W. B.; Dunitz, J. D. *J. Chem. Soc., Chem. Commun.* **1984**, 853.

(11) Williard, P. G.; Carpenter, G. B. *J. Am. Chem. Soc.* **1985**, *107*, 3345.

(12) Seebach, D.; Amstutz, R.; Laube, T.; Schweizer, W. B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1985**, *107*, 5403.

(13) Williard, P. G.; Carpenter, G. B. *J. Am. Chem. Soc.* **1986**, *108*, 462.

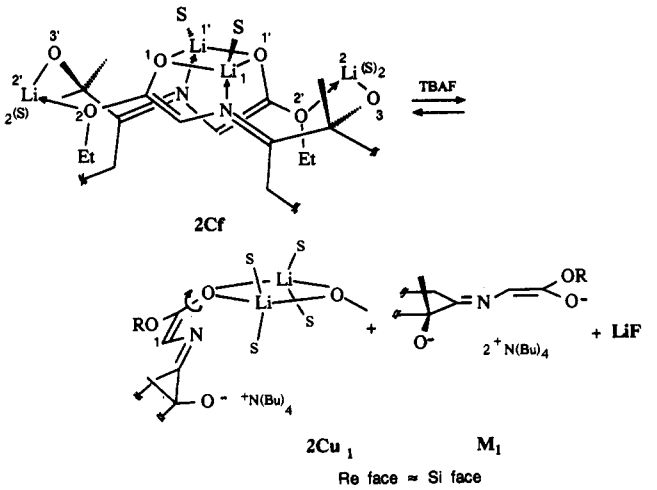
(14) Williard, P. G.; Salvino, J. M. *J. Chem. Soc., Chem. Commun.* **1986**, 153.

(15) Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1987**, *109*, 5539.

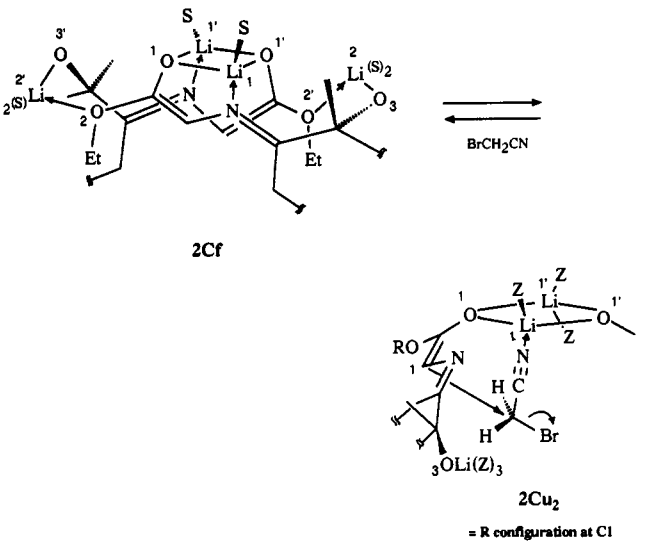
(16) (a) Bottin-Strzalko, T.; Seyden-Penne, J. *J. Chem. Soc., Chem. Commun.* **1976**, 905. (b) Solladié-Cavallo, A.; Mioskowski, C. *Org. Magn. Reson.* **1981**, *4*, 273.

(17) Jastrzebski, J. T.; Van Koten, G.; Van De Mieroop, W. F. *Inorg. Chim. Acta* **1988**, *142*, 169.

Scheme IV



Scheme V



correctly positioned to complex the O2 oxygen of the other enolate unit, thus reinforcing the folding.

This folded dimer **2C*f*** (Scheme II) could then account for the high diastereoselectivity observed and for the *S* absolute configuration obtained (entries 1 and 5, Table I) through an *outer approach* (Scheme II) of the alkylating agent.

This model accounted also for the decrease in diastereoselectivity observed when the temperature increased (entries 1,2 and 5,6), in consistency with the known effect of temperature on exchange rates and degree of aggregation.

Therefore, magnesium having a stronger coordinating ability, the addition of $MgBr_2$ into the lithium enolate was expected (if the model was correct) to slow down exchange, to reinforce the dimer's folding, and thus to increase the diastereoselectivity, *which was indeed observed* (entries 3 and 7, Table I). The fact that 0.5 equiv of $MgBr_2$ was enough for the maximum effect is also in favor of the dimeric type model proposed; however, we do not know yet if metal exchange occurs or if extra bridges are formed.

Upon addition of TBAF[18] into the enolate, one expects from this model that the "naked" fluorine would quench the Li^+ (because of the high Li–F bond energy) and unfold the dimeric aggregate (the O3–Li2–O2 bridges being cut) to give the unfolded dimer **2C*u*$_1$**, which could then be in equilibrium with the monomer $\mathbf{M}_1$ (Scheme IV). A decrease in diastereoselectivity should thus be expected which *was, indeed, observed* (compare entries 1 with 4 and 5 with 8, Table I).[19]

When tBuOLi was used as a base, the alkylation with benzyl bromide proceeded with smaller but still high diastereoselectivity, 84/16 (compare entry 6 with 9, Table I) and addition of $MgBr_2$ (entry 10) increased the diastereoselectivity to 95/5. *These results hinted that the model **2Cf** may also be used in this case.*

When tBuOK was used as a base (entries 11–15, Table I), the same trend was observed: (a) a high diastereoselectivity (~70% and 82% at −78 °C) and (b) an increase in diastereoselectivity upon addition of $MgBr_2$ (from 60% to 86% at −50 °C; entries 14 and 15, Table I). *Hence, again the same folded/unfolded dimeric aggregate could be used as a model to rationalize the K-enolate's results,* and this was consistent with literature results.[13] However, one must notice that the diastereoselectivity obtained with tBuOK as base did not exceed 86%.

Alkylation with Bromoacetonitrile and Ethyl Iodoacetate. Monoalkylation of the lithium enolate (formed from LDA) with bromoacetonitrile (**3c**) and ethyl iodoacetate (**3d**) led either to a small diastereoselectivity (30% *S*, entry 1, Table II) or to a small and reverse diastereoselectivity (30% *R*, entry 5, Table II).

It was reasonable to postulate that bromoacetonitrile (**3c**) and ethyl iodoacetate (**3d**), having extra heteroatoms, *were able to unfold the lithium dimeric aggregate* probably through complexation of the Li1 and Li2 atoms by the nitrile nitrogen lone pair in **3c** and, even more strongly, by the ester oxygen lone pairs in **3d** (Scheme V), leading to the unfolded aggregate **2C*u*$_2$**, to a lower face differentiation, *and thus to the low diastereoselectivity observed.* Besides, from examination of the molecular models, it appeared that the alkylating agents **3c,d**, when complexed in positions 1 and 1′ (Li1 and Li1′) on the **2C*u*$_2$** aggregate, were correctly positioned to react with the enolate units from the *Re* faces *via* an *intraaggregate* reaction, thus leading to the *R* diastereoselectivity.[20]

Therefore, the higher the percentage of **2C*u*$_2$**, the higher the percentage of *R* diastereoselectivity. Then, due to the weaker complexing ability of nitrogen compared to that of oxygen toward lithium, one could expect that the population of **2C*u*$_2$** (eq 1) would be smaller with bromoacetonitrile (**3c**) than with ethyl iodoacetate (**3d**), leading to a smaller percentage of *R* configuration in the case of **3c**, *as observed* (compare entry 1, 35% *R*, with entry 5, 65% *R*, Table II).

Then, as expected from the model **2C*f***, addition of $MgBr_2$ (in reinforcing the folding) should restore high to complete *S* diastereoselectivity if, of course, reagents **3c,d**

(18) The chemical yields in the presence of TBAF being very close to those without, it appears that the three molecules of H_2O which are always present in THF solutions of TBAF are so strongly H-bonded that they become inactive toward anions.

(19) The *R* absolute configuration obtained in experiment 8 is not clearly understood but might be related to the presence of the phenyl ring, as already observed by McIntosh and co-workers (McIntosh, J. M.; Leavitt, R. K.; Mishra, P.; Cassidy, K. C.; Drake, J. E.; Chadha, R. *J. Org. Chem.* **1988**, *53*, 1945).

(20) When the alkylating agents **3c** and/or **3d** are complexed (through the N or the O lone pairs) in positions 2 and 2′ (Li2, Li2′), the CH_2 groups undergoing the reaction do not appear (on the molecular models) to be correctly positioned to react. However, this would also lead to the *R* configuration.

$$\underset{\substack{\text{leads to } S \text{ configuration}\\ \textit{via interaggregate} \text{ reaction}}}{\mathbf{2Cf}} + n\mathrm{RX} \rightarrow \underset{\substack{\text{leads to } R \text{ configuration}\\ \textit{via intraaggregate} \text{ reaction}}}{\mathbf{2Cu_2}} + (n-x)\mathrm{RX} \quad (1)$$

are not able to unfold **2Cf** (or at least not much), which *was indeed observed*: 99/1 with **3c**, and 92/8 with **3d**.

The results obtained in the presence of TBAF (entries 4 and 7, Table II) deserve no further comment and could also be rationalized using the **2C** model (unfolding of the aggregate and/or formation of monomer $\mathbf{M_1}$ accounted for the decrease in diastereoselectivity as with alkyl halides; see above).

The result obtained when the anion was formed from tBuLi (entry 8, Table II) was similar to that obtained with LDA.

When tBuOK was used as the base and when the alkylating agent was bromoacetonitrile, an increase in *R* diastereoselectivity was observed (compare entries 1 and 9, Table II). This result could also be understood on the basis of the model **2Cf** = **2Cu₂** invoking a higher percentage of **2Cu₂** due to the greater affinity of the nitrogen lone pair of $BrCH_2CN$ toward K (compared to Li). Examination of molecular models (using K–O–K and Li–O–Li bond lengths given in ref 13) suggested also that the CH_2 undergoing the substitution was better positioned for an *intraaggregate* reaction in the **2Cu₂** K-aggregate than in the **2Cu₂** Li-aggregate, thus explaining the greater *R* diastereoselectivity observed.

In the case of ethyl iodoacetate there was no modification of the *R* diastereoselectivity on passing from Li to K (entries 5 and 11, Table II).

Here again addition of $MgBr_2$ reversed the selectivity toward a high *S* diastereoselectivity in consistency with an increase in population of the folded dimer **2Cf** (entries 10 and 12, Table II) and an *interaggregate* reaction.

Conclusion

The dimer **2C**, which was designed using the X-ray literature information and which could be folded (**2Cf**) or unfolded (**2Cu₁**/**2Cu₂**) according to the nature of the alkylating agent and/or of the added salts, has been able to fully rationalize the following results: (a) the *S* configuration (*S* diastereoselectivity) obtained at C1 upon alkylation with alkyl halides, (b) the *R* diastereoselectivity obtained with alkylating agents which possess extra heteroatoms (and can unfold the dimer **2Cf**, leading to the unfolded dimer **2Cu₂** and to the possibility of an *intraaggregate* reaction), (c) the decrease in diastereoselectivity when the temperature increased, (d) the increase in *S* diastereoselectivity upon addition of $MgBr_2$ into the enolates before alkylation (thus reinforcing the folding and favoring the outer approach), and (e) the decrease in diastereoselectivity upon addition of TBAF into the enolates before alkylation (thus disrupting the dimer and lowering the face differentiation).

It is thus reasonable to postulate that this model is more than a model and that aggregates of this type might well be involved as reacting species.

Therefore, the diastereoselectivity could be due but indirectly to the chiral auxiliary, the main origin of the diastereoselectivity being the *self-clustering of the polyfunctionalized three-dimensional anion enolate*, probably favored by the rigidity of the bifunctionalized chiral fragment.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 257 spectrometer (ν in cm^{-1}). ^1H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded on a Bruker AC-200 (δ in ppm referenced to TMS, $\Delta\nu$ and J in Hz, signs of the J_{AB} coupling constants not given). Rotations were measured on a Perkin-Elmer Model 241MC polarimeter. Melting points (uncorrected) were determined on a Reichert microscope. Flash chromatography was performed using silica gel (70–230 mesh) purchased from Merck, Kieselgel 60 F_{254} plates (from Merck) were used for TLC. THF was distilled before use over Na/benzophenone. Diisopropylamine was dried by distillation over KOH. All the reagents were reagent grade, purchased from Aldrich and/or Janssen and used without further purification. Elemental analyses were performed by the "Service d'analyse du CNRS", Strasbourg, France.

(+)-(1*R*,2*R*,5*R*)-2-Hydroxypinan-3-one (1) was prepared by $KMnO_4$ oxidation of (−)-α-pinene ($[\alpha]_D = -42°$ (neat), 81% optical purity) by following a known procedure.[21] The distilled pinanone was recrystallized three times from pentane: yield 35%; colorless prisms, mp 36 °C (lit.[22] mp 34.5–35.5 °C); $[\alpha]_D = +40°$ (c = 2.11, $CHCl_3$) (lit.[22] $[\alpha]_D = -41°$ (c = 0.04, $CHCl_3$)); optical purity about 98%. ^1H NMR ($CDCl_3$): 0.89 (s, 3H, Me_1); 1.36 (s, 3H, Me_2); 1.37 (s, 3H, Me_3); 1.67 (d, 1H, H1, J_{1-2} = 10 Hz); 2.12 (~d, 2H, H3 and H6); 2.47 (dtt, 1H, H2, J_{1-2} = 10 Hz, $J_{2-3} = J_{2-6}$ = 6 Hz, $J_{2-4} = J_{2-5}$ = 1.5 Hz); 2.62 (dd, 2H, H4 and H_5, J = 1.5 Hz, J = 1 Hz). ^{13}C NMR ($CDCl_3$): 22.9, 25.2, and 27.3 (CH_3); 28.4 (CH_2); 38.3 (CH); 39.3 (C); 43.0 (CH_2); 49.7 (CH); 77.1 (C); 214.2 (C=O). IR ($CHCl_3$): ν_{OH}(free) = 3580 cm^{-1}, ν_{OH}(bonded) = 3420 cm^{-1}, $\nu_{C=O}$ = 1710 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.41; C, 9.59.

(1*R*,2*R*,5*R*)-Ethyl ((2-Hydroxypinan-3-ylene)amino)acetate (2). A mixture of glycine ethyl ester[23] (54 mmol, 2 equiv), 2-hydroxypinan-3-one (27 mmol), benzene (80 mL), and boron trifluoride etherate (0.1 g) was refluxed for 4–5 h under argon using a Dean–Stark apparatus. After evaporation of the benzene under vacuum, the yellow oil was purified by chromatography (Et_2O, silica gel pretreated with a 5% solution of Et_3N in Et_2O). Crystals could be obtained by recrystallization in Et_2O/hexane (8/2): yield 90% (after chromatography); white crystals; mp 80–81 °C; $[\alpha]_D = +6°$ (c = 2.54, $CHCl_3$). ^1H NMR ($CDCl_3$): 0.88 (s, 3H, Me_1); 1.30 (t, 3H, Me, J = 7 Hz); 1.34 (s, 3H, Me_2); 1.53 (s, 3H, Me_3); 1.57 (d, 1H, H1, J_{1-2} = 10 Hz); 2.07 (m, 2H, H3 and H6); 2.36 (dtt, 1H, H2, J_{1-2} = 10 Hz, $J_{2-3} = J_{2-6}$ = 6 Hz, $J_{2-4} = J_{2-5}$ = 1.5 Hz); 2.50 (dd, 2H, H4 and H5, J = 1.5 Hz, J = 1 Hz); 2.61 (s, 1H, OH); 4.17 (s, 2H, =N-CH_2); 4.23 (q, 2H, CH_2Me, J = 7 Hz). IR ($CHCl_3$): ν_{OH}(free) = 3540 cm^{-1}, ν_{OH}(bonded) = 3420 cm^{-1}, $\nu_{C=O}$ = 1720 cm^{-1}, $\nu_{C=N}$ = 1640 cm^{-1}. ^{13}C NMR ($CDCl_3$): 13.8, 22.4, 26.9, and 27.7 (CH_3); 27.6 and 33.3 (CH_2); 37.9 (CH); 38.1 (C); 50.1 (CH); 52.0 and 60.4 (CH_2); 75.9 (C); 169.8 (C=N); 179.5 (C=O). Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15; N, 5.53. Found: C, 66.13; H, 9.32; N, 5.49.

General Method for Alkylation of the Imino Ester 2 with Electrophiles. To the base (1.6 mmol, 2 equiv) in anhydrous THF (2 mL) was added the imino ester **2** (0.8 mmol; 1 equiv) in anhydrous THF (2 mL) at −78 °C under argon, and the mixture was stirred for 15 min at −78 °C. If desired, $MgBr_2$ (freshly prepared in THF) was added and the temperature was allowed to increase to −35 °C for 1 h. The solution was then cooled down again to −78 °C (or −50 °C) and the electrophile (2–3 equiv) was added dropwise. The mixture was then stirred at −78 °C (or at

(21) Carlson, R. G.; Pierce, J. K. *J. Org. Chem.* **1971**, *36*, 2319.
(22) Delépine, M.; Horeau, A.; Grandperrin-Harispe, M. *Ann. Chim. (Paris)* **1943**, *18*, 250.
(23) The ethyl glycinate was obtained by bubbling gaseous ammonia in a suspension of glycinate chlorohydrate in benzene followed by filtration of the ammonium chloride formed.

−50 °C) for 4 h (the reaction was followed by TLC). The mixture was then poured into a cold saturated solution of NH_4Cl (15 mL). The aqueous phase was extracted with Et_2O (3 × 15 mL); the combined organic layers were dried over Na_2SO_4, filtered, and evaporated under vacuum, and the residue was chromatographed on silica gel pretreated with a 5% solution of Et_2N in Et_2O (Et_2O/hexane 70/30).

Ethyl 2′-((2-Hydroxypinan-3-ylene)amino)-2′-methylacetate (4a): yellow oil. Anal. Calcd for $C_{15}H_{25}NO_3$: C, 67.38; H, 9.43; N, 5.24. Found: C, 67.29; H, 9.40; N, 5.19. Diastereomer I (1*R*,2*R*,5*R*,2′S): R_f 0.49 (Et_2O/hexane, 70/30); $[\alpha]_D$ = −34° (*c* = 6.08, $CHCl_3$). ^1H NMR ($CDCl_3$): 0.85 (s, 3H, Me_1); 1.27 (t, 3H, Me, J = 7 Hz); 1.33 (s, 3H, Me_2); 1.41 (d, 3H, Me, J = 7 Hz); 1.48 (s, 3H, Me_3); 1.57 (d, 1H, H1, J_{1-2} = 10 Hz); 2.03 (tt, A part of $ABXA_1B_1$, 1H, H3, $J_{3-6} = J_{3-2}$ = 6 Hz, $J_{3-4} = J_{3-5}$ = 2.5 Hz); 2.07 (B part of $ABXA_1B_1$, 1H, H6, $J_{6-3} = J_{6-2}$ = 6 Hz); 2,33 (dtd, X part of $ABXA_1B_1$, 1H, H2, J_{1-2} = 10 Hz, $J_{2-6} = J_{2-3}$ = 6 Hz, J_{2-5} = 2.5 Hz); 2.54 (A_1B_1 part of $ABXA_1B_1$, 2H, H4 and H5, J_{4-5} = 18 Hz, $J_{5-3} = J_{5-2} = J_{4-3}$ = 2.5 Hz, $\Delta\nu$ = 59 Hz); 2.74 (s, 1H, OH); 4.17 (q, 2H, CH_2Me, J = 7 Hz); 4.29 (q, 1H, CHMe, J = 7 Hz). IR ($CHCl_3$): ν_{OH}(free) = 3690 cm^{-1}, ν_{OH}(bonded) = 3550 cm^{-1}, $\nu_{C=O}$ = 1730 cm^{-1}, $\nu_{C=N}$ 1650 cm^{-1}. Diastereomer II (1*R*,2*R*,5*R*,-2′R): ^1H NMR ($CDCl_3$) 0.90 (s, 3H, Me_1), 1.25 (t, 3H, Me); the other signals overlap. Diastereomers I and II can also be distinguished by ^1H NMR in C_6D_6: 0.73 (s, 3H, Me_1, I); 1.05 (t, 3H, Me, I); 1.2 (s, 3H, Me_2, I); 1.53 (d, 3H, Me, I); 1.70 (s, Me_3, I) and 0.92 (s, 3H, Me_1, II); 1.02 (t, 3H, Me, II); 1.22 (s, 3H, Me_2, II); 1.56 (d, 3H, Me II); 1.74 (s, 3H, Me_3, II).

Ethyl 2′-((2-Hydroxypinan-3-ylene)amino)-2′-benzylacetate (4b): yellow oil. Anal. Calcd for $C_{15}H_{25}NO_3$: C, 73.44; H, 8.51; N, 4.08. Found: C, 73.32; H, 8.47; N, 3.99. Diastereomer I (1*R*,2*R*,5*R*,2′*S*): R_f 0.52 (Et_2O/hexane, 70/30); $[\alpha]_D$ = −74 ° (*c* = 8.95, $CHCl_3$). ^1H NMR ($CDCl_3$): 0.29 (s, 3H, Me_1); 1.20 (s, 3H, Me_2); 1.27 (t, 3H, Me, J = 7 Hz); 1.38 (s, 3H, Me_3); 1.45 (d, 1H, H1, J_{1-2} = 10 Hz); 1.85 (tt, 1H, H3, $J_{3-6} = J_{3-2}$ = 6 Hz, J_{3-5} = 3 Hz); 1.95 (B part of ABX, 1H, H5, J_{5-4} = 17 Hz; $J_{5-3} = J_{5-2}$ = 3 Hz); 1.96 (t, 1H, H6, J = 6 Hz); 2.24 (dtd, 1H, H2, J_{1-2} = 10 Hz, $J_{2-6} = J_{2-3}$ = 6 Hz, J_{2-5} = 3 Hz); 2.47 (A part of ABX, 1H, H4, J_{4-5} = 17 Hz, J_{4-3} = 3 Hz); 2.66 (s, 1H, OH); 3.23 (AB part of ABX, 2H, CH_2Ph, J_{AB} = 13 Hz, J_{AX} = 3 Hz, J_{BX} = 10 Hz, $\Delta\nu$ = 48 Hz); 4.20 (q, 2H, CH_2, J = 7 Hz); 4.46 (X part of ABX, 1H, =NCH–); 7.20 (m, 5H, H arom). IR ($CHCl_3$): ν_{OH}(free) = 3690 cm^{-1}, ν_{OH}(bonded) = 3550 cm^{-1}, $\nu_{C=O}$ = 1730 cm^{-1}, $\nu_{C=N}$ = 1650 cm^{-1}. Diastereomer II (1*R*,2*R*,5*R*,2′*R*): ^1H NMR ($CDCl_3$) 0.80 (s, 3H, Me_1), 1.50 (s, 3H, Me_3), 4.50 (X part of ABX, 1H, =NCH).

Ethyl 2′-((2-Hydroxypinan-ylene)amino-2′-(cyanomethylene)acetate (4c): yellow oil. Anal. Calcd for $C_{16}H_{24}N_2O_3$: C, 65.73; H, 8.27; N, 9.58. Found: C, 65.59; H, 8.23; N, 9.49. Diastereomer I (1*R*,2*R*,5*R*,2′*S*): R_f 0.32 (Et_2O/hexane, 70/30); $[\alpha]_D$ = −90° (*c* = 6.41, $CHCl_3$). ^1H NMR ($CDCl_3$): 0.93 (s, 3H, Me_1); 1.28 (t, 3H, Me, J = 7 Hz); 1.35 (s, 3H, Me_2); 1.53 (s, 3H, Me_3); 1.58 (d, 1H, H1, J_{1-2} = 10 Hz); 2.1 (m, 2H, H3 and H6); 2.40 (m, 2H, H2 and OH); 2.71 (∼d, 2H, H4 and H5); 2.95 (AB of ABX, 2H, CH_2CN, J_{AB}, J_{AX}, and J_{BX} were not determined); 4.21 (q, 2H, CH_2O, J = 7 Hz); 4.55 (X of ABX, 1H, =NCH–). IR ($CHCl_3$): ν_{OH}(free) = 3680 cm^{-1}, ν_{OH}(bonded) = 3560 cm^{-1}, $\nu_{C=N}$ = 1650 cm^{-1}. Diastereomer II (1*R*,2*R*,5*R*,2′*R*): R_f 0.18 (Et_2O/hexane, 70/30). $[\alpha]_D$ = +85° (*c* = 5.1, $CHCl_3$). ^1H NMR ($CDCl_3$): 0.91 (s, 3H, Me_1); 1.25 (t, 3H, Me, J = 7 Hz); 1.35 (s, 3H, Me_2); 1.50 (s, 3H, Me_3); 1.61 (d, 1H, H1, J_{1-2} = 10 Hz); 2.09 (m, 2H, H3 and H6); 2.36 (m, 2H, H2 and OH); 2.68 (∼d, 2H, H4 and H5); 2.95 (AB of ABX, 2H, CH_2CN, J_{AB} = 15 Hz, J_{AX} ≈ 5 Hz, J_{BX} ≈ 7 Hz, $\Delta\nu$ = 15 Hz); 4.22 (AB of ABX_3, 2H, CH_2, J_{AB} was not determined); 4.51 (X of ABX, 1H, =NCH, J_{AX} ≈ 5 Hz, J_{BX} ≈ 7 Hz). IR ($CHCl_3$): ν_{OH}(free) = 3680 cm^{-1}, ν_{OH}(bonded) = 3560 cm^{-1}, ν_{CN} = 2240 cm^{-1}, $\nu_{C=O}$ = 1730 cm^{-1}, $\nu_{C=N}$ = 1650 cm^{-1}.

Ethyl 2′-(2-hydroxypinan-3-ylene)amino(carbethoxymethylene)acetate (4d): yellow oil. Anal. Calcd for $C_{18}H_{29}NO_5$: C, 63.69; H, 8.61; N, 4.12. Found: C, 63.58; H, 8.62; N, 4.08. Diastereomer I (1*R*,2*R*,5*R*,2′*S*): ^1H NMR ($CDCl_3$): 0.85 (s, 3H, Me_1); 1.25 (t, 3H, Me); 1.35 (s, 3H, Me_2); 1.47 (s, 3H, Me_3); 1.52 (d, 1H, H1, J_{1-2} = 10 Hz); 2.05 (m, 2H, H3 and H6); 2.32 (m, 2H, H2 and OH); 2.72 (m, 2H, H4 and H5); 2.80 (A part of ABX, 1H, J_{AB} = 15 Hz, J_{AX} ≈ 8 Hz); 3.07 (B part of ABX, J_{BX} ≈ 5 Hz); 4.15 (m, 4H, $2CH_2O$); 4.67 (t, 1H, X part of ABX, =NCH). Diastereomer II (1*R*,2*R*,5*R*,2′R): ^1H NMR ($CDCl_3$): 0.82 (s, 3H, Me_1); 1.25 (t, 3H, Me); 1.35 (s, 3H, Me_2); 1.42 (s, 3H, Me_3); 1.57 (d, 1H, H1, J_{12} = 10 Hz); 2.05 (m, 2H, H3 and H6); 2.32 (m, 2H, H2 and OH); 2.72 (m, 2H, H4 and H5); ∼2.80 (slightly deshielded with respect to diastereomer I, A part of ABX, J_{AB} = 15 Hz, J_{AX} ≈ 9 Hz); 3.02 (B part of ABX, J_{BX} ≈ 4 Hz); 4.15 (m, 4H, $2CH_2O$); 4.72 (t, 1H, X part of ABX, =NCH).

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