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# Diastereodivergent additions of aluminum and magnesium reagents to [(S)*S*]-3,6-dimethoxy-2-(*p*-tolylsulfinyl)-benzaldehyde

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**Abstract**—Enantiomerically pure [(S)*S*]-3,6-dimethoxy-2-(*p*-tolylsulfinyl)-benzaldehyde, prepared in two steps from commercially available 2,5-dimethoxybenzyl alcohol, reacted with organomagnesium and organoaluminum derivatives in a highly diastereodivergent way giving rise respectively to the (*S*) or (*R*) alkyl aryl or diaryl carbinols in excellent chemical and optical yields. Enantiopure (*S*) and (*R*)-2,5-dimethoxyphenyl methyl carbinols were obtained through a two-steps sequence comprising nucleophilic addition of MeMgBr or $AlMe_3$ and desulfinylation with *n*-BuLi.


Enantiopure chiral secondary carbinols are important starting materials for the total synthesis of natural products.[1] Enzymatic resolution of racemic derivatives,[2] catalytic asymmetric hydrogenation[3] or asymmetric reduction of prochiral ketones with chirally modified hydrides[4] are general methods for the synthesis of optically enriched secondary alcohols. Although the catalytic asymmetric dialkylzinc addition to benzaldehydes has also been successfully applied to the synthesis of aryl alkyl carbinols,[5] to the best of our knowledge, 2,5-dimethoxy benzaldehyde has only been used as substrate in the quinine-catalyzed additions of diethylzinc[6] and di-*n*-propylzinc[7] en route to a natural pyranonaphthoquinone, but no addition of $Me_2Zn$ has been described. Thus, the corresponding 2,5-dimethoxyphenyl methyl carbinol is only available in enantiomerically enriched form by asymmetric reduction of the substituted acetophenone,[8–10] and by enzymatic resolution.[11] In all cases but the last one, only one enantiomer is available with a maximum enantiomeric purity of 91%. The presence of a 2,5-dimethoxy aryl moiety in such carbinol is of huge interest for the synthesis of natural quinones[1a,12] since such aromatic moiety can be easily oxidized into the quinone by a variety of mild procedures.

The asymmetric approach to enantiopure carbinols based on the simplest addition of the widely used Grignard reagents or other organometallic compounds to benzaldehydes bearing a chiral auxiliary, has been scarcely investigated.[13] In our continous search for new applications of sulfoxides in asymmetric synthesis,[14] we were interested in knowing whether enantiopure *ortho*-sulfinylbenzaldehydes can control the diastereoselective addition of organometallic reagents by a 1,4 asymmetric induction process. Several reports have been published concerning the addition of nucleophiles to carbonyl groups in molecules containing a chiral sulfoxide, that posses the reaction site remote from the sulfinyl group (1,>3 asymmetric induction). These studies have mainly focused on acyclic,[15] heterocyclic[16] and naphthalenic systems.[17] In spite of the good diastereoselectivities achieved in general, only one recent example[13] dealt with molecules containing a simple benzene ring. In that report the use of the bulky 2,4,6-triisopropylphenylsulfinyl group as chiral inductor was necessary to obtain only one of the two possible carbinols in a diastereoselective way.

In this communication, we report that the common *p*-tolylsulfinyl group, easily accessible from commercially available starting materials, is very efficient in directing the nucleophilic addition of different organometallic derivatives on the carbonyl group of [(S)*S*]-3,6-dimethoxy-2-(*p*-tolylsulfinyl)-benzaldehyde (**1**), and allows the diastereodivergent synthesis of the corresponding sulfinyl-substituted (*S*) or (*R*) alkyl aryl or diaryl carbinols, by simply choosing the appropriate organometallic reagent. A final desulfinylation step on methyl derivatives, illustrates the usefulness of the process to synthesize in optically pure form both enantiomers of 2,5-dimethoxyphenyl methyl carbinol in a short and efficient manner.

*Keywords*: asymmetric synthesis; benzaldehydes; diastereoselection; organometallic additions; sulfoxides.
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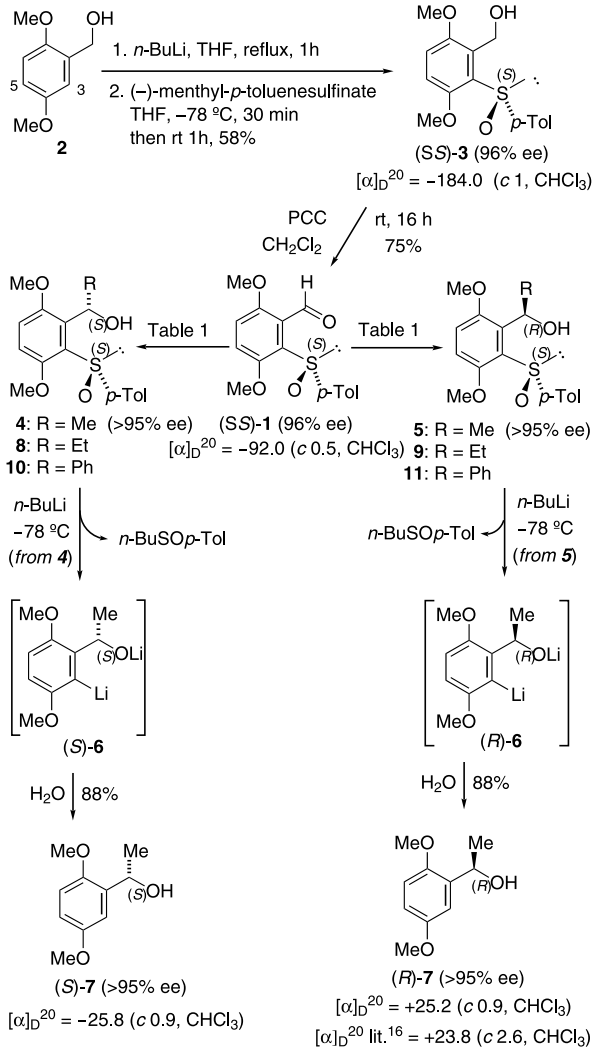
The synthesis of [(S)*S*]-**1**, depicted in Scheme 1, started from commercially available 2,5-dimethoxybenzyl alcohol (**2**). After many synthetic effort, we found that the




**Scheme 1.**

*ortho*-directed[18] lithiation of **2** using *n*-BuLi in refluxing THF followed by addition of (1*R*,2*S*,5*R*,S*S*)-(–)-menthyl *p*-toluenesulfinate[19] at –78°C afforded exclusively the 3-sulfinyl regioisomer [(S)*S*]-**3** in 21% isolated yield (58% based on recovered starting material **2**) showing 90% ee.[20] After one recrystallization, the optical purity of **3** was shown to be 96%. When the lithiation step was performed at rt, a 70:30 mixture of **3** and its 5-sulfinyl substituted regioisomer was formed in 60% isolated yield (85% based on recovered **2**). PCC oxidation of alcohol **3** (Scheme 1) gave aldehyde [(S)*S*]-**1** in 75% yield and 96% ee.[20]

With [(S)*S*]-**1** in hand, we began the study of nucleophilic additions by using different methyl substituted organometallic reagents as models to determine the role of the metal in the control of the diastereoselectivity. The best results of this study are summarized in Table 1.

The addition of MeMgBr in THF at –78°C occurred in 4 h (entry 1) affording exclusively diastereoisomer **4** $\{[\alpha]_D^{20} = -129$ (*c* 1, $CHCl_3)\}$, which was shown to be enantiomerically pure from its Mosher's esters,[21] bearing the (*S*) absolute configuration at the newly created stereogenic center. This result was in agreement with that reported by Toru[13] in the Grignard addition on unsubstituted 2-(2,4,6-triisopropylphenylsulfinyl)-benzaldehyde but contrasted with the poor selectivity achieved (67:33) by using the *p*-tolylsulfinyl analogue.

With the aim of inverting the diastereoselection, we tried to mix $ZnBr_2$ with [(S)*S*]-**1**, prior to the reaction with MeMgBr, but an identical diastereoselectivity resulted, being diastereomer [*S*,(S)*S*]-**4** formed as major (entry 2). Other Lewis acids such as $TiCl_4$ (entry 3), $Ti(O^iPr)_3Cl$ (entry 4) or $AlCl_3$ (entry 5), as well as the methyl titanium reagent $MeTi(O^iPr)_3$[22] (entry 6), gave poorer conversions and/or lower diastereoselections.

When [(S)*S*]-**1** was submitted to reaction with $Me_2Zn$ in $CH_2Cl_2$ at rt for 16 h (entry 7), compound **4** was again

**Table 1.** Diastereoselective organometallic additions to [(S)*S*]-3,6-dimethoxy-2-(*p*-tolylsulfinyl)-benzaldehyde (**1**)

| Entry | R-metal | Solvent | *T* (°C) | Time (h) | Carbinols (ratio) | D.e. (%) | Yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | MeMgBr | THF | –78 | 4 | **4** (>98):**5** (<2) | 98 | 91 |
| 2 | $MeMgBr/ZnBr_2$ | THF | –48 | 8 | **4** (98):**5** (2) | 96 | [a] |
| 3 | $MeMgBr/TiCl_4$ | $CH_2Cl_2$ | –48 | 3.5 | **4** (92):**5** (8) | 84 | [a] |
| 4 | $MeMgBr/Ti(O^iPr)_3Cl$ | THF | –48 | 4.5 | **4** (90):**5** (10) | 80 | [b] |
| 5 | $MeMgBr/AlCl_3$ | $CH_2Cl_2$ | –48 | 5.5 | **4** (64):**5** (36) | 28 | [c] |
| 6 | $MeTi(O^iPr)_3$ | $CH_2Cl_2$ | 0 | 4.5 | **4** (92):**5** (8) | 84 | [d] |
| 7 | $Me_2Zn$ | $CH_2Cl_2$ | 20 | 16 | **4** (98):**5** (2) | 96 | 90 |
| 8 | $Me_3Al$ | $CH_2Cl_2$ | –78 | 0.3 | **4** (<2):**5** (>98) | 98 | 92 |
| 9 | $Me_2AlCl$ | $CH_2Cl_2$ | –78 | 1 | **4** (3):**5** (97) | 94 | 84 |
| 10 | EtMgBr | THF | –78 | 5 | **8** (>98):**9** (<2) | 98 | 68 |
| 11 | $Et_3Al$ | $CH_2Cl_2$ | –78 | 1 | **8** (<2):**9** (>98) | 98 | 64 |
| 12 | PhMgBr | THF | –78 | 8 | **10** (>98):**11** (<2) | 98 | 76 |

[a] Not determined.
[b] 11% conversion.
[c] 85% conversion.
[d] 10% conversion.

generated with an excellent diastereoselectivity (98:2), in 90% yield. This high reactivity was noteworthy because it is well documented that dialkylzinc reagents react only sluggishly with aldehydes in the absence of catalysts,[23] and suggested an activation by the sulfoxide which could interact with the organozinc reagent, favoring the addition. This was confirmed by performing the reaction on 2,5-dimethoxybenzaldehyde, lacking the sulfoxide. Under the same conditions ($Me_2Zn$, $CH_2Cl_2$, rt, 16 h), only a 5% of conversion was observed.

Gratifyingly, when the reaction of [(S)*S*]-**1** was carried out with $Me_3Al$ in $CH_2Cl_2$ at −78°C, only diastereoisomer **5** {$[\alpha]_D^{20}=-156$ (*c* 0.7, $CHCl_3$)}, showing the (*R*) configuration at the hydroxylic carbon was obtained after 20 min (Table 1, entry 8). Carbinol **5** was isolated with 92% yield in enantiomerically pure form (Mosher's esters).[21] In the absence of the sulfoxide, the addition of $Me_3Al$ to 2,5-dimethoxybenzaldehyde was comparatively slow (35% conversion after 20 min). This result suggested an essential role of the sulfoxide controlling both the diastereoselectivity and the reaction rate of the process.

Finally, $Me_2AlCl$ also showed a high reactivity ($CH_2Cl_2$, −78°C, 1 h) as nucleophile (Table 1, entry 9) for the transfer of a methyl group, and its addition to [(S)*S*]-**1** followed a similar pattern. Compound **5** was again formed with an excellent diastereoselectivity (de 94%). The same reaction on 2,5-dimethoxybenzaldehyde at −78 °C for 9 h took place with only a 40% conversion.

Cleavage of the sulfoxide of **4** and **5** was achieved with *n*-BuLi at −78°C (Scheme 1) through the dilithiated intermediates (*S*)-**6** and (*R*)-**6** which were trapped with $H_2O$ to give enantiomerically pure (Mosher's esters)[21] aryl methyl carbinols (*S*)-**7** and (*R*)-**7**[9a] (88% yield). This desulfinylation step is of huge interest since intermediates **6** could be trapped by other electrophiles opening access to differently tetrasubstituted aromatic carbinols.

With the aim of determining the generality of this diastereodivergent process, we added other organometallic reagents to [(S)*S*]-**1**. Thus, EtMgBr (Table 1, entry 10) gave exclusively diastereomer [*S*,(S)*S*]-**8** {$[\alpha]_D^{20}=-107$ (*c* 0.4, $CHCl_3$)}, whereas $AlEt_3$ afforded the [*R*,(S)*S*] epimer **9** {$[\alpha]_D^{20}=-146$ (*c* 0.2, $CHCl_3$)}, as a sole diastereomer (entry 11). Phenyl magnesium bromide (entry 12) reacted with [(S)*S*]-**1** leading to the exclusive formation of diaryl carbinol [*S*,(S)*S*]-**10** {$[\alpha]_D^{20}=-173$ (*c* 0.5, $CHCl_3$). Upon treatment of [(S)*S*]-**1** with $Ph_2Zn$ at rt for 24 h in $CH_2Cl_2$, the starting material was recovered unchanged. This lack of reactivity was surprising tacking into account that diphenylzinc is able to react with benzaldehydes even without catalysts.[5a]

In order to check if a phenyl aluminum derivative was able to invert the diastereoselectivity of the process, we tried to perform the nucleophilic addition of $Ph_3Al$ generated in situ from $AlCl_3$ and PhLi.[24] When this reagent was added over a solution of [(S)*S*]-**1** in $CH_2Cl_2$, no reaction occurred even at room temperature for 24 h. A similar negative result was observed when [(S)*S*]-**1** was treated with $PhAlMe_2$, generated in situ from a 1:1 mixture of $Me_2AlCl$ and PhLi.[25] Under the same conditions, 2,5-dimethoxybenzaldehyde disappeared in 24 h upon reaction with $PhAlMe_2$ giving a complex mixture where the addition products resulting from the transfer of the Me and Ph groups could be detected. This result suggested that the sulfoxide was difficulting the reaction of bulky diphenylzinc or aryl aluminum reagents with [(S)*S*]-**1**. Thus, the sulfinyl group seems to play a crucial role facilitating the addition of alkyl groups from the organometallics and difficulting the phenyl transfer.

The high reactivity and stereochemical outcome of $R_3Al$ (R = Me, Et) additions to [(S)*S*]-**1** could be explained through the initial formation of a species such as **A** (Fig. 1), where the aluminum is associated to the sulfinylic oxygen. The most favored disposition of sulfur substituents is the one shown in **A** where the small non-bonding electron pair is situated in the *s-cis* disposition close to the carbonyl oxygen, which is forced to be far from the *ortho*-methoxy group to avoid electronic repulsions. The intramolecular transfer of the alkyl R group to the most accesible *Re*-face of the aldehyde, through a seven-membered cyclic transition state, explains the formation of (*R*) carbinols.

The opposite diastereoselection observed in the additions of Mg or Zn derivatives, is explained from the evolution of a chelate such as **B** (Fig. 1), where the metal is associated to the sulfinyl and carbonyl oxygens. The attack of a second equivalent of the organometallic reagent to the *Si*-face of the carbonyl, justifies the formation of the (*S*)-carbinols. A key structural feature of **B** is the disposition of the non-bonding electron pair at sulfur which could also interact with the electrophilic organometallic reagent favoring the *Si* face attack. Both mechanistic proposals explain the enhanced reactivity observed for $R_3Al$ (favored intramolecular transfer) and $Me_2Zn$ or Grignard reagents (activation of the carbonyl group by chelation) due to the presence of the sulfoxide. The lack of reactivity observed for the aryl zinc or aluminum reagents could be due to their bulkyness and lower electrophilicity. This avoids the assoca-

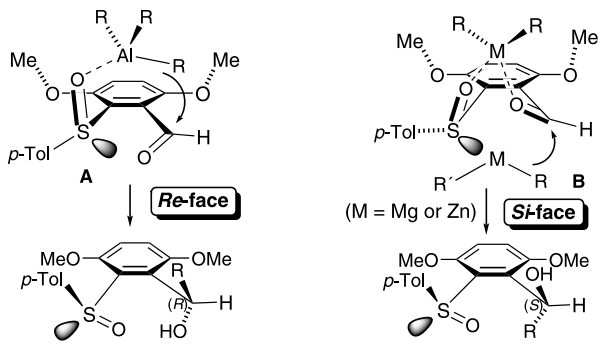



**Figure 1.**

tion to the basic centers of [(S)*S*]-**1**, essential for the effective transfer of aryl groups.

In summary, we have described a short and diastereodivergent synthesis of both diastereomers of alkyl aryl sulfinylcarbinols **4**–**5** and **8**–**9**, as well as the [*S*,(S)*S*] diastereomer of diarylcarbinol **10** in excellent chemical and optical yields, simply by selecting the organometallic reagent which makes the nucleophilic addition. Methyl aryl carbinols **4** and **5** have been desulfinylated to the corresponding enantiomers of alcohol **7**, showing that the nucleophilic addition/desulfinylation process is an efficient strategy for the synthesis of enantiopure (*S*)-**7** and (*R*)-**7**.

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