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Salicylaldehyde Schiff bases derived from 2-ferrocenyl-2-amino alcohols. Part 2: Stereochemical divergence in the titanium-promoted enantioselective diketene addition to benzaldehyde

Rosa M[a] Moreno and Albert Moyano*

Unitat de Recerca en Síntesi Asimètrica, Departament de Química Orgànica, Universitat de Barcelona, Facultat de Química, C. Martí i Franquès 1-11, 08028 Barcelona, Spain

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Abstract—Chiral Schiff bases arising from the condensation of a set of diversely substituted (*S*)-2-amino-2-ferrocenyl ethanol derivatives **1a–e** with salicylaldehydes **2A–B** have been tested in the asymmetric, titanium-promoted diketene addition to benzaldehyde. This study has revealed that the enantiofacial selectivity of this reaction depends strongly on the substitution pattern of the amino alcohol component. Molecular mechanics calculations have led to the identification of a transition state model that explains these observations.

1. Introduction

Chiral Schiff bases derived from the condensation of salicylaldehydes with 2-amino alcohols have found widespread use as ligands in asymmetric synthesis. These compounds act as tridentate *O*,*N*,*O* ligands, and a great number of metallic complexes derived from them have been described in the literature. Depending upon the nature of the metal centre, these chiral complexes are able to promote a variety of enantioselective transformations.[1] Up till now, a relatively small number of 2-amino alcohols, most of which derived from α-amino acids, have been used for their preparation.

In connection with a research program devoted to the development of new chiral auxiliaries and ligands based on 2-amino-2-ferrocenylalkanols,[2] we have prepared a set of salicylaldehyde Schiff base ligands **3aA–dB** derived from 2-amino-2-ferrocenylethanols **1a–e**,[3] with different degrees of substitution both at the C_1 and C_2 positions, and from aldehydes **2A–B** (see Fig. 1), in order to investigate the catalytic efficiency of their titanium alkoxide complexes in asymmetric additions to aldehydes. In the preceding paper in this issue, we have described the synthesis of these novel chiral complexes, and have shown that they are able to catalyze the enantioselective reaction of trimethylsilyl cyanide with aldehydes. Herein, we report on their use as chiral controllers in another important enantioselective transformation: the asymmetric synthesis of 5-hydroxy-3-keto esters by the titanium-promoted addition of diketene to aldehydes.

2. Results and discussion

2.1. Enantioselective reaction of diketene with benzaldehyde

Building upon a reaction previously reported by Mukaiyama,[4] Oguni et al. disclosed in 1994[5] that the reaction of diketene with aldehydes in the presence of chiral Schiff base–titanium alkoxide complexes proceeded with moderate to good enantioselectivity to afford the corresponding 5-hydroxy-3-oxoesters (Scheme 1). In their initial studies,[5,6] these workers found that the enantioselectivity of the reaction depended on the nature of the Schiff base used: on the one hand, the existence of a *tert*-butyl group at the 3-position of the salicylaldehyde moiety was essential for achieving sizable asymmetric induction, and on the other best results were obtained with monosubstituted 2-amino alcohols such as valinol or *tert*-leucinol. In order to obtain a satisfactory yield, equimolar, or at least more than 50 mol % amounts of titanium complexes were necessary. Subsequently, Oguni found that the replacement of the salicylaldehyde component by a 2-hydroxybenzophenone

* Corresponding author. Tel.: +34 93 4021245; fax: +34 93 3397878; e-mail: amoyano@ub.edu

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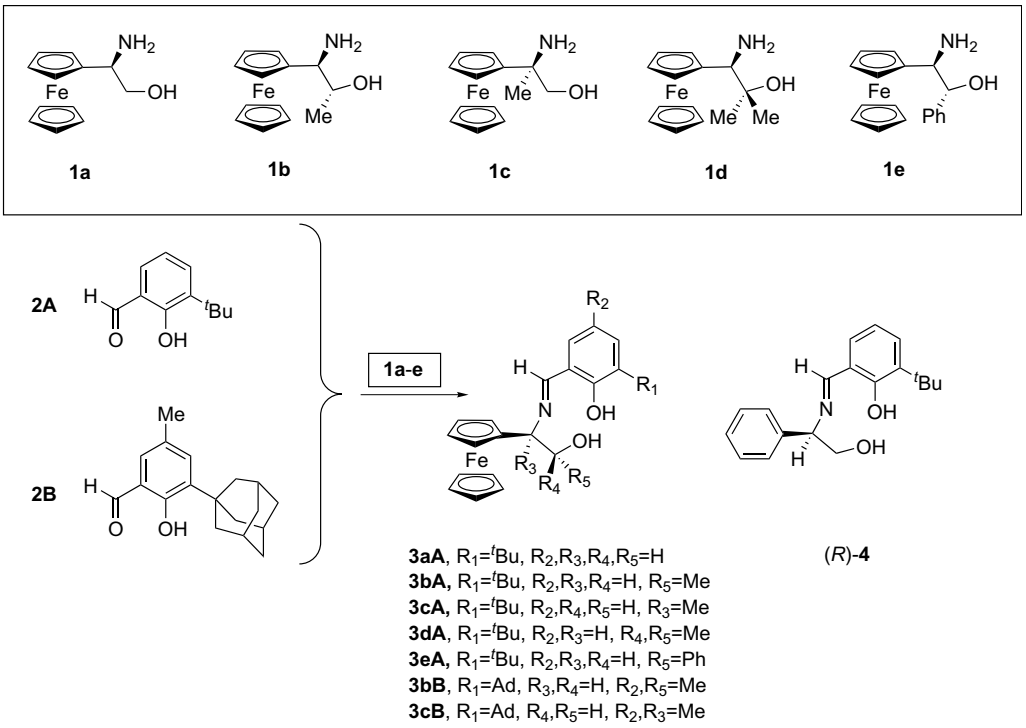
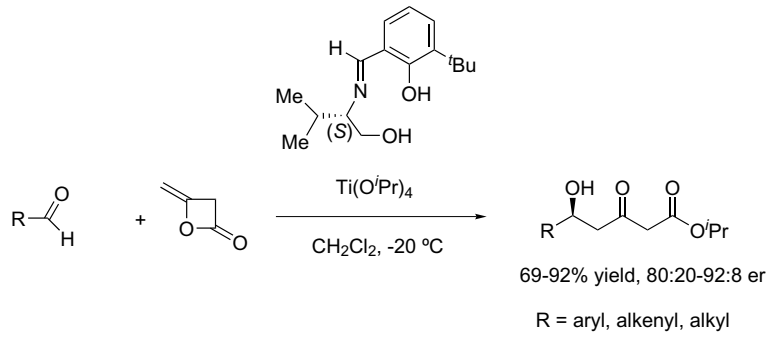


Figure 1. Chiral salicylaldehyde Schiff base ligands used in this work.



Scheme 1. Oguni's enantioselective approach to 5-hydroxy-3-oxoesters (Ref. 6a).

allowed the reaction to be performed with a 20 mol % amount of the Schiff base.[7] The diketene addition was assumed to proceed through an aldol type reaction of the aldehyde with a titanium enolate formed from diketene and the titanium alkoxide complex. When Schiff bases derived from (*S*)-valinol were used, the aldehydes were attacked from the *si* face by this enolate: a stereochemical outcome that was rationalized[6a] by the putative transition state depicted in Figure 2A. In this model, the octahedral titanium(IV) is coordinated in the same plane by the tridentate Schiff base and the enolate arising from diketene. The aldehyde is coordinated below this plane, *syn* to the isopropyl group of valinol, and oriented in such a way that the formyl hydrogen points towards the phenolic oxygen. In this way, the *si* face of benzaldehyde is attacked intramolecularly by the titanium enolate, leading to the predominant formation of the (*S*)-configured 5-hydroxy-3-oxoester. Shortly thereafter, Corey[8] suggested an alternative model for this reaction, based on the formation of a CH–O hydrogen bond. In the transition state model proposed by Corey (Fig. 2B), the octahedral titanium(IV) is also coordinated in the same plane by the tridentate Schiff base and the enolate. The benzaldehyde molecule occupies an apical position, now *anti* to the isopropyl substituent. The formation of an intramolecular hydrogen bond between the formyl hydrogen and the valinol oxygen orientates the aldehyde in order to expose its *si* face to the titanium enolate.

Optically active 5-hydroxy-3-oxoesters are useful intermediates in the synthesis of inhibitors of HMG–CoA reductase.[9] Over the past few years a number of other approaches to their enantioselective preparation have appeared in the literature;[10] Oguni's method, however, still stands out for the ready availability of both the reagents and the chiral ligand, as well as for the simplicity of the experimental procedure. We therefore felt that a re-examination of this reaction with Schiff bases derived from 2-

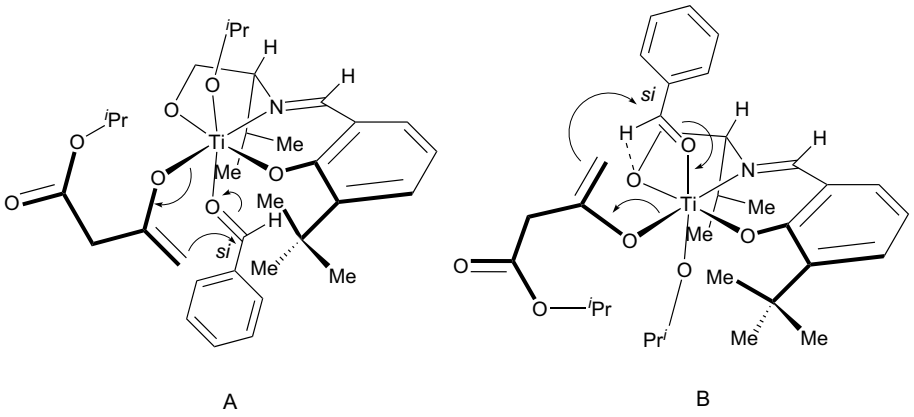


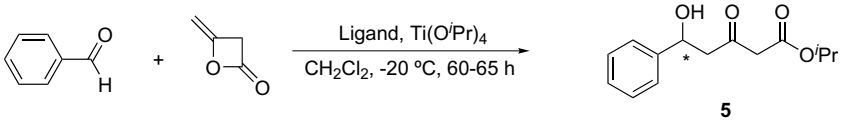
Figure 2. Transition state models for the enantioselective titanium-promoted diketene addition to benzaldehyde according to Oguni (A, Ref. 6a) and to Corey (B, Ref. 8).

ferrocenyl-2-amino alcohols would be worthwhile. Moreover, we reasoned that an investigation of the influence of the substitution of the amino alcohol moiety on the stereochemical outcome of the reaction could offer some clues on the mechanism of the reaction, by testing the predictive ability of both Oguni's[6a] and Corey's[8] models.

We began our study by performing the addition of diketene to benzaldehyde with the Schiff base ligand (*R*)-**4**, since we have previously observed that the degree of asymmetric induction exerted by the ferrocenyl group in chiral auxiliaries or ligands derived from amino alcohol **1a** is very similar to that of a phenyl group.[2f] According to the general protocol developed by Oguni,[6] a preformed dichloromethane solution of the titanium di(isopropoxide) complex of the Schiff base was stirred at −20 °C with an equimolar amount of benzaldehyde and two molar equivalents of diketene for 60–65 h. After the hydrolysis of the complex, isopropyl 5-hydroxy-5-phenyl-3-oxopropanoate **5** was isolated in 54% yield and with a 61:39 er (Table 1, entry 1). The result described by Oguni for this reaction, with the ligand (*S*)-**4**, was 56% yield and 55:45 er.[6a,b] Although Oguni did not specify the absolute configuration of oxoester **5** obtained under these conditions, it could be assumed, by inspection of the transition state models depicted in Figure 2, that the major enantiomer of our product would have an (*R*)-configuration, resulting from the addition to the *re*-face of the aldehyde with a ligand of configuration opposite to that of (*S*)-valinol. We were surprised to find, however, that both polarimetric and chromatographic data clearly showed that, in fact, the (*S*)-enantiomer of **5** was predominant in our mixture. This gave us a first indication of the fact that the predictive power of the transition state models previously proposed for this reaction[6a,8] was very limited.

In the presence of imine **3aA** (Table 1, entry 2), (*S*)-**5** was again obtained, in practically the same yield (53%) and enantiomeric purity (60:40 er). This result emphasizes the steric similarity of the ferrocenyl and the phenyl groups in the absence of conformational control of the former.[2f] According to the results reported in the preceding paper in this issue, the introduction of additional substituents at C_1 should modify the conformational preferences of the ferrocenyl group, bringing about significant changes in the stereochemical outcome of the product. In effect, the use of the Schiff base **3bA** (entry 3) reversed the enantiofacial selectivity of the addition, leading to the formation of (*R*)-**5** with increased enantioselectivity (85:15 er).

Table 1. Asymmetric addition of diketene to benzaldehyde promoted by chiral Schiff base (**3**, **4**)–titanium isopropoxide complexes



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Entry	Ligand	Yield[a] (%)	er[b]	Configuration[c]
1	(*R*)-**4**	54	61:39	(*S*)
2	**3aA**	53	60:40	(*S*)
3	**3bA**	51	15:85	(*R*)
4	**3cA**	69	77:23	(*S*)
5	**3dA**	18	0	—
6	**3eA**[d]	34	30:70	(*R*)
7	**3bB**	50	17:83	(*R*)
8	**3cB**	45	75:25	(*S*)

[a] Yield of isolated product **5** after chromatographic purification.
[b] By HPLC (Chiral PAK AD).
[c] By comparison of the sign of specific rotation values with those in the literature.[6a]
[d] Generated in situ by condensation of **2A** with **1e** before the addition of titanium tetra(isopropoxide).

A smaller increase in enantioselectivity with regard to **3aA** (up to 70:30 er) was observed in the case of ligand **3eA** (entry 6). Rather unexpectedly,[2f] the presence of a *gem*-dimethyl moiety at C_1 (ligand **3dA**, entry 5) produced racemic **5** in very low yield. Since the formation of the titanium alkoxide complex was also complete in this case, we speculated that the increased steric hindrance of this complex prevented the coordination of the aldehyde and/or the generation of the titanium enolate from diketene. The adamantyl-substituted Schiff base **3bB** (entry 7) behaved analogously to **3bA** (83:17 er in (*R*)-**5**). The presence of a methyl substituent at C_2 in amino alcohol **1c** did not bring about a reversal of the enantioface selectivity of the reaction with respect to ligands derived from **1a**; when using both **3cA** (entry 4) and **3cB** (entry 8) as chiral ligands, the (*S*)-enantiomer of **5** was again the major product of the diketene addition. On the other hand, the enantiomeric purity of the product was substantially increased (up to 77:23 er; 80:20 er when corrected for the enantiomeric purity of **1c**[2g]) with respect to that obtained with **3aA**. In summary, even if the best ligand identified in this study (**3bA**) afforded the addition product **5** in moderate yield and enantioselectivity, the intriguing trends observed in the variation of the stereochemical outcome of the reaction with the substitution pattern of the Schiff base ligands were not easily accommodated with current mechanistic models, and we concluded that a more detailed investigation of this issue was warranted.

2.2. Molecular modelling of intermediate complexes

Since imines **3bA** and **3cA** led to the formation of **5** with the highest enantiomeric purities, albeit with opposite absolute configuration (Table 1, entries 3 and 4), we selected these ligands to build a transition state model that could account for these results. Thus, we proposed that the reaction could take place via the titanium(IV) complexes depicted in Figure 3. In these complexes, the titanium atom has an approximately octahedral geometry and is coordinated by the *O*,*N*,*O* atoms of the Schiff base. The remaining three coordination sites are occupied by an isopropoxide ligand, benzaldehyde and the enolate derived from diketene, respectively. In this way, there are four possible geometrical isomers for each complex, depending on the position occupied by the enolate (*fac* or *mer* with respect to the Schiff base) and on the relative disposition of the isopropoxide and the ferrocenyl moieties (*syn* or *anti*). In each of these geometrical isomers, the coordinated benzaldehyde is oriented so as to minimize the steric interactions of the phenyl group with the rest of the complex. With this nomenclature, Oguni's model (Fig. 2A) corresponds to a *mer-anti* isomer, and Corey's model (Fig. 2B) is of the *mer-syn* type. As it can be seen in Figure 3, only the *fac-syn* isomer would lead to the predominant formation of (*R*)-**5**, by attack of the enolate to the *re* face of benzaldehyde; in the other three isomers, the (*S*)-enantiomer of **5** should be produced preferentially.

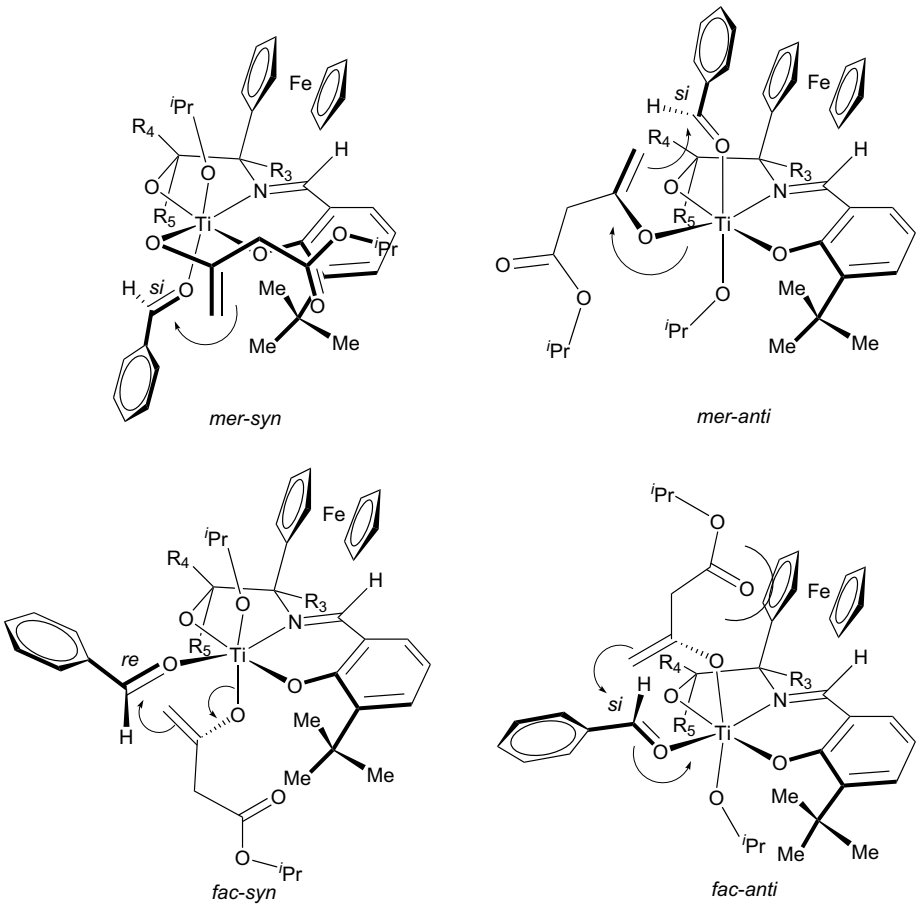

Figure 3. Geometrical isomers for the transition state complexes.

For both imines **3bA** and **3cA**, we optimized the geometries of these isomers by means of the SYBYL force-field[11] as implemented in the SPARTAN[12] package of programs. Two energetic minima were located for each isomer, corresponding to two different conformational arrangements of the ferrocenyl group:[2f] IN (when oriented towards the metallic centre) and OUT (when directed away from it). The calculated relative energies of the optimized structures are shown in Table 2. In all instances, the OUT conformer is less stable than the IN, due to the unfavourable interactions of the ferrocenyl group with the aromatic fragment (Fig. 4). Inspection of the molecular models shows that if the R_4 substituent is different from hydrogen, then the IN conformers are also destabilized, by repulsive interactions of this substituent with the ferrocenyl group. This could explain the low reactivity associated with the disubstituted ligand **3dA** (Table 1, entry 5). Finally, it is worth noting that the *fac-anti* isomers are much less stable than the other ones, because of the repulsion between the large enolate and the ferrocenyl fragments.

Table 2. Calculated relative energies (in kcal mol^{-1}) of the transition state models for the asymmetric addition of diketene to benzaldehyde promoted by the chiral Schiff base (**3bA**,**3cA**)–titanium isopropoxide complexes

Entry	Ligand	Isomer[a]	Rel. energy[b]	Configuration[c]
1	**3bA**	*mer-syn*-IN	3.8	(*S*)
2	**3bA**	*mer-syn*-OUT	4.9	(*S*)
3	**3bA**	*mer-anti*-IN	3.9	(*S*)
4	**3bA**	*mer-anti*-OUT	4.4	(*S*)
5	**3bA**	*fac-syn*-IN	2.9	(*R*)
6	**3bA**	*fac-syn*-OUT	4.5	(*R*)
7	**3bA**	*fac-anti*-IN	11.2	(*S*)
8	**3bA**	*fac-anti*-OUT	11.7	(*S*)
9	**3cA**	*mer-syn*-IN	0.5	(*S*)
10	**3cA**	*mer-syn*-OUT	2.7	(*S*)
11	**3cA**	*mer-anti*-IN	0.0	(*S*)
12	**3cA**	*mer-anti*-OUT	3.7	(*S*)
13	**3cA**	*fac-syn*-IN	0.7	(*R*)
14	**3cA**	*fac-syn*-OUT	4.7	(*R*)
15	**3cA**	*fac-anti*-IN	7.4	(*S*)
16	**3cA**	*fac-anti*-OUT	7.5	(*S*)

[a] See Figures 3 and 4.
[b] Relative final strain energies (in kcal mol^{-1}).
[c] Absolute configuration of the product obtained by intramolecular attack of the titanium enolate to the less hindered face of benzaldehyde.

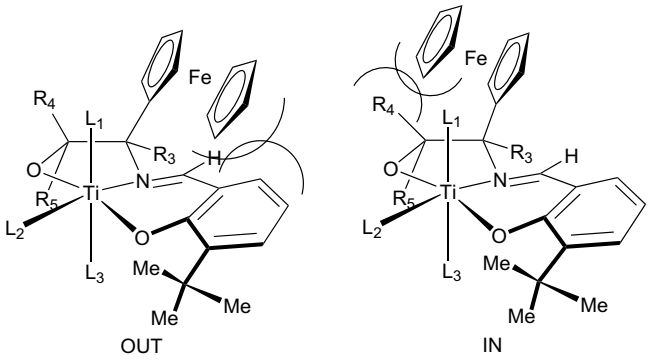

Figure 4. Limiting conformations of the ferrocenyl group in octahedral Schiff base titanium(IV) complexes. The OUT conformers are destabilized by repulsive interactions of the ferrocenyl group with the salicylaldehyde fragment. When R_4 is different from hydrogen, the IN conformers are also destabilized, by repulsive interactions of this substituent with the ferrocenyl group.

The two most stable isomers for imine **3cA** are the *mer-syn*-IN (Table 2, entry 9) and the *mer-anti*-IN (Table 2, entry 11); both lead to the predominant formation of product (*S*)-**5**. In Figure 5, we show the evolution of the *mer-syn*-IN transition state complex corresponding to **3cA** into the addition complex of (*S*) configuration.

In the case of imine **3bA**, the *mer-syn* and the *mer-anti* complexes are relatively destabilized with respect to the analogous ones in **3cA** (compare entries 1 and 3 with entries 9 and 11 in Table 2) because of steric repulsion between the methyl substituent at C_1 with the aldehyde (see Fig. 6 for an example). For this ligand, then, the most stable transition state complex is the *fac-syn*-IN (Table 2, entry 5), leading to the formation of (*R*)-**5** (see Fig. 7). Moreover, the energy difference between the *fac-syn*-IN complex and

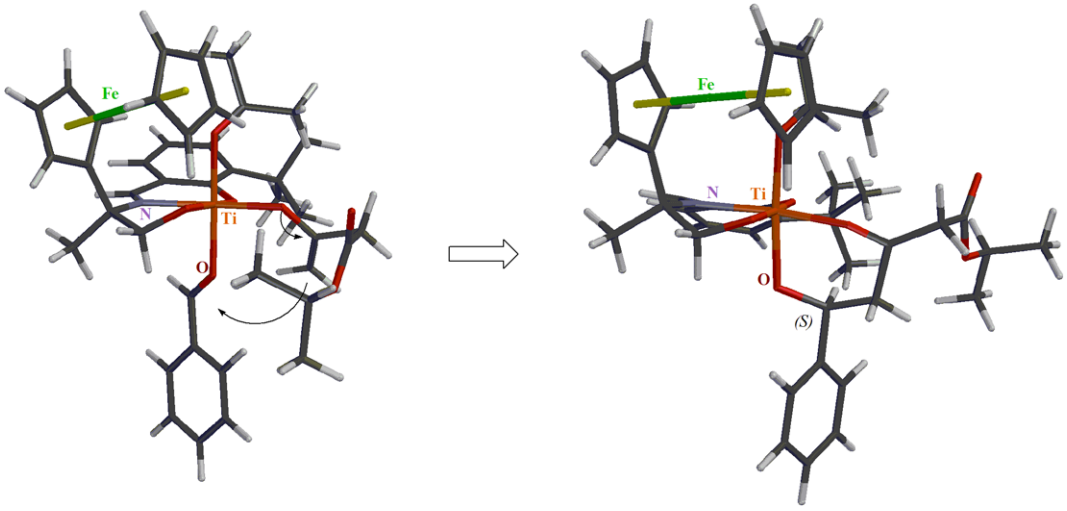

Figure 5. For imine **3cA**, the *mer-syn*-IN isomer of the transition state complex leads to the formation of (*S*)-**5**.

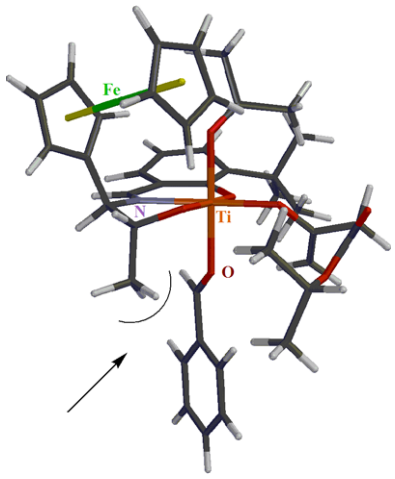

Figure 6. *mer-syn* Isomer of the transition state complex for imine **3cA**, showing the destabilizing interaction between the methyl substituent at C_1 and the coordinated aldehyde.

the most stable of the complexes leading to (*S*)-**5** (*mer-syn*-IN and *mer-anti*-IN, entries 1 and 3 of Table 2, respectively) is of 0.9–1.0 kcal mol^{-1}. In the case of **3cA**, the minimum energy gap between the most stable of the complexes leading to (*R*)-**5** (*fac-syn*-IN, entry 13, Table 2) and a complex leading to (*S*)-product (*mer-syn*-IN, entry 9, Table 2) is of 0.2 kcal mol^{-1} only; this is a fact that correlates well with the smaller enantioselectivity observed for this ligand.

3. Conclusions

In conclusion, the incorporation of 2-amino-2-ferrocenylalkanols **1a**–**e** into salicylaldehyde Schiff bases gives rise to a new class of chiral ligands whose titanium alkoxide complexes are able to promote the asymmetric addition of diketene to benzaldehydes. Both the enantioselectivity and the stereochemical outcome of these processes are controlled by the positioning of substituents in the 2-amino-2-ferrocenylethanol moiety. In particular, the titanium complexes of Schiff bases derived from (1*S*,2*R*)-1-amino-1-ferrocenyl-2-propanol **1b** and from (*S*)-2-amino-2-ferrocenyl-1-propanol **1c** exhibit strongly divergent enantiofacial selectivities in the reaction of benzaldehyde with diketene (preferential *re*-face addition and preferential *si*-face addition, respectively), a result for which no precedent can be found in the literature. Molecular mechanics calculations on the transition state complexes have led to a mechanistic model that is more comprehensive than those previously proposed for this reaction.

4. Experimental

4.1. General materials and methods

Optical rotations were measured at room temperature (23 °C); concentrations are given in g 100 ml^{-1}. Infrared spectra were recorded in a Fourier transform mode, using NaCl film techniques. NMR spectra were recorded in $CDCl_3$ solution. The reactions were run in flame- or oven-dried glassware under a N_2 atmosphere. Commercially available reagents (with the exception of benzaldehyde, which was distilled prior to use) were employed as received. Dichloromethane was distilled from calcium hydride. The preparation of Schiff bases **3aA**–**cB** is described in the preceding paper in this issue.

4.2. General procedure for the asymmetric addition of diketene to benzaldehyde mediated by Schiff base–titanium isopropoxide complexes

To a stirred solution of the Schiff base (1.0 mmol) in anhydrous dichloromethane (5.5 ml), under an argon atmosphere, titanium tetra(isopropoxide) (0.27 ml, 0.91 mmol) was added with the aid of a syringe and the resulting red-coloured solution was stirred at room temperature for 1 h. After cooling to −20 °C, freshly distilled benzaldehyde (92 μl, 0.91 mmol) and diketene (0.14 ml, 1.82 mmol) were sequentially added via a syringe and stirring was maintained for 60–65 h at the same temperature. After the addi-

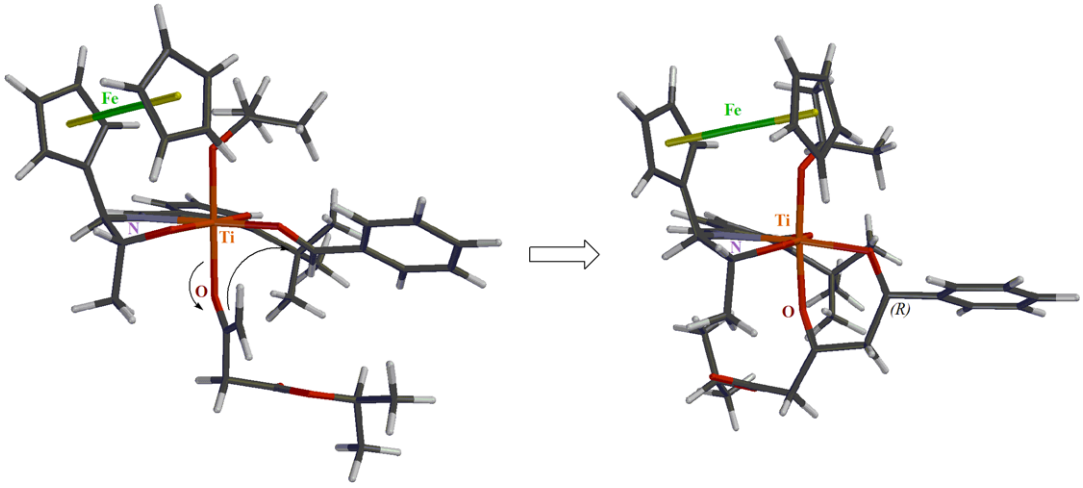

Figure 7. For imine **3bA**, the *fac-syn*-IN isomer of the transition state complex leads to the formation of (*R*)-**5**.

tion of isopropyl alcohol (0.36 ml), the reaction mixture was stirred at room temperature for 4 h, poured over a mixture of aqueous 0.1 M HCl (12 ml) and diethyl ether (12 ml) and stirred vigorously for 20–24 h at room temperature. The mixture was then extracted with diethyl ether (3×25 ml) and the combined extracts were washed with saturated aqueous sodium bicarbonate (2×25 ml) and with brine (2×25 ml), dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent, hexane–ethyl acetate mixtures of increasing polarity) to give isopropyl 5-hydroxy-5-phenyl-3-oxopentanoate **5**. The IR and the ^{1}H NMR spectra of this compound fully coincided with those described in the literature.[6a] $[\alpha]_D^{23}$ [(*R*)-**5**, 85:15 er] = +42.4 (*c* 0.66, $CHCl_3$) {lit.[6a] $[\alpha]_D^{24}$ [(*S*)-**5**, 92:8 er] = −40.8 (*c* 1.0, $CHCl_3$)}.

Conditions for the determination of the enantiomeric composition of **5**: Chiral PAK AD column, 95% hexane–5% isopropyl alcohol + 0.2% TFA, $\Phi = 1$ ml min^{-1}, $T = 25$ °C, $\lambda = 254$ nm, $t_{R((+)\text{-}(R)\text{-}\mathbf{5})} = 13.3$ min, $t_{R((-)\text{-}(S)\text{-}\mathbf{5})} = 21.8$ min.

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References

1. For some leading references, see: (a) Aratani, T.; Yoneyoshi, Y.; Nagase, T. *Tetrahedron Lett.* **1975**, 1707–1710; (b) Aratani, T. *Pure Appl. Chem.* **1985**, *57*, 1839–1844; (c) Desimoni, G.; Quadrelli, P.; Righetti, P. P. *Tetrahedron* **1990**, *46*, 2927–2934; (d) Bolm, C.; Bienewald, F. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2640–2642; (e) Fleischer, R.; Braun, M. *Synlett* **1998**, 1441–1443; (f) Cogan, D. A.; Liu, G.; Kim, K.; Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 8011–8019; (g) Oguni, N.; Miyagi, Y.; Itoh, K. *Tetrahedron Lett.* **1998**, *39*, 9023–9026; (h) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2398–2400; (i) Cai, L.; Mahmoud, H.; Han, Y. *Tetrahedron: Asymmetry* **1999**, *10*, 411–427; (j) Li, Z.; Liu, G.; Zheng, Z.; Chen, H. *Tetrahedron* **2000**, *56*, 7187–7191; (k) Flores-López, L. Z.; Parra-Hake, M.; Somanathan, R.; Walsh, P. J. *Organometallics* **2000**, *12*, 2153–2160; (l) Gademann, K.; Chavez, D. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2002**, *41*, 3059–3061; (m) Ruck, T. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 2882–2883; (n) Chavez, D. E.; Jacobsen, E. N. *Org. Lett.* **2003**, *5*, 2563–2565; (o) Gao, X.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 9038–9039.
2. (a) Catasús, M.; Bueno, A.; Moyano, A.; Maestro, M. A.; Mahía, J. *J. Organomet. Chem.* **2002**, *642*, 212–226; (b) Catasús, M.; Moyano, A.; Aggarwal, V. K. *Tetrahedron Lett.* **2002**, *43*, 3475–3479; (c) Moreno, R. M.; Bueno, A.; Moyano, A. *J. Organomet. Chem.* **2002**, *660*, 62–70; (d) Moyano, A.; Rosol, M.; Moreno, R. M.; López, C.; Maestro, M. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1865–1869; (e) Rosol, M.; Moyano, A. *J. Organomet. Chem.* **2005**, *609*, 2328–2333; (f) Bueno, A.; Moreno, R. M.; Moyano, A. *Tetrahedron: Asymmetry* **2005**, *16*, 1763–1778; (g) Moreno, R. M.; Bueno, A.; Moyano, A. *J. Org. Chem.* **2006**, *71*, 2528–2531.
3. A few ferrocenyl imines derived from the condensation of chiral ferrocenylamines with aromatic aldehydes have been used as ligands in asymmetric synthesis. See: (a) Hayashi, T.; Hayashi, C.; Uozomi, Y. *Tetrahedron: Asymmetry* **1995**, *6*, 2503–2506; (b) Kim, T.; Lee, H.; Ryu, E.; Park, D.-K.; Cho, C.; Shim, S. C.; Jeong, J. H. *J. Organomet. Chem.* **2002**, *649*, 258–267; (c) Hu, X.; Chen, H.; Dai, H.; Zheng, Z. *Tetrahedron: Asymmetry* **2003**, *14*, 3415–3421.
4. Izawa, T.; Mukaiyama, T. *Chem. Lett.* **1975**, 161–164.
5. Hayashi, M.; Inoue, T.; Oguni, N. *J. Chem. Soc., Chem. Commun.* **1994**, 341–342.
6. (a) Hayashi, M.; Inoue, T.; Miyamoto, Y.; Oguni, N. *Tetrahedron* **1994**, *50*, 4385–4398; (b) Oguni, N.; Hayashi, M.; Harada, M.; Matsushita, A. U.S. Patent 5,457,225; (c) Hayashi, M.; Kaneda, H.; Oguni, N. *Tetrahedron: Asymmetry* **1995**, *6*, 2511–2516.
7. (a) Hayashi, M.; Tanaka, H.; Oguni, N. *Tetrahedron: Asymmetry* **1995**, *61*, 1833–1836; (b) Oguni, N.; Tanaka, K.; Ishida, H. *Synlett* **1998**, 601–602.
8. Corey, E. J.; Barnes-Seeman, D.; Lee, T. W. *Tetrahedron Lett.* **1997**, *38*, 4351–4354.
9. (a) Tobert, J. A. *Nat. Rev. Drug Discov.* **2003**, *2*, 517–526; (b) Bagi, C. M. *IDrugs* **2002**, *5*, 266–277; (c) Illingworth, D. R.; Tobert, J. A. *Adv. Protein Chem.* **2001**, *56*, 77–114; (d) McFarlane, I. M.; Newton, C. G.; Pitchen, P. Synthesis of the common lactone moiety of HMG–CoA reductase inhibitors. In *Process Chemistry in the Pharmaceutical Industry*; Gadamasetti, K. G., Ed.; M. Dekker: New York, 1999; pp 243–259; (e) Roth, B. D.; Blankley, C. J.; Chucholowski, A. W.; Ferguson, E.; Hoefle, M. L.; Ortwine, D. F.; Newton, R. S.; Sekerke, C. S.; Sliskovic, D. R.; Stratton, C. D.; Wilson, M. W. *J. Med. Chem.* **1991**, *34*, 357–366.
10. (a) Singer, R. A.; Carreira, E. M. *J. Am. Chem. Soc.* **1995**, *117*, 12360–12361; (b) Krüger, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837–838; (c) Krüger, J.; Carreira, E. M. *Tetrahedron Lett.* **1998**, *39*, 7013–7016; (d) Pagenkopf, P. L.; Krüger, J.; Stojanovic, A.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 3124–3126; (e) Keck, G. E.; Yu, T. *Org. Lett.* **1999**, *1*, 289–291; (f) Soriente, A.; De Rosa, M.; Villano, R.; Scettri, A. *Tetrahedron: Asymmetry* **2000**, *11*, 2255–2258; (g) De Rosa, M.; Soriente, A.; Scettri, A. *Tetrahedron: Asymmetry* **2000**, *11*, 3187–3195; (h) Soriente, A.; De Rosa, M.; Stanzione, M.; Villano, R.; Scettri, A. *Tetrahedron: Asymmetry* **2001**, *12*, 959–963; (i) Snider, B. B.; Song, F. *Org. Lett.* **2001**, *3*, 1817–1820; (j) Brennan, C. J.; Campagne, J.-M. *Tetrahedron Lett.* **2001**, *42*, 5195–5197; (k) 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*, 669–685; (l) Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J. *J. Am. Chem. Soc.* **2000**, *122*, 10033–10046; (m) Yanagisawa, A.; Matsumoto, Y.; Asakawa, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 892–893; (n) Denmark, S. E.; Beutner, G. L. *J. Am. Chem. Soc.* **2003**, *125*, 7800–7801; (o) Denmark, S. E.; Beutner, G. L.; Wynn, T.; Eastgate, M. D. *J. Am. Chem. Soc.* **2005**, *127*, 3774–3789; (p) Kawase, T.; Takizawa, S.; Jayakrapash, D.; Sasai, H. *Synth. Commun.* **2004**, *34*, 4487–4492; (q) Gondi, V. B.; Gravel, M.; Rawal, V. H. *Org. Lett.* **2005**, *7*, 5657–5660.
11. Clark, M.; Cramer, R. D., III; van Opdenbosch, N. *J. Comput. Chem.* **1989**, *10*, 982–1012.
12. SPARTAN, version 4.1.1, Wavefunction Inc., 18401 Von Karman Ave., Suite 370, Irvine, CA 92162.