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The Enantioselective Michael Reaction of Tin(II) Enolates

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The enantioselective Michael addition reaction of tin(II) enolates to various α,β-unsaturated ketones is successfully achieved by employing chiral diamine ligands.

The Michael addition reaction of metal enolates to α,β-unsaturated carbonyl compounds is a reaction which has a great potential for stereoselective synthesis.$^{1)}$ Development of the asymmetric Michael additions is of special importance as such reactions would open new routes to a wide range of optically active compounds. However, efforts towards achieving high enantioselectivity in this reaction have as yet rarely been successful.$^{2)}$ Furthermore, although several asymmetric reactions in which a high degree of diastereoselectivity is achieved through the use of chiral carbonyl substrates have been reported,$^{3)}$ asymmetric induction in the Michael reactions of achiral substrates by the employment of chiral additives has proved to be extremely difficult.$^{4)}$

In a previous communication,$^{5)}$ we reported the Michael addition reaction of tin(II) enolates to α,β-unsaturated ketones. Furthermore, we have already established that chiral diamines strongly coordinate to tin(II) enolates and have utilized this characteristic in the enantioselective aldol reaction of tin(II) enolates.$^{6)}$ In this communication, we wish to report the first example of an asymmetric Michael addition reaction of preformed achiral metal enolates which proceeds under kinetic control conditions and in which enantioselectivity is achieved by the addition of chiral ligands.

We first examined the reaction between 3-propanoyl-1,3-oxazolidin-2-one and benzalacetone. Following the procedure reported in our previous communication,$^{5)}$ tin(II) enolate was generated from 3-propanoyl-1,3-oxazolidin-2-one, then, to the mixture, chiral diamine $\underline{A}$, chlorotrimethylsilane(TMSCl) and benzalacetone were added successively. However, by this procedure, the reaction failed to proceed. We concluded that this negative result was due to the weak Lewis acidity of TMSCl, and next attempted the same reaction using a stronger activator, trimethylsilyl trifluoromethanesulfonate(TMSOTf). In this case the reaction proceeded even at -78 °C to give, although in low yield, the desired Michael adduct. The optical purity of this compound, determined by the use of chiral shift reagent Eu(hfc)$_3$, was 80 % e.e. Subsequent examination of reaction conditions showed that the chemical yield was greatly improved by using two equivalents of the enolate to the

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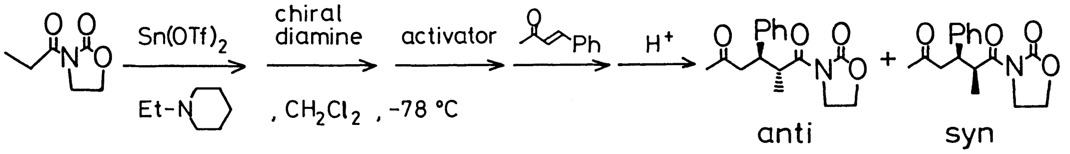
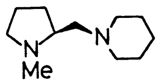


Table 1.

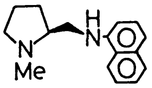
	Activator	Chiral diamine[a)]	Yield/%	anti : syn	Optical yield/%[b)]
1.	TMSCl	A	0		
2.	TMSOTf	A	35	>95 : 5	80
3.	TMSOTf	A	70	>95 : 5	80
4.	TMSOTf	B	72	>95 : 5	93

Molar ratio of propanoyloxazolidone : $Sn(OTf)_2$: N-ethylpiperidine : benzalacetone = 0.8 : 1.0 : 1.2 : 1.2 : 0.7 in entries 1,2, 0.8 : 1.0 : 1.2 : 1.2 : 0.4 in entries 3,4.

a) Diamine A



B



b) Absolute stereochemistry not determined.

unsaturated ketone. Furthermore, after extensive screening of chiral diamine ligands, we found that when diamine B was used, the enantiomeric excess achieved in this reaction rose to 93 % e.e. Thus, we established that chiral diamines could be successfully utilized to induce a high degree of enantioselectivity in this Michael reaction of tin(II) enolates. However, as an excess amount of tin(II) enolate had to be employed in this reaction, we turned our attention to thiocarbonyl compounds which are expected to exhibit greater reactivity.[7)]

Tin(II) triflate($Sn(OTf)_2$) was treated with dithioacetic acid methyl ester in the presence of N-ethylpiperidine to generate the tin(II) enethiolate. After the addition of diamine, TMSOTf, benzalacetone, the reaction proceeded smoothly to give the desired Michael adduct in 82% yield. As expected, the dithioester showed high reactivity and only one equivalent of the tin(II) enethiolate was required to obtain the Michael adduct in good yield. The optical purity of this product was determined as 70 % e.e. Next, the effect of the diamine ligand on the enantioselectivity in this reaction was examined, and, as shown in Table 2, it was found that in this reaction as well, diamine B gave the highest enantioselectivity. The results of the Michael addition reaction of dithioacetic acid methyl ester and various α,β-unsaturated ketones are shown in Table 3. In all cases the corresponding Michael adduct was obtained in good yield, and when α,β-unsaturated ketones with aromatic substituents in the β-position were employed, moderate to high optical purity was obtained.

A typical procedure is described for the reaction of dithioacetic acid methyl ester and benzalacetone. To a suspension of $Sn(OTf)_2$ (288 mg, 0.69 mmol) and N-ethylpiperidine (98 mg, 0.87 mmol) in 2 ml of dichloromethane was added dithioacetic acid methyl ester (57 mg, 0.54 mmol) in 1.5 ml of dichloromethane with stirring at -78 °C under an argon atmosphere. After stirring for 1 h, (S)-1-methyl-2-[(N-1-naphthylamino)methyl]pyrrolidine (196 mg, 0.82 mmol) in 1.5 ml of

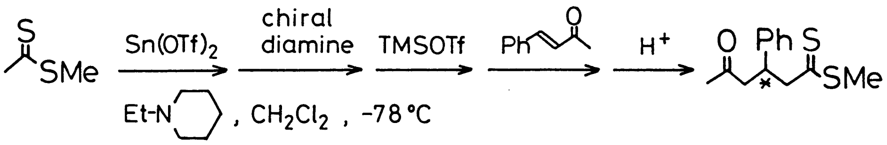
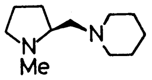
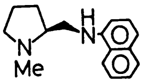
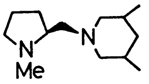
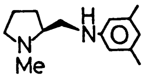


Table 2.

Chiral diamine[a]		Yield/%	Optical yield/%e.e.[b)c)]
1.	A	73	26
2.	B	82	70
3.	C	67	46
4.	D	65	36

a) Diamine A  B  C  D 

b) Determined by measurement of the ^{1}H-NMR spectrum of the corresponding methyl ester using Eu(hfc)$_3$ as a chiral shift reagent. The methyl ester was obtained by treating the dithioester with $(CF_3CO_2)_2Hg$ in methanol.

c) Absolute stereochemistry not determined.

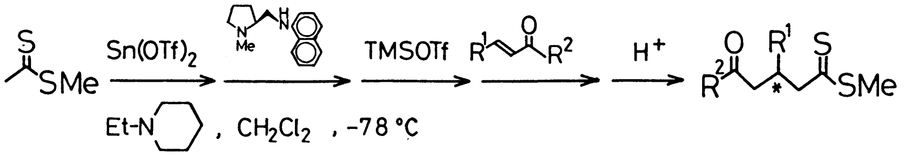
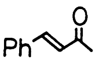
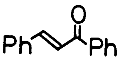
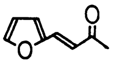
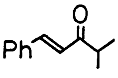
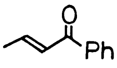
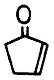


Table 3.

α,β-Unsaturated ketone		Yield/%	Optical yield/%e.e.[a)b)]
1.		82	70
2.		75	40
3.		79	60
4.		79	60
5.		62	15
6.		44	30

a) Determined by measurement of the ^{1} H-NMR spectrum of the corresponding methyl ester using Eu(hfc)$_3$ as a chiral shift reagent. The methyl ester was obtained by treating the dithioester with $(CF_3CO_2)_2Hg$ in methanol.

b) Absolute stereochemistry not determined.

dichloromethane was added dropwise and the mixture was stirred for 5 min. TMSOTf (180 mg, 0.81 mmol), and benzalacetone (68 mg, 0.47 mmol) were added successively to the reaction mixture after which stirring was continued for another hour. The reaction was quenched with a 10% citric acid solution, and the organic materials were extracted with dichloromethane. To completely hydrolyze the trimethylsilylether product, the crude Michael product obtained after evaporation of the solvent was dissolved in methanol and citric acid was added to this solution. After stirring for 1 h the reaction was quenched with ph7 phosphate buffer. The organic layer was extracted with dichloromethane and the combined extracts were dried over anhydrous sodium sulfate. After evaporation of the solvent, the crude product was purified by preparative thin layer chromatography to afford the desired Michael adduct. (98 mg, 82% yield)

It is noted that the asymmetric Michael addition reaction of tin(II) enolates is achieved in moderate to high optical purities, starting from achiral substrates, by the utilization of the coordination of chiral diamine ligands to the intermediate tin(II) enolate.

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