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Stereocontrolled Cyclopropanation of α,β-Unsaturated Carboxamides Derived from Bicyclic Amino Alcohols

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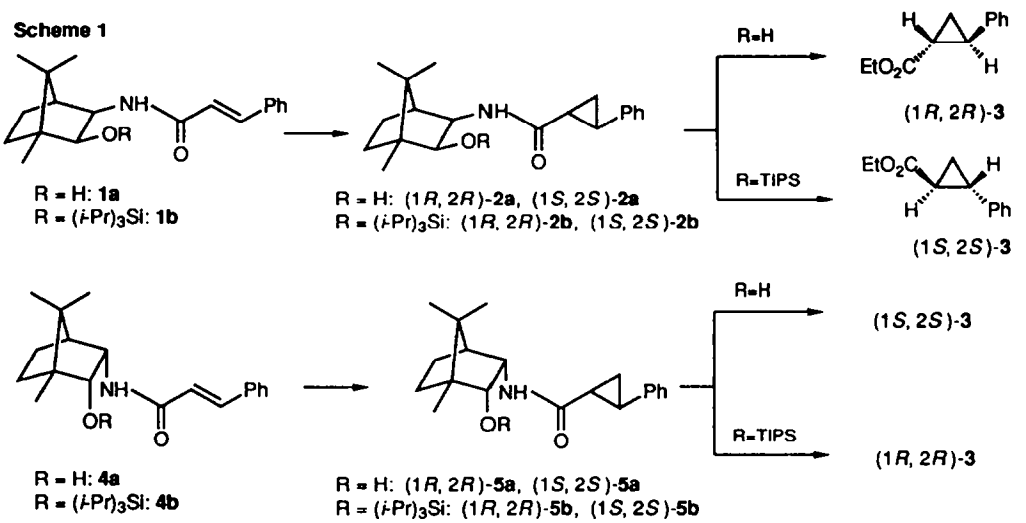
Abstract: The asymmetric cyclopropanation of the *exo*-*N*-[(1*R*,2*S*,3*R*,4*S*)-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]hept-3-yl]-3-phenyl-2-propenamide and the *endo*-(1*R*,2*R*,3*S*,4*S*)-isomer with Et_2Zn/CH_2I_2 proceeded with predictable absolute stereochemistry. The *exo*-amide gave the (1*R*,2*R*)-cyclopropane derivative selectively (de ≤ 80%), while the *endo*-amide gave the (1*S*,2*S*)-isomer (de ≤ 58%). Complete reversal of the stereoselectivity (98% de) was observed when *O*-triisopropyl derivatives of the amides were used in the cyclopropanation.

The asymmetric synthesis of cyclopropane derivatives has attracted considerable interest from synthetic chemists, because optically active cyclopropanes can serve as useful intermediates for the preparation of naturally occurring compounds[1] or biologically active substances.[2] High levels of diastereoselectivity[3] and enantioselectivity[4] in the cyclopropanation reaction have been achieved either by use of chiral auxiliaries such as 2-hydroxy-β-D-glucopyranose[3l] and $[\eta^5\text{-}(C_5H_5)Fe(CO)(PPh_3)]$,[3g] or by use of chiral ligands such as semicorrin metal complex[4g] and bis(oxazoline) copper complex.[4f]

Scheme 1



We wish to report the diastereofacially controlled cyclopropanation of α,β-unsaturated carboxamides (**1a** and **4a**) prepared from *exo*- and *endo*-3-amino-2-hydroxybornanes as chiral auxiliaries. Thus, the reaction of *exo*-**1a** with Et_2Zn/CH_2I_2[5] at room temperature gave a 76% yield of a diastereomeric mixture of *trans*-(1*R*,2*R*)-**2a** and (1*S*,2*S*)-**2a** in a ratio of 90:10. The absolute configurations of **2a** were determined by

measuring the specific rotations of 3[4q] after *N-tert*-butoxycarbonylation (94%)[6] and ethanolysis (78%) (Scheme 1).

We found that the stereoselectivity was completely reversed when *endo*-**4a** was employed in the cyclopropanation (Table 1). An important feature of the bicyclic amides derived from D-camphor is that the diastereomeric cyclopropanecarboxamides are readily separated by silica gel chromatography to give optically pure amides. These diastereomers were transformed into the corresponding ethyl 2-phenylcyclopropanecarboxylates with 100% ee, which are important intermediates for the synthesis of *N,N*-dialkylated 2-phenylcyclopropylamine, the potent 5-hydroxytryptamine receptor agonists.[7]

Table 1. Asymmetric cyclopropanation of α,β-unsaturated carboxamides (**1a** and **4a**).

Entry	Amide	Solvent	temp.	time (h)	Yield[a] (%)	Diastereomer of cyclopropanes (**2a** or **5a**) (1*R*,2*R*) : (1*S*,2*S*)	% de
1[b]	**1a**	CH_2Cl_2	r.t.	7	76	(**2a**) 90 : 10	80
2	**1a**	CH_2Cl_2	reflux	6	83	(**2a**) 88 : 12	76
3	**1a**	ether	r.t.	24	12	(**2a**) 50 : 50	0
4	**1a**	benzene	r.t.	24	72	(**2a**) 78 : 22	56
5	**1a**	hexane	r.t.	24	42	(**2a**) 51 : 49	2
6	**4a**	CH_2Cl_2	reflux	6	100	(**5a**) 21 : 79	58
7	**4a**	CH_2Cl_2	r.t.	24	92	(**5a**) 32 : 68	36

[a] 3 eq of Et_2Zn and 5 eq of CH_2I_2 were used. [b] 0.03 eq of CuI was added.

Table 2. Asymmetric cyclopropanation of Silylated α,β-unsaturated carboxamides (**1b** and **4b**).

Entry	Amide	Additive	time (h)	Yield[a] (%)	Diastereomer of cyclopropanes (**2b** or **5b**) (1*R*,2*R*) : (1*S*,2*S*)	% de
1	**1b**	none	72	16	(**2b**) 1 : 99	98
2	**1b**	L-(+)-DT[b] (0.5 eq)	40	62	(**2b**) 1 : 99	98
3	**1b**	D-(-)-DT[b] (0.5 eq)	40	46	(**2b**) 1 : 99	98
4	**1b**	meso-DT[b] (0.5 eq)	72	47	(**2b**) 1 : 99	98
5	**4b**	none	24	20	(**5b**) 99 : 1	98
6	**4b**	L-(+)-DT[b] (0.5 eq)	48	56	(**5b**) 99 : 1	98
7	**4b**	D-(-)-DT[b] (0.5 eq)	48	56	(**5b**) 99 : 1	98

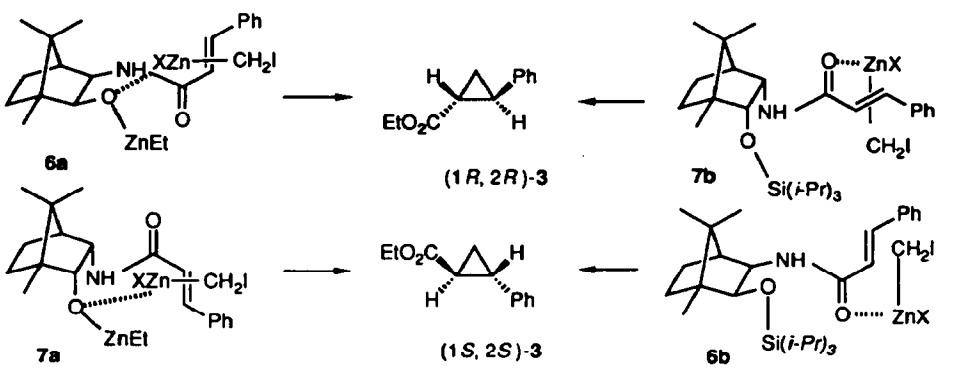
[a] 3eq of Et_2Zn and 5 eq of CH_2I_2 were used in CH_2Cl_2 at room temperature. [b] DT: diethyl tartrate.

In contrast to the reaction of **1a** and **4a**, the cyclopropanation of α,β-unsaturated carboxamides (**1b** and **4b**) possessing an *O*-triisopropylsilyl group proceeded with reversal of the original stereoselectivity. Thus, the reaction of **1b** with Et_2Zn/CH_2I_2 in CH_2Cl_2 gave (1*S*,2*S*)-**2b** exclusively, but in poor yield. It is interesting to note that the addition of 0.5 equiv of L-(+)- or D-(-)-diethyl tartrate increased the chemical yield from 16% to 62%, although the mechanistic details are unclear at present.[4p] When the reaction was carried out with *endo*-

4b, the stereoselectivity of the cyclopropanation was completely reversed to give (1*R*,2*R*)-**5b** in 98% de (Table 2).

The observed stereoselectivity can be rationalized by assuming "(iodomethyl)zinc reagent" (ICH_2ZnX)[8] as a reactive species, and the *syn*-directing effect of hydroxy function.[3i] The front side attack of the reagent to the secondary amides in the *Z*-configuration[9] is favored by the proximal oxygen substituent of **1a** and **4a**,[3i,8] leading to the formation of (1*R*,2*R*)-**2a** from **1a** and (1*S*,2*S*)-**5a** from **4a** (Scheme 2). On the other hand, the *O*-triisopropylsilyl group of the amides (**1b** and **4b**) cannot direct the cyclopropanation reaction and causes nonbonding interaction to restrict rotation about C_1-C_2 bond and covers the front face of the amides moiety. Thus, the (iodomethyl)zinc reagent approaches from back side of the amide group, resulting in higher diastereoselectivity.

Scheme 2



In summary, we have demonstrated interesting features of four kinds of α,β-unsaturated carboxamides derived from D-camphor, which provide both enantiomers of *trans*-2-phenylcyclopropanecarboxylates with high stereoselectivity in the (iodomethyl)zinc cyclopropanation reaction. Applications of these chiral auxiliaries to the synthesis of other optically pure substances will be reported in due course.

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