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Enantioselective Catalytic Conjugate Addition of Dialkylzinc Reagents using Copper–Phosphoramidite Complexes; Ligand Variation and Non-linear Effects

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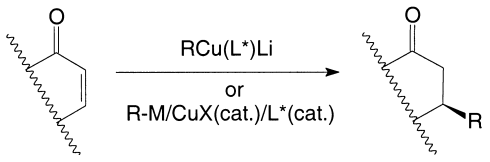
Abstract—A variety of new chiral phosphoramidites was synthesised and tested in the copper-catalysed enantioselective conjugate addition of diethylzinc to cyclohexenone and chalcone in order to assess the structural features that are important for stereocontrol. A sterically demanding amine moiety is essential to reach high e.e.'s. Enantioselectivities for chalcones up to 89% and for cyclic enones up to 98% were found. Studies on non-linear effects with the best ligands for both cyclohexenone and chalcone showed clear non-linear effects for both cyclic and acyclic enones. © 2000 Elsevier Science Ltd. All rights reserved.

Conjugate addition reactions of organometallic reagents to α,β-unsaturated compounds constitute an important part of our standard repertoire of synthetic methods for carbon–carbon formation.[1] Although organocuprates and copper-catalysed 1,4-additions of Grignard- and organolithium reagents are most frequently employed[2,3] a number of alternatives based on, for example, the use of other metal catalysts (Ni, Co) or organometallic reagents (R_2Zn, R_3Al) has been reported in recent years.[4,5]

The potential of conjugate addition reactions in synthesis is partly due to the large variety of organometallic reagents and substrates that can be employed and these features have been a strong impetus in the search for enantioselective conjugate additions. A number of organocopper reagents with chiral non-transferable ligands and organocuprates modified with additional chiral ligands are known today that provide e.e.'s at the >95% level.[2,6–8]

Until recently a highly enantioselective catalytic version of the conjugate addition of organometallic reagents to enones was lacking[9] (Scheme 1). Despite numerous attempts, the rational design of new chiral catalysts for enantioselective conjugate addition has met limited success, presumably due to the fact that several factors that might govern the 1,4-addition step have to be taken into consideration. Among these are: (i) the nature of the organometallic reagent $(R)_nM$, (ii) the ligands associated with it, (iii) the aggregation of most of these reagents in solution (often solvent dependent), (iv) the effect on regio- and stereoselectivity by additional ligands, coordinating solvents and salts, (v) the activation of the enones by metal ion complexation or via additional Lewis acid.

Lippard and co-workers[10] described the first catalytic conjugate addition of *n*-BuMgBr to 2-cyclohexenone employing an in situ prepared chiral copper(I) complex derived from *N*,*N*′-dialkylaminotropone-imine in the presence of HMPA and *t*-butyldiphenylsilyl chloride leading to e.e.=74%. A number of copper and zinc catalysed enantioselective conjugate additions of Grignard reagents to enones have subsequently been reported with e.e's up to 92%.[7] Chiral ligands include aminothiols,[11] mercaptophenyloxazolines,[12] sugar-derived thiolates,[13] phosphines,[14] diamines and amino-alcohols[15] and Taddols.[16] Significant enantioselectivities in catalytic alkyllithium additions to enones have not been reported until Tanaka and co-workers realised an impressive e.e. of 99% in the chiral diamino-alkoxycuprate catalysed addition of MeLi to (*E*)-2-cyclopentadecenone affording (*R*)-muscone, although a high amount of catalyst (36 mol%) was required to reach these selectivities.[17]



Scheme 1.

Keywords: phosphoramidite ligand; copper; enantioselective conjugate addition; enones; non-linear effect; diethyl zinc; catalytic 1,4-addition.

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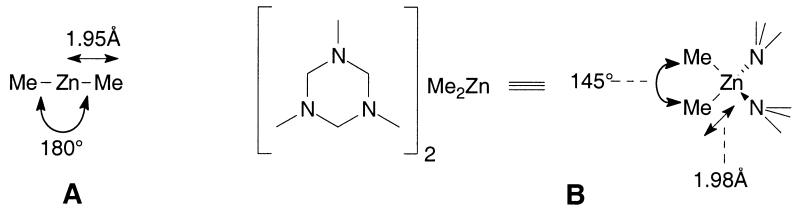


Scheme 2.

Ligand accelerated catalysis[18] of 1,4-additions of aryllithium reagents, employing chiral diethers, showed enantioselectivities up to 75%.[19]

Enantioselective carbon–carbon bond formation using organozinc reagents has become one of the most successful areas of asymmetric synthesis in recent years.[20] Although dialkylzinc reagents react extremely sluggish with carbonyl compounds, effective catalysis has been achieved by several ligands and transition metal complexes. The catalytic effect can be explained either by alkyl transfer or by changes in geometry and bond energy of the zinc reagents.[21] For example, dimethylzinc has a linear structure and is not reactive towards aldehydes or ketones (Scheme 2). Upon coordination of triazine a tetrahedral configuration at the zinc atom and an elongated zinc–carbon bond is found, resulting in enhanced reactivity of the dialkylzinc reagent.

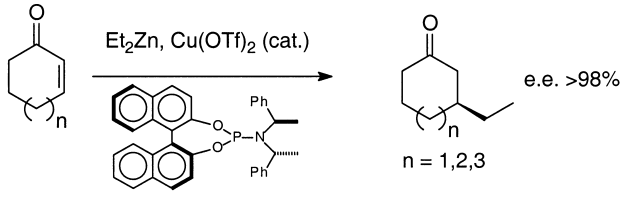
A number of catalytic 1,4-additions of diethylzinc to enones employing chiral nickel complexes have been reported. Based on the work of Luche and Greene,[22] an enantioselective modification of the nickel catalysed alkyl transfer from diethylzinc to chalcone was found by Soai and co-workers.[4b,23] A variety of chiral ligands have subsequently been used in Ni-catalysed 1,4-additions; these include chiral (bi)pyridines, aminoalcohols, β-hydroxysulfoximines, proline amides, arene–chromium aminoalcohols, thiazolidin-4-ones and diamines.[24–30]

The following main features emerged from these studies with different organometallic reagents and a large variety of ligands: (i) although appreciable e.e's were found the results did not reveal the key elements to realise complete stereocontrol and point to a rather complex nature of these catalytic systems, (ii) most successful catalysts for cyclic enones do not show significant enantioselectivity for acyclic enones and vice versa.

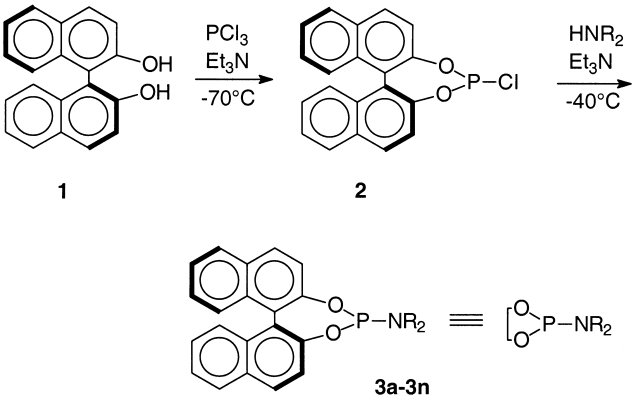
Alexakis and co-workers reported the first example of copper catalysed enantioselective conjugate addition (10 mol% of catalyst, e.e.=32%) of diethylzinc to 2-cyclohexenone employing a trivalent phosphorus ligand .[31] Under the same conditions chalcone gave racemic product. Despite all these efforts, which represent major advances in the field of catalytic enantioselective conjugate addition of organometallic reagents, the problem of accomplishing efficient and highly enantioselective catalysis for a wide variety of enones remained a major challenge.

Recently we have introduced phosphoramidites as chiral ligands in copper catalysed 1,4-addition of dialkylzinc reagents and found strong ligand accelerated catalysis and relatively high e.e. values for the 1,4-adducts of both acyclic and cyclic enones.[32] The introduction of a chiral amine moiety in 2,2′-binaphthol-based phosphoramidite ligands allowed for the first time catalytic 1,4-addition reactions of R_2Zn reagents to cyclic enones with complete enantiocontrol (Scheme 3).[33] Employing this new chiral catalyst e.e.'s >98% were obtained for 6-, 7- and 8-membered cycloalkenones. Applications of the copper–phosphoramidite catalysts include tandem conjugate addition-aldol reactions (e.e. >90%),[33] the synthesis of arylnitroalkanes (e.e.'s up to 92%),[34] enantioselective synthesis of cycloalkenones (e.e. >96%),[35] kinetic resolution of diene epoxides (e.e.'s up to 94%)[36] and ring annulations (e.e.'s >96%).[37] For cyclopentenones, Taddol-based phosphoramidites were introduced leading to e.e.'s of 62%.[38] However e.e.'s up to 72% were found by Pfaltz et al.[39] using chiral phosphites whereas (*S*)-2,2′-binaphthol based bisphosphites resulted in e.e.'s up to 88.7%.[40] A number of related copper catalysed 1,4-additions of dialkylzinc reagents, employing PN[41] and PO[42] type chiral ligands, have recently been reported.

We describe here the synthesis of a variety of phosphoramidites and their application as ligands in the copper catalysed conjugate addition of dialkylzinc reagents to assess the effect of ligand variation in the asymmetric catalysis. Highly enantioselective copper–phosphoramidite catalysed conjugate addition of dialkylzinc reagents to



Scheme 3.



Scheme 4.

Table 1. Chiral phosphoramidites based on (*S*)-2,2′-binaphthol

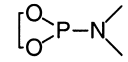
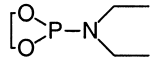
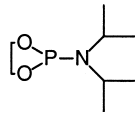
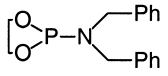
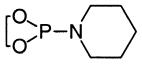
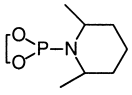
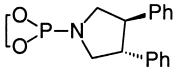
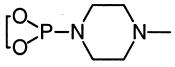
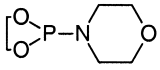
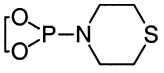
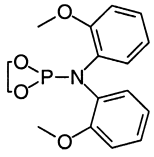
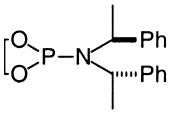
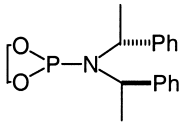
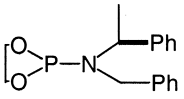
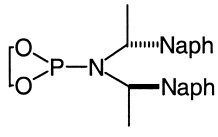
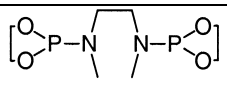
Entry	Phosphoramidite		Yield(%)	^{31}P NMR δ (ppm)
1		**3a**	80	148.7
2		**3b**	59	149.8
3		**3c**	38	151.7
4		**3d**	54	144.7
5		**3e**	65	145.5
6		**3f**	32	146.5
7		**3g**	81	148.9
8		**3h**	30	145.0
9		**3i**	61	144.6
10		**3j**	43	145.0
11		**3k**	45	139.8
12		**3l**	41	145.3
13		**3m**	41	145.3
14		**3n**	53	141.0
15		**3o**	46	147.6

Table 1 (*continued*)

Entry	Phosphoramidite		Yield(%)	^{31}P NMR δ (ppm)
16		**3p**	45	148.9

acyclic enones is reported. Furthermore the results of a study of non-linear effects in these catalytic reactions are presented and possible mechanistic implications are discussed.

Synthesis of novel phosphoramidites

Phosphoramidites [$P(NR_2)(OR)_2$] represent a class of trivalent phosphorus compounds hardly recognised as ligands for catalytic transformation despite the prominent role that organophosphorus ligands, especially trivalent phosphines and phosphites, have played in asymmetric catalysis.[43] Recently achiral phosphoramidites have been applied as ligands for rhodium catalysed hydroformylation of 1-octene and styrene.[44] The χ-value of the applied phosphoramidites (R=aryl, approximately 21)[44,45] is lower than the χ-factor of arylphosphites (31) and higher than the χ-value of arylphosphines (13), indicating a moderate electron withdrawing ability. As the introduction of a chiral amine moiety in phosphoramidites **3** resulted in a dramatic increase of the enantioselectivity in our preliminary catalytic 1,4-additions[32,33]we examined several novel phosphoramidites by varying the amine and binaphthol parts of the ligands.

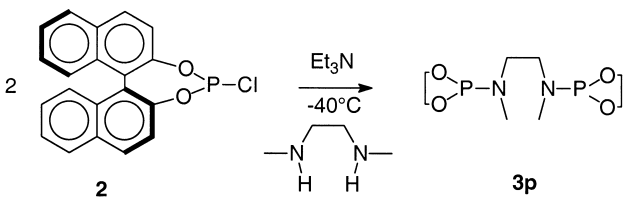
Modification of the amine moiety

The *N*,*N*-dimethyl substituted ligand **3a** (R=Me) was obtained by reaction of (*S*)-2,2′-binaphthol and HMPT,[46] but due to lack of availability of the analogous phosphortriamides another route had to be developed for the modified phosphoramidites (Scheme 4).

Starting from phosphoryl chloride **2**[47] phosphoramidites **3b**–**3n** were synthesised by nucleophilic substitution with a wide variety of secondary amines. The phosphoramidites were purified by column chromatography (SiO_2, hexane/CH_2Cl_2) and were remarkably stable to air and moisture. The new ligands are compiled in Table 1.

With diethylamine, dibenzylamine and piperidine the corresponding amidites **3b**,**3d** and **3e** were synthesised in satisfactory yields, but with the sterically demanding di-*i*-propylamine and *cis*-2,6-dimethylpiperidine the isolated yield of amidites **3c** and **3f** was rather low. The yield **3c** was slightly improved by using LDA instead of triethylamine as base. Attempts to increase the steric hindrance at the amine part of **3** further using 2,2,6,6-tetramethylpiperidine were not successful.

No general trend towards decreased shielding at phosphorus (downfield shift) is observed in the ^{31}P NMR spectra of the ligands with different amine groups. A downfield shift of the



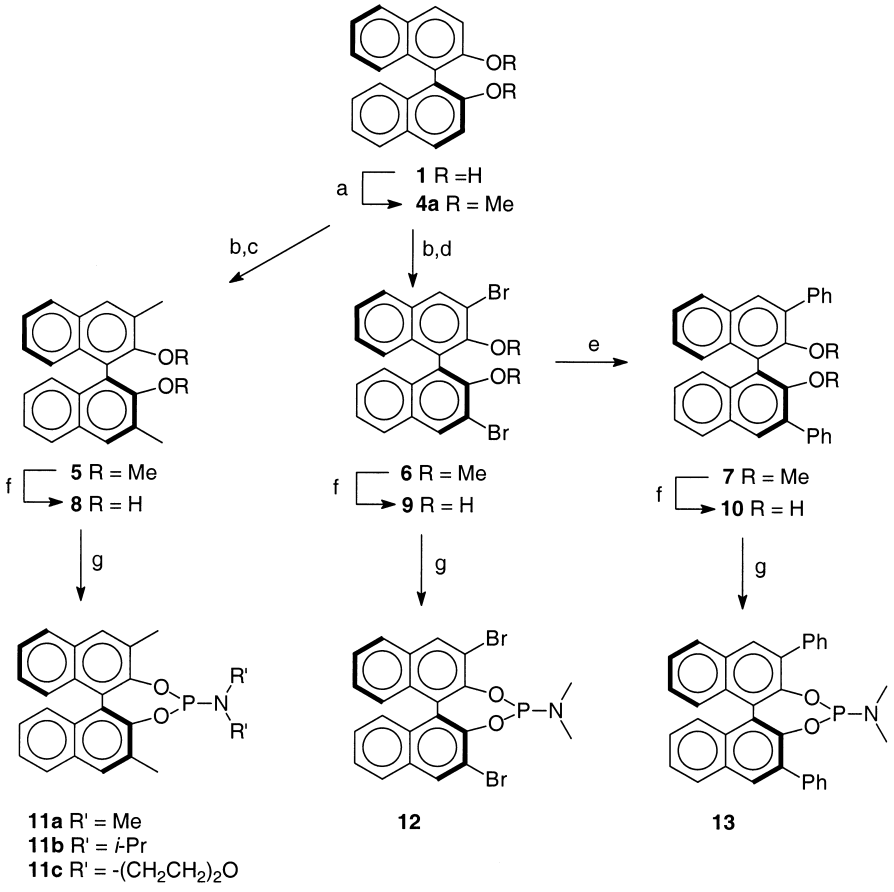
Scheme 5.

phosphorus resonance has been attributed to a decrease of the *s* character in the phosphorus lone pair orbital[45] probably induced by an increased phosphorus–nitrogen bond length. A remarkably high yield of phosphoramidite **3g** (81%) was achieved with (3*R*,4*R*)-3,4-diphenylpyrrolidine. Employing *N*-methylpiperazine, morpholine and thiomorpholine, an additional heteroatom was introduced in the amine moiety of amidites **3**. Compared to piperidine substituted phosphoramidite **3e** no substantial shift of the phosphorus resonance was observed for **3h**–**3j**, indicating a minor influence of the heteroatom in the amine part on the phosphorus lone pair.

Using di(2-methoxyphenyl)amine a phosphoramidite was prepared with oxygen donor groups present at a position capable of forming a chelated six-membered ring upon binding of copper to the phosphorus atom. Since ligand **3k** was not stable upon column chromatography isolation was accomplished by repeated precipitation with hexane. Compared to the other amidites the phosphorus resonance is shifted upfield in this ligand indicating an increased shielding at phosphorus. The diastereomeric ligands **3l**, **3m** and **3n** were prepared from (*S*)-2,2′-binaphthol **1** and (*S*,*S*)-bis(1-phenylethyl)amine and (*R*,*R*)-bis(1-phenylethyl)-amine and (*S*)-benzyl(1-phenylethyl)amine, respectively.[32] In an attempt to enhance the steric effect on the chiral amine part of the corresponding bis[(*R*)-(1-naphthyl)ethyl]amine derived ligand **3o** was prepared via the route outlined in Scheme 4. Finally the bidentate ligand **3p**, corresponding to monodentate phosphoramidite **3a**, was readily obtained from *N*,*N*′-dimethylethylenediamine and phosphoryl chloride **2** in the presence of Et_3N (Scheme 5). The phosphorus resonance of bisamidite **3p** is nearly the same as found for the monoamidite **3a** indicating the same shielding at phosphorus in both ligands.

Modification at the binaphthol moiety

Examination of the molecular structure of the CuI complex of ligand **3a**[32] showed that besides the amine part the 3- and 3′-positions of the binaphthyl part of the ligand are crucial for ligand modification. Model studies indicate that substituents at these positions could affect the binding mode of alkyl group and enone on the copper in the actual catalyst. Considerable effort has been devoted to the synthesis of



Scheme 6. Synthesis of 3,3′-substituted binaphthols and their conversion to the corresponding phosphoramidites. (a) MeI (excess), K_2CO_3, acetone (98%) (b) *n*-BuLi (2.2 equiv.), TMEDA, diethylether (c) MeI, diethylether (d) bromine, diethylether (e) phenylboronic acid, $Pd(PPh_3)_4$ (0.06 equiv.), dimethoxyethane, $NaHCO_3$, water (f) BBr_3, CH_2Cl_2 (g) HMPT, toluene.

3,3′-substituted binaphthols as they have shown promising asymmetric induction in a variety of reactions.[39,48] Methodology includes the use of Mannich intermediates,[49] cross-couplings of 3,3′-dibromo-binapthols[50] and *ortho*-lithiation of 2,2′-bisMOM-substituted binaphthalene.[51] The synthesis of a number of 3,3′-disubstituted binaphthols and their conversion to phosphoramidites is outlined in Scheme 6.

Following Crams procedure[49] (*S*)-2,2′-binaphthol (**1**) was successively methylated to **4a**, dilithiated and quenched with bromine to afford dibromide **6** in 48% yield. The dilithio-compound was also quenched with methyl iodide furnishing dimethyl-derivative **5** in 63% yield. For comparison, by *ortho*-lithiation, methyl iodide quenching and deprotection with MeOH/HCl starting with the MOM protected analogue of **1**[51] we obtained **8** in 70% overall yield. For the preparation of 3,3′-diphenyl substituted binaphthol, the dibromo compound **6** was treated with phenyl boronic acid under Suzuki cross coupling conditions[52] to furnish **7** in 95% yield. This method resulted in a much higher yield than via the Grignard cross coupling method.[50]

The 2,2′-dimethoxy-3,3′-disubstituted derivatives **5**–**7** were deprotected quantitatively with BBr_3 in CH_2Cl_2 and the resulting binaphthols **8**–**10** converted to the corresponding phosphoramidites **11**–**13** with HMPA in toluene (yields >75%). Phosphoramides **11b** and **11c** were prepared from 3,3′-dimethyl-2,2′-dihydroxy-binaphthyl **8** using the improved synthesis (see Experimental section). The ^{31}P NMR shifts of **11b** (149.2 ppm) and **11c** (142.1 ppm) are in good agreement with those determined for the unsubstituted amidites **3c** and **3i**.

Substituted phosphoramidites as ligands in conjugate additions of diethylzinc

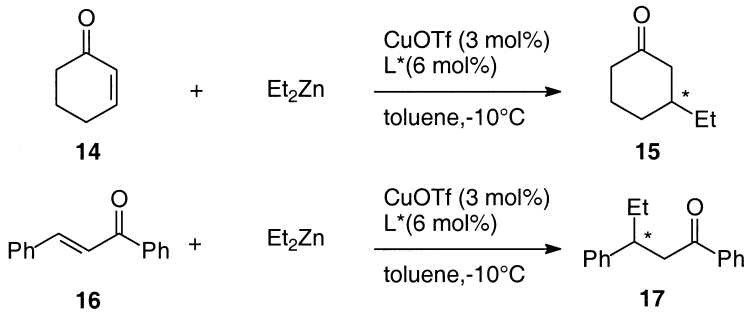
The effect of the ligand modification was examined in the enantioselective copper catalysed diethylzinc addition to two model substrates cyclohexenone **14** and chalcone **16** (Scheme 7). Initially ligands **3b**, **3d**, **3e**, **3i**, **3o** and **11a** were tested in the CuI catalysed addition of Et_2Zn to **14** but the reactions were much slower (2d at −10°C) and the regioselectivity for the 1,4-adduct **15** lower (ca. 80%) compared to CuI/**3a** catalysed reaction.[32] Lower isolated yields and e.e.'s were also found.

This lack of efficient catalysis is probably due to solubility problems with the in situ generated phosphoramidite copper complexes as contrary to the copper complex of **3a**. No clear solutions were obtained with these modified ligands. In order to enhance the solubility of the catalyst complexes the CuOTf catalysed conjugate addition was investigated as it is known that dissociation of the triflate counterion in solution occurs.[53] With a catalytic amount (3 mol%) of phosphoramidite **3a** (2.2 equiv. to CuOTf) strong ligand-acceleration was observed in the conjugate addition of Et_2Zn both to **14** and **16**. High yields of adducts **15** (82%) and **17** (91%) were obtained with e.e.'s slightly higher for **15** (39%) and significantly higher for **17** (65%) compared to those found for the CuI/**3a** catalysed reactions.[31] Furthermore the addition reactions shown in Scheme 7 appeared to proceed with the same regio- and enantioselectivities in CH_2Cl_2 as in toluene.

With this knowledge the effect of the ligand modification on the enantioselectivity of the ethyl transfer from diethylzinc to cyclic (**14**) and acyclic enones (**16**) could be examined. In general a solution of a catalytic amount of (CuOTf)·benzene (3–5 mol%) and chiral ligand (2.2 equiv. to copper) in toluene (3–5 ml) were stirred at ambient temperature for 1 h under Ar, furnishing a clear solution of the catalyst complex. In case the solution was not clear, appropriate amounts of CH_2Cl_2 were added. After addition of the substrate the mixture was cooled to −20°C, Et_2Zn in toluene was added and stirring continued at −10°C for 16 h. The conversion was determined by GC analysis and in all cases regioselectivities for the 1,4-adducts were higher than 90% at >95% conversion. The 1,4-adducts were isolated and purified by column chromatography (yields >75%) prior to e.e. determination. Control experiments indicated that this purification procedure did not effect the e.e. value. The results are summarised in Table 2.

Except for ligand **3h** all phosphoramidites showed enantioselectivity in the 1,4-addition. In the case of the catalytic reaction employing **3h**, ligand decomposition takes place, as besides the 1,4-adduct 2,2′-binaphthol was isolated. The following features are emerging when one considers the various ligand modifications:

- Sterically demanding achiral substituents on the amine moiety improve the e.e values up to 60 and 83% for **15** and **17**, respectively (entries 1–4).
- Ligands with substituents containing heteroatoms in the amine part retain the ceiling e.e.'s found for **17** (entries 8,9), whereas ligands with aromatic groups at the amine part furnish **17** with lower e.e.'s (entries 4,6) or showed to be detrimental for enantioselective ethyl transfer (entry 10).



Scheme 7.

Table 2. Chiral ligand effect in catalytic 1,4-addition

Entry	Chiral ligand	e.e. of **15** (%) (*S*)	e.e. of **17** (%) (*S*)
1	**3a**	39	65
2	**3b**	27	–
3	**3c**	60	83
4	**3d**	53	53
5	**3f**	43	79
6	**3g**	47	50
7	**3h**	0	–
8	**3I**	50	71
9	**3j**	55	70
10	**3k**	48	13
11	**3l**	75[a]	40[a]
12	**3m**	>98[a]	75[a]
13	**3n**	72[a]	72[a]
14	**3o**	94[a]	42[a]
15	**3p**	37	–
16	**11a**	56	52
17	**11b**	59	81
18	**11c**	51	76
19	**12**	51	23
20	**13**	35	<20[b]

[a] Using $Cu(OTf)_2$ at −25°C instead of CuOTf at −10°C.
[b] No base line separation.

- The introduction of methyl substituents at the 3- and 3′-positions of the binaphthol part of the ligand has an effect only on the enantioselective ethyl addition to cyclohexenone (e.e. is increased) and chalcone (e.e. is decreased) when the amine group is small (compare entry 1 with entry 16). With di-*i*-propyl or morpholine based phosphoramidites comparable e.e.'s are observed as with the unsubstituted analogues (compare entries 17, 18 with entries 3,8).
- Phenyl or bromide substituents at the 3- and 3′- positions of the ligand (entry 19,20) are detrimental for the enantioselectivity in the case of chalcone whereas marginal effects on the e.e.'s are found for cyclohexenone.
- The introduction of the sterically demanding (*R*,*R*)-bis(1-phenylethyl)amine moiety results in a matched combination with exceptional high enantioselectivities (>98%) for **15**.[33] The mismatched combination derived from (*S*,*S*)-bis(1-phenylethyl)amine and (*S*)-binaphthol still affords 75% e.e for **15**, a value exceeding those of di-*i*-propylamine and dibenzyl amine based ligands. When the (*S*)-*N*-benzyl-1-phenylethyl phosphoramidite is used the e.e. value for **15** is slightly lower but for **17** a drastic increase in the enantioselectivity is observed. (compare entry 13 with entry 11).
- Surprisingly further increase of the steric hindrance using **3o** lead to a drastic decrease of enantioselectivity for **17**.
- Employing the bidentate phosphoramidite **3p** (ligand/Cu=1.1) in the CuOTf catalysed 1,4-addition to cyclohexenone comparable e.e.'s were found as in the case of the monodentate ligand **3a** (ligand/Cu=2.2) (entry 1, 15). This observation indicates the presence of two monodentate chiral ligands in the catalytically active complex (or catalyst aggregate).

It is evident from these findings that there is no straightforward relation between the molecular architecture of the phosphoramidite ligand, for instance steric requirements, and the enantioselectivities observed in the conjugate addition. So far we observed a major influence of the nature of the amine part of the ligand whereas the effects of variation in the binaphthol unit are less prominent. A delicate balance seems to exist between the increase of steric hindrance (a rather bulky amine is required to achieve high e.e.'s) and the chirality of the amine moiety.

Dialkylzinc Additions to Acyclic Enones

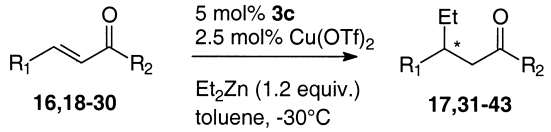
During our studies of the enantioselective conjugated addition to cyclic enones it was found[32] that the catalyst prepared in situ from $Cu(OTf)_2$ was more active than using CuOTf and slightly enhanced the enantioselectivity. The reactions of a number of acyclic enones was examined with the $Cu(OTf)_2$/phosphoramidite **3c** based catalyst. It should be noted that so far ligand **3c** has shown to give the highest e.e.'s with acyclic enones and the best ligand **3m** for cyclohexenone (**14**) gave only e.e=75% in the case of chalcone (**16**). Conjugated additions were performed with 2.5 mol% of in situ prepared catalyst (copper/ligand ratio=2) in toluene at −30°C. Under these conditions a typical aliphatic α,β-unsaturated ketone 3-penten-2-one (**18**) did not provide the 1,4-adduct. On the contrary aryl-substituted enones were converted to the β-substituted ketones with high chemo-, regio-, and in several cases excellent enantioselectivities. The results are given in Table 3.

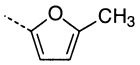
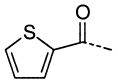
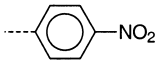
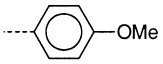
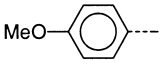
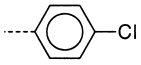
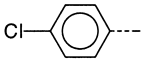
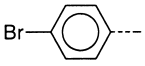
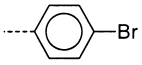
Thus diethylzinc addition to chalcone **16** provided **17** in 85% isolated yield and e.e=89%. Only a small temperature effect was observed leading to e.e.'s ranging from 87–90% (reaction temperatures −10 to −50°C). The presence of an arylketone moiety seems to be important to reach high e.e's as the enantioselectivity decreased to 60% when benzylideneacetone **19** was employed. Low yields and enantioselectivities were found for heteroaromatic enones **20**–**23**, presumably due to competitive binding of the copper catalysts to the heteroarene moiety favouring alternative, non-selective, reaction pathways. The use of *p*-substituted chalcones allows the study of possible electronic effects on the enantioselectivities in these conjugated additions. Towards this goal the diethylzinc addition to chalcones **24**–**30**, with various donor and acceptor substituents at 4- and 4′-positions, was performed under identical conditions (Table 3). In all cases complete conversion was found and the β-substituted ketones **37**–**43** were isolated with high yields and enantioselectivities (except for nitro-substituted chalcone **24**). Presumably again the nitro group interferes with the coordination of the catalyst to the enone moiety although we recently found that 1,4-additions to nitrocoumarines proceed with e.e's up to 92%.[34] From the results with substituted chalcones it is evident that the electron donating or withdrawing properties of the substituents are not of great importance for the stereoselection. The e.e.'s show only modest variation ranging from 75 to 89%.

Non-linear Effects

The study of non-linear effects in asymmetric catalysis has become an important mechanistic tool[20a,54] and the enantiomeric excess observed in the product can be linear proportional to the enantiomeric excess of the catalyst or shows a

Table 3. Catalytic enantioselective 1,4-addition to acyclic enones



Entry	Enone	R_1	R_2	Product	Yield (%)	e.e.[a] (%)
1	**16**	Ph	Ph	**17**	85	89
2	**18**	CH_3	CH_3	**31**	0	–
3	**19**	Ph	CH_3	**32**	75	60
4	**20**			**33**	40	15
5	**21**			**34**	48	40
6	**22**			**35**	30	60
7	**23**	Ph		**36**	69	29
8	**24**	Ph		**37**	64	15
9	**25**	Ph		**38**	85	80
10	**26**		Ph	**39**	86	70
11	**27**	Ph		**40**	94	75
12	**28**		Ph	**41**	65	88
13	**29**			**42**	80	75
14	**30**			**43**	85	89

[a] Configurations or optical rotations of the prevailing enantiomers were not determined.

non-linear relationship which can be either positive (asymmetric amplification) or negative (asymmetric depletion) according to Kagan's models.[55] The effect of the change in the enantiomeric composition of the chiral ligand on the e.e. values of the 1,4-adduct in the copper catalysed conjugate addition of diethylzinc was examined both for chalcone and cyclohexenone with the best phosphoramidites so far found for acyclic and cyclic enones.

The 1,4-addition of diethylzinc to chalcone catalysed by $Cu(OTf)_2$ and di-*i*-propylamine based ligand **3c** in toluene at −20°C provided pure **17** in 85–95% yield. An e.e. of max. 88% for **17** was found with enantiomerically pure ligand. The correlation between the % e.e. of ligand **3c** and % e.e. of product **17** is shown in Fig. 1. A clear negative non-linear correlation is observed.

For the 1,4-addition to cyclohexenone **14** both (*S*,*R*,*R*)-**3m** and (*R*,*S*,*S*)-**3m** were employed and reproducibilities using these enantiomeric ligands were within 2%, whereas duplicate experiments were all within 1%. The $e.e._{max}$ for enantiomerically pure ligand **3m** is >98%. The relationship

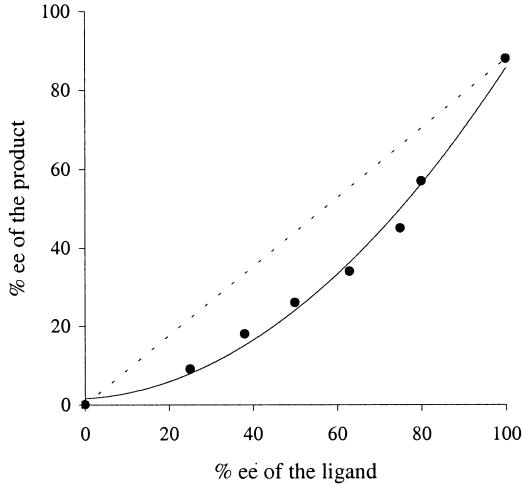


Figure 1. Correlation between the enantiomeric excess of the ligand **3c** and the e.e. of **17**.

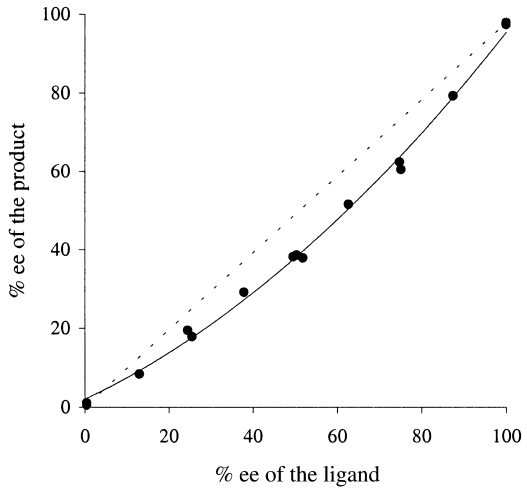
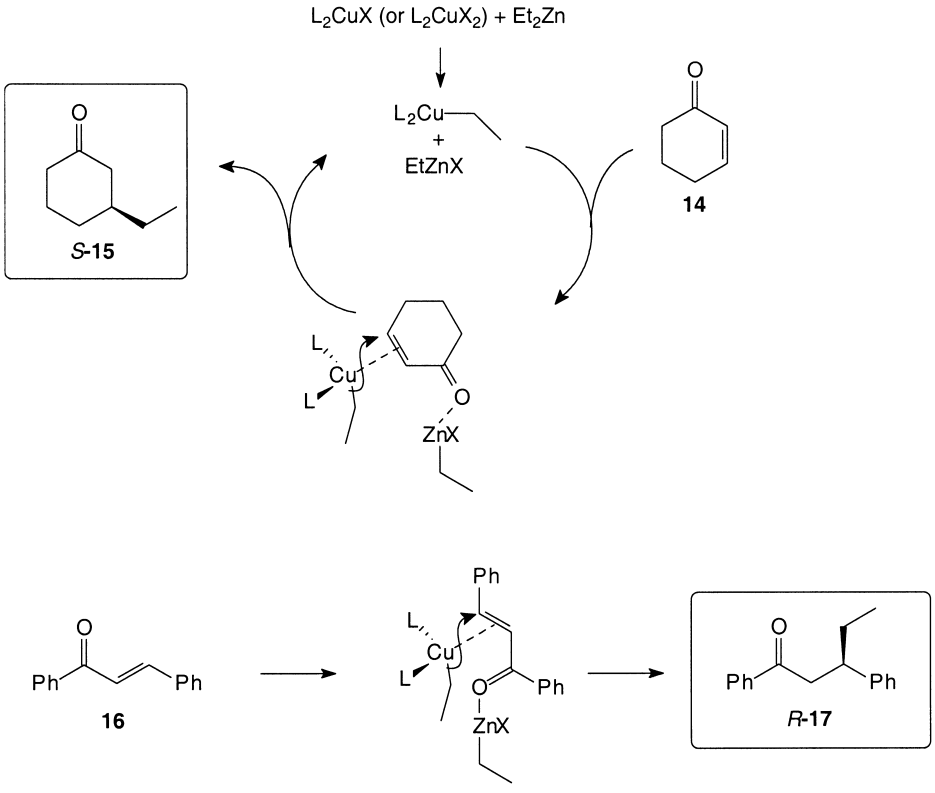


Figure 2. Correlation between the enantiomeric excess of the ligand **3m** and the e.e. of 3-ethyl-cyclohexanone **15** following standard reaction procedures.

between e.e.'s of ligand **3m** and product **15** is shown in Fig. 2. Although less pronounced, as in the previous case, again a negative non-linear effect is observed.

In all cases the most effective catalyst was made with a ligand to copper ratio of 2 pointing to an ML_2 system.[55] The negative non-linear effects for cyclic and acyclic enones might then be explained by Kagan's model system[55,56] in which fast ligand exchange occurs at the Cu-centre in a reactive complex bearing two chiral phosphoramidite ligands (*R*)-**3c** and (*S*)-**3c** (or (*S*, *R*, *R*)-**3m** and (*R*,*S*,*S*)-**3m**, respectively. Three complexes can be formed when non-enantiomerically pure ligand is employed: M-(*R*)-**3c**, (*R*)-**3c**; M-(*S*)-**3c**, (*S*)-**3c**; M-(*R*)-**3c**, (*S*)-**3c**. The first two complexes will provide enantiomeric adducts whereas the meso complex M-(*R*)-**3c**, (*S*)-**3c** generates racemic product. A negative non-linear relationship points to a greater reactivity of the heterochiral (*meso*) catalyst than the reactivity of the homochiral catalyst. An alternative explanation might be found in the so called 'reservoir effect' in which aggregation leads to unproductive catalyst complexes which influences the enantiomeric composition of the effective catalyst.

Based on the data obtained so far the pathways shown in Scheme 8 are proposed for the copper phosphoramidite catalysed 1,4-addition of diethylzinc to enones. Starting with either the Cu(I)-complex or the Cu(II)-complex (which is most probably in situ reduced to the corresponding Cu(I)-complex) and diethylzinc first an ethyl group is transferred to the copper.[21b,57] The enone coordinates to the ethyl copper species by π-complexation of the olefinic bond.[58] The Lewis acidic Zn(II) centre probably activates the enone through complexation to the carbonyl group. This substrate binding and activation could well involve a (bridged) bimetallic complex. The remaining sites in the tetrahedral coordination sphere of the copper ion are occupied by two phosphoramidite ligands providing a favourable pathway for π-face selective ethyl transfer. The smaller electronegativity of zinc (1.6) relative to that of copper (1.9) suggests the generation of the zinc enolate instead of a copper enolate.[59] Via chiral intermediates and (with the same chiral coordination sphere) 1,4-adduct with the *S*-configuration will be formed for *s-trans* enones (i.e.



Scheme 8.

ethylcyclohexanone **15**) and products with the R configuration for *s-cis* enones (i.e. **17**). These predictions are in accordance with the experimental observations for cyclohexenone and chalcone type substrates.

In depth mechanistic studies are required to substantiate the proposed pathways and intermediates and to obtain insight into ligand parameters that govern π-face selection in the case of cyclic and acyclic enones. The combined results of these studies will allow us to rationalize the high enantioselectivities encountered.

Experimental

General

Toluene and diethylether were distilled from sodium and dichloromethane (CH_2Cl_2) was distilled from P_2O_5. All solvents were stored under nitrogen. All secondary amines were purchased from Aldrich, Fluka or Acros and distilled before use. The following substances were commercially available and used without further purification: (*S*)-binaphthol (Syncom, Groningen), phenyl boronic acid (Acros), hexamethylphosphorus triamide (Aldrich), $Cu(OTf)_2$ (Aldrich) was dried before use, Et_2Zn (1.1 M toluene) (Aldrich). The substituted unsaturated ketones were commercially available (Lancaster) or synthesised.[60] All reactions were carried out under argon atmosphere using dried glassware. Chromatography: silica gel Merk Typ 9385 230–400 mesh, TLC: silica gel 60, Merk, 0.25 mm. Optical rotations were measured on a Perkin–Elmer 241 MC (at RT). Mass spectra (HRMS) were obtained in an AEI MS-902. HPLC analysis was performed on a Water 480 with a LC spectrophotometer or a Water 600E system controller with a Waters 991 photodiode array detector. ^{1}H NMR, ^{13}C NMR and ^{31}P NMR ($CDCl_3$): δ in ppm (δ=7.2 ppm) for protons, (δ=77 ppm) for carbon atoms and (H_3PO_4): (δ=0.0 ppm) for phosphorus atoms.

Synthesis of phosphoramidite ligands

Under argon atmosphere: To a cooled solution (−60°C) of PCl_3 (270 μl, 3.0 mmol), Et_3N (860 μl, 6.0 mmol), and toluene (5 ml) was added a warm solution (60°C) of (*S*)-2,2′-binaphthol (**1**) (860 mg, 3.0 mmol) and toluene (25 ml) in 5 min. After stirring for 2 h the reaction mixture was warmed up to room temperature and filtered under argon atmosphere. The filtrate was treated with Et_3N (410 μl, 2.9 mmol) and 2.9 mmol of the corresponding secondary amine at −40°C. After 16 h at ambient temperature, the reaction mixture was filtered and purified by chromatography (SiO_2, hexane: CH_2Cl_2) to give the pure amidite as a colorless amorphous compound. Stripping with CH_2Cl_2 furnished the phosphoramidite as foamy solids with still some solvent molecules incorporated. Crystallisation from diethyl ether/CH_2Cl_2 mixtures gave crystalline material.

Improved synthesis for 3c, 3l, 3m, 3n, 3o. The general procedure as described above was applied to prepare the phosphoryl chloride (**2**). This mixture was filtered in a preformed cooled (−40°C) solution of (2.8 mmol secondary amine and 2.8 mmol *n*-BuLi) in THF (10 ml). After 16 h at ambient temperature, the reaction mixture was filtered over celite, concentrated and purified by chromatography (SiO_2, hexane: CH_2Cl_2) to give the pure amidite.

***O,O′*-(*S*)-(1,1′Dinaphthyl-2,2′-diyl)-*N,N*-diethylphosphoramidite (3b).** $[\alpha]_D^{20}$=+501° (*c*=0.50, CH_2Cl_2). ^{1}H NMR δ=1.08 (t, *J*=7.2 Hz, 6H), 2.79–3.21 (m, 4H), 7.18–7.58 (m, 8H), 7.89–8.05 (m, 4H). ^{13}C NMR δ=14.01, 44.22, 121.97, 122.14, 122.91, 123.98, 124.11, 124.41, 124.65, 126.07, 126.93, 128.20, 129.85, 130.11, 130.65, 131.34, 123.50, 149.17, 149.69. ^{31}P NMR δ149.8. HRMS calcd for $C_{24}H_{22}NO_2P$: 387.139, found 387.139.

***O,O′*-(*S*)-(1,1′-Dinaphthyl-2,2′-diyl)-*N,N*-di-*i*-propylphosphoramidite (3c).** $[\alpha]_D^{20}$=+591° (*c*=0.68, $CHCl_3$). ^{1}H NMR δ=1.19 (d, *J*=6.84 Hz, 6H), 1.24 (d, *J*=6.84 Hz, 6H), 3.37 (heptet, *J*=6.84 Hz, 1H), 3.42 (heptet, *J*=6.84 Hz, 1H), 7.55–7.22 (m, 8H), 7.99–7.89 (m, 4H). ^{13}C NMR δ=24.27, 24.43, 44.48, 44.74, 121.69, 122.26, 122.32, 123.91, 124.10, 124.45, 125.63, 125.72, 126.96, 128.04, 128.10, 129.18, 130.00, 130.32, 131.16, 132.54, 132.67, 150.03, 150.22, 150.35. ^{31}P NMR δ=151.7. HRMS calcd for $C_{22}H_{26}NO_2P$: 415.170, found 415.170.

***O,O′*-(*S*)-(1,1-Dinaphthyl-2,2′-diyl)-*N,N*-dibenzylphosphoramidite (3d).** $[\alpha]_D^{20}$=+163° (*c*=0.54, CH_2Cl_2). ^{1}H NMR δ=3.47 (AB system, *J*=15.0 Hz, 1H), 3.53 (AB system, *J*=15.0 Hz, 1H), 4.25 (AB system, *J*=15.0 Hz, 1H), 4.29 (AB system, *J*=15.0 Hz, 1H), 7.16–7.51(m, 17H), 7.68–7.88 (m, 3H), 7.98 (d, *J*=8.1 Hz, 1H), 8.07 (d, *J*=8.65 Hz, 1H). ^{13}C NMR δ=47.90, 48.33, 121.48, 122.16, 122.90, 123.63, 123.85, 124.62, 124.86, 126.10, 126.91, 127.06, 127.35, 128.21, 128.40, 128.84, 130.15, 130.31, 130.64, 131.24, 132.48, 137.83, 149.22, 149.80. ^{31}P NMR δ=144.7. HRMS calcd for $C_{34}H_{26}NO_2P$: 511.170, found 511.170.

***O,O′*-(*S*)-(1,1′-2,2′-Diyl)-*N*-(1-piperidinyl)phosphoramidite (3e).** ^{1}H NMR δ=1.36–1.61 (m, 6H), 2.88–3.11 (m, 4H), 7.21–7.56 (m, 8H). ^{13}C NMR δ=24.88, 26.89, 26.97, 45.10, 45.50, 122.08, 122.18, 122.74, 123.93, 124.08, 124.45, 124.68, 125.97, 126.95, 128.25, 129.75, 130.17, 130.65, 131.33, 132.58, 149.27, 149.90. ^{31}P NMR δ=145.5. HRMS calcd for $C_{25}H_{23}NO_2P$: 400.147, found 400.147.

***O,O′*-(*S*)-(1,1′-2,2 Dinaphthyl-2,2′-diyl)*N*-[1-(2,6-dimethyl)-piperidinyl]phosphoramidite (3f).** $[\alpha]_D^{20}$=+472° (*c*=0.76, CH_2Cl_2). ^{1}H NMR δ=1.17 (d, *J*=7.1 Hz, 3H), 1.30 (d, *J*=7.1 Hz, 3H), 1.46–1.91 (m, 6H), 3.42–3.52 (m, 1H), 3.86–3.98 (m, 1H), 7.21–7.58 (m, 8H), 7.90–8.01 (m, 4H). ^{13}C NMR δ=14.43, 23.61, 23.96, 30.99, 31.42, 45.65, 45.81, 46.27, 47.01, 121.89, 122.36, 124.30, 124.62, 125.80, 125.92, 127.09, 128.21, 129.32, 130.15, 130.54, 131.31, 132.65, 132.72, 149.64, 150.02. ^{31}P NMR δ=146.5. HRMS calcd for $C_{27}H_{26}NO_2P$: 427.170, found 427.170.

***O,O′*-(*S*)-(1,1′-Dinaphthyl-2,2′-diyl)-*N*-[1-((3*R*,4*R*)-3,4-diphenyl)pyrrolidinyl]phosphoramidite (3g).** $[\alpha]_D^{20}$=+164° (*c*=1.35, CH_2Cl_2). ^{1}H NMR δ=3.39–3.62 (m, 6H), 7.16–7.34 (m, 12 H), 7.43–7.51 (m, 4H), 7.64 (t, *J*=8.8 Hz, 2H),

7.96–8.08 (m, 4H). ^{13}C NMR δ=52.27, 52.31, 53.19, 53.40, 121.52, 121.73, 122.83, 123.77, 123.83, 124.48, 124.61, 125.14, 125.92, 125.99, 126.73, 126.83, 128.06, 128.12, 128.17, 128.89, 129.79, 130.11, 130.61, 131.18, 132.46, 132.65, 139.99, 149.55, 149.86, 149.92. ^{31}P NMR δ=148.9. HRMS calcd for $C_{36}H_{28}NO_2P$: 537.186, found 537.186.

***O,O′*-(*S*)-(1,1′-Dinaphthyl-2,2′-diyl)-*N*-(1-(*N*-methyl)piperazidinyl)phosphoramidite (3h).** ^{1}H NMR δ=2.15–2.26 (m, 7H), 2.91–3.11 (m, 4H), 7.11–7.58 (m, 8H), 7.85–8.05 (m, 4H). ^{13}C NMR δ=44.31, 44.67, 47.28, 56.54, 56.71, 121.93, 123.06, 123.97, 124.14, 124.86, 125.01, 126.20, 126.82, 128.33, 130.53, 130.81, 131.13, 131.44, 132.34, 132.92, 149.26, 150.01. ^{31}P NMR δ=145.0. HRMS calcd for $C_{24}H_{20}N_2O_2P$: 414.150, found 414.150.

***O,O′*-(*S*)-(1,1′-Dinaphthyl-2,2′-diyl)-*N*-(1-morpholinyl)-phosphoramidite (3i).** $[\alpha]_D^{20}$=+364° (*c*=0.19, CH_2Cl_2). ^{1}H NMR δ=2.93–3.21 (m, 4H), 3.53–3.61 (m, 4H), 7.24–7.60 (m, 8H), 7.92–8.04 (m, 4H). ^{13}C NMR δ=44.37, 44.73, 67.78, 67.87, 121.90, 122.87, 123.83, 123.95, 124.75, 124.90, 126.20, 126.92, 128.37, 130.09, 130.41, 130.78, 131.42, 132.34, 132.96, 149.32, 149.80. ^{31}P NMR δ=144.6. HRMS calcd for $C_{24}H_{20}NO_3P$: 401.118, found 401.118.

***O,O′*-(*S*)-(1,1′-Dinaphthyl-2,2′-diyl)-*N*-(1-thiomorpholinyl)-phosphoramidite (3j).** $[\alpha]_D^{20}$=+383° (*c*=0.39, CH_2Cl_2). ^{1}H NMR δ=2.41–2.53 (m, 4H), 3.20–3.38 (m, 4H), 7.22–7.58 (m, 8H), 7.91–8.03 (m, 4H). ^{13}C NMR δ=42.53, 44.41, 44.77, 122.02, 122.64, 123.86, 123.91, 124.65, 124.89, 126.12, 126.92, 128.31, 130.10, 130.43, 130.77, 131.40, 132.41, 132.83, 149.43, 149.88, 150.04. ^{31}P NMR δ=145.0 HRMS calcd for $C_{24}H_{20}NO_2PS$: 417.095, found 417.095.

***O,O′*-(*S*)-(1,1′-Dinaphthyl-2,2′-diyl)-*N,N′*-di(2-methoxyphenyl)phosphoramidite (3k).** ^{1}H NMR δ=3.80 (s, 6H), 6.51 (dt, *J*=7.7 Hz, *J*=1.3 Hz, 2H), 6.80 (dd, *J*=8.1 Hz, *J*=1.3 Hz, 2H), 6.96 (dt, *J*=7.7 Hz, *J*=1.3 Hz, 2H), 7.12–7.43 (m, 9H), 7.49–7.57 (m, 2H), 7.75 (d, *J*=8.1 Hz, 1H), 7.93 (t, *J*=9.4 Hz, 2H). ^{13}C NMR δ=55.82, 112.24, 120.14, 121.62, 122.13, 124.05, 124.62, 125.38, 125.86, 126.30, 126.74, 127.06, 127.73, 128.73, 128.22, 128.52, 130.05, 130.22, 130.53, 130.62, 131.31, 132.75, 132.97, 155.28. ^{31}P NMR δ=139.9 HRMS calcd for $C_{34}H_{26}NO_4PS$: 543.160, found 543.160.

***O,O′*-(*S*)-(1,1′-Dinaphthyl-2,2′-diyl)-*N,N′*-di-(*S,S*)-1-phenylethylphosphoramidite (3l).** $[\alpha]_D$=+202.1° (*c*=0.79, $CHCl_3$). ^{1}H NMR δ=8.08–7.78 (m, 4), 7.65–7.24 (m, 18H), 4.47 (q, *J*=7.2 Hz, 2H), 1.75 (d, *J*=7.2 Hz, 6H). ^{13}C NMR δ=150.45, 150.20, 149.80, 143.13, 132.77, 131.38, 130.47, 129.60, 129.25, 128.33, 128.06, 127.99, 127.79, 127.26, 126.71, 126.05, 125.87, 124.80, 124.36, 122.54, 54.55, 54.34, 23.07, 22.83. ^{31}P NMR δ=150.4. HRMS calcd for $C_{36}H_{30}NO_2P$: 539.201, found 539.208.

***O,O′*-(*S*)-(1,1′-Dinaphthyl-2,2′-diyl)-*N,N′*-di-(*R,R*)-1-phenylethylphosphoramidite (3m).** $[\alpha]_D$=+456.0° (c=0.79, $CHCl_3$). ^{1}H NMR δ=7.98–8.08 (m, 4H), 7.17–7.74 (m, 18), 4.63 (q, *J*=7.2 Hz, 2H), 1.85 (d, *J*=7.2 Hz, 6H). ^{13}C NMR δ=150.2, 149.6, 142.8, 132.8, 131.4, 130.5, 130.5, 130.3, 129.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.2, 127.1, 126.7, 126.0, 124.7, 124.5, 122.4, 52.3, 51.1, 21.8. ^{31}P NMR δ=145.3. HRMS calcd for $C_{36}H_{30}NO_2P$: 539.201, found 539.208.

***O,O′*-(*S*)-(1,1′-Dinaphthyl-2,2′-diyl)-*N*-benzyl-*N′*-(*S*)-1-phenylethylphosphoramidite (3n).** $[\alpha]_D$=+196° (c 0.84, $CHCl_3$). ^{1}H NMR δ=8.06–7.10 (m, 22H), 4.15 (m, 1H), 4.11 (d, *J*=15 Hz, 1H), 3.08 (d, *J*=15 Hz, 1H), 1.76 (m, 3H). ^{13}C NMR δ=150.13, 150.09, 149.55, 143.67, 138.58, 132.77, 132.44, 131.37, 130.51, 130.22, 130.09, 128.53, 128.44, 128.27, 128.13, 127.41, 127.33, 127.03, 126.89, 125.99, 124.76, 124.46, 124.10, 122.44, 122.26, 121.64, 57.59, 57.40, 48.27, 23.55, 23.29. ^{31}P NMR δ=141.0. HRMS calcd for $C_{35}H_{28}N\,O_2P$ 525.186 found 525.185

***O,O′*-(*S*)-(1,1′-Dinaphthyl-2,2′-diyl)-*N,N′*-di-(*R,R*)-1-naphthylethylphosphoramidite (3o).** $[\alpha]_D$=+49.7° (c 0.9, $CHCl_3$). ^{1}H NMR δ=8.05–7.21 (m, 24H), 6.73 (t, *J*=7.8 Hz, 2H), 5.60 (m, 2H), 1.78 (d, *J*=6.6, 6H). ^{13}C NMR δ=150.42, 150.36, 149.49, 138.27, 133.04, 132.86, 131.46, 130.46, 129.69, 128.33, 128.19, 127.17, 127.14, 126.87, 126.11, 126.09, 125.26, 124.86, 124.78, 124.50, 124.37, 124.28, 124.24, 123.11, 122.73, 122.18, 121.80, 49.60, 49.53, 23.16. ^{31}P NMR (200 MHz) δ=147.6. HRMS calcd for $C_{44}H_{34}N\,O_2P$ 639.233, found 639.232.

***N,N′*-Bis[*O,O′*-(*S*)-(1,1′-dinaphthyl-2,2′-diyl)-*N*-methylphosphoramidite]ethylenediamine (3p).** ^{1}H NMR δ=2.37 (s, 3H), 2.40 (s, 3H), 3.01–3.19 (m, 2H), 3.29–3.42 (m, 2H), 7.24–7.62 (m, 16H), 7.90–8.04 (m, 8H). ^{13}C NMR δ=32.21, 47.09, 47.85, 122.06, 122.26, 122.47, 123.93, 124.05, 124.59, 124.81, 126.09, 126.91, 127.04, 128.27, 128.34, 130.11, 130.30, 130.72, 131.38, 132.56, 132.83, 149.45, 149.98, 150.10. ^{31}P NMR δ=148.9 HRMS calcd for $C_{44}H_{34}N_2O_4P$: 716.199, found 716.199.

Synthesis of 3,3′-substituted binaphthols

3,3′-Dimethyl-2,2′-dimethoxy-1,1′dinaphthyl (5). A solution of (*S*)-(**4**) (0.72 g, 2.29 mmol), prepared according to a published procedure,[49] and TMEDA (1.81 ml, 12.0 mmol) in 40 ml of diethylether was cooled with ice/water. A 2.0 M solution of *n*-BuLi in hexane (4.9 ml, 9.8 mmol) was added dropwise over a period of 25 min. The mixture was stirred at 0°C for 30 min and was then slowly warmed to reflux. After refluxing for 20 h the resulting orange suspension was cooled to 0°C and MeI (1.56 ml, 25 mmol) was added dropwise over a period of 45 min resulting in a white suspension. After stirring for 16 h at ambient temperature the white mixture was poured into 200 ml of aqueous 1 N HCl. The mixture was extracted with $CHCl_3$ (250 ml) and the organic layer was washed with saturated solution of $NaHCO_3$ (200 ml), brine (200 ml), dried (Na_2SO_4) filtered and evaporated to give the crude product as a yellow solid (0.94 g). The crude product was filtered over a short column (SiO_2, hexane: EtOAc: CH_2Cl_2 10:1:1) and recrystallised from hexane: EtOAc (10:1, 35 ml) to give **5** (0.46 g, 63%) as colourless crystals. ^{1}H NMR δ=2.57 (s, 6H), 3.33 (s, 6H), 7.11–7.41 (m, 6H), 7.79–7.86 (m, 4H). ^{13}C NMR δ=17.23,

60.07, 124.54, 124.60, 125.29, 125.72, 127.12, 129.56, 130.71, 131.56, 133.11, 155.74.

3,3′-Diphenyl-2,2′-dimethoxy-1,1′dinaphthyl (7). A mixture of (*S*)-**6** (1.04 g, 2.20 mmol), prepared according to the published procedure,[50] and $Pd(PPh_3)_4$[61] (0.153 g, 0.132 mmol) in 10 ml of dimethoxyethane was stirred at room temperature for 30 min. After addition of $PhB(OH)_2$ (0.59 g, 4.84 mmol) and $NaHCO_3$ (1.1 g in 13 ml of H_2O) the suspension was refluxed for 16 h resulting in a colourless solution above a brownish gum. After cooling to room temperature the mixture was washed with brine (25 ml), dried (Na_2SO_4) filtered, and evaporated to give the crude product as a foam (1.22 g). The crude product was purified by column chromatography (SiO_2, hexane:toluene 1:1) to give **7** (0.977 g, 95%) as a colourless powder. ^{1}H NMR δ=3.21 (s, 6H), 7.21–7.53 (m, 12H), 7.80 (d, J=6.8 Hz, 4H), 7.92–8.01 (m, 4H).

Deprotection of compounds 5, 6, 7

All 3,3′-disubstituted-2,2′-dimethoxy-1,1′-dinaphthyls were deprotected with BBr_3 according to literature procedure[49,51] furnishing the corresponding diols **8**, **9**, **10** in high yields (>90%). Spectroscopic data (NMR and $[\alpha]_D^{20}$) of the compounds **8** and **10** were in good agreement with data in the literature.[49–51]

3,3′-Dibromo-2,2′-dihydroxy-1,1′-dinaphthyl (9). $[\alpha]_D^{20}$= −89° (c=0.58, CH_3OH). ^{1}H NMR δ=5.58 (s, 2H), 7.08 (d, J=7.6 Hz, 2H), 7.23–7.46 (m, 4H), 7.81 (d, J=7.7 Hz, 2H), 8.23 (s, 2H). ^{13}C NMR ($CD_3OD/CDCl_3$) δ=116.65, 119.26, 128.24, 128.44, 130.94, 133.40, 136.47, 136.84, 152.78.

General procedure for the synthesis of compounds 11a, 12, 13

To a mixture of a 3,3′-disubstituted-2,2′-dihydroxy-1,1′-dinaphthyl (1 mmol) in 5 ml of toluene hexamethylphosphorus triamide (1.5 mmol) was added. The mixture became clear and after 1 h a white solid precipitated. The mixture was stirred for 3 h at ambient temperature, 3 ml diethyl ether was added, and a white solid precipitated. The solid was collected by filtration, washed with diethyl ether (3 ml), and dried in vacuo to give the pure phosphoramidites **11a**, **12**, **13**. Yields >75%.

***O,O′*-(1,1′-Dinaphthyl-2,2′-diyl-3,3′-dimethyl)-*N,N′*-dimethylphosphoramidite (11a).** $[\alpha]_D^{20}$=+554° (c=0.14, CH_2Cl_2). ^{1}H NMR δ=2.51 (s, 6H), 2.60 (d, J=9.4 Hz, 6H), 7.12–7.43 (m, 6H), 7.73–7.89 (m, 4H). ^{31}P NMR δ=145.9. HRMS calcd for $C_{24}H_{22}NO_2P$: 387.139, found 387.139.

***O,O′*-(1,1′-Dinaphthyl-2,2′-diyl-3,3′-dibromide)-*N,N′*-dimethylphosphoramidite (12).** $[\alpha]_D^{20}$=+554° (*c*=0.54, CH_2Cl_2). ^{1}H NMR δ=2.59 (d, J=9.4 Hz, 6H), 7.23–7.31 (m, 4H), 7.41–7.49 (m, 2H), 7.84 (d, J=7.7 Hz, 2H), 8.27 (d, J=9.0 Hz, 2H). ^{31}P NMR δ=148.8 HRMS calcd for $C_{22}H_{16}Br_2NO_2P$: 514.929, found 514.929.

***O,O′*-(1,1′-Dinaphthyl-2,2′-diyl-3,3′-diphenyl)-*N,N′*-dimethylphosphoramidite (13).** $[\alpha]_D^{20}$=+446° (*c*=0.50, CH_2Cl_2). ^{1}H NMR δ=1.96 (d, J=9.4 Hz), 7.17–7.52 (m, 12H), 7.70–7.82 (m, 4H), 7.95–8.05 (m, 4H). ^{13}C NMR δ=34.01, 34.40, 124.32, 124.73, 124.97, 125.87, 126.63, 126.84, 127.18, 127.93, 127.98, 128.11, 128.21, 128.30, 129.70, 129.83, 129.91, 130.58, 130.75, 130.95, 132.21, 132.39, 134.12, 134.88, 138.03, 147.28. ^{31}P NMR δ=147.4 HRMS calcd for $C_{34}H_{26}NO_2P$: 511.170, found 511.170.

Synthesis of compounds 11b and 11c

These compounds were prepared according to the general procedure given for compounds **3c**, **3l**, **3m**, **3n**, **3o** using 3,3′-dimethyl-2,2′-dihydroxy-1,1′;dinaphthyl and the corresponding deprotonated amines.

***O,O′*-(1,1′-Dinaphthyl-2,2′-diyl-3,3′-dimethyl)-*N,N′*-di-*i*-propylphosphoramidite (11b).** Yield 37%. $[\alpha]_D^{20}$=+522° (*c*=1.00, CH_2Cl_2). ^{1}H NMR δ=1.19 (d, J=4.8 Hz, 12H), 2.58 (s, 3H), 2.60 (s, 3H), 3.32–3.40 (m, 2H), 7.12–7.38 (m, 6H), 7.75–7.82 (m, 4H). ^{13}C NMR δ=17.25, 18.19, 24.84, 24.91, 45.00, 45.18, 121.93, 123.98, 124.18, 124.44, 124.76, 124.86, 126.85, 127.09, 127.35, 127.45, 129.03, 129.50, 130.28, 130.35, 131.12, 131.70, 149.41, 149.84. ^{31}P NMR δ=149.2 HRMS calcd for $C_{28}H_{30}NO_2P$: 443.201, found 443.201.

***O,O′*-(1,1′-Dinaphthyl-2,2′-diyl-3,3′-dimethyl)-*N*-(1-morpholinyl)phosphoramidite (11c).** Yield 51%. $[\alpha]_D^{20}$= +467° (*c*=0.30, CH_2Cl_2). ^{1}H NMR δ=2.50 (d, J=9.4 Hz, 6H), 2.82–3.18 (m, 4H), 3.41–3.64 (m, 4H), 7.14–7.43 (m, 6H), 7.75–7.88 (m, 4H). ^{31}P NMR δ=142.1 HRMS calcd for $C_{26}H_{24}NO_3P$: 429.149, found 429.149.

General procedure for the conjugate addition of diethylzinc to α,β-unsaturated ketones employing a chiral catalyst derived from $Cu(OTf)_2$ and a phosphoramidite

A solution of $Cu(OTf)_2$ (0.025 mmol) and 0.05 mmol of phosphoramidite in 5 ml freshly distilled toluene was stirred under a nitrogen atmosphere at ambient temperature for 1 h. The substrate was added 1.0 mmol, the mixture was cooled to −20°C and 1.4 ml of diethylzinc in toluene (1.1 M) was added. Stirring was continued at −20°C for 16 h. The conversion was determined by TLC. After complete conversion, the reaction mixture was poured in 25 ml of 1 M HCl and extracted three times with diethyl ether (60 ml). The combined organic layers were dried with brine (25 ml) and Na_2SO_4, filtered and evaporated to yield the crude 1,4-products. After purification by column chromatography (SiO_2 and hexane/diethyl ether), the e.e.'s were determined by HPLC or GC analyses.

1,3-Diphenylpentan-1-one (17). e.e. determination by HPLC analyses; Daicel (Chiralcel OD), 0.25% iPrOH in hexane, flow rate 1.0 ml/min, UV detector (254 nm); retention times 16.3 min; 19.0 min. ^{1}H NMR δ=0.85 (t, J=7.3 Hz, 3H), 1.60–1.84 (m, 2H), 3.24–3.33 (m, 3H), 7.18–7.33 (m, 5H), 7.41–7.60 (m, 3H), 7.92–7.96 (m, 2H). ^{13}C NMR δ=12.12 (q), 29.23 (t), 43.00 (d), 45.60

(t), 126.27 (d), 127.65 (d), 128.05 (d), 128.40 (d), 128.52 (d), 132.90 (d), 137.25 (s), 144.67 (s), 199.19 (s).

1-(2-Furyl)-3(5-methyl-2-furyl)pentan-1-one (33). e.e. determination by HPLC analyses; Daicel (Chiralcel OD), 0.25% *i*PrOH in hexane, flow rate 1.0 ml/min, UV detector (254 nm); retention times 15.2 min; 18.0 min. ^{1}H NMR δ=0.862 (t, J=7.3 Hz, 3H), 1.60–1.74 (m, 2H), 2.21 (s, 3H), 2.93–3.33 (m, 3H), 5.78–5.80 (m, 1H), 5.84–5.88 (m, 1H), 6.49–6.51 (m, 1H), 7.14–7.17 (m, 1H), 7.55–7.57 (m, 1H). ^{13}C NMR δ=11.40 (q), 13.25 (q), 26.55 (t), 36.18 (d), 42.36 (t), 105.47 (d), 105.81 (d), 111.97 (d), 117,01 (d), 146.22 (d), 150.30 (s), 155.18 (s), 194.78 (s). HRMS calcd for $C_{13}H_{14}O_3$: 219.556, found 219.556.

1,3-Di(2-thiophene)pentan-1-one (34). e.e. determination by HPLC analyses; Daicel (Chiralcel OD), 0.25% *i*PrOH in hexane, flow rate 1.0 ml/min, UV detector (294 nm); retention times 18.3 min; 20.1 min. ^{1}H NMR δ=0.89 (t, J=7.4 Hz, 3H), 1.60–1.90 (m, 2H), 3.20–3.24 (m, 2H), 3.56–3.67 (m, 1H), 6.83–6.91 (m, 2H), 7.11–7.14 (m, 2H), 7.59–7.68 (m, 2H). ^{13}C NMR δ=11.18 (q), 30.36 (t), 44.88 (d), 45.17 (t), 122.35 (d), 122.76 (d), 124.53 (d), 125.19 (d), 126.29 (d), 126. 96 (d), 201.18 (s). HRMS calcd for $C_{13}H_{14}OS_2$: 251.555, found 251.557.

1,4-Di(2-thiophene)-2-ethyl-1,4-butadione (35). e.e. determination by HPLC analyses; Daicel (Chiralcel OD), 10% *i*PrOH in hexane, flow rate 1.0 ml/min, UV detector (254 nm); retention times 10.1 min, 12.9 min. ^{1}H NMR δ=0.962 (t, J=7.5 Hz, 3H), 1.67–1.79 (m, 2H), 3.12–3.30 (m, 1H), 3.80–3.87 (m, 2H), 7.10–7.16 (m, 2H), 7.61–7.66 (m, 2H), 7.76–7.85 (m, 2H). ^{13}C NMR δ=11.16 (q), 28.17 (t), 46.11 (d), 57.93 (d), 122.52 (d), 122.87 (d), 124.61 (d), 124.81 (d), 126.33 (d), 127.29 (d), 139.48 (s), 154.53 (s), 201.53 (s), 202.13 (s) HRMS calcd for $C_{14}H_{14}O_2S_2$: 279.668, found 279.664.

1-(2-Pyridyl)-3-phenyl-1-pentanone (36). e.e. determination by HPLC analyses; Daicel (Chiralcel OD), 10% *i*PrOH in hexane, flow rate 1.0 ml/min, UV detector (240 nm); retention times 18.2 min, 25.4 min. ^{1}H NMR δ=0.81 (t, J=7.4 Hz, 3H), 1.60–1.85 (m, 2H), 3.19–3.34 (m, 1H), 3.45–3.69 (m, 2H), 7.10–7.23 (m, 1H), 7.24–7.47 (m, 4H), 7.40–7.47 (ddd, 1H), 7.74–7.82 (dt, 1H), 7.92–7.98 (dt, 1H), 8.65–8.68 (ddd, 1H). ^{13}C NMR δ=11.79, 29.32, 42.42, 43.98, 121.66, 125.92, 126.84, 127.63, 128.09, 126.68, 144.77, 148.69, 153.45, 200.70.

1-(4-Nitrophenyl)-3-phenyl-1-pentanone (37). e.e. determination by HPLC analyses; Daicel (Chiralcel OD), 10% *i*PrOH in hexane, flow rate 1.0 ml/min, UV detector (270 nm); retention times 8.7 min, 23.8 min. ^{1}H NMR δ=0.876 (t, J=7.4 Hz, 3H), 1.63–1.88 (m, 2H), 3.18–3.40 (m, 3H), 7.18–7.37 (m, 5H), 8.04 (d, J=6.3 Hz, 2H), 8.32 (d, J=6.3 Hz, 2H). ^{13}C NMR δ=12.33 (q), 28.16 (t), 41.36 (d), 45.17 (t), 123.16 (d), 125.47 (d), 128.3 (d), 128.73 (d), 129,48 (d), 141.83 (d), 142.41 (d), 148.09 (s), 203.56 (s).

1-(4-Methoxyphenyl)-3-phenyl-1-pentanone (38). e.e. determination by HPLC analyses; Daicel (Chiralcel OD), 0.25% *i*PrOH in hexane, flow rate 1.0 ml/min, UV detector (254 nm); retention times 25.4 min, 27.2 min. ^{1}H NMR δ=0.82 (t, J=7.2 Hz, 3H), 1.41–1.58 (m, 2H), 2.21 (s, 3H), 3.18–3.33 (m, 3H), 7.01–7.34 (m, 7H), 7.64 (d, J=6.8 Hz, 2H). ^{13}C NMR δ=12.73 (q), 31.45 (t), 41.54 (d), 46.82 (t), 54.25 (q), 112.87 (d), 124.26 (s), 125.42 (d), 127.48 (d), 128.13 (d), 130.75 (d), 137.32 (s), 138.40 (s), 202.76 (s).

1-Phenyl-3-(4-methoxyphenyl)pentan-1-one (39). e.e. determination by HPLC analyses; Daicel (Chiralcel OD), 0.25% *i*PrOH in hexane, flow rate 1.0 ml/min, UV detector (254 nm); retention times 29.7 min, 34.8 min. ^{1}H NMR δ=0.79 (t, J=7.2 Hz, 3H), 1.43–1.63 (m, 2H), 2.16 (s, 3H), 3.21–3.24 (m, 3H), 7.11–7.53 (m, 7H), 7.89 (d, J=6.8 Hz, 2H). ^{13}C NMR δ=11.82 (q), 29.10 (t), 42.00 (d), 45.61 (t), 54.97 (q), 113.59 (d), 123.73 (s), 127.84 (d), 127.92 (d), 128.37 (d), 132.75 (d), 138,45 (s), 138.96 (s), 197.68 (s).

1-(4-Chlorophenyl)-3-phenyl-1-pentanone (40). e.e. determination by HPLC analyses; Daicel (Chiralcel OD), 0.25% *i*PrOH in hexane, flow rate 1.0 ml/min, UV detector (254 nm); retention times 16.0 min, 17.5 min. ^{1}H NMR δ=0.83 (t, J=7.6 Hz, 3H), 1.58–1.83 (m, 2H), 3.17–3.31 (m, 3H), 7.21–7.31 (m, 5H), 7.40 (d, J=7.1 Hz, 2H), 7.84 (d, J=7.2 Hz, 2H). ^{13}C NMR δ=11.83 (q), 28.98 (t), 42.83 (d), 45.34 (t), 126.24 (d), 127.47 (d), 128.32 (d), 128.69 (d), 129.35 (d), 135.41 (s), 139.98 (s), 144.31 (s), 197.96 (s).

1-Phenyl-4-(4-chlorophenyl)pentan-1-one (41). e.e. determination by HPLC analyses; Daicel (Chiralcel OD), 0.25% *i*PrOH in hexane, flow rate 1.0 ml/min, UV detector (254 nm); retention times 32.9 min, 37.9 min. ^{1}H NMR δ=0.80 (t, J=7.3 Hz, 3H), 1.56–1.80 (m, 2H), 3.20–3.27 (m, 3H), 7.14–7.59 (m, 7H), 7.89 (d, J=6.8 Hz, 2H). ^{13}C NMR δ=11.74 (q), 28.89 (t), 42.10 (d), 45.15 (t), 127.87 (d), 128.38 (d), 128.44 (d), 128.88 (d), 132.80 (s), 132.91 (d), 137.56 (s), 143.02 (s), 198.77 (s).

1,3-Di-(4-chlorophenyl)pentan-1-one (42). e.e. determination by HPLC analyses; Daicel (Chiralcel OD), 0.25% *i*PrOH in hexane, flow rate 1.0 ml/min, UV detector (254 nm); retention times 22.3 min, 24.6 min. ^{1}H NMR δ=0.79 (t, J=7.1 Hz, 3H), 1.38.1.64 (m, 2H), 3.11–3.31 (m, 3H), 7.42 (d, J=6.8 Hz, 1H), 7.57 (d, J=6.8 Hz, 1H), 7.64 (d, J=6.8 Hz, 1H), 7.79(d, J=6.8 Hz, 1H). ^{13}C NMR δ=12.36 (q), 28.14 (t), 1.56 (d), 44.13 (t), 128.33 (d), 128.56 (d), 129.57 (d), 129.88 (d), 134.94 (s), 135.16 (s), 140.40 (s), 143.36 (s), 203.16 (s).

1,3-Di-(4-bromophenyl)pentan-1-one (43). e.e. determination by HPLC analyses; Daicel (Chiralcel OD), 0.25% *i*PrOH in hexane, flow rate 1.0 ml/min, UV detector (251 nm); retention times 24.8 min, 27.9 min. ^{1}H NMR δ=0.80 (t, J=7.3 Hz, 3H), 1.48–1.84 (m, 2H), 3.05–3.13 (m, 3H), 7.23 (d, J=6 Hz, 1H), 7.39 (d, J=6 Hz, 1H), 7.59 (d, J=6 Hz, 1H), 7.74 (d, J=6 Hz, 1H). ^{13}C NMR δ=11.88 (q), 31.46 (t), 40.18 (d), 43.61 t), 122.01 (s), 122.73 (s), 129.04 (d), 129.94 (d), 131.13 (d), 131.74 (d), 141.20 (s), 142.39 (s), 201.83 s).

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