Asymmetric Simmons-Smith Cyclopropanation of *E*-Allylic Alcohols Using 1,1'-Bi-2-naphthol-3,3'-dicarboxamide as a Chiral Auxiliary

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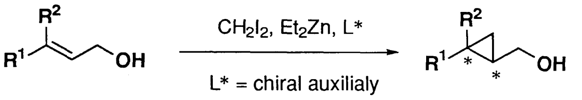
N,N,N'N'-Tetraethyl-1,1'-bi-2-naphthol-3,3'-dicarboxamide (**1b**) was found to be an effective chiral auxiliary for asymmetric Simmons-Smith cyclopropanation and high enantioselectivity greater than 85% ee was achieved in the reaction of *E*-allylic alcohols.

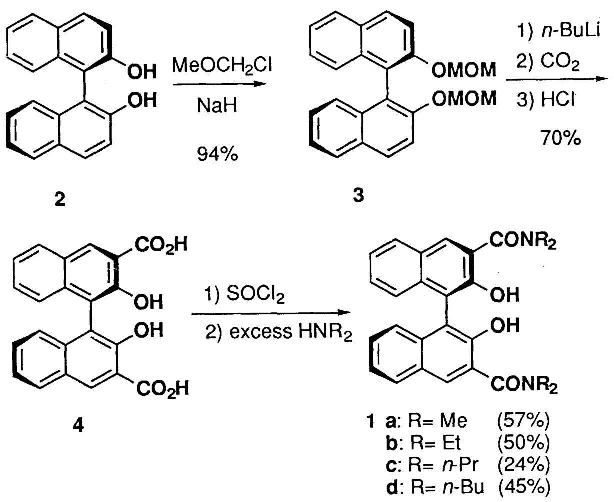
The chirality of cyclopropyl subunits in natural and non-natural products of worth often exerts a great influence on their biological activities,[1,2] and many efforts have been directed toward the development of asymmetric cyclopropanation. Among the methodologies for this purpose, asymmetric Simmons-Smith reaction of allylic alcohols has aroused chemist's interest due to easy availability of starting allylic alcohols and mild reaction conditions (Scheme 1), and moderate to excellent enantioselectivity has been achieved in the reactions using chiral auxiliaries such as disulfonamide,[3] diethyl tartrate,[4] and *N,N,N',N'*-tetramethyltartaramide.[5] In these reactions, complex formation among the reagent, the substrate, and the chiral auxiliary has been considered to play an important role in inducing high asymmetry into the product.[3,5,6] Thus, we expected that conformationally flexible chiral diol derivatives bearing a coordinating functional group would make good chiral auxiliaries, because they might provide a chelate complex more appropriate for high asymmetric induction. It is well known that binaphthol has high conformational freedom. Accordingly, we designed new chiral auxiliaries, 1,1'-bi-2-naphthol-3,3'-dicarboxamides (**1a**-**d**).



Scheme 1.

The synthesis of **1a**-**d** started from commercially available (a*R*)-binaphthol (**2**). Compound **2** was protected as MOM ether **3** and treated successively with *n*-butyllithium and with dried carbon dioxide to give dicarboxylic acid which was exposed to alcoholic hydrogen chloride to give hydroxy carboxylic acid **4**. Compound **4** was converted into the desired amides (**1a**-**d**) by treatment with thionyl chloride followed by the exposure of the resulting acid chloride to excess (>10 equiv.) dialkylamine. The optical purity of **1a**-**d** was confirmed to be >99% ee by HPLC analysis using an optically active column (Daicel Chiralpak AD; Hexane/ *i*-PrOH 9:1).

Since it has been reported that enantioselectivity of asymmetric Simmons-Smith reaction is strongly dependent on experimental conditions and that it is not easy to obtain reproducible enantioselectivity,[3c,d] we first examined



Scheme 2.

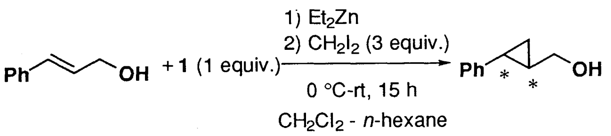


Table 1. Asymmetric Simmons-Smith reaction of cinnamyl alcohol using **1a**-**d** as chiral auxiliaries

Entry	Chiral Auxiliary	Et_2Zn	Yield (%)	% Ee[a]	Confign.[b]
1	**1a**	2 equiv.	7	14	1*S*, 2*S*
2	"	3 equiv.	34	14	1*R*, 2*R*
3	"	4 equiv.	85	26	1*R*, 2*R*
4	"	5 equiv.	84	64	1*R*, 2*R*
5	"	6 equiv.	90	67	1*R*, 2*R*
6	"	6 equiv. + ZnI_2	87	75	1*R*, 2*R*
7	**1b**	6 equiv.	55	94	1*R*, 2*R*
8	"	6 equiv. + ZnI_2	87	90	1*R*,2*R*
9	**1c**	6 equiv.	51	85	1*R*, 2*R*
10	"	6 equiv. + ZnI_2	88	79	1*R*, 2*R*
11	**1d**	6 equiv.	58	89	1*R*, 2*R*
12	"	6 equiv. + ZnI_2	75	78	1*R*, 2*R*

[a]Determined by HPLC analysis using DAICEL Chiralcel OJ (hexane/*i*-PrOH 9:1). [b]Determined by chiroptical comparison with the literature value (Reference 3a).

cyclopropanation of cinnamyl alcohol under various reaction conditions by using diethylzinc and diiodomethane as reagents and **1a** as a chiral auxiliary. The Denmark's conditions[7] using the preformed $(ICH_2)_2Zn$ and the Ukaji's conditions[4] using a stoichiometric amount of diethylzinc and diiodomethane did not give satisfactory results. However, we found that the stoichiometry of diethylzinc strongly affects the degree and sense of enantioselectivity (Table 1). Although the use of <2 equiv. of diethylzinc gave (1*S*,2*S*)-isomer as the major product (entry 1), (1*R*,2*R*)-isomer was obtained preferentially when much excess (>3 equiv.) diethylzinc was used (entries 2-5). Enantioselectivity was also improved as the amount of diethylzinc was increased, and the highest enantioselectivity was achieved, when 6 equiv. of diethylzinc was used (entry 5). Under these optimized conditions, we next examined the effect of the amide alkyl group on enantioselectivity (entries 7, 9, and 11) and found that diethylamide **1b** showed the highest enantioselectivity of 94% ee (entry 7). Based on the Denmark's report,[8] we examined also the reaction in the presence of 1 equiv. of zinc iodide (entries 8, 10, and 12). Interestingly, however, the addition of ZnI_2 gave a negative effect on enantioselectivity in the reactions using **1b**, **1c**, and **1d**, but a positive effect only in the reaction using **1a**.

We examined also the cyclopropanation of other substrates by using **1b** as a chiral auxiliary (Table 2). Both conjugated and non conjugated *E*-allylic alcohols showed excellent enantioselectivity greater than 85% ee, but the reaction of *Z*-allylic alcohol gave unsatisfactory result (entry 6). For example, the reaction of (*Z*)-4-trityloxy-2-butene-1-ol showed only 65% ee.

Typical experimental procedure is as follows: To a solution of (a*R*)-**1b** (48 mg, 0.1 mmol) and *p*-methoxycinnamyl alcohol (16 mg, 0.1 mmol) in anhydrous dichloromethane (1 ml) were added a hexane solution of diethylzinc (1.0 M, 0.6 ml) and diiodomethane (24 µl, 0.3 mmol) successively at 0 °C under a nitrogen atmosphere, and the mixture was stirred for 15 h at the temperature. The reaction was allowed to warm to room temperature, and quenched with aqueous NaOH solution (2 M). After extraction with ether (x3), the combined organic layer was successively washed with aqueous NaOH and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by TLC on silica gel (diisopropyl ether) to give *trans*-[2-(*p*-methoxyphenyl)-cyclopropyl]methanol (13.9 mg) as a colorless oil (78%). Compound **1b** was recovered in 87% yield without loss of the optical purity by acidification of the aqueous layer and the extraction with chloroform.

In conclusion, we have demonstrated that *N*,*N*,*N'*,*N'*-tetraethyl-1,1'-bi-2-naphthol-3,3'-dicarboxamide **1b** of axial chirality is an efficient chiral auxiliary for asymmetric Simmons-Smith reaction of *E* allylic alcohols. Study on the mechanism of this reaction is under way in our laboratory.

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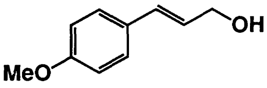
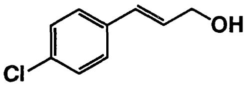
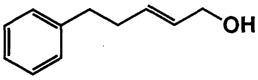
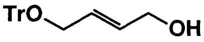
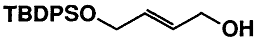
Table 2. Asymmetric Simmons-Smith reaction of allylic alcohols using **1b** as a chiral auxiliary[a]

Entry	Substrate	Yield (%)	% Ee	Confign.[b]
1		78	94[c]	
2		50	90[d]	
3		65	89[e]	
4		64	88[e]	1*R*, 2*R*
5		59	87[e]	
6		34	65[f]	1*R*, 2*S*

[a] All the reaction was carried out under the same conditions as described in general procedure, unless otherwise mentioned. [b] Absolute configuration was assigned by chiroptical comparison with the literature value (Reference 3a). [c] Determined by HPLC analysis using DAICEL Chiralcel OD (hexane/*i*-PrOH 9:1). [d] Determined by HPLC analysis using DAICEL Chiralcel OD (hexane/*i*-PrOH 100:1) after acetylation. [e] Determined by HPLC analysis using DAICEL Chiralcel OD (hexane/*i*-PrOH 15:1). [f] Determined by HPLC analysis using DAICEL Chiralcel OD (hexane/*i*-PrOH 30:1).

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† Research Fellow of the Japan Society for the Promotion of Science.

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8 Denmark have reported that the addition of ZnI_2 increases the enantioselectivity in Simmons-Smith reaction of allylic alcohols with optically active disulfonamides as chiral ligands (Reference 3c).