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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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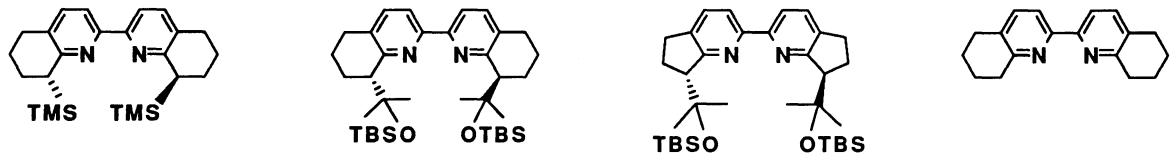
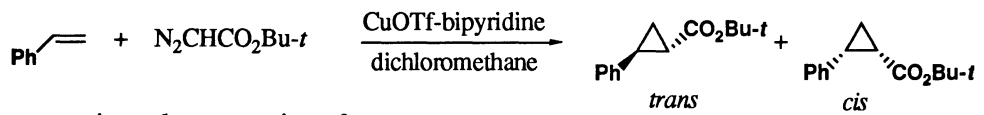
Copper complex of (7*R*,7*R'*)-7,7'-di(1-*t*-butyldimethylsiloxy-1-methylethyl)-6,6',7,7'-tetrahydro-5*H*,5'*H*-2,2'-bi-1,1'-pyrindine (**3**) was found to be an effective catalyst for asymmetric carbene insertion reaction into the C-O bond of oxetanes. For example, the reaction of *dl*-2-phenyloxetane 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 substances[1] 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 reported[4] 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 C_2-symmetric bipyridine **1** was an effective catalyst for asymmetric cyclopropanation.[5] In order to extend further the possibility of bipyridine ligands, we



1 **2** **3** **4**



trans *cis*

Table 1. Asymmetric cyclopropanation of styrene

Entry	Bipyridine	Yield/%	*trans* : *cis* [a]	% ee (*trans*)[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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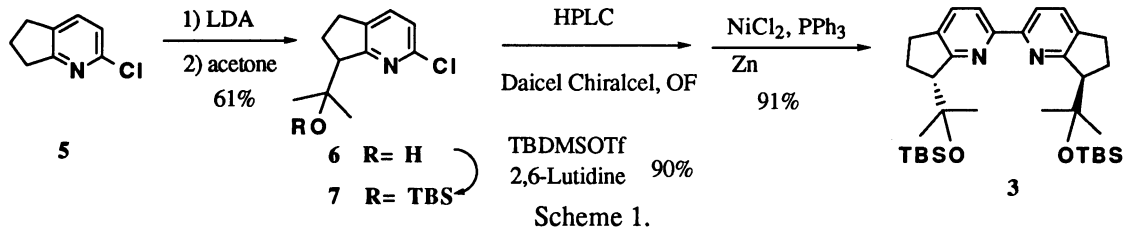
examined carbene C-O insertion reaction. Herein we describe asymmetric carbene C-O insertion of oxetanes using the new chiral bipyridine-copper complex as a catalyst.

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'-pyrindine 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-pyrindine **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 reaction[8] to give the desired bipyridine **3**.[7]



Scheme 1.

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 derivatives[10] 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

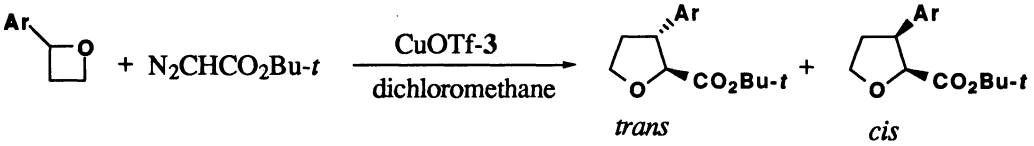


Table 2. Carbene C-O insertion reaction of 2-phenyloxetane with Cu-3 complex as a catalyst

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

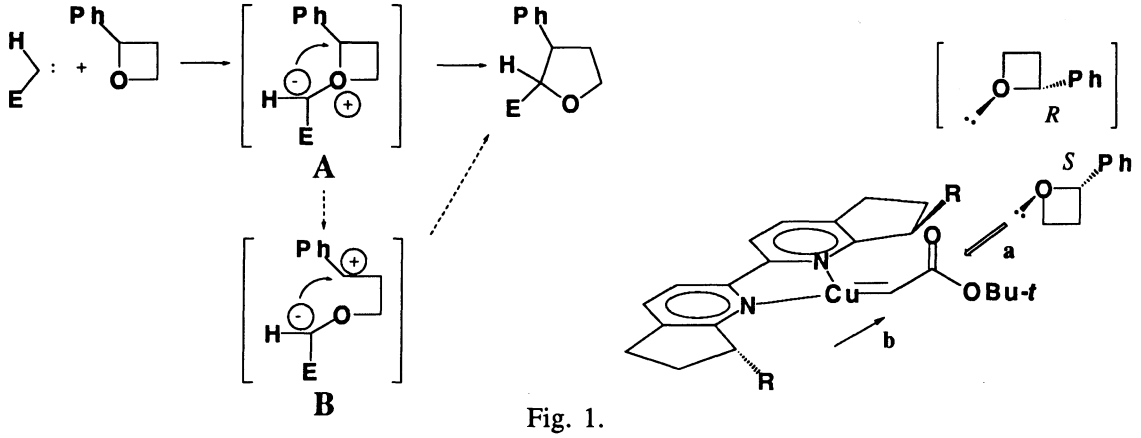


Fig. 1.

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•0.5C_6H_6 (0.7 mg, 2.8 μmol) in CH_2Cl_2 (0.5 ml) was added a solution of **3** (1.8 mg, 3.1 μmol) in CH_2Cl_2 (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 CH_2Cl_2 (0.125 ml) over a period of 30 min at room temperature. The reaction mixture was directly subjected to preparative TLC (Hexane/*i*-Pr_2O 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.

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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 7*R*,7*R'* and 7*R*, respectively, from the following observations. i) Compound **7** showed the same behavior in HPLC analysis using chiral column as (7*R*)-2-chloro-7-methyl-6,7-dihydro-5*H*-1-pyrindine (**i**). That is, compound (7*R*)-**i** was less polar than (7*S*)-**i**. ii) Both **3** and (7*R*,7*R'*)-7,7'-dimethyl-6,6',7,7'-tetrahydro-5*H*,5'*H*-2,2'-bi-1,1'-pyrindine (**ii**) showed negative optical rotation in chloroform. iii) Copper complexes of **3** and (7*R*,7*R'*)-**ii** showed the same sense of asymmetric induction in cyclopropanation.
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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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