Pure & Appl. Chem., Vol. 66, Nos 10/11, pp. 2115–2118, 1994.
Printed in Great Britain.

Stereospecific addition of thiophenol to electron-deficient double bond and its application to natural product synthesis

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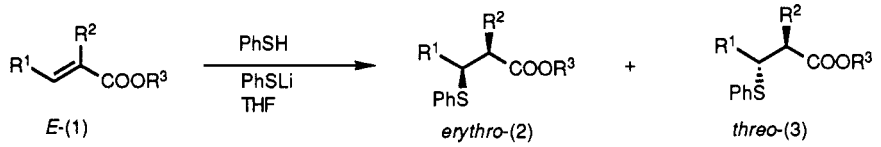
Abstract Stereospecific addition of thiophenol to electron-deficient double bond was developed and applied to the synthesis of biologically active compounds, *i.e.*, β-lactams and lactones.

During the course of synthetic study of indole alkaloids, we have encountered the geometrical isomerism of an ethylidene side chain in isositsirikines and succeeded in synthesizing all the isomers by applying a synthetic method for the conversions of *E* to Z and *Z* to *E* which are consisting of a combination of *anti*-addition of HX to olefin and thermal *syn*-elimination.[1] Since then we have tackled with this addition of thiol to an electron-deficient olefin aiming at the development of a new stereoselective addition reaction. In this paper, we summarized the results on the stereoselective Michael-type addition reaction and its application to the synthesis of natural products.

1. Study on the Stereoselectivity of Addition of Thiol to Olefinic Double Bond.[3]

With success in the conversion of geometrical isomers of *E* and *Z* in isositsirikines,[1] our focus has been centered on the stereoselective addition reaction. The stereochemistry of nucleophilic addition of thiophenol to α, β-unsaturated esters has not been well investigated except only a few cases. Recently Morig *et al* reported a stereoselective addition of t-butylmercaptan to crotonates in the presence of base but obtained the same adduct from both *Z*- and *E*-esters, thus showing no stereospecificity.[2]

We carried out the addition of thiophenol to an electron-deficient olefin by using a pair of α, β-unsaturated esters with E and Z geometry, methyl tiglate *E*-(1) and methyl angelicate *Z*-(4), in the presence of base. The reaction conditions and the results are shown in SCHEME 1.



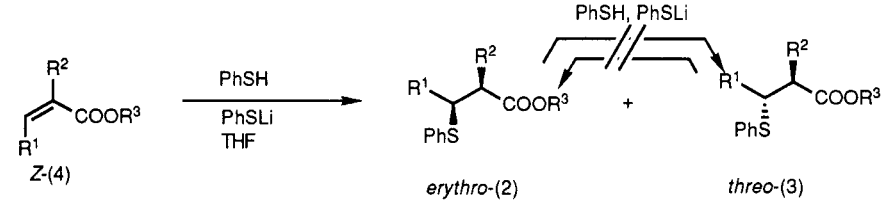
E-(1) *erythro*-(2) *threo*-(3)

a; R^1=R^2=R^3=Me
b; R^1=Et, R^2=R^3=Me
c; R^1=n-Pr, R^2=Me, R^3=Et
d; R^1=Ph, R^2=R^3=Me
e; R^1=t-Bu, R^2=Me, R^3=Et

Entry	Substrate	PhSLi (eq)	PhSH (eq)	Temp. (°C)	Yield (%)	Ratio (2) : (3)
1	(1a)	3	3	20	90	91 : 9
2	(1a)	0.1	10	20	99	96 : 4
3	(1a)	0.1	1.2	20	95	94 : 6
4	(1a)	0.1	10	0	59	96 : 4
5	(1a)	-	10	20	-	-
6	(1a)	Et_3N(3)	3	20	53	93 : 7
7	(1a)	1.2	MeOH	20	-	-
8	(1a)	1.2	-	20	-	-
9	(1a)	PhSNa(0.1)	10	20	87	93 : 7
10	(1b)	0.1	10	20	85	87 : 13
11	(1c)	0.1	10	20	95	85 : 15
12	(1d)	0.1	10	20	99	81 : 19
13	(1e)	0.1	10	20	25	57 : 43

SCHEME 1

The best result was obtained as in the entry 2, giving the adducts quantitatively with the ratio (*erythro/threo*) of 94:6, showing preferential formation of the *erythro*-adduct.



Z-(4) *erythro*-(2) *threo*-(3)

a; R^1=R^2=R^3=Me
b; R^1=Et, R^2=R^3=Me
c; R^1=n-Pr, R^2=Me, R^3=Et
d; R^1=Ph, R^2=R^3=Me

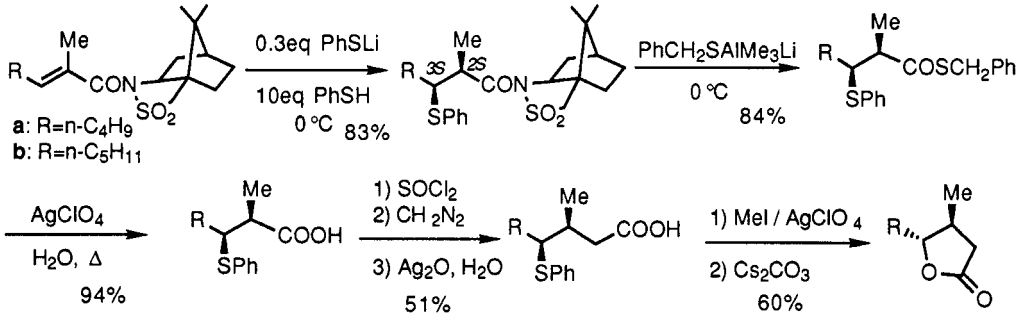
Entry	Substrate	PhSLi (eq)	PhSH (eq)	Temp. (°C)	Yield (%)	Ratio (2) : (3)
1	(4a)	0.1	10	20	85	14 : 86
2	(4a)	1.2	-	20	-	-
3	(4a)	PhSNa(0.1)	10	20	83	22 : 78
4	(4b)	0.1	10	20	61	17 : 83
5	(4c)	0.1	10	20	86	28 : 72
6	(4d)	0.1	10	20	82	66 : 34

SCHEME 2

Similarly, the addition reaction to the *Z*-ester *Z*-(4) proceeded smoothly as shown in SCHEME 2, giving the *threo*-adduct as the major product. Since interconversion of these two stereoisomeric products, *erythro* and *threo*, was not observed, the results show these adducts as the products were kinetically controlled. This provided the first example showing both stereoselectivity and stereospecificity in this Michael-type addition reaction.

2. Application of Stereoselective Addition Reaction to the Synthesis of Natural γ -Lactones [Application to Asymmetric Synthesis][4]

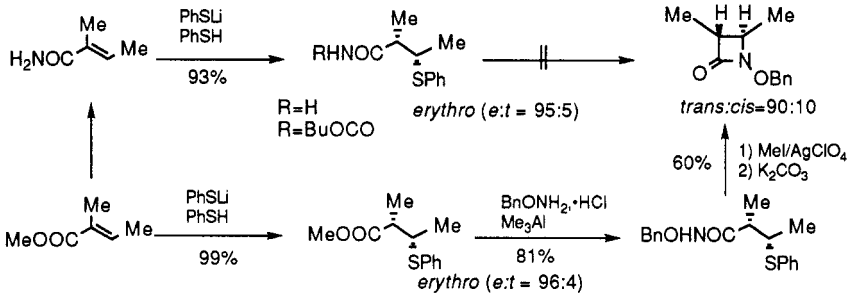
For the synthesis of chiral natural products, we introduced chiral auxiliaries of (+)-sultam developed by Oppolzer and the oxazolone by Evans into the starting ester. Syntheses of γ -lactones,(+)-*trans*-whisky and cognac lactones were carried out as in SCHEME 3 by using (+)-sultam as a chiral auxiliary. In order to remove the auxiliary, a new procedure had to be developed, that is, treatment with aluminum thiobenzyloxy "ate" complex. The lactone ring was formed *via* the route involving the conversion of a phenylthio group to the sulfonium salt and its cleavage with cesium carbonate.



SCHEME 3

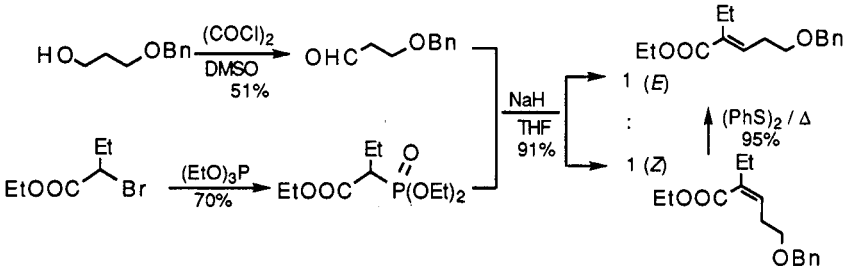
3 Application to the β -Lactam Synthesis and the Synthesis of (+)-PS-5.[5]

The route for the lactone formation was further applied to the synthesis of β -lactam. Methyl tiglate was converted, upon stereoselective addition of thiophenol, into three types of amides(amide, hydroxamate and carbamate) as in SCHEME 4 for the following β -lactam formation. However, only the hydroxamate gave *trans*-β -lactam in ca 60% yield with high selectivity (90:10) in a preliminary study.

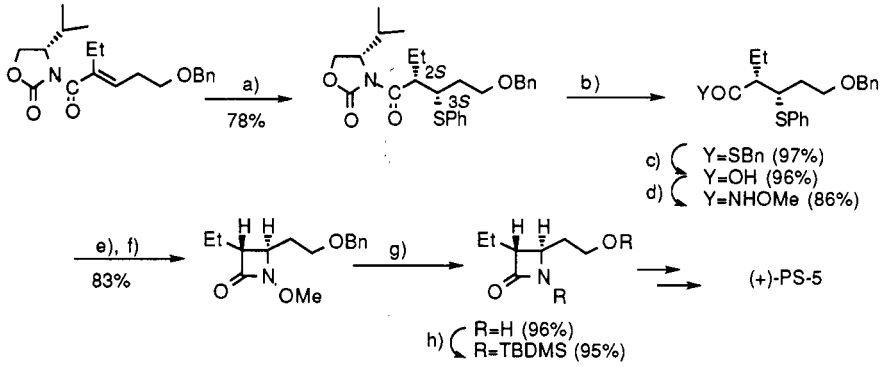


SCHEME 4

Then we picked PS-5, a carbapenem antibiotic, as our synthetic target *via* the route including steps of diastereoselective addition of thiophenol, conversion of the adduct to the hydroxamate and its intramolecular substitution *via* the sulfonium salt. Accordingly, total synthesis of (+)-PS-5 was carried out as in SCHEME 6 upon the preparation of the starting unsaturated ester homogeneously as in SCHEME 5.



SCHEME 5



a). 5 eq PhSLi / 10 eq PhSH, b). $BnSAlMe_3Li$, c). CF_3COOAg / H_2O-THF, d). $MeONH_2$•HCl /WSC., e). MeI / $AgClO_4$, f). K_2CO_3 / Δ, g). Ca. liq. NH_3, h). TBDMSOTf / 2,6-lutidine.

SCHEME 6

ACKNOWLEDGEMENT

The authors thank Dr. T. Shinada for his great contribution to this work.

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