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Asymmetric cycloetherification based on a chiral auxiliary for 4-acyloxy-1-butene substrates during oxidation with iodosylbenzene via a 1,3-dioxan-2-yl cation

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ABSTRACT

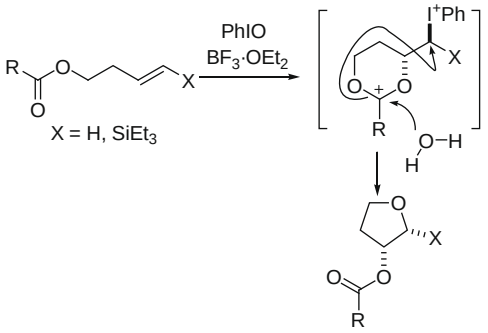
Reaction of but-3-enyl camphanate and its derivatives with iodosylbenzene yielded tetrahydrofuran-3-yl camphanate with high diastereomeric ratio via a 1,3-dioxan-2-yl cation intermediate. The reaction using (1*S*)-camphanate as a chiral auxiliary preferentially gave (*S*)-3-acyloxytetrahydrofuran and (2*S*,3*S*)-3-acyloxy-2-silyltetrahydrofuran.

Development of highly stereoselective construction of substituted tetrahydrofurans as enantiomerically pure form is of great interest because many biologically active compounds have such oxygen heterocycles.[1,2] Enantiomerically pure tetrahydrofurans were prepared by a combination of stereoselective reaction steps in many cases, for example, asymmetric epoxidation followed by diastereoselective cycloetherification.[1] In this Letter, we describe asymmetric synthesis of optically active tetrahydrofuran during oxidation of acyloxybutenes with hypervalent iodine(III).[3,4] The reaction has an advantage of stereoselectively forming two stereogenic centers at the 2,3-position of tetrahydrofuran in a single step from alkene substrates.[5]

We recently found that the tetrahydrofuranylation with hypervalent iodine(III) proceeded via a 1,3-dioxan-2-yl cation intermediate. The intermediate was generated by nucleophilic participation of the internal acyloxy group of acyloxyalkene substrates during electrophilic attack of hypervalent iodine(III) toward the substrate (Scheme 1).[5] The cyclic structure of the intermediate cation contributed to the stereoselective preparation of 2,3,5-trisubstituted tetrahydrofurans.[5a] An enantio-differentiating variant of the reaction using a lactate-derived hypervalent iodine(III) resulted in moderate enantioselectivity (up to 64% ee).[5b] A chiral auxiliary was introduced as the acyloxy group of the substrate to improve the stereoselectivity in the cycloetherification described in this Letter.

A series of chiral but-3-enyl carboxylates **1a–e** were prepared and subjected to reaction with iodosylbenzene in the presence of $BF_3{\cdot}OEt_2$ in dichloromethane (Table 1). The reaction gave a diastereomeric mixture of 3-acyloxytetrahydrofuran, *R*-**2** and *S*-**2**. The diastereomeric ratio of the product **2** was determined by GLC or ^{1}H NMR (600 MHz).[6,7] The camphanate of **1e** induced highest diastereoselectivity among the chiral auxiliaries employed.

In order to examine further improvement of the stereoselectivity, derivative substrates **1e–g** with the camphanate auxiliary were subjected to the diastereo-differentiating tetrahydrofuranylation



Scheme 1. Cycloetherification via a 1,3-dioxan-2-yl cation.

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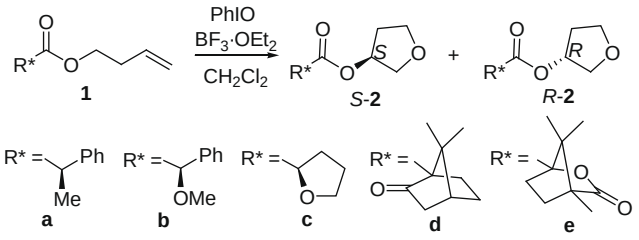
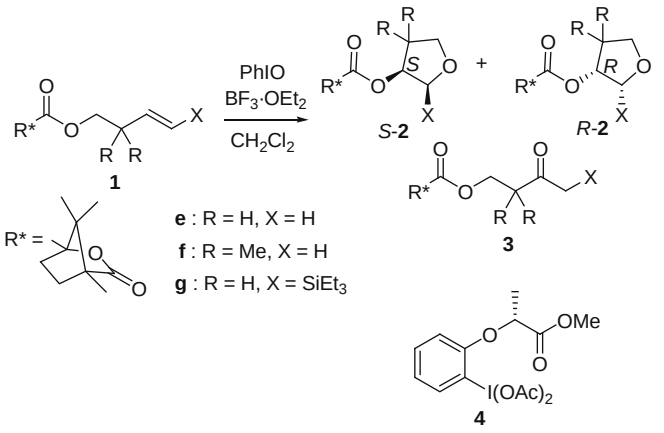
Table 1
Chiral auxiliary screening for tetrahydrofuranylation[a]



Entry	Subst.	Temp (°C)	Yield (%)	*R*-**2**:*S*-**2**
1	**1a**[b]	−30	55	9:11[c,d]
2	**1b**[b]	−40	57	1:1[c,d]
3	**1c**	−40	40	44:56[e]
4	**1d**	−40	23	60:40[e]
5[f]	**1d**	−40	46	54:46[e]
6	**1e**	0	39	29:71[e]
7	**1e**	−40	37	23:77[e]
8[f]	**1e**	−40	55	23:77[e]

[a] The reaction was typically carried out in dichloromethane (8 mL) containing a substrate (0.4 mmol), PhIO (0.8 mmol), and $BF_3{\cdot}OEt_2$ (1.6 mmol) for 1–2 h.
[b] Racemic **1** was employed for the reaction.
[c] The diastereomeric ratio was determined by ^1H NMR.
[d] Stereochemistry of **2** was not determined.
[e] The diastereomeric ratio was determined by GLC equipped with a TC-1 column.
[f] (Hydroxy(tosyloxy)iodo)benzene was employed in place of iodosylbenzene.

Table 2
Camphanate as a chiral auxiliary in tetrahydrofuranylation[a]



Entry	Subst.	Yield (%)		*R*-**2**:*S*-**2**[b]
		2	**3**	
9[c]	**1e**	51	0	4:96
10[c,d]	**1e**	55	0	5:95
11	**1f**	81	0	47:53[e]
12[c]	**1f**	60[f]	0	27:73[e]
13	**1g**	3	77	8:92[g]
14[d]	**1g**	40	0	<3:97[g]
15[c,d]	**1g**	49	0	<3:97[g]

[a] The reaction was typically carried out in dichloromethane (8 mL) containing substrate (0.4 mmol), PhIO (0.8 mmol), and $BF_3{\cdot}OEt_2$ (1.6 mmol) at −40 °C for 1-2 h.
[b] The diastereomeric ratio was determined by GLC equipped with a TC-1 column unless otherwise noted.
[c] An optically active reagent **4** was employed in place of iodosylbenzene.
[d] A hypervalent iodine reagent was treated with *p*-toluenesulfonic acid, and the (hydroxy(tosyloxy)iodo)arene obtained was employed for the reaction instead of iodosylbenzene.
[e] Stereochemistry of **2** was not determined.
[f] Substrate **1f** was recovered in 13% yield.
[g] The diastereomeric ratio was determined by ^1H NMR.

(Table 2). Reaction conditions were also optimized for enhancement of stereoselectivity; optically active (*R*)-methyl 2-(2-(diacetoxyiodo)phenoxy)propanoate **4**[5b] was employed for the reaction of **1e** (entries 9 and 10). The double asymmetric induction resulted in higher stereoselectivity (92% de of *S*-**2e**). The (*R*)-reagent **4** preferentially gave (*S*)-3-benzoyloxytetrahydrofuran with 46% ee in the reaction of achiral but-3-enyl benzoate.[5b] Enantioface-differentiation in the simple asymmetric cycloetherification similarly works for preferential formation of *S*-**2e** in the double asymmetric induction.

The reaction of dimethyl-substituted substrate **1f** gave high yield of tetrahydrofuran product **2f** (entry 11), but the diastereoselectivity was poor (53:47). Introduction of the dimethyl group may accelerate the cyclization by the Trope–Ingold effect to give the product in high yield.[8] Double asymmetric induction in the tetrahydrofuranylation of **1f** using **4** improved the diastereoselectivity (entry 12).

The reaction with a silyl-substituted substrate **1g** gave a small amount of tetrahydrofuran product **2g** together with a considerable amount of α-silyl ketone **3g** (entry 13). The yield of **2g** was increased by using a (hydroxyl(tosyloxy)iodo)arene reagent (entries 14 and 15). Under these conditions, a 1,3-dioxan-2-yl cation intermediate may effectively be trapped with water to prevent the 1,2-elimination pathway giving the α-silyl ketone **3g**.[5a–c] Diastereomeric ratio of the tetrahydrofuran product **2g** was high even in the reaction with an achiral reagent; only the (3*S*)-isomer *S*-**2g** was obtained (entry 14).[9] The preferential formation of (3*S*)-configuration agrees with the stereoselectivity in the reaction of a simple butenyl camphanate **1e**. Stereodifferentiation by the camphanate auxiliary may sterically be enhanced by the silyl substituent. The silyl-substituted tetrahydrofuran products *R*-**2g** and *S*-**2g** have a 2,3-cis configuration, and no 2,3-trans-product was observed.[10] The stereospecific formation of the 2,3-cis-product from the (*E*)-substrate was observed in the reaction of achiral acyloxy substrates[5c] as well, and was rationalized by *anti*-participation of the acyloxy group and ensuing S_N2 in the departure of the phenyliodonio group.[5c] The chiral auxiliary of *S*-**2g** was readily removed by hydrolysis under basic conditions, and (2*S*,3*S*)-3-hydroxy-2-(triethylsilyl)tetrahydrofuran was obtained as enantiomerically pure form in 77% yield.[11]

To obtain further insight into the diastereo-differentiating mechanism, some experiments were carried out. Does diastereoselective decomposition of the tetrahydrofuran product affect the product distribution? Treatment of a 50:50 mixture of *R*-**2e** and *S*-**2e** with $BF_3{\cdot}OEt_2$ (23 mmol dm^{-3}) in dichloromethane at 0 °C for 4 h resulted in slight change in the diastereomeric ratio of the recovered **2** (*R*-**2e**:*S*-**2e** = 48:52). When the reaction of **1e** was quenched at the point when half of substrate **1e** remained, the diastereomeric ratio was 25:75 (=*R*-**2e**:*S*-**2e**). The ratio was similar to that of the completed reaction (*R*-**2e**:*S*-**2e** = 23:77 in entry 7). These results suggest that diastereo-differentiating decomposition of the tetrahydrofuran products is not a major factor of the diastereomeric ratio of the stereoselective tetrahydrofuranylation of **1e**.

The diastereo-differentiation caused by the camphanate moiety is discussed using theoretical calculations. For the stereo-induced cycloetherification of pent-4-enyl carboxylates, the stereoselectivity is rationalized by thermodynamic stability of a 1,3-dioxan-2-yl cation intermediate.[5a] Theoretical calculations were carried out for discussing thermodynamic stability between diastereomers of a camphanate-derived dioxanyl cation intermediate. 4-Methyl-1,3-dioxan-2-yl cations were calculated as a model intermediate in place of 4-(phenyliodonio)methyl-1,3-dioxan-2-yl cations (see Supplementary data). Diastereomeric difference in energy of the camphanate-derived dioxanyl cation was small (0.11 kcal mol^{-1}) at the level of B3LYP/6-31G(d), and was not consistent with the diastereoselectivity of the tetrahydrofuranylation. Thus, it is neces-

sary to estimate the steric effect of camphanate in the transition state including the participation of the internal camphanate. Alternative explanation for the stereoselectivity is intramolecular interaction between the oxy group of camphanate and iodonio group of the actual intermediate, but this seems unlikely because of high strain of the interaction.

In summary, the (1*S*)-camphanate auxiliary promotes a highly stereoselective cycloetherification giving (*S*)-3-acyloxytetrahydrofuran and (2*S*,3*S*)-3-acyloxy-2-silyltetrahydrofuran.

Acknowledgment

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Supplementary data

Supplementary data associated with this Letter can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.012.

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6. An authentic sample of *S*-**2** was prepared by esterification of (*S*)-3-hydroxytetrahydrofuran (TCI).
7. If epimerization at the α-position of the carboxylate of **1a**–**c** (**2a**–**c**) took place during the reaction, diastereomeric ratio should be affected. No experimental examination for the epimerization was carried out. The poor diastereomeric ratio obtained is not suitable for asymmetric synthesis whether it takes place or not.
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9. Absolute stereochemistry of **2g** was determined by chiral HPLC analyses of the benzoate given by transesterification of the **2g** obtained from **1g**; only (2*S*,3*S*)-3-benzoyloxy-2-(triethylsilyl)tetrahydrofuran[5b] was detected by HPLC equipped with a chiral column (Daicel chiralpak AD).
10. Relative stereochemistry of **2g** was determined by ^{1}H NMR (600 MHz) in comparison with that of an authentic sample. The authentic sample was prepared by transesterification of *cis*-3-benzoyloxy-2-(triethylsilyl)tetrahydrofuran, which was obtained by the reaction of (*E*)-4-(triethylsilyl)but-3-enyl benzoate.[5c]
11. Enantiomeric purity of the hydroxytetrahydrofuran was determined by HPLC analysis (Daicel chiralpak AD column) of *cis*-3-benzoyloxy-2-(triethylsilyl) tetrahydrofuran derived from the hydroxytetrahydrofuran.