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Asymmetric Ring Cleavage Reaction Based on Crossed Aldol Condensation

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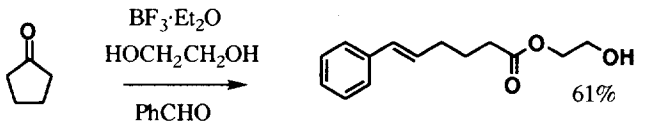
Abstract: Ring cleavage reaction based on crossed aldol condensation of carbobicyclic ketones with benzaldehyde under acetalization conditions (BF_3·Et_2O/ethylene glycol) was studied. By using optically active 1,2-diols instead of ethylene glycol, an asymmetric version of this reaction could be developed for the first time.

We previously reported a new type of ring transformation based on tandem intramolecular aldol condensation and ring cleavage using a combination of Lewis acid and 1,2-diol. In the intramolecular system, this reaction including its asymmetric version,[1] was found to be widely applicable to various types of ring transformation. Furthermore, the preliminary studies of this reaction in the intermolecular system, that is to say, ring cleavage based on unimolecular aldol condensation and/or crossed aldol condensation, were recently reported by us.[2] We describe here the first attempt for the asymmetric version of this reaction using optically active 1,2-diols of C_2-symmetry as a chiral source and carbobicyclic ketones of σ-symmetry as a substrate.

Reaction of carbobicyclic ketones with benzaldehyde

Reaction of cyclopentanone and benzaldehyde under acetalization conditions (BF_3·Et_2O/ethylene glycol/CH_2Cl_2/r.t.) afforded styrene derivative in 61% yield (Scheme 1).[2] A similar reaction using six-membered ketones such as cyclohexanone and/or 4-methylcyclohexanone did not give satisfactory results,[3] and the desired products were obtained in only 5-20% yields.

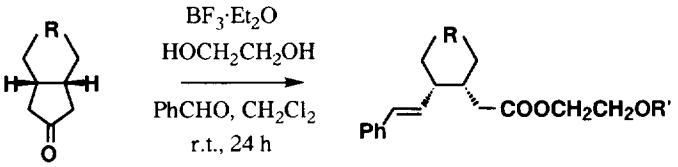
Scheme 1



To develop an asymmetric version of this type of reaction, we set up three kinds of carbobicyclic compounds **1-3** of σ-symmetry as a substrate. At first, reaction of these compounds with benzaldehyde (1.05 equiv.) in the presence of BF_3·Et_2O (3 equiv.) and ethylene glycol (5 equiv.) in CH_2Cl_2 at room temperature was carried out, and the results are summarized in Scheme 2. In all cases, the desired reaction proceeded to give the corresponding ring-cleaved products **4-6**. Chemical yields of **4** (53%) and **5+5'** (total yield 72%) were moderate, but that of **6+6'** (total yield 29%) was low. The structure of these products was determined based on spectroscopic analyses and chemical conversion into the corresponding methyl esters (85-93% yields) by

treatment with K_2CO_3/MeOH. As a typical example, ^{1}H-NMR spectrum of compound **5** showed signals assignable to the hydroxyethyl ester [δ 4.18 (2H, m, CO_2CH_2), 3.77 (2H, m, CH_2OH)], two olefinic protons [δ 6.38, 6.36 (1H each)] and aromatic protons [δ 7.37-7.17 (5H)]. From the coupling constant (J=17 Hz) between the olefinic protons, the geometry of the double bond was determined to be *trans*. Relative stereochemistry between two substituents on the cyclohexane skeleton of **5** was determined to be *cis*, retaining the stereochemistry of substrate **2**, by chemical conversion into diol **12** as aftermentioned, and diastereomeric *trans*-isomer could not be detected.

Scheme 2. Ring cleavage of carbobicyclic ketones with benzaldehyde in the presence of BF_3-Et_2O/ethylene glycol.



1 : R = -CH_2-

2 : R = -CH_2CH_2-

3 : R = -CH=CH- (Z)

4 : R = -CH_2-, R'= H (53%)

5 : R = -CH_2CH_2-, R'= H (66%)
5' : R = -CH_2CH_2-, R'= CH_2CH_2OH (6%)

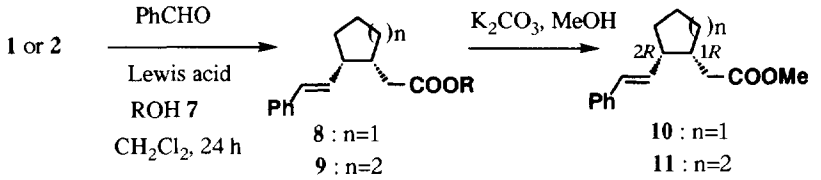
6 : R = -CH=CH- (Z), R'= H (14%)
6' : R = -CH=CH- (Z), R'= CH_2CH_2OH (15%)

Application into asymmetric version

Next, an asymmetric ring cleavage based on intermolecular aldol condensation was studied by using compounds **1** and **2** as a substrate and optically active 1,2-diols **7a-c** of C_2-symmetry as a chiral source. Results are summarized in Table 1. Several reaction conditions relative to the ratio of diol/Lewis acid and reaction temperature were also studied. In all entries, the desired reaction proceeded to give ring-cleaved products **8** or **9**. The obtained products were converted into the corresponding methyl esters[4] **10** or **11** by treatment with K_2CO_3/MeOH in 85-94% yields. Enantiomeric excess (e.e.) was estimated from 270 MHz ^{1}H-NMR spectrum in the presence of chiral shift reagent (Eu(hfc)$_3$). Among the reactions of compound **1** having a bicyclo[3.3.0]-octane skeleton (entries 1-3), (*S,S*)-cycloheptane-1,2-diol **7b** gave the best result as regards the chemical yield of ring-cleaved product **8b** (81% yield, entry 2). But in these cases, e.e. values of **10** were extremely low (12-26% e.e.). In cases of using substrate **2** with a bicyclo[4.3.0]nonane skeleton, asymmetric induction was improved. In connection with the chemical yield of products **9a-c**, it was found that 7-membered diol **7b** (**9b**: 79%, entry 5) and acyclic diol **7c** (**9c**: 72%, entry 8) were superior to 6-membered diol **7a** (**9a**: 30%, entry 4), which is similar to the results in entries 1-3. The chemical yield of **9** was found to be strongly affected by reaction temperature (entries 5, 6, 8 and 9) and reaction at -20°C was so slow that a satisfactory result was not obtained.

For the e.e. value of **11**, the best enantioselectivity was obtained in entry 7 ((-)-**11** of 69% e.e.) by using (*R,R*)-**7b** and TMSOTf at 0°C. Asymmetric induction by chiral diol into **11** was obviously supported from the results in entries 5 and 6, in which (1*R*,2*R*)-**11** was obtained by using (*R,R*)-**7b**, and (1*S*,2*S*)-**11** by using (*S,S*)-**7b**. Absolute configuration of **11** was determined by comparison with the authentic sample after conversion into **12**.[5]

Table 1. Asymmetric ring cleavage reaction.

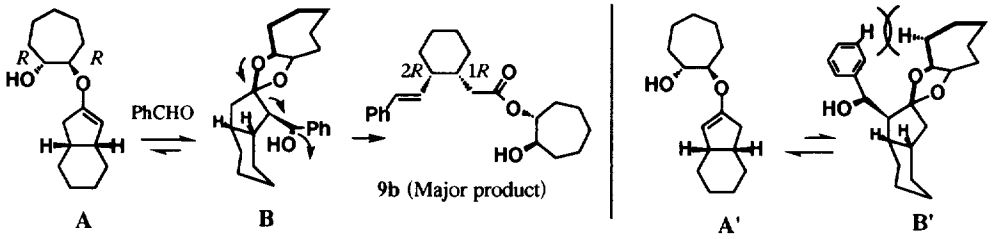


Entry	Substrate	ROH 7	Lewis acid	Temp.	Yield of **8** or **9** (%)	%e.e. of **10** or **11** (Abs. config.)*
1	**1**	 (*R,R*)-**7a** 2 equiv.	BF_3·Et_2O 3 equiv.	r. t.	**8a**: 34	(-)-**10** : 26
2	**1**	 (*S,S*)-**7b** 2 equiv.	BF_3·Et_2O 3 equiv.	r. t.	**8b**: 81	(+)-**10** :14
3	**1**	 (*R,R*)-**7c** 2 equiv.	BF_3·Et_2O 3 equiv.	r. t.	**8c**: 72	(-)-**10** : 12
4	**2**	(*R,R*)-**7a** 2 equiv.	BF_3-Et_2O 4 equiv.	r. t.	**9a**: 30	(-)-**11** : 49 (1*R*, 2*R*)
5	**2**	(*R,R*)-**7b** 3 equiv.	BF_3-Et_2O 3 equiv.	r. t.	**9b**: 79	(-)-**11** : 60 (1*R*, 2*R*)
6	**2**	(*S,S*)-**7b** 3 equiv.	BF_3-Et_2O 3 equiv.	0°C	**9b**: 34	(+)-**11** : 64 (1*S*, 2*S*)
7	**2**	(*R,R*)-**7b** 2 equiv.	TMSOTf 2 equiv.	0°C	**9b**: 54	(-)-**11** : 69 (1*R*, 2*R*)
8	**2**	(*R,R*)-**7c** 2 equiv.	BF_3-Et_2O 3 equiv.	r. t.	**9c**: 72	(-)-**11** : 63 (1*R*, 2*R*)
9	**2**	(*R,R*)-**7c** 2 equiv.	TMSOTf 2 equiv.	0°C	**9c**: 31	(-)-**11** : 53 (1*R*, 2*R*)

* Absolute configuration of **10** was not determined.

Reaction mechanisms, tentatively proposed as shown in Scheme 3, include three steps: 1. Formation of chiral enol ether[6] **A**; 2. Acetal-formation and subsequent aldol condensation to form **B**; 3. Grob's fragmentation into ring-cleaved product **9b**. Steps 1 and 2 including four reaction intermediates **A**, **A'**, **B** and **B'** are considered to be in equilibrium, and step 3 is irreversible. By comparing **B** and **B'** with the Dreiding stereomodel, **B'** was considered to be more highly hindered than **B**, which might cause the asymmetric induction into the ring-cleaved product.

Scheme 3



References and Notes

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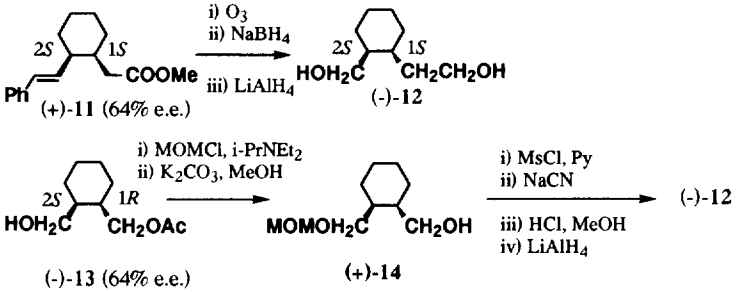
4. Selected spectroscopic data: **(-)-10**: 26% e.e., Colorless oil, $[\alpha]_D^{20}$ -12.4 (c=1.5, $CHCl_3$). IR (neat): 1735, 1600, 1450, 1435, 1280 cm^{-1}. 270 MHz ^{1}H-NMR δ ($CDCl_3$): 7.35-7.19 (5H, m), 6.36 (1H, d, *J*=16 Hz), 6.11 (1H, dd, *J*=8.9, 16 Hz), 3.60 (3H, s). FDMS *m/z*: 244 (M^+). (-)-**11**: 69% e.e., Colorless oil, $[\alpha]_D^{22}$ -53.3 (c=1.3, $CHCl_3$). 270 MHz ^{1}H-NMR δ ($CDCl_3$): 7.37-7.17 (5H, m), 6.37 (1H, d, *J*=17 Hz), 6.35 (1H, dd, *J*=8, 17 Hz), 3.62 (3H, s). FDMS *m/z*: 258 (M^+).
5. Absolute configuration of (+)-**11** was determined as follows. Product (+)-**11** (64% e.e.) obtained in entry 6 was converted into diol (-)-**12** ($[\alpha]_D^{20}$ -21.9 (c=1.0, $CHCl_3$)) *via* ozonolysis followed by two-step reduction with $NaBH_4$ and $LiAlH_4$. The authentic sample of optically active (-)-**12** was synthesized from (-)-(1*R*,2*S*)-**13** of 64% e.e., which was prepared by porcine pancreas lipase-catalyzed hydrolysis of the corresponding meso-diacetate according to Jones' procedure.[7] Protection of the hydroxy group of **13** as MOM ether and solvolysis of the acetate function gave the compound (+)-**14**. Subsequent conversion into (-)-**12** was achieved *via* the usual four-step sequence. The specific rotation of the obtained (1*S*,2*S*)-**12** showed $[\alpha]_D^{22}$ -22.8 (c=2.7, $CHCl_3$).



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