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Enantioselective addition of organozinc reagents to carbonyl compounds*

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Abstract: Different chiral camphorsulfonamide derivatives containing a hydroxy or a sulfonamido functionality, as well as chiral 1,2-hydroxysulfonamides, have been evaluated as chiral promoters in the classical enantioselective addition of dialkylzinc reagents to aldehydes in the presence of titanium tetraisopropoxide (ee up to 96 %). Surprisingly, ligands with a structure of isoborneol are able to promote the related unknown addition to ketones (ee >99 %), the best ligand being the *exo*-diol derived from 1,2-*trans*-biscamphorsulfonamidocyclohexane (HOCSAC).

Keywords: Enantioselective; organozinc reagents; camphorsulfonamide; hydroxysulfonamides; dialkylzinc; titanium tetraisopropoxide.

INTRODUCTION

Catalytic enantioselective synthesis [1] is a very valuable method for preparing optically active substances. In contrast to stoichiometric methods, the asymmetric information of the ligand is transferred to several product molecules through a catalytic cycle. The reactivity of the active species bearing the chiral ligand is enhanced due to the so-called "ligand acceleration effect" [2]. Among the enantioselective catalytic transformations, those involving carbon–carbon bond formation are probably the most attractive for synthesis [3]. Concerning this subject, the stereoselective addition of organometallics to one of the two heterotopic faces of a carbonyl group has been extensively studied [4]. Particularly, the addition of diethylzinc to benzaldehyde has become a prototype in the evaluation of any new chiral ligand [5] due to the low nucleophilicity of organozinc reagents, which permits the modulation of their reactivity by addition of different substances.

There is a version of the above reaction promoted by the use of titanium alkoxides [6], which has as a general advantage its homogenous enantioselectivity independent of the nature of the aldehyde. The majority of ligands used in this case have a C_2-symmetry owing to the low number of possible transition states (C_1-ligands have theoretically a double amount of transition states) that favor the enantioselectivity.

DISCUSSION OF RESULTS

We thought that a C_1-ligand with one approach to the reactive area biased by the presence of a bulky moiety could minimize the possible number of transition states and therefore behaves as a C_2-one.

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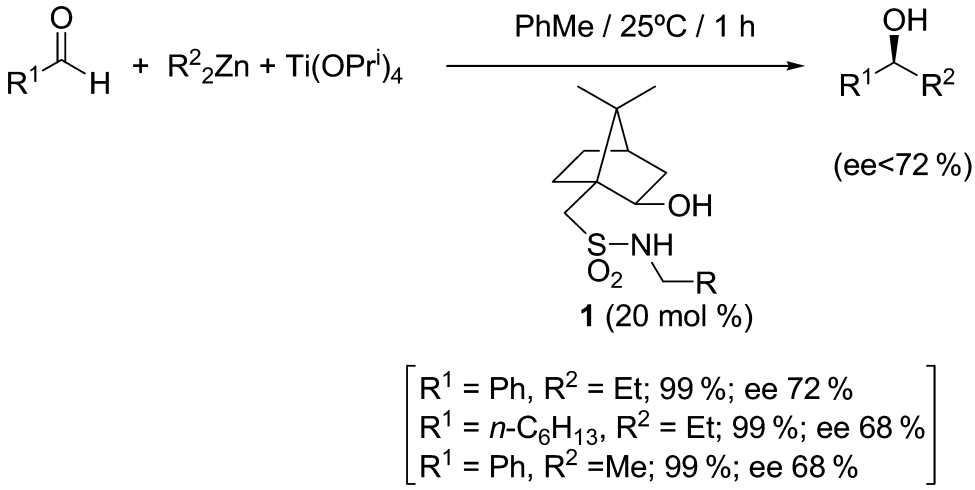
One of the classical examples of biased face compounds appears in the addition of organometallic reagents to bicyclo[2.2.1]hept-2-one derivatives. Thus, the additions of different nucleophiles to 2-norbornanone yield almost exclusively the *endo*-alcohol, whereas in the case of camphor the *exo*-alcohol is the obtained product. This reversal behavior has been explained by the presence of methyl groups at the position 7 of the bicyclic structure, which bias the *exo*-approach (more favored thermodynamically) to the second ketone [7].

With this example in mind, we thought that a chiral ligand having a camphor structure could be a good candidate for C_1-ligand with restricted number of transition states. The designed ligands were *N*-substituted isobornyl-10-sulfonamides **1**, which can be easily obtained by successive reaction of chiral camphorsulfonyl chloride with the corresponding primary amine followed by standard reduction using $NaBH_4$. It should be pointed out that the starting chiral chloride is very cheap and commercially available in both enantiomeric pure forms.

Ligands of type **1** were tested in the classical catalytic enantioselective addition of dialkylzinc to aldehydes (Scheme 1). After optimization of the reaction conditions such as temperature, solvent, and titanium alkoxide, and after testing 15 different ligands of type **1**, the best results (for R = Ph) were unsatisfactory [8] as far as the enantioselectivity concerned.

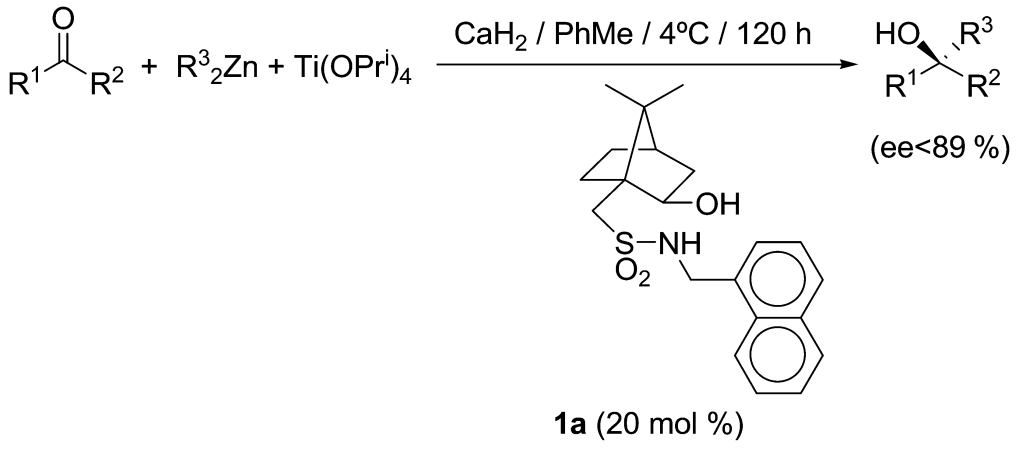


Scheme 1

Despite these disappointing results, we inferred that our ligand design was correct and that the problem arose from the electrophile. Thus, it was expected that substitution of aldehydes with less electrophilic substrates, such as ketones, might improve enantioselectivity. However, the concept of enantioselective addition of organozinc reagents to ketones was unknown at the time that this investigation commenced, and early experimental work met with failure [9].

Nevertheless, when the reaction of dialkylzinc reagents with ketones was performed using titanium tetraisopropoxide and the hydroxylsulfonamide **1a**, the corresponding tertiary alcohols were obtained with a moderate chemical yield (56–95 %) and enantioselectivities ranging from 68 to 72 % [10]. The best results were obtained using alkyl aryl ketones (ee 85–90 %), with α,β-unsaturated ketones the enantioselectivities being lower (ee about 50 %), whereas the reaction failed with dialkyl ketone derivatives (Scheme 2). This new reaction supposed a new entry to the synthesis of chiral molecules bearing an oxido-functionalized quaternary stereocenter [11] and implied the addition of unreactive zinc reagents to poor electrophilic ketones [12].

In order to improve the previous results, the next step was the modification of hydroxy group in the ligand **1** by preparation of the corresponding camphordisulfonamide system of type **2** [13]. This

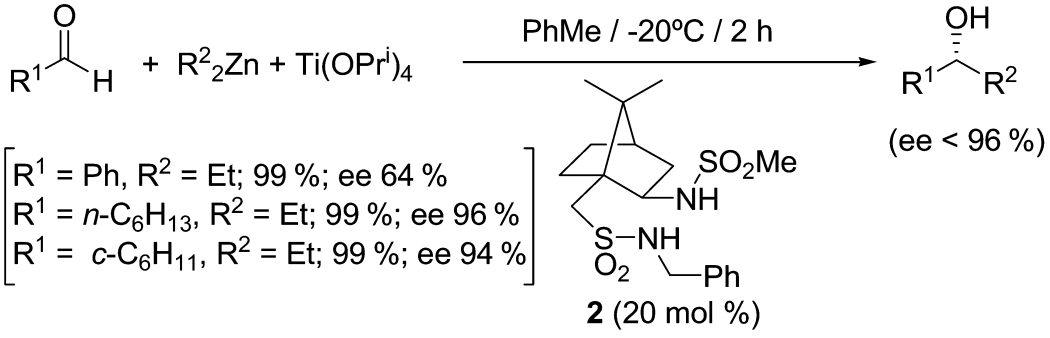


Scheme 2

ligand was obtained from the corresponding Oppolzer sultam [14] by deprotanation reaction with sulfonyl chloride to yield the corresponding sulfonyl imide, which was finally treated with an excess of lithium amide to give, after a ring-opening process, the ligand **2**. However, when the addition of diethylzinc to acetophenone was conducted in its presence, surprisingly, the starting ketone was recovered unchanged.

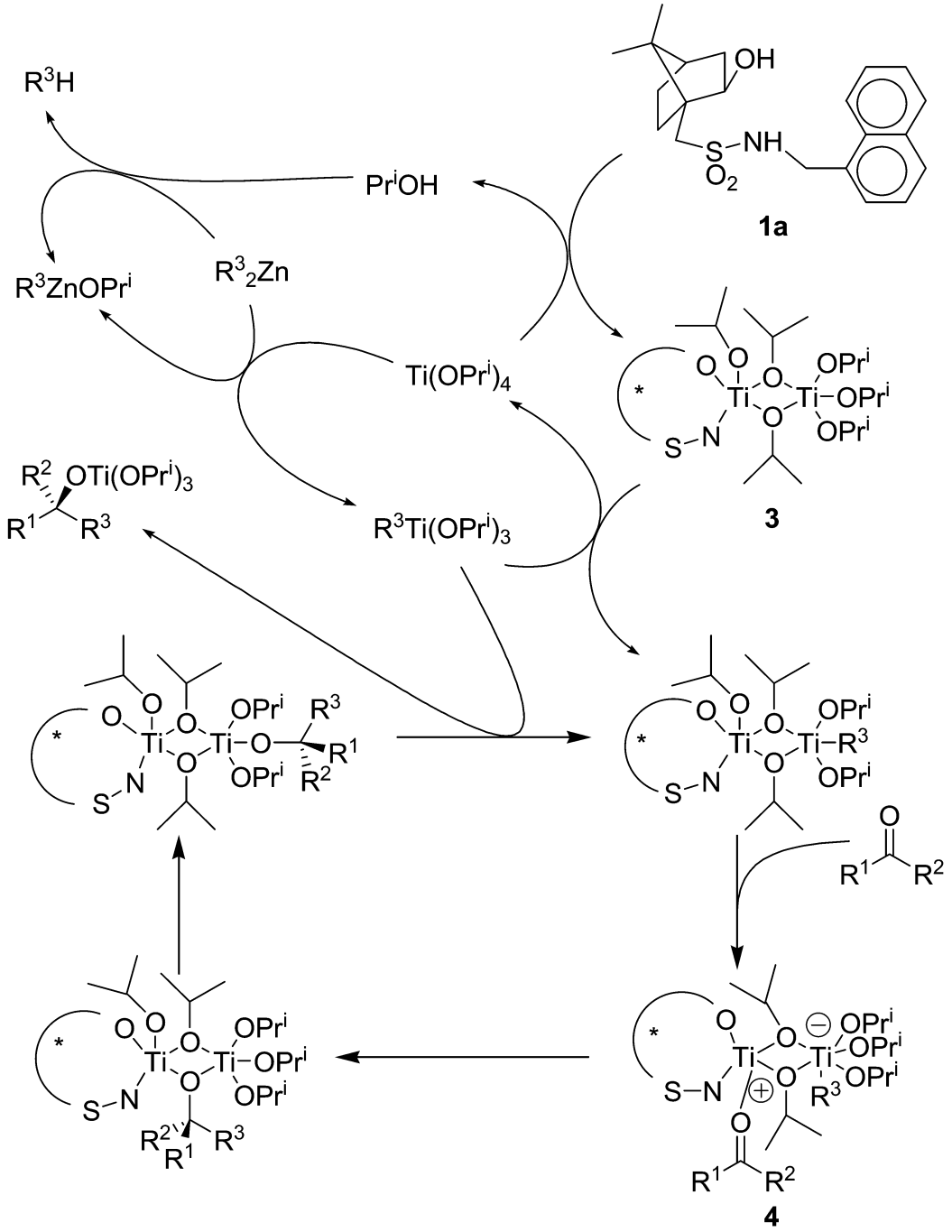
It should be pointed out that ligand **2** is an excellent promoter for the classical enantioselective addition of dialkylzinc reagents to aldehydes, giving the expected secondary alcohol with excellent chemical yields and enantioselectivities (Scheme 3) [13]. Some comments should be made about these results: (a) as usual, low temperature gave the best ee values; (b) the best results were obtained for aliphatic aldehydes (ee about 95 %), the use of more crowded or more acid systems than ligand **2** giving worse results (9 different sulfonamides of type **2** were tested); (c) the absolute configuration of the secondary alcohol obtained using system **2** was the opposite one to that obtained using the related isobornyl-10-sulfonamide **1**.

In order to improve the results outlined in Scheme 2, we turned our attention to the mechanistic studies. The first fact was the presence of a small positive nonlinear effect when the reaction was per-



Scheme 3

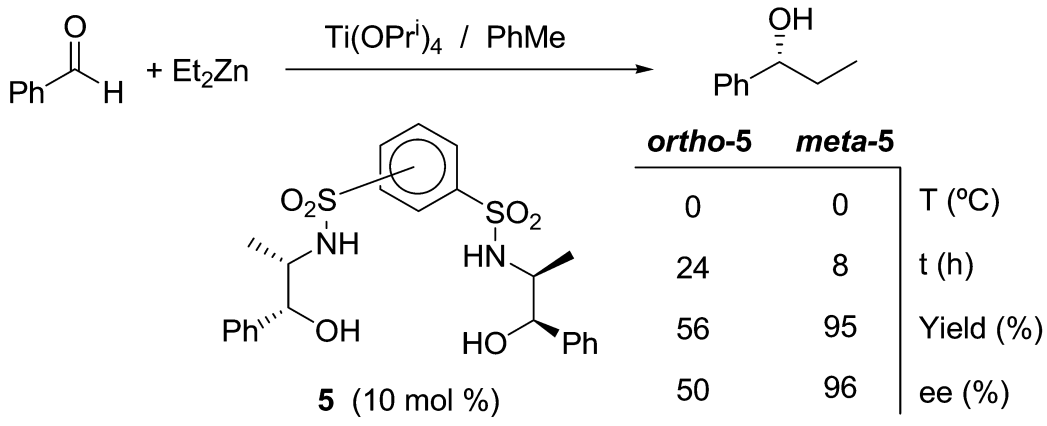
formed using stoichiometric amounts of titanium and the chiral ligand **1a**. This result is usually attributed to the presence of a bimetallic species in the catalytic cycle. However, when the amount of ligand was reduced to 20 %, the aforementioned nonlinear effect disappeared, which would indicate that there is only one chiral ligand in the bimetallic species (**3** in Scheme 4).



Scheme 4

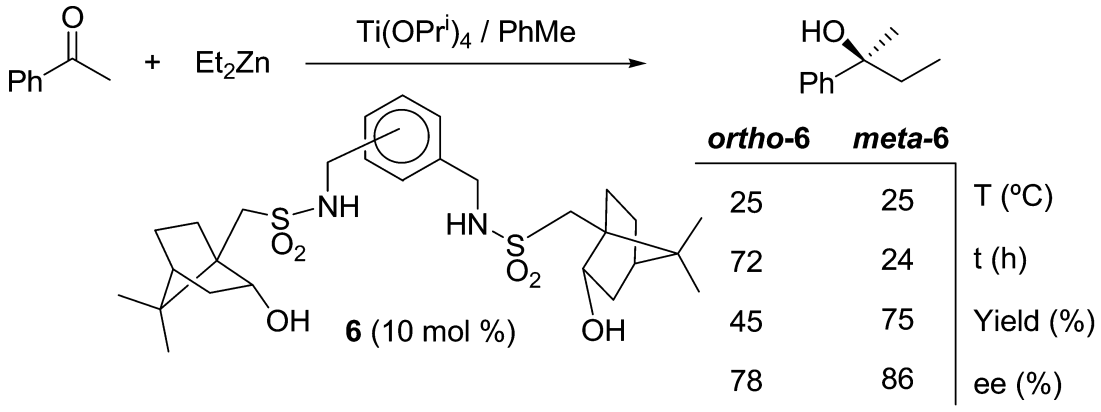
The enantioselectivity was practically independent of the chemical yield (no autocatalysis effect was detected) and strongly dependent on the size of both the ligand and ketone. All these facts were similar to those previously described for the well-known alkylation of aldehydes [15]. As a consequence, and assuming that the catalytic species has a pentacoordinated positively charged titanium center **4** [16], a similar catalytic cycle and bimetallic species were postulated for this new reaction [17]. These assumptions prompted us to synthesize ligands able to chelate two atoms of titanium at the same time. In this way, the catalytic enantioselective species of type **4** might be improved by playing with the length and angles between both isobornyl moieties.

After becoming engaged in this enterprise, we tested our idea in the classical and simpler ethylation of benzaldehyde, and for that purpose, ligands of type **5** were synthesized [18]. To our delight, the results (time, chemical yield, as well as the enantioselectivity) were found to be a function of the relative positions of both hydroxysulfanoamido moieties (Scheme 5), which corroborates our initial hypothesis. The level of enantioselectivity was also affected by the size of substituents on the 1,2-amido alcohol and their relative configuration.



Scheme 5

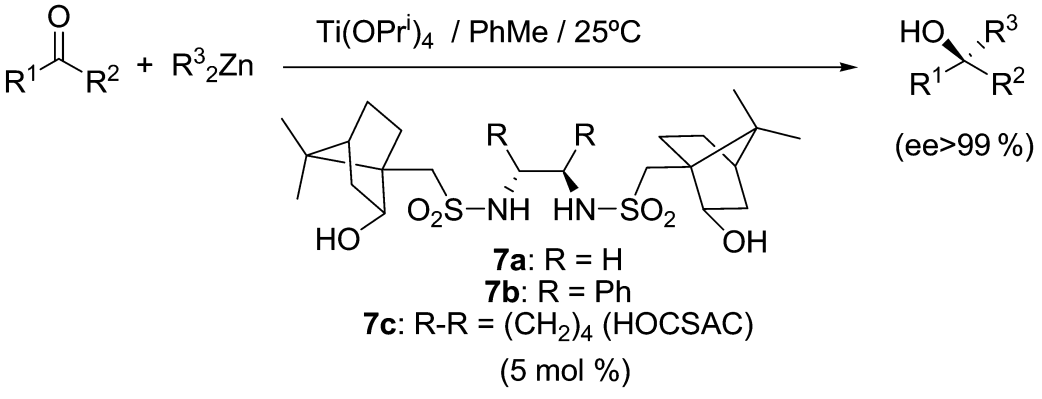
As a consequence of this finding, ligands of type **6** were synthesized starting from different diamines and the corresponding camphorsulfonyl chloride, in the hope of achieving a significant improvement of the results outlined in Scheme 2. The enantioselective addition of diethylzinc to acetophenone showed the previous behavior, that is, the relative position between both isobornyl-10-sulfonyl moieties have a significant impact over reaction time, yield, and enantioselectivity [19] (Scheme 6). In fact, all these parameters were slightly better for ligand *meta*-**6** than for ligand **1a**, using a higher amount of ligand for the last ligand (20 mol %). Other diamines used as linker for isobornyl-10-sulfonyl moieties, including chiral 1,1'-binaphthyl-2,2'-diamine, gave worse results. These unsatisfactory results were rationalized as a consequence of an excessive length between the amine groups in the linker, which diminished the supposed synergistic effect of both titanium atoms hosted in the chiral ligand.



	ortho-6	meta-6	
	25	25	T (ºC)
	72	24	t (h)
	45	75	Yield (%)
	78	86	ee (%)

Scheme 6

Finally, we concluded that a closer relative position between both isobornyl-10-sulfonyl moieties could yield better results, and therefore the ethylendiamine derivatives **7** were synthesized and tested in the enantioselective addition of dialkylnzinc reagents to ketones (Scheme 7), finding that system **7c** (*exo*-diol derived from 1,2-*trans*-biscamphorsulfonamidocyclohexane; HOCSAC) gave excellent results even using a lower-loading catalyst, with enantioselective excess higher than 99 % for α,β-unsaturated ketones, around 95 % for simple alkyl aryl ketones [20] and being able to promotes the addition to dialkyl ketone derivatives.



7a	7b	7c	
96	48	8	t (h)
60	15	80	Yield (%)
92	23	98	ee (%)

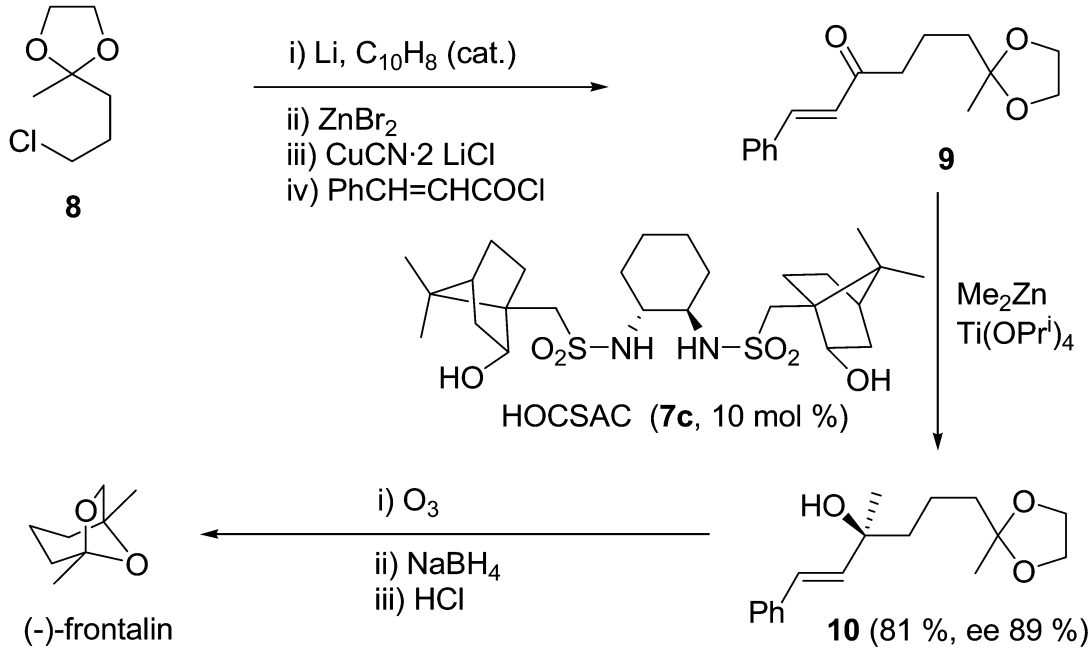
HOCSAC (**7c**)

R^1	R^2	R^3	Yield (%)	ee (%)
PhCH=CH	Me	Et	90	>99
4-BrC$_6$H$_4$	Me	Ph	98	96
c-C$_6$H$_{11}$	Bu^n	Me	70	65

Scheme 7

The ligand HOCSAC (**7c**) showed that it is an excellent promoter not only for the alkylation of ketones, but also for the reaction using diphenylzinc, the improvements with this new ligand being focused not only in the enantioselectivities but also in the chemical yields, catalyst loading, and in the reaction times. The catalytic enantioselective arylation of ketones can be performed not only using pure diphenylzinc, but also using functionalized zinc reagents, obtained in turn by transmetallation from functionalized boronic acids with diethylzinc and trapping the in situ formed functionalized arylzinc reagents by reaction with ketones [21]. The results found under these new conditions were practically identical to those obtained using pure diphenylzinc, making evidence of the ample scope of this new ligand for this addition.

The enantioselective addition of dimethylzinc to an α,β-unsaturated ketone **9** using the ligand HOCSAC (**7c**) has been used as the asymmetric key step in the synthesis of (–)-frontalin [22]. The starting ketone **9** was prepared by a naphthalene-catalyzed lithiation [23] of chloroketal **8** and reaction, after lithio-zinc transmetallation, with cinnamoyl chloride. The final transformation of the tertiary alcohol **10** in (–)-frontalin was accomplished by standard reductive ozonolysis and final acidic hydrolysis (Scheme 8).



Scheme 8

The success of these isorbonyl-10-sulfonamide ligands has been proved not only by the results presented herein, but also by the results from other authors in related processes [24–26].

CONCLUSIONS

Although the catalytic enantioselective addition of dialkylzinc reagents to aldehydes has become a mature method, it still permits some improvements, such as the use of other zinc reagents such as vinyl and aryl as well as the corresponding functionalized derivatives. Another open challenge is the use of less electrophilic systems such as ketones. In this case, the use of ligands derived from isobornyl-10-sulfonamide does not have competence, the combination HOCSAC (**7c**) and titanium tetraisopropoxide giving excellent results. All these facts make the search for new chiral ligands necessary.

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