



Highly enantioselective addition of dialkylzinc reagents to ketones promoted by titanium tetraisopropoxide

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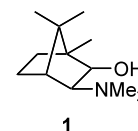
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Abstract—The preparation of several 1,2-bis(hydroxycamphorsulfonamido)cyclohexenes from the corresponding 1,2-cyclohexenediamine and camphorsulfonyl chloride is described. The use of these ligands to promote the enantioselective addition of dialkylzinc to ketones in the presence of titanium tetraisopropoxide gives the expected *tertiary* alcohols with very high enantiomeric excess (>99%). © 2002 Elsevier Science Ltd. All rights reserved.

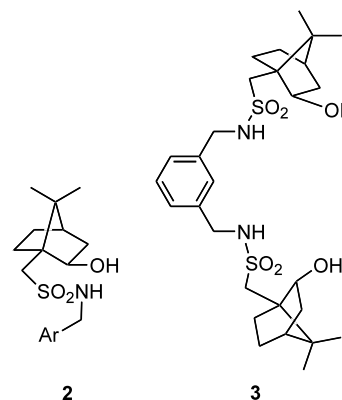
The synthesis of chiral building blocks containing a stereogenic quaternary carbon centre is a considerable challenge in organic synthesis.¹ The simplest approach to the construction of the corresponding heteroatom-substituted quaternary carbon stereocentres is the enantioselective addition of organometallic reagents to carbonylic derivatives.² Among other organometallics, dialkylzinc reagents are ideal alkyl nucleophile synthons since it is very easy to obtain many different functionalised reagents.³ However, their low reactivity towards electrophilic compounds represents a significant drawback. This drawback has been transformed into an advantage by the use of several promoters in order to perform different types of additions: A plethora of chiral ligands has been used in the enantioselective addition of dialkylzinc to aldehydes,⁴ this reaction being the typical reaction to prove the efficiency of different type of ligands.

On the other hand, the reaction of dialkylzinc reagents with ketones does not yield the addition product (*tert*-alcohol),⁵ giving instead the corresponding secondary alcohol, arising from a reduction process.⁶ Only very recently, have the first examples of chiral ligands that enable the addition of organozinc reagents to ketones been described independently and simultaneously.^{7,8}

The addition of diphenylzinc to phenones has been reported, using a mixture of aminoalcohol **1** and methanol as promoter. The success of the addition was ascribed to the higher reactivity of the zinc reagent, as well as the higher acidic character of the system due to the presence of methoxy groups.⁷



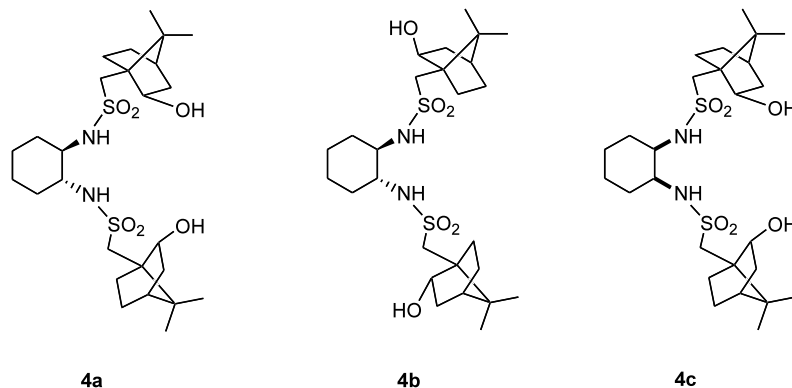
Investigation into the use of hydroxysulfonamides as chiral ligands in the enantioselective addition of dialkylzinc reagents to aldehydes promoted by titanium tetraalkoxides⁹ has been an ongoing concern in our laboratory for some time.¹⁰ We have reported the first sulfonamide-type chiral ligand **2**, which is able to promote the enantioselective addition of dialkylzinc reagents to ketones in the presence of titanium tetraisopropoxide.⁸ A further evolution of this ligand was introduced by the use of different C_2 -symmetric derivatives, the bis sulfonamide **3** being the best among the corresponding C_2 -symmetric ligands, giving better enantioselection under milder conditions than ligand **2**.¹¹



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After being informed of the preliminary results obtained by Walsh using the ligand **4a**, we report herein our independent work with ligands **4a–c** in the enantioselective addition of dialkylzinc reagents to ketones promoted by titanium tetraisopropoxide.¹²

The synthesis of ligands **4** was performed by reaction of the corresponding commercially available 1,2-cyclohexanediamines and chiral camphorsulfonyl chloride to give the expected 1,2-bis(camphorsulfonamido)-cyclohexane,¹³ which were subsequently reduced using DIBAL-H to give a mixture from which it was easy to isolate the expected ligands **4a**, **b** and **c** in 58, 55 and 46% yield, respectively.



Once ligands **4** were prepared, the next aim was to find the best one for the enantioselective addition of diethylzinc to acetophenone in the presence of titanium tetraisopropoxide to give the expected *tert*-alcohol (see Table 1). The reaction using 10% of chiral ligand **4a** at room temperature in toluene gave, after only 8 h, the expected 1-phenyl-2-butanol with an excellent enantiomeric excess. However, when the ligands **4b** or **c** were used under the same reaction conditions, the corre-

sponding *tert*-alcohol was obtained in both poor yield as well as enantiomeric excess (compare entries 1–3).

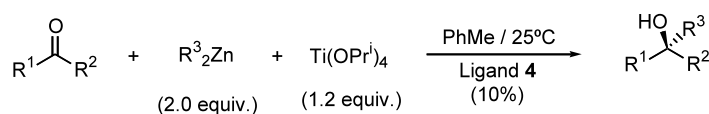
Having established that ligand **4a** was the appropriate system, the influence of different ketones, as well as dialkylzinc reagent, on the enantioselection was studied (Table 1, entries 4–10). The first observation is that the enantioselectivity of the reaction is not influenced by the alkylzinc reagent used. Thus, the same level of enantioselectivity was obtained using dimethylzinc instead of diethylzinc (compare entries 1 and 4).

The influence of different *para*-substituted acetophenone derivatives on the enantioselectivity was also stud-

ied. Thus, we used 4-methylacetophenone and 4-(trifluoromethyl)acetophenone as electrophiles. The enantiomeric excess found in these cases was similar to that found for acetophenone (compare entries 1, 5 and 6). We can conclude that there is no relationship between the enantiomeric excess found and the electronic character of the group placed at the *para*-position.

It is interesting to note that the reaction using a more

Table 1.



Entry	Ketone		R ³	Ligand	<i>t</i> (h)	<i>tert</i> -Alcohol		
	R ¹	R ²				Yield (%) ^a	E.e. ^b	Absolute configuration
1	Me	Ph	Et	4a	8	80	98	<i>S</i>
2	Me	Ph	Et	4b	120	20 ^c	36	<i>R</i>
3	Me	Ph	Et	4c	72	16 ^d	24	<i>R</i>
4	Et	Ph	Me	4a	8	>95	97.5	<i>R</i>
5	Me	4-MeC ₆ H ₄	Et	4a	8	90	95	–
6	Me	4-CF ₃ C ₆ H ₄	Et	4a	8	90	93	–
7	Me	2-C ₁₀ H ₈	Et	4a	8	>95	86	–
8	BrCH ₂	Ph	Et	4a	0.2	70	50	<i>S</i>
9	Me	(<i>E</i>)-PhCH=CH	Et	4a	8	90	>99	–
10	Me	PhC≡C	Et	4a	8	>95	>99	–

^a Isolated yields after bulb-to-bulb distillation.

^b Determined by GLC analysis using a γ -CD column.

^c Starting ketone was recovered in 8% yield.

^d Starting ketone was recovered in 40% yield.

crowded ketone such as 2-acetylnaphthalene gave significantly lower enantioselectivity (entry 7). However, in the case of using a ketone with a chelating functionality close to the carbonyl group, such as 2-bromoacetophenone, the enantiomeric excess fell to 50%, the reaction time being only 15 min (entry 8).

Finally, when the addition was performed using α,β -unsaturated ketones, the enantioselection was higher than 99%, the minor of the enantiomers being undetectable by chiral GLC analysis.

In summary, we can conclude that *trans*-1,2-bis-(hydroxy-camphorsulfonamide)cyclohexane **4a** is an extraordinary ligand for promotion of the enantioselective addition of dialkylzinc reagents to ketones in the presence of titanium tetraisopropoxide. In most cases, the otherwise difficult to obtain *tert*-alcohol was formed in good chemical yields and with excellent levels of enantioselection.

The scope and the mechanism of catalytic species described herein is currently under further investigation.

Acknowledgements

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