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Peri- and Enantioselectivity of Thermal, Scandium-, and [Pybox/Scandium]-Catalyzed Diels–Alder and Hetero-Diels–Alder Reactions of Methyl (*E*)-2-Oxo-4-aryl-butenoates with Cyclopentadiene

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Abstract: The cycloaddition between methyl (*E*)-2-oxo-4-aryl-3-butenoates (**2a–d**) and cyclopentadiene, in addition to the expected normal Diels–Alder (DA) adducts *endo*-**3a–d** and *exo*-**4a–d**, gives the less expected *endo*-**5a–d** products of the [4+2] hetero-Diels–Alder (HDA) reaction in which the α-ketoester behaves as a heterodiene. If a comparison is made between the thermal and the scandium(III) triflate-catalyzed conditions, the periselectivity changes and whereas under thermal conditions the main products are those from the DA reaction (**3a–d**), in the presence of $Sc(OTf)_3$ (OTf = triflate), the HDA products **5a–d** become largely predominant. The reactions are enantioselectively catalyzed by the scandium(III) triflate complex of (4′*S*,5′*S*)-2,6-bis[4′-(triisopropylsilyl)-oxymethyl-5′-phenyl-1′,3′-oxazolin-2′-yl]pyridine (**1**) and both the DA and the HDA products are obtained with excellent enantiomeric excess, up to >99% *ee*. The X-ray crystallographic structure determination of **5c** assigns it the 4*R*,4a*S*,7a*R* absolute configuration. The thermal retro-Claisen rearrangement of **3c** into (4*R*,4a*S*,7a*R*)-**5c** allows the correlation of their absolute configuration, and **3c** has therefore the 2*R*,3*R* configuration. By analogy the same absolute configuration can be assigned to **3a**,**b**,**d** and **5a**,**b**,**d**, and the stereospecific thermal Claisen rearrangement of the optically active **5a**,**b**,**d** into **3a**,**b**,**d** completes the correlation between their absolute configuration. The [3,3]-sigmatropic rearrangements can be easily carried out under catalytic conditions with scandium(III) triflate, which promotes the equilibration between **3a–d** and **5a–d**, with a different degree of enantioselectivity characterizing the process starting from **3a–d** or **5a–d**. The unambiguous attributions of the configuration to the products allows us to propose a rationale of the stereochemical outcome of the catalyzed cycloaddition and to investigate the reaction mechanism of the competing DA and HDA reactions and shifts in products distribution by acid catalysis.

Keywords: asymmetric catalysis · cycloaddition · enantioselectivity · periselectivity · pybox

Introduction

The [4+2] cycloaddition between two different dienes,[1–3] such as that involving a diene and an heterodiene, is an up-to-date argument from both the theoretical and synthetic points of view.[4–9] The periselectivity of the competing Diels–Alder (DA) and hetero-Diels–Alder (HDA) reactions may arise from 1) two distinct reaction pathways; 2) a single reaction pathway that bifurcates after the transition state; 3) a partial conversion of the primary cycloadduct of the pericyclic reaction into the second one. A way to infer these different options can be the comparison of the change of the periselectivity observed in the uncatalyzed and Lewis acid catalyzed reactions.

A typical example is given by the reaction of cyclopentadiene (Cp) with an α,β-unsaturated carbonyl derivative: Cp may behave either as the 4π component to give the normal DA cycloadduct or, less usually, as the 2π component to furnish the HDA cycloadduct. Two specific cycloadditions that satisfy such features have been studied: the reactions of Cp with either α-keto-β,γ-unsaturated phosphonates or (*E*)-2-oxo-4-phenyl-butenoate.

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Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author. pybox = pyridine-bis(oxazoline).

In the first case, synthetic studies were carried out independently by Evans et al.[10,11] and Hanessian and Compain[12] with and without a Lewis acid catalyst, whereas a computational investigation has been more recently been reported by Houk and co-workers.[13] Evans further contributed to insight into the reaction by investigating enantioselective catalysis with a Cu^{II} complex of 4-*tert*-butylbis(oxazoline): both the DA and HDA cycloadducts were obtained with good or excellent diastereo- and enantioselectivities.

The second example concerns the catalyzed reaction between Cp and methyl (*E*)-2-oxo-4-phenyl-butenoate (**2a**). After initial studies by Kanemasa et al.[14] and Zhou and Tang,[15] the effect of the lanthanide–triflate complexes of (4′*S*,5′*S*)-2,6-bis[4′-(triisopropylsilyl)oxymethyl-5′-phenyl-1′,3′-oxazolin-2′-yl]pyridine (**1**) as chiral catalysts was investigated (Scheme 1).[16] It was found that the best enantioselective catalyst was based on the Sc^{III} ion since both the DA product, *endo*-**3a**, and the HDA product, *endo*-**5a**, were obtained with almost complete enantioselectivity.

Whereas the absolute configuration of the DA product between Cp and dimethyl (but-2-enoyl)phosphonate was determined through chemical correlation,[11] the absolute configuration of product **3a**, with a negative optical rotation, was assumed to be the 2*R*,3*R* isomer[14–16] on the basis of confident considerations about the structure of the reactive intermediates. Furthermore, the stereospecific [3,3]-Claisen rearrangement of **5a** into **3a**, carried out under thermal conditions, allowed the correlation of the absolute configuration of these products.[16]

With these results in hand, the cycloaddition involving methyl (*E*)-2-oxo-4-aryl-butenoates (**2**) was chosen as a model to further infer the periselectivity between DA and HDA reactions under either thermal or catalyzed conditions, to determine the absolute configuration of the products, and to verify the possible interconversion between **3** and **5**.

Results and Discussion

To test the selectivity of several α,β-unsaturated carbonyl derivatives, four different methyl (*E*)-2-oxo-4-aryl-but-3-enoates (**2a**–**d**) were synthesized, and their reactions with Cp were investigated in the absence of any catalyst at ambient temperature. The reaction conditions and the results are reported in Table 1 (entries 1–4): the yields were excellent

Table 1. Uncatalyzed and Sc^{III}-catalyzed DA and HDA reactions between **2a**–**d** and Cp in CH_2Cl_2.

Entry	Substrate	Catalyst[a]	*T* [°C]	Time	Yield [%]	[**3**+**4**]/[**5**]	[**3**]/[**4**]
1	**2a**	–	ambient	24 h	quant.	82:18	83:17
2	**2b**	–	ambient	5 days	quant.	89:11	87:13
3	**2c**	–	ambient	10 h	quant.	92:8	81:19
4	**2d**	–	ambient	4 days	quant	92:8	77:23
5	**2a**	$Sc(OTf)_3$	−50	15 min	quant.	35:65	89:11
6	**2b**	$Sc(OTf)_3$	−70	15 min	quant.	86:14	95:5
7	**2c**	$Sc(OTf)_3$	−70	15 min	quant.	90:10	92:8
8	**2d**	$Sc(OTf)_3$	−70	5 h	55[b]	38:62	91:9
9	**2a**	$Sc(OTf)_3$	−50	3 days	quant.	41:59	92:8
10	**2b**	$Sc(OTf)_3$	−70	3 days	97	73:27	>95:<5
11	**2c**	$Sc(OTf)_3$	−70	3 days	quant.	85:15	91:9
12	**2d**	$Sc(OTf)_3$	−70	3 days	80[b]	47:53	89:11

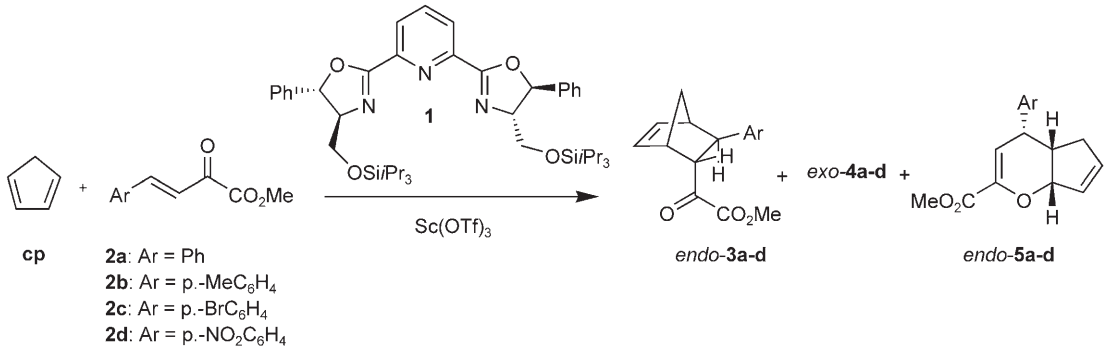
[a] Loading = 10 mol%. [b] Consistent amount of **2d** was isolated.

and in each case the main product was derived from the *endo*-DA pathway (**3a**–**d**), with the DA selectivity ranging from 82 to 92% and the *endo* selectivity from 77 to 87%.

When the same reactions were run in the presence of $Sc(OTf)_3$ (OTf = triflate) at low temperature, no significant change in the periselectivity was evident in the case of **2b** and **2c** (Table 1, entries 6 and 7), while cycloadditions starting from **2a** and **2d** clearly showed an inversion of the periselectivity in favor of the HDA adducts **5a** and **5d** (Table 1, entries 5 and 8), which became the main reaction products as previously observed in the reaction involving α-keto-β,γ-unsaturated phosphonates.[12]

The next step was the investigation of the same reactions under enantioselective catalytic conditions with the complex of $Sc(OTf)_3$ and (4′*S*,5′*S*)-2,6-bis[4′-(triisopropylsilyl)oxymethyl-5′-phenyl-1′,3′-oxazolin-2′-yl]pyridine) (**1**). The reactions were carried out with 10% of catalyst and 3-Å molecular sieves (MS; Table 2).

The DA products **3** and **4** were separated from **5** by column chromatography, the DA adduct ratios were determined by ^1H NMR spectroscopic analysis and the enantiomeric excess of **3**–**5** by chiral HPLC (Table 2), except in the



cp

2a: Ar = Ph
2b: Ar = p.-MeC$_6$H$_4$
2c: Ar = p.-BrC$_6$H$_4$
2d: Ar = p.-NO$_2$C$_6$H$_4$

endo-**3a-d**

endo-**5a-d**

Scheme 1. The lanthanide triflate complexes of **1** as chiral catalysts in the DA and HDA reactions between **cp** and **2**.

Table 2. DA and HDA reactions between **2a–d** and Cp in CH_2Cl_2 in the presence of 10 mol% of the **1**/Sc(OTf)$_3$ complex and 3-Å MS.

Entry	Substrate	T [°C]	Time	Yield [%][a]	[3+4]/[5]	[3]/[4]	**3** % *ee*[b] conf.	**5** % *ee*[c] conf.
1[d]	**2a**	−50	15 min	99	34:66	95:5	99.5 (2*R*,3*R*)-**3a**	99.5 (4*R*,4a*S*,7a*R*)-**5a**
2	**2b**	−70	15 min	93	33:67	95:5	99.5 (2*R*,3*R*)-**3b**	>99.5 (4*R*,4a*S*,7a*R*)-**5b**
3	**2c**	−70	15 min	99	35:65	95:5	99 (2*R*,3*R*)-**3c**	99.5 (4*R*,4a*S*,7a*R*)-**5c**
4	**2d**[e]	−70	4 h	84	39:61	93:7	99 (2*R*,3*R*)-**3d**	99 (4*R*,4a*S*,7a*R*)-**5d**

[a] Yields of the isolated products. [b] Determined by HPLC with a Chiralpak AD column (for adduct **3c**, see the Experimental Section for details). [c] Determined by HPLC with a Chiralcel OJ column (for adducts **5b** and **5d**, see the Experimental Section for details). [d] Data confirming those of ref. [16]. [e] Compound **2d** is poorly soluble in CH_2Cl_2.

cases of **3c** and **5b** whose enantiomers could not be separated. In the case of **5c**, an accurate crystallization allowed us to obtain crystals suitable for X-ray crystal structure determination: the absolute configuration of **5c** was therefore unambiguously determined to be 4*R*,4a*S*,7a*R* (Figure 1).

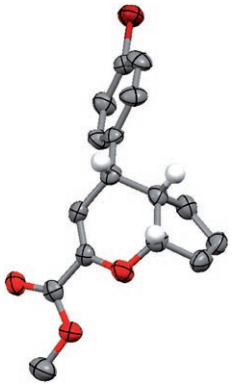


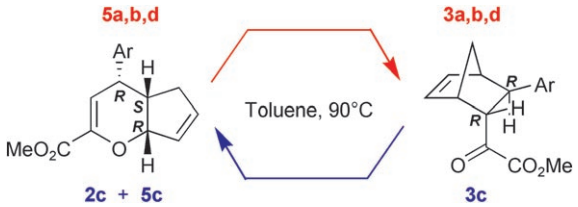
Figure 1. X-ray structure of **5c**, thus confirming the absolute 4*R*,4a*S*,7a*R* configuration.

Having determined the absolute configuration of **5c**, the relationship between **5c** and **3c** was a key point in assigning an absolute configuration to the DA adduct.

Previously, we easily obtained the correlation between HDA and DA cycloadducts by a thermal conversion of **5a** into **3a** following a stereospecific Claisen [3,3]-sigmatropic rearrangement, whereas, under the same conditions, **3a** gave only the retro-DA reaction.[16] Hence, the stereospecific sigmatropic rearrangement **3**→**5** could be a useful tool both to correlate absolute configurations and to determine the enantiomeric purity when chiral HPLC analysis is unable to separate the enantiomers of **3c** or **5b** or when the separation is somewhat difficult (e.g., **5d**).

Following the protocol used for **5a**, the enantiomeric purity of **5b**,**d** was easily obtained by determining the enantiomeric excess of **3b**,**d**, derived from their thermal conversion (Table 2, entries 2 and 4). In the case of **3c**, despite the possibility of the retro-DA reaction, the importance of determining its absolute configuration forced us to attempt the **3c**→**5c** conversion under thermal conditions (Scheme 2). Besides **2c** deriving from the retro-DA process, the enantiomer (4*R*,4a*S*,7a*R*)-**5c** was isolated with 99% *ee*, which allows us to attribute the 2*R*,3*R* configuration to the DA adduct **3c** as well its enantiomeric purity (Table 2, entry 3).

From the univocal attribution of the absolute configuration of **3c** and **5c**, by analogy, the same absolute configurations 2*R*,3*R* and 4*R*,4a*S*,7a*R* can be proposed for the DA adducts **3a**,**b**,**d** and the HDA adducts **5a**,**b**,**d**, respectively. This attribution confirms the previous proposal based on considerations about the structure of the octahedral reactive intermediate **6** involved in the catalytic process (Figure 2).[16]



Scheme 2. The interconversion between **3** and **5** under thermal conditions.

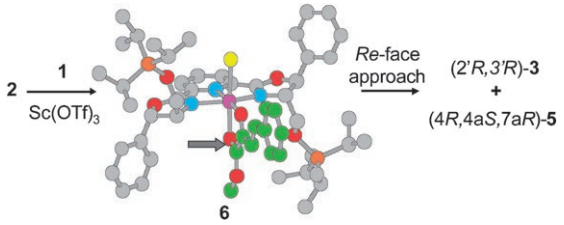
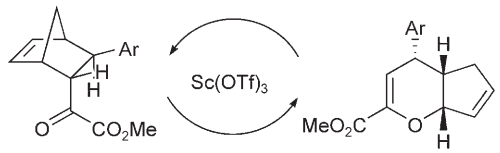


Figure 2. The assumed reactive intermediate **6** in the DA and HDA reactions between **2** and Cp catalyzed by the Sc(OTf)$_3$ complex of pybox **1**, which gives (2*R*,3*R*)-**3** and (4*R*,4a*S*,7a*R*)-**5**. pybox = pyridinebis(oxazoline).

To exclude the possibility that the periselectivity of the competing DA and HDA reactions arises from a partial conversion between primary cycloadducts, the stability of **3a–d** and **5a–d** toward Sc(OTf)$_3$ and the possible loss of stereochemistry during their eventual conversion must be checked (Scheme 3).

First, the reactions of **2a–d** with Cp at low temperature in the presence of Sc(OTf)$_3$ were carried out for a longer reaction time (3 days) to show possible equilibration of the products (Table 1, entries 5–8 versus 9–12). The yields were again good, but the isomer distribution was somewhat changed. These results suggest that the periselectivity obtained from the Sc(OTf)$_3$-catalyzed reaction may be altered (even if not dramatically) by product isomerization occurring under the reaction conditions.



(2*R*,3*R*)-**3a-d** (4*R*,4a*S*,7a*R*)-**5a-d**

Scheme 3. Investigation into the stability of **3a–d** and **5a–d** to $Sc(OTf)_3$.

In the study of DA/HDA cycloadditions, the retro-Claisen rearrangement of products catalyzed with a Lewis acid has been already reported in the case of the DA product of diethyl α-crotonylphosphonate,[12] therefore it should be interesting to study the conversions of **3** and **5** in the presence of $Sc(OTf)_3$ and to extend the study to the optically active products to check the eventual loss of stereochemistry, a subject that to our knowledge has not yet been explored. The conditions first employed were those under which the catalyzed reaction was carried out (Table 1, entries 5–8); if the adducts were stable, then they were warmed up at ambient temperature (Table 3).

Table 3. [3,3]-Sigmatropic rearrangement of (2*R*,3*R*)-**3** and (4*R*,4a*S*,7a*R*)-**5** catalyzed by $Sc(OTf)_3$.[a]

Entry	Reagent	*T* [°C]	Time	Product distribution (**3**/**5**)[b]
1	**3a**	−50	24 h[c]	89:11 (**3a**/**5a**)
2	**3a**	ambient	24 h	85:15 (**3a**/**5a**)
3	**5a**	−50	15 min	decomposition of **5a** (no **3a**)
4	**5a**[d]	−50	24 h	38:62 (**3a**/**5a**)
5	**5a**[d]	ambient	3 h	85:15 (**3a**/**5a**)
6	**3b**	−50	24 h[e]	89:11 (**3b**/**5b**)
7	**3b**	ambient	6 h	86:14 (**3b**/**5b**)
8	**5b**	−70	15 min	decomposition of **5b** (no **3b**)
9	**5b**[f]	−70	24 h[g]	8:92 (**3b**/**5b**)
10	**5b**[f]	ambient	3 h	81:19 (**3b**/**5b**)
11	**3c**	−70	10 h	**3c**
12	**3c**	ambient	45 min	89:11 (**3c**/**5c**)
13	**5c**	−70	10 h	**5c**
14	**5c**	ambient	8 h	87:13 (**3c**/**5c**)
15	**3d**	−70	5 days	**3d**
16	**3d**	ambient	3 h	86:14 (**3d**/**5d**)
17	**5d**	−70	5 days	**5d**
18	**5d**	ambient	3 h	83:17 (**3d**/**5d**)

[a] About 0.1 mmol of reagent (when **3** is used as the reagent, it is contaminated with **4**); 10% catalyst in CH_2Cl_2. [b] Variable amounts **4** are present. [c] Compound **5a** begins to form after 35 min. [d] Addition of 0.05 mmol of **2a**. [e] Compound **5b** begins to form after 35 min. [f] Addition of 0.05 mmol of **2b**. [g] Compound **3b** begins to form after 1 h.

The data in Table 3 show a significant constancy in the product distribution at ambient temperature (with a preference for the DA products), starting either from **3a–d** or **5c**,**d**, the ratio of which can be the result of an equilibrium. Two results (Table 3, entries 3 and 8) seem at a first glance to be illogical. In the presence of $Sc(OTf)_3$, **5a** and **5b** decompose at −50 (−70) °C within a short time. On the other hand, adducts **5a**,**b** have been obtained under similar conditions from the reaction of **2a**,**b** and Cp catalyzed by $Sc(OTf)_3$ and were found to be stable for a longer reaction time (Table 1, entries 5, 6, 9, and 10). Since their formation occurs in the presence of **2a** and **2b**, respectively, the test of the stability of the HDA products at −50 °C was therefore repeated in the presence of 0.5 equivalents of either **2a** or **2b**, thus simulating, as far as possible, the reaction conditions (see the Supporting Information). Under these conditions, the equilibration of the HDA products to the corresponding DA adducts occurred without any decomposition (Table 3, entries 4, 5, 9, and 10), and the influence of the α-dicarbonyl fragment of **2a**,**b**, able to coordinate the scandium cation, cannot be ignored.

The conversion of **3a–d** into **5a–d** (or vice versa) catalyzed by $Sc(OTf)_3$ could either occur through a process that does not modify the chiral centers of the DA and HDA adducts (in analogy to the thermal processes) or through a non-stereoselective rearrangement. To cast aside any doubt, a pair of enantiopure isomers must be submitted to the catalyzed conversion, thus checking the variation of the optical purity of each stereoisomer. Only **3d** and **5d** ensure easy HPLC analysis and product stability, therefore they were treated with $Sc(OTf)_3$ at ambient temperature (Table 4).

Table 4. [3,3]-Sigmatropic rearrangement of (2*R*,3*R*)-**3d** and (4*R*,4a*S*,7a*R*)-**5d** catalyzed by $Sc(OTf)_3$.[a]

Entry	Starting isomer	Time [min]	**3d** Yield [%]	**3d** *ee* [%]	**4d** Yield [%][b]	**4d** Yield [%]	**5d** *ee* [%]
1	**3d**	0	96	99	4	–	–
2	**3d**	10	85	99	5	10	99
3	**3d**	60	71	49	15	14	61
4	**5d**	0	–	–	–	100	99
5	**5d**	10	70	99	3	27	99
6	**5d**	60	81	99	4	15	99
7	**5d**	300	52	*rac*	30	18	37

[a] At ambient temperature. [b] *exo*-**4d** has always a significant *ee* value.

Both **3d** (containing 4% **4d**) and **5d**, which are stable at −70 °C, begin to rearrange within five minutes when treated with $Sc(OTf)_3$ at ambient temperature. The composition of the mixtures obtained from both **3d** and **5d** after 10 and 60 minutes was determined to check the enantiomeric excess of both the residual and developing products. After 10 minutes the mixtures were not yet fully equilibrated, and the enantiomeric excess was that of the starting product (Table 4, entries 2 and 5). After one hour, either starting from **3d** or **5d**, the ratio of **3d**(+**4d**)/**5d** was the same as that found in the previous equilibrations (Table 3, entries 16 and 18), but two different results were observed. When **3d** is the starting product, the enantiomeric excess of both **3d** and **5d** drops and the amount of **4d** strongly increases (Table 4, entry 3). When **5d** is the starting product (Table 4, entry 6), after one hour the enantiomeric purities of both the developing **3d** and the residual **5d** do not change and the rearrangement is stereospecific. When **5d** is in the presence of scandium triflate for 5 hours, the amount of **4d** strongly increases, both **3d** and **5d** loose their enantiomeric purities, and the behavior of **5d** tends to that observed for **3d** (Table 4, entry 7).

Therefore, the beginning of the scandium-catalyzed rearrangement can be classified as a stereospecific [3,3]-sigmatropic rearrangement as in the case of the thermal reaction. Then, starting either from **3d** or **5d**, the prolonged interaction between the substrate and Lewis acid promotes other processes whose mechanisms deserve further investigation.[17]

Finally, about the isomer distribution and the competing DA and HDA cycloadditions in the enantioselective reactions catalyzed by the complex between **1** and $Sc(OTf)_3$, the same enantiomeric excess obtained for both the DA and HDA products (Table 2) certainly does not suggest two distinct reaction pathways. To understand whether their formation occurs from a single reaction pathway that bifurcates after the transition state, thus giving the different products, or from the partial stereospecific conversion of one single product into the second one, (2*R*,3*R*)-**3a–d** and (4*R*,4a*S*,7a*R*)-**5a–d** were treated with the $Sc(OTf)_3$/pybox **1** complex under the reaction conditions (Table 2) and no product equilibration was observed. This control experiment has been already been carried out by Evans et al.[11] on the enantiopure DA and HDA adducts obtained from the reaction between α-keto-β,γ-unsaturated phosphonates and Cp catalyzed by a *tert*-butyl-box/$Cu(SbF_6)_2$ (box = bis(oxazoline)) complex, and also in this case no product conversion occurred. Hence, also the DA and HDA cycloadducts obtained in the reactions between **2a–d** and Cp in the presence of the $Sc(OTf)_3$/pybox **1** catalyst are primary products, thus confirming the existence of a single transition state that leads to adducts **3** and **5**.

Conclusions

Pybox units are excellent ligands that give rise to catalysts for several enantioselective reactions.[18] Especially, the lanthanide complexes of pybox **1** have already been used as efficient catalysts in the enantioselective DA and Mukaiyama–Michael reactions with acryloyl- and crotonoyloxazolidinones[19] and in the Mukaiyama–aldol reaction of pyruvates.[20] The complex **1**/$Sc(OTf)_3$ is a very efficient stereoselective catalyst of the DA and HDA reactions between cyclopentadiene and methyl (*E*)-2-oxo-4-aryl-3-butenoates (**2a–d**), thus allowing excellent control of both the diastereo- and enantioselectivities, both in the DA (**3a–d**) and HDA (**5a–d**) reactions, with enantiomeric excess not easily obtainable with other optically active catalysts.[14,15]

The X-ray structure of **5c** allowed us to determine its absolute configuration as 4*R*,4a*S*,7a*R*, and the conversion of (4*R*,4a*S*,7a*R*)-**5c** into **3c**, through a stereospecific retro-Claisen rearrangement, allowed us to determine the absolute configuration of the latter as 2*R*,3*R*, thus confirming the previously proposed configuration on the basis of mechanistic considerations.[16] By analogy, the same absolute configuration can be attributed to **3b**,**d** and **5b**,**d**. In this context, the stereospecific rearrangement between **3** and **5** has been found to be a useful tool to correlate absolute configurations and to determine the enantiomeric purity of products not separable by chiral HPLC analysis.

The stability of either racemic **3a–d** and **5a–d** or enantiopure **3d** and **5d** in the presence of $Sc(OTf)_3$ was checked at low and ambient temperature, with and without **1**. From the results the following features can be pointed out:

1. The equilibrations set up at ambient temperature starting from racemic **3a–d** and **5a–d** are complete within a few hours, thus giving rise to a DA/HDA product ratio of about 85:15 independent of the starting materials.
2. If the previous reactions are carried out at low temperature, equilibration is slower and incomplete in the case of **3a**,**b** and **5a**,**b** or completely absent for **3c**,**d** and **5c**,**d**.
3. The complex **1**/$Sc(OTf)_3$ does not promote any isomerization under the reaction conditions, and both the DA and HDA products are stable.

From this evidence, great care is required in the comparison between the periselectivity observed in the uncatalyzed and the $Sc(OTf)_3$-catalyzed reactions, and it cannot be excluded that the DA/HDA ratio could sometimes be altered from a partial equilibration of the primary reaction products induced by the Sc^{III} cation. These problems are fully avoided when the reactions are catalyzed by the complex **1**/$Sc(OTf)_3$ since cycloadducts **3a–d** and **5a–d** have been found to be the kinetically controlled products. Since the enantiomeric purities of both the DA and HDA isomers are the same, we can conclude that the discovery by Houk and co-workers[13] that the competition between the DA and HDA processes can arise from a single reaction pathway that bifurcates after the transition state rationalizes the results of the above study concerning the enantioselective reaction between **2a–d** and Cp catalyzed by the complex **1**/$Sc(OTf)_3$.

Experimental Section

General: Melting points were determined by the capillary method and are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively ($CDCl_3$, 25 °C, trimethylsilane (TMS)). IR spectra were registered on a Perkin-Elmer RX I spectrophotometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Separation and purification of the products was carried out by column chromatography on Merck silica gel 60 (230–400 mesh). The enantiomeric excess (*ee*) of the products was determined by HPLC using Daicel columns: Chiralpak AD for **3a**,**b**,**d** and Chiralcel OJ for **5a**,**c**,**d**.

Materials: Dichloromethane, hydrocarbon-stabilized ACS grade from Aldrich, was distilled from calcium hydride and used immediately. Scandium triflate was obtained from Aldrich as the ACS reagent. Powdered molecular sieves (3 Å) were obtained from Aldrich and were heated under vacuum at 300 °C for 5 h and kept in sealed vials in a dryer. (4′*S*,5′*S*)-2,6-Bis[4′-(triisopropylsilyl)oxymethyl-5′-phenyl-1′,3′-oxazolin-2′-yl]pyridine (**1**) was prepared as previously described.[19] (*E*)-2-Oxo-4-phenylbut-3-enoic acid methyl ester (**2a**) was prepared, following a previously reported method,[21,22] from esterification with methanol of the potassium salt, obtained from benzaldehyde and pyruvic acid in the presence of KOH. Yellow needles were obtained from diisopropyl ether (m.p. 69–70 °C, ref. [22] m.p. 70–71 °C). Following the same procedure, and starting from the suitable aldehyde, the following products were prepared: (*E*)-2-

oxo-4-(4-methylphenyl)but-3-enoic acid methyl ester (**2b**) in a yield of 45% (a sample suitable for this study was purified by crystallization from diisopropyl ether to give yellow needles (m.p. 80–81°C, ref. [23] m.p. 81°C)); (*E*)-2-oxo-4-(4-bromophenyl)but-3-enoic acid methyl ester (**2c**) in a yield of 35% as yellow needles from methanol (m.p. 120°C, ref. [24] m.p. 122°C); (*E*)-2-oxo-4-(4-nitrophenyl)but-3-enoic acid methyl ester (**2d**) in a yield of 32% as bright-orange crystals from ethyl acetate (m.p. 182–183°C, ref. [25] m.p. 182.5–183.5°C).

General procedure for the reaction between cyclopentadiene and (*E*)-2-oxo-4-arylbut-3-enoic acid methyl ester (2a–d):

Uncatalyzed reactions (Table 1, entries 1–4): Cyclopentadiene (300 μL; approximately 4.5 mmol) was added by microsyringe to a solution of **2a–d** (0.30 mmol) in anhydrous CH_2Cl_2 (0.3 mL) at ambient temperature in a rubber-septum-sealed vial. Stirring of the reaction mixture was continued for the time reported in Table 1 until the disappearance of **2** was shown by TLC. The reaction mixture was separated by column chromatography (silica gel, 30 cm length, 1.5 cm diameter).

Adducts from 2a: Cyclohexane/ethyl acetate (90:10) was the eluant, and the inseparable mixture of the Diels–Alder products **3a** and **4a** was eluted first, then the hetero-Diels–Alder product **5a** was separated. The ratio **3a**/**4a** was determined by ^{1}H NMR spectroscopic analysis from the vinylic protons at $\delta = 5.97$ (**3a**) and 6.10 ppm (**4a**).

3a: Colorless crystals; m.p. 45°C (hexane); IR (Nujol): $\tilde{\nu} = 1726\ cm^{-1}$ (C=O); ^{1}H and ^{13}C NMR spectra are in accordance with those previously reported.[16]

5a: Colorless needles; m.p. 50–55°C (diisopropyl ether/pentane); IR (Nujol): $\tilde{\nu} = 1734$ (C=O), 1646 cm^{-1} (C=C); ^{1}H and ^{13}C NMR spectra are in accordance with those previously reported.[16]

Adducts from 2b: The products were isolated following the procedure described for **2a**; the ratio **3b**/**4b** was determined by ^{1}H NMR spectroscopic analysis from the vinylic protons at $\delta = 5.97$ (**3b**) and 6.11 ppm (**4b**).

3b: ^{1}H NMR ($CDCl_3$): $\delta = 7.20$–7.05 (m, 4H, aromatic protons), 6.47 (dd, ^3J(H,H) = 5.5 and 3.3 Hz, 1H, vinylic proton), 5.97 (dd, ^3J(H,H) = 5.5 and 2.7 Hz, 1H, vinylic proton), 3.87 (s, 3H, OCH_3), 3.76 (dd, ^3J(H,H) = 5.1 and 3.4 Hz, 1H, CH), 3.50 (m, 1H, CH), 3.23 (dd, ^3J(H,H) = 5.1 and 1.2 Hz, 1H, CH), 3.05 (m, 1H, CH), 2.35 (s, 3H, CH_3), 1.96 (d, ^3J(H,H) = 8.7 Hz, 1H, CH*H*), 1.65 ppm (dd, ^3J(H,H) = 8.7 and 1.8 Hz, 1H, CH*H*); ^{13}C NMR ($CDCl_3$): $\delta = 193.7$, 161.8, 139.8, 139.4, 135.3, 132.1, 128.7, 126.8, 56.1, 52.3, 48.8, 47.2, 46.7, 44.7, 20.4 ppm; IR (film): $\tilde{\nu} = 1726\ cm^{-1}$ (C=O); elemental analysis calcd (%) for $C_{17}H_{18}O_3$ (270.3): C 75.53, H 6.71; found: C 75.17, H 6.55.

5b: ^{1}H NMR ($CDCl_3$): $\delta = 7.15$ (m, 4H, aromatic protons), 6.33 (dd, ^3J(H,H) = 3.0 Hz, ^4J(H,H) = 1.2 Hz, 1H, H-3), 6.05 (s, 2H, H-6 and H-7), 5.13 (dd, ^3J(H,H) = 6.0 Hz and 1.8 Hz, 1H, CH), 4.5 (dd, ^3J(H,H) = 6.7 Hz and 3.0 Hz, 1H, CH), 3.82 (s, 3H, OCH_3), 2.89 (m, 1H, CH), 2.36 (s, 3H, CH_3) 2.12 (dd, ^2J(H,H) = 16.7 Hz, ^3J(H,H) = 8.4 Hz, 1H, CH*H*), 1.75 ppm (ddd, ^2J(H,H) = 16.7 Hz, ^3J(H,H) = 7.2 and 1.1 Hz, 1H, CH*H*); ^{13}C NMR ($CDCl_3$): $\delta = 162.9$, 145.6, 138.3, 137.9, 135.7 130.2, 128.7, 127.1, 112.1, 81.8, 51.6, 43.2, 37.3, 33.3, 20.5 ppm; IR (Nujol): $\tilde{\nu} = 1733$ (C=O), 1646 cm^{-1} (C=C); elemental analysis calcd (%) for $C_{17}H_{18}O_3$ (270.3): C 75.53, H 6.71; found: C 75.38, H 6.83.

Adducts from 2c: The products were isolated following the procedure described for **2a**; the ratio **3c**/**4c** was determined by ^{1}H NMR spectroscopic analysis from the vinylic protons at $\delta = 5.96$ (**3c**) and 6.05 ppm (**4c**).

3c: ^{1}H NMR ($CDCl_3$): $\delta = 7.43$ (d, ^3J(H,H) = 8.2 Hz, 2H, aromatic protons), 7.13 (d, ^3J(H,H) = 8.2 Hz, 2H, aromatic protons), 6.45 (dd, ^3J(H,H) = 5.4 and 3.3 Hz, 1H, vinylic proton), 5.96 (dd, ^3J(H,H) = 5.6 and 2.7 Hz, 1H, vinylic proton), 3.87 (s, 3H, OCH_3), 3.68 (dd, ^3J(H,H) = 5.0 and 3.5 Hz, 1H, CH), 3.51 (broad s, 1H, CH), 3.21 (dd, ^3J(H,H) = 5.0 and 1.5 Hz, 1H, CH), 3.04 (broad s, 1H, CH), 1.89 (d, ^2J(H,H) = 8.8 Hz, 1H, CH*H*), 1.65 ppm (dd, ^2J(H,H) = 8.8 Hz, ^3J(H,H) = 1.5 Hz, 1H, CH*H*); ^{13}C NMR ($CDCl_3$): $\delta = 193.3$, 161.6, 141.9, 139.2, 132.3, 131.1, 128.6, 119.5, 56.3, 52.4, 48.4, 47.2, 46.7, 44.5 ppm; IR (film): $\tilde{\nu} = 1726\ cm^{-1}$ (C=O); elemental analysis calcd (%) for $C_{16}H_{15}BrO_3$ (335.2): C 57.33, H 4.51; found: C 57.12, H 4.55.

5c: ^{1}H NMR ($CDCl_3$): $\delta = 7.47$ (d, ^3J(H,H) = 8.3 Hz, 2H, aromatic protons), 7.13 (d, ^3J(H,H) = 8.3 Hz, 2H, aromatic protons), 6.25 (dd, ^3J(H,H) = 3.0 Hz, ^4J(H,H) = 1.3 Hz, 1H, H-3), 6.06 (s, 2H, H-6 and H-7), 5.11 (dd, ^3J(H,H) = 5.8 Hz, ^4J(H,H) = 1.3 Hz, 1H, CH), 4.05 (dd, ^3J(H,H) = 6.8 and 2.8 Hz, 1H, CH), 3.82 (s, 3H, OCH_3), 2.86 (m, 1H, CH), 2.07 (dd, ^2J(H,H) = 16.3 Hz, ^3J(H,H) = 8.4 Hz, 1H, CH*H*), 1.73 ppm (dd, ^2J(H,H) = 16.3 Hz, ^3J(H,H) = 7.4 Hz, 1H, CH*H*); ^{13}C NMR ($CDCl_3$): $\delta = 162.7$, 145.9, 140.4, 137.8, 131.1, 130.2, 128.9, 120.0, 110.6, 81.6, 51.8, 42.8, 37.2, 33.2 ppm; IR (Nujol): $\tilde{\nu} = 1721$ (C=O), 1653 cm^{-1} (C=C); elemental analysis calcd (%) for $C_{16}H_{15}BrO_3$ (335.2): C 57.33, H 4.51; found: C 57.45, H 4.36.

Adducts from 2d: The products were isolated following the procedure described for **2a**; the ratio **3d**/**4d** was determined by ^{1}H NMR spectroscopic analysis from the aromatic protons at $\delta = 7.41$ (**3d**) and 7.30 ppm (**4d**).

3d: ^{1}H NMR ($CDCl_3$): $\delta = 8.17$ (d, ^3J(H,H) = 8.7 Hz, 2H, aromatic protons), 7.41 (d, ^3J(H,H) = 8.7 Hz, 2H, aromatic protons), 6.47 (dd, ^3J(H,H) = 5.6 and 3.0 Hz, 1H, vinylic proton), 6.00 (dd, ^3J(H,H) = 5.6 and 3.0 Hz, 1H, vinylic proton), 3.89 (s, 3H, OCH_3), 3.71 (dd, ^3J(H,H) = 5.1 and 3.5 Hz, 1H, CH), 3.57 (bs, 1H, CH), 3.37 (d, ^3J(H,H) = 4.8 Hz, 1H, CH), 3.12 (bs, 1H, CH), 1.89 (d, ^2J(H,H) = 8.9 Hz, 1H, CH*H*), 1.70 ppm (m, 1H, CH*H*); ^{13}C NMR ($CDCl_3$): $\delta = 192.8$, 161.4, 150.8, 145.9, 139.1, 132.6, 127.7, 123.3, 56.4, 52.6, 48.2, 47.2, 46.8, 45.0 ppm; IR (film): $\tilde{\nu} = 1726\ cm^{-1}$ (C=O); elemental analysis calcd (%) for $C_{16}H_{15}NO_5$ (301.3): C 63.78, H 5.02, N 4.65; found: C 63.92, H 5.48, N 4.67.

5d: Colorless needles; m.p. 145–146°C (diisopropyl ether); ^{1}H NMR ($CDCl_3$): $\delta = 8.23$ (d, ^3J(H,H) = 8.7 Hz, 2H, aromatic protons), 7.44 (d, ^3J(H,H) = 8.7 Hz, 2H, aromatic protons), 6.26 (dd, ^3J(H,H) = 2.8 Hz, ^4J(H,H) = 1.1 Hz, 1H, H-3), 6.08 (s, 2H, H-6 and H-7), 5.15 (d, ^3J(H,H) = 5.8 Hz, 1H, CH), 4.22 (dd, ^3J(H,H) = 6.7 and 2.8 Hz, 1H, CH), 3.84 (s, 3H, OCH_3), 2.91 (m, 1H, CH), 2.07 (dd, ^2J(H,H) = 16.9 Hz, ^3J(H,H) = 7.7 Hz, 1H, CH*H*), 1.70 ppm (ddd, ^2J(H,H) = 16.9 Hz, ^3J(H,H) = 7.5 and 1.6 Hz, 1H, CH*H*); ^{13}C NMR ($CDCl_3$): $\delta = 162.5$, 149.0, 146.4, 146.3, 137.7, 130.2, 128.1, 123.4, 109.0, 81.5, 51.9, 42.5, 37.7, 33.0 ppm; IR (Nujol): $\tilde{\nu} = 1726$ (C=O), 1652 cm^{-1} (C=C); elemental analysis calcd (%) for $C_{16}H_{15}NO_5$ (301.3): C 63.78, H 5.02, N 4.65; found: C 64.02, H 4.98, N 4.77.

Reaction catalyzed by scandium triflate: A mixture of **2a–d** (0.30 mmol) and scandium triflate (14 mg, 0.03 mmol) in anhydrous CH_2Cl_2 (0.3 mL) was stirred for 15 min at ambient temperature in a rubber-septum-sealed vial and then cooled at the temperature reported in Table 1. Cyclopentadiene (100 μL; approximately 1.5 mmol) was added by microsyringe and stirring of the reaction mixture was continued at the temperature and for the time reported in Table 1. The reaction mixture was decomposed in water, extracted with CH_2Cl_2, dried, and the mixture of adducts was separated by column chromatography as previously described.

Reaction catalyzed by the scandium triflate/pybox 1 complex: Compounds **2a–d** (0.30 mmol), pybox **1** (22 mg, 0.03 mmol), scandium triflate (14 mg, 0.03 mmol), and MS (about 0.040 g) were added to anhydrous CH_2Cl_2 (0.3 mL) at ambient temperature in a rubber-septum-sealed vial. The reaction mixture was stirred for 15 min and then cooled at the temperature reported in Table 2. Cyclopentadiene (100 μL; approximately 1.5 mmol) was added by a microsyringe, and stirring of the reaction mixture was continued for the time reported in Table 2, when all **2** disappeared. The reaction was decomposed in water, extracted with CH_2Cl_2, dried, and the mixture of adducts was separated by column chromatography (silica gel, 30 cm L^{-1}, 1.5 cm diameter).

The reaction mixture from **2a** was separated by eluting with cyclohexane/ethyl acetate (90:10). The mixture of DA products **3a** and **4a** (colorless oil) was analyzed on a Chiralpak AD column with hexane/2-propanol (96:4) as the eluant (1.0 mL min^{-1}), and the average retention times were 13 and 15.5 min for methyl (2*S*,3*S*)- and (2*R*,3*R*)-3-phenylbicyclo-[2.2.1]hept-5-en-2-ylglyoxylate (**3a**), respectively, and 12 and 14 min for the *exo* enantiomers **4a**.[16]

The HDA product 2-methoxycarbonyl-4-phenyl-4,4a,5,7a-tetrahydrocyclopenta[*b*]pyran (**5a**) was analyzed on a Chiralcel OJ column with hexane/2-propanol (90:10) as the eluant (1.0 mL min^{-1}), and the average retention times were 20 and 36 min for (4*R*,4a*S*,7a*R*)-**5a** and (4*S*,4a*R*,7a*S*)-**5a**,

respectively. The sample from entry 1 of Table 2, for which $[\alpha]_D^{20} = -226.4$ ($c = 1.2$ in $CHCl_3$),[16] could be crystallized from diisopropyl ether/hexane; m.p. 70–71 °C.

The reaction mixture from **2b** was separated by eluting with cyclohexane/ethyl acetate (90:10). The mixture of DA products **3b** and **4b** was analyzed on a Chiralpak AD column with hexane/2-propanol (98:2) as the eluant (1.0 mL min^{-1}), and the average retention times were 8.8 and 10.1 min for methyl (2*S*,3*S*)- and (2*R*,3*R*)-3-(4-methylphenyl)bicyclo-[2.2.1]hept-5-en-2-ylglyoxylate (**3b**), respectively, and 7.3 and 9.4 min for the *exo* enantiomers **4b**.

The HDA product 2-methoxycarbonyl-4-(4-methylphenyl)phenyl-4,4a,5,7a-tetrahydrocyclopenta[b]pyran (**5b**) was analyzed on a Chiralcel OJ column with hexane/2-propanol (90:10) as the eluant (1.0 mL min^{-1}), and the enantiomers of **5b** overlap (retention time = 24 min). The sample from entry 2 of Table 2, for which $[\alpha]_D^{20} = -198.1$ ($c = 2.2$ in $CHCl_3$), could be crystallized from cyclohexane/hexane; m.p. 96–97 °C.

The reaction mixture from **2c** was separated by eluting with cyclohexane/ethyl acetate (95:5). The mixture of DA products **3c** and **4c** was analyzed on a Chiralpak AD column with hexane/2-propanol (96:4) as the eluant (1.0 mL min^{-1}), and the average retention times were 11 and 13.5 min for *exo* enantiomers **4c**, whereas the enantiomers of **3c** overlap at 14 min.

The HDA product 2-methoxycarbonyl-4-(4-bromophenyl)-4,4a,5,7a-tetrahydrocylopenta[*b*]pyran (**5c**) was analyzed on a Chiralcel OJ column with hexane/2-propanol (90:10) as the eluant (1.0 mL min^{-1}), and the average retention times were 22 and 26 min for (4*R*,4a*S*,7a*R*)-**5c** and (4*S*,4a*R*,7a*S*)-**5c**, respectively. The sample from entry 3 of Table 2, which is nearly enantiomerically pure (4*R*,4a*S*,7a*R*)-**5c** with $[\alpha]_D^{20} = -156.1$ ($c = 2.4$ in $CHCl_3$), crystallizes from diisopropyl ether/pentane as colorless needles; m.p. 105–106 °C.

The reaction mixture from **2d** was separated by eluting with cyclohexane/ethyl acetate (90:10). The mixture of DA products **3d** and **4d** was analyzed on a Chiralpak AD column with hexane/2-propanol (96:4) as the eluant (1.0 mL min^{-1}), and the average retention times were 26.5 and 30.5 min for methyl (2*R*,3*R*)- and (2*S*,3*S*)-3-(4-nitrophenyl)bicyclo-[2.2.1]hept-5-en-2-ylglyoxylate (**3d**), respectively, and 19 and 24.5 min for the *exo* enantiomers **4d**.

The HDA product 2-methoxycarbonyl-4-(4-nitrophenyl)-4,4a,5,7a-tetrahydrocyclopenta[*b*]pyran (**5d**) was analyzed on a Chiralcel OJ column with hexane/2-propanol (90:10) as the eluant (1.0 mL min^{-1}), and the average retention times were 79 and 84 min for (4*S*,4a*R*,7a*S*)- and (4*R*,4a*S*,7a*R*)-**5d**, respectively. The sample from entry 4 of Table 2 has $[\alpha]_D^{20} = -147.2$ ($c = 1.3$ in $CHCl_3$).

General procedure for the [3,3]-sigmatropic rearrangements of 3a–d and 5a–d catalyzed by Sc(OTf)$_3$ (Table 3): Compounds **3a–d** or **5a–d** (about 0.1 mmol) were dissolved in anhydrous CH_2Cl_2 (1.0 mL), and $Sc(OTf)_3$ (4.8 mg, 0.01 mmol) was added to the stirred solution kept at the temperature and for the time reported in Table 3. The reaction mixture was quenched with water and extracted with CH_2Cl_2. The organic layer was dried, the solvent was evaporated, and the composition of the residue (**3a–d**/**5a–d** ratio) was determined by ^{1}H NMR spectroscopic analysis. In the case of entry 5, **2a** (0.05 mmol) and $Sc(OTf)_3$ (0.01 mmol) in anhydrous CH_2Cl_2 (0.5 mL) were stirred at ambient temperature for 15 min, the solution was cooled at −50 °C, a cooled solution of **5a** (0.1 mmol) was added, and the reaction mixture was warmed to ambient temperature for 3 h and worked up as described above. Compound **2a** did not interfere with the determination of the ratio of **3a**/**5a**.

Determination of the enantiomeric excess of 5b: A sample of **5b** (12 mg, 0.044 mmol) from entry 2 in Table 2 was dissolved in anhydrous toluene (5 mL) and heated at 90 °C for 12 h. The solvent was evaporated and the residue purified by column chromatography on silica gel (eluant: cyclohexane/ethyl acetate (90:10)). The first fraction was (2*R*,3*R*)-**3b** (6 mg, 50 % yield), and HPLC analysis gave (2*R*,3*R*)-**3b** with >99.5 % *ee* and $[\alpha]_D^{20} = -95.3$ ($c = 0.2$ in $CHCl_3$). The second fraction was (4*R*,4a*S*,7a*R*)-**5b** (5 mg), which was identical in every respect to the starting product, whose enantiomeric excess was therefore >99.5 % *ee*.

Determination of the enantiomeric excess of 3c: A sample of **3c** (15 mg, 0.045 mmol) from entry 3 in Table 2 was dissolved in anhydrous toluene (5 mL) and heated at 90 °C for 12 h. The solvent was evaporated, and the residue was purified by column chromatography on silica gel (eluant: cyclohexane/ethyl acetate (95:5)). The first fraction was starting material **3c**, then a very small amount of **2c** was isolated, followed by **5c** (5 mg, 33 % yield). This latter compound was submitted to HPLC analysis on a Chiralcel OJ column with hexane/2-propanol (90:10) as the eluant (1.0 mL min^{-1}), and the major enantiomer was (4*R*,4a*S*,7a*R*)-**5c** with 99 % *ee*, thus allowing the determination of both the absolute configuration and enantiomeric excess of starting material **3c**.

Determination of the enantiomeric excess of 5d: A sample of **5d** (10 mg, 0.033 mmol) from entry 4 in Table 2 was dissolved in anhydrous toluene (5 mL) and heated at 90 °C for 12 h. The solvent was evaporated, and the residue was purified by column chromatography on silica gel (eluant: cyclohexane/ethyl acetate (85:15)). The first fraction was (2*R*,3*R*)-**3d** (5 mg, 50 % yield), and HPLC analysis performed on a Chiralpak AD column with hexane/2-propanol (96:4) as the eluant (1.0 mL min^{-1}) gave a mixture of (2*S*,3*S*)- and (2*R*,3*R*)-**3d** in the ratio 0.5:99.5 with $[\alpha]_D^{20} = -107.3$ ($c = 0.3$ in $CHCl_3$). The second fraction was (4*R*,4a*S*,7a*R*)-**5d** (5 mg), which was identical in every respect to the starting product, and whose enantiomeric excess was therefore 99 % *ee*.

General procedure for the [3,3]-sigmatropic rearrangements of (2*R*,3*R*)-3d and (4*R*,4a*S*,7a*R*)-5d catalyzed by Sc(OTf)$_3$ (Table 4): Compounds (2*R*,3*R*)-**3d** or (4*R*,4a*S*,7a*R*)-**5d** (about 0.1 mmol) were dissolved in anhydrous CH_2Cl_2 (1.0 mL), and $Sc(OTf)_3$ (4.8 mg, 0.01 mmol) was added to the stirred solution kept at the temperature and for the time reported in Table 4. The reaction mixture was quenched with water and extracted with CH_2Cl_2. The organic layer was dried, the solvent was evaporated, and the composition of the residue (ratio of **3d**/**4d**/**5d**]) was determined by ^{1}H NMR spectroscopic analysis. The overall residue was purified by column chromatography on silica gel (eluant: cyclohexane/ethyl acetate (85:15)). The first fraction was **3d**(+**4d**), and HPLC analysis performed on a Chiralpak AD column with hexane/2-propanol (96:4) as the eluant (1.0 mL min^{-1}) allowed both a precise determination of the ratio of **3d**/**4d** and the enantiomeric composition of **3d**. The second fraction was **5d**, and its enantiomeric purity was determined either by HPLC (Chiralcel OJ column) and the optical rotation of the product.

CCDC-649656 (**5c**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.[26]

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