DOI: 10.1002/chem.200901577

Copper-Catalyzed Asymmetric Conjugate Addition with Chiral SimplePhos Ligands**

Laëtitia Palais and Alexandre Alexakis*[a]

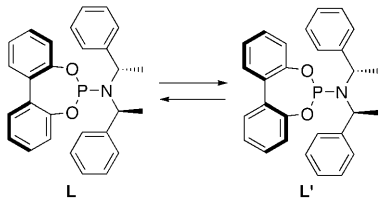
Abstract: SimplePhos ligands represent a novel class of monodentate chiral ligands based on a chiral amine moiety and flexible diaryl groups on the phosphorous atom. They can be easily prepared by two different pathways and they can be highly functionalised. Herein we report the copper-catalysed asymmetric conjugate addition of diethyl zinc and trialkylaluminium reagents with SimplePhos ligands, which gives high enantioselectivity with cyclic enones, acyclic enones and nitro-olefins, with up to 98.6% *ee*. Of particular interest is the reaction of trialkylaluminium reagents with a wide range of 3-substituted enones, thus allowing the formation of stereogenic quaternary carbon centres.

Keywords: asymmetric catalysis · conjugate addition · copper · enones · P ligands

Introduction

Transition-metal-catalysed asymmetric transformations require an efficient chiral ligand to induce high levels of enantioselectivity. The art of designing these ligands still remains, in many respects, quite empirical. A way to simplify this problem is to rely on modular structures that can easily afford a huge diversity of ligands. Due to strong substrate dependence in most cases, it is desirable that such ligands remain tunable in terms of steric and/or electronic properties and can be easily synthesised. Subtle changes in conformational, steric and/or electronic properties of the chiral ligand can often lead to dramatic variation of the reactivity and enantioselectivity.

Although bidentate ligands (C_2 symmetric or not) were almost exclusively used until the last decade, more and more monodentate ligands are currently being investigated, particularly in the field of conjugate addition.[1] Of particular interest to our group were the copper-catalysed reactions in which monodentate ligands are of prime importance. The asymmetric copper-catalysed conjugate addition is nowadays a well-developed methodology to create C–C bonds.[2] Many efforts have been made in designing efficient systems and identifying new ligands to improve enantioselectivities. Phosphoramidite ligands appear to be among the most efficient for the copper-catalysed asymmetric conjugate addition (ACA).[3] In 2001, we introduced tropos phosphoramidites, in which the rigid binaphthol unit was replaced by a flexible biphenol unit.[4a] The success of these ligands was based on the different turnover frequency (TOF) provided by each conformer. A simple disconnection of the biphenol and the chiral amine allows the synthesis of many variants, both on the biphenol and the amine part.[4b]



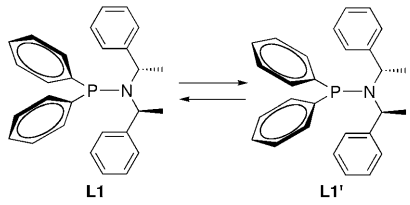
In keeping the same amine part, we felt that it could be possible to replace the biphenol part by another type of chirality, that is, helicity. Here again, we are dealing with two conformers that may not provide the same TOF in the Cu-catalysed ACA.

This new concept seemed quite successful, and we have recently described the synthesis of some of these new effi-

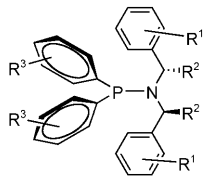
[a] L. Palais, Prof. Dr. A. Alexakis
Département de chimie organique
Université de Genève
30 quai Ernest Ansermet
1211 Geneve 4 (Switzerland)
Fax: (+41) 223-793-215
E-mail: alexandre.alexakis@unige.ch

[**] SimplePhos ligands = phosphorus ligands based on the induced helicity of a diaryl group and a chiral amine.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200901577.



cient chiral ligands called SimplePhos ligands.[5] The modularity of these ligands allows for easy variations of the amino unit[6] as well as the diaryl part on the phosphorus atom. Moreover, SimplePhos ligands have shown their efficiency not only for asymmetric conjugate addition of Et_2Zn to cyclohexenone and cycloheptenone (with *ee* values up to 95%) but also for the addition of Me_3Al and Et_3Al species to methylcyclohexenone and phenylcyclohexenone catalysed by copper to form quaternary stereogenic carbon centres. These ligands seemed to be very efficient for ACA, since high enantioselectivity was obtained in experiments in which phosphoramidite-type ligands gave inferior results.



We herein report a full account of our results in the synthesis of several members of the SimplePhos family of ligands. Modifications were made to both the amine and aryl scaffold with different electronic or steric requirements. All these new ligands were tested for the copper-catalysed ACA on several substrates, such as cyclic and acyclic enones, nitro-olefins and substituted cyclohexenones for the formation of quaternary carbon centres.

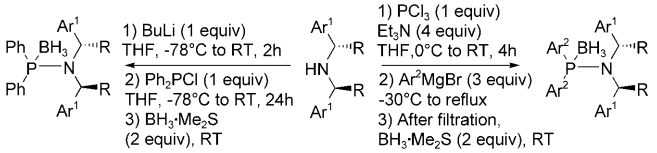
Results and Discussion

Synthesis of SimplePhos ligands: Starting from a chiral C_2-symmetric amine (except for **L8**–**L11**), SimplePhos ligands have been prepared by two different pathways (Table 1). For the first one, ligands **L4** to **L11** were obtained by deprotonation of the chiral amine by *n*BuLi followed by the addition of Ph_2PCl (pathway 1). Some ligands are stable towards oxidation in the solid state but slightly air-sensitive in solution. Although traces of oxide do not impede catalysis, we have decided to protect our ligands with borane to form phosphine–borane complexes,[7] which are air-stable and easily purified by chromatography on alumina. It should be noted, however, that hindered ligands such as **L5**, **L12**, **L13**, **L17**, **L19**, **L20**, **L22** and **L23** are perfectly stable and do not easily form the borane complexes.

For the other strategy (pathway 2), the same methodology as for the synthesis of phosphoramidite ligands was used. After formation of the aminophosphine dichloride, prepared in situ from bis-(*S*)-(1-phenylethyl)amine or bis-(*S*)-(1-2-naphthylethyl)amine (**L22** and **L23**) and a solution of PCl_3/Et_3N, three equivalents of aryl Grignard reagent[8] (prepared in THF) were added to form the free ligand after one night of heating at reflux. Some were not protected because it was observed that these ligands crystallised spontaneously in pentane without oxidation. Due to the presence of magnesium salts, the ligands could not be protected in situ and needed prior filtration on neutral alumina under an inert atmosphere.

These ligands have a high potential modularity because the amine part could be modified by the presence of electron-withdrawing or electron-donating substituents on the Ar^1 aryl moiety or by using more sterically hindered amine

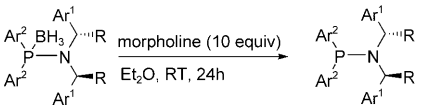
Table 1. Synthesis of SimplePhos–borane ligands by two different pathways.



Entry	Ligand	Ar^1	Ar^2	R	Isolated yield [%]
1	**L1**	Ph	Ph	Me	68
2	**L1**-BH3	Ph	Ph	Me	82
3	**L2**-BH3	Ph	Ph	Et	84
4	**L3**-BH3	*o*-OMe(C_6H_4)	Ph	Me	58
5	**L4**-BH3	2-naphthyl	Ph	Me	41
6	**L5**	1-naphthyl	Ph	Me	78
7	**L6**-BH3	*o*-tolyl	Ph	Me	57
8	**L7**	*p*-OMe	Ph	Me	63
9	**L8**-BH3	Ph, 2-naphthyl	Ph	Me	94
10	**L9**	Ph	Ph	Me, *i*Pr	4
11	**L10**-BH3	Ph,	Ph	Me, $(CH_2)_2Ph$	41
12	**L11**-BH3	Ph, 1-pyridine	Ph	Me	50
13	**L12**	Ph	*o*-Me(C_6H_4)	Me	94
14	**L13**	Ph	*p*-Me(C_6H_4)	Me	94
15	**L14**-BH3	Ph	*p*-OMe(C_6H_4)	Me	70
16	**L15**-BH3	Ph	*m*-CF_3(C_6H_4)	Me	25
17	**L16**-BH3	Ph	*m*-OMe(C_6H_4)	Me	71
18	**L17**	Ph	xylyl	Me	67
19	**L18**	Ph	3,5-CF_3(C_6H_3)	Me	40
20	**L19**	Ph	2-naphthyl	Me	30
21	**L20**	Ph	1-naphthyl	Me	59
22	**L21**	Ph	1-furyl	Me	8
23	**L22**-BH3	2-naphthyl	xylyl	Me	66
24	**L23**	2-naphthyl	*m*-CF_3(C_6H_4)	Me	46

with 2-naphthyl and 1-naphthyl as Ar^1 aryl groups. Coordination effects can also expected by an *ortho*-OMe group.[9,10] We have shown that these effects have an important consequence for the enantioselectivity in the copper-catalysed ACA with phosphoramidite-type ligands. On the amine part, the C_2 symmetry is not a requirement because we have also synthesised non-symmetric chiral amines (two different Ar^1 aryl groups). Again, electronic or coordination effects can be tuned by variation of R (methyl, ethyl or phenyl groups) and Ar^1 (*o*-Me and *o*-OMe).

Table 2. Deprotection of SimplePhos–borane ligands by using morpholine.



Entry[a]	Ligand	Ar^1	Ar^2	R	Isolated yield [%]
1	**L2**	Ph	Ph	Et	98
2	**L3**	*o*-OMe(C_6H_4)	Ph	Me	93
3	**L4**	2-naphthyl	Ph	Me	97
4	**L6**	*o*-tolyl	Ph	Me	100
5	**L8**	Ph, 2-naphthyl	Ph	Me	81
6	**L10**	Ph	Ph	Me, $(CH_2)_2$Ph	88
7	**L11**	Ph, 1-pyridine	Ph	Me	87
8	**L14**	Ph	*p*-OMe(C_6H_4)	Me	80
9	**L15**	Ph	*m*-CF_3(C_6H_4)	Me	83
10	**L16**	Ph	*m*-OMe(C_6H_4)	Me	77
11	**L22**	2-naphthyl	xylyl	Me	97

On the Ar^2 aryl part on the phosphorus atom, similar variations can be applied. For example, the xylyl group on **L17** and **L22** can decrease the free rotation around phosphorus and modify the general helicity and consequently act on the enantioselectivity. Such beneficial effects have been observed with *ortho*-substituted biphenol phosphoramidite ligands.[4b] Moreover, and in contrast to phosphoramidite ligands, the substituents on Ar^2 can have a direct electronic effect on the coordination properties of the phosphorus atom. This is why we have synthesised ligands **L12–L16**, **L18** and **L23** with CF_3 or OMe groups in various positions. Combination of these various effects were undertaken according to the results of the conjugate additions we attempted.

Aromatic heterocycles may also be introduced as Ar^2 groups. Ligand **L21**, with a 2-furyl group, is representative of this class. A possible coordination of the heteroatom with copper could be envisaged. This ligand was prepared according the modified procedure 2 using 2-lithiofuran instead of Grignard reagent. An excess of this lithium reagent had to be added to the solution of phosphine amine dichloride and, after one night of heating at reflux, ligand **L21** was obtained with very low yield.

In addition to these variations, it could be possible to create a stereogenic phosphorus atom if the two Ar^2 aromatic substituents were different. Thus, by adding successively two different aromatic Grignard reagents to the amine–PCl_2 intermediate, we observed two signals by ^{31}P NMR spectroscopy on the resulting diastereomeric ligand. Unfortunately, a 2:1 ratio indicated a low asymmetric induction by the chiral amine.

SimplePhos ligands complexed by BH_3 should be deprotected for further use because the borane[11] complex did not provide good results in terms of enantioselectivity for the addition of Et_2Zn to cyclohexenone. For this reason, all the borane complexes were deprotected with of morpholine (10 equiv) in diethyl ether at room temperature.[7] A simple filtration on neutral alumina under an inert atmosphere gave the desired ligands with high yields (Table 2).

All the free ligands displayed a single set of signals in the ^{1}H, ^{13}C and ^{31}P NMR spectra. This is a good indication of the rapid interconversion of the two helical conformers. Only the most hindered ligand, **L22**-BH3, gave rise to two signals at low temperature (Figure 1). Thus, the free and borane variants of ligand **L22** were studied by variable-temperature ^{31}P NMR spectroscopy. From −90 °C (183 K) to room temperature a single set of sharp signals was observed with the free ligand. Concerning borane ligand **L22**-BH3,

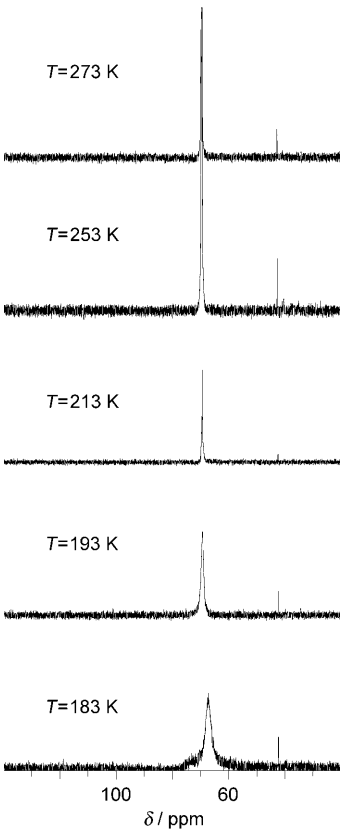
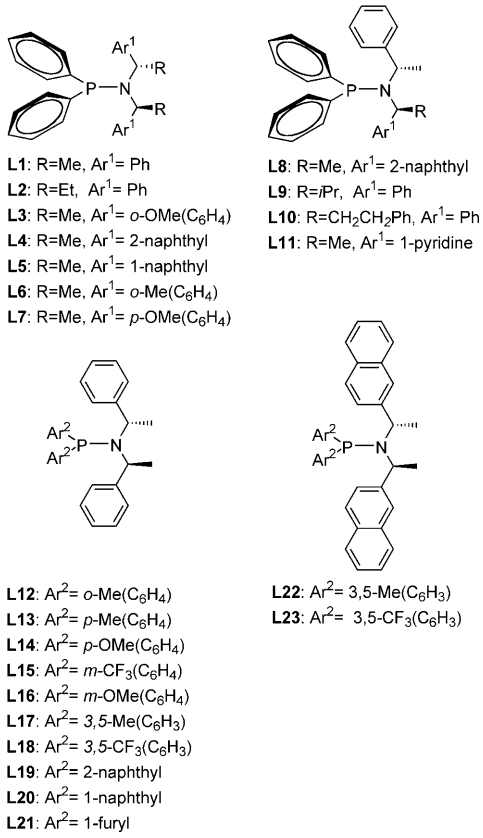


Figure 1. Variable-temperature ^{31}P NMR spectra of ligand **L22**-BH3 in [D_8]toluene.

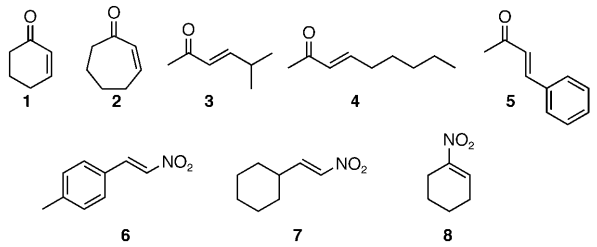
the multiplicity did not change over the temperature range of 25 °C (298 K) to −70 °C (203 K). However, by lowering the temperature below −70 °C, the singlet broadened and split into two signals with a coalescence temperature at −80 °C (193 K). Further cooling to −90 °C resulted in the generation of two resolved signals originating from two helical conformers in approximately 1:3.5 ratio. This slower interconversion of the two conformers should be ascribed to the increased rigidity of the borane complex.

Copper-catalysed asymmetric conjugate addition of R_2Zn: We first investigated the conjugate addition of diethyl zinc reagent to cyclic enones using the same conditions as those described previously[4b,5] with copper thiophene carboxylate (CuTC; 5 mol%) and chiral ligand (10 mol%; Scheme 1).



Scheme 1. SimplePhos ligands tested for conjugate addition.

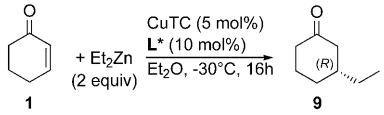
The cyclic and acyclic enones and nitroalkenes used for this study with R_2Zn are compiled in Scheme 2. All of them are commercially available except for the nitroalkene **7**, which was prepared according to the literature.[12] In the following study, the full screening of SimplePhos ligands is only described for cyclohexenone **1**. For the other Michael acceptors, we only summarised the interesting results. The full screening of ligands with all the substrates are reported in the Supporting Information.



Scheme 2. Michael acceptors used in this study.

Cyclohexenone **1** is the archetypical enone in the copper-catalysed ACA. With this substrate, we have tested all the synthesised ligands for the addition of Et_2Zn (Table 3). Among the variations on the amine part, ligands **L4**, **L22** and **L23** with Ar^1 = 2-naphthyl afforded the best results with complete conversions and very high enantioselectivities up to 95% *ee* (Table 3, entry 4). As we have observed previously for biphenol-based phosphoramidite ligands, an increase of the steric bulk on the amine favours the enantioselectivity.[13] But with a too sterically hindered Ar^1, such as the 1-naphthyl group in **L5** (entry 5), the enantiomeric excess decreased to 70%. Moreover, *ortho* substituents on this same aryl group on the amine part is not favourable. Indeed, ligands **L3** and **L6**, which respectively have a methoxy and methyl group, show lower results (entries 3 and 6). Concern-

Table 3. Addition of Et_2Zn to cyclohexenone catalysed by CuTC in the presence of various ligands.



Entry	Ligand	Conv. [%][a]	*ee* [%][b]
1	**L1**	97 (90)[c]	80 (83)[c]
2	**L2**	100	81
3	**L3**	100	63
4	**L4**	100 (100)[c]	95 (96)[c]
5	**L5**	100	70
6	**L6**	100	51
7	**L7**	100	88
8	**L8**	99	86
9	**L9**	100	24
10	**L10**	100	83
11	**L11**	60	2
12	**L12**	100	4
13	**L13**	100	67
14	**L14**	100	42
15	**L15**	100	90
16	**L16**	100	75
17	**L17**	100	73
18	**L18**	100	82
19	**L19**	100	56
20	**L20**	100	23
21	**L21**	100	75
22	**L22**	100	91
23	**L23**	100	95

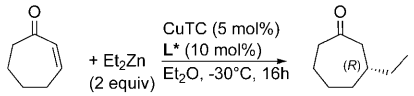
[a] Determined by GC–MS. [b] Determined by chiral GC. [c] Reaction was carried out at −10 °C.

ing the modification of the R^1 group, the replacement of the methyl (**L1**) by an ethyl group (**L2**) did not have a considerable effect (entries 1 and 2). On the amine part, the C_2 symmetry is not a requirement because ligand **L8**, on account of having two different R or Ar^1 groups (entry 8), was more efficient than the simple **L1**.

Concerning the diaryl scaffold, the first striking result showed that the bulkier, electron-rich substituent in the *ortho* position on the Ar^2 part on the phosphorus atom (**L12** and **L20**) was detrimental to enantioselectivity (Table 3, entries 12 and 20). The enantioselectivity also dropped using ligands **L13** and **L14** with an electron-donating group in the *para* position, such as methyl or methoxy moieties (entries 13 and 14). In contrast, the presence of a substituent in the *meta* position on Ar^2 seemed to improve the enantioselectivity. However, an electron-rich methoxy group (**L16**) afforded lower enantiomeric excess values than an electron-withdrawing group such as *m*-CF_3 (**L15**) (entries 15 and 16). This surprising electronic effect was not observed with phosphoramidite ligands. As we were hoping to increase the enantioselectivity by limiting the free rotation of aryl groups around the phosphorus atom, we investigated ligands **L17**–**L19** with more sterically hindered substituents: for example, with methyl and CF_3 groups in 3,5-positions or with Ar^2=2-naphthyl. Once again, electronic effects had a strong influence on the enantioselectivity. Ligand **L18** with an electron-withdrawing group (CF_3) gave better results than ligand **L17** with an electron-rich group (CH_3) (entries 17 and 18). On the other hand, when Ar^2=2-naphthyl, the system was too sterically hindered to enhance the enantioselectivity (entry 19). In some cases, we tried to perform the reaction at higher temperature (−10 °C) but enantioselectivities were almost the same (Table 3, entries 1 and 4).

The same observations were made with the cycloheptenone **2** (Table 4) but with slightly lower results in terms of enantioselectivity, although up to 95 % *ee* could be obtained with **L23** (Table 4, entry 5).

Table 4. Addition of Et_2Zn to cycloheptenone catalysed by CuTC in the presence of various ligands.



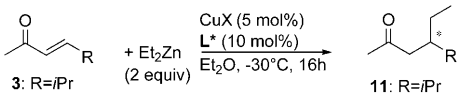
2 **10**

Entry[a]	Ligand	Conv. [%][a]	*ee* [%][b]
1	**L1**	100	67
2	**L4**	100 (100)[c]	92 (93)[c]
3	**L15**	100	90
4	**L22**	100	91
5	**L23**	100	95

[a] Determined by GC–MS. [b] Determined by chiral GC. [c] Reaction was carried out at −10 °C.

Then the challenge was to apply this methodology to other Michael acceptors such as acyclic enones and nitroalkenes. We first screened some of these ligands with 5-methyl-3-hexen-2-one (**3**) under the same experimental conditions and the results are summarised in Table 5. The test reaction for addition of Et_2Zn was realised with the most simple ligand, **L1**, in the presence of CuTC. In contrast to cyclic enone, low enantioselectivities were observed under these conditions (Table 5, entry 1). However, we chose to screen various copper sources with ligand **L1** and we managed to improve the enantiomeric excess with copper trifluoroacetylacetonate ($Cu(F_3acac)_2$) up to 58 % *ee* (entry 2). Then we applied this new condition to other ligands and the best result was obtained with ligand **L17** (Ar^2=xylyl), with up to 80 % *ee* (entry 4). Similar enantioselectivities of around 76 % *ee* were observed with ligands bearing a 2-naphthyl group on the amine moiety, **L4** and **L22** (entries 3 and 5). Ligand **L23**, which previously gave high enantiomeric excess, showed only 54 % *ee* (entry 6). On the aryl part, it seemed that steric hindrance overcame the beneficial electronic effects.

Table 5. Addition of Et_2Zn to various acyclic enones catalysed by copper in the presence of various SimplePhos ligands.



3: R=*i*Pr
4: R=C_5H_9
5: R=Ph

11: R=*i*Pr
12: R=C_5H_9
13: R=Ph

Entry	Substrate	CuX	Ligand	Conv. [%][a]	*ee* [%][b]
1[a]	3	CuTC	**L1**	99	32 (*R*)
2	3	$Cu(F_3acac)_2$	**L1**	100	58 (*R*)
3	3	$Cu(F_3acac)_2$	**L4**	100	75 (*R*)
4	3	$Cu(F_3acac)_2$	**L17**	96	80 (*R*)
5	3	$Cu(F_3acac)_2$	**L22**	100	77 (*R*)
6	3	$Cu(F_3acac)_2$	**L23**	94	54 (*R*)
7	4	CuTC	**L2**	100	52 (*R*)
8	4	CuTC	**L5**	100	52 (*R*)
9	5	CuTC	**L1**	100	0
10	5	CuTC	**L23**	100	68 (*S*)

[a] Determined by GC–MS. [b] Absolute configuration; determined by chiral GC.

Next we studied the addition of the diethyl zinc reagent to linear acyclic enone **4** catalysed by CuTC (Table 5, entries 7 and 8). Only some of the ligands were tested in this reaction but moderate enantioselectivity was obtained with ligands **L2** and **L5**, with up to 52 % *ee* (entries 7 and 8). The screening of a large range of copper salts to afford better results was unsuccessful.

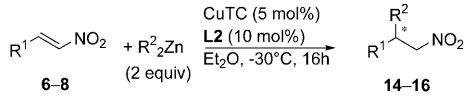
The last acyclic α,β-unsaturated ketone used in this study was benzalacetone (**5**). First, we tested some SimplePhos ligands under classical conditions. Ligand **L22** could catalyse the asymmetric conjugate addition of Et_2Zn with complete conversion and 68 % *ee* (Table 5, entry 10). Many ligands were unable to provide efficient asymmetric induction in this reaction. Therefore, we tested an array of different copper salts with ligand **L1**. A small improvement of enantioselectivity was observed with $[Cu(OTf)]_2{\cdot}C_6H_6$ (Tf=trifluoromethansulfonate). But after trying this new copper source for the addition of Et_2Zn to this substrate, we were

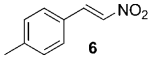
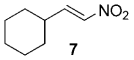
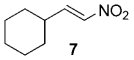
unable to increase the enantiomeric excess. Surprisingly, ligand **L22** catalysed the reaction with CuTC (68% *ee*) but not with $[Cu(OTf)]_2 \cdot C_6H_6$.

Finally, we envisaged another type of Michael acceptor such as nitroalkenes. *para*-Methylnitrostyrene (**6**) was chosen as the substrate because high enantioselectivity has been reported for the asymmetric conjugate addition of the diethyl zinc reagent with phosphoramidite-based ligands.[4b,14] Moreover, to see the influence of the substituent, an acyclic nitroalkene bearing an alkyl group (**7**) and a cyclic nitroalkene (**8**) were selected.

Classical conditions, with CuTC (5 mol%) and chiral ligand (10 mol%), were used at −30°C in Et_2O. Several SimplePhos ligands were screened, and the product formed by addition of Et_2Zn to substrate **6** gave the best enantiomeric excess (61%) with **L2** (Table 6, entry 1).

Table 6. Addition of R_2Zn to nitroalkenes catalysed by CuTC SimplePhos ligand **L2**.



Entry	Substrate	R^2	Adduct	Conv. [%][a]	*ee* [%][b]
1	 **6**	Et	**14**	100	61 (*S*)
2	 **7**	Et	**15a**	100	50 (*S*)
3	 **7**	Me	**15b**	100	89 (*S*)
4	 **8**	Et	**16**	100[c]	92 (*cis*)

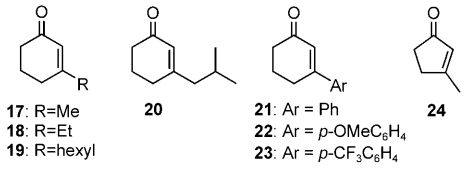
[a] Determined by GC–MS. [b] Absolute configuration; determined by chiral GC or supercritical fluid chromatography (SFC). [c] *cis*/*trans* 85:15.

We then applied this methodology to nitroalkene **7** and, as previously, ligand **L2** catalysed the reaction with full conversion but moderate enantiomeric excess (50% *ee*) (Table 6, entry 2). In addition, we also tried the addition of Me_2Zn to **7**. This was more challenging because it is known that dimethyl zinc is much less reactive than diethyl zinc. By combining this reagent with **L2**, the corresponding adduct was obtained with a remarkable 89% *ee* (entry 3).

Finally, the addition of Et_2Zn to the cyclic nitroalkene **8** gave the desired compound in full conversion and high enantioselectivity: up 92% *ee* for the *cis* product (entry 4). Unfortunately, Me_2Zn was not reactive enough to give the corresponding adduct of cyclic substrate **8**.

Copper-catalysed asymmetric conjugate addition of R_3Al reagents: Another more demanding copper-catalysed conjugate addition was tested: the addition of R_3Al to trisubstituted cyclic enones to induce the formation of stereogenic quaternary carbon centres. The synthesis of biologically active natural products and drugs bearing quaternary stereocentres still remains a highly demanding task.[15] Over the last few years, new methodologies for the construction of quaternary carbon centres have appeared in the literature.[16] Powerful catalytic methods using copper-catalysed asymmetric conjugate reactions were described with reactive substrates such as nitroalkenes[17] or doubly activated enones.[18] To avoid the problem of a lack of reactivity of β-trisubstituted enones, both our group[19] and those of Hoveyda[20] and Tomioka[21] have developed efficient catalyst systems that tolerate this type of substrate.

Trisubstituted α,β-unsaturated ketones used for this study are summarised in Scheme 3. Some of them were commercially available; the others were prepared according to literature procedures.[22]



Scheme 3. Trisubstituted enones used in this study.

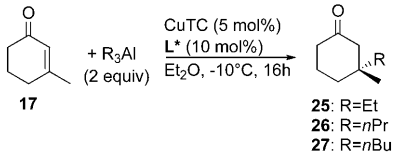
We first investigated the conjugate addition of Et_3Al to 3-methylcyclohexen-2-one (**17**). As we have recently reported, the best experimental conditions are to perform the reaction at −10°C in diethyl ether with 5 mol% CuTC and 10 mol% chiral ligand.[5] At a lower temperature (−30°C), some problems of conversion were observed and more than two equivalents of organometallic reagents were needed, yet this was without any improvement of the enantioselectivity. The results with all the ligands are compiled in Table 7.

As for conjugate addition of Et_2Zn, bulky groups on the amine part of the ligand such as the 2-naphthyl group (**L4** and **L22**) led to an increased enantioselectivity (up to 95% *ee*; Table 7, entries 4 and 22) except with ligand **L23** (entry 23), for which both conversion and enantioselectivity dropped. In contrast to the previous results obtained for the ACA of Et_2Zn, electron-withdrawing substituents R^3 on the diaryl group were not favourable. However, the bulky R part (**L2**) gave good enantiomeric excess (entry 2). As we have previously shown, ligand **L8** with a non-symmetric chiral amine (entry 8) gave a comparable enantiomeric excess (92% *ee*) to those obtained with **L1** and **L4** (90 and 93% *ee*; entries 1 and 4, respectively).

As previously observed, *ortho* substitution on the diaryl groups of the ligand is highly detrimental. Only 1% conversion was observed (Table 7, entry 8). On the other hand, the presence of an electron-donating group (methyl and methoxy) in the *para* position has a more positive effect and gave good enantiomeric excess (entries 9 and 10). However, a methoxy group in the *meta* position (**L16**) did not improve the enantioselectivity and even showed a deleterious effect (entry 16).

In contrast to dialkyl zinc species for conjugate addition, an electron-withdrawing CF_3 group in the *meta* position (**L15**) was not as good and it was even worse with two

Table 7. Addition of Et_3Al to 3-methyl-2-cyclohexenone (**17**) catalysed by CuTC in the presence of various SimplePhos ligands.



Entry	R	Ligand	Conv. [%][a] (yield [%])	*ee* [%][b]
1	Et	**L1**	85	90
2	Et	**L2**	100 (71)	93
3	Et	**L3**	98 (73)	86
4	Et	**L4**	100	93
5	Et	**L5**	99	70
6	Et	**L6**	100	66
7	Et	**L7**	100	88
8	Et	**L8**	100	92
9	Et	**L9**	87	20
10	Et	**L10**	100	90
11	Et	**L11**	48	10
12	Et	**L12**	1	–
13	Et	**L13**	100 (60)	90
14	Et	**L14**	44	91
15	Et	**L15**	82	80
16	Et	**L16**	100	27
17	Et	**L17**	100 (81)	92
18	Et	**L18**	3	24
19	Et	**L19**	100	92
20	Et	**L20**	34	27
21	Et	**L21**	100	74
22	Et	**L22**	91 (71)	95
23	Et	**L23**	85	51
24[c]	*n*Pr	**L22**	100 (52)	96
25[c]	*n*Bu	**L22**	100 (66)	95

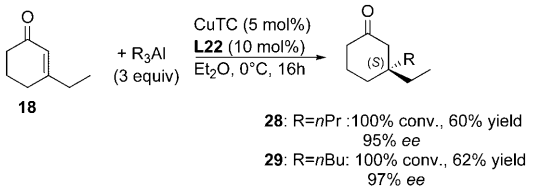
[a] Determined by GC–MS. [b] Determined by chiral GC. [c] Reaction was carried out at 0 °C with 3 equiv of R_3Al.

groups in this same position (**L18**; Table 7, entries 15 and 14). One of the best previous ligands, **L23**, showed lower enantiomeric excess for the addition of triethylaluminium to this substrate (entry 23).

Then, to enlarge the scope of organoaluminium reagents, we decided to use tri-*n*-butyl- and tri-*n*-propylaluminium, which are also commercially available at a low price. These types of reagent had never been used for the formation of quaternary carbon centres to substituted enones. After optimisation of the experimental conditions, we found that the reaction should be performed at higher temperature (0 °C) with three equivalents of nPr_3Al or nBu_3Al to get total conversion. As previously, the best ligand for addition of such a trialkylaluminium reagent is **L22**, with high enantioselectivities close to 96 % *ee* for the addition of nPr_3Al and 95 % *ee* with nBu_3Al (Table 7, entries 24 and 25).

The same procedure was applied for the ACA of nPr_3Al and nBu_3Al to 3-ethylcyclohexen-2-one (**18**; Scheme 4). Once again, ligand **L22** showed its efficiency with full conversion and high enantioselectivities up to 97 % *ee*.

The experimental conditions were further optimised by copper-catalysed asymmetric conjugate addition of various aluminium species to the bulkier cyclohexenone substrate,

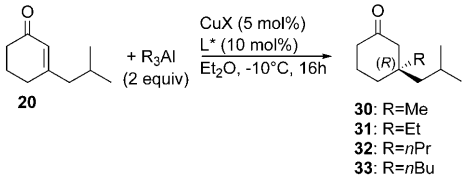


Scheme 4. ACA of R_3Al to ethylcyclohexen-2-one (**18**) catalysed by CuTC in the presence of ligand **L22**.

3-isobutylcyclohex-2-en-1-one (**20**) to determine the limits of our system. In this case, the results obtained with SimplePhos ligands gave better yield and enantioselectivities than with phosphoramidite counterparts.

We first envisaged the addition of a methyl group on **20** (Table 8). In the case of phosphoramidite ligands, Me_3Al gave better enantioselectivities than Et_3Al.[19b] To check if

Table 8. Addition of R_3Al to 3-isobutyl-2-cyclohexenone (**20**) catalysed by CuX in the presence of various SimplePhos ligands.



Entry	R	CuX	Ligand	Conv. [%][a] (yield [%])	*ee* [%][b]
1	Me	CuTC	**L1**	100	85
2	Me	$Cu(OAc)_2 \cdot H_2O$	**L1**	100	85
3	Me	$[Cu(OTf)]_2 \cdot C_6H_6$	**L1**	100	83.5
4	Me	$Cu(acac)_2$	**L1**	100 (81)	85.5
5	Me	$Cu(acac)_2$	**L2**	97 (79)	95
6	Me	$Cu(acac)_2$	**L17**	100 (90)	96
7	Me	$Cu(acac)_2$	**L19**	97 (78)	94
8	Me	$Cu(acac)_2$	**L22**	90	97
9	Et	CuTC	**L1**	98 (77)	94
10	Et	CuTC	**L4**	75 (60)	95
11	Et	CuTC	**L17**	10 (85)	96
12	Et	CuTC	**L22**	>99 (66)	98.6
13[c]	*n*Pr	CuTC	**L22**	79 (55)	97
14	*n*Bu[c]	CuTC	**L22**	100 (71)	96

[a] Determined by GC–MS. [b] Determined by chiral GC. [c] Reaction was carried out at 0 °C with 3 equiv of R_3Al.

this was also the case with SimplePhos ligands, we tried to add various groups such as methyl, ethyl, *n*-propyl and *n*-butyl. Surprisingly, the reaction of Me_3Al with ligand **L1** gave a moderate 85 % *ee* (Table 8, entry 1). Some optimisations of the experimental conditions were made by changing the copper salts. Copper acetylacetonate appeared to be an optimum one (entry 4). Then other ligands were tested under these new optimised conditions. This test substrate **20** gave at best 98 % *ee* with a biphenol-based phosphoramidite ligand.[19c] Three SimplePhos ligands, **L2** and, again, **L17** and **L22**, gave respectively close enantiomeric excess values from 95 to 97 % (entries 5, 6 and 8). Once again, the bulkier ligand **L22** proved its efficiency for the formation of quater-

nary carbon centres. This was not the case for all ligands because some of them showed a deleterious effect both on conversions and enantioselectivities (for example, with groups in *meta* positions for the diaryl part). To our surprise, ligand **L19**, which generally did not give good results, catalysed the reaction with full conversion and high enantiomeric excess up to 94% (entry 7).

Next the scope of the aluminium reagents was studied. After some optimisations, we found that 5 mol% CuTC and 10 mol% chiral ligand in diethyl ether offered the best conditions (Table 8). With Et_3Al, the first attempt with the simple ligand **L1** gave both high conversion and 94% enantioselectivity (Table 8, entry 9). Moreover, ligands **L4** (2-naphthyl group on the amine part) and **L17** (xylyl groups on P) also gave good results (entries 10 and 11). However, ligand **L22**, which is a mix of these two best ligands, improved the results with 98.6% *ee* (entry 12). For all the other ligands, the reaction gave good enantioselectivities but low conversions. The addition of a propyl chain to this substrate worked perfectly with ligand **L22**, with 55% isolated yield and 97% *ee* (entry 13). In the case of enone **20**, SimplePhos ligands were very efficient for the addition of Et_3Al, nPr_3Al, and nBu_3Al species to this bulky trisubstituted cyclohexenone, clearly better than phosphoramidite-type ligands, which gave no conversion with Et_3Al.[19c]

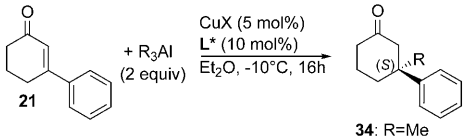
Interestingly, the absolute configuration of the adducts obtained by the addition of Me_3Al, Et_3Al, nPr_3Al or nBu_3Al was the same as with a less bulky substrate (methylcyclohexenone **17**). Thus the ACA of R_3Al showed that the face selectivity is the same whatever the R substituent (small or bulky).

3-Arylcyclohex-2-en-1-ones **21–23** were quite problematic substrates since both steric and electronic effects were combined. In our preliminary study,[5] we reported that 3-phenylcyclohex-2-en-1-one (**21**) gave the desired adduct with Me_3Al using CuTC as the copper salt with **L17**, and did so in good conversion and with 86% *ee*. Having many new ligands in hand, we screened all our SimplePhos ligands to find the best one (only a selection appear in Table 9). In addition, we also tested Et_3Al, nPr_3Al and nBu_3Al.

Ligand **L22** gave similar enantioselectivity as **L17** (up to 87% *ee*) (Table 9, entry 7), even if the conversion was not full. Other ligands did not perform well, with either low conversions and enantiomeric excesses (not shown in the table), except for ligands **L1**, **L4**, **L8**, **L13** and **L16**, which gave quite good conversions and *ee* values close to 75–81%.

We then investigated the addition of Et_3Al on this same substrate **21**, first with optimised experimental conditions. Thus, CuTC and ligand **L1** catalysed the reaction with 85% conversion and 81% *ee* (Table 9, entry 8). The same result was obtained at a higher temperature (entry 9). Variation of the copper salts allowed us to find that $[Cu(CH_3CN)_4]BF_4$ gave complete conversion, but the enantioselectivity was lower (entry 10). $Cu(acac)_2$ gave a better enantiomeric excess (entry 11) but using $Cu(OAc)_2{\cdot}H_2O$ improved the conversion with the same enantioselectivity (entry 12). Consequently, all the ligands were tested under these new conditions. Once again, ligand **L22** with the amine 2-naphthyl moiety gave the best results of up to 90% *ee* (entry 15). Ligands **L4** and **L17** also showed high conversions and good *ee* values up to 86% (entries 13 and 14). But for the addition of a longer alkyl chain (propyl or butyl), ligand **L17** was the best one with 88% *ee* in the both cases (Table 9, entries 16 and 17).

Table 9. Addition of R_3Al to 3-phenyl-2-cyclohexenone (**21**) catalysed by copper salt in the presence of various SimplePhos ligands.



34: R=Me
35: R=Et
36: R=*n*Pr
37: R=*n*Bu

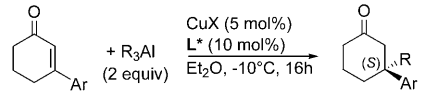
Entry	R	CuX	Ligand	Conv. [%][b] (yield [%])	*ee* [%][c]
1	Me	CuTC	**L1**	98	76
2	Me	CuTC	**L4**	69 (63)	81
3	Me	CuTC	**L8**	86 (63)	81
4	Me	CuTC	**L13**	94	75
5	Me	CuTC	**L16**	79	71
6	Me	CuTC	**L17**	98 (71)	86
7	Me	CuTC	**L22**	74 (61)	87
8	Et	CuTC	**L1**	85	81
9[a]	Et	CuTC	**L1**	84	81
10	Et	$[Cu(CH_3CN)_4]BF_4$	**L1**	>99	75
11	Et	$Cu(acac)_2$	**L1**	94	82
12	Et	$Cu(OAc)_2{\cdot}H_2O$	**L1**	98	81
13	Et	$Cu(OAc)_2{\cdot}H_2O$	**L4**	95 (70)	86
14	Et	$Cu(OAc)_2{\cdot}H_2O$	**L17**	73 (64)	86
15	Et	$Cu(OAc)_2{\cdot}H_2O$	**L22**	95 (69)	90
16[d]	*n*Pr	CuTC	**L17**	97 (63)	88
17[d]	*n*Bu	CuTC	**L17**	79 (56)	88

[a] Reaction was carried out at 0°C. [b] Determined by GC–MS. [c] Determined by chiral GC. [d] Reaction was carried out at 0°C with 3 equiv of R_3Al.

To check the influence of the electronic effects on the β position of the enone, copper-catalysed asymmetric additions of trialkylaluminium reagents were carried out on two other 3-arylcyclohexen-2-ones, **22** and **23**, with electron-withdrawing or electron-donating groups. For this study, we tested just four different ligands (Table 10).

First, we investigated the addition of Me_3Al to **22** bearing an electron-donating OMe group in the *para* position. The classical conditions with CuTC seemed to be the best and the desired adduct could be obtained with 81% *ee* and good yield with **L17** (entry 2). This result was much better than those obtained with phosphoramidite-based ligands (20% conversion, 60% *ee*).[19c] Et_3Al was tested with CuTC; however, low conversion was observed (Table 10, entry 4). We have already seen that copper acetate monohydrate could lead to increased reactivity (see Table 9). Therefore, the three other ligands were tested with these new conditions and good conversion and enantioselectivities were obtained with **L4**, with up to 90% *ee* (Table 10, entry 6). Ligand **L22** gave quite similar enantioselectivity but lower conversion (89%; entry 8).

Table 10. Addition of R_3Al to 3-aryl-2-cyclohexenones **22** and **23** catalysed by copper in the presence of various SimplePhos ligands.



22: Ar =*p*-OMe(C_6H_4)
23: Ar =*p*-CF_3(C_6H_4)

38: Ar =*p*-OMe(C_6H_4), R= Me
39: Ar =*p*-OMe(C_6H_4), R=Et
40: Ar =*p*-CF_3(C_6H_4), R=Me
41: Ar =*p*-CF_3(C_6H_4), R=Et

Entry	Substrate	R	CuX	Ligand	Conv. [%][a] (yield [%])	*ee* [%][b]
1	**22**	Me	CuTC	**L1**	91	73
2	**22**	Me	CuTC	**L17**	100 (72)	81
3	**22**	Me	CuTC	**L22**	68	79
4	**22**	Et	CuTC	**L1**	48	85
5	**22**	Et	$Cu(OAc)_2{\cdot}H_2O$	**L1**	80	82
6	**22**	Et	$Cu(OAc)_2{\cdot}H_2O$	**L4**	100 (71)	90
7	**22**	Et	$Cu(OAc)_2{\cdot}H_2O$	**L17**	71	89
8	**22**	Et	$Cu(OAc)_2{\cdot}H_2O$	**L22**	89 (60)	90
9	**23**	Me	$Cu(OAc)_2{\cdot}H_2O$	**L22**	100 (79)	91
10	**23**	Et	CuTC	**L22**	100 (73)	93

[a] Determined by GC–MS. [b] Determined by chiral GC.

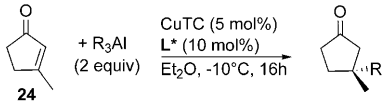
Then we tested the addition of Me_3Al to enone **23** bearing an electron-withdrawing group (CF_3) in the *para* position. Copper acetate monohydrate was the best copper salt and both good conversion and enantioselectivity were obtained with ligand **L22**, with up to 91% *ee* (Table 10, entry 9). Biphenol phosphoramidite-based ligand gave only 93% conversion and a moderate enantiomeric excess of 66%.[19c] The addition of Et_3Al showed also full conversion and high *ee* values of up to 93% with the same ligand (entry 10).

As expected, substrate **23** bearing an electron-withdrawing group on the aromatic moiety had a higher reactivity than **22** bearing an electron-donating group in the same *para* position. Phenylcyclohexenone **21** presented an intermediate reactivity; this is because electron-withdrawing groups tend to decrease the electronic density of the β position and make it more electrophilic and reactive. This remark is true for the addition of Me_3Al. In the case of the addition of Et_3Al, we only observed an improvement of the conversion.

Finally, an even more challenging substrate was 3-methylcyclopenten-2-one (**24**), representative of five-membered ring systems.[19b] For the first attempt, we tested the simple ligand **L1** under the same experimental conditions described above. Moderate enantioselectivity was observed (up to 58% *ee*), although with good conversion, whereas the six-membered ring system gave better results both in terms of conversion and enantioselectivity with the same ligand (Table 7, entry 1 versus Table 10, entry 1). We extensively tried to optimise these conditions but whatever the copper salt, the solvent, the catalyst loading or the temperature, we did not manage to improve these results. Consequently, we have screened some ligands to find a better one (Table 11).

Once again, the ligand with a 2-naphthyl group on the amine scaffold, **L4**, gave the best result, even if we did not manage to obtain more than 77% *ee* (Table 11, entry 2).

Table 11. Addition of Et_3Al to 3-methyl-2-cyclopentenone (**24**) catalysed by CuTC in the presence of various SimplePhos ligands.



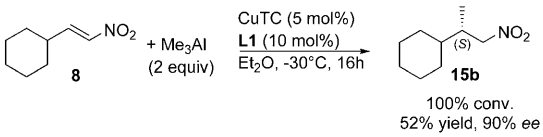
42: Et
43: *n*Bu

Entry	R	Ligand	Conv. [%][a] (yield [%])	*ee* [%][b]
1	Et	**L1**	97	58
2	Et	**L4**	100	77
3	Et	**L8**	100	71
4	Et	**L19**	93	57
5	*n*Bu	**L4**	27	75
6	*n*Bu	**L22**	100 (65)	74

[a] Determined by GC–MS. [b] Determined by chiral GC.

The second best, **L8**, was also the ligand with a non-C_2-symmetric amine (entry 3). But bulkier substituents on the diaryl part seemed to be very detrimental; a decrease in enantioselectivity was observed with ligand **L19** (entry 4). Moreover, electronic effects on the diaryl part did not have a strong influence on the enantioselectivity. The amine part was more important for the control of the catalytic system. Another aluminium reagent, nBu_3Al, was also tested. Using the best conditions with ligand **L4**, the adduct **43** was obtained in low conversion but with 75% *ee* (entry 5). After screening some ligands, we found that ligand **L22**, which was inefficient for the addition of Et_3Al (not shown in Table 11), gave the desired compound with complete conversion and the same enantiomeric excess value (74%; entry 6). This result shows that the length of the alkyl chain does not have any influence on the enantioselectivity.

It was reported that Me_3Al was a better reagent than Me_2Zn for the ACA to nitroalkene with phosphoramidite ligands.[14] To test if this was also the case with SimplePhos ligands, the addition of the Me_3Al reagent to nitroalkene **8** was attempted (Scheme 5). Using the simplest ligand, **L1**,

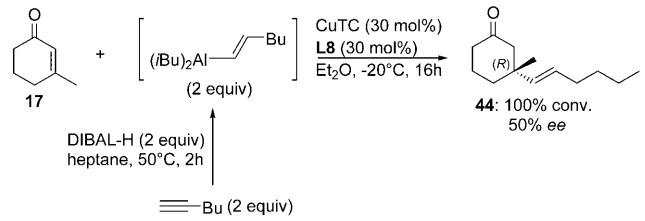


Scheme 5. Addition of Me_3Al to nitroalkene **8** catalysed by CuTC and SimplePhos ligand **L1**.

we could obtain the adduct with the same enantiomeric excess value as with Me_2Zn (90 versus 89% *ee* with Me_2Zn).

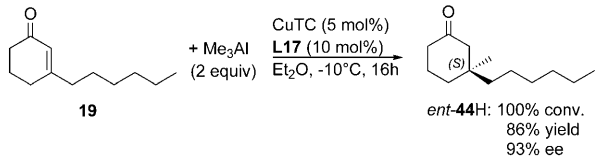
To enlarge the scope of reaction, we examined a tandem hydroalumination–ACA reaction (Scheme 6).[19c] As with phosphoramidite ligands, we expected the preferential transfer of the vinylic group. After some experimental optimisations, the desired product **44** was obtained in full conversion but with only 50% *ee* with ligand **L8**. No transfer of the *i*Bu group was observed.

To ascertain if the face selectivity of the transfer was the same as usual, we hydrogenated **44** to **44**H (H_2, Pd/C,



Scheme 6. Tandem hydroalumination–ACA hydrogenation reaction (DIBAL-H = diisobutylaluminium hydride).

MeOH). In turn, *ent*-**44**H could be obtained by the conjugate addition of Me_3Al to **18** bearing a long alkyl chain in the β position (Scheme 7).

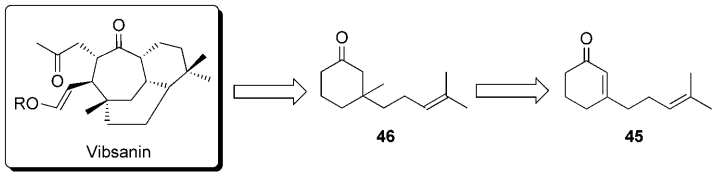


Scheme 7. Addition of Me_3Al to 3-hexyl-2-cyclohexenone (**19**) catalysed by CuTC and SimplePhos ligand **L17**.

The adduct *ent*-**44**H was obtained with high yield and enantioselectivity (up to 93% *ee*) with ligand **L17** and the absolute configuration of *S* was assigned. This was determined by analogy with the general trend observed for the adducts of R_3Al to 3-methylcyclohexen-2-one (**17**; see Table 7). Thus, the alkenylalane attacked with the same facial selectivity as Me_3Al and Et_3Al when using substrates **17**, **18**, **20** and **24**.

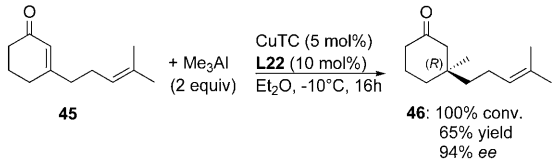
Synthetic applications: The asymmetric conjugate addition is an essential method for the specific introduction of a hydrocarbon unit to the β position of a carbonyl function. Furthermore, the eminent nucleophilicity of the metal enolate intermediate allows for reaction with various electrophiles, thereby affording the α,β-vicinal structural modification of enones and providing a powerful tool for the synthesis of complex molecules.

To illustrate these two aspects, we have applied our methodology to create stereogenic quaternary carbon centres for the preparation of key intermediates in the synthesis of natural products. Firstly, we were interested in the formation of product **46** in an enantio-enriched version (Scheme 8), which is an intermediate for the synthesis of several natural products such as the Vibsane family,[23a–e] isolated from *Viburnum awabuki*, the axane family[23f] or the ambra derivatives.[23g] All these previous syntheses were described in a racemic version.



Scheme 8. Retrosynthesis.

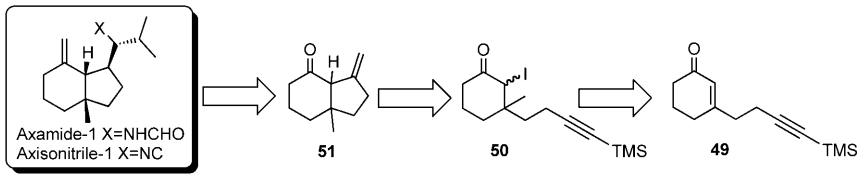
The synthesis of product **45** was prepared according to the usual procedure, by addition of the corresponding Grignard reagent to ethoxycyclohexenone with 86% yield (see the Supporting Information). Finally, the ACA of the trimethylaluminium reagent to enone **45** catalysed by copper thiophene carboxylate in the presence of **L22** allowed the formation of the chiral adduct **46** in 65% yield and 94% *ee* (Scheme 9).



Scheme 9. Synthesis of **46**.

Another interesting target for natural product synthesis has recently been described. Combining ACA with R_3Al and α iodination of trisubstituted adducts, we have finally envisaged the formation of a chiral key intermediate for the synthesis of axane derivatives, which were isolated from the marine sponge *Axinella cannabia*. The synthesis of such natural products has been reported in a racemic version.[24]

The proposed sequential retrosynthesis involves the bicyclic compound **51**, which is easily prepared by radical cyclisation of the intermediate **50**.[24] This could be obtained by tandem ACA of Me_3Al with a SimplePhos ligand to the trisubstituted cyclic enone **49** and then an α iodination of the corresponding enol acetate (Scheme 10).



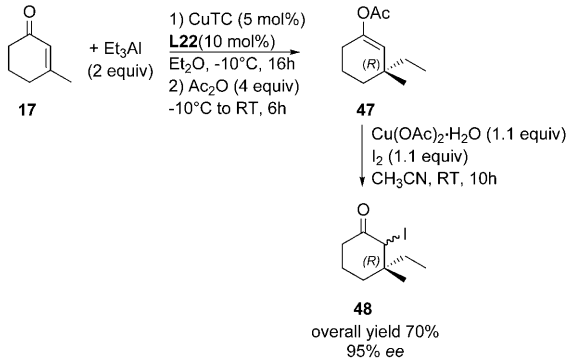
Scheme 10. Retrosynthesis.

We have previously described the formation and the use of aluminium enolates generated from the ACA of R_3Al with a phosphoramidite ligand to form the corresponding enol silyl ethers and acetates.[19a] As it was not possible to functionalise directly the α position of the aluminium enolate, probably due to the strong bond between the alumini-

um and the oxygen atom, we have envisaged the α halogenation of the adduct starting from the corresponding enol acetate **47**. To avoid any problems with the alkyne, a test reaction was done by ACA of the Et_3Al reagent to 3-methylcyclohexenone (**17**) followed by trapping of the corresponding aluminium enolate with Ac_2O.

Many methods have been tested for the α iodination, and we chose a modified procedure developed by Cort[25] using Cu^{II} salt and iodine as reagents in acetonitrile at room temperature.

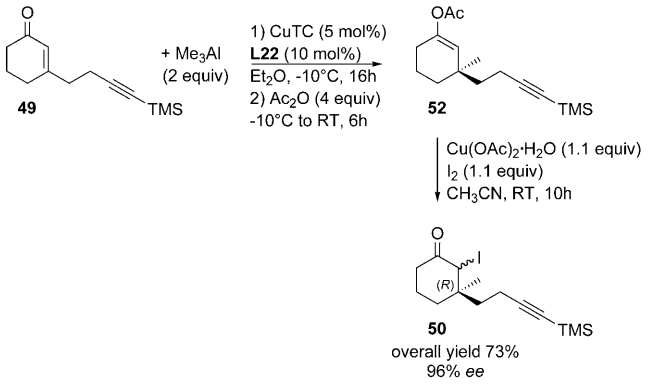
The corresponding adduct **48** was obtained in a good overall yield (70%) and 95% *ee* (Scheme 11). It is important to note that no loss of enantioselectivity was observed in comparison with the corresponding hydrolysed adduct (see Table 7, entry 22).



Scheme 11. α-Iodination of the adduct **48**.

The synthesis of product **49** was prepared according to the classical procedure by addition of the corresponding Grignard reagent to ethoxycyclohexenone, which gave 71% yield (see the Supporting Information).

Then product **49** could undergo the asymmetric conjugate addition of Me_3Al catalysed by CuTC and the most efficient ligand, **L22**. Keeping in mind that no racemisation of the chiral centre occurred during the formation of the enol acetate nor during the α iodination, the enantiomeric excess was measured just before quenching the aluminium enolate with Ac_2O. For reasons of chiral separation, the de-silylated corresponding adduct gave 96% *ee* (Scheme 12). The absolute configuration was determined on the corresponding saturated product, obtained after hydrogenation, and the methyl group came, as usual, from the back face of the substrate. Then, after quenching the aluminium enolate with acetic anhydride, the enol acetate **52** could be reacted with iodine in presence of a stoichiometric amount of copper acetate to allow the formation of the iodo adduct **50** with 73% overall isolated yield. Finally, as described in the literature,[24] we could envisage a radical cyclisation to afford the bi-cyclic product **51**. It is interesting to note that the iodination procedure did not interfere with the triple bond, nor with the trimethylsilyl group.



Scheme 12. Synthesis of **50**.

Conclusion

In summary, we have described a series of versatile new phosphorus ligands based on the induced helicity of a diaryl part and C_2-symmetric chiral amine. In many cases, some ligands could provide high enantioselectivities, except for the copper-catalysed addition of the Et_2Zn reagent to acyclic enones and nitroalkenes, for which only moderate *ee* values were obtained.

Concerning the formation of stereogenic quaternary carbon centres by addition of trialkylaluminium species, some ligands, and particularly **L22**, afforded much better results than the parent phosphoramidite-based ligand and sometimes the best reported in the literature. Ligand **L22** showed generally high enantioselectivity on a large scope of substituted enones and seemed to be an optimal ligand for this study. Theoretical studies are underway to gain a deeper insight into the importance of the helicity of the diaryl part on the phosphorus atom.

Finally, SimplePhos ligand **L22** showed its efficiency for the formation of chiral intermediates in the synthesis of natural products.

Experimental Section

Full experimental details are provided in the Supporting Information (111 pages).

Typical procedure for ligand synthesis

Pathway 1: *n*BuLi (solution in hexane, 1 equiv) was added dropwise to a stirred solution of amine (1 equiv) in THF at −78°C. The reaction mixture was stirred at −78°C for 10 min, then allowed to warm up to room temperature. After stirring for 2 h, the mixture was cooled to −78°C and a solution of Ph_2PCl (1 equiv) in THF was slowly added dropwise. The reaction mixture was allowed to warm to room temperature and was stirred overnight. A solution of dimethylsulfide complex (2 equiv) was added dropwise at room temperature. The reaction was stirred overnight at this temperature. Then the reaction mixture was concentrated under reduced pressure. The desired product was purified by flash chromatography on neutral alumina with toluene as eluent.

Pathway 2: A solution of amine (1 equiv) in THF was added to a stirred mixture of Et_3N (5 equiv) and PCl_3 (1 equiv) at 0°C in THF under a nitrogen atmosphere, and the reaction mixture was stirred at room temper-

ature for 4 h. Then, the solution was cooled to −30 °C and a solution of Grignard reagent (3 equiv) was added slowly. The reaction mixture was allowed to warm at room temperature and then was heated to reflux overnight. Then, the solution was directly evaporated under vacuum. The product was purified by filtration on neutral alumina under an inert atmosphere.

Then, under an inert atmosphere, free ligand was dissolved in dry THF and a solution of dimethylsulfide complex (2 equiv) was added dropwise at room temperature. The reaction was stirred overnight at this temperature. Then the reaction mixture was concentrated under reduced pressure. The desired product was purified by flash chromatography on neutral alumina with toluene as eluent.

Typical procedure for ligand deprotection: Phosphine borane ligand (1 equiv) was dissolved in diethyl ether under a nitrogen atmosphere and a solution of morpholine (10 equiv) was added at room temperature. The solution was stirred at this temperature for 2 d.

After complete deprotection, the solution was filtered on neutral alumina under a nitrogen atmosphere and with toluene as eluent.

Typical procedure for 3-substituted enone synthesis: A flame-dried flask was charged with Grignard reagent (2.0 equiv) and cooled to 0 °C. Then 3-ethoxycyclohex-2-en-1-one (50 mmol) in THF (40 mL) was added dropwise. Once the addition was complete, the reaction mixture was left at room temperature until complete disappearance of the starting material. The reaction was hydrolysed by the addition of aqueous sulfuric acid (5% w/w). Et_2O (50 mL) was added and the aqueous phase was separated and extracted further with Et_2O (3×20 mL). The combined organic fractions were washed with $NaHCO_3$, brine and water, dried over Na_2SO_4, filtered and concentrated in vacuo. The oily residue was purified by flash chromatography on silica gel (pentane/Et_2O 5:1).

Typical procedure for enantioselective copper-catalysed conjugate addition with diethyl zinc: A solution of CuTC (0.025 mmol) and chiral ligand (0.05 mmol) in dry diethyl ether (2 mL) was stirred for 30 min at room temperature and then cooled to −30 °C. Diethyl zinc (1 mL, 1 M in hexane) was slowly added to the reaction mixture and the solution was stirred for 15 min at the same temperature. Michael acceptor (0.5 mmol) was then added dropwise in 1 min. The reaction mixture was stirred at −30 °C overnight before being quenched by MeOH/saturated aqueous NH_4Cl solution. Enantiomeric excess was determined by chiral GC.

Typical procedure for enantioselective copper-catalysed conjugate addition with trialkylaluminium reagent: A flame-dried Schlenk tube was charged with copper (5 mol%) and the ligand (10 mol%). Diethyl ether (1 mL) was added and the mixture was stirred at room temperature for 30 min. Then the Michael acceptor (0.5 mmol) in ether (1 mL) was added at room temperature and the reaction mixture was stirred for a further 5 min before being cooled to −10 °C. Then trialkylaluminium (2 equiv) was introduced dropwise over 1 min. Once the addition was completed, the reaction was left at −10 °C overnight. The reaction was hydrolysed by the addition of MeOH followed by saturated aqueous NH_4Cl solution. Enantiomeric excess was determined by chiral GC.

Tandem hydroalumination—ACA procedure: A 1 N solution of diisobutylaluminium hydride in *n*-heptane (1 mmol, 1 mL) was added to 1-hexyne (1 mmol, 88 μL) while maintaining the temperature below 40 °C. When the initial exothermic reaction had subsided, the reaction mixture was heated for 2 h at 50 °C. The vinylalane formed was used in solution in heptane. A flame-dried Schlenk tube was charged with CuTC (28.8 mg, 30 mol%) and the chiral ligand **L8** (68.9 mg, 30.0 mol%). Dry Et_2O (1 mL) was added and the mixture was stirred at room temperature for 20 min. Then, the reaction mixture was cooled to −20 °C and the freshly prepared vinylalane in solution in heptane was introduced dropwise over 1 min. After 15 min at this temperature, the 3-methylcyclohexenone (48 μL, 0.5 mmol) in Et_2O (1 mL) was added dropwise and, once the addition was complete, the reaction mixture was left at −20 °C overnight. The reaction was hydrolysed by the addition of MeOH at −30 °C, followed by 2 N HCl (3 mL) at room temperature. Diethyl ether (10 mL) was added and the aqueous layer was separated and extracted further with diethyl ether (3×3 mL). The combined organic fractions were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo.

Finally, the corresponding adduct was hydrogenated with palladium on charcoal in MeOH at room temperature over 2 d to afford the adduct **44**H after filtration on Celite.

Acknowledgements

The authors thank the Swiss National Research Foundation (grant no. 200020-113332) and COST action D40 (SER contact no. C07.0097) for financial support, as well as BASF for the generous gift of chiral amines, Stefan Kerhli for a generous gift of trisubstituted enones and Stephane Rosset for his help with chiral separations.

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Received: June 10, 2009
Published online: August 28, 2009

