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Aldol Reaction under Solvent-Free Conditions: Highly Stereoselective Synthesis of 1,3-Amino Alcohols

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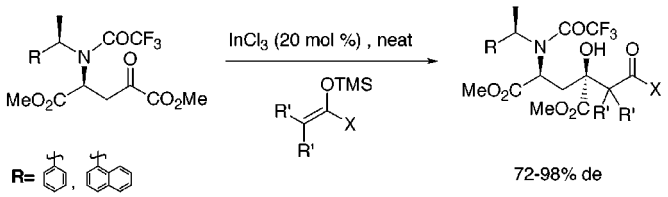
ABSTRACT



A method for the highly stereoselective synthesis of 1,3-amino alcohols based on the indium trichloride-catalyzed Mukaiyama aldol reaction of keto ester (*R,S*)-1 under solvent-free conditions has been developed. The high selectivity observed can be explained on the basis of the shielding of one face by a remote substituent.

Organic reactions under solvent-free conditions have gained in popularity in recent years.[1] This is because no-solvent reactions usually need shorter reaction times and simpler reactors and result in simple and efficient workup procedures. This relatively unfamiliar territory lends itself to exploration in terms of reaction characteristics and stereochemical behavior. Furthermore, reactions that are performed under organic solvent-free conditions especially important and have attracted much attention.

Recent research from our group has shown that indium trichloride can function as a Lewis acid for many C−C bond formation reactions such as an aldol reaction in aqueous media as well as under solvent-free conditions.[2] Our interest in the application of this indium trichloride-catalyzed aldol reaction under solvent-free conditions for the total synthesis of a natural product has encouraged us to investigate the aldol reaction of keto ester (*R,S*)-**1a** and (*R,S*)-**1b** with silyl enol ethers as well as ketene silyl acetals. In this paper, we report an efficient and highly stereoselective aldol reaction of keto ester (*R,S*)-**1a** or (*R,S*)-**1b** with various silyl enol ethers and ketene silyl acetals (Scheme 1). A new stereochemical model based on the remote substituent effect is proposed to explain the excellent level of 1,3-induction observed for these reactions.

First, we investigated the reactivity as well as the selectivity of ketone (*R,S*)-**1a**[3] with acetophenone-derived silyl enol ether under neat conditions with a wide variety of Lewis

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(3) Excellent stereoselectivity has also been observed in the indium-mediated allylation of ketone ester (*R,S*)-**1a** in aqueous media. Submitted for publication.

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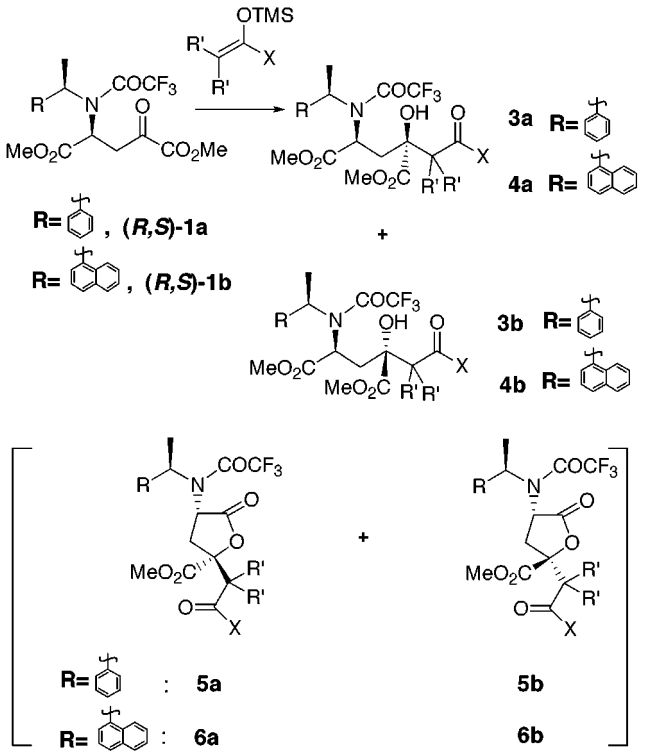
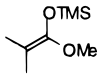
Scheme 1



acids. This neat Mukaiyama aldol reaction was performed by first activating the ketone (solid, 1 equiv) using Lewis acid (0.2 equiv) and then adding the silyl enol ether or ketene silyl acetal (5 equiv). The reaction mixture was then stirred at room temperature for 16 h. THF and 1 M hydrochloric acid were then added followed by stirring for 2 h before normal aqueous work up. The pure product was obtained after purification by flash column chromatography. The results are shown in Table 1.

It should be noted that the use of classical Lewis acids such as $BF_3{\cdot}OEt_2$ (1 equiv) in dichloromethane under strict anhydrous condition (−78 °C to room temperature, 20 h) afforded no desired product (run 1).[4] We also did a comparative study of indium trichloride with lanthanide triflates[5] such as $Sc(OTf)_3$, $Yb(OTf)_3$, and $La(OTf)_3$. Our study demonstrated the superiority of $InCl_3$ in terms of yield and selectivity under solvent-free conditions. The $InCl_3$-catalyzed aldol reaction in water afforded the product in lower yield although excellent selectivity was observed (run 4). Therefore, subsequent studies were carried out using indium trichloride as the catalyst for the aldol reactions of keto ester (*R*,*S*)-**1a** with a wide variety of silyl enol ethers and ketene silyl acetals under solvent-free conditions. In all cases, the reactions were clean and only the excess silyl enol ethers or ketene silyl acetals and the aldol products were detected after aqueous workup. The desired aldol products **4** were obtained in moderate to good yields with very high 1,3-induction (runs 5−9). The reactions with ketene silyl acetal furnished the cyclized aldol products **5** in high diastereoselectivity (runs 8 and 9). Similarly, the reaction of (*R*,*S*)-**1b** with various silyl enol ethers or ketene silyl

Table 1. Reaction of Silyl Enol Ethers and Ketene Silyl Acetals with (*R*,*S*)-**1a** and (*R*,*S*)-**1b**

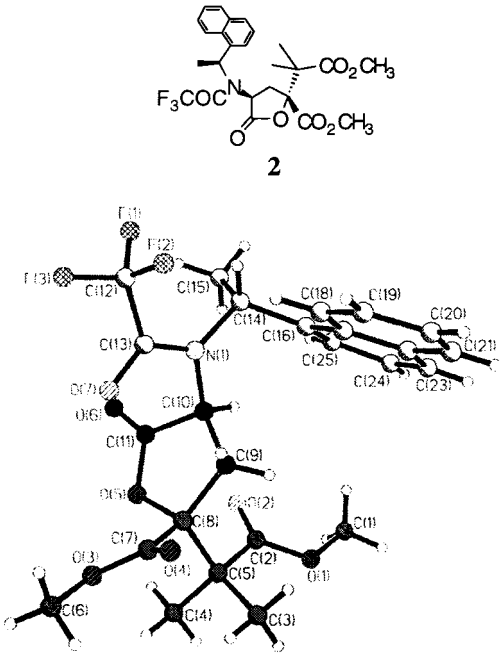
run		conditions	(*R*, *S*)-**1a** **3a**:**3b**[a] (yield,%)	(*R*, *S*)-**1b** **4a**:**4b**[a] (yield,%)
1		$BF_3{\cdot}OEt_2$	no reaction	-
2		$La(OTf)_3$	trace	-
3		$Yb(OTf)_3$ or $Sc(OTf)_3$	90 : 10 (40)	-
4		$InCl_3$ H_2O	90 : 10 (40)	-
5		$InCl_3$	90 : 10 (73)	96 : 4 (73)
6		$InCl_3$	86 : 14 (72)	92 : 8 (72)
7		$InCl_3$	99 : 1 (56)	99 : 1 (55)
8		$InCl_3$	87 : 13 (58)[b]	87 : 13 (54)[c]
9		$InCl_3$	99 : 1 (72)[b]	99 : 1 (74)[c]

[a] Selectivity was determined by ^1H NMR and ^{13}C NMR analyses. [b] **5a** and **5b** were obtained instead of **3a** and **3b**. [c] **6a** and **6b** were obtained instead of **4a** and **4b**.

acetals afforded the aldol products in very high selectivity. Especially noteworthy is the higher selectivity observed when ketone ester (*R*,*S*)-**1b** (R = 1-naphthyl) was used instead of (*R*,*S*)-**1a** (R = phenyl) (runs 5 and 6).

The determination of the stereochemistry deserves comment. The absolute stereochemistry of one of the products **2** (run 9) was determined by X-ray crystallographic analysis (Figure 1). All the other products were determined on the basis of the similarities of the polarities and the ^1H NMR and ^{13}C NMR chemical shifts.

The X-ray structure of the olefin analogue (*R*,*S*)-**7b** was obtained, and the structure is depicted in Figure 2. NMR spectroscopy of the olefin analogues provides hints of the molecular structure in solution (Figure 3). The proximity of the naphthyl ring and the alkene double bond in (*R*,*S*)-**7b** is indicated by the high field chemical shift of one of the vinyl protons Ha (δ = 4.47 ppm), which is in the plane of the aromatic ring and hence is shielded by the ring current compared to that of (*R*,*R*)-**7b** (δ = 5.79 ppm). On the other hand, the proximity of the naphthyl group with the α-amino ester in (*R*,*R*)-**7b** manifests itself by the unusual high



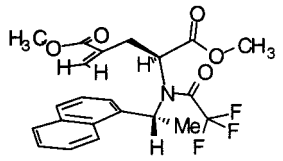
2

Figure 1. Crystal structure of **2**.

chemical shift of the methyl ester ($\delta = 2.73$ ppm) compared with that ($\delta = 3.73$ ppm) in (*R*,*S*)-**7b.** This difference in chemical shift of the α-amino methyl ester is preserved in the corresponding ketone series.

The increase in diastereoselectivity for keto ester (*R*,*S*)-**1b** where R is a more π-basic substituent provides possible involvement of π-stacking in the transition state. To prove whether $\pi-\pi$ interaction is playing a role in this reaction, we investigated the indium trichloride-catalyzed aldol reaction of ketone **10** in which the phenyl group was replaced by a cyclohexyl group. To our surprise, the product was obtained in 72% yield with excellent diastereoselectivity (Scheme 2). This results obtained provide evidence that $\pi-\pi$ attractive interaction plays no significant role in the control of the stereoselectivity.

On the basis of the above evidence and the observed stereochemistry of the products, we propose that the reaction proceeded via transition state as shown in Scheme 3. The phenyl group serves to shield one face of the carbonyl group, thereby rendering the nucleophilic addition processes highly stereoselective.



(*R*, *S*)-**7 b**

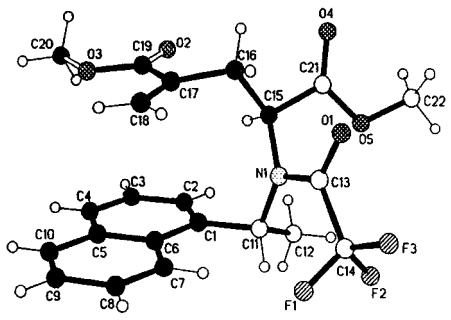


Figure 2. Crystal structure of (*R*,*S*)-**7b**.

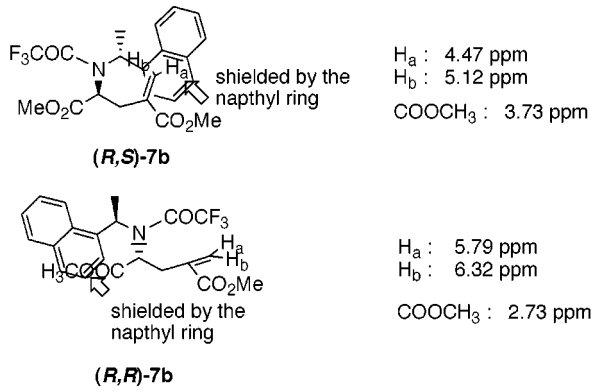
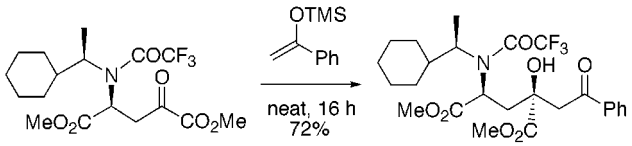
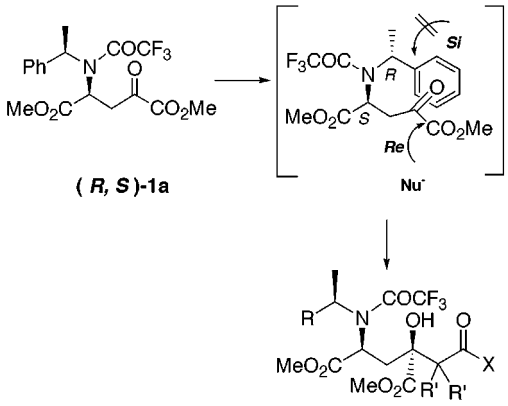


Figure 3. ^{1}H NMR spectra of (*R*,*S*)-**7b** and (*R*,*R*)-**7b**.

Scheme 2



Scheme 3



The traditional acyclic stereochemical control methods usually derive their controlling power from steric repulsion in a chelated rigid cyclic transition state; however, this method of controlling chirality based on the remote substituent effect due to conformational preference has further been demonstrated to be a useful method for acyclic stereocontrol in the absence of any cyclic transition state.[6]

In conclusion, this work demonstrates that a remote substituent can be used as a controlling element in the indium trichloride-catalyzed aldol reaction under solvent-free conditions. Efforts to apply this new acyclic stereocontrol model to other organic transformations are under way.

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Supporting Information Available: Preparation of (*R*,*S*)-**1**, X-ray crystallographic data of (*R*,*S*)-**7** and **2**, procedure of indium trichloride-catalyzed aldol reaction of (*R*,*S*)-**1a**, (*R*,*S*)-**1b**, and **10** and ^{1}H, ^{13}C NMR, mass spectra of all the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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