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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 1829–1831

Enantioselective allylation of aldehydes promoted by chiral sulfur reagents

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Received 14 September 2005; revised 27 December 2005; accepted 5 January 2006

Abstract—The addition of allylzinc bromide to aldehydes was studied with different chiral sulfur compounds acting as a catalyst. Yield differences and enantiomeric excesses were observed.

The availability of efficient synthetic methods for achieving absolute stereoselectivity by catalytic processes in the production of enantiomerically pure compounds are of considerable interest because such products can be used as building blocks for the synthesis of valuable chiral substances.[1] Asymmetric allyl-transfer reactions provide excellent stereoselective routes for converting aldehydes into the corresponding homoallylic alcohols, which are important building blocks for the synthesis of many natural and biologically active compounds,[2] and materials such as liquid crystals.[3]

The enantioselective addition of allylsilanes,[4] allylstannanes,[5] allylindium,[6] and allylboranes[7] to aldehydes has been extensively studied using several catalysts devised for this purpose.

Chiral sulfur compounds have been employed as efficient stereochemical controllers in many classical keystone C–C bond-forming reactions.[8] The efficacy of sulfur compounds in diastereoselective auxiliary-induced reactions is mainly due to the steric and stereoelectronic differences existing between the substituents of the stereogenic sulfur atom: a lone electron pair, an oxygen, and two different carbon ligands, which are able to differentiate the diastereotopic faces of a proximal or even remote reaction center.[9]

We describe herein the results obtained in the asymmetric allylation of aromatic and aliphatic aldehydes. The catalysts investigated **2a**–**e** (Table 1) consisting of monodentated and bidentated ligands and were easily prepared according to the literature procedures.[10]

Allylzinc bromide is also easily prepared by treatment of allyl bromide with zinc powder and is compatible with most functional groups.[11]

With the appropriate ligands, we then examined the enantioselective allylation of benzaldehyde catalyzed by different chiral sulfur reagents. The reactions were performed under standard conditions: the allylzinc reagent was added to a solution of a catalytic amount of the chiral ligand (**2a**–**e**) (0.5 mol %) in THF at −78 °C and stirred for 5 min followed by the addition of benzaldehyde (Scheme 1). Table 1 summarizes the results obtained in the reaction.

The conversion was complete in 15 min, and alcohol **3a** was obtained in good yields in all cases but with modest enantioselectivities (Table 1).

The majority of catalytic asymmetric reactions rely on the use of chiral Lewis acids, which bind to the electrophile activating it toward nucleophilic attack.[12] The chiral Lewis bases catalyzed reactions are conceptually distinct and involve the binding of the nucleophile with the catalyst, which can further coordinate the electrophile. This dual mechanism of activation could provide high reaction rates and excellent transfer of stereochemical

Keywords: Lewis base catalysis; Allylation; Enantioselective addition; Chiral sulfur reagents.
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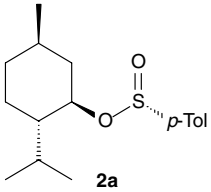
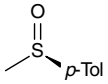
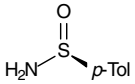
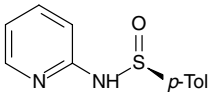
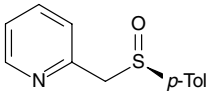
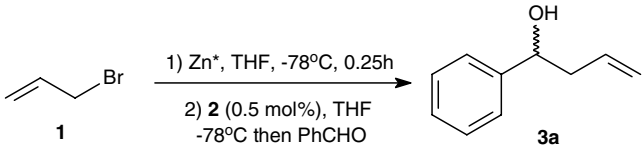
doi:10.1016/j.tetlet.2006.01.014

Table 1. Allylation of benzaldehyde with allylzinc using different chiral sulfur compounds

Entry	2	Yield (%)[a]	ee (%)[b] (confgn)[c]
1	 **2a**	80	24 (*S*)
2	 **2b**	82	15 (*S*)
3	 **2c**	75	13 (*S*)
4	 **2d**	65	20 (*S*)
5	 **2e**	87	41 (*S*)

[a] Isolated yield.
[b] Determined by converting the obtained alcohol into the corresponding MTPA-ester.
[c] Configuration assignment by comparison to the literature values of optical rotations.



Scheme 1.

information because the reaction proceeds through a closed assembly transition state.[13]

Very different levels of enantiocontrol were observed in the reaction. Although low stereoselectivities were observed with monodentate ligands, a significantly higher and more homogeneous enantiocontrol were found when bidentate **2e** ligand was used.

This decrease in the enantioselectivity could be attributed to the interaction of monodentate catalysts **2a**–**c** via an oxygen coordination or via some unidentified electronic effect (Table 1, entries 1–3). However, for the more rigid N,O bidentade catalyst **2e** a possible chelation between the oxygen atom of the sulfoxide molecule and the nitrogen atom of the pyridine ring with the zinc atom was found to be fairly effective for enhancing the ee of the reaction (Table 1, entry 5). In all cases, the reactions took place smoothly and the ligands employed could be recovered at the end of the reaction.[14] Additionally, it is worthwhile to note the allylzinc reagent with relatively acidic functionalities of the ligands such as the sulfinamide **2c** and **2d**, which are also compatible.

When the reaction was performed without the presence of the catalysts, longer reaction times were required indicating that the ligands are catalyzing the reaction.

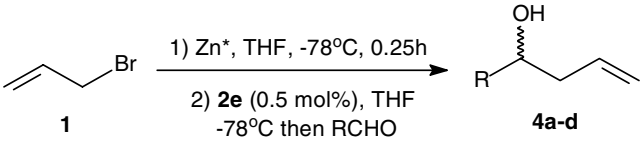
It is notable that increasing the catalyst loading (2.0 mol %) proved to have no effect on the enantioselectivity. Furthermore, increasing the temperature from the original −78 °C to room temperature or 0 °C resulted only in the decomposition of the allylzinc compound. The use of toluene as a solvent in the reaction surprisingly led to lower enantioselectivity. This fact is probably due to the low solubility of the allylzinc compound as well as due to the ligands in this solvent.

Having optimized the reaction conditions, we extended the enantioselective allylation to a variety of aldehydes using the chiral ligand **2e** as a catalyst. The results are summarized in Table 2.

As shown in Table 2, the methodology gave the desired products in good yields after 15 min and with modest ee's in all cases.

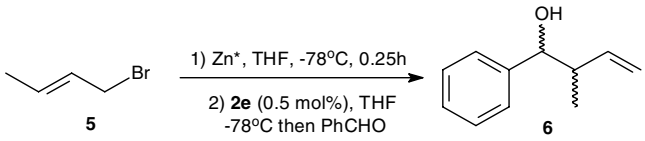
The electronic effects of the aldehyde were briefly studied. Both *para*-substituted aldehydes proved to have

Table 2. Allylation of aldehydes with allylzinc using the chiral ligand **2e**



Entry	Compound	R	Yield (%)[a]	ee (%)[b] (confgn)[c]
1	**4a**	2-CN–C_6H_4	80	20 (*S*)
2	**4b**	3-CN–C_6H_4	80	7 (*S*)
3	**4c**	4-CN–C_6H_4	85	10 (*S*)
4	**4d**	2-MeO–C_6H_4	68	42 (*S*)
5	**4e**	4-Cl–C_6H_4	86	17 (*S*)
6	**4f**	$C_6H_5CH_2CH_2$	80	26 (*S*)
7	**4g**	2-Naphthyl	78	21 (*S*)
8	**4h**	2-NO_2–C_6H_4	—	—
9	**4i**	4-NO_2–C_6H_4	—	—
10	**4j**	C_3H_7	70	0
11	**4k**	C_6H_{13}	75	0

[a] Isolated yield.
[b] Determined by converting the obtained alcohol into the corresponding MTPA-ester.
[c] Configuration assignment by comparison to the literature values of optical rotations.



Scheme 2.

similar reactivities giving the desired products in good yields but low ee (Table 2, entries 3 and 5). Similar reactivity but higher selectivity was observed with *ortho*-substituted aldehydes **4a** and **4d** (Table 2, entries 1 and 4). Aliphatic aldehydes gave good chemical yields, but no enantioselectivity was observed (Table 2, entries 10 and 11). It is also noteworthy that both *o*- and *p*-nitrobenzaldehyde did not react at all (Table 2, entries 8 and 9).

Furthermore, this method is also useful for the allylation of substituted allyl bromides. Crotyl bromide **5** was also used as allylating agent and the reaction was found to be regioselective, giving only the γ-regioisomer **6** (Scheme 2). The reaction was, however, less diastereoselective, giving an inseparable 6:4 mixture of *syn*- and *anti*-diastereomers.

In summary, we have demonstrated the effectiveness of the use of chiral sulfur compounds as chiral Lewis bases in the enantioselective addition of allylzinc to aldehydes. To the best of our knowledge, there are few precedents dealing with the use of sulfoxides as chiral ligands in this kind of reaction, with the reported enantioselectivity of the process being very modest.[15] The present methodology provides the first example that utilizes chiral sulfoxides as ligands in a Lewis base catalyzed reaction. Furthermore, the reaction was characterized by low catalyst loading (0.5 mol %), high tolerance to certain aldehydes and short reaction time. Studies on the mechanism of this reaction as well as the synthesis of other chiral sulfoxides to further enhance the enantioselectivity are currently in progress.

Acknowledgements

We gratefully acknowledge the financial support from CNPq/PROFIX (54045/01-4), FACEPE and CAPES. R.P.A.M. is grateful to Dr. André L. M. Porto (University of São Paulo) for his help in obtaining optical rotations. The authors also thank CNPq for their Fellowships.

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14. *Representative procedure for the asymmetric allylation of aldehydes*: Zinc (100 mg; 1.5 mmol) in anhydrous THF was activated successively with 1,2-dibromoethane and chlorotrimethylsilane, which were stirred under argon for 5 min. Allyl bromide (0.14 mL; 1.35 mmol) was added at −78 °C and the mixture was stirred for 10 min. Chiral ligand (0.5 mol %) in THF was then added at −78 °C and stirred for 10 min, followed by aldehyde (1.2 mmol) addition at −78 °C. The reaction mixture was allowed to warm to room temperature and was then quenched by the addition of HCl (0.1 M). The mixture was then extracted with AcOEt (2 × 10 mL) and the organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude product was purified by chromatography using silica gel to yield the desired homoallylic alcohols.
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