Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 4885–4893

TETRAHEDRON: *ASYMMETRY*

On the origin of changes in topicity observed in Diels–Alder reactions catalyzed by Ti–TADDOLates

Belén Altava, M. Isabel Burguete, Eduardo García-Verdugo, Santiago V. Luis,* Juan F. Miravet and María J. Vicent

Department of Inorganic and Organic Chemistry, ESTCE, University Jaume I, E-12080 Castellón, Spain

Received 19 October 2000; accepted 17 November 2000

Abstract

New C_2 symmetric TADDOLs containing different groups at the 2-position of the dioxolane ring have been prepared. The Ti catalysts derived from these have been studied in the Diels–Alder reaction of cyclopentadiene and (*E*)-2-butenoyl-1,3-oxazolidin-2-one. Substituents at the C-2 position of the dioxolane ring can play an important role in determining the selectivity as well as the nature of the major isomer. This effect is more important for TADDOLs containing bulky aromatic groups such as 3,5-dimethylphenyl- or 1-naphthyl at the α-positions. Experimental evidence supports the hypothesis that π–π interactions between aromatic groups at the C-2 and the ones at the α-positions are critical in this respect.

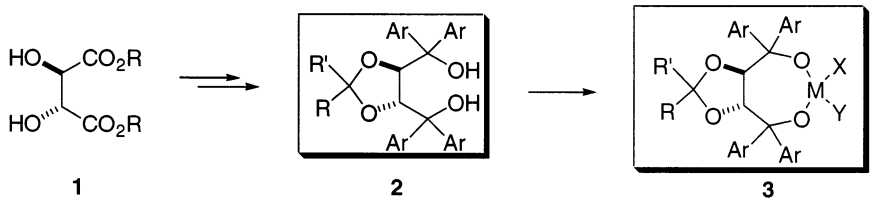
1. Introduction

TADDOLs (α,α′-tetraaryl-1,3-dioxolane-4,5-dimethanols) represent a very useful class of chiral ligands that have been widely used for the preparation of enantioselective catalysts and reagents and for other applications.[1] They can be easily prepared in both enantiomeric forms from simple materials and, moreover, their general structure **2** presents a high potential for molecular diversity through changes in the nature of R, R′, Ar, M, X and Y groups, and this allows for a better tuning of the desired properties (Scheme 1).

Most efforts have been dedicated, in general, to understand the role played by changes in the nature of the Ar groups on the final properties of metal TADDOLates such as **3**.[2] Nevertheless, much less is known about the exact role played by the R and R′ substituents at the 2-position of the dioxolane ring. In most instances, their role has been mainly associated with the presence or absence of a C_2 symmetry, which is usually considered as an advantageous feature for enantioselective catalysts.[3] However, experimental evidence has been gathered that shows that

* Corresponding author. Tel: +34 964 728239; fax: +34 964 788214; e-mail: luiss@mail.uji.es

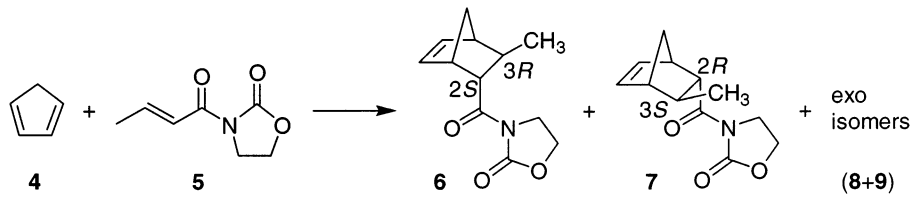
0957-4166/00/$ - see front matter
PII: S0957-4166(00)00464-X



Scheme 1.

this is an oversimplification. In recent years we have been involved in the preparation and study of supported TADDOL derivatives that could be useful for practical applications.[4–6] In this respect, the 2-position of the dioxolane ring is always key for linking to the heterogeneous support. Accordingly, a better knowledge of the implications that structural modifications in this position have on their efficiency is required for a better design of the supported systems.

Here we present experimental evidence that aids rationalizing how, in some instances, substituents at the C-2 position can have a decisive influence on the extent and direction of the asymmetric induction in the benchmark Diels–Alder reaction of cyclopentadiene and (*E*)-2-butenoyl-1,3-oxazolidin-2-one (Scheme 2).



Scheme 2.

2. Results and discussion

Results gathered in Table 1 clearly reveal that the presence of C_2 symmetry in the structure of TADDOLs **2** (R = R′) is not always reflected in higher enantioselectivities. Very large *ee* values have been obtained for the simple dialkyl derivative **2a** (R = R′ = CH_3) (see entry 1), but a complete lack of enantioselectivity was observed for the diphenyl derivative **2c** (R = R′ = Ph) (see entry 3).[2a]

On the other hand, results from different groups have shown that the presence of very bulky aryl groups at the α positions, like 3,5-dimethylphenyl or 1-naphthyl, but not 2-naphthyl, is usually accompanied by a reversal in the topicity of the major isomer.[1,2] In those cases, the (2*R*,3*S*)-*endo*-isomer **7** is obtained instead of the *normal* (2*S*,3*R*)-*endo*-isomer **6** (compare, for instance, entries 2 and 6). Preliminary Molecular Mechanics calculations suggest that π–π stacking interactions between one aromatic ring at the 2-position of the dioxolane ring and one 3,5-dimethylphenyl group could be the origin of this phenomenon. The presence of such π–π interactions seems to decrease the relative energy of the intermediates leading to the formation of the *abnormal* (2*R*,3*S*)-*endo*-isomer.[2a]

The result shown in entry 1 is in good agreement with this hypothesis. In this case, the absence of aromatic groups at the 2-position leads to the formation of the *normal* (2*S*,3*R*)-iso-

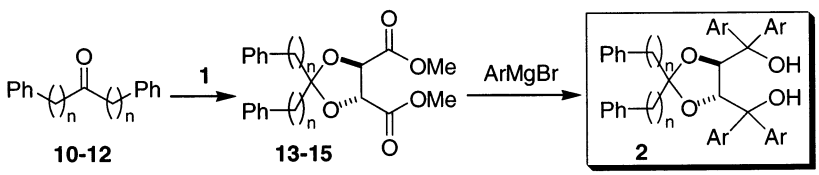
Table 1
Results obtained in the Diels–Alder reaction of **4** and **5** catalyzed by Ti–TADDOLates **3** in toluene at 0°C in 24 h

Entry	Catalyst	R	R′	Ar	Yield (%)[a]	*endo*/*exo*[a]	Ee (%)[b]
1	**3a**	CH_3	CH_3	3,5-$(CH_3)_2C_6H_3$	95	89:11	82 (2*S*,3*R*)[c]
2	**3b**	Ph	H	3,5-$(CH_3)_2C_6H_3$	100	70:30	24 (2*R*,3*S*)[d]
3	**3c**	Ph	Ph	3,5-$(CH_3)_2C_6H_3$	22	80:20	0[d]
4	**3d**	CH_2Ph	CH_2Ph	3,5-$(CH_3)_2C_6H_3$	96	75:25	61 (2*R*,3*S*)
5	**3e**	$(CH_2)_2Ph$	$(CH_2)_2Ph$	3,5-$(CH_3)_2C_6H_3$	100	79:21	33 (2*S*,3*R*)
6	**3f**	Ph	H	2-Naphthyl	96	74:26	61 (2*S*,3*R*)[d]
7	**3g**	CH_2Ph	CH_2Ph	2-Naphthyl	99	83:17	65 (2*S*,3*R*)
8	**3h**	$(CH_2)_2Ph$	$(CH_2)_2Ph$	2-Naphthyl	97	87:13	79 (2*S*,3*R*)
9	**3i**	$(CH_2)_2Ph$	$(CH_2)_2Ph$	Ph	100	83:17	30 (2*S*,3*R*)
10	**3j**	$(CH_2)_2Ph$	$(CH_2)_2Ph$	4-$MeOC_6H_4$	91	87:13	41 (2*S*,3*R*)

[a] Determined by ^1H NMR.
[b] Determined by ^1H NMR in the presence of $Eu(hfc)_3$.
[c] Data from Ref. 1d.
[d] Data from Ref. 2a.

mer as the major product. The substitution of alkyl groups by phenyl groups at C-2 seems to be always accompanied by an increase in the amount of the (2*R*,3*S*)-isomer formed (entries 2 and 3) that leads to a lack of selectivity for catalyst **3c** and to a reversal of topicity when **3b** is used.

In order to obtain additional experimental evidence regarding this general hypothesis, a series of new TADDOL derivatives was prepared as shown in Scheme 3. Those compounds (**2c**–**2e**, **2g**–**2j**) were designed to maintain a C_2 symmetry and to have aromatic rings separated from the ketalic carbon atom by a variable number of methylene groups ($n=0$–2). As the aryl groups at the α and α′ positions we initially selected the 2-naphthyl **2g**–**2h** and 3,5-dimethylphenyl groups **2c**–**2e**. Ti–TADDOLates containing the first one are described to give always the *normal* (2*R*,3*S*)-isomer with high enantioselectivities, whereas with the second group the *abnormal* (2*S*,3*R*)-isomer is often obtained.



Ar = 3,5-$(CH_3)_2$-C_6H_3-, n = 0, **2c**
n = 1, **2d**
n = 2, **2e**
Ar = 2-naphthyl-, n = 1, **2g**
n = 2, **2h**
Ar = C_6H_5-, n = 2, **2i**
Ar = 4-$(CH_3O)C_6H_4$-, n = 2, **2j**

Scheme 3.

The desired TADDOLs were prepared in the usual way starting from ketones **10**–**12** as shown in Scheme 3. Compounds **10** and **11** are commercially available, and ketone **12** was obtained, in good yields, by catalytic hydrogenation of dibenzylideneacetone. Ketalization of **10** and **11** to afford compounds **13** and **14** was difficult to be accomplished efficiently (60 and 29% yields, respectively). This might be expected from electronic considerations for **10**, but it is more difficult to rationalize for ketone **11**. Initial Molecular Mechanics and Molecular Dynamics calculations suggest that the preferred conformations both for **11** and for its hemiketal result from close π–π intramolecular interactions. This is reflected in the existence of a strong steric hindrance for the attack to the carbonylic or hemiketalic carbon, making ketal formation difficult.

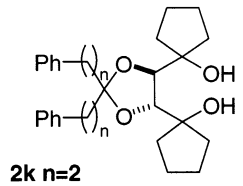
The corresponding Ti–TADDOLates were obtained by treatment of TADDOLs **2** with $Ti(OPr^i)_2Cl_2$ in toluene and were used as catalysts for the Diels–Alder reaction between cyclopentadiene and (*E*)-2-butenoyl-1,3-oxazolidin-2-one (Scheme 2).[2,4] If π–π interactions between one phenyl group bound to C-2 and one 3,5-dimethylphenyl group at the α position play a key role to explain the abnormal enantioselectivity behavior of catalysts such as **3b**, it was to be expected that increasing the separation between the ketalic carbon and the phenyl group (catalysts **3c**–**3e**) would have a large influence on the selectivity observed. This influence was expected to be much lower for catalysts such as **3g** and **3h** containing 2-naphthyl groups at the α and α′ positions. This situation was clearly observed in the experimental results, as shown in Table 1.

If the TADDOLs containing 3,5-dimethylphenyl groups (catalysts **3a**–**3e**) are considered, it can be seen that the *normal* (2*S*,3*R*)-isomer is obtained with very good enantioselectivity (82% ee) when the C_2 symmetric TADDOL **2a** having alkyl groups at C-2 is used. However, a complete lack of enantioselectivity is observed for catalyst **3c** for which phenyl groups have substituted both methyl groups at C-2. This indicates that the formation of the otherwise minor isomer (2*R*,3*S*) is now as favorable as that of the (2*S*,3*R*)-isomer as a result of the presence of those phenyl groups. The change in topicity is even more dramatic when the catalyst derived from TADDOL **2d** ($n=1$) is used. In this case a 61% ee is observed, (2*R*,3*S*) being the preferred isomer. A further increase in the length of the aliphatic spacer linking the ketalic carbon and the phenyl group seems to hinder the π–π interactions of the phenyl group and one of the 3,5-dimethylphenyl substituents, as could be expected. As a consequence, the formation of the isomer with the reversal topicity is much less favorable and the *normal* (2*S*,3*R*)-isomer is again obtained as the major product, with 33% ee.

As it was predicted, TADDOLs having 2-naphthyl substituents at the α and α′ positions are not very much affected by the changes in the length of the methylenic spacer between C-2 and the phenyl group. The *normal* (2*S*,3*R*)-isomer is always obtained as the major product with good enantioselectivities. For TADDOL **2h** ($R=R'=Ph(CH_2)_2$, Ar = 2-naphthyl) the enantioselectivity found was almost as good (79% ee) as that reported for **2a** (82% ee). When other aryl groups such as phenyl or 4-methoxyphenyl were introduced at the α and α′ positions, instead of 3,5-dimethylphenyl or 2-naphthyl, results were similar to those found for the latter, but selectivities were lower as has been usually described for this kind of structural changes (see entries 9 and 10 in Table 1).

The crucial role played by the aromatic rings in the TADDOL-derived catalysts can also be exemplified by the results obtained with TADDOL **2k** containing aliphatic substituents at α and α′ positions. This compound was synthesized in good yield by reaction of the Grignard reagent prepared from 1,4-dibromobutane with the ketal **15**. When the corresponding Ti–TADDOLate was assayed for the Diels–Alder reaction in Scheme 2 (catalyst:crotonate ratio 1:10, 0°C, 24 h)

much lower activities (63% after 24 hours) and selectivities [*endo*/*exo*: 3.53, ee: 13%, major *endo* isomer: (2*S*,3*R*)] were observed when compared to those obtained with catalysts obtained from TADDOLs containing aryl groups at the α positions (Scheme 4).[7,8]



Scheme 4.

In conclusion, the present results support the hypothesis, suggested by previous Molecular Mechanic calculations, that π–π interactions play an important role in determining the topicity changes observed in Diels–Alder reactions catalyzed by Ti–TADDOLates. The occurrence of such interactions favor the formation of the unusual (2*R*,3*S*)-isomer. Those changes are only observed for very rigid TADDOL derivatives containing very bulky aryl groups (3,5-dimethylphenyl or 1-naphthyl) at the α positions. For those systems, the introduction of aliphatic spacers between the ketalic carbon atom and the phenyl group provide a way for regulating the above-mentioned π–π interactions. For a given length of the linker ($n=2$), the interaction between the aromatic group in the substituent at C-2 and the aryl group at the α position starts to be hindered and the normal topicity is again observed. More work is needed to fully understand the exact mechanisms for this kind of Ti–TADDOLate catalyzed reactions, but results in this work allow to rationalize previous observations on this subject with homogeneous and supported TADDOL derivatives.

3. Experimental

3.1. Synthesis of 1,5-diphenyl-3-pentanone ***12***

Benzylideneacetone (6.94 g, 0.03 mol) was dissolved in EtOH (100 mL) in a 600 mL Parr reactor and 5% Pd/C (0.2 g) was added. Hydrogenation was carried out at 8.3 bar (initial pressure). When the pressure dropped to 4.2 bar, the reactor was opened, the mixture of reaction was filtered through Celite and the resulting solution was vacuum evaporated to give **12** as colorless oil of high purity (6.72 g, 96.8%). IR (KBr, cm^{-1}): 3085, 3062, 2927, 2860, 1712, 1603, 1495, 1459, 1179, 1092, 747, 698. ^{1}H NMR ($CDCl_3$, δ): 2.75 (m, 4H), 2.96 (m, 4H), 7.3 (m, 10H). ^{13}C NMR ($CDCl_3$, δ): 29.8, 44.6, 125.9, 128.4, 128.5, 141.0, 209.2. Anal. calc. for $C_{17}H_{18}O$: C, 85.7; H, 7.6%. Found: C, 85.7; H, 7.4%.

*3.2. Synthesis of (4*R*,5*R*)-2,2-diphenyl-1,3-dioxolane-4,5-dicarboxylic acid dimethyl ester* ***13***

Benzophenone **10** (4 g, 23 mmol) was dissolved in MeOH (12 mL) and trimethyl orthoformate (5 mL, 48.6 mmol) and a catalytic amount of *p*-toluenesulfonic acid (PTSA) were added. The mixture was heated under reflux until a white solid was formed. After cooling, a solution of 1N NaOH (20 mL) was added. The resulting solution was extracted with diethyl ether (30 mL, 3×), and the organic phase was washed with brine and water, dried over $MgSO_4$ and evaporated

under vacuum to obtain a white solid. This solid (4.05 g, 18.2 mmol) was dissolved in dry benzene (100 mL) (CAUTION: the reaction must be carried out in a well-ventilated hood) and then (*R*,*R*)-dimethyl tartrate (3.8 g, 21 mmol) and a catalytic amount of PTSA were added. Distillation of the benzene/methanol azeotrope was carried out at 60°C, and, after cooling, Et_3N was added to neutralize the acid. The solvent was evaporated under vacuum to give a red oil. The crude product was purified by crystallization from hexane to give a white solid (3.74 g, 60% yield). Mp 80–81°C; $[\alpha]^{20}=+54.2$ (*c* 0.964, $CHCl_3$). IR (KBr, cm^{-1}): 3060, 2945, 1750, 1590, 1250, 1120, 760, 705. ^1H NMR ($CDCl_3$, δ): 3.62 (s, 6H), 4.39 (s, 2H), 7.13–7.50 (m, 10H). ^{13}C NMR ($CDCl_3$, δ): 52.8, 76.9, 126.2, 127.9, 128.1, 128.8, 130.1, 132.6, 137.9, 140.0, 169.4, 196.5. Anal. calc. for $C_{19}H_{18}O_6$: C, 66.6; H, 5.3%. Found: C, 66.7 H, 5.2%.

*3.3. Synthesis of (4*R,*5*R*)-2,2-Dibenzyl-1,3-dioxolane-4,5-dicarboxylic acid dimethyl ester* ***14***

1,3-Diphenylacetone **11** (4 g, 19 mmol) was dissolved in dry benzene (100 mL) (CAUTION) and trimethyl orthoformate (4.2 mL, 38 mmol) and a catalytic amount of *p*-toluenesulfonic acid (PTSA) were added. The reaction was heated at 70°C during 2 h and then (*R*,*R*)-dimethyl tartrate (4 g, 22 mmol) was added. Distillation of the benzene/methanol azeotrope was carried out at 60°C, and, after cooling, Et_3N was added to neutralize the acid. The solvent was evaporated under vacuum to give a yellow oil. The crude product was purified by column chromatography (SiO_2) using hexanes/EtOAc 4:1 as the eluent to give a yellow oil (2.05 g, 29% yield). IR (KBr, cm^{-1}): 3062, 2945, 1750, 1590, 1250, 1120, 760, 705. ^1H NMR ($CDCl_3$, δ): 3.0 (s, 4H), 3.7 (s, 6H), 4.2 (s, 2H), 7.3 (m, 10H). ^{13}C NMR ($CDCl_3$, δ): 45.0, 53.2, 77.8, 116.1, 127.1, 128.4, 131.4, 135.6, 168.9. Anal. calc. for $C_{21}H_{22}O_6$: C, 68.1; H, 6.0%. Found: C, 68.2 H, 5.9%.

*3.4. Synthesis of (4*R,*5*R*)-2,2-bis(2-phenylethyl)-1,3-dioxolane-4,5-dicarboxylic acid dimethyl ester* ***15***

1,5-Diphenyl-3-pentanone **12** (5 g, 22 mmol) was dissolved in dry benzene (100 mL) (CAUTION) and trimethyl orthoformate (3.27 ml, 29 mmol) and a catalytic amount of *p*-toluenesulfonic acid (PTSA) were added. The reaction was stirred for 2 h and then (*R*,*R*)-dimethyl tartrate (3.8 g, 22 mmol) was added. Distillation of the benzene/methanol azeotrope was carried out at 60°C, and, after cooling, Et_3N was added to neutralize the acid. The solvent was evaporated under vacuum to give a yellow oil. The crude product was purified by column chromatography (SiO_2) using as eluent mixtures of hexanes/EtOAc 1:0, 10:0.5, 10:1 to give a yellow oil (6.7 g, 76% yield). $[\alpha]^{20}=+12.4$ (*c* 0.04, THF). IR (KBr, cm^{-1}): 3085, 3062, 1715, 1603, 1210, 989, 749, 700. ^1H NMR ($CDCl_3$, δ): 2.15 (m, 4H), 2.81 (m, 4H), 3.87 (s, 6H), 4.88 (s, 2H), 7.24–7.40 (m, 10H). ^{13}C NMR ($CDCl_3$, δ): 29.8, 39.1, 52.78, 77.19, 116.1, 125.8, 128.2, 128.3, 141.5, 169.6. Anal. calc. for $C_{23}H_{26}O_6$: C, 69.3; H, 6.5%. Found: C, 69.1 H, 6.4%.

3.5. General procedure for the preparation of C_2 *substituted TADDOL derivatives. Synthesis of* ***2d***

A solution of (3,5-dimethylphenyl)magnesium bromide, obtained from 3,5-dimethylbromobenzene (4.1 mL, 34 mmol) and Mg (0.80 g, 34 mmol) in dry THF (40 mL), was carefully added to compound **14** (0.45 g, 1.3 mmol) in dry THF (20 mL). When the addition was complete,

the mixture was refluxed for 20 h. After cooling, a saturated solution of NH_4Cl was added and, after filtering, the resulting solution was extracted with EtOAc. The organic phase was dried ($MgSO_4$) and the solvent evaporated under vacuum. The oil obtained was purified by column chromatography (SiO_2) using hexane/EtOAc mixtures as the eluent to give a white solid (0.57 g, 60% yield). Mp: 115°C; $[\alpha]^{25} = -47.5$ (*c* 0.05, $CHCl_3$). IR (KBr, cm^{-1}) 3365, 3028, 3010, 2855, 1612, 1495, 1454, 1114, 1031, 812, 758, 699. ^1H NMR ($CDCl_3$, δ): 1.8 (s, br, 8H), 2.2 (s, br, 24H), 5.2 (s, br, 2H), 6.8–7.6 (m, 22H). ^{13}C NMR ($CDCl_3$, δ): 21.1, 45.8, 81.4, 112.5, 125.5, 126.1, 127.3, 128.0, 129.3 130.5, 133.2, 136.8, 138.6. Anal. calc. for $C_{51}H_{54}O_4$: C, 83.8; H, 7.4%. Found: C, 84.0%; H, 7.5%.

3.6. Synthesis of TADDOL **2e**

This compound was obtained as before starting from **15**. Yellow solid (1.64 g, 86% yield). Mp: 97–99°C; $[\alpha]^{20} = +9.3$ (*c* 0.046, THF). IR (KBr, cm^{-1}) 3558, 3226, 2920, 1612, 1454, 1378, 1234, 1047, 812, 698. ^1H NMR ($CDCl_3$, $T = 50$°C, δ): 2.09 (s, 6H), 2.47–2.79 (s+s+m, 18H), 5.33 (s, broad, 2H), 5.82 (s, br, 1H), 7.08–7.96 (m, 22H).^{13}C NMR ($CDCl_3$, $T = 50$°C, δ): 20.6, 20.7, 21.2, 22.5, 30.0, 30.3, 38.7, 43.5, 78.7, 81.2, 111.9, 125.5, 125.6, 126.1, 126.4, 126.6, 127.2, 128.0, 128.1, 129.2, 133.0, 136.6, 136.7, 137.5, 138.1, 141.9. Anal. calc. for $C_{53}H_{58}O_4 \cdot H_2O$: C, 87.8; H, 7.7%. Found: C, 81.9; H, 7.6%.

3.7. Synthesis of TADDOL **2g**

This compound was obtained as described above starting from **14** and a Grignard reagent prepared from 2-bromonaphthalene. Brown solid (0.68 g, 64% yield). Mp: 103°C; $[\alpha]^{20} = -44.0$ (*c* 0.007, $CHCl_3$). IR (KBr, cm^{-1}) 3550, 3055, 1650, 1629, 1600, 1505, 1453, 1272, 1121, 858, 817, 795, 746, 699. ^1H NMR ($CDCl_3$, δ): 2.81 (dd, 4H, $J = 14$ Hz), 4.44 (s, br, 2H) 7–8.5 (m, 38H). ^{13}C NMR ($CDCl_3$, δ): 43.7, 78.3, 81.4, 109.3, 117.7, 123.2, 124.7, 127.9, 130.3, 136.1, 140.7, 141.5, 142.2. Anal. calc. for $C_{59}H_{46}O_6$: C, 86.5; H, 5.6%. Found: C, 86.6; H, 5.6%.

3.8. Synthesis of TADDOL **2h**

This compound was obtained as described above starting from **15** and a Grignard reagent prepared from 2-bromonaphthalene. Yellow solid (0.84 g, 38% yield). Mp: 118°C; $[\alpha]^{20} = -33.9$ (*c* 0.009, THF). IR (KBr, cm^{-1}) 3531, 3314, 3057, 3023, 2927, 1600, 1505, 1453, 1273, 1050, 925, 857, 819, 754, 699. ^1H NMR ($CDCl_3$, $T = 50$°C, δ): 1.75 (m, 4H), 2.52 (m, 4H), 4.93 (s, 1H), 6.81–8.22 (m, ^{13}C NMR ($CDCl_3$, δ): 30.3, 39.2, 78.9, 81.4, 111.4, 124.9, 125.5, 125.7, 125.9, 126.0, 126.2, 126.3, 126.35 126.4, 126.9, 127.2, 127.4, 127.5, 127.7, 127.9, 128.0, 128.27, 128.33, 128.5, 128.6, 128.65, 129.0, 132.77, 132.8, 132.9, 140.1, 141.6, 142.9. Anal. calc. for $C_{61}H_{50}O_4 \cdot H_2O$: C, 84.6; H, 6.0%. Found: C, 84.3; H, 6.1%.

3.9. Synthesis of TADDOL **2I**

This compound was obtained as described above from **15** and phenyl magnesium chloride. Yellow solid (0.8 g, 50% yield). Mp: 68–70°C; $[\alpha]^{20} = +23.15$ (*c* 0.007, THF). IR (KBr, cm^{-1}) 3550, 3027, 2931, 1602, 1449, 1127, 1045, 916, 812, 743. ^1H NMR ($CDCl_3$, $T = 50$°C, δ): 1.70 (m, 4H), 2.49 (m, 4H), 4.18 (s, 1H), 4.61 (s, 1H), 4.65 (s, 1H), 7.02–7.67 (m, 30H). ^{13}C NMR

($CDCl_3$, $T=50°C$, δ): 30.0, 39.1, 78.3, 80.6, 111.7, 125.8, 125.9, 125.95, 127.3, 127.4, 127.45, 127.5, 128.0, 128.3, 128.7, 129.0, 129.1, 141.8, 142.3, 146.0. Anal. calc. for $C_{45}H_{42}O_4 \cdot 2H_2O$: C, 79.2; H, 6.7%. Found: C, 79.6; H, 6.9%.

3.10. Synthesis of TADDOL **2j**

This compound was obtained as described above starting from **15** and a Grignard reagent prepared from bromoanisole. Yellow solid (1.2 g, 42% yield). Mp: 169°C; $[\alpha]^{20}=+19.2$ (c 0.009, THF). IR (KBr, cm^{-1}) 3529, 3350, 2932, 1608, 1511, 1455, 1298, 1250, 1175, 1033, 831, 694. ^1H NMR ($CDCl_3$, $T=50°C$, δ): 1.70 (m, 4H), 2.5 (m, 4H), 3.75 (s, 6H), 3.83 (s, 6H), 4.5 (s, 2H), 6.8–7.5 (m, 26H). ^{13}C NMR ($CDCl_3$, $T=50°C$, δ): 30.9, 39.0, 55.1, 55.2, 77.7, 80.7, 110.7, 112.6, 113.5, 125.8, 128.2, 128.4, 129.0, 129.2, 129.8, 130.0, 134.7, 138.6, 158.7, 158.8. Anal. calc. for $C_{49}H_{52}O_4 \cdot H_2O$: C, 75; H, 6.6%. Found: C, 75.7; H, 6.7%.

3.11. Synthesis of TADDOL **2k**

This compound was obtained as described above, starting from **15** and a Grignard reagent prepared from 1,4-dibromobutane. White solid (1.2 g, 42% yield). Mp: 140°C; $[\alpha]^{20}=+7.15$ (c 0.021, $CHCl_3$). IR (KBr, cm^{-1}) 3529, 3350, 2932, 1608, 1511, 1455, 1298, 1250, 1175, 1033, 831, 694. ^1H NMR ($CDCl_3$, δ): 1.7 (m, 16H), 1.9 (dd, 4H, $J=6$ Hz, $J=9$ Hz), 2.7 (dd, 4H, $J=6$ Hz, $J=9$ Hz), 3.9 (s, 2H), 7.2 (m, 10H). ^{13}C NMR ($CDCl_3$, δ): 23.8, 24.0, 30.4, 34.7, 38.6, 40.1, 81.6, 81.8, 108.8, 125.7, 125.7, 125.7, 128.2, 128.3, 141.9. Anal. calc. for $C_{29}H_{38}O_4$: C, 77.3; H, 8.5%. Found: C, 77.4: H, 8.5%.

3.12. General procedure for the Diels–Alder reactions

Under argon, a solution of $TiCl_2(O^iPr)_2$ (1 M solution in toluene) was added to a solution of 1 mmol of the corresponding TADDOL **2a**–**k** in 20 mL of dry toluene and 3.56 g of molecular sieves (4 Å). The mixture was stirred at 0°C for 60 min. After this time, a solution of (*E*)-3-butenoyl-1,3-oxazolidin-2-one (10 mmol) in 30 mL of dry toluene and freshly distilled cyclopentadiene (120 mmol) were added. The mixture was stirred at 0°C for 24 h. After this period 200 mL of 1N HCl were added and the mixture was stirred for 15 min. The organic phase was separated, filtered through Celite, and the Celite washed with 200 mL of diethyl ether. The organic phase was dried ($MgSO_4$) and the solvent evaporated under vacuum. The conversion and the *endo*/*exo* selectivity determined by means of ^1H NMR spectroscopy by integration of the signals of the methyl groups (**8**+**9**: 0.81 ppm, **6**+**7**: 1.10 ppm, **5**: 1.94 ppm). The e*ndo* cycloadducts were purified by column chromatography on silica gel using hexanes/EtOAc (2:1) as the eluent, and the enantiomeric excess in the *endo* cycloadducts was determined by ^1H NMR in presence of $Eu(hfc)_3$ (L/S molar ratio = 0.3) and confirmed by polarimetry. The absolute configuration was assigned taking into account the specific rotation of the pure enantiomer.[1c]

Acknowledgements

Financial support has been provided by the CICYT (project MAT99-1176) and the Fundació Caixa Castelló-Bancaixa (project P1B97-10).

References

1. (a) Seebach, D.; Weidmann, B.; Widler, L. In *Modern Synthetic Methods*; Scheffold, R.; Salle, D., Eds.; Wiley: New York, 1983; Vol. 3, pp. 217–353; (b) Narasaka, K.; Inoue, M.; Yamada, T.; Sugimori, J.; Iwasawa, N.; Nakashima, M. *J. Am. Chem. Soc.* **1989**, *111*, 340; (c) Narasaka, K. *Synthesis* **1991**, 1; (d) Seebach, D.; Dahinden, R.; Marti, R. E.; Beck, A. K.; Plattner, D. A.; Kühnle, F. N. M. *J. Org. Chem.* **1995**, *60*, 1788–1799; (e) Sellner, H.; Seebach, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 1918–1920; (f) Rheiner, P. B.; Seebach, D. *Chem. Eur. J.* **1999**, *5*, 3221–3237.
2. (a) Altava, B.; Burguete, M. I.; Fraile, J. M.; García, J. I.; Luis, S. V.; Mayoral, J. A.; Royo, A. J.; Vicent, M. J. *Tetrahedron: Asymmetry* **1997**, *8*, 2561–2570; (b) For different mechanistic models, see: Ito, Y. N.; Ariza, X.; Beck, A. K.; Bohác, A.; Ganter, C.; Gawley, R. E.; Kühnle, F. N. M.; Tuleja, J.; Wang, Y. M.; Seebach, D. *Helv. Chim. Acta* **1994**, *77*, 2071–2110; (c) Gothelf, K. V.; Jørgensen, K. A. *J. Org. Chem.* **1995**, *60*, 6847–6851; (d) Haase, C.; Sarko, C. R.; DiMare, M. *J. Org. Chem.* **1995**, *60*, 1777–1787; (e) Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1995**, *117*, 4435–4436.
3. (a) Whitesel, J. K. *Chem. Rev.* **1989**, *89*, 1581–1590; (b) Levacher, V.; Moberg, C. *J. Org. Chem.* **1995**, *60*, 1755–1762; (c) Halm, C.; Kurth, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 510–512.
4. Fraile, J. M.; Mayoral, J. A.; Royo, A. J.; Altava, B.; Burguete, M. I.; Escuder, B.; Luis, S. V.; Salvador, R. V. *J. Org. Chem.* **1997**, *62*, 3126–3134.
5. Altava, B.; Burguete, M. I.; Fraile, J. M.; Garcia, J. I.; Mayoral, J. A.; Luis, S. V.; Vicent, M. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 1503–1506.
6. For other approaches to the preparation of polymer-supported TADDOLs, see: (a) Seebach, D., Marti, R. E.; Hintermann, T. *Helv. Chim. Acta* **1996**, *79*, 1710–1740 and references cited therein. (b) Irurre, J.; Fernandez-Serrat, A.; Altayo, M.; Riera, M. *Enantiomer* **1998**, *3*, 103–120. (c) Santora, B. P.; White, P. S.; Gagné, M. R. *Organometallics* **1999**, *18*, 2557–2560.
7. Braun, M. *Angew. Chem., Int. Ed.* **1996**, *35*, 519–522.
8. For the development and use of chiral ligands containing cyclopentanol fragments see, for instance: (a) Wilken, J.; Kossenjans, M.; Gröger, H., Martens, J. *Tetrahedron: Asymmetry* **1997**, *8*, 2007–2015. (b) Wassmann, S.; Wilken, J.; Martens, J. *Tetrahedron: Asymmetry* **1999**, *10*, 4437–4445.