

Chiral tertiary alcohols from a *trans*-1-arenesulfonyl-amino-2-isoborneolsulfonylamino-cyclohexane-catalyzed addition of organozincs to ketones

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Dedicated to Professor Josep Castells on the occasion of his 80th birthday

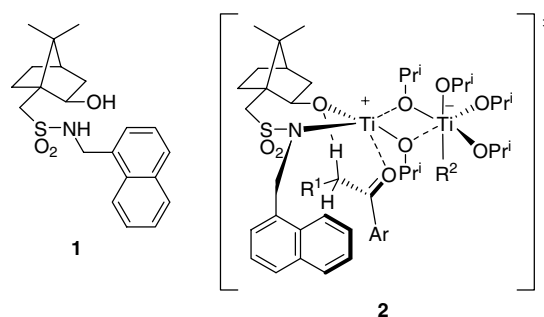
Abstract—The catalytic enantioselective addition of different organozinc reagents, such as alkyl, or in situ generated aryl, allyl, alkenyl and alkynyl derivatives to simple aryl ketones, was accomplished using titanium tetraisopropoxide and chiral ligands derived from 1-arenesulfonylamino-2-isoborneolsulfonylamidocyclohexane, giving the corresponding tertiary alcohols with enantioselectivities up to >99%. A simple and efficient procedure for the synthesis of the disulfonamide ligands used is described.
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1. Introduction

Nowadays the catalytic enantioselective generation of compounds with stereogenic tertiary carbon atoms can be easily achieved in most cases.¹ However, the related approach to compounds bearing quaternary stereocenters is still an enormous challenge for synthetic organic chemistry. Thus, every new enantioselective procedure for the construction of a fully substituted carbon center is of great value,² the simplest approach for the preparation of chiral tertiary alcohols being the enantioselective 1,2-addition of organometallic reagents³ to ketones.⁴

Recently, we have introduced isoborneolsulfonamide⁵ **1** as the first chiral ligand⁶ able to promote the catalytic enantioselective addition of dialkylzinc reagents to simple ketones⁷ in the presence of titanium isopropoxide.⁸ Simple initial mechanistic studies suggested that the catalytic cycle could be similar to that proposed for the classical enantioselective addition of dialkylzinc reagents to aldehydes,⁹ by only changing the corresponding electrophile.¹⁰ The stereochemical outcome of the reaction was rationalized by the formation of a catalytic bimetallic¹¹ species **2**, in which the ketone was coordinated to a

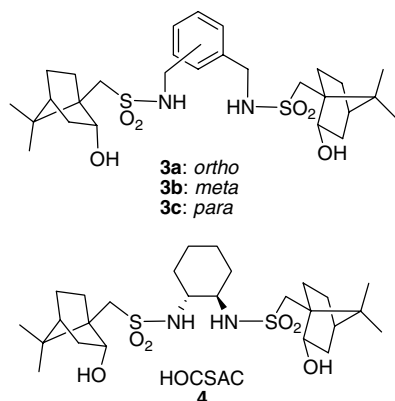
cationic titanium center bearing the chiral ligand¹² favoring a possible π -stacking effect between aryl moieties, and showing a hydrogen bond between the α -proton of the ketone and the oxygen atom of the chiral ligand.¹³



The possible participation of a catalytic bimetallic species **2** suggested the synthesis of chiral ligands **3**¹⁴ and **4** (HOCSAC)¹⁵ able to accommodate two titanium atoms at the same time. In this way, the previous results could be improved depending on the length and angles between the isoborneolsulfonamide moieties; this concept was also applicable to aldehydes.¹⁶ The ligand HOCSAC gave the best enantiomeric excess (only one enantiomer detected) for the alkylation of α,β -unsaturated ketones, being used as the asymmetric key step

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in the synthesis of (–)-frontalin.¹⁷ HOCSAC **4** is also an excellent ligand for the arylation of ketones using boronic acids as the starting nucleophile source.¹⁸



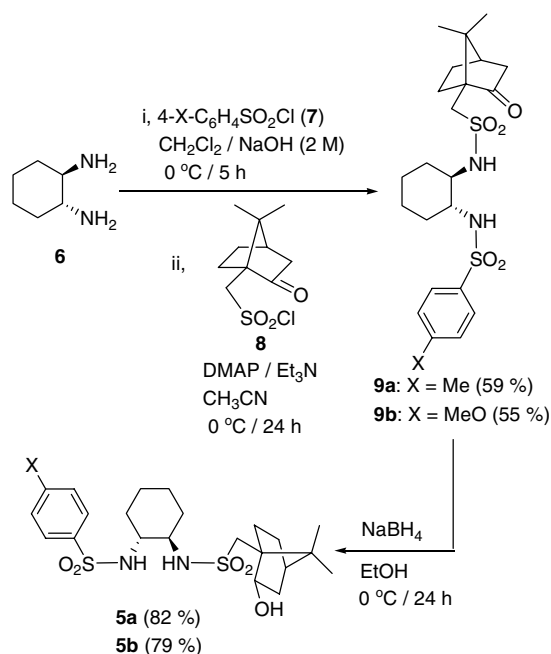
Following our ongoing project on the development of new chiral ligands based on isborneolsulfonamide structures, we herein report the first synthesis of chiral *trans*-1-arenesulfonylamino-2-isborneolsulfonylamino-cyclohexane derivatives **5** and the preliminary results on their use as chiral promoters in the catalytic enantioselective addition of different zinc reagents to aryl ketones.

2. Results and discussion

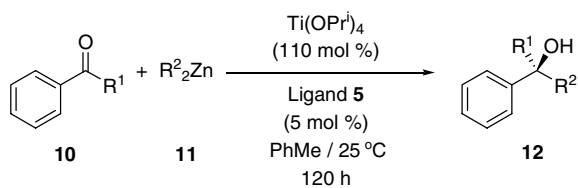
Chiral ligands **5** were prepared from the corresponding chiral (1*R*,2*R*)-*trans*-1,2-diaminocyclohexane **6** by reaction with the corresponding arenesulfonyl chloride **7** in a biphasic media at 0 °C, followed by the standard coupling reaction of the in situ prepared amine with (1*S*)-(+)-10-camforsulfonyl chloride **8** to yield the corresponding ketones **9** with good chemical yields. These ketones were diastereoselectively reduced to the expected tridentate ligands **5** with good chemical yields and diastereoselectivities higher than 80% (Scheme 1). The major diastereoisomer **5** was easily isolated in pure form (>99%) by column chromatography.

Once ligands **5** were prepared, they were first tested in the enantioselective addition of commercially available dialkylzincs **11** to simple phenyl alkyl ketones, in the presence of Ti(OPrⁱ)₄. The reaction gave the expected tertiary alcohols **12** after 5 days at room temperature (Scheme 2). Although the reaction rate was slow, the enantioselectivity was excellent for all the tested cases, the minor enantiomer not being detected by chiral column GC analysis. The reaction using dimethylzinc **11a** as the initial source of the nucleophile gave a lower yield than for diethylzinc **11b** independent of the ligand used, **5a** or **5b**.

After the success was found for the enantioselective alkylation of simple ketones, we turned our attention to the zinc reagent. The first example studied was the allylation process, which was accomplished by reaction of cinnamyl acetate **13** with diethylzinc **11b** catalyzed by palladium(0)tetrakis(triphenylphosphine) to yield the corresponding allyl zinc reagent (Scheme 3).¹⁹ The

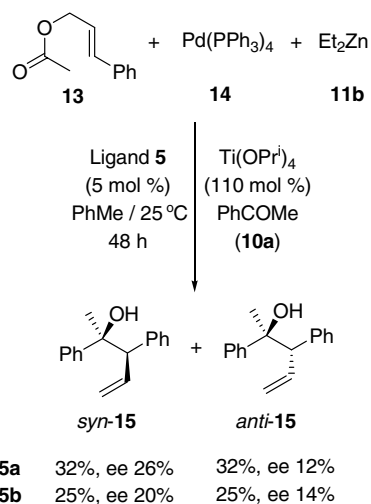


Scheme 1.

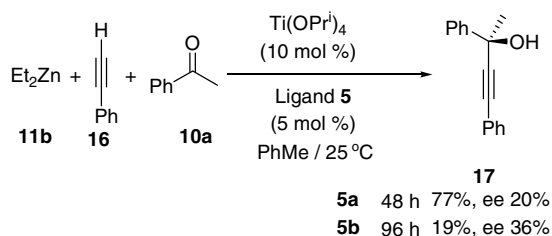


Ligand 5a				Ligand 5b			
R ¹	R ²	Yield (%)	ee (%)	R ¹	R ²	Yield (%)	ee (%)
Me	Et	55	>99	Me	Et	65	>99
Et	Me	25	>99	Et	Me	29	>99

Scheme 2.



Scheme 3.



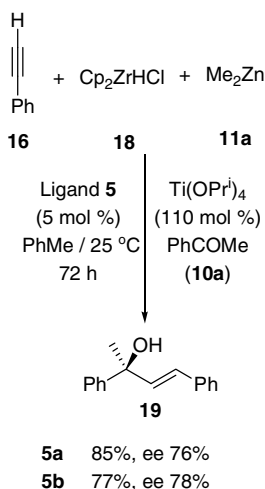
Scheme 4.

in situ formed cinnamyl zinc derivative was trapped by reaction with acetophenone **10a** in the presence of titanium tetraisopropoxide to yield, after hydrolysis with an aqueous saturated solution of ammonium chloride, equimolar amounts of both diastereoisomers **15**.²⁰ The ee values were poor and similarly independent of ligand **5** used.

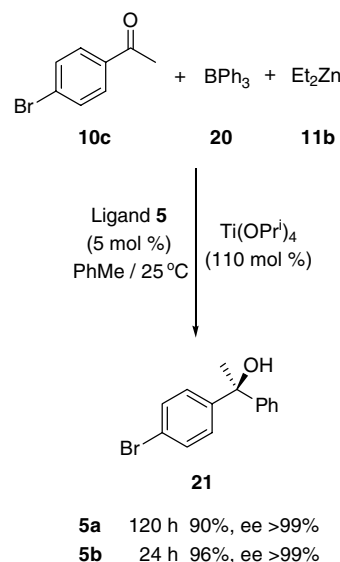
The next process studied was the alkylation process performed by deprotonation of phenylacetylene **16** to yield the corresponding alkynyl zinc reagent, which was trapped by reaction with acetophenone **10a** in the presence of substoichiometric amounts of chiral ligand **5** and titanium tetraisopropoxide²¹ to yield the propargylic alcohol **17** (Scheme 4). Although the results obtained are modest, they show that typical transmetalation processes can be used in the addition of ketones just by a fine tuning of the ligand choice.

The alkenylation process was far more successful. The hydrozirconation of phenylacetylene to yield the corresponding terminal alkenylzirconium derivative followed by transmetalation with dimethylzinc **11a** gave the expected alkenylzinc reagent,²² which was trapped as above by the reaction with acetophenone in the presence of an excess of titanium tetraisopropoxide and substoichiometric amounts of chiral ligands **5** (Scheme 5), both ligands rendering similar results.

We finally studied the catalytic enantioselective arylation of ketones. The corresponding phenyl zinc interme-



Scheme 5.



Scheme 6.

diolate was obtained starting from commercially available triphenylboron **20** by transmetalation with dimethylzinc **11b** by heating in toluene at 70 °C.²³ This intermediate was reacted in situ with *para*-bromoacetophenone **10c** in the presence of substoichiometric amounts of ligands **5** and a small excess of titanium tetraisopropoxide giving the expected diaryl ethanol derivative **21** with excellent enantioselectivities. The minor enantiomer was not detected by chiral column HPLC analysis. Surprisingly, the reaction rate seemed to be quite different for both chiral ligands, with **5b** catalyzing the enantioselective more efficiently. We currently do not have any explanation for this behavior (Scheme 6).

3. Conclusion

In conclusion, we have described herein an easy and simple synthesis of different chiral *trans*-1-arenesulfonylamino-2-isborneolsulfonylamino-cyclohexane derivatives, which permits the highly modular preparation of this type of compound. These ligands have shown to be excellent promoters for the catalytic enantioselective alkylation and arylation of ketones (only one enantiomer being detected), very good for the alkenylation process and modest for the allylation and alkylation reactions. This strategy sheds light on the possibility of using any known transmetalation process to obtain in situ the starting zinc derivatives for this unusual addition to ketones. Work is currently in progress in order to the fine tune the properties of the chiral ligands by changes on the substitution of the arenesulfonyl moiety and improving the results for the allylation and alkylation reactions.

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