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Asymmetric activation of tropos catalysts in the stereoselective catalytic conjugate additions of R_2Zn to α,β-enones: an efficient synthesis of (−)-muscone

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Abstract—The preparation of a new phosphoramidite starting from (*R*)-BINOL and a biphenylamine is presented. In such a compound the chirality is due only to atropisomerism and this molecule possesses a flexible biphenylamine residue. Therefore it can work as a tropos catalyst. The catalytic efficiency of this new phosphoramidite has been tested in some asymmetric conjugate additions of dialkylzinc reagents to α,β-enones and compared with that of an analogous already known non-tropos ligand. Interestingly, while comparable results were obtained in the addition of $ZnEt_2$ to chalcone and cyclohexenone, in the case of the addition of $ZnMe_2$ to (*E*)-cyclopentadec-2-en-1-one, the new ligand provides (−)-muscone, a valuable ingredient of the perfume industry, in 84% ee, while the non-tropos ligand gives a much lower (57%) ee value.

1. Introduction

Configurationally stable biaryl compounds (i.e. 2,2′,6,6′-tetrasubstituted biphenyls and 2,2′-disubstituted-1,1′-binaphthyls) have received a lot of attention as chiral[1] ligands and catalysts in asymmetric synthesis. More recently, even non-atropisomerically stable, flexible biaryl compounds have been employed towards the same end.[2] From this point of view, excellent results have been obtained by Mikami and co-workers who introduced[2] the concept of 'asymmetric activation of tropos catalysts': here, if a tropos species (say a flexible biphenyl compound) is linked to a metal which, in turn, is linked to a stable enantiopure ligand (the chiral activator) a single diastereoisomeric compound can be formed, since a preferred sense of twist is induced in the tropos moiety by the stable chiral activator. This may cause an increase of the catalytic activity and of the asymmetric induction: many examples of highly enantioselective processes carried out within this scheme have been described. Interestingly, the same concept has also been applied[3] in a related topic: the assignment of the absolute configuration of aliphatic 1,*n*-diols ($n=2$–4) by exploiting the sense of twist induced in a biphenyl moiety when a diol, reacting with a suitable flexible biphenyl ketone, forms the corresponding ketal. Herein, we want to show a further example of this concept in which it becomes possible to carry out a highly enantioselective synthesis of (−)-muscone,[4] a valuable ingredient of the perfume industry, by means of the asymmetric conjugate addition of dimethylzinc to (*E*)-cyclopentadec-2-en-1-one.[5] The last few years have witnessed significant progresses[6] in the field of the catalytic asymmetric conjugate addition of organozinc compounds to α,β-unsaturated ketones, allowing the construction of C–C bonds in high chemical yields and efficient stereocontrol, thus providing the synthetic organic chemist with a very powerful tool to assemble even large and polyfunctional molecules.[7] The success obtained in such of process relies mainly in the development of efficient catalytic precursors which are constituted by Cu(II) or Cu(I) salts coordinated by enantiopure phosphorus ligands. The family of phosphoramidites, the use of which has been pioneered by Feringa and co-workers,[6a,7a,b,8] has been particularly successful in this respect. In these ligands the chiral source is often derived from enantiopure 2,2′-dihydroxy-1,1′-binaphthyl, BINOL, or modified binaphthols, coupled to another achiral or chiral residue, so the phenomenon of double asymmetric induction may also result.[9] Our attention was captured by a recent paper of Feringa et al. where a systematic study of the relationship between structure of the chiral ligand and asymmetric induction was carried out:[8a] of the several ligands tested, compound **1** (Scheme 1) seemed to us particularly attractive because we immediately saw in it the possibility to make a

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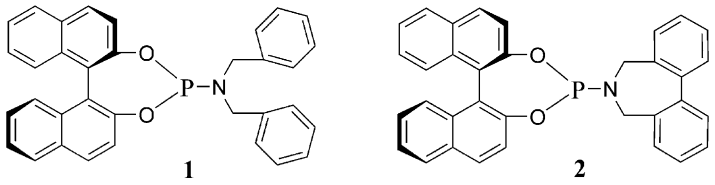


Scheme 1.

comparison with the properties of the structurally related ligand **2** (Scheme 1).

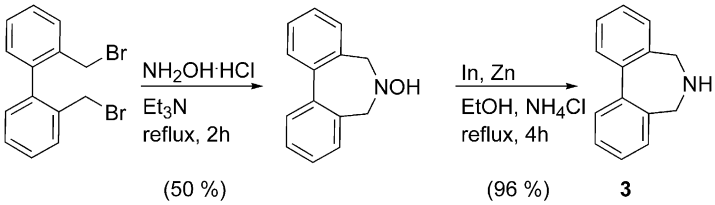
The possibility of asymmetric activation exists in compound **2** and this is not possible in **1**.[2,5e] Previous examples of phosphoramidite catalysts based on the principle of asymmetric activation made use[5e] of a centrochiral amine residue and phenolic part derived from flexible biphenol. Interestingly, ligand **2** derives from a part coming from enantiopure BINOL and an achiral, flexible biphenyl amine; in other words **2** shows a completely new design: chiral phenol, flexible biphenyl amine and overall chirality only due to atropisomerism.

2. Results and discussion

We synthesized the phosphoramidites **1** and **2** simply by adding a solution of (*R*)-BINOL in THF to a solution of dichloroamidite of dibenzylamine or amine **3** respectively, prepared in situ by treating the suitable amine with PCl_3 and NEt_3, according to the Alexakis procedure.[10] Amine **3** was prepared (Scheme 2) starting from 2,2′-bis(bromomethyl)-biphenyl,[11a,b] obtained from diphenic acid, by transforming it in the corresponding hydroxylamine and successive reduction with In/Zn in boiling ethanol.[11c]

It is well known[3,12] that biphenyl compounds like **3** present an M–P equilibrium and that the activation energy for this transformation is about 14–15 kcal/mol, so the inversion of the biphenyl sense of twist is really fast at room temperature and the two enantiomers of **3** cannot be isolated. In principle, starting from (*R*)-BINOL two diastereoisomeric phosphoramidites could be obtained, taking into account that the biphenyl group could be P or M twisted, i.e. (*R*,P)-**2** and (*R*,M)-**2**. However, also in compounds where the biphenyl moiety is linked to a chiral group, a fast P–M interconversion still occurs:[3,12] thus, this fact ensures that the stereoisomeric ratio between (*R*,P)-**2** and (*R*,M)-**2** is only determined by their thermodynamic stability. The ^{31}P NMR spectrum of **2** showed the presence of only one peak (δ= 146.38). Taking into account that diastereoisomeric phosphoramidites[8a] (and phosphites[13]) show different ^{31}P signals, it is tempting to assume that in the case of **2** a single diastereoisomer is present in solution. We also measured the CD spectrum of **1** and **2**: the difference spectrum, CD(**2**)–CD(**1**), could afford a reasonable estimate[14] of the CD coming from a distorted biphenyl group. Interestingly, in the spectrum (Fig. 1) two Cotton effects can be recorded below 280 nm (i.e. in the region where the biphenyl chromophore absorbs): a broad positive one (220–260 nm), which clearly results from the contribution of two bands of the same positive sign at about 220 and 240 nm, and a negative one at about 215 nm. The Cotton effect at 240 nm is reasonable due to the A transition of the biphenyl chromophore which is a probe of the sense of twist of the biphenyl group: a positive Cotton effect from the A band indicates[3,12] a negative (M) torsion of the biphenyl.

Asymmetric conjugate additions of dialkylzinc reagents to the enones **4**–**6** (Scheme 3) were carried out in toluene (at −40 °C for **4** and **5** and at 0 °C for **6**) with a catalytic precursor deriving from $Cu(OTf)_2$/**1** or **2** (ratio substrate/Cu/chiral ligand = 1/0.03/0.06). The results are collected in Table 1. In the presence of **1** diethyl zinc adds quickly (4 h) and smoothly to both **4** (run 1) and **5** (run 2) affording the corresponding ketones in high yields and moderate enantiomeric excesses. It is noteworthy that the same results have been obtained[8a] by Feringa et al. who used slightly different experimental conditions (CuOTf instead of $Cu(OTf)_2$, −10 °C for 16 h instead of −40 °C for 4 h). A moderate value of enantiomeric excess has also been obtained with the same ligand for ketone **6**[15] (run 3): (−)-muscone is prepared in 57% ee, i.e. a value which is not of practical interest for the perfume industry. Then the same reactions were repeated (under the same experimental conditions) using phosphoramidite **2**. Also, ligand **2** gives rise to an efficient catalytic system: in the cases of **4** (run 4) and **5** (run 5) the addition products are obtained in good yields and short reaction times (2 h ca.), but we could not observe a substantial 'asymmetric activation' effect. In fact, while in the case of chalcone (Table 1, run 1 vs run 4) we had an increase from 52 to 65%, in the case of cyclohexenone (Table 1, run 2 vs run 5) we had a slight reduction of stereoselectivity (from 54% with **1** to 45% with **2**). However, much to our delight, significant increase of ee was observed just in the case of ketone **6**: in fact, (run 6) with **2** derived from (*R*)-BINOL, (−)-muscone having 84% ee was obtained. Of course, using (*S*)-BINOL for the preparation of **2**, the (+) antipode is obtained with the same



Scheme 2.

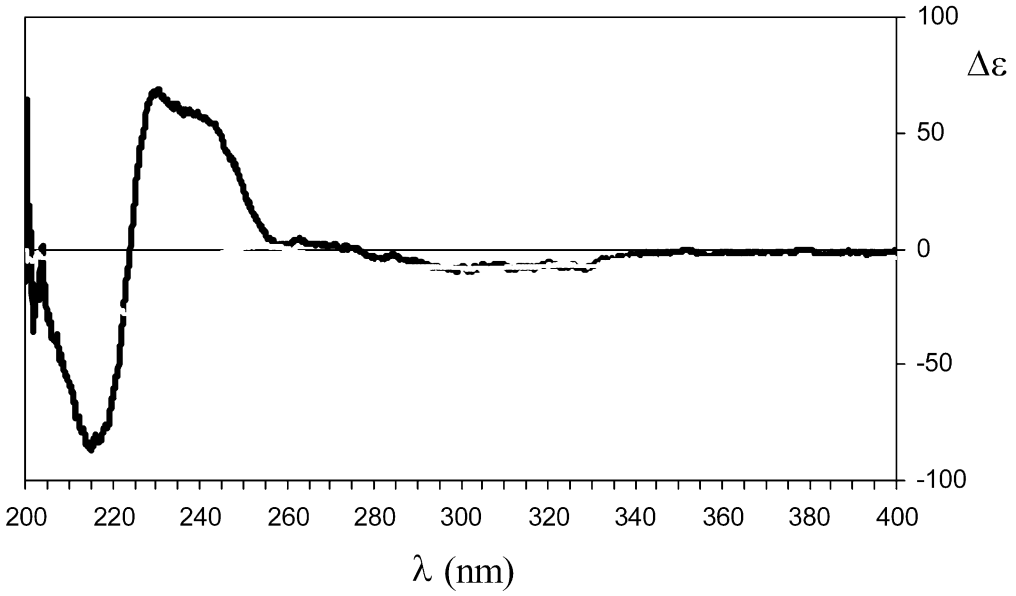
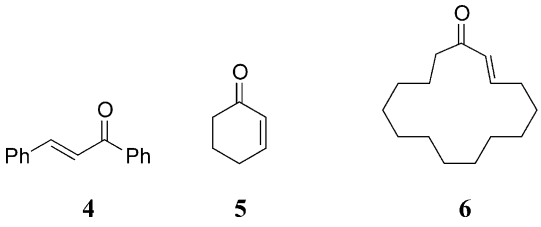


Figure 1. Difference spectrum (CD-2)–(CD-1) in THF.

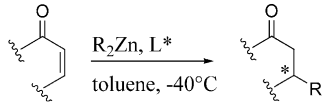


4 **5** **6**

Scheme 3.

enantiomeric excess (run 7). Another interesting observation is the result with a different amount of $Cu(OTf)_2$. Using enone/$Cu(OTf)_2$/L^* = 1/0.01/0.02 (i.e. with only 1% of metal) the ee goes to 61% ee (run 8). These results are very important from a practical point of view: the use of (*R*)-**2** guarantees a truly catalytic synthesis of the natural antipode of (−)-muscone having high enantiomeric purity and this certainly constitutes an economic access to this valuable fine chemical. From a more theoretical point of view, this result demonstrates the importance of the concept of asymmetric activation: here the (*R*)-chirality of BINOL imposes the biphenyl moiety of the ligand **2** to assume a preferred M sense of twist. The pair (*R*,M) obtained in this way allows an efficient enantioselective conjugate addition of dimethylzinc to (*E*)-cyclopentadec-2-en-1-one. On the other hand, the same ligand **2** does not work with the same efficiency in the cases of **4** and **5**, indicating that the asymmetric activation effect is strongly dependent on the substrate employed. However, it is interesting to note that, if the results provided by **2** are compared with those obtained in the case of **1**, an increase of the ee is observable for addition to **4** and **6** (13 and 27%, respectively) whilst a small

Table 1. Asymmetric conjugated addition of R_2Zn to α,β-enones in the presence of ligands **1** and **2**



Run	Enone	Ligand	R_2Zn	Yield[a]	ee (a.c.)[b]
1	**4**	**1**	Et_2Zn	68	52[c] (*S*)
2	**5**	**1**	Et_2Zn	95	54[d] (*R*)
3	**6**	**1**	Me_2Zn	60[e]	57[f] (*R*)
4	**4**	**2**	Et_2Zn	70	65[c] (*S*)
5	**5**	**2**	Et_2Zn	98	45[d] (*R*)
6	**6**	**2**	Me_2Zn	72[e]	84[f] (*R*)
7	**6**	**2**[g]	Me_2Zn	68[e]	84[f] (*S*)
8	**6**	**2**[h]	Me_2Zn	50[g]	61[f] (*R*)

[a] Carried out at −40 °C in toluene; enone/$Cu(OTf)_2$/L^* = 1/0.03/0.06; yield calculated on the isolated and purified product.
[b] Determined by the sign of optical rotatory power.
[c] Determined by HPLC on chiral column Chiralcel OJ, hexane/isopropanol 99.5: 0.5, 1.0 ml/min, 254 nm.
[d] Determined by HPLC on chiral column Chiralcel OD, hexane/isopropanol 99.7: 0.3, 0.5 ml/min, 254 nm, on the corresponding dioxolane obtained with (*R*,*R*)-1,2-diphenylethane-1,2-diol.
[e] Carried out at 0 °C in toluene; enone/$Cu(OTf)_2$/L^* = 1/0.03/0.06; yield calculated on isolated and purified product.
[f] Determined by ^1H NMR spectroscopy in the presence of $Eu(hfc)_3$ as described by Yamamoto.[16] When the same measurament has been carried out by polarimetry [for (−)-muscone: $[\alpha]_D = -12.7$ (c = 0.9, MeOH), lit. 4g] the slightly higher value of 89% is obtained.
[g] **2** has been prepared from (*S*)-BINOL.
[h] Carried out at 0 °C in toluene; enone/$Cu(OTf)_2$/L^* = 1/0.01/0.02.

reduction (9% ca.) is observed in the case of **5**. Therefore, (*R*,M)-**2** behaves like a matched pair of the BINOL and biphenyl chiralities in the cases of chalcone and (*E*)-cyclopentadec-2-en-1-one, while it looks like a mismatched pair in the case of cyclohexenone. This different outcome could be related to a different conformational behavior[6c] of the α,β-unsaturated ketones. In fact, whilst **4** and **6** are flexible compounds, **5** is fixed in a pure *s-trans* situation. In other words, a pure *s-trans* system is not a very good substrate for the Cu/**2** catalyst since the enantioselectivity is only moderate, on the contrary flexible α,β-unsaturated ketones afford higher values of asymmetric induction, the macrocyclic ketone **6** providing the highest ee. It is noteworthy that the present results are at variance with those reported by Alexakis et al.[5e] who employed a phosphoramidite ligand where the amine part was centro chiral and the phenolic part derived from the flexible biphenol. Here, in fact, ketone **5** is a good substrate whilst **4** and **6** are not, giving rise only to moderate enantioselectivities (27 and 49%, respectively).

3. Conclusions

This work describes some important results in the field of the asymmetric conjugate addition to α,β-unsaturated ketones: first, the completely new designed phosphoramidite ligand **2**, where the chirality is due only to atropisomerism and where the amine residue constitutes the tropos part, has been prepared and tested. In this way, a protocol has been set up by which a valuable fine chemical, (−)-muscone, can be easily prepared. Second, it has been possible to make a comparison between the previously reported ('asymmetrically activated') phosphoramidites (where the amine moiety was centrochiral and the phenolic counterpart a flexible biphenol) and **2** (without stereogenic centers, deriving from enantiopure BINOL and showing the flexible biphenyl amine **3**). This comparison shows that the two kinds of phosphoramidites have opposite behavior versus rigid or flexible ketones. Understanding the origin of this correlation could be an extremely useful key to understand the reaction stereochemistry and thus to reliably predict the enantioselectivity of this reaction.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker Aspect300 300 MHz NMR and Varian AS500 500 MHz NMR spectrometers, using TMS as external standard. The ^{31}P NMR spectrum was recorded at the frequency of 242.88 MHz with an Inova 600 instrument. The sample was dissolved in CD_2Cl_2 and the chemical shift of the signals were calculated with respect to H_3PO_3 85% (0 ppm) by replacement. TLC analyses were performed on silica gel 60 Macherey–Nagel sheets; flash chromatography separations were carried out on suitable columns using silica gel 60 (230–400 mesh) or neutral aluminum oxide. HPLC analyses were performed on a JASCO PU-1580 intelligent HPLC pump equipped with a Varian 2550 UV detector. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. Melting points were taken using a Kofler Reichert–Jung Thermovar apparatus and are uncorrected. Mixture compositions were determined by GC–MS on a Hewlett Packard 6890 chromatograph equipped with a HP-5973 mass detector. IR spectra were performed with a Perkin–Elmer 883 spectrometer. Toluene and dichloromethane were refluxed over sodium–benzophenone and calcium hydride respectively and distilled before the use. Unless otherwise specified the reagents were used without any purification.

4.1.1. Synthesis of 2,2′-(2-azapropane-1,3-diyl)-1,1′-biphenyl (3). 2,2′-Bis(bromomethyl)-1,1′-biphenyl was prepared by PBr_3 bromination of 2,2′-bis(hydroxymethyl)-1,1′-biphenyl, in turn obtained by Red-Al reduction of dimethyl ester of commercially available diphenic acid.

To a solution of Et_3N (53 ml) and hydroxylamine hydrochloride (3.7 g, 54 mmol), under nitrogen atmosphere, 2,2′-bis(bromomethyl)-1,1′-biphenyl (5.4 g, 16 mmol) was added and the mixture was heated to reflux for 2 h. The mixture was filtered under vacuum and the resulting solution was distilled to remove the Et_3N. The crude product was purified on silica gel (petroleum ether/ethyl ether 4:1–petroleum ether/ethyl ether 2:1) affording the pure 2,2′-(2-azapropane-1,3-diyl)-1,1′-biphenyl-*N*-hydroxide (1.7 g, 50%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.15 (d, J= 12.1 Hz, 2H), 3.95 (d, J=12.1 Hz, 2H), 7.5 (m, 9H); ^{13}C NMR (75 Mz, $CDCl_3$): δ 60.44, 127.81, 129.51, 130.15, 133.92, 149.50.

To a 1:1 solution of EtOH/satd. NH_4Cl (40 ml, pH≅6) 2,2′-(2-azapropane-1,3-diyl)-1,1′-biphenyl-*N*-hydroxide (1.7 g, 8 mmol) was added. Indium (5%, 46 mg, 0.4 mmol) and zinc (1.04 g, 16 mmol) were then added and the mixture was refluxed for 7 h. After cooling, the mixture was filtered on Celite and concentrated. A satd. Na_2CO_3 solution was added and the mixture was extracted with ethyl acetate. The collected organic phases were dried over anhydrous Na_2SO_4 and the solvent evaporated in vacuo to afford the biphenylazepine **3** (1.5 g, 7.6 mmol, 95%) as a white solid. Mp=229–231 °C; IR (neat): ν_{max} 3310, 3140, 2910, 1450, 1380, 1200, 760 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.04 (s, 5H), 7.47–7.49 (m, 2H), 7.55–7.60 (m, 4H), 7.64 (d, 2H, J=7.5 Hz); ^{13}C NMR (125 Mz, $CDCl_3$): δ 45.90, 128.61, 129.22, 129.54, 130.50, 131.27, 140.81.

4.1.2. Synthesis of O,O′-(*R*)-(1,1′-dinaphthyl-2,2′-diyl)-*N*,*N*′-dibenzylphosphoramidite (1). Under nitrogen atmosphere, at 0 °C, to a stirred mixture of freshly distilled PCl_3 (174 μL, 20 mmol) and Et_3N (3.9 mL, 28 mmol) in dry THF (4 mL) freshly distilled dibenzylamine (384 μL, 2.0 mmol) was added and the mixture was stirred for 3 h at room temperature. Slowly, a solution of enantiopure (*R*)-BINOL (572 mg, 2.0 mmol) in dry THF (6 mL) was added at 0 °C. After stirring (19 h) at room temperature, the resulting mixture was diluted with toluene and filtered on neutral aluminum oxide. The solution was concentrated and purified by flash chromatography on neutral aluminum oxide using CH_2Cl_2 as eluent obtaining 417 mg (0.81 mmol, 41%) of the pure ligand as a foamy white solid. Stripping with petroleum ether gave the product as white solid.

Mp = 132–134 °C. Spectroscopic data (NMR and $[\alpha]_D^{20}$) were in good agreement with data reported in literature.[8a]

4.1.3. Synthesis of O,O′-(*R*)-(−)-(1,1′-dinaphthyl-2,2′-diyl)-*N*-2-[2,2′-(2-azapropane-1,3-diyl)-1,1′-biphenylyl] phosphoramidite (2). Under nitrogen atmosphere, at 0 °C, to a stirred solution of PCl_3 (174 μL, 20 mmol) and Et_3N (3.9 mL, 28 mmol) in dry THF (4 mL) the biphenylazepine **3** (390 mg, 2.0 mmol) was added and the mixture was stirred for 3 h at room temperature. Slowly, a solution of enantiopure (*R*)-BINOL (572 mg, 2.0 mmol) in dry THF (6 mL) was added at 0 °C. After 18 h of stirring at room temperature, the resulting mixture was diluted with toluene and filtered on neutral aluminum oxide. The solution was concentrated and purified by flash chromatography on neutral aluminum oxide using CH_2Cl_2 as eluent obtaining 630 mg (1.24 mmol, 62%) of the pure ligand as a foamy solid. Stripping with petroleum ether gave the phosphoramidite **2** as a white solid. Mp = 152–154 °C; $[\alpha]_D^{20} = -246$ ($c = 0.45$; CH_2Cl_2); IR (neat): ν_{max} 3080, 2860, 1580, 1460, 1230, 1050, 930, 820, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.67 (dd, 2H, $J_1 = 13.0$ Hz, $J_2 = 9.5$ Hz), 4.00 (dd, 2H, $J_1 = 13.0$ Hz, $J_2 = 6.5$ Hz), 7.08 (d, 1H, $J = 8.5$ Hz), 7.19–7.21 (m, 1H), 7.27–7.30 (m, 4H), 7.35 (d, 1H, $J = 9.0$ Hz), 7.39–7.48 (m, 8H), 7.57 (d, 1H, $J = 8.5$ Hz), 7.80 (d, 1H, $J = 8.5$ Hz), 7.88 (d, 1H, $J = 7.5$ Hz), 7.95 (d, 1H, $J = 8.5$ Hz), 8.01 (d, 1H, $J = 9.0$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 47.65, 47.82, 122.21, 122.31, 124.83, 125.06, 126.32, 127.18, 127.30, 128.06, 128.43, 128.50, 128.59, 129.51, 130.25, 130.56, 131.05, 131.67, 133.20, 135.20, 141.25, 149.29, 149.90; ^{31}P NMR (242.88 MHz, CD_2Cl_2) δ 146.38. Anal. calcd for $C_{34}H_{24}NO_2P$: C 80.14; H 4.75; N 2.74; P 6.08. Found: C, 80.85; H, 5.10; N 2.90; P 6.30.

4.1.4. Synthesis of cyclopentadec-2-en-1-one (6). To a solution of 30% H_2O_2 (2.0 mL, 18 mmol) and 1,1,1-trifluoromethylacetone (0.3 mL, 3.3 mmol) a solution of 2-phenylthiocyclopentadecanone (obtained from 2-cyclopentadecanone as reported)[15] (5.0 g, 15 mmol) in $CHCl_3$ (15 ml) was added at 0 °C. After 1 h of stirring at 0 °C, the mixture was diluted with $CHCl_3$ and the organic layer was separated, dried with anhydrous Na_2SO_4 and the solvent evaporated in vacuo. The crude sulfoxide was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate 3/1) obtaining the pure product (4.2 g, 12 mmol, 80%) and the starting sulfide (300 mg, 6%).

Under nitrogen atmosphere, the sulfoxide (4.2 g, 12 mmol) was dissolved in anhydrous toluene (100 mL) and calcium carbonate (160 mg, 1.6 mmol) was added. The mixture was stirred 12 h at room temperature and refluxed for 2 h. After cooling at room temperature, water (50 mL) was added and the organic layer was separated, washed with brine, dried with anhydrous Na_2SO_4 and the solvent evaporated in vacuo. The crude product was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate 3/1) affording 2.38 g (89%) of 2-cyclopentadecenone.

4.1.5. Enantioselective conjugate addition of diethylzinc to chalcone (4). A solution of $Cu(OTf)_2$ (5 mg, 0.014 mmol) and chiral ligand (0.030 mmol) in toluene (4 mL) was stirred for 1 h at room temperature under nitrogen atmosphere. To this catalyst solution, chalcone (104 mg, 0.5 mmol) was added and, after cooling to −40 °C, diethylzinc (1.0 M in hexane, 1.0 mL, 2 equiv) was added dropwise. The reaction was monitored by TLC. After stirring for 2 h at −40 °C the reaction mixture was poured in 10 mL of 1.0 M HCl solution and extracted three times with ethyl ether. The combined organic phases were washed with brine, dried with anhydrous Na_2SO_4 and the solvent evaporated in vacuo. The crude product was purified by column chromatography (SiO_2, petroleum ether/ethyl ether 8:2), affording pure 1,3-diphenyl-pentanone (70%). The ee was determined by HPLC analyses: Daicel Chiralcel OJ, hexane/2-propanol 99.5:0.5, 1.0 mL/min, $\lambda = 254$ nm, $t_r = 18.63$ min (*S*); $t_r = 28.29$ min (*R*).

4.1.6. Enantioselective conjugate addition of diethylzinc to 2-cyclohexen-1-one (5). A solution of $Cu(OTf)_2$ (5 mg, 0.014 mmol) and chiral ligand (0.03 mmol) in toluene (4 mL) was stirred for 1 h at room temperature under nitrogen atmosphere. The solution was cooled to −40 °C and 2-cyclohexen-1-one (48 mg, 0.5 mmol) followed by Et_2Zn (1.0 M in hexane, 1.0 mL, 2 equiv) were added slowly. The reaction was monitored by GC–MS. After stirring for 2 h at −40 °C the reaction mixture was poured in 10 mL of 1 M HCl solution and extracted three times with ethyl ether. The combined organic phases were washed with brine, dried with anhydrous Na_2SO_4 and filtered. Removal of ethyl ether under reduced pressure, 700–350 mbar, at room temperature yielded the crude product in toluene which was purified by flash column chromatography (SiO_2, pentane/ethyl ether 5:1) to afford 3-ethylcyclohexanone (98%) as a colorless liquid. The ee was determined by HPLC analyses after derivatization with (*R*,*R*)-1,2-diphenylethan-1,2-diol: to a solution of 3-ethylcyclohexanone (62 mg, 0.49 mmol) in CH_2Cl_2 (5 mL) actived 4 Å molecular sieves were added at room temperature followed by (*R*,*R*)-1,2-diphenylethan-1,2-diol (128 mg, 0.6 mmol) and by traces of *p*-toluensulfonic acid. After stirring for 2 h the 4 Å molecular sieves were removed by filtration and the reaction mixture was dried with anhydrous Na_2SO_4, and the solvent removed under reduced pressure. The crude product was purified by column chromatography (petroleum ether/ethyl ether 98:2) to afford the desired ketal as a colorless liquid. The ee was determined by HPLC analyses: Daicel Chiralcel OD, hexane/2-propanol 99.7:0.3, 0.5 mL/min, $\lambda = 254$ nm, $t_r = 8.0$ min (*R*,*R*,*R*), $t_r = 10.0$ min (*S*,*R*,*R*).

4.1.7. Enantioselective conjugate addition of dimethylzinc to 2-cyclopentadecen-1-one (6). A solution of $Cu(OTf)_2$ (5.6 mg, 0.015 mmol) and chiral ligand (0.03 mmol) in toluene (4 mL) was stirred for 1 h at room temperature under nitrogen atmosphere. After cooling to 0 °C, Me_2Zn (2.0 M in toluene, 0.38 mL, 1.5 equiv) was added followed by 2-cyclopentadecenone (111 mg, 0.5 mmol). The reaction was monitored by GC–MS analysis. After stirring for 1.5 h at 0 °C 1 M HCl solution (10 mL) and ethyl ether (5 mL) were added and stirred for a few minutes. Then, the solution was extracted three times with ethyl ether. The combined organic phases were washed with brine, dried with anhydrous Na_2SO_4 and the solvent removed in vacuo. The crude product was purified by flash column chromatography (SiO_2, petroleum ether/ethyl ether 95:5), affording (−)-muscone (70%) as colorless oil. $[\alpha]_D = -11.3$ ($c = 0.85$, MeOH). The ee was determined

by the following NMR method:[16] a solution of $Eu(hfc)_3$ (107 mg) and (+) or (−)-muscone (3.6 mg) in 0.5 ml of $CDCl_3$ was subjected to analysis by NMR. The peak (doublet) caused by methyl group of the (*R*) enantiomer shifted to 3.72 ppm, while that of the (*S*) shifted to 3.59 ppm. The ee were calculated from the area peak ratio.

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15. To prepare (*E*)-cyclopentadec-2-en-1-one, the procedure of Tanaka, K.; Ushio, H.; Kawabata, Y.; Suzuki, H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1445 has been followed. Here, the C═C bond of **6** derives from an elimination reaction involving an intermediate sulfoxide, in turn produced by oxidation of the corresponding sulfide by oxone. However, instead of using oxone to oxidize the sulfide to sulfoxide, we used the method of H_2O_2/CF_3COCH_3, described by Lupattelli, P.; Ruzziconi, R.; Scafato, P.; Degl'Innocenti, A.; Paolobelli, A. *Synth. Commun.* **1997**, *27*, 441. In this way, no sulfone is formed; this allows an easy separation of the desired sulfoxide from the starting sulfide which can be recycled, increasing the overall conversion.
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