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New bidentate chiral phosphoramidites in copper-catalyzed asymmetric 1,4-addition of diethylzinc to cyclic α,β-enones: enantioselective tandem 1,4-addition-aldol reactions with 2-cyclopentenone

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Abstract—New bidentate phosphoramidites were prepared starting from α,α,α′,α′-tetraphenyl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol (TADDOL) or 1,1′-bi-2-naphthol (BINOL) and either 1,2-ethylene- or 1,3-propylenediamine *N*,*N*′-disubstituted with achiral or chiral groups. The use of these ligands in the copper-catalyzed enantioselective conjugate addition of diethylzinc to 2-cyclohexenone and 2-cyclopentenone afforded products with e.e.s of up to 89 and 83%, respectively.

1. Introduction

In recent years considerable progress has been achieved in the development of catalytic versions of the synthetically important[1] enantioselective 1,4-addition of organometallic reagents to α,β-unsaturated compounds,[2–4] especially in the case of the copper-mediated conjugate addition of organozinc reagents to enones. Among the different chiral ligands proposed for this purpose the phosphoramidites **1a, 1b** and **1c**, introduced by us,[5,6] have proven highly effective, with ligand **1a** (Fig. 1) allowing virtually complete stereocontrol in the reaction of (functionalized) dialkylzinc R_2Zn compounds with six-, seven- and eight-membered 2-cycloalkenones,[7] hence, opening a direct route to homochiral products containing cyclohexane and larger rings in their structure.[8] The addition of organozinc reagents to 2-cyclopentenone was more difficult to achieve. Surprisingly, the use of the BINOL derived phosphoramidite **1a** resulted in very low diastereoselectivity (10% e.e.)[6,8a] with this enone. On the other hand, cyclopenten-3,5-dione monoacetals, highly functionalized 2-cyclopentenone derivatives, were successfully used (e.e.s of up to 97%) in the conjugate addition–aldol reaction with dialkylzincs in the presence of aldehydes using ligand **1a**.[9] Employing TADDOL-derived[10] ligands such as **2**, we achieved e.e.s of up to 62%, in the presence of molecular sieves (MS), using 2-cyclopentenone as substrate.[11] Chan[12] obtained 89% e.e. in the 1,4-addition of diethylzinc to 2-cyclopentenone using the BINOL-based diphosphite **3**, whereas Pfaltz[13] enhanced the enantioselectivity further to 94% using phosphite **4a** containing a chiral oxazoline group. Recently Hoveyda[14] reported e.e. values of up to 97% using a chiral peptide-based phosphine ligand **4b** in the catalytic 1,4-addition with diethylzinc to 2-cyclopentenone.

In the continuing pursuit to develop effective ligands for the asymmetric conjugate addition to enones in particular 2-cyclopentenones and realizing that most of the phosphanes successfully employed in asymmetric catalysis are of the bidentate type,[15] we focussed on the screening of new bidentate phosphoramidites. In this respect, it is worth noting that early observations from our group demonstrated that Cu(I) can accommodate up to three monodentate ligands **1b**[5] and further experimental evidence actually points to the presence of more than one ligand bound to the copper ion during the reaction.[16] In view of the present lack of detailed

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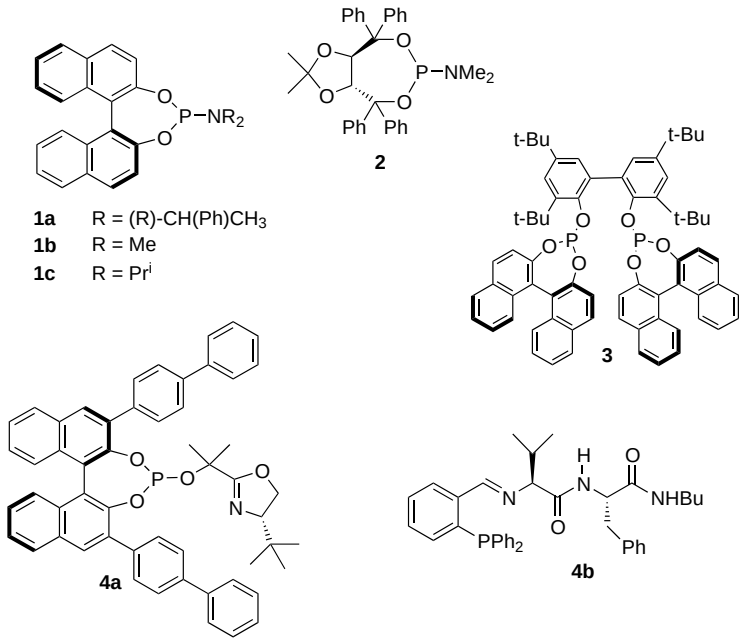


Figure 1. Effective chiral ligands for the copper-catalyzed conjugate addition of R_2Zn to cyclic enones.

knowledge of the actual catalytic system, which prevents a fully rational approach to the design of chiral ligands, several inherent aspects of the reaction were addressed in the course of this investigation: encompassing the importance of the bridge length and the nature of the bridge between the phosphoramidite moieties, TADDOL versus BINOL chiral backbone effectiveness, effect of steric hindrance and chirality of the nitrogen substituents. Herein, we disclose the results of this study of the asymmetric conjugate addition of diethylzinc to 2-cyclopentenone and 2-cyclohexenone in a tandem 1,4-addition–aldol protocol. Remarkable improvements in the enantioselectivity of the reactions of five-membered cyclic enones were seen using bidentate phosphoramidite ligands.

2. Results

2.1. Synthesis of the ligands

The new bidentate phosphoramidites **8** and **9** were prepared in 40–60% isolated yields, according to the general procedure already applied to the synthesis of **9a**,[5] by reacting the enantiomerically pure chlorophosphites **5** or **6** with the appropriate 1,2- or 1,3-diamines **7a**–**7e** in toluene in the presence of triethylamine (Scheme 1).

The ligands were purified by chromatography. The MS and spectroscopic data of the new ligands were in accordance with their proposed structures; in particular ^{31}P NMR chemical shifts closely matched those of the corresponding monomeric phosphoramidites (Section 5).

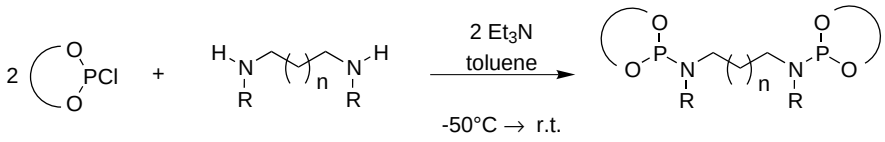
2.2. Asymmetric conjugate addition of Et_2Zn to 2-cyclohexenone

TADDOL and BINOL derived bidentate ligands **8a**–**8b** and **9a**–**9g** were first screened in the Cu-catalyzed addition of diethylzinc to 2-cyclohexenone **10.** Complete chemoselectivity was found, affording 3-ethylcyclohexanone **11** in almost quantitative yield. Unless noted otherwise, the conditions adopted were those of Scheme 2, i.e. reaction at −35°C, with 0.2 M enone **10** in toluene, 1.2 mol% $Cu(OTf)_2$ and a 1.1:1 ligand to copper ratio.

The results of the catalytic runs with the various bidentate ligands are collected in Table 1.

2.3. Tandem asymmetric conjugate addition–aldol reaction of Et_2Zn to 2-cyclopentenone

As conjugate addition of R_2Zn reagents to 2-cyclopentenone commonly results in low yields, the newly synthesized TADDOL and BINOL phosphoramidites **8a**–**8b** and **9b**–**9g**, as well as the previously reported ligand **9a**,[5] were examined in the tandem conjugate addition–aldol reaction of diethylzinc with 2-cyclopentenone **12** in the presence of benzaldehyde **13** (Scheme 3). Adopting this protocol, ratios of the *trans-erythro*:*trans-threo* aldol products **14**, ranging from 45:55 to 35:65, were isolated in 75–85% yield. PCC oxidation of **14** afforded the β-diketone **15** that was subjected to HPLC analysis to assess the enantiomer composition (Scheme 3).[11] Unless indicated otherwise, the conditions employed were those shown in Scheme 3, i.e. reaction at −35°C, with 0.2 M enone **12** and aldehyde **13** in toluene, 1.2 mol% $Cu(OTf)_2$ and a 1.1:1 ligand to copper ratio.



	R	n	diamine	Phosphoramidite
(R,R)-**5**	Me	0	**7a**	**8a**
	Me	1	**7b**	**8b**
(R)-**6**	Me	0	**7a**	**9a**
	Me	1	**7b**	**9b**
	Pr^i	1	**7c**	**9c**
	Me, Ph	0	**7d**	**9d**
	Me, Ph	1	**7e**	**9e**
(S)-**6**	Me, Ph	0	**7d**	**9f**
	Me, Ph	1	**7e**	**9g**

Scheme 1. Preparation of bidentate phosphoramidites.

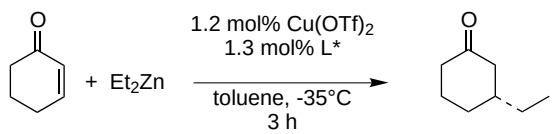
The results of the catalytic reactions are shown in Table 2.

3. Discussion

3.1. TADDOL based bidentate ligands

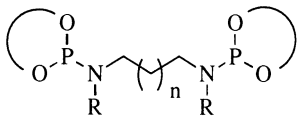
On the basis of the promising results recently obtained with TADDOL-derived phosphoramidite **2**,[11] the analogous dimeric ligand **8a**, featuring an ethylene bridge was investigated first. In spite of the surprisingly low solubility of **8a** in most common organic solvents, briefly heating the free ligand with 0.9 equiv. of $Cu(OTf)_2$ in toluene resulted in an almost clear solution of the copper complex, which proved to be catalytically active in the conjugate addition of diethylzinc to 2-cyclohexenone **10** and 2-cyclopentenone **12**. As generally found in all the experiments described here, the reactions were considerably faster in the presence of the ligand than those completed with $Cu(OTf)_2$ alone, demonstrating that a *ligand acceleration effect* (LAE)[17] is a general feature of copper-catalyzed conjugate addition with phosphoramidites.

When **8a** was employed in the reaction of diethylzinc with 2-cyclohexenone, (*R*)-3-ethylcyclohexanone **11** was isolated with an e.e. of 33% (Table 1, entry 1), corresponding to a lower stereoselectivity than observed with the monodentate counterpart **2** (54% e.e. with **2**: $Cu(OTf)_2 = 2{:}1$).[11] As expected on the basis of the previous findings,[11] when the ligand **8a** to copper molar ratio was lowered to 0.6, a decrease of enantioselectivity was observed (16% e.e., Table 1, entry 2). However, in the present case increasing the phosphoramidite ratio with respect to $Cu(OTf)_2$ to 2.2 was not detrimental to the observed stereoselectivity and the product **11** was obtained with 30% e.e. (Table 1, entry 3).



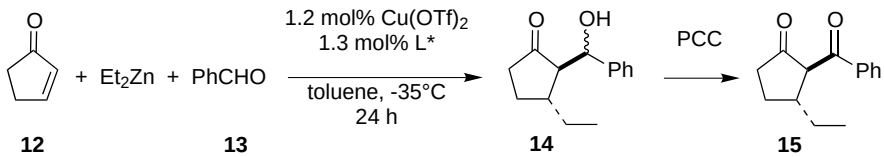
Scheme 2. Asymmetric conjugate addition to 2-cyclohexenone.

Table 1. Asymmetric conjugate addition of Et_2Zn to 2-cyclohexenone **10** catalyzed by $Cu(OTf)_2$-bidentate phosphoramidite



Entry[a]	Ligand	OH / OH	R	*n*	**11** e.e.%[b]	Configuration[c]
1	**8a**	(*R*,*R*)-**5**	Me	0	33	(*R*)
2	**8a**[d]	(*R*,*R*)-**5**	Me	0	16	(*R*)
3	**8a**[e]	(*R*,*R*)-**5**	Me	0	30	(*R*)
4	**8a**[f]	(*R*,*R*)-**5**	Me	0	38	(*R*)
5	**8a**[g]	(*R*,*R*)-**5**	Me	0	18	(*R*)
6	**8b**	(*R*,*R*)-**5**	Me	1	34	(*R*)
7	**9a**	(*R*)-**6**	Me	0	27	(*R*)
8	**9b**	(*R*)-**6**	Me	1	50	(*R*)
9	**9c**	(*R*)-**6**	Pr^i	1	50	(*R*)
10	**9d**	(*R*)-**6**	(*S*)-CH(Ph)CH_3	0	88	(*R*)
11	**9d**[e]	(*R*)-**6**	(*S*)-CH(Ph)CH_3	0	89	(*R*)
12	**9d**[h]	(*R*)-**6**	(*S*)-CH(Ph)CH_3	0	69	(*R*)
13	**9d**[i]	(*R*)-**6**	(*S*)-CH(Ph)CH_3	0	88	(*R*)
14	**9d**[j]	(*R*)-**6**	(*S*)-CH(Ph)CH_3	0	52	(*R*)
15	**9e**	(*R*)-**6**	(*S*)-CH(Ph)CH_3	1	62	(*R*)
16	**9f**	(*S*)-**6**	(*S*)-CH(Ph)CH_3	0	53	(*S*)
17	**9g**	(*R*)-**6**	(*S*)-CH(Ph)CH_3	1	76	(*S*)

[a] Conditions, see Scheme 2 and text.
[b] Determined by chiral GC (HP 5890 4 GC, Chiraldex G-TA column, 95°C).
[c] From elution order (See also Refs. 19,21).
[d] Ligand:$Cu(OTf)_2$ = 0.6:1.
[e] Ligand:$Cu(OTf)_2$ = 2.2:1.
[f] With molecular sieves (4 Å).
[g] With molecular sieves (4 Å), 30% wt/wt H_2O.
[h] 0.6 mol% $Cu(OTf)_2$and 0.66 mol% ligand.
[i] With hydrated $Cu(OTf)_2$.
[j] At 23°C.



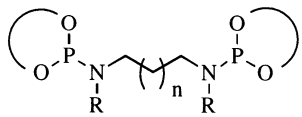
Scheme 3. Asymmetric tandem conjugate addition–aldol reaction with 2-cyclopentenone.

The effect of the addition of molecular sieves on the catalytic system was next examined: although the use of powdered MS (4 Å), equilibrated with water vapor for 3 h, allowed the isolation of **11** with 38% e.e. (Table 1, entry 4), no dramatic improvement in enantioselectivity was observed, in contrast to the observations for the monomeric phosphoramidite **2**. In addition, a window for optimal water concentration seems to be present for this catalytic system, because employing MS containing 30% w/w water a marked reduction of the e.e. value of **11** was observed (Table 1, entry 5).

Ligand **8a** was also inferior to its monomeric counterpart **2** in the asymmetric tandem 1,4-addition-aldol reaction with 2-cyclopentenone in the presence of **13**, affording **14** with a *trans-erythro*:*trans-threo* ratio of 45:55. After oxidation compound **15** was obtained with 18% e.e. (Table 2, entry 1) whereas an e.e. of 37% was obtained with ligand **2** without added MS.[11]

Considering that the steric hindrance of the TADDOL fragments might reduce the complexation ability of the phosphoramidite moieties in **8a**, an attempt was made to increase the flexibility of the ligand using the homologue **8b**. Unfortunately, the introduction of an additional carbon atom in the ligand bridge did not lead to any appreciable improvement in the enantioselectivity of the conjugate addition to 2-cyclohexenone (34% e.e., Table 1, entry 6) and resulted in the formation of racemic product with 2-cyclopentenone with a ratio of 41:59 for the *trans-erythro*:*trans-threo* aldol products **14** (Table 2, entry 2).

Table 2. Asymmetric tandem conjugate addition–aldol reaction with Et_2Zn/2-cyclopentenone **12**/PhCHO **13**, catalyzed by $Cu(OTf)_2$-bidentate phosphoramidite



Entry[a]	Ligand		R	*n*	*Trans-erythro*:*trans-threo* **14**[f]	**15** e.e.%[b]	Configuration[c]
1	**8a**	(*R*,*R*)-**5**	Me	0	45:55	18	(2*S*,3*R*)
2	**8b**	(*R*,*R*)-**5**	Me	1	41:59	2	(2*S*,3*R*)
3	**9a**	(*R*)-**6**	Me	0	37:63	54	(2*S*,3*R*)
4	**9b**	(*R*)-**6**	Me	1	39:61	22	(2*S*,3*R*)
5	**9d**	(*R*)-**6**	(*S*)-CH(Ph)Me	0	35:65	72	(2*S*,3*R*)
6	**9e**	(*R*)-**6**	(*S*)-CH(Ph)Me	1	44:56	62	(2*S*,3*R*)
7	**9f**	(*S*)-**6**	(*S*)-CH(Ph)Me	0	44:56	79	(2*R*,3*S*)
8	**9f**[d]	(*S*)-**6**	(*S*)-CH(Ph)Me	0	42:58	79	(2*R*,3*S*)
9	**9f**[e]	(*S*)-**6**	(*S*)-CH(Ph)Me	0	44:56	83	(2*R*,3*S*)
10	**9g**	(*S*)-**6**	(*S*)-CH(Ph)Me	1	42:58	72	(2*R*,3*S*)
11	**9g**[d]	(*S*)-**6**	(*S*)-CH(Ph)Me	1	46:54	65	(2*R*,3*S*)

[a] Conditions, see Scheme 3 and text.
[b] Determined by chiral HPLC (Daicel–Chiralcel OD, 0.25% *iso*-PrOH in hexane, flow rate 1.0 ml/min, UV detector (254 nm); ret. times 16.3 min; 19.0 min).
[c] From elution order (see also Ref. 21).
[d] Substrates concentration 0.1 M.
[e] With molecular sieves (4 Å).
[f] Determined by ^{1}H NMR.

From these observations it can be concluded that bidentate phosphoramidites derived from TADDOL shows little potential in asymmetric copper-catalyzed conjugate addition to cyclic enones, a result presumably related to the low tolerance of this class of ligands to modifications that results in increasing the steric hindrance around the phosphorus atom and as a consequence a depletion of e.e. in the catalytic 1,4-addition, as was observed previously for their monodentate counterparts.[11]

3.2. BINOL based bidentate ligands

During previous studies from our laboratory it was demonstrated that in the conjugate addition to 2-cyclohexenone **10**, the catalyst derived from the bidentate ligand **9a** and $Cu(OTf)_2$ (1:1 molar ratio) afforded the same e.e. as the catalyst formed from the monomeric ligand **1b** (2:1 molar ratio).[5]

Much to our delight when **9a** was employed with 2-cyclopentenone **12** under the conditions of the tandem 1,4-addition–aldol reaction protocol, adducts **14** (37:63 ratio of *trans-erythro*:*trans-threo*) were obtained, with 54% e.e. (Table 2, entry 3). This surprising improvement in the enantioselectivity compared to the monodentate ligand **1b** (that affords almost racemic **15** under the same conditions)[18] prompted us to systematically modify the structure of bidentate ligand **9a** in an effort to optimize the catalyst stereoselectivity.

Whereas ligand **9b**, with an additional carbon atom in the bridge, furnished a catalytic system with improved enantioselectivity towards 2-cyclohexenone (50% e.e., Table 1, entry 8 versus 27% e.e. with **9a**, Table 1, entry 7), the opposite effect was observed in the case of 2-cyclopentenone (22% e.e., Table 2, entry 4). The *iso*-propyl substituted ligand **9c** was also evaluated, taking into account that in the case of BINOL based monodentate phosphoramidites **1c** an increase in steric hindrance at the nitrogen center is known to improve the enantioselectivity of the catalytic system in the conjugate addition to 2-cyclohexenone.[5]

Although no variation in the e.e. of product **11** could be observed in comparison with the methyl substituted ligand **9b** (Table 1, entries 8 and 9), it is worth noting that both bidentate ligands **9b** and **9c** led to significant asymmetric induction (50% e.e.) which is intermediate between those of the monodentate analogues **1b** and **1c** (35 and 60% e.e., respectively).[5]

Realizing that in the development of monomeric phosphoramidites very high enantioselectivities for the addition to 2-cyclohexenone **10** could only be obtained by the introduction of additional stereogenic centers in the substituents attached to nitrogen,[6] we set out to evaluate the diastereomeric pairs of C_2-symmetry ligands **9d**–**9g**, prepared from *N*,*N*′-bis[(*S*)-1-phenylethyl]-ethane- and *N*,*N*′-bis[(*S*)-1-phenylethyl]propanediamine **7d** and **7e**, respectively.

These modifications indeed resulted in an increase of the enantioselectivity in the formation of 3-ethylcyclohexanone **11**. The stereoselectivity depends on the configurations of the BINOL and phenylethylamine moieties and on the bridge length.

In fact, for the pair of C-2 bridged diastereoisomers **9d** and **9f**, the presence of (*R*)-BINOL fragments and (*S*)-phenylethyl substituents in the **9d** (*unlike* relative configuration, *ul*), proved to be the matched case affording **11** with 88% e.e. (Table 1, entry 10), while the alternative *like* (*lk*) combination in **9f** led to only 53% e.e. (Table 1, entry 16). In contrast, in the case of C-3 bridged phosphoramidites, the *lk* diastereoisomer **9g** turned out to represent the matched combination between chiral elements (76% e.e., Table 1, entry 17) compared to the *ul* one **9e** (62% e.e., Table 1, entry 15). With the exception of **9f**, that affords enantioselectivities comparable to those obtained with ligands **9b** and **9c** (devoid of additional chiral substituents at nitrogen), it is interesting to note that these new bidentate phosphoramidites approaching the synthetically useful enantioselectivity range of 88% e.e. in the case of **9d**. With bidentate ligand **9d**, the importance of some of the experimental parameters was evaluated. As in the case of TADDOL derived ligand **8a** (vide supra), increasing the ligand **9d** to copper ratio to 2.0 did not cause significant variations in the e.e. of the addition product **11** (Table 1, entry 11), but the reaction was slower. However, after reduction the amount of the catalyst to 0.6 mol% $Cu(OTf)_2$ and 0.66 mol% ligand **9d**, a marked decrease in the enantioselectivity was observed (Table 1, entry 12). The catalytic system proved tolerant towards tiny amounts of water, as confirmed by the fact that the direct use of $Cu(OTf)_2$ weighed under air (pale blue in color) did not result in any change of enantioselectivity in comparison to the standard procedure (flame drying of the copper salt; compare entries 10 and 13 of Table 1). This result is not entirely unexpected, knowing that with TADDOL ligand **2** the addition of small amounts of water actually causes an increase of the enantiomeric excess of the product.[11] Finally, although a comprehensive study of the effect of temperature on stereoselectivity was not carried out, it is interesting to note that the catalytic system obtained from **9d** afforded a still remarkable 52% e.e. when the addition was conducted at 23°C (Table 1, entry 14). Despite the fact that the last result suggests that the structure of **9d** is rather well suited for the discrimination of the enantiotopic faces of the olefinic double bond of 2-cyclohexenone **10**, it has to be emphasized that, with respect to stereoselectivity, none of the new bidentate ligands **9a**–**9g** could reach the effectiveness of monodentate **1a** with six-membered enones.

As anticipated, the use of the new bidentate phosphoramidites proved much more convenient in the tandem reaction with 2-cyclopentenone. Indeed, when ligands **9d**–**9g** were employed under the conditions shown in Scheme 3, we were pleased to find that the aldol products **14** were formed with diastereomeric ratios between 35:65 and 46:54 (*trans-erythro*:*trans-threo*) and with e.e. values for products **15** exceeding 60% in each case (Table 2). This corresponds to a substantial stereoselectivity improvement with respect to previous ligands employed by us in the reactions of 2-cyclopentenones. Similar to the observations in the 1,4-addition to the six-membered enone **10** (vide supra), the extent of asymmetric induction was found to depend upon the relative configuration of BINOL and amine fragments and on the number of carbon atoms of the linker moiety between the phosphorus centers. However in the case of 2-cyclopentenone, regardless of the bridge length, the *lk* ligands **9f** and **9g** uniformly represented the matched case, affording e.e. values (79 and 72% e.e., respectively, Table 2, entries 7, 10) 7–10% higher than the alternative *ul* diastereoisomers **9d** and **9e** (Table 2, entries 5, 6). The effect of catalyst concentration[12] was briefly investigated in the case of the ligands **9f** and **9g**. While the catalytic system obtained from **9f** proved insensitive to a two-fold dilution ([**12**] = 0.1 M, Table 2, entry 8), a slight decrease in e.e. was recorded with **9g** (Table 2, entry 11). In general, the effect of lowering reagents and catalyst concentrations appears therefore of minor importance when compared to the marked decrease of stereoselectivity which is caused by the reduction of the catalyst to substrate ratio (vide supra).

As in the case of the dimeric TADDOL phosphoramidite **8a** discussed above, only a limited increase in enantioselectivity was observed with the ligand **9f**, when the tandem 1,4-addition–aldol reaction was performed in the presence of MS 4 Å. Nevertheless it is worth noting that under these conditions we were able to isolate the product **14** in 83% e.e. (Table 2, entry 9), which represents a relatively high enantioselectivity for a catalytic conjugate addition of organometallic reagents to a simple substrate such as 2-cyclopentenone.

Although at this moment a satisfactory rationale of the influence of reaction conditions and phosphoramidite structure on the enantioselectivity seems difficult, some features can be noted on the basis of the data discussed:

1. For 2-cyclohexenones, the present bidentate ligands cannot fully replicate the optimal combination of chirality elements found for the monodentate phosphoramidite **1a**; the latter therefore remains the ligand of choice for the asymmetric conjugate addition to cyclic six- to eight-membered enones;
2. Regardless of the nature of the substrate, in all the cases studied the sense of asymmetric induction maintained constant, i.e. (*R*,*R*)-TADDOL or (*R*)-BINOL derived phosphoramidites uniformly afforded the (3*R*)-adducts **11** or **14** as the prevailing enantiomers. Unlike the findings of Chan et al.[12] for phosphite ligands, no dependence of product absolute configuration on ring size was observed. In addition, even if the most effective bidentate ligands for 2-cyclopentenone and 2-cyclohexenone showed to have a diastereomeric relationship (*ul* and *lk* structures **9d** and **9f**, respectively), the homologues **9e** and **9g** afforded an unprecedented regular matching between the e.e. values obtained with both types of cyclic enones;

3. In analyzing the influence of the bridge length, it can be noted that the best ligands for both enone substrates proved to be the C-2-bridged homologues **9d** and **9f**. Furthermore, with 2-cyclopentenone the ethylene linked systems actually performed better than the corresponding propylene bridged ones in all the cases studied (Table 2). However, such consistent behavior was not recorded with 2-cyclohexenone, where the lengthening of the bridge occasionally resulted in enantioselectivity improvement (Table 1, entries 7, 8 and 16, 17);
4. Only a relatively minor impact on the stereocontrol for the aldol products **14** (*trans-erythro*:*trans-threo*) can be identified for any of the ligands. It is worth mentioning that regardless of the configuration of the ligands the *trans-erythro* product is the minor product in all cases.
5. With the limitations discussed above the findings that the bidentate phosphoramidites derived of BINOL are in generally superior for reactions of 2-cyclopentenone with respect to their monodentate counterparts and the C-2 bridged systems over C-3 homologues. Together with the observation that no significant improvement in e.e. could be gained by raising the ligand to copper ratio over 1.1, apparently support the view of a bidentate coordination of these new ligands to the copper center. Nevertheless, the present lack of detailed structural information on the reactive species involved in the actual catalysis does not allow to rule out alternative explanations, such as the occurrence of copper clusters,[19] or the coordination of different metal centers (Cu, Zn) by the bidentate phosphoramidites.

4. Conclusions

In the present investigation the new bidentate phosphoramidites **8a**–**8b** and **9a**–**9g** were synthesized and screened as chiral ligands in the copper-catalyzed enantioselective conjugate addition of Et_2Zn to 2-cyclohexenone **10** and 2-cyclopentenone **12**. While the use of TADDOL derived ligands **8a** and **8b**, did not result in any advantage over the corresponding monodentate ligand **4**, very promising results were obtained with BINOL derived bidentate ligands **9d**–**9g**.

In particular, in the case of 2-cyclopentenone a remarkable improvement of enantioselectivity was observed with respect to the monomeric phosphoramidites evaluated to date, leading to an enhancement of the enantioselectivity from 10 to 83% in the tandem conjugate addition–aldol reaction. Unfortunately, the influence of the ligand during the subsequent aldol reaction is minor, resulting in *trans-erythro* and *trans-threo* products with ratios up to 35:65.

The fine-tuning of the ligand structure, the elucidation of the structure of the actual catalyst complex and the evaluation of the scope of this new class of ligands with respect to other substrates are currently under way.

5. Experimental

5.1. General experimental procedures

^1H, ^{13}C and ^{31}P NMR spectra were recorded on a Varian Gemini-200 or a Varian 300 spectrometer in $CDCl_3$; Chemical shift values are given in ppm; (reference $\delta = 7.24$ ppm for proton NMR, reference $\delta = 77$ ppm for carbon NMR and (H_3PO_4) reference $\delta = 0.0$ ppm for phosphorus NMR). Mass spectra (HRMS) were recorded on an AEI MS-902MS. All catalytic experiments were carried out in oven-dried glassware and under an atmosphere of purified nitrogen. Solvents, benzaldehyde, triethylamine and commercially available diamines were dried by standard methods, distilled before use and stored under nitrogen. Except when specified, commercially available reagents were used as received. Diamines **7d**–**7e**[20] were synthesized by reaction of the corresponding 1,*n*-dibromide with excess (*S*)-α-phenylethylamine. Prior to use, powdered molecular sieves 4 Å (Merck) were equilibrated for 3 h with water vapors in a close vessel. Asymmetric conjugate addition reactions to 2-cyclohexenone and tandem conjugate addition/aldol reactions to 2-cyclopentenone as well as the determination of e.e. values were carried out as described previously;[11] modified conditions are discussed in the text and footnotes to tables. Despite the fact that all the ligands appeared to be homogeneous by TLC analysis, a minor (5%) component was present in the ^{31}P NMR spectra of some of the samples.

5.2. Preparation of bidentate TADDOL phosphorus amidites 8a and 8b. Typical procedure

To a cooled (−70°C) solution of PCl_3 (0.52 mL, 6.0 mmol) and Et_3N (1.7 mL, 12.0 mmol) in toluene (7.5 mL), (*R*,*R*)-TADDOL (2.80 g, 6.0 mmol) in toluene (50 mL) was added dropwise over 20 min. The reaction mixture was allowed to warm to rt over 5 h and then filtered under N_2. The clear filtrate was cooled to −50°C and treated sequentially with Et_3N (0.84 mL, 6.0 mmol) and the appropriate *N*,*N*′-dimethyl-1,*n*-diamine **7a** or **7b** (3.0 mmol) The solution was allowed to warm to rt overnight, resulting in the formation of a thick white suspension that was filtered, and the residue washed with toluene (3×30 mL) and diethyl ether (2×10 mL). After drying, the solid was finely ground and stirred with water (3×20 mL), followed by absolute EtOH (2×10 mL) and diethyl ether (3×20 mL). The last traces of solvent were removed in vacuo and the product was dried by storing over silica gel.

5.2.1. *N*,*N*′ - Bis[(1*R*,7*R*) - 9,9 - dimethyl - 2,2,6,6 - tetraphenyl-3,5,8,10-tetraoxo-4-phosphabicyclo[5,3,0]decane-4-yl]-*N*,*N*′-dimethylethylenediamine 8a. ^1H NMR ($CDCl_3$): δ 7.72 (m, 4H), 7.57 (m, 4H), 7.42 (m, 8H), 7.12–7.32 (m, 24H), 5.16 (dd, $J_A = 3.1$ Hz, $J_B = 8.9$ Hz, 2H), 4.80 (d, $J = 8.8$ Hz, 2H), 3.02–3.32 (m, 4H), 2.75 (d, $J = 5.4$ Hz, 6H), 1.29 (s, 6H), 0.28 (s, 6H).^{31}P NMR ($CDCl_3$): δ 140.1. HRMS calcd for $C_{66}H_{66}N_2O_8P_2$: 1076.429; found 1076.431. Due to the low solubility in common organic solvents, no satisfactory ^{13}C NMR spectrum could be recorded.

5.2.2. *N,N′* - Bis[(1*R*,7*R*) - 9,9 - dimethyl - 2,2,6,6 - tetraphenyl-3,5,8,10-tetraoxo-4-phosphabicyclo[5,3,0]decane-4-yl]-*N,N′*-dimethylpropylenediamine 8b. ^{1}H NMR ($CDCl_3$): δ 7.72 (m, 4H), 7.56 (m, 4H), 7.42 (m, 8H), 7.12–7.30 (m, 24H), 5.15 (dd, $J_A=3.3$ Hz, $J_B=8.4$ Hz, 2H), 4.77 (d, $J=8.4$ Hz, 2H), 2.94–3.14 (m, 4H), 2.73 (d, $J=7.8$ Hz, 6H), 1.76 (quint., $J=6.9$ Hz, 2H), 1.29 (s, 6H), 0.27 (s, 6H).^{13}C NMR ($CDCl_3$): δ 146.9, 146.6, 142.3, 141.9, 129.0, 128.8, 128.7, 128.0, 127.6, 127.4, 127.1, 127.0, 111.6, 82.5, 82.0, 81.7, 81.3,, 81.2, 47.4, 46.8, 31.7, 31.5, 27.5, 25.3. ^{31}P NMR ($CDCl_3$): δ 139.4. HRMS calcd for $C_{67}H_{68}N_2O_8P_2$: 1090.445; found 1090.447.

5.3. Preparation of bidentate BINOL phosphorus amidites 9b–9g. Typical procedure

The related procedure for monodentate phosphoramidites[16] was followed, monitoring the consumption of the chlorophosphite **6** by ^{31}P NMR (12–48 h). The crude reaction products were purified by chromatography (SiO_2, hexane–CH_2Cl_2 mixtures).

5.3.1. *N,N′*-Bis{(*R*)-1,2-dihydro-[2′,1′-c:1′,2′-e]dinaphtho-2,7-dioxa-7*H*-phosphepine-1-yl}-*N,N′*-dimethylpropylenediamine 9b. ^{1}H NMR ($CDCl_3$): δ 7.95 (d, $J=8.7$ Hz, 2H), 7.91 (d, $J=8.1$ Hz, 2H), 7.84 (d, $J=8.7$ Hz, 4H), 7.50 (d, $J=8.7$ Hz, 2H), 7.28–7.44 (m, 10H), 7.16–7.27 (m, 4H), 2.94–3.14 (m, 4H), 2.29 (d, $J=5.7$ Hz, 6H), 1.75 (quint., $J=7.2$ Hz, 2H).^{13}C NMR ($CDCl_3$): δ 150.0, 149.4, 132.8, 132.6, 131.4, 130.7, 130.3, 130.0, 128.3, 128.2, 127.0, 126.9, 126.0, 124.8, 124.5, 122.1, 121.9, 47.1, 46.3, 32.0. ^{31}P NMR ($CDCl_3$): δ 148.1. HRMS calcd for $C_{45}H_{36}N_2O_4P_2$: 730.215; found: 730.215.

5.3.2. *N,N′*-Bis{(*R*)-1,2-dihydro-[2′,1′-c:1′,2′-e]dinaphtho-2,7-dioxa-7*H*-phosphepine-1-yl}-*N,N′*-diisopropylpropylenediamine 9c. ^{1}H NMR ($CDCl_3$): δ 7.94 (d, $J=8.7$ Hz, 2H), 7.90 (d, $J=8.4$ Hz, 2H), 7.78–7.86 (m, 4H), 7.16–7.50 (m, 16H), 3.26–3.44 (m, 2H), 2.32–2.58 (m, 4H), 1.48–1.63 (m, 2H), 0.95–1.07 (m, 12H).^{13}C NMR ($CDCl_3$): δ 150.3, 150.2, 149.7, 132.8, 132.6, 131.3, 130.5, 130.1, 129.6, 128.2, 128.1, 127.0, 126.9, 125.9, 125.8, 124.7, 124.3, 122.1, 121.9, 47.8, 47.4, 40.6, 40.3, 34.5, 23.1, 23.0, 22.9, 22.7. ^{31}P NMR ($CDCl_3$): δ 150.7. HRMS calcd for $C_{49}H_{44}N_2O_4P_2$: 786.277; found: 786.278.

5.3.3. *N,N′*-Bis{(*R*)-1,2-dihydro-[2′,1′-c:1′,2′-e]dinaphtho-2,7-dioxa-7*H*-phosphepine-1-yl}-*N,N′*-bis[(*S*)-(1-phenylethyl)]ethylenediamine 9d. ^{1}H NMR ($CDCl_3$): δ 7.80–7.96 (m, 8H), 7.07–7.46 (m, 26H), 3.87–4.06 (m, 2H), 2.49–2.75 (m, 4H), 1.05 (d, $J=7.2$ Hz, 6H).^{13}C NMR ($CDCl_3$): δ 149.7, 149.6, 149.4, 143.1, 143.0, 132.7, 131.3, 130.6, 130.2, 129.7, 129.1, 128.3, 128.2, 128.1, 127.2, 127.1, 127.0, 126.9, 126.1, 126.0, 125.2, 125.0, 124.7, 124.6, 123.9, 123.8, 122.1, 121.9, 56.0, 55.4, 45.2, 21.4, 21.0. ^{31}P NMR ($CDCl_3$): δ 149.2. HRMS calcd for $C_{58}H_{46}N_2O_4P_2$: 896.293; found 896.296.

5.3.4. *N,N′*-Bis{(*R*)-1,2-dihydro-[2′,1′-c:1′,2′-e]dinaphtho-2,7-dioxa-7*H*-phosphepine-1-yl}-*N,N′*-bis[(*S*)-(1-phenylethyl)]propylenediamine 9e. ^{1}H NMR ($CDCl_3$): δ 7.97 (d, $J=8.7$ Hz, 2H), 7.91 (d, $J=8.4$ Hz, 2H), 7.80 (d, $J=8.7$ Hz, 2H), 7.60 (d, $J=8.4$ Hz, 2H), 7.51 (dd, $J_A=8.7$ Hz, $J_B=1.5$ Hz, 2H), 7.07–7.45 (m, 22H), 7.03 (d, $J=7.5$ Hz, 4H), 4.37–4.57 (m, 2H), 1.82–2.28 (m, 4H), 1.45 (quint., $J=7.5$ Hz, 2H), 1.19 (d, $J=6.8$ Hz, 6H).^{13}C NMR ($CDCl_3$): δ 150.1, 149.3, 142.6, 132.8, 132.6, 131.3, 130.4, 130.2, 129.7, 128.3, 128.1, 127.4, 127.0, 126.9, 126.0, 124.7, 124.4, 122.1, 121.8, 55.1, 54.5, 41.0, 34.1, 20.2, 20.0. ^{31}P NMR ($CDCl_3$): δ 148.7. HRMS calcd for $C_{59}H_{48}N_2O_4P_2$: 910.308; found 910.306.

5.3.5. *N,N′*-Bis{(*S*)-1,2-dihydro-[2′,1′-c:1′,2′-e]dinaphtho-2,7-dioxa-7*H*-phosphepine-1-yl}-*N,N′*-bis[(*S*)-(1-phenylethyl)]ethylenediamine 9f. ^{1}H NMR ($CDCl_3$): δ 7.85–8.03 (m, 8H), 7.31–7.51 (m, 10H), 7.20–7.31 (m, 4H), 6.95–7.12 (m, 8H), 6.62 (d, $J=7.2$ Hz, 4H), 3.93–4.05 (m, 2H), 2.24–2.44 (m, 2H), 1.37–1.54 (m, 2H), 0.80–0.98 (m, 6H).^{13}C NMR ($CDCl_3$): δ 150.3, 150.2, 149.7, 142.8, 142.7, 132.9, 131.4, 130.6, 130.3, 129.9, 129.5, 128.3, 128.2, 128.0, 127.1, 127.0, 126.8, 126.7, 126.4, 126.1, 125.8, 124.8, 124.7, 124.0, 123.9, 122.3, 122.1, 121.7, 55.7, 55.0, 41.9, 21.0, 20.6. ^{31}P NMR ($CDCl_3$): δ 147.4. HRMS calcd for $C_{58}H_{46}N_2O_4P_2$: 896.293; found 896.291.

5.3.6. *N,N′*-Bis{(*S*)-1,2-dihydro-[2′,1′-c:1′,2′-e]dinaphtho-2,7-dioxa-7*H*-phosphepine-1-yl}-*N,N′*-bis[(*S*)-(1-phenylethyl)]propylenediamine 9g. ^{1}H NMR ($CDCl_3$): δ 8.02 (d, $J=8.7$ Hz, 2H), 7.95 (d, $J=8.1$ Hz, 2H), 7.72 (d, $J=8.1$ Hz, 2H), 7.50–7.62 (m, 4H), 7.16–7.48 (m, 22H), 6.98 (d, $J=8.7$ Hz, 4H), 4.11–4.30 (m, 2H), 2.20–2.38 (m, 2H), 1.86–2.05 (m, 2H), 1.54 (d, $J=5.7$ Hz, 6H), 1.02–1.20 (m, 2H).^{13}C NMR ($CDCl_3$): δ 150.3, 150.2, 149.4, 142.8, 142.7, 132.9, 131.4, 130.6, 130.3, 129.9, 129.5, 128.3, 128.2, 128.0, 127.1, 127.0, 126.8, 126.7, 126.4, 126.1, 125.8, 124.8, 124.7, 124.0, 123.9, 122.3, 122.1, 121.7, 55.7, 55.0, 41.9, 28.3, 21.6, 21.2. ^{31}P NMR ($CDCl_3$): δ 148.1. HRMS calcd for $C_{59}H_{48}N_2O_4P_2$: 910.308; found 910.309.

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