

Asymmetric Carbene C-O Insertion Reaction Using Optically Active Bipyridine-Copper
Complex as a Catalyst. Ring Expansion of Oxetanes to Tetrahydrofurans

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Copper complex of (7*R*,7*R'*)-7,7'-di(1-*t*-butyldimethylsiloxy-1-methylethyl)-6,6',7,7'-tetrahydro-5*H*,5'*H*-2,2'-bi-1,1'-pyrindine (**3**) was found to be an effective catalyst for asymmetric carbene insertion reaction into the C-O bond of oxetanes. For example, the reaction of *dl*-2-phenyloxetane and *t*-butyl diazoacetate in the presence of Cu-**3** complex provided *trans*- and *cis*-*t*-butyl 3-phenyltetrahydrofuran-2-carboxylate of 75% ee and 81% ee, respectively.

Tetrahydrofurans are important structural units as parts of naturally occurring biologically active substances¹⁾ and a considerable effort has been directed toward the stereoselective construction of tetrahydrofuran systems.²⁾ In 1966, Nozaki et al. for the first time reported metal-catalyzed asymmetric cyclopropanation and C-O insertion reactions.³⁾ Since then, many effective methodologies for catalytic asymmetric cyclopropanation have been reported⁴⁾ but asymmetric C-O insertion reaction has been left without attracting chemist's notice, although it may provide a new entry to asymmetric synthesis of tetrahydrofuran derivatives. Recently, we found that the copper complex of chiral C₂-symmetric bipyridine **1** was an effective catalyst for asymmetric cyclopropanation.⁵⁾ In order to extend further the possibility of bipyridine ligands, we

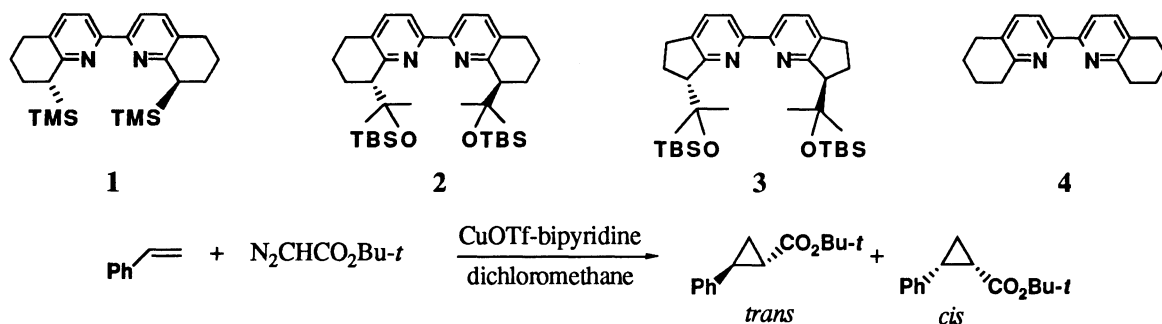


Table 1. Asymmetric cyclopropanation of styrene

Entry	Bipyridine	Yield/%	<i>trans</i> : <i>cis</i> ^{a)}	% ee (<i>trans</i>) ^{b)}
1	1	75	86 : 14	92
2	2	85	81 : 19	92
3	3	76	81 : 19	94

a) Ratio of *trans*- and *cis*-isomers was determined by using capillary GC (NEUTRA BOND-1; 130 °C).

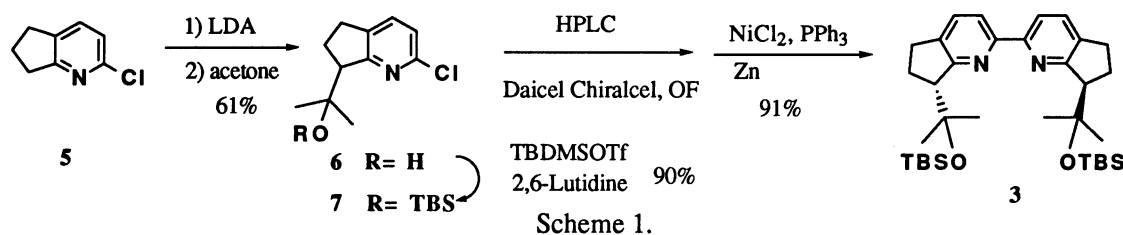
b) E.e. was determined by the reported procedure (Ref. 11).

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examined carbene C-O insertion reaction. Herein we describe asymmetric carbene C-O insertion of oxetanes using the new chiral bipyridine-copper complex as a catalyst.

In our previous communications, we have reported that the copper complex of chiral bipyridine **1** is a good catalyst for the cyclopropanation of olefins (Table 1, entry 1).^{5b,c} However, quite recently, we found that chiral ligand **3** bearing 6,6',7,7'-tetrahydro-5*H*,5'*H*-2,2'-bi-1,1'-pyridine structure showed a slightly improved asymmetric induction than chiral ligands (**1** and **2**) bearing 5,5',6,6',7,7',8,8'-octahydro-2,2'-biquinoline structure (entry 3). Accordingly, we examined carbene C-O insertion reaction using the copper complex of **3** as a catalyst.

The new bipyridine **3** was prepared from 2-chloro-6,7-dihydro-5*H*-1-pyridine **5**⁶) (Scheme 1). Compound **5** was successively treated with LDA and acetone at -78 °C to give alcohol **6**, which was silylated with *tert*-butyldimethylsilyl triflate in the presence of 2,6-lutidine giving silylether **7**. Resolution of *dl*-**7** was performed by HPLC using optically active column (Daicel Chiralcel OF) and the enantiomer eluted first from the column was used for the next reaction.⁷) Optically active **7** (>99% ee) was then subjected to nickel-mediated homocoupling reaction⁸) to give the desired bipyridine **3**.⁷)



With chiral bipyridine **3** in hand, we first examined the reaction of 2-phenyloxetane with 0.5 equiv. of *t*-butyl diazoacetate in the presence of the copper complex of **3**, expecting the kinetic resolution of *dl*-2-phenyloxetane (Table 2). Reaction proceeded smoothly at room temperature but, against our expectation, the optical purity of the remaining oxetane was very poor (<5% ee), suggesting that the efficiency of kinetic resolution was very low (entry 1). However, *cis*- and *trans*-tetrahydrofuran derivatives¹⁰) were obtained in almost equimolar amounts with good enantioselectivity, respectively (entry 1). Since the reaction using the copper complex of **4** showed *trans*-selectivity (entry 2), the above results strongly suggested that each enantiomer of *dl*-oxetane showed opposite *cis-trans* selectivity in the presence of chiral catalyst. To answer this question, we prepared (*R*)- and (*S*)-2-phenyloxetane and examined asymmetric insertion reaction (entries 3 and 4). As expected, reaction of (*R*)-2-phenyloxetane gave *trans*-isomer preferentially, and that of (*S*)-2-phenyloxetane gave *cis*-isomer preferentially.

Next we examined the reaction of several other substrates. The reaction of 2-(4-chlorophenyl)oxetane showed the same level of enantioselectivity as 2-phenyloxetane, while that of 2-(4-methylphenyl)oxetane exhibited the diminished enantioselectivity to some extent (entries 5 and 6). Although the origin of this substituent effect is unclear, the same phenomena have been observed in the cyclopropanation of styrene derivatives catalyzed by Cu-**1** complex.^{5b}) Carbene-insertion reaction of styrene oxide was also examined. However, in agreement with the result of Nozaki et al.,^{3a,c}) the reaction gave a complicated mixture (entry 7).

It has been proposed that carbene C-O insertion reaction proceeds through oxygen-ylide intermediate (A).^{3c}) If we could assume that the oxygen-ylide formation step is a crucial step for the face selection of the prochiral carbenoid carbon and that oxetanes approach from the same side as olefins do in asymmetric

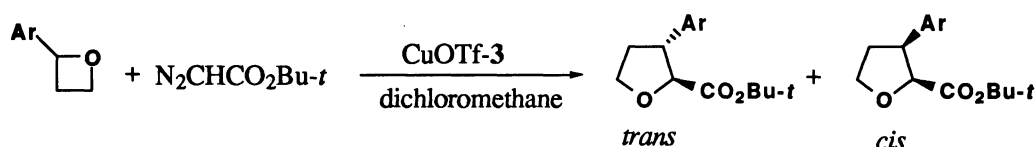


Table 2. Carbene C-O insertion reaction of 2-phenyloxetane with Cu-3 complex as a catalyst

Entry	Oxetane	Yield/%, (% ee) (recovered oxetane)	Yield/% (<i>trans</i> : <i>cis</i> ^a) (tetrahydrofuran)	% ee (<i>trans</i>)	% ee (<i>cis</i>)
1	<i>dl</i> -2-phenyloxetane	30, (<5) ^b	36 (59 : 41)	75 (2 <i>S</i> ,3 <i>R</i>) ^{c,d}	81 (2 <i>S</i> ,3 <i>S</i>) ^{c,d}
2	<i>dl</i> -2-phenyloxetane ^e	-	31 (76 : 24)	-	-
3	(<i>R</i>)-2-phenyloxetane (89% ee) ^f	30, (87) ^b	35 (89 : 11)	92 (2 <i>S</i> ,3 <i>R</i>) ^{c,d}	16 (2 <i>S</i> ,3 <i>S</i>) ^{c,d}
4	(<i>S</i>)-2-phenyloxetane (85% ee) ^f	36, (87) ^b	30 (25 : 75)	11 (2 <i>S</i> ,3 <i>R</i>) ^{c,d}	93 (2 <i>S</i> ,3 <i>S</i>) ^{c,d}
5	<i>dl</i> -2-(<i>p</i> -chlorophenyl)oxetane	35, (1) ^g	40 (54 : 46)	75 ^h	80 ^h
6	<i>dl</i> -2-(<i>p</i> -methylphenyl)oxetane	- ⁱ	31 (50 : 50)	50 ^b	76 ^j
7	styrene oxide	-	-		

a) Ratio of *trans*- and *cis*-isomers was determined by using capillary GC (FFAP Bonded; 200 °C).b) Determined by HPLC using optically active column: (Daicel Chiralcel OJ; Hexane/*i*-PrOH 400:1).c) Determined by HPLC using optically active column: (Daicel Chiralcel OJ; Hexane/*i*-PrOH 15:1).

d) See the note 9 for the determination of absolute configuration of products.

e) Complex 4 was used instead of 3.

f) Reaction was carried out with 0.5 equiv. of diazoacetate, since the starting oxetane was not optically pure.

g) Determined by HPLC using optically active column: (Daicel Chiralpack AD; Hexane/*i*-PrOH 100:1).h) Determined by HPLC using optically active column: (Daicel Chiralcel OF; Hexane/*i*-PrOH 9:1).

i) The unreacted oxetane was decomposed under the reaction conditions.

j) Determined by HPLC using optically active column: (Daicel Chiralcel OJ; Hexane/*i*-PrOH 100:1).

cyclopropanation using Cu-1 or Cu-2 as a catalyst, the stereochemistry observed can be rationalized as follows. Oxetanes approach the carbenoid-carbon along the pathway **a** preferentially, because the approach along the pathway **b** causes steric repulsion between the carbenoid ester group and C7(7')- substituent R on the bipyridine ligand as the reaction proceeds.¹¹⁾ Thus, the lone pair electrons *trans* to 2-phenyl group attack the *si* face of carbenoid carbon. The oxygen-ylid thus formed rearranges preferential with retention of the configuration. Accordingly the reaction with (*R*)-2-phenyloxetane gives *trans*-isomer preferentially and that with (*S*)-2-phenyloxetane gives *cis*-isomer. However, the oxygen-ylid partially rearranges through a zwitterionic species (**B**), causing partial epimerization. The presence of the latter pathway is supported from the absolute configuration of the minor isomer in which the configuration of C3-carbon is reversed. Although the precise

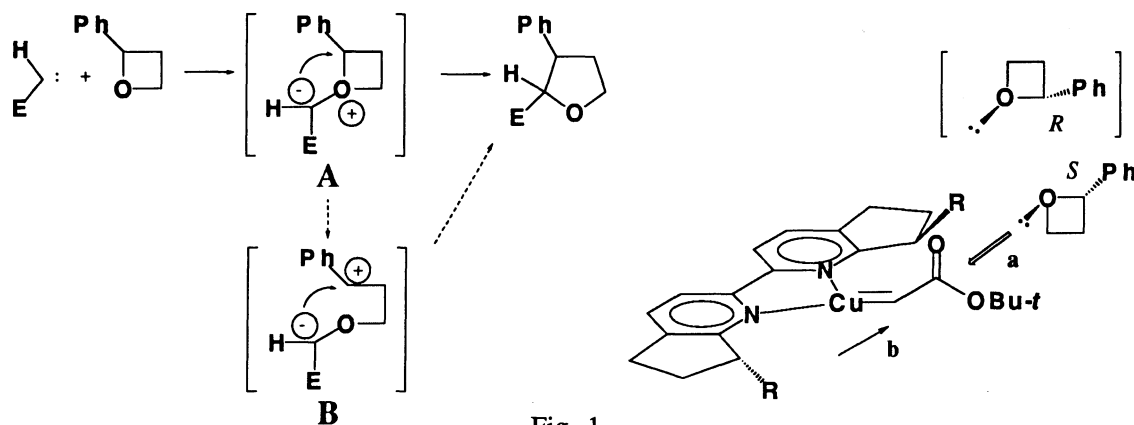


Fig. 1.

reaction mechanism is unclear at present, this proposal well explains our results.

Typical experimental procedure was exemplified by the reaction of *dl*-2-phenyloxetane using CuOTf·3 complex as a catalyst: To a suspension of CuOTf·0.5C₆H₆ (0.7 mg, 2.8 μmol) in CH₂Cl₂ (0.5 ml) was added a solution of **3** (1.8 mg, 3.1 μmol) in CH₂Cl₂ (0.15 ml). After 30 min, the mixture was filtered through a packed adsorbent cotton under argon and to the filtrate was added *dl*-2-phenyloxetane (33.5 mg, 0.25 mmol). To the solution was added dropwise a solution of *t*-butyl diazoacetate (17.8 mg, 0.125 mmol) in CH₂Cl₂ (0.125 ml) over a period of 30 min at room temperature. The reaction mixture was directly subjected to preparative TLC (Hexane/*i*-Pr₂O 5:1), giving the recovered starting material (30%), *trans*-isomer (21%), and *cis*-isomers (15%). Optical purities of these materials were determined by HPLC as described in the footnote of Table 2.

In conclusion, we described a new approach to the optically active tetrahydrofuran derivatives, though there is still a room for improvement.

Financial supports from the Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture, Japan and Ono pharmaceutical Company Ltd., are greatly acknowledged.

References

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- 6) A. I. Meyers and G. Garcia-Munoz, *J. Org. Chem.*, **29**, 1435 (1964).
- 7) Although absolute configurations of **3** and **7** were not determined yet, their configurations were presumed to be *7R,7R'* and *7R*, respectively, from the following observations. i) Compound **7** showed the same behavior in HPLC analysis using chiral column as (*7R*)-2-chloro-7-methyl-6,7-dihydro-5*H*-1-pyridine (**i**). That is, compound (*7R*)-**i** was less polar than (*7S*)-**i**. ii) Both **3** and (*7R,7R'*)-**7,7'**-dimethyl-6,6',7,7'-tetrahydro-5*H,5'H*-2,2'-bi-1,1'-pyridine (**ii**) showed negative optical rotation in chloroform. iii) Copper complexes of **3** and (*7R,7R'*)-**ii** showed the same sense of asymmetric induction in cyclopropanation.
- 8) M. Tiecco, L. Testaferri, M. Tingoli, D. Chianelli, and M. Montanucci, *Synthesis*, **1984**, 736.
- 9) The absolute configurations of *cis*- and *trans*-products were determined by chiroptical comparison with the published value [A. I. Meyers, R. K. Smith, and C. E. Whitten, *J. Org. Chem.*, **44**, 2250 (1979).] after their conversion to 4-phenyltetrahydro-2*H*-pyran-2-one by the sequence: i) reduction with SmI₂-THF-HMPA in methanol and ii) acid-catalyzed lactonization of the resulting hydroxy ester with TFA.
- 10) The stereochemistry of *cis*- and *trans*-isomers was ascertained by the NOE experiment. In the case of the *trans*-isomer, NOE was observed between the C2-proton and the *ortho*-proton of phenyl group.
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(Received July 14, 1994)