Enantioselective copper-catalysed addition of organometallic reagents using phosphoramidite ligands

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Chapter 6

Copper-catalyzed enantioselective conjugate addition of organometallic reagents to acyclic dienones

The enantioselective copper/phosphoramidite-catalyzed 1,4-addition of dialkylzinc reagents and trimethylaluminum to acyclic dienones is described. The products of this reaction, obtained with enantioselectivities of up to 95%, can be further functionalized by a second conjugate addition, or employed in an enolate trapping, ring-closing metathesis protocol.

Part of this chapter has been published:

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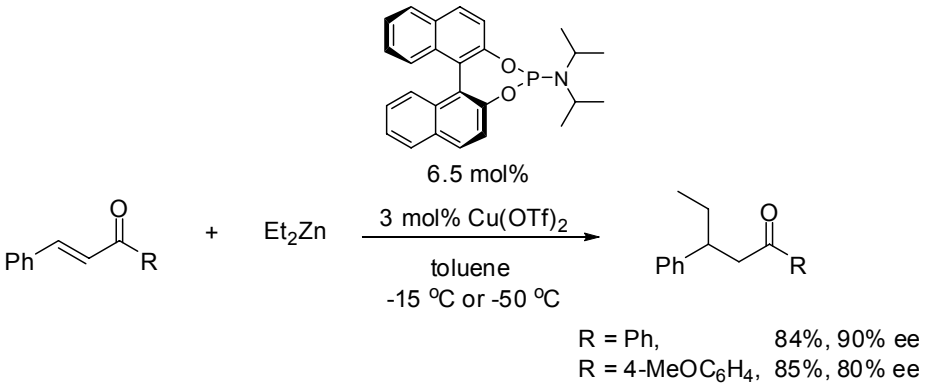
6.1 Introduction

The conjugate addition of organometallic reagents to α,β-unsaturated systems is an important transformation in synthetic organic chemistry.[1] Considerable effort has been devoted over the past decade to the development of enantioselective copper-catalyzed conjugate addition reactions.[2] Copper complexes based on chiral phosphoramidite ligands are established versatile catalysts for the enantioselective 1,4-addition of dialkylzinc reagents to a range of enones.[3] Although more recently a variety of other chiral ligands has been introduced for this C-C bond forming reaction,[2,4] acyclic α,β-unsaturated systems constitute a considerable challenge as it has proven to be much more dificult to obtain high enantioselectivity with these types of substrates. Recently several structurally diverse chiral ligands were reported to be suitable for a number of important acyclic substrates. [3b,4b,5] A short survey, with focus on the most efficient methods available, is presented in the next paragraph.

6.1.1 Enantioselective copper-catalyzed conjugate addition of organozinc reagents to acyclic substrates

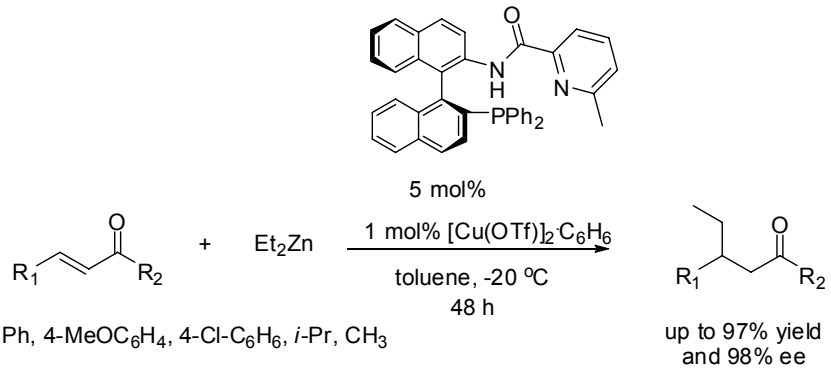
BINOL-based phosphoramidites were the first class of chiral ligands reported to achieve high enantioselectivities in the copper catalyzed conjugate addition of organozinc reagents to acyclic substrates.[3b]



Scheme 6.1

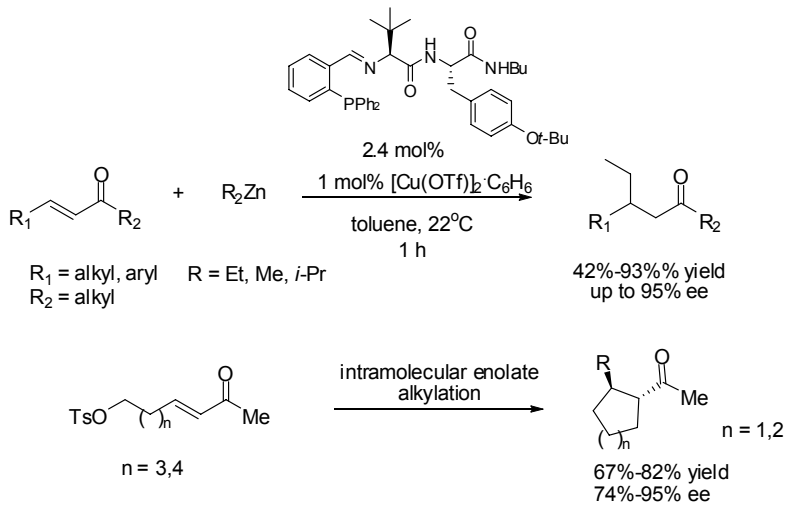
The addition of Et_2Zn to chalcone in the presence of $Cu(OTf)_2$ and a chiral ligand in a ratio of 1:2 afforded the desired product in 84% yield and with 90% ee (Scheme 6.1).

A further improvement in the enantioselective addition of Et_2Zn to chalcone and its derivatives was achieved using the P,N chiral ligand depicted in Scheme 6.2, in combination with $[Cu(OTf)]_2 \cdot C_6H_6$.[4b] However, long reaction times (48 h) are required.



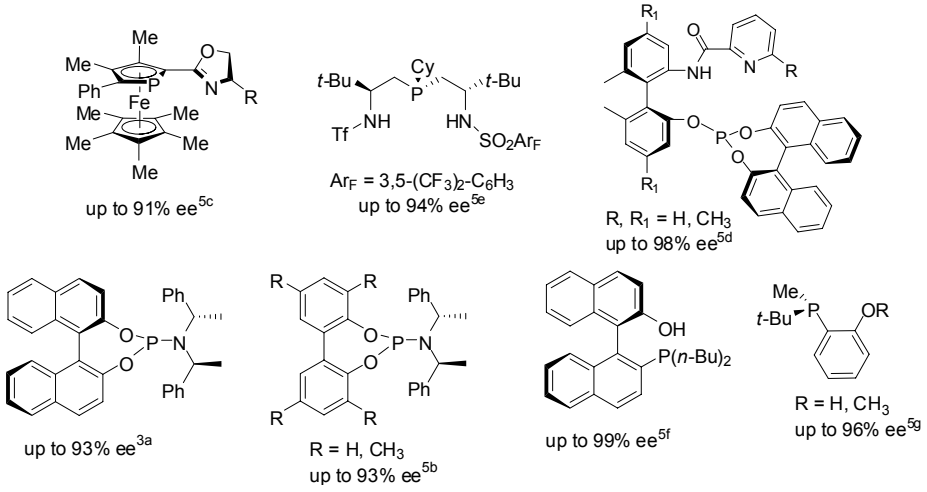
Scheme 6.2

Employing a new class of chiral diphenyl phosphine ligands, Hoveyda and coworkers[5a] extended in 2002 the scope of the copper-catalyzed conjugate addition to linear α,β-unsaturated ketones to a wide range of dialkylzinc reagents. The copper complex of the chiral dipeptide phosphine ligand afforded the 1,4-products in moderate to high yields (42%-93%) and high enantioselectivities (up to 95%) (Scheme 6.3). The possibility of inter- and intramolecular enolate alkylation was investigated as well. In the latter case substituted cyclopentyl and cyclohexyl ketones were obtained in good yield and enantioselectivities of up to 95%. This catalytic reaction was applied in the total synthesis of *erogorgiaene*,[6] in which the asymmetric conjugate addition of Me_2Zn to an acyclic α,β-unsaturated ketone is the key step (see Chapter 1).



Scheme 6.3

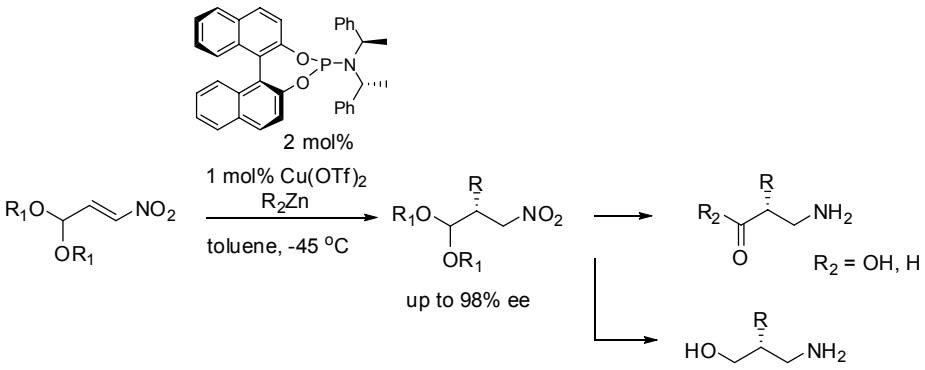
Since this report, several other chiral ligands for the copper catalyzed conjugate addition of dialkylzinc reagents to α,β-unsaturated ketones have been described.[3a,5b-g] Amongst the most efficient are those depicted in Scheme 6.4.



Scheme 6.4

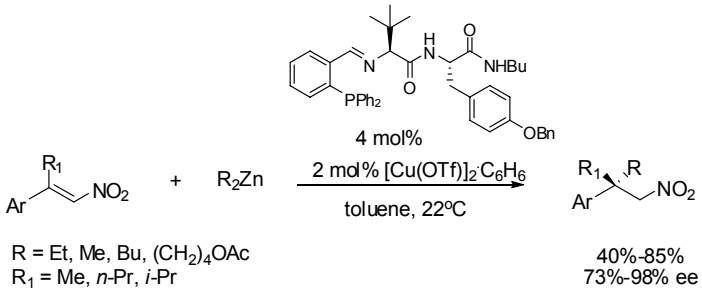
With regard to substrate scope, phosphoramidite ligands stand out with respect to efficiency. Full conversion and enantioselectivities of up to 99% were observed in the addition to aromatic acyclic nitroalkenes using chiral BINOL- or biphenyl-based phosphoramidites in combination with $Cu(OTf)_2$.[7a,d]

In particular, the use of functionalized substrates such as 3-nitropropanoates[7b] or acetal substituted nitroalkenes[7a] provides a catalytic enantioselective route to β[2]-amino aldehydes, acids and aminoalcohols (Scheme 6.5).



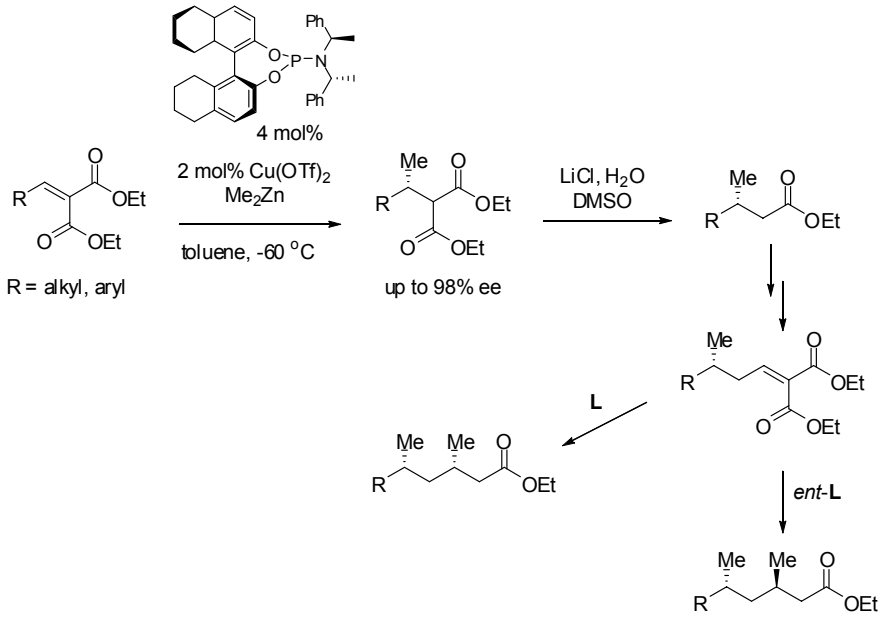
Scheme 6.5

A particular achievement is the addition of dialkylzinc reagents to β-substituted nitroalkenes described by Hoveyda and coworkers for the formation of quaternary stereogenic centers.[7f] The β-disubstituted nitroalkanes were obtained in moderate to good yields and with enantioselectivities of up to 98% using chiral dipeptide phosphine ligands in combination with $[Cu(OTf)]_2{\cdot}C_6H_6$ (Scheme 6.6).



Scheme 6.6

High enantioselectivities were observed for the addition of dimethylzinc to acyclic esters, also. Acyclic malonates are the substrates of choice since simple α,β-unsaturated esters are unreactive toward the conjugate addition of dialkylzinc reagents. It is possible to convert the 1,4-addition product to a mono-ester via decarboxylation (Scheme 6.7). This method can be extended to an iterative procedure to yield either *syn*- or *anti*-3,5-dimethyl carbonyl compounds.



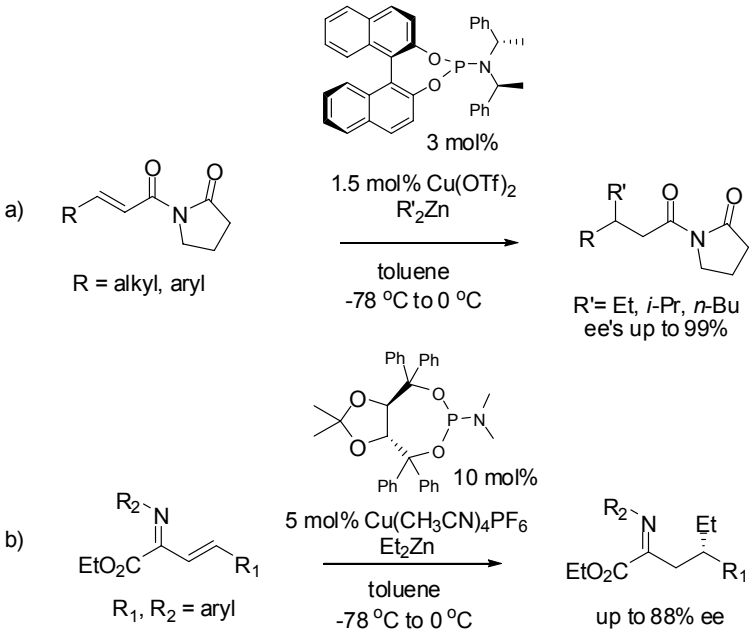
Scheme 6.7

TADDOL- and BINOL-based phosphoramidite ligands were also employed successfully in the copper-catalyzed addition of diorganozinc reagents to α,β-unsaturated imides and imines, respectively.[8]

N-acyl-pyrrolidinones have been used for the first time as α,β-unsaturated carboxylic acids derivatives (Scheme 6.8a).[8a] Good conversion and typically high ee are achieved in the addition of different dialkylzinc reagents (Et_2Zn, *i*-Pr_2Zn, *n*-Bu_2Zn). The β-substituted-*N*-acylpyrrolidones can be converted to the

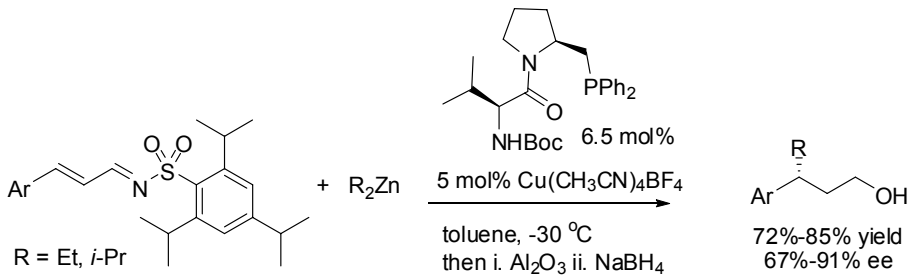
corresponding esters, using a catalytic amount of $[Er(OTf)_3]$ in EtOH, or by hydrolysis to the carboxylic acid.

In the second case α-iminoesters bearing a stereogenic center in the γ-position were obtained in good yield and with enantioselectivities of up to 88%.[8b] $[Cu(CH_3CN)_4]PF_6$ provided better results compared to the more commonly used $Cu(OTf)_2$. High regioselectivities in favor of the 1,4-adduct were observed (Scheme 6.8b).



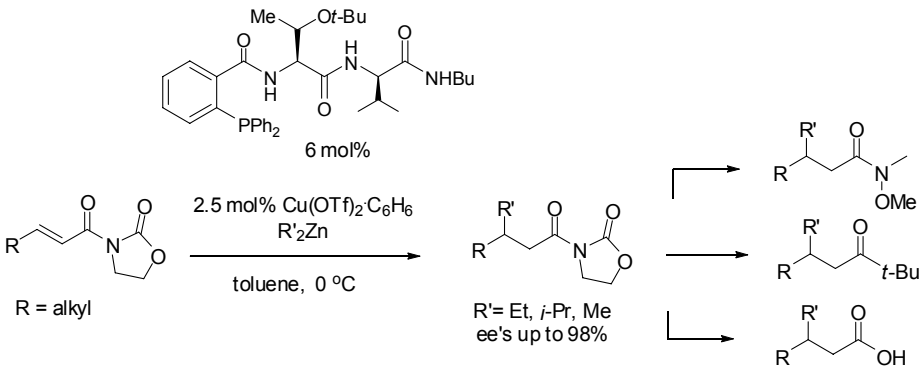
Scheme 6.8

Unsaturated sulfonylaldimines have been shown to undergo conjugate addition of dialkylzinc reagents to afford the 1,4-adducts with high regio- and enantioselectivity in presence of copper complexes with chiral amidophosphane ligands (Scheme 6.9).[9] Deprotection of the imine after the conjugate addition and reduction of the corresponding aldehyde yields the corresponding β-alkylated alkanols with up to 91% ee.



Scheme 6.9

A further broadening of the substrate scope for the copper-catalyzed addition of diorganozinc reagents to acyclic α,β-unsaturated systems was achieved through the use of *N*-acyloxazolidinones, whose masked functionality can be used to give a wide range of carbonyl derivatives such as ketones, Weinreb amides and carboxylic acids[10] (Scheme 6.10).



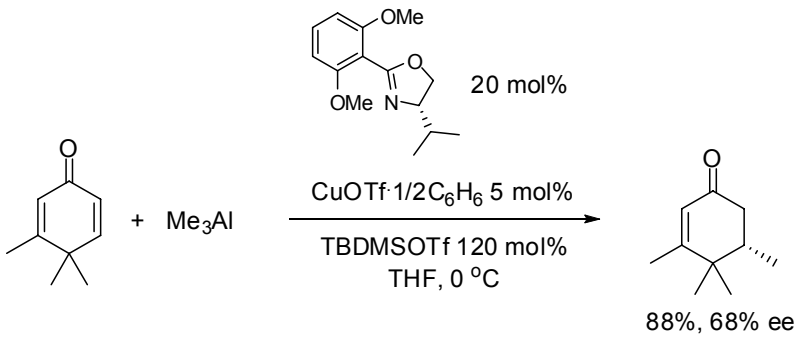
Scheme 6.10

6.1.2 Enantioselective copper catalyzed conjugate addition of organozinc and organoaluminum reagents to cyclic dienones

Much less effort has been devoted to dienones, although these compounds offer considerable potential for further functionalization after the conjugate addition through the second enone moiety. Thus far, only enantioselective

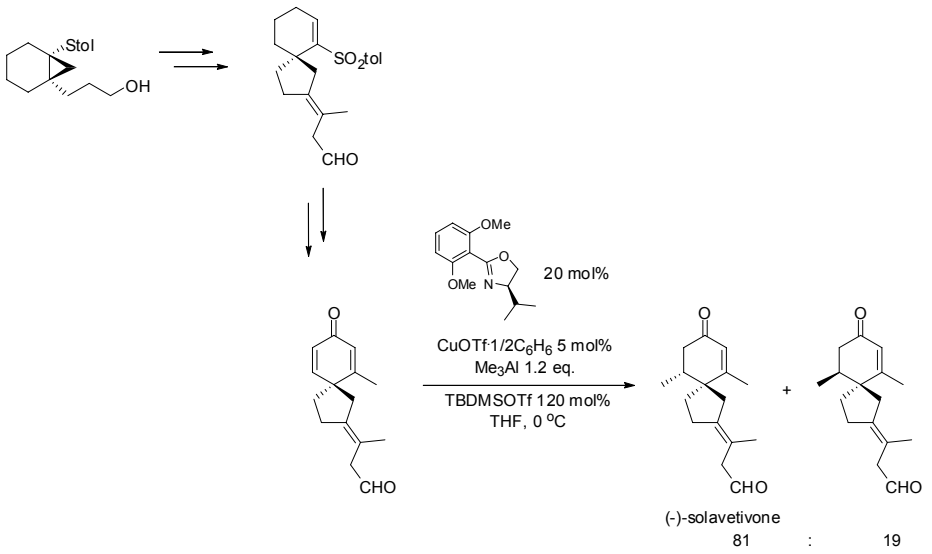
catalytic additions of organozinc reagents and trimethylaluminum to cyclic dienones have been reported and shown to provide versatile chiral synthons for natural product synthesis.

The first example of a copper-catalyzed conjugate addition to a dienone, in the presence of an external chiral ligand, concerns the addition of trimethylaluminum to a substituted cyclohexa-2,5-dienone.[11] 5 mol% of [CuOTf·1/2C_6H_6] in combination with 20 mol% of a chiral 2-aryloxazoline were used to catalyze the addition of Me_3Al to 3,4,4-trimethylcyclohexane-2,5-dienone in 88% isolated yield and 68% ee. The addition of 120 mol% of TBDMSOTf was found to be crucial in achieving high enantioselectivity (Scheme 6.11).



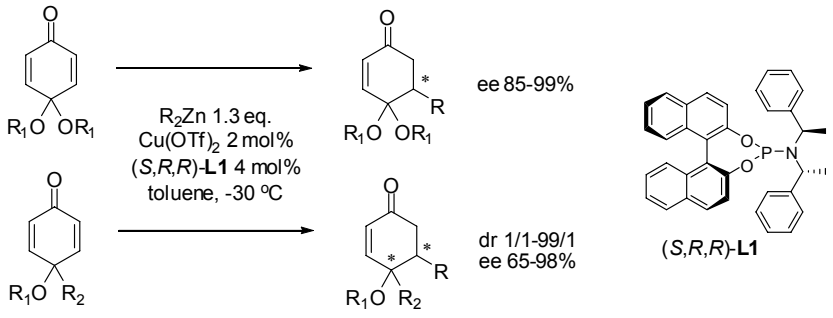
Scheme 6.11

This reaction was used by the same group as a key step in the enantioselective synthesis of (-)-solavetivone,[12] a phytoalexin[13] isolated from potato tubers infected with the blight fungus *Phytophthora infestans* or air cured tobacco leaves. The reaction afforded two diastereoisomers in a 81:19 ratio in favor of the desired product. Separation by HPLC chromatography provided enantiomerically pure (-)-solavetivone in 72% yield (Scheme 6.12).



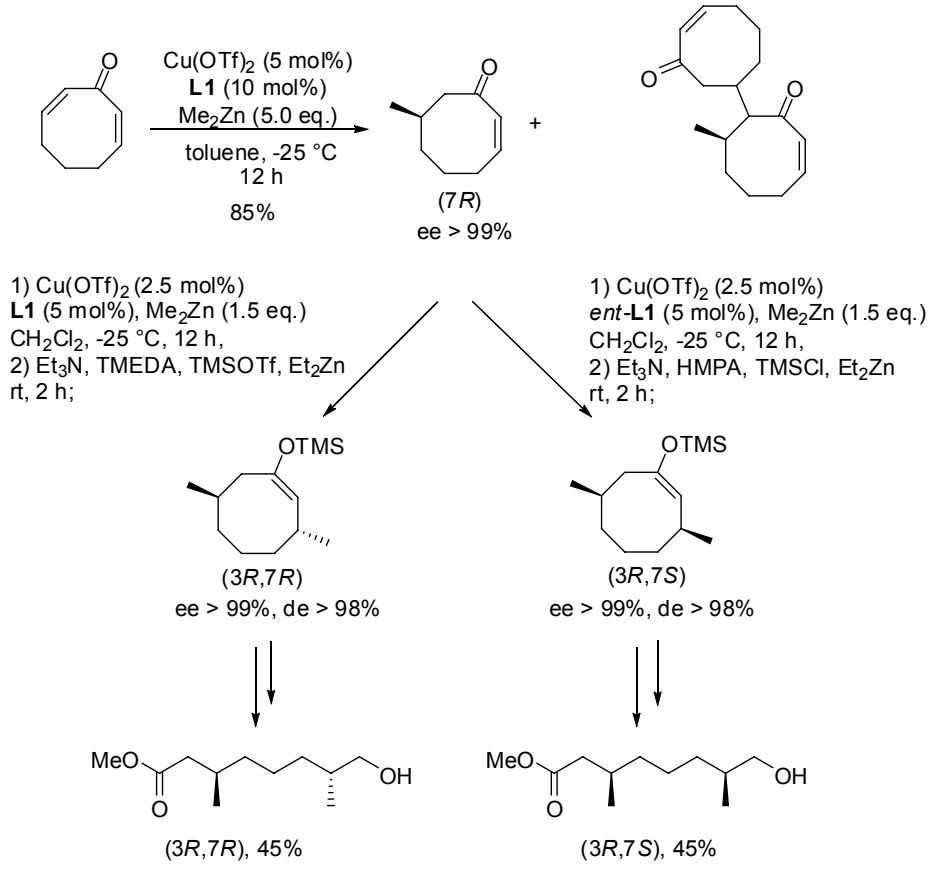
Scheme 6.12

The use of the phosphoramidite ligand (*S*,*R*,*R*)-**L1** allowed high stereoselectivity in the copper-catalyzed addition of organozinc reagents to 4,4-disubstituted cyclohexadienones.[14] In particular, an enantioselectivity of up to 97% was obtained in the desymmetrization of prochiral dienones bearing equal substituents at the 4 position. For substrates substituted with two different groups, two stereogenic centers are formed at the same time during the reaction. Diastereomeric ratio's ranging between 1/1 and 99/1 and moderate to high ee's of the isomers were observed (Scheme 6.13).



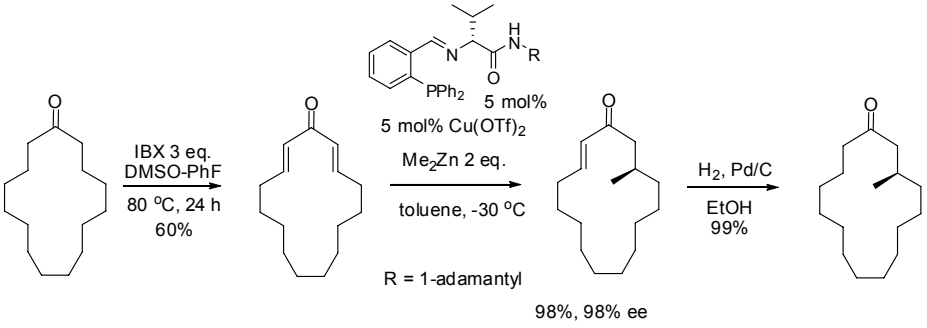
Scheme 6.13

A further example of the synthetic possibilities afforded by the products of the conjugate addition of organozinc reagents to dienones is represented by the procedure, developed in our group, for the addition of Me_2Zn to cycloocta-2,7-dienone (Scheme 6.14).[15] This catalytic procedure allows for the preparation of all four diastereoisomers of a versatile isoprenoid derivative which has been employed as building block in the synthesis of apple leafminer pheromones and of the *β*-mannosyl phosphomycoketide, a potent mycobacterial antigen for T-cells, isolated from *Mycobacterium tuberculosis*[16] (see Chapter 1 for a detailed description).



Scheme 6.14

Recently, Pfaltz et al. reported an enantioselective route to (-)-(*R*)-muscone based on the copper-catalyzed addition of Me_2Zn to cyclopentadecane-2,14-dienone.[17] The starting material can be obtained from commercially available cyclopentadecanone via double IBX dehydrogenation. The introduction of a methyl group, catalyzed by 5 mol% of $Cu(OTf)_2$ and a valine-derived phosphine ligand, proceeds in nearly quantitative yield and 98% ee. Hydrogenation of the remaining double bond over Pd/C gives the (-)-(*R*)-muscone (Scheme 6.15).



Scheme 6.15

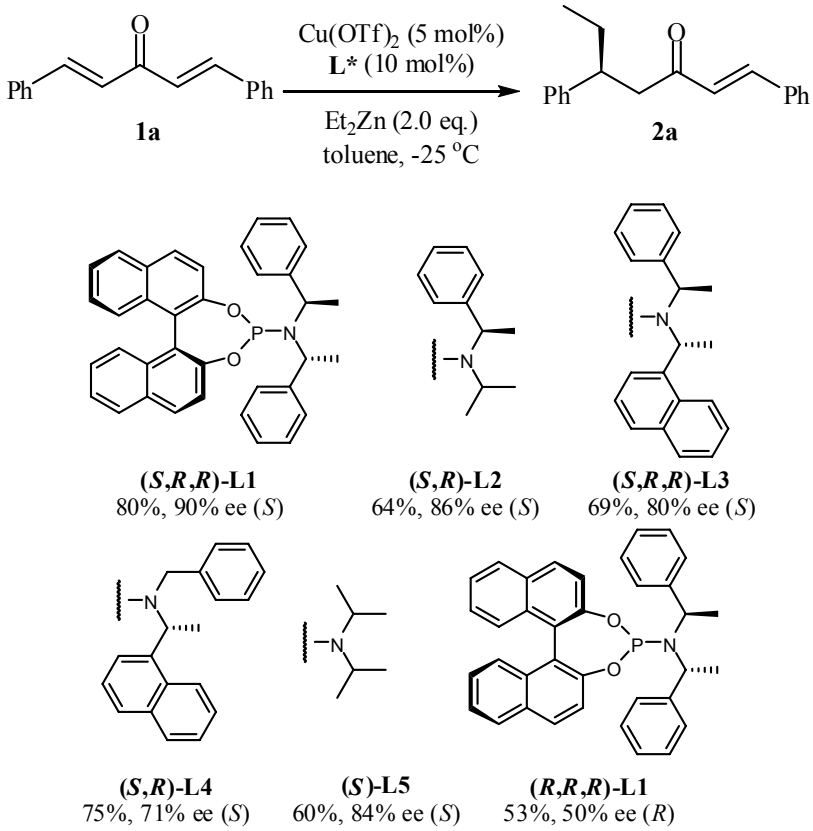
6.2 Copper-catalyzed enantioselective conjugate addition of organozinc reagents and trimethylaluminum to acyclic dienones

Encouraged by the promising results obtained using phosphoramidite ligands for the organozinc addition to acyclic substrates[3b,5b,18] and the high enantioselectivities observed with cyclic dienones,[14,15] we decided to test the catalytic system developed in our group in the enantioselective addition of diethylzinc to α,β-unsaturated acyclic dienones. The possibility of performing double 1,4-addition as well as the introduction of new functionalities in the molecule via trapping of the intermediate enolate are considered.

trans,trans-Dibenzylideneacetone **1a** was used as a model substrate for preliminary investigation. The addition of diethylzinc was performed using 5 mol% of a copper complex prepared *in situ* from $Cu(OTf)_2$ and the phosphoramidite ligand (*S*,*R*,*R*)-**L1** in a ratio of 1:2. Two equivalents of Et_2Zn

were employed. The ethyl substituted product **2a** was obtained, after overnight reaction, in 80% isolated yield and with 90% enantioselectivity (Scheme 6.16).

In order to achieve an improvement in enantiocontrol, several structurally related ligands **L1**–**L5**[3b,5b,19] were tested. (Scheme 6.16).



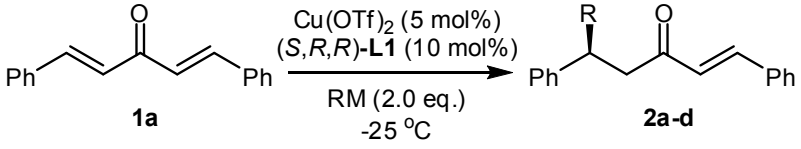
Scheme 6.16 *Screening of phosphoramidite ligands.*

Under the same reaction conditions a slightly lower ee of 86% was achieved using (*S*,*R*)-**L2** in which the steric hindrance of the amine moiety has been reduced and a stereogenic center was removed. Ligand (*S*,*R*,*R*)-**L3**, where a phenyl ring has been replaced by a naphthyl substituent, afforded the product

with 80% ee. In comparison with (*S*,*R*,*R*)-**L3**, the removal of a methyl group in ligand (*S*,*R*)-**L4** resulted in a further decrease in enantioselecivity to 71%. Better results (84% ee) were achieved using ligand (*S*)-**L5** where the chirality is present only in the binaphthol part and the amine moiety is derived from diisopropylamine. The isolated yields of product **2a** using the ligands **L2**-**L5** range between 60% and 75%. The use of the diastereoisomer (*R*,*R*,*R*)-**L1** afforded the product **2a** in low yield (53%) and enantioselectivity (50%) indicating a mismatch combination of the binaphthol and amine chiral moieties. Moreover, the formation of the opposite enantiomer of **2a** indicates that the binaphthol part determines the sign of the chiral induction.

The phosphoramidite ligand (*S*,*R*,*R*)-**L1** proved to be the most efficient, therefore it was used as ligand of choice for further investigations.

Table 6.1 *Addition of organometallic reagents to **1a** catalyzed by $Cu(OTf)_2$ and (S,R,R)-**L1**.*



1a **2a-d**

Entry	RM	Solvent	Product	Yield (%)	ee (%)
1	Et_2Zn	toluene	**2a**	73	92(*S*)
2	Me_2Zn	toluene	**2b**	12	95(*S*)
3	Me_3Al	toluene	**2b**	8	92(*R*)
4	Me_3Al[a]	THF	**2b**	8	92(*R*)
5	Me_3Al[a]	Et_2O	**2b**	16	96(*R*)
6	MeMgBr[b]	*t*-BuOMe	**2b**	50	88(*S*)
7	*i*-Pr_2Zn	toluene	**2c**	60	73(*S*)
8	Bu_2Zn	toluene	**2d**	61	89(*S*)

[a] -50 °C; [b] $CuBr{\cdot}SMe_2$ (5 mol%), (*R*,*S*)-Josiphos (6 mol%), MeMgBr (1.5 eq.), -75 °C.

The introduction of several other alkyl groups using commercially available organozinc reagents was investigated (Table 6.1). The addition of *i*-Pr_2Zn and *n*-Bu_2Zn afforded the corresponding products **2c** and **2d** in 60% isolated yield and with 73% and 89% enantioselectivity, respectively (entries 7 and 8).

The reaction with Me_2Zn afforded the addition product **2b** with 95% ee but in only 12% isolated yield. Furthermore, the formation of several by-products was detected, probably due to the occurrence of addition reactions between the enolate formed and the starting material. Attempts were made to obtain the methyl substituted product **2b** in higher yield. Me_3Al was used instead of the less reactive Me_2Zn. Full conversion was observed after reaction in toluene overnight, at -50 °C. The desired product **2b** was isolated with high enantioselectivity (92%) but in only 8% yield (entry 3). Also in this case the low yield can be ascribed to the presence of side products. A significant improvement was not observed upon changing the solvent to THF or Et_2O where **2b** was obtained in 8% and 16% yield and with 92% and 96% ee, respectively (entries 5 and 6). The introduction of a methyl substituent was achieved in higher yield (50%) and with good enantioselectivity (88%) via the copper-catalyzed addition of MeMgBr using Josiphos as chiral ligand.[20]

Interestingly, the addition reaction of Me_3Al to **1a** afforded the methyl substituted product **2b** with opposite absolute configuration compared to Me_2Zn under the same reaction conditions. The same situation had been observed previously in the copper/phosphoramidite addition of organometallic reagents to *N*-formylimines (see Chapter 4). A possible rationalization of this observation is given in section 4.5.

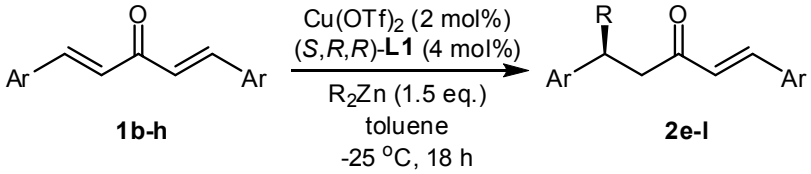
It was possible to decrease the catalyst loading to 2 mol% and the amount of the organozinc reagent to 1.5 equiv without affecting the enantioselectivity of the reaction, although a modest decrease of the isolated yield (to 73%) was observed (Table 6.2, entry 1). Similar results were obtained when the reaction was performed on a larger scale (Table 6.2, entry 2).

The scope of the reaction was explored further by performing the Et_2Zn addition on a series of substituted dienones **1b**–**h** (Table 6.2). The corresponding products **2e** and **2g**–**l** were obtained in good yield and with high enantiomeric excess.

The reaction of dienone **1b** with Et_2Zn affords product **2e** with a lower enantioselectivity of 77% (entry 3), indicating sensitivity to steric bulk near the β-carbon atom. The 34% ee obtained in the addition of *i*-Pr_2Zn to substrate **1b** is in agreement with these results.

Comparison of entries 5-6 and 7-8, where the dienones are substituted at the *meta* and *para* position with electron-withdrawing and electron-donating groups respectively, indicates that electronic effects do not play a major role. Slightly higher enantioselectivities were obtained with *para*-substituted substrates. Good enantioselectivities were obtained with the dienones **1g** and **1h** (entries 9 and 10), although the corresponding products **2k** and **2l** were isolated in lower yields.

Table 6.2 *Addition of organozinc reagents to dienones **1b-h**.*



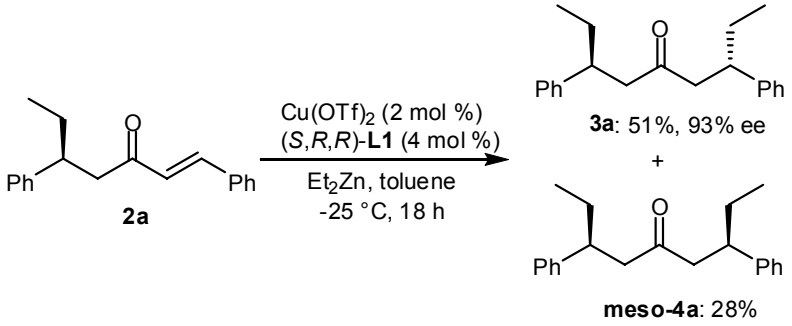
1b-h **2e-l**

Entry	Dienone	Ar	R_2Zn	Product	Yield (%)	ee (%)
1	**1a**	C_6H_5	Et_2Zn	**2a**	73	92(*S*)
2	**1a**[a]	C_6H_5	Et_2Zn	**2a**	75	92(*S*)
3	**1b**	2-Cl-C_6H_4	Et_2Zn	**2e**	79	77(*S*)
4	**1b**	2-Cl-C_6H_4	iPr_2Zn	**2f**	53	34(*S*)
5	**1c**	3-Br-C_6H_4	Et_2Zn	**2g**	66	90(*S*)
6	**1d**	3-Me-C_6H_4	Et_2Zn	**2h**	69	88(*S*)
7	**1e**	4-Cl-C_6H_4	Et_2Zn	**2i**	71	95(*S*)
8	**1f**	4-MeO-C_6H_4	Et_2Zn	**2j**	59	94(*S*)
9	**1g**	2-thienyl	Et_2Zn	**2k**	48	87(*S*)
10	**1h**	1-naphthyl	Et_2Zn	**2l**	53	93(*S*)

[a] Reaction carried out on 4.27 mmol scale of dienone.

6.2.1 Sequential conjugate addition

Conjugate addition to dienone **1a** yielded, again, an α,β-unsaturated system as the final product that can undergo a second conjugate addition reaction (Scheme 6.17).



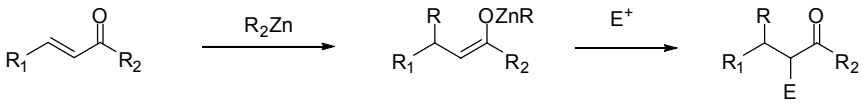
Scheme 6.17 *Sequential conjugate addition.*

Enone **2a** (92% ee) was subjected to Et_2Zn addition under standard conditions. When the introduction of the second ethyl substituent occurs in *trans*-fashion, the chiral C2-symmetric ketone **3a** is obtained. On the other hand if the two ethyl groups have *cis*-relationship, compound **4a** has a meso configuration, in which the enantioselectivity of the first conjugate addition step is lost. The diastereoselectivity observed for the sequential conjugate addition of Et_2Zn to **2a** was in favor of the *trans*-product affording **3a** in 51% yield and with 93% ee together with product **4a** in 28% yield.

6.2.2 Tandem conjugate addition

The actual product of the addition of organozinc reagents to an α,β-unsaturated ketone is, in fact, a zinc enolate which, after acidic hydrolysis, affords the desired β-substituted compound. In the acidic quenching, H_3O^+ is the electrophiilic species that reacts with the zinc enolate generating the saturated ketone. It is possible to use a different electrophile in order to obtain, in a one-pot reaction, an α,β-disubstituted product (Scheme 6.18).

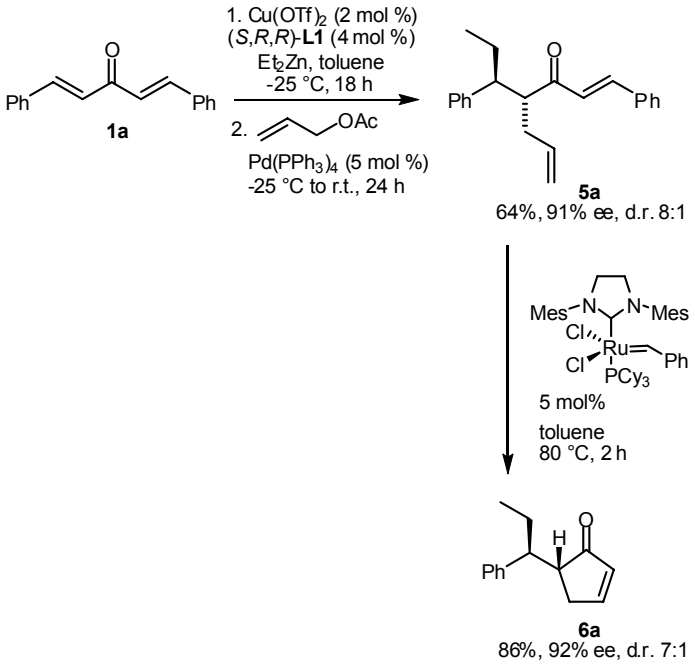
Several examples of the use of this tandem procedure have appeared in the literature.[21] In a number of cases the tandem products have been used in the synthesis of natural products.[22]



Scheme 6.18 *Tandem conjugate addition.*

Considering that the product of the Et_2Zn addition to the acyclic dienone **1a** contains a second double bond, the introduction of an allylic substituent in the α-position would provide an interesting substrate for further functionalization (Scheme 6.19). For example, a substituted cyclopentenone can be obtained by performing a ring-closing metathesis.

Accordingly, the enolate formed from Et_2Zn and dienone **1a** was trapped in a diastereoselective Pd-catalyzed allylation.[22b,c,23] The resulting product **5a** was obtained with 91% ee and 8:1 de in favor of the *trans*-compound (Scheme 6.19).



Scheme 6.19 *Tandem conjugate addition/ring-closing metathesis.*

Ring-closing metathesis (RCM) using 5 mol% of the second generation Grubbs catalyst[24] in toluene, at 80 °C, afforded the 5-substituted cyclopentenone **6a** in 86% yield and with a 7:1 diastereomeric ratio (Scheme 6.19).

6.3 Conclusions

The first enantioselective catalytic addition of organometallic reagents to acyclic dienones is reported. The catalytic system formed using $Cu(OTf)_2$ and the phosphoramidite ligand (*S*,*R*,*R*)-**L1** can be used to introduce alkyl groups such as Et, *i*-Pr and *n*-Bu in good yield and with high enantioselectivity. The introduction of a methyl substituent, a key motif in the structure of several natural products, has been accomplished via the $CuBr{\cdot}SMe_2$-catalyzed addition of MeMgBr using Josiphos as chiral ligand. The co-existence of two enone moieties in the same molecule makes these substrates prone to undergo a sequential conjugate addition, even though the diastereoselectivity observed is modest. The potential of this class of substrates in conjugate additions was demonstrated with the combination of three sequential catalytic steps comprising of a tandem conjugate addition-allylation-RCM resulting in optically active cyclopentenones. This catalytic asymmetric C-C bond formation provides alternative methods to a efficient route to cyclopentenoid natural products.

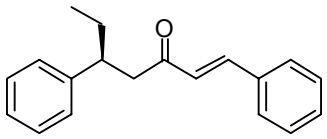
6.4 Experimental

General Methods. For general information see Chapter 2. Absolute configurations were assigned on the basis of the facial selectivity observed using the same catalysts (*S*,*R*,*R*)-**L1** with chalcone.[18]

General procedure for the copper/phosphoramidite catalyzed conjugate addition of dialkylzinc reagents to dienones.

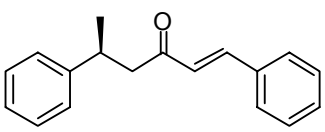
$Cu(OTf)_2$ (3.6 mg, 0.010 mmol) and ligand (*S*,*R*,*R*)-**L1** (10.8 mg, 0.020 mmol) were dissolved in anhydrous toluene (3 mL) and stirred for 40 min at r.t. The substrate (0.50 mmol) was added to this solution and the mixture was cooled to -25 °C. A solution of a R_2Zn (0.75 mmol) was added dropwise and the reaction mixture was stirred for 18 h at -25 °C, then quenched with sat. aq. NH_4Cl and extracted with AcOEt (3x). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography.

(*S*)-*E*-1,5-Diphenyl-hept-1-en-3-one (2a).



The crude product was purified by flash chromatography (*n*-heptane/AcOEt = 97:3) to give pure **2a** in 73% yield as a white solid, m.p. = 78-79 °C (lit.[25] m.p. = 87 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.81 (t, *J*=7.3 Hz, 3H), 1.58-1.77 (m, 2H); 2.95 (m, 2H), 3.14 (m, 1H); 6.65 (d, *J*=16.5 Hz, 1H), 7.16-7.50 (m, 11H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 12.0, 29.2, 43.3, 48.0, 126.3, 126.5, 127.6, 128.2, 128.4, 128.9, 130.4, 134.5, 142.5, 144.5, 199.3. HRMS calc. for $C_{19}H_{20}O$ 264.1514, found 264.1516. HPLC on Chiralpak AD column (*n*-heptane/propan-2-ol = 96:4, flow = 1.0 mL/min): t_R 7.56 min (minor), t_R 8.62 min (major). $[\alpha]_D$ = +34.0 (c 0.50, $CHCl_3$), 90% ee. Anal. calcd for $C_{19}H_{20}O$: C 86.32, H 7.63 found C 86.30, H 7.62.

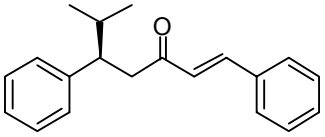
(*S*)-*E*-1,5-Diphenyl-hex-1-en-3-one (2b).



The crude product was purified by flash chromatography (*n*-heptane/AcOEt = 97:3) to give pure **2b** as a white solid, m.p. = 66-68 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.33 (d, *J*=7.0 Hz,

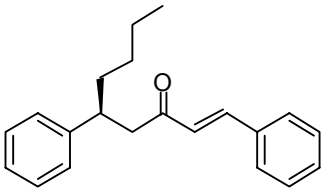
3H), 2.85-3.03 (m, 2H), 3.43 (q, *J*=7.3 Hz, 1H), 6.69 (d, *J*=16.1 Hz, 1H), 7.18-7.53 (m, 11H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 21.8, 35.8, 49.3, 126.3, 126.4, 126.8, 128.2, 128.5, 128.9, 130.4, 134.5, 142.6, 146.4, 199.1. HRMS calc. for $C_{18}H_{18}O$ 250.1358, found 250.1368. HPLC on Chiralpak AD column (*n*-heptane/propan-2-ol = 96:4, flow = 1.0 mL/min): t_R 7.52 min (minor), t_R 8.37 min (major). $[\alpha]_D$ = +20.5 (c 0.20, $CHCl_3$), 95% ee.

(*S*)-*E*-1,5-Diphenyl-6-methyl-hept-1-en-3-one (2c).



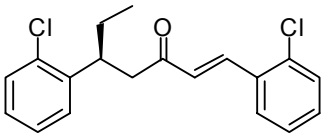
The crude product, obtained by the general procedure, was purified by flash chromatography (*n*-heptane/AcOEt = 97:3) to give pure **2c** in 60% yield as a white solid, m.p. = 97-98 °C (lit.[26] m.p. = 95 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.80 (d, *J*=6.6 Hz, 3H), 1.00 (d, *J*=6.6 Hz, 3H), 1.93 (m, 1H), 3.07 (m, 3H); 6.64 (d, *J*=16.1 Hz, 1H), 7.16-7.50 (m, 11H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 20.3, 20.9, 33.3, 45.1, 48.2, 126.2, 126.3, 128.1, 128.2, 128.3, 128.9, 130.3, 134.5, 142.2, 143.4, 226.3. HRMS calc. for $C_{20}H_{22}O$ 278.1671, found 278.1673. HPLC on Chiralpak AD column (*n*-heptane/propan-2-ol = 96:4, flow = 1.0 mL/min): t_R 7.76 min (minor), t_R 8.66 min (major). $[\alpha]_D$ = +13.2 (c 0.50, $CHCl_3$), 73% ee.

(*S*)-*E*-1,5-Diphenyl-non-1-en-3-one (2d).



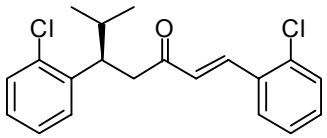
The crude product was purified by flash chromatography (*n*-heptane/AcOEt = 97:3) to give pure **2d** in 61% yield as a white solid, m.p. = 89-90 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.83 (t, *J*=7.0 Hz, 3H), 1.10-1.31 (m, 4H), 1.62-1.71 (m, 2H), 2.94 (dd, *J*=7.0, 2.9 Hz, 2H), 3.23 (m, 1H), 6.64 (d, *J*=16.1 Hz, 1H), 7.18-7.50 (m, 11H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.0, 22.6, 29.7, 36.0, 41.6, 48.4, 126.3, 126.5, 127.6, 128.2, 128.4, 128.9, 130.4, 134.5, 142.5, 144.8, 199.3. Elem. anal. calcd. for $C_{21}H_{24}O$ C 86.26, H 8.27; found C 85.90, H 8.30. HRMS calc. for $C_{21}H_{24}O$ 292.1827, found 292.1819. HPLC on Chiralpak AD column (*n*-heptane/propan-2-ol = 96:4, flow = 1.0 mL/min): t_R 6.88 min (minor), t_R 7.55 min (major). $[\alpha]_D$ = +15.7 (c 0.37, $CHCl_3$), 89% ee. Anal. calcd for $C_{21}H_{24}O$: C 86.26, H 8.27 found C 85.90, H 8.30.

(*S*)-*E*-1,5-Bis-(2-chlorophenyl)-hept-1-en-3-one (2e).



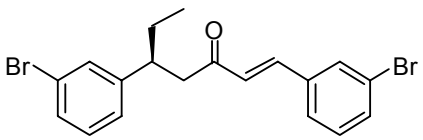
The crude product was purified by flash chromatography (*n*-heptane/AcOEt = 97:3) to give pure **2e** in 76% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.84 (t, *J*=7.3 Hz, 3H), 1.77 (m, 2H), 3.00 (m, 2H),. 3.80 (m, 1H), 6.66 (d, *J*=16.1 Hz, 1H), 7.10-7.43 (m, 7H), 7.58 (m, 1H), 7.93 (d, *J*=16.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 11.8, 28.0, 39.0, 46.5, 127.0, 127.1, 127.4, 127.5, 127.9, 128.6, 129.7, 130.2, 131.1, 132.8, 134.3, 135.2, 138.4, 141.4, 198.6. MS (EI) calc. for $C_{19}H_{18}Cl_2O$ 332, found 332 (It was not possible to obtain an exact mass). HPLC on Chiralpak AD column (*n*-heptane/propan-2-ol = 97:3, flow = 1.0 mL/min): t_R 7.22 min (minor), t_R 7.78 min (major). $[\alpha]_D$ = +35.5 (c 0.80, $CHCl_3$), 78% ee.

(*S*)-*E*-1,5-Bis-(2chlorophenyl)-6-methyl-hept-1-en-3-one (2f).



The crude product was purified by flash chromatography (*n*-heptane/AcOEt = 97:3) to give pure **2f** in 53% yield as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.84 (d, *J*=6.6 Hz, 3H), 1.03 (d, *J*=6.6 Hz, 3H), 2.00 (m, 1H), 3.04 (m, 2H), 3.68 (m, 1H), 6.61 (d, *J*=16.1 Hz, 1H), 7.07-7.57 (m, 8H), 7.87 (d, *J*=16.1 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 20.2, 20.7, 33.2, 43.9, 126.7, 127.0, 127.3, 127.5, 128.3, 128.6, 129.7, 130.1, 131.1, 132.8, 135.2, 138.2, 141.1, 198.9. MS (CI) calc. for $C_{20}H_{21}Cl_2O$ (MH^+) 347, found 347; ($M+NH4^+$) calc. 364, found 364. (It was not possible to obtain an exact mass). HPLC on Chiralpak AD column (*n*-heptane/propan-2-ol = 96:4, flow = 1.0 mL/min): t_R 6.59 min (minor), t_R 6.99 min (major). $[\alpha]_D$ = -6.2 (c 0.50, $CHCl_3$), 34% ee.

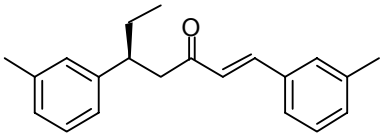
(*S*)-*E*-1,5-Bis-(3-bromophenyl)-hept-1-en-3-one (2g).



The crude product was purified by flash chromatography (*n*-heptane/AcOEt = 97:3→95:5) to give pure **2g** in 66% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.81 (t, *J*=7.3 Hz, 3H), 1.60-1.74 (m, 2H), 2.93 (d, *J*=7.0 Hz, 2H), 3.11 (m, 1H), 6.63 (d, *J*=16.1 Hz, 1H), 7.15-7.64 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 12.0, 29.1, 42.8, 47.9,

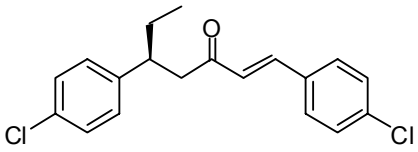
123.0, 126.5, 126.9, 127.3, 127.9, 129.5, 130.0, 130.4, 130.5, 130.8, 133.2, 136.5, 140.8, 146.9, 198.2. HRMS calc. for $C_{19}H_{18}Br_2O$ 419.9724, found 419.9755. HPLC on Chiralcel OD column (*n*-heptane/propan-2-ol = 99:1, flow = 1.0 mL/min): t_R 23.0 min (minor), t_R 26.0 min (major). $[\alpha]_D$ = +3.1 (c 0.32, $CHCl_3$), 90% ee.

(*S*)-*E*-1,5-Bis-(3-methylphenyl)-hept-1-en-3-one (2h).



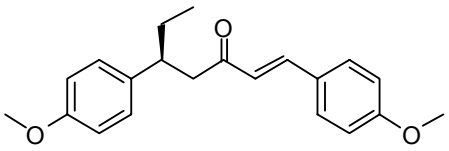
The crude product was purified by flash chromatography (*n*-heptane/AcOEt = 97:3→95:5) to give pure **2h** in 69% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.80 (t, *J*=7.3 Hz, 3H), 1.59-1.77 (m, 2H), 2.33 (s, 3H), 2.36 (s, 3H), 2.93 (d, *J*=7.0 Hz, 2H), 3.11 (m, 1H), 6.64 (d, *J*=16.5 Hz, 1H), 6.99-7.30 (m, 8H), 7.44 (d, *J*=16.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 12.1, 21.3, 21.5, 29.1, 43.2, 48.0, 124.6, 125.4, 126.3, 127.0, 128.2, 128.4, 128.7, 128.8, 131.2, 134.4, 137.8, 138.5, 142.6, 144.5, 199.4. HRMS calc. for $C_{21}H_{24}O$ 292.1827, found 292.1823. HPLC on Chiralpak AD column (*n*-heptane/propan-2-ol = 98:2, flow = 1.0 mL/min): t_R 7.50 min (minor), t_R 7.98 min (major). $[\alpha]_D$ = +31.3 (c 0.61, $CHCl_3$), 88% ee.

(*S*)-*E*-1,5-Bis-(4-chlorophenyl)-hept-1-en-3-one (2i).



The crude product was purified by flash chromatography (*n*-heptane/AcOEt = 97:3) to give pure **2i** in 71% yield as a white solid, m.p. = 76-77 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.80 (t, *J*=7.3 Hz, 3H), 1.54-1.77 (m, 2H), 2.92 (d, *J*=7.3 Hz, 2H), 3.13 (m, 1H), 6.60 (d, *J*=16.1 Hz, 1H), 7.14 (d, *J*=8.1 Hz, 2H), 7.24-7.43 (m, 7H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 12.0, 29.2, 42.5, 48.0, 126.6, 128.5, 129.0, 129.2, 129.4, 131.9, 132.9, 136.4, 141.1, 142.9, 198.5. Elem. anal. calcd. for $C_{19}H_{18}Cl_2O$ C 68.48, H 5.44; found C 68.40, H 5.52. HRMS calc. for $C_{19}H_{18}Cl_2O$ 332.0735, found 332.0729. HPLC on Chiralpak AD column (*n*-heptane/propan-2-ol = 95:5, flow = 1.0 mL/min): t_R 9.94 min (minor), t_R 13.71 min (major). $[\alpha]_D$ = +33.9 (c 0.75, $CHCl_3$), 95% ee. Anal. calcd for $C_{19}H_{18}Cl_2O$: C 68.48, H 5.44 found C 68.40, H 5.51.

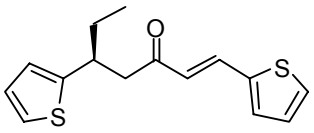
(*S*)-*E*-1,5-Bis-(4-methoxyphenyl)-hept-1-en-3-one (2j).



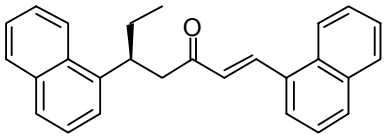
The crude product was purified by flash chromatography (*n*-heptane/AcOEt = 95:5→80:20) to give pure **2j** in 59% yield as a white solid, m.p. = 84-86 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.79 (t, *J*=7.3 Hz, 3H), 1.56-1.76 (m, 2H), 2.89 (d, *J*=7.0 Hz, 2H), 3.09 (m, 1H), 3.77 (s, 3H), 3.84 (s, 3H), 6.53 (d, *J*=16.1 Hz, 1H), 6.83 (d, *J*=8.8 Hz, 2H), 6.89 (d, *J*=8.8 Hz, 2H), 7.13 (d, *J*=8.4 Hz, 2H), 7.42 (d, *J*=16.5 Hz, 1H), 7.44 (d, *J*=8.8 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 12.0, 29.3, 42.6, 48.1, 55.1, 55.3, 113.7, 114.3, 124.3, 127.1, 128.5, 129.9, 136.6, 142.2, 157.9, 161.5, 199.4. HRMS calc. for $C_{21}H_{24}O_3$ 324.1725, found 324.1724. HPLC on Chiralpak AD column (*n*-heptane/propan-2-ol = 92:8, flow = 1.0 mL/min): t_R 12.26 min (minor), t_R 16.46 min (major). $[\alpha]_D$ = +17.6 (c 0.50, $CHCl_3$), 94% ee. Anal. calcd for $C_{21}H_{24}O_3$: C 77.75, H 7.46 found C 77.44, H 7.43.

(*S*)-*E*-1,5-Dithiophene-2-yl-hept-1-en-3-one (2k).

The crude product was purified by flash chromatography (*n*-heptane/AcOEt = 97:3→95:5) to give pure **2k** in 48% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.80 (t, *J*=7.3 Hz, 3H), 1.62-1.82 (m, 2H), 2.94 (m, 2H), 3.51 (m, 1H), 6.49 (d, *J*=15.7 Hz, 1H), 6.83-7.07 (m, 3H), 7.13 (d, *J*=5.1 Hz, 1H), 7.27 (m, 1H), 7.39 (d, *J*=4.8 Hz, 1H), 7.62 (d, *J*=15.8 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 11.9, 30.3, 38.5, 48.7, 122.9, 124.1, 125.0, 126.5, 128.2, 128.8, 131.7, 135.1, 139.8, 148.4, 198.1. HRMS calc. for $C_{15}H_{16}OS_2$ 276.0643, found 276.0659. HPLC on Chiralpak AD column (*n*-heptane/propan-2-ol = 96:4, flow = 1.0 mL/min): t_R 8.16 min (minor), t_R 9.32 min (major). $[\alpha]_D$ = +5.6 (c 0.61, $CHCl_3$), 87% ee.

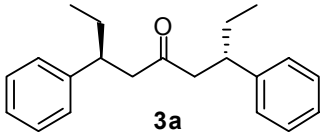


(*S*)-*E*-1,5-Dinaphthalene-1-yl-hept-1-en-3-one (2l).

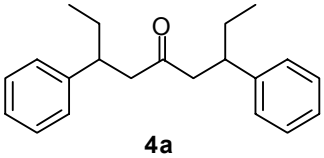


The crude product was purified by flash chromatography (*n*-heptane/AcOEt = 97:3→95:5) to give pure **2l** in 53% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.90 (t, *J*=7.3 Hz, 3H), 1.97 (m, 2H), 3.18 (d, *J*=6.6 Hz, 2H), 4.23 (m, 1H), 6.77 (d, *J*=15.8 Hz, 1H), 7.43-8.34 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 12.0, 28.7, 48.0, 123.2, 123.3, 125.0, 125.35, 125.41, 126.0, 126.2, 126.75, 126.8, 128.7, 128.8, 128.9, 130.6, 131.5, 131.8, 132.0, 133.6, 134.0, 139.3, 140.7, 199.1. HRMS calc. for $C_{27}H_{24}O$ 364.1827, found 364.1831. HPLC on Chiralcel OD column (*n*-heptane/propan-2-ol = 95:5, flow = 1.0 mL/min): t_R 23.19 min (minor), t_R 26.30 min (major). $[\alpha]_D$ = +90.6 (c 0.88, $CHCl_3$), 93% ee.

(*S*,*S*)-3,7-Diphenyl-nonan-5-one (3a/4a).



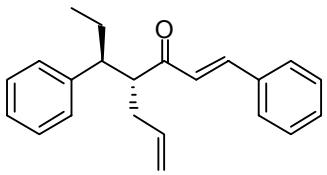
3a



4a

The crude product was purified by flash chromatography (*n*-heptane/AcOEt = 98:2) to give pure **3** (the diastereoisomers could not be separated) in 51% yield as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) (signals for the *meso* compound **4a** are in italic) δ = 0.71 (t, *J*=7.3 Hz, 6H), *0.73* (t, *J*=7.3 Hz), 1.45-1.57 (m, 4H), 2.48-2.66 (m, 4H), 2.97 (m, 2H), 7.09-7.30 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.9, *11.91*, 29.1, *42.55*, 42.6, *50.2*, 50.4, 126.2, *127.46*, 127.5, 128.3, 144.4, 209.0. HRMS calc. for $C_{21}H_{26}O$ 294.1984, found 294.1987. HPLC on Chiralpak AD column (*n*-heptane/propan-2-ol = 99:1, flow = 1.0 mL/min): t_R 6.01 min (minor), t_R 6.72 min (meso), 8.53 min (major). $[\alpha]_D$ = -40.1 (c 0.85, $CHCl_3$), 93% ee, **3a**/**4a** = 72:28.

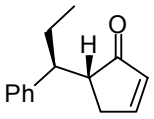
(*4R*,*5S*)-1-Phenyl-4-(1-phenylpropyl)-*n*-heptane-1,6-dien-3-one (5a).



$Cu(OTf)_2$ (3.6 mg, 0.010 mmol) and (*S*,*R*,*R*)-**L1** (10.8 mg, 0.020 mmol) were dissolved in anhydrous toluene (3 mL) and stirred 40 min at r.t. Dibenzylideneacetone (117 mg, 0.50 mmol)

was added and the resulting yellow solution was cooled to -25 °C. Et_2Zn (1.1M in toluene, 0.68 mL, 0.75 mmol) was added and the reaction mixture was stirred for 18 h at -25°C. Subsequently a solution of $Pd(PPh_3)_4$ (87 mg, 0.075 mmol) and allyl acetate (0.16 mL, 150 mg, 1.5 mmol) in toluene (3 mL), was added and the mixture was stirred for 24 h allowing the temperature to rise gradually to r.t. The reaction mixture was treated with sat. aq. NH_4Cl solution and extracted with AcOEt (3x). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (*n*-heptane/AcOEt=98:2) to give pure **5a** in 64% yield as a slightly yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ = 0.65 (t, *J*=7.3 Hz, 3H), 1.52-1.69 (m, 2H), 2.00 (m, 1H), 2.21 (m, 1H), 2.82 (dt, *J*=10.6, 3.7 Hz, 1H), 3.17 (dt, *J*=10.3, 4.0 Hz, 1H), 4.85 (m, 2H), 5.58 (m, 1H), 6.85 (d, *J*=16.1 Hz, 1H), 7.12-7.65 (m, 11H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 12.2, 27.4, 35.7, 50.1, 56.2, 116.6, 126.5, 126.6, 128.2, 128.4, 128.7, 128.9, 130.5, 134.6, 135.3, 142.3, 142.7, 203.3. HRMS calc. for $C_{22}H_{24}O$ 304.1827, found 304.1833. HPLC on Chiralpak AD column (*n*-heptane/propan-2-ol = 98:2, flow = 1.0 mL/min): t_R 7.37 min (major), t_R 8.03 min (minor), 8.80 min (minor diastereoisomer). $[\alpha]_D$ = +24.7 (c 0.76, $CHCl_3$), 91% ee, d.r. 8:1.

(*5R,1'S*)-5-(1-Phenylpropyl)-cyclopent-2-enone (6a).

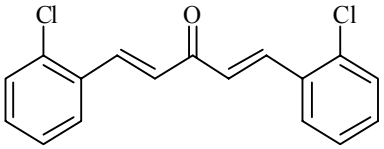


Grubbs 2nd gen. catalyst[24] (17 mg, 0.020 mmol) was dissolved in toluene (5 mL) and to this solution the diene **5a** (122 mg, 0.40 mmol) in toluene (5 mL) was added. The resulting red-brown solution was stirred for 2 h at 80 °C. After cooling, the solvent was evaporated and the residue was purified by flash chromatography (*n*-heptane/AcOEt = 95:5) to afford 69 mg (86%) of pure **6a** as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) (signals for the minor diastereoisomer are in italic) δ = *0.79* (t, *J*=7.3 Hz), 0.85 (t, *J*=7.3 Hz, 3H), 1.81 (m, 1H), 2.02 (m, 1H), 2.39 (m, 1H), 2.63 (m, 2H), 3.05 (m, 1H), *3.15* (m), 6.00 (m, 1H), *6.17* (m), 7.12-7.28 (m, 5H), 7.46 (m, 1H), *7.64* (m). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 12.1, *12.4*, *22.7*, 26.1, *32.1*, 32.5, 47.4, 49.3, *50.9*, 126.4, 128.0, 128.1, *128.4*, 128.6, 134.1, *134.6*, *141.2*, 163.6, *163.9*, 211.6. HRMS calc. for $C_{14}H_{16}O$ 200.1201, found 200.1210. HPLC on Chiralpak AD column (*n*-heptane/propan-2-ol = 99.5:0.5, flow = 1.0 mL/min): t_R 11.25 min (minor), t_R 13.90 min (major), 16.61 min (minor diastereoisomer). $[\alpha]_D$ = -127.7 (c 0.73, $CHCl_3$), 92% ee, d.r. 7:1.

Synthesis of the starting materials 1b-h

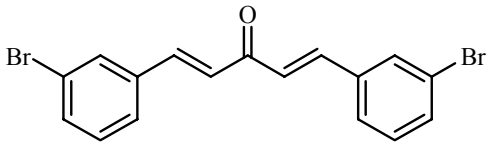
Dienone substrates were prepared by condensation of 2 moles of aldehyde with 1 mole of acetone in an aq. NaOH/EtOH solution according to known procedures.[27] The resulting products were recrystallized from AcOEt to obtain pure *trans,trans*-dienones.

1,5-Bis-(2-chlorophenyl)-pentane-1,4-dien-3-one (1b)[28]



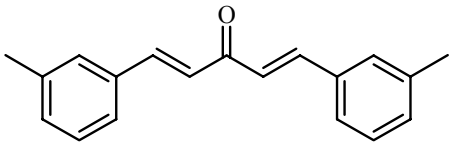
M.p. = 117-118 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, *J*=16.1 Hz, 2H), 7.30-7.47 (m, 6H), 7.73 (m, 2H), 8.15 (d, *J*=15.7 Hz, 2H).

1,5-Bis-(3-bromophenyl)-pentane-1,4-dien-3-one (1c)[29]



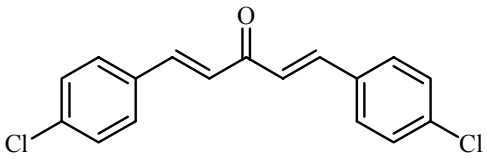
M.p. = 133-134 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (d, *J*=16.1 Hz, 2H), 7.30 (m, 2H), 7.53 (m, 4H), 7.65 (d, *J*=16.0 Hz, 2H), 7.77 (m, 2H).

1,5-Bis-(3-methylphenyl)-pentane-1,4-dien-3-one (1d)[30]



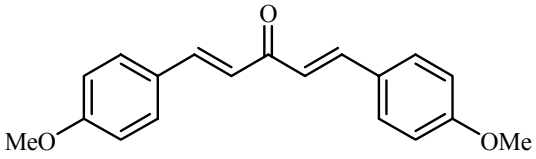
M.p. = 75-76 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.40 (s, 6H), 7.08 (d, *J*=15.8 Hz, 2H), 7.27 (m, 4H), 7.43 (m, 4H), 7.72 (d, J=16.1 Hz, 2H).

1,5-Bis-(4-chlorophenyl)-pentane-1,4-dien-3-one (1e)[31]



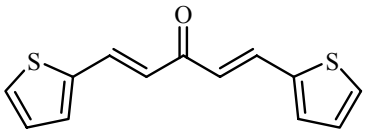
M.p. = 192-193 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (d, *J*=16.1 Hz, 2H), 7.39 (d, *J*=7.0 Hz, 4H), 7.55 (d, *J*=7.0 Hz, 4H), 7.68 (d, *J*=15.7 Hz, 2H).

1,5-Bis-(4-methoxyphenyl)-pentane-1,4-dien-3-one (1f)[27a]



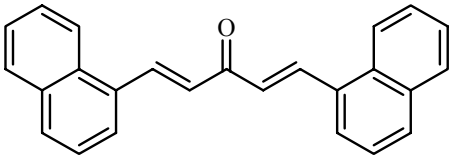
M.p. = 128-129 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85 (s, 6H), 6.93 (d, J=8.8 Hz, 4H), 6.96 (d, J=15.7 Hz, 2H), 7.57 (d, J=8.4 Hz, 4H), 7.70 (d, J=15.7 Hz, 2H).

1,5-Bis-(2-thienyl)-pentane-1,4-dien-3-one (1g)[27a]



M.p. = 119-120 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (d, *J*=15.4 Hz, 2H), 7.08 (m, 2H), 7.34 (m, 2H), 7.42 (m, 2H), 7.85 (d, *J*=15.4 Hz, 2H).

1,5-Bis-(1-naphthyl)-pentane-1,4-dien-3-one (1h)[32]



M.p. = 134-135 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J*=15.8 Hz, 2H), 7.57 (m, 6H), 7.92 (m, 6H), 8.29 (m, 2H), 8.66 (d, *J*=15.4 Hz, 2H).

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