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ENANTIOSELECTIVE, RHODIUM CATALYZED INTRAMOLECULAR CYCLOPROPANATIONS OF HOMOALLYLIC DIAZOACETATES.

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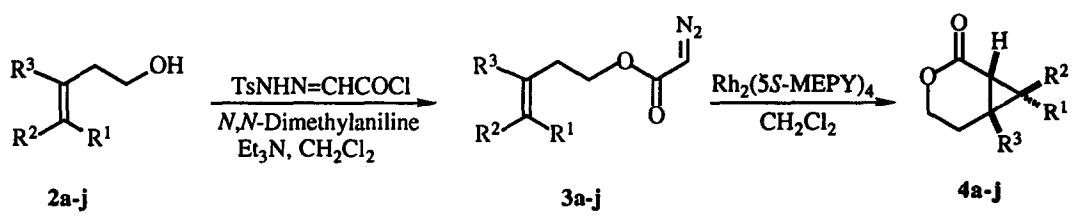
Abstract. The homoallylic diazoacetates **3a-j** underwent enantioselective intramolecular cyclopropanation with the rhodium catalyst Rh_2(5*S*-MEPY)$_4$ (**1**) to give the oxabicyclo[4.1.0]heptanes **4a-j** in 71-90% enantiomeric excess and in 55-80% chemical yield.

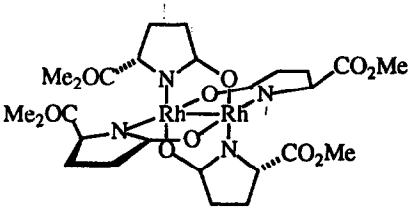
Interest in cyclopropanes has been stimulated over the years as a consequence of its occurrence in natural products,[1] its biological significance,[2,3] its ability to function as a mechanistic probe,[4] and its synthetic utility.[5] The importance of cyclopropanes has fostered numerous efforts directed toward the development of stereoselective methods for its synthesis, and a variety of methods have been developed for its asymmetric synthesis.[6-8]

As part of a general program directed toward the invention of novel replacements of peptide secondary structure, we have focused upon trisubstituted cyclopropanes as rigid surrogates of the extended, β-strand conformation of oligopeptides.[3] The requisite cyclopropanes for our initial studies were prepared by a procedure that featured the highly enantioselective, intramolecular cyclopropanation of allylic diazoacetates catalyzed by dirhodium(II) tetrakis[methyl 2-pyrrolidinone-5-(*S*)-carboxylate] [Rh_2(5*S*-MEPY)$_4$] (**1**).[7,9] We have recently extended the scope of this process and now wish to report the use of **1** as an effective catalyst for promoting the enantioselective cyclopropanation of homoallylic diazoacetates (Scheme 1).

Scheme 1



2a-j **3a-j** **4a-j**



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The homoallylic alcohols **2a-e** are commercially available, whereas **2f-j** were prepared by stereoselective reduction[10] of the corresponding acetylenes that were synthesized by modification of known procedures.[11,12] The subsequent conversion of **2a-j** into the homoallylic diazoacetates **3a-j** [(a) TsNHN=CHCOCl (1.1 equiv); *N,N*-dimethylaniline (1.25 equiv); CH_2Cl_2; 0 °C; 10 min. (b) Et_3N (5.3 equiv); 0 °C (15 min) → RT (30 min)] proceeded in 80-92% yield.[13] When a solution of **3a-j** (0.04 M in CH_2Cl_2) was added dropwise (8 h) via syringe pump to a refluxing solution of Rh_2(5*S*-MEPY)$_4$ (**1**) (0.01 equiv) in an equal volume of CH_2Cl_2, the cyclopropanes **4a-j** were obtained in 71-90% enantiomeric excess and in yields ranging from 55-80% (unoptimized) (Table 1).[14]

Table 1. Enantioselectivity of Rh_2(5*S*-MEPY)$_4$ Catalyzed Intramolecular Cyclopropanation Reactions of Homoallylic Diazoacetates 3a-j → 4a-j

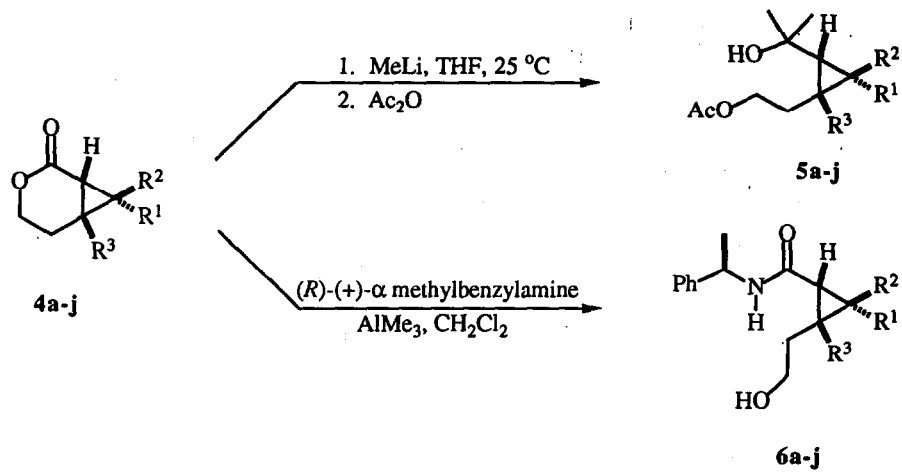
Entry	R^1	R^2	R^3	yield, %	e.e., %
a	H	H	H	80	71[b]
b	H	H	CH_3	76	79[b]
c	CH_3	CH_3	H	74	77[b]
d	C_2H_5	H	H	80	90[b,c]
e	H	C_2H_5	H	65	82[b]
f	C_6H_5	H	H	73	88[c]
g	H	C_6H_5	H	55[a]	73[b]
h	*c*-$C_6H_{11}CH_2$	H	H	77	80[c]
i	$C_6H_5CH_2$	H	H	68	80[b]
j	$(CH_3)_3Si$	H	H	65	86[c]

[a]Reaction run starting with an initial concentration of of **3g** 0.02 M; with initial concentration of 0.04 M, the yield was 32%. [b]Determined according to Method A. [c]Determined according to Method B. (See text)

The enantiomeric excesses obtained in these cyclizations were determined by two different methods. In the first (Method A), the lactones **4a-e,g,i** were converted into the corresponding monoacetates **5a-e,g,i** [(a) MeLi (4.0 equiv); THF; 25 °C; 30 min. (b) Ac_2O (4.0 equiv); 15 min.] (Scheme 2), and the relative amounts of the two enantiomers were established by integration of the signals of the diastereotopic protons of the ***geminal*** dimethyl groups of the dimethyl carbinol moiety in the presence of the chiral shift reagent Eu(tfc)$_3$ (0.2-0.6 equiv) in C_6D_6. Another technique (Method B) was developed in which the lactones **4d,f,h,j** were transformed into the corresponding diastereomeric amides **6d,f,h,j** according to the method of Weinreb[15] [(*R*)-(+)-α methylbenzylamine (3.0 equiv); $AlMe_3$ (3.0 equiv); CH_2Cl_2; 40 °C; 16 *h*], and the mixtures were analyzed by HPLC. In all cases, control experiments were performed using racemic lactones **4a-j** [**3a-j**, Cu(TBS)$_2$ (0.05 equiv); toluene; 110 °C].[16]

In general, the intramolecular cyclopropanations of the homoallylic diazoacetates **3a-j** follow the trends previously observed for their allylic counterparts,[7] although the yields and enantioselectivities seem to be slightly higher for the latter. The absolute sense of the asymmetric induction also appears to be the same based upon the determination of the structures of the (*R*)-(+)-α-methylbenzylamide derivatives **6d** and **6j** by single crystal X-ray analyses. Based upon the examples shown, it appears that the cyclizations of the (*Z*)-homoallylic diazoacetates proceed with higher enantioselectivity as well as in higher yields than corresponding (*E*)-isomers. In this context it

Scheme 2



should be noted that the yield of lactone **4g** obtained upon cyclization of **3g** increased significantly at concentrations lower than 0.04 M with dimerization of the carbene being the major side reaction. The effect of further lowering the concentrations with the other substrates was not examined.

These results further illustrate the effectiveness of the chiral rhodium catalyst [Rh_2(5*S*-MEPY)$_4$] (**1**) for inducing enantioselective cyclopropanations of unsaturated diazoacetates. The uses of **1** and related catalysts for the asymmetric syntheses of cyclopropanes that may be exploited in a variety of biologically relevant applications is under active investigation, the results of which will be reported in due course.

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