

Improved Methodology for the Asymmetric Alkylation of Aldehydes Employing Bis(sulfonamide) Complexes

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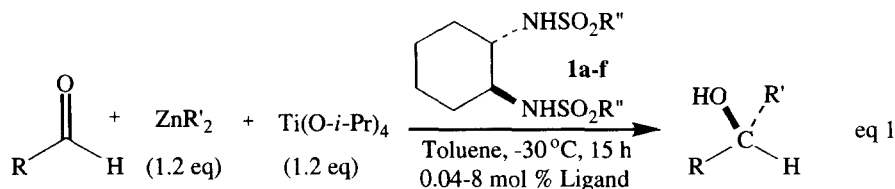
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Abstract: We report an improved procedure for the asymmetric transfer of alkyl groups from zinc to aldehydes utilizing bis(sulfonamide) ligands. The new methodology is easier to perform and, in some cases, provides the alcohol products with higher enantioselectivities than the original methodology.

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The formation of carbon-carbon bonds is one of the most fundamental and important constructions in chemistry. Consequently, efforts to conduct this reaction in an asymmetric fashion have attracted considerable interest.¹ The most common strategy involves the asymmetric addition of organometallic reagents to aldehydes,² and more recently, ketones.^{3,4} Perhaps the most practical and efficient asymmetric addition to aldehydes is that introduced by Ohno and Kobayashi⁵⁻⁷ employing bis(sulfonamide) ligands (eq 1). Knochel broadened the scope of this reaction by employing highly functionalized aldehydes and organozinc reagents to produce elaborate alcohols with high ee's.⁸

In our efforts to understand the mechanism of this reaction, we have developed a more practical procedure which, with certain ligands, gives better enantioselectivity and reproducibility.



The original procedure⁵⁻⁷ called for combination of titanium tetraisopropoxide and ligand in toluene. The solution was heated to 40 °C, then cooled to -78 °C. Diethylzinc (in hexanes) then aldehyde were added. The reaction vessel was then placed in a -30 °C bath until completion of the reaction. One drawback of this procedure is that the bis(sulfonamide) ligands are polar, highly crystalline compounds, and are often difficult to solubilize in the relatively non-polar reaction mixture. Incomplete dissolution of the ligand can erode the enantioselectivity in this ligand accelerated process.⁹

Contrary to the initially proposed mechanisms, we have found that titanium tetraisopropoxide does not react with the bis(sulfonamide) ligand.¹⁰ We postulated that the ligand initially reacts with the diethylzinc and is transferred to titanium in a subsequent step. Support for this pathway has recently been provided by Denmark, who has elegantly shown that diethylzinc reacts with bis(sulfonamide) ligands of the type 1, to liberate ethane and to generate bis(sulfonamido)zinc complexes.¹¹

We anticipated that initial reaction of the bis(sulfonamide) ligand with the diethylzinc might overcome the ligand solubility problem. Thus, addition of the ligand (1-2 mol%) to diethylzinc (in toluene) resulted in generation of the bis(sulfonamido)zinc species.¹² After stirring for 10 m at rt, the

homogenous solution was cooled to -30 °C. Titanium tetraisopropoxide (in hexanes) was added and the solution turned orange. Aldehyde was then injected and the mixture was stirred until completion of the reaction. The results of this procedure are compared to the results of the original procedure in Table 1.

Table 1	1a	1b	1c	1d	1e	1f
Procedure:	4-C ₆ H ₄ -Me	2,5-C ₆ H ₃ -Me ₂	1-Naphthyl	CF ₃	2,4,5-C ₆ H ₂ -Cl ₃	4-C ₆ H ₄ -NO ₂
New (ee) ^a	98	84	93	98	98	98
Original (ee) ^a	97	84	92	98	76-95	87

^aThe ee's were determined by GC using a 30-m Supelco β -DEXTM. Error is (+/-) 1 % ee. Final concentrations of solvent and reagents were identical in both procedures. Ligands used at 2 mol%.

Inspection of Table 1 show that the ee's were the same using both procedures with ligands **1a-1d**. Ligand **1e** is highly crystalline and gives erratic ee's using the original methodology due to solubility problems. In nine runs with **1e**, the ee's obtained under the original procedure were 86, 88, 76, 95, 78, 77, 84, 85 and 79. In four experiments using the new conditions, the ee's were 98, 97, 98 and 98. With the original procedure, traces of undissolved ligand remained, however, the new procedure gave clear solutions. Similar behavior was observed with ligand **1f**.

In summary, our improved procedure involves cooling the reaction mixture to -30 °C whereas the original methodology required heating to 40-50 °C followed by cooling to -78 °C and finally warming to -30 °C. Additionally, this methodology reduces problems caused by the insolubility of the polar bis(sulfonamide) ligands and gives more consistent ee's and yields.

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- 12) **Sample procedure:** Under a nitrogen atmosphere, the ligand **1a** (23.9 mg, 5.65 X 10⁻⁵ mol, 2 mol %) was combined with a 1.0 M solution of diethylzinc in toluene (3.34 mL, 3.39 X 10⁻³ mol, 1.2 eq), stirred for 10 m and cooled to -30 °C. Titanium tetraisopropoxide in hexanes (1.4 M, 2.36 mL, 3.39 x 10⁻³ mol, 1.2 eq) was added slowly by syringe to give an orange solution. The solution was stirred for 5 m and benzaldehyde was added (0.29 mL, 2.82 X 10⁻³ mol, 1 eq). After 15 h the reaction was quenched with 10 mL of 2M HCl and extracted with 3 X 20 mL of ethyl acetate. The product was chromatographed on silica (5 % ethyl acetate / 95 % hexanes). Isolated yields of 1-phenyl-1-propanol ranged from 85 - 95 %.