

Asymmetric Synthesis of 2,3-Dihydro-4-pyranones by Reaction of Chiral 3-Alkoxycyclobutanone and Aldehydes

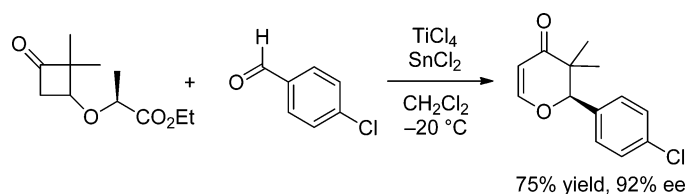
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ABSTRACT



Chiral cyclobutanone which had ethyl L-lactate as a chiral auxiliary at the 3-position reacted with aldehydes to give 2,3-dihydro-4-pyranones in up to 93% ee by combined use of titanium(IV) chloride and tin(II) chloride.

Chiral pyrans are versatile building blocks for the synthesis of many biologically active compounds, such as pheromones, antitumor agents, and terpenoids.¹ Chiral dihydropyranones **1** (Figure 1, R¹, R² = H) have been prepared by enantioselective hetero-Diels–Alder (HDA) reactions² between siloxydienes and aldehydes by using various chiral Lewis acid catalysts such as BINOL–metal (Mg,^{3a} Ti,^{3b} Zn,^{3c} or Al^{3d}) complexes, Cu(II)^{4a} or Rh(II)^{4b} carboxamidates, and salen–metal (Cr(III) or Mn(III)) complexes.^{5a–c} Chiral organo-catalysts⁶ such as TADDOL (α,α,α′,α′-tetraaryl-1,3-dioxo-

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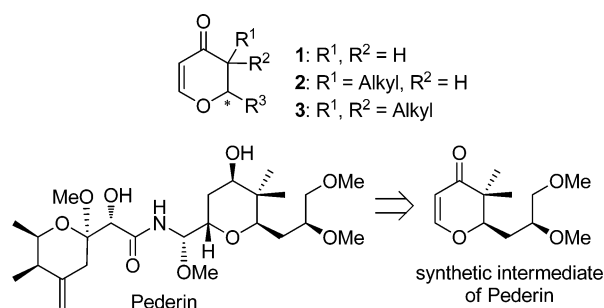


Figure 1. 2,3-Dihydro-4-pyranones (**1–3**) and synthetic intermediate of pederin.

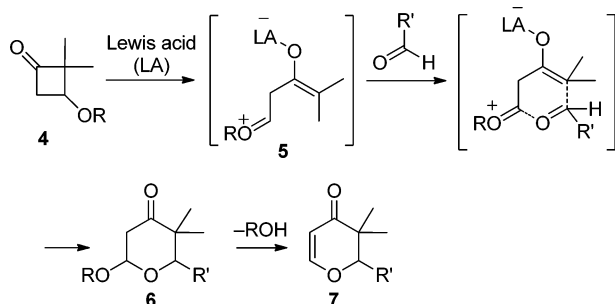
lane-4,5-dimethanol),^{7a,b} BAMOL (1,1′-biaryl-2,2′-dimethanol),^{7c} or oxazolines,^{7d} which activate aldehydes through hydrogen bonds, have also promoted enantioselective HDA reactions between 1-amino-3-siloxy-1,3-butadienes⁸ and al-

(6) Recent review: Merino, P.; Marqués-López, E.; Tejero, T.; Herrera, R. P. *Synthesis* **2010**, 1.

dehydes. Synthesis of dihydropyranones **2** bearing alkyl groups at their 3-position ($R^1 = \text{alkyl}$, $R^2 = \text{H}$) is more difficult, and only a few methods have been reported for their preparation by using dirhodium(II) chiral carboxamidate^{9a} catalysts, Cu(II) bisoxazoline,^{9b} or BINOL–metal (Al^{3d} or Zr^{9c}) complexes. Chiral dihydropyranones **3** having dialkyl groups at their 3-position are seen in the structure of natural products such as the pederin family of natural products.¹⁰ However, preparation of chiral dihydropyranones **3** needs many steps which include asymmetric aldol reaction.^{11a,b}

We have reported a Lewis acid-catalyzed reaction between 3-alkoxycyclobutanones **4** and aldehydes¹² to afford various types of 2,3-dihydro-4-pyranones **7** (Scheme 1). A zwitterionic

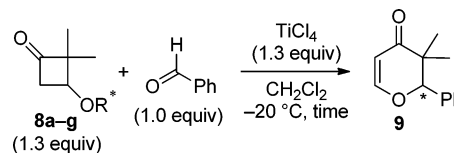
Scheme 1. Lewis Acid-Catalyzed Reaction between Cyclobutanone **4** and Aldehyde to Dihydropyranone **7**



intermediate **5** was generated by Lewis acid-catalyzed ring opening of 3-alkoxycyclobutanone **4**. Compound **6** was formed by reaction of **5** and aldehyde, and elimination of alcohol from adduct **6** gave dihydro-4-pyranone **7**. It was then thought that introducing a chiral auxiliary into the 3-alkoxy group of cyclobutanone **4**¹³ would give chiral dihydropyranone **7**.

First, screening for an effective chiral auxiliary for asymmetric induction between 3-alkoxycyclobutanone **4** and aldehyde was carried out by reaction between cyclobutanone **8a–g** and benzaldehyde in the presence of titanium(IV) chloride (Table 1). Reaction of cyclobutanones **8a** and **8b**,

Table 1. Effect of Chiral Auxiliary on Diastereoselective Cycloaddition between Cyclobutanone **8a–g** and Benzaldehyde



entry	cyclobutanone ^a	time (h)	yield (%) ^b	% ee ^c
1		0.5	42	7 (<i>S</i>)
2		5.0	43	3 (<i>S</i>)
3		3.0	60	79 (<i>R</i>)
4		8.0	73	77 (<i>R</i>)
5		8.0	43	44 (<i>R</i>)
6 ^d		55.0	43	58 (<i>R</i>)
7		30.0	67	19 (<i>S</i>)

^a Diastereomer ratios: **8a** (49:51), **8b** (45:55), **8c** (60:40), **8d** (36:64), **8e** (31:69), **8f** (36:64), **8g** (15:85). ^b Isolated yield. ^c Determined by chiral HPLC. For the absolute configuration, see the text. ^d The reaction was carried out at -20 to 0 °C.

which were prepared from (–)-menthol and (*S*)-1-(benzyloxy)-propane-2-ol, respectively, gave dihydro-4-pyranone **9** in low ee's (7–3% ee, entries 1 and 2). Moderate to good asymmetric induction was observed in the reaction of cyclobutanones **8c–e**, which were derived from L-lactic esters (44–79% ee, entries 3–5). The reaction of cyclobutanones **8f** and **8g**, which were prepared from L-malic acid dimethyl ester and D-pantolactone, afforded cycloadduct **9** in 58% and 19% ee, respectively (entries 6 and 7). Therefore, L-ethyl lactate was chosen as a chiral auxiliary for the present asymmetric reaction.

The chiral cyclobutanone **8c** was prepared from L-ethyl lactate in three steps (Scheme 2). 1-Ethoxyethyl ether of L-ethyl lactate **10** was prepared in 92% yield by reaction of L-ethyl lactate and ethyl vinyl ether in the presence of a catalytic amount of TFA. Treating **10** with triethylamine and TMSOTf gave vinyl ether **11** (79% yield).¹⁴ [2 + 2]

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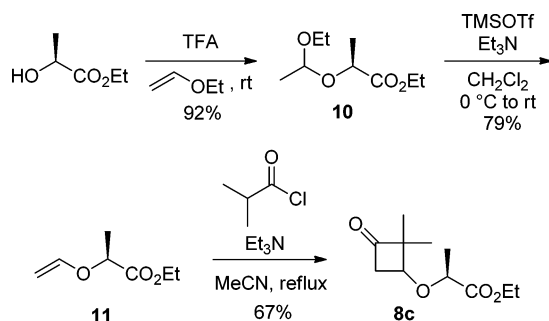
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Scheme 2. Preparation of Cyclobutanone **8c**



Cycloaddition by using vinyl ether **11**, isobutyryl chloride, and triethylamine afforded cyclobutanone **8c** in 67% yield as a mixture of two diastereomers (60:40).

Interestingly, it was proven that addition of some metal chlorides in a titanium(IV) chloride-promoted asymmetric reaction between **8c** and benzaldehyde improved the enantioselectivity of product **9** (Table 2). The use of copper(II)

Table 2. Effect of Metal Chloride on Diastereoselective Cycloaddition between Chiral Cyclobutanone **8c** and Benzaldehyde

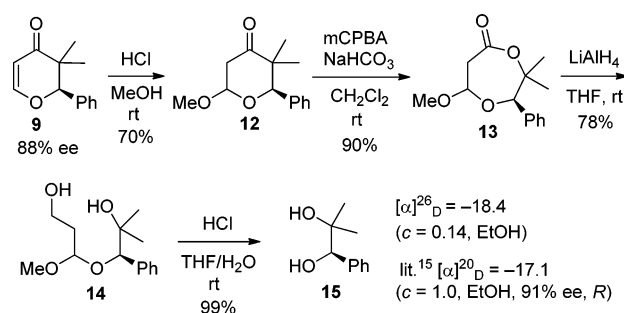
entry	metal chloride	time (h)	yield (%) ^a	% ee ^b
1	none	3.0	60	79
2	CuCl ₂	6.0	26	81
3	ZnCl ₂	1.5	58	83
4	SnCl ₂	8.0	70	88

^a Isolated yield. ^b Determined by chiral HPLC.

chloride and zinc(II) chloride slightly improved the ee of adduct **9**, but yields were decreased (entries 2 and 3). Among the metal chlorides tested, the use of tin(II) chloride gave **9** in 70% yield with the best enantioselectivity (88% ee, entry 4). The role of tin(II) chloride in this reaction has not yet been clarified. The use of each separated diastereomer of **8c** gave almost the same results as those obtained by employing a mixture of two diastereomers of **8c**.

The absolute configuration of **9** was determined by comparison with the specific rotation of known diol **15**¹⁵ (Scheme 3). Baeyer–Villiger oxidation of **12**, which was prepared by reaction of compound **9** (88% ee) with methanolic hydrogen chloride,¹⁶ gave lactone **13** in 90% yield. Reduction of **13** with lithium aluminum hydride gave diol

Scheme 3. Determination of the Absolute Configuration of **9**



14 in 78% yield, and hydrolysis of **14** gave diol **15** in 99% yield. The specific rotation of obtained **15** ($[\alpha]_D^{26} = -18.4$) suggested that its absolute configuration was *R*.¹⁵

Next, the scope and limitations of diastereoselective reaction of **8c** were investigated by using various aldehydes (Table 3). When electron-withdrawing groups were substi-

Table 3. Diastereoselective Cycloaddition with Various Aromatic Aldehydes

entry	aldehyde	time (h)	yield (%) ^a	% ee ^b
1	R' = CF ₃ (16a)	12.5	68	89
2	R' = F (16b)	10.0	67	91
3	R' = Cl (16c)	8.0	75	92
4	R' = Br (16d)	12.0	64	90
5	R' = I (16e)	12.5	78	88
6	R' = Me (16f)	8.0	59	77
7	R' = Ph (16g)	11.5	70	77
8	(16h)	5.0	60	93
9	(16i)	6.0	58	75
10	(16j)	10	43	78
11	(16k)	6.5	47	76

^a Isolated yield. ^b Determined by chiral HPLC analysis. The absolute configuration was deduced from compound (*R*)-**9**.

tuted at the para-position of the phenyl group of benzaldehyde **16a–e**, the corresponding 2,3-dihydropyranones **17a–e** were obtained in good yields (64–78%) and with high ee's

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(88–92% ee, entries 1–5). On the other hand, aldehydes bearing a methyl or phenyl group at the para-position of the phenyl group gave lower ee's (77% ee, entries 6 and 7). In comparison with 2-naphthylaldehyde **16h**, which gave cycloadduct **17h** in 60% yield and 93% ee (entry 9), the reaction with 1-naphthylaldehyde **16i** gave the desired adduct **17i** in a lower yield (58%) and with lower ee's (75% ee, entry 10). These results suggest that this reaction was influenced by steric effects. Reactions between **8c** and aliphatic aldehydes **16j** and **16k** gave the desired products **17j** and **17k** in moderate yields (43% and 47%) and with good ee's (76% and 78% ee, entries 10 and 11).

In summary, chiral 2,3-dihydro-4-pyranones were prepared by a diastereoselective asymmetric reaction of aldehyde and 3-alkoxycyclobutanone bearing L-ethyl lactate as a chiral auxiliary. It is expected that these chiral cyclobutanones will be effective for other reactions with imines,¹⁷ allylsilanes,¹⁸

and silyl enol ethers¹⁹ to afford the corresponding chiral dihydropyranones and cyclohexanones.

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Supporting Information Available: Detailed experimental procedures and full spectroscopic characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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