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Enantioselective alkynylation and phenylation of aromatic aldehydes promoted by atropisomeric 1,1′-binaphthylazepine-based amino alcohols

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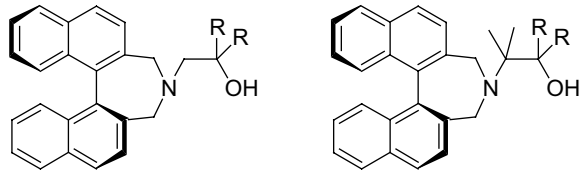
Dedicated to Professor Victor Snieckus in recognition of his significant contributions in the field of synthetic organic chemistry

Abstract—The atropisomeric 1,1-binaphthylazepine-based 1,2-amino alcohols **1b** and **1c** were tested as catalysts in the enantioselective addition of zinc phenylacetylide and diphenylzinc to aromatic aldehydes in order to achieve, respectively, optically active propargyl alcohols and diarylcarbinols. In both these reactions, ligand **1c** proved to be more efficient than **1b**, affording ees up to 70% in the addition of phenylacetylene to arylaldehydes and ees up to 54% in the diphenylzinc addition.

1. Introduction

The 1,1′-binaphthylazepine skeleton has frequently been used to design efficient auxiliaries and ligands for asymmetric synthesis.[1] Moreover, chiral ammonium salts based on this peculiar backbone have been successfully employed in enantioselective phase transfer catalysis.[2] We recently approached the rational design of new 1,1′-binaphthylazepine amino alcohols, determining the structural features which affect their efficiency as chiral ligands, and improving their performances[3,4] in the enantioselective addition of $ZnEt_2$ to arylaldehydes,[5] taken as a benchmark reaction. The computational study of Goldfuss and Houk[6] on the chiral induction mechanism in such a reaction given by the Noyori's ligand (*S*)-**1a**[1d] (Fig. 1) gave an important input to our investigation, by pointing out the crucial role of the substituents at C(O). Taking into account this study and starting from mechanistic considerations, we demonstrated that by simply tuning the size of the substituents on the C(O), with no changes on the chiral atropisomeric binaphthyl backbone, a very high increase in enantioselectivity could be achieved. In fact while (*S*)-**1a** afforded[1d] only a moderate 49% ee in the $ZnEt_2$ addition to benzaldehyde, the use of **1b**, which has a diphenylhydroxymethyl moiety, gave an increased ee of 87%.[4] We then imagined that a further improvement in enantioselectivity could be obtained by inserting suitable groups on the C(N) of the amino ethanol moiety, which giving rise to steric interaction with both the chiral binaphthyl moiety and the substituents on the C(O), could ensure a better chirality transfer. We then designed the new tetrasubstituted amino alcohol **1c**, which as expected, afforded an ee increase of 7–10% with respect to **1b** in the ethylation of different arylaldehydes and a 95% ee with benzaldehyde.[7]



1a R = H
1b R = Ph

1c R = Ph

Figure 1.

These studies allowed us to provide a qualitative rationale of the stereochemical outcome of the reaction with these ligands and to better define the influence of the substituents present on the amino alcoholic moiety. Once the structural features of the binaphthylazepine

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amino alcohols had been optimized we decided to test their efficiency in more synthetically useful enantioselective organozinc additions. Our attention was attracted by the addition of zinc phenylacetylide and diphenylzinc to aromatic aldehydes in order to achieve optically active propargyl alcohols and diarylcarbinols, respectively.

Chiral propargylic alcohols are in fact very important synthetic intermediates[8] and their synthesis in optically active form has attracted much effort. Together with the asymmetric reduction of propargyl ketones,[9] the enantioselective addition of alkynes to carbonyl compounds proved to be one of the most efficient synthetic approaches to this class of compounds. Dating back to the pioneering work of Soai and Niwa,[10] the enantioselective addition of zinc acetylides to aldehydes, in the presence of catalytic amounts of either chiral amino alcohols[1q,11] or BINOL derivatives,[12] has been the first approach followed.[13] This method, where the zinc acetylide is formed in situ by reaction of terminal alkynes with a dialkylzinc, is clearly strictly related to the diethylzinc addition to aldehydes, but the values of the ee obtained are usually not so high as in the ethylation reaction. Better results in terms of enantioselectivity have been achieved when the zinc acetylide addition is catalyzed by titanium complexes of BINOL derivatives,[14] sulfonamides,[15] and alkaloids.[16] An alternative approach was reported by Carreira et al.[17] who performed the direct addition of terminal alkynes to aldehydes in the presence of stoichiometric amounts of $Zn(OTf)_2$, triethylamine, and *N*-methylephedrine. Later on, a sub-stoichiometric version of the reaction was developed[17d] while other authors[18] described the use of different chiral amino alcohols in the same conditions. Despite all these efforts the asymmetric alkynylation of aldehydes has not yet reached the high levels of enantioselectivity, generality, and practicability of the parent ethylation reaction.[19] Quite often stoichiometric or sub-stoichiometric amounts of the chiral ligand are needed and large amounts of co-reagents (e.g., $Ti(O^iPr)_4$) or additives are required.

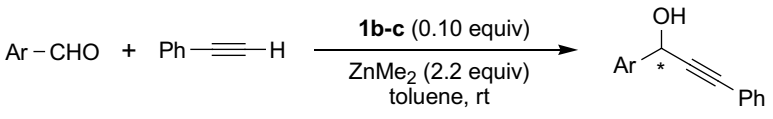
The related enantioselective addition of $ZnPh_2$ to aldehydes is also a synthetically relevant procedure, leading to optically active diarylmethanols, intermediates for the preparation of important therapeutic agents.[20] The main problem to overcome in such a reaction is that $ZnPh_2$ is much more reactive than the dialkylzinc species, giving addition to aldehydes in the absence of catalysts. Competition between the uncatalyzed aryl addition and the asymmetric catalyzed one can then occur, with lowering of the enantioselectivity. Only very recently Fu et al.[21] reported an enantioselective $ZnPh_2$ addition to arylaldehydes promoted by a chiral ferrocenyl amino alcohol, although in moderate ees. Working at low concentrations Pu et al.[22] were able to minimize the competing non-stereoselective addition, then achieving good levels of enantioselection in the presence of BINOL-derived ligands, while other authors[23] obtained good results employing binaphthyl amino alcohols. Bolm et al.[24] were then able to suppress the background reaction in a more convenient way by using $ZnPh_2$/$ZnEt_2$ (1:2 mixture). Under such conditions the uncatalyzed addition was minimized and the ee of the resulting diaryl carbinols highly enhanced. By using both ferrocenyl and rhenium-tricarbonyl chiral oxazolines, these authors obtained highly enantioselective phenylation on a variety of arylaldehydes. Interestingly, only the phenyl transfer occurs under such conditions and no ethylation products were observed. A theoretical investigation by the same authors provided evidence, which accounts for both suppression of the uncatalyzed $ZnPh_2$ addition and the preferential phenyl transfer.[25] In a recent report, Pericàs et al.[26] showed that the same mixed $ZnPh_2$/$ZnEt_2$ system proves to be also very efficient, in terms of enantioselectivity, with simpler amino alcohol ligands such as 2-piperidino-1,1,2-triphenylethanol, providing very high ees in the phenylation of arylaldehydes.

The high synthetic interest of such reactions and the need for practical and reliable procedures affording high enantioselectivity, then prompted us to test in the addition of zinc phenylacetylene and diphenylzinc to aromatic aldehydes the atropisomeric 1,1′-binaphthylazepine amino alcohols **1b** and **1c**, which in our previous studies afforded the highest enantioselectivity in the diethylzinc addition to arylaldehydes.

2. Results and discussion

The efficiency of both **1b** and **1c** was first tested in the enantioselective alkynylation of benzaldehyde. The addition of phenylacetylene to benzaldehyde (Scheme 1) was performed in dry toluene at room temperature by reacting first the alkyne (2.4 equiv) and $ZnMe_2$ (2.2 equiv) for 30 min, then adding the ligand (10 mol %) and, after further 30 min, the aldehyde. The reaction was monitored by TLC until complete conversion of the aldehyde was detected and then quenched by the addition of 5% aqueous HCl. After extraction with Et_2O, drying, and evaporation of solvent, the product was purified by column chromatography while the ee of the propargyl alcohol was determined by HPLC on a chiral stationary phase.

The results in Table 1 show that, in the presence of catalytic amounts of compounds **1b** and **1c**, the zinc phenylacetylide smoothly adds to benzaldehyde, thus



Scheme 1.

Table 1. Addition of phenylacetylene to arylaldehydes mediated by ligands (*S*)-**1b**,**c**[a]

Run	Ligand	Ar	Time (h)	Yield (%)[b]	ee (%)[c] (ac)[d]
1	(*S*)-**1b**	Ph	24	30	15 (+)-(*R*)
2	(*S*)-**1c**	Ph	24	40	70 (+)-(*R*)
3[e]	(*S*)-**1c**	Ph	24	7	3 (+)-(*R*)
4	None	Ph	24	50	0
5	(*S*)-**1b**	2-Naphthyl	24	25	24 (+)
6	(*S*)-**1c**	2-Naphthyl	24	95	60 (+)
7	(*S*)-**1b**	4-Cl–Ph	24	50	20 (+)
8	(*S*)-**1c**	4-Cl–Ph	24	45	46 (+)
9	(*S*)-**1b**	2-Cl–Ph	12	90	20 (+)
10	(*S*)-**1c**	2-Cl–Ph	12	95	30 (+)
11	(*S*)-**1b**	2-CF_3–Ph	5	45	13 (+)
12	(*S*)-**1c**	2-CF_3–Ph	5	77	40 (+)

[a] Reactions performed in toluene at rt; reagent ratio: aldehyde/$ZnMe_2$/phenylacetylene/ligand = 1.0:2.2:2.4:0.1.
[b] Isolated yields.
[c] Determined by HPLC on Chiralcel OD.
[d] Determined by comparison of $[\alpha]_D$ with literature values.[9h]
[e] Reaction in THF.

providing the corresponding propargyl alcohol in good yield with no traces of by-products due to reduction or methylation of the aldehyde. In the presence of amino alcohol (*S*)-**1b**, addition of phenylacetylene to benzaldehyde (run 1) afforded the corresponding (*R*) propargyl alcohol in only 15% ee, while ligands (*S*)-**1c** gave a higher 70% ee. Both yield and enantioselectivity of the reaction dropped when performed in a more coordinating solvent, such as THF (run 3). Although in the literature,[11c] the uncatalyzed addition is reported to be much slower than in the presence of an amino alcohol, we observed (run 4) that the background reaction can effectively compete with the catalyzed one, eventually decreasing the overall enantioselectivity of the process. The alkynylation reaction was then tested on different substituted arylaldehydes (Table 1). The higher efficiency of **1c** in the alkynylation was confirmed, affording ees about 30% higher than (*S*)-**1b**. In the addition to 2-naphthaldehyde, (*S*)-**1b** afforded a 24% ee, and (*S*)-**1c** a 60% ee while, in the addition to the *para*-substituted 4-Cl benzaldehyde, ligand (*S*)-**1b** and (*S*)-**1c** provided, respectively, 20% and 46% ee. The *ortho*-substituted 2-Cl and 2-CF_3 benzaldehydes reacted faster than benzaldehyde although affording lower ees, showing a reactivity enhancement due to the EWG substituents, but a detrimental effect of *ortho* steric hindrance on enantioselectivity. The observed higher efficiency of **1c** confirms the valuable effect of the *gem*-dimethyl moiety associated with the diphenylhydroxymethyl portion in inducing a better transfer of chirality to the C(O) carbon.

The asymmetric addition of $ZnPh_2$ to arylaldehydes (Scheme 2) was performed following the mixed zinc species approach, which as described in the literature,[24,26] allows suppression of the uncatalyzed background reaction and provides higher enantioselection. Therefore a solution of $ZnPh_2$ (1.1 equiv) and $ZnEt_2$ (2.5 equiv) in toluene was first prepared, at which point the ligand (10 mol %) and the aldehyde were then added at room temperature. The mixture was monitored by TLC and when no more traces of the aldehyde were detected, the reaction mixture was quenched by the addition of 5% aqueous HCl, extracted with Et_2O, and the recovered residue purified by column chromatography. The ee of the diarylcarbinol produced was then determined by HPLC on a chiral stationary phase. The addition was tested on 4-chlorobenzaldehyde, 2-naphthaldehyde, and 1-naphthaldehyde, chosen as the model compounds having different electronic and steric features.

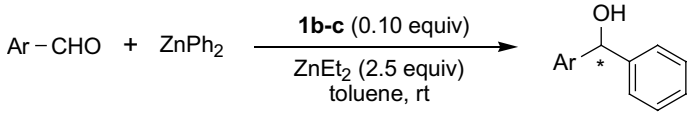
As inferred from Table 2, ligand (*S*)-**1c** provided higher ees than (*S*)-**1b**. In the $ZnPh_2$ addition to 4-Cl-benzaldehyde, the (*S*)-diarylcarbinol was obtained in 54% ee using (*S*)-**1c** and with only 3% ee using ligand (*S*)-**1b**. A similar trend was observed in the $ZnPh_2$ addition to 2-naphthyl and 1-naphthyl aldehyde, where (*S*)-**1b** afforded very low ees, while higher, but still moderate ees were achieved using (*S*)-**1c**.

Table 2. Addition of diphenylzinc to arylaldehydes mediated by ligands (*S*)-**1b**,**c**[a]

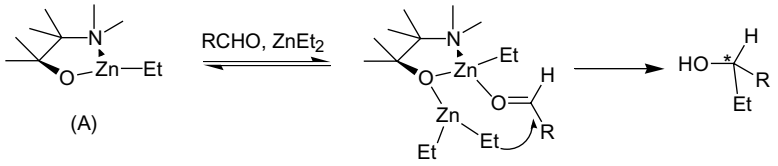
Run	Ligand	Ar	Time (h)	Yield (%)[b]	ee (%)[c] (ac)[d]
1	(*S*)-**1b**	4-Cl–Ph	1	65	3 (*S*)
2	(*S*)-**1c**	4-Cl–Ph	1	82	54 (*S*)
3	(*S*)-**1b**	2-Naphthyl	2	85	5 (*S*)
4	(*S*)-**1c**	2-Naphthyl	2	84	30 (*S*)
5	(*S*)-**1b**	1-Naphthyl	2	30	16 (*S*)
6	(*S*)-**1c**	1-Naphthyl	2	84	40 (*S*)

[a] Reactions performed in toluene at rt; reagent ratio: aldehyde/$ZnEt_2$/ligand = 1:2.5:0.1.
[b] Isolated yields.
[c] Determined by HPLC on either c.s.p. Chiralcel OD or OB.
[d] Determined by elution order on c.s.p. Chiralcel OD or OB.[24f,26]

It is noteworthy that employing (*S*)-configured 1,1′-binaphthylazepine ligands, in both alkynylation and phenylation the organozinc species (i.e., zinc phenylacetylide and diphenylzinc), attack the *Si* face of the carbonyl, as observed in our previous studies on the $ZnEt_2$ addition.[4,7] Moreover, in all these organozinc additions, the tetrasubstituted ligand **1c** constantly provided higher enantioinduction than **1b**. This parallelism between the stereochemical outcomes of such diethylzinc, diphenylzinc, and zinc phenylacetylide additions can therefore envisage an analogous induction mechanism for these reactions.



Scheme 2.



Scheme 3.

A great number of experimental,[27] and theoretical[6,28] studies on the mechanism of the asymmetric diethylzinc addition to aldehydes have been reported, defining the intermediates of the reaction and providing some proposals about the possible transition states involved. Many evidences point out that the stereoselective ethylation of aldehydes is promoted by the chelated ethylzinc alkoxide (A), which coordinates both the carbonyl compound and a second molecule of $ZnEt_2$ (Scheme 3).[5a] The migration of an ethyl moiety to the carbonyl then occurs through a tricyclic transition state.[28a] Much less is known about both alkynylation and phenylation reactions however, on the basis of the present results and the literature, transition states similar to the $ZnEt_2$ addition can be reasonably imagined and a qualitative rationale of the stereochemical outcome of such reactions with 1,1′-binaphthylazepine amino alcohols **1b** and **1c** can be tentatively provided.

In the case of the alkynyl addition, by mixing in situ equimolar quantities of dimethyl zinc and phenylacetylene, a mixed methyl alkynyl organozinc species can be generated. It is known that in alkylzinc acetylides, the alkynyl moiety is the more reactive one[29] and therefore, upon reaction with the amino alcohol, such a moiety is released and a methylzinc alkoxide is formed. This intermediate corresponds to the catalytic species (A) present in the enantioselective dialkylzinc addition to carbonyls (Scheme 3) and can analogously coordinate both a second molecule of methylzinc acetylide and the aldehyde. As for analogy with the ethylation case[7] we can then presume that in the alkynylation with (*S*)-**1b** and (*S*)-**1c**, the two most stable TS's are *anti*-(*S*) and *anti*-(*R*) (Fig. 2a) and therefore that the enantioselectivity of the reaction is primarily determined by their energy difference. From Figure 2a, we can see that in *anti*-(*R*) the axial phenyl Ph* and the methyl group on zinc (Me*) are on the same side of the ring, while in *anti*-(*S*), the Ph* and Me* moieties are on the opposite sides. The latter transition state, which leads to an alkynyl transfer on the *Si* face of the carbonyl is therefore the most stable one. The methyl groups on the C(N) in **1c** force the Ph* group even more toward the Me*, enhancing the energy difference between *anti*-(*S*) and *anti*-(*R*) transition states and then ensuring a higher enantioselectivity.

More detailed theoretical[25] and experimental[26] studies on the mechanism of the Ph_2Zn addition to aldehydes in the presence of a mixed Ph_2Zn/Et_2Zn species and amino alcohols have recently been reported. In particular Pericàs et al.[26] showed that when diphenylzinc and diethylzinc are mixed in a 1:2 ratio, the new EtPhZn complex generated, reacts very slowly with the aldehyde in the absence of the catalyst, thus minimizing the background reaction. When EtPhZn interacts with the amino alcohol, the phenyl moiety reacts faster with the hydroxyl group than the ethyl one, so that the ethylzinc alkoxide catalyst (A) (Scheme 3) is formed. Also in this case, such an intermediate coordinates both another molecule of EtPhZn and the aldehyde, thus catalyzing the enantioselective phenyl transfer. By means of PM3 calculations, the same authors also found that the most stable transition state was again a tricyclic *anti*-(*S*) one. Therefore also in the phenylation with (*S*)-**1b** and (*S*)-**1c** the transition state *anti*-(*S*) in Figure 2b, minimizing the steric interactions between the axial Ph* and the Et*, is the more stable one. Such a transition state again leads to a phenyl transfer on the *Si* face of the carbonyl as experimentally found. Also in this case, the higher enantioselection afforded by **1c** can be explained by

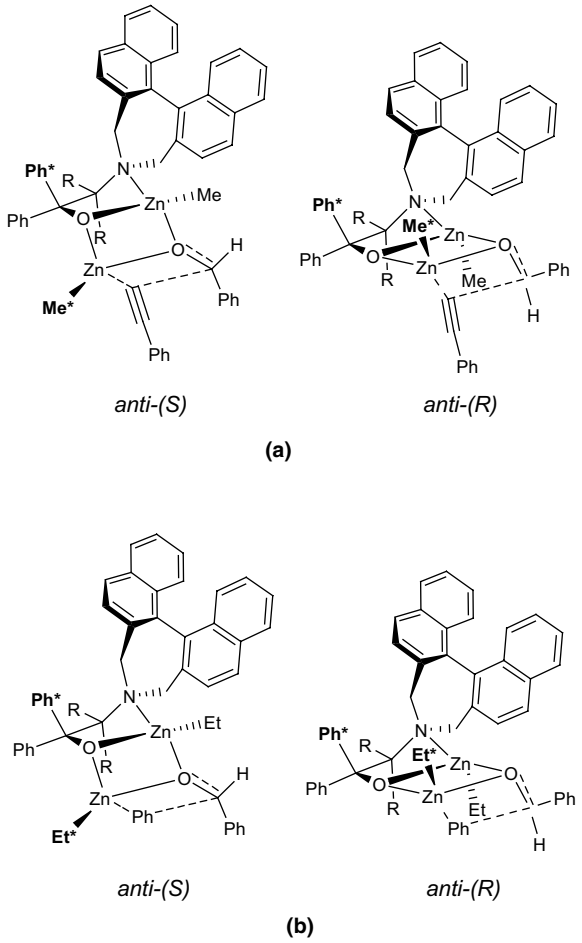


Figure 2.

taking into account that the introduction of two more methyls on the C(N) in this amino alcohol further destabilizes the transition state leading to the opposite facial attack.[30] The definition of the mechanism of enantioinduction can allow us to foresee the stereochemical outcome of the present addition reactions. On this basis an (*R*)-configuration can be tentatively assigned to all the dextrorotatory propargyl alcohols in Table 1 coming from the phenylacetylene addition in the presence of (*S*)-binaphthylazepine amino alcohols.

In summary, in ligand **1b**, and even more in **1c**, by simple steric interactions, an efficient chirality transfer from the atropisomeric chiral binaphthyl backbone to the achiral amino alcoholic moiety can occur, generating a chiral environment around the zinc atom in the zinc aminolkoxide complex (A). In these compounds the chirality transfer occurs even if no stereogenic centers are close to the complexing zinc atom, affording enantiodiscrimination in both the alkynylation and phenylation reactions. The level of enantioselectivity provided by these ligands in such reactions is however considerably lower than in the diethylzinc addition. This can be due to both the possible competition with uncatalyzed background reaction and to the presence of larger alkynyl and phenyl zinc moieties, which can destabilize the *anti*-(*S*) transition state.

3. Conclusions

We have demonstrated that the rationally designed (*S*)-**1b** and (*S*)-**1c**, which showed excellent enantioselection in the ethylation of arylaldehydes, also efficiently catalyze the enantioselective addition of zinc phenylacetylide and diphenylzinc to aromatic aldehydes. In particular, (*S*)-**1c** was markedly more efficient than (*S*)-**1b**, affording ees up to 70% in the alkynylation of benzaldehyde and ees up to 54% in the phenylation of 4-Cl benzaldehyde. A qualitative explanation of the stereochemical outcome of both reactions has been tentatively provided, showing that simple structural modifications, with no changes in the chiral backbone, can significantly improve the efficiency of the ligand. Although the enantioselectivity provided in these reactions is still moderate, we believe that 1,1′-binaphthylazepine amino alcohols can constitute a new class of promising chiral ligands. Their peculiar structures can in fact be easily modified allowing us to prepare, from commercially available enantiopure 1,1′-binaphthol, and in both enantiomeric forms, tailor-made ligands for asymmetric catalysis. Work is currently in progress on their use of catalytic precursors in other enantioselective transformations.

4. Experimental

4.1. General procedures

^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ on a Bruker Aspect 300 spectrometer. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. Addition of organometallics was performed using a syringe-septum cap technique under a nitrogen atmosphere. Toluene and THF were freshly distilled prior to their use on sodium benzophenone ketyl under a nitrogen atmosphere. Commercially available (Aldrich) dimethylzinc (2.0 M solution in toluene), diethylzinc (1.0 M solution in hexanes), and diphenylzinc were used as purchased. Commercially available (Aldrich) benzaldehyde, 4-chlorobenzaldehyde, and 2-trifluoromethylbenzaldehyde were distilled prior to their use and stored under a nitrogen atmosphere. Commercially available (Aldrich) 2-naphthaldehyde and 1-naphthaldehyde were used as purchased. All the 1-aryl-3-phenyl-prop-2-yn-ols and diaryl carbinols showed analytical and spectroscopic data in full agreement with the literature data. Enantiomeric excesses of the optically active carbinols were determined by HPLC analysis performed on a JASCO PU-1580 pump with a Varian 2550 UV detector and Daicel Chiralcel OD or OB columns. Analytical TLC was performed on a 0.2 mm silica gel plate Merck 60 F-254. Gas-chromatographic analysis was performed by GLC-MS on a Hewlett Packard 6890 chromatograph equipped with a HP-5973 mass detector. The ligands were prepared after the procedure previously reported by the authors.[4,7]

4.2. Typical procedure for the phenylacetylene addition to arylaldehydes

To a solution of phenylacetylene (52.7 μL, 0.48 mmol) in dry toluene (2.0 mL) under a nitrogen atmosphere at room temperature was added a solution of $ZnMe_2$ in toluene (2.0 M, 220 μL, 0.44 mmol). The mixture was stirred for 30 min, then the ligand (0.02 mmol, 10 mol %) was added and, after a further 30 min, the arylaldehyde (0.20 mmol) was added. The mixture was monitored by TLC and when no more traces of the aldehyde were detected, the reaction mixture was quenched by the addition of 5% aqueous HCl. The mixture was extracted with Et_2O and the organic phase washed with brine, and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the recovered residue was purified by column chromatography (SiO_2; petroleum ether/ethyl acetate 10:1).

4.3. Typical procedure for the diphenylzinc addition to arylaldehydes

To a solution of $ZnEt_2$ (1.0 M in hexanes, 50 μL, 0.50 mmol) in dry toluene (3.0 mL) was added the ligand (0.02 mmol). The solution was stirred for 15 min at room temperature and then $ZnPh_2$ (50 mg, 0.23 mmol) was added. After a further 15 min of stirring, the aldehyde (0.2 mmol) was added. The mixture was monitored by TLC and when no more traces of the aldehyde were detected, the reaction mixture was quenched by the addition of 5% aqueous HCl. The mixture was extracted with Et_2O and the organic phase washed with brine, and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the recovered residue was purified by column chromatography (SiO_2; petroleum ether/diethylether 7:3).

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