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Enantiodifferentiating tetrahydrofuranylation of but-3-enyl carboxylates using optically active hypervalent iodine(III) reagents via a 1,3-dioxan-2-yl cation intermediate

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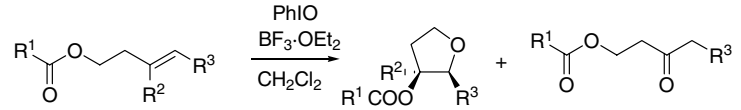
Abstract—Optically active methyl 2-[2-(diacetoxyiodo)phenoxy]propanoate and its derivative were prepared and used for oxygenation of but-3-enyl carboxylates leading to tetrahydrofuran-3-yl carboxylates as an enantiomerically enriched form.

(Diacyloxyiodo)arenes and iodosylarenes are practically useful hypervalent iodine(III) reagents, which have been employed as a mild oxidant toward various substrates such as alcohols, phenols, and alkenes.[1–3] Some optically active hypervalent iodine(III) reagents have been prepared to investigate the structure and reactivities.[4–7] However, few examples have been successful in asymmetric oxidations using optically active derivatives of (diacyloxyiodo)arenes; moderate selectivities were obtained for oxygenation of sulfides to sulfoxides (up to 57% ee)[6] and dioxytosylation of olefins (up to 65% ee).[7]

We have recently found that the reaction of (*E*)-4-(triethylsilyl)but-3-enyl carboxylates, (*E*)-**1a** and **1b**, with iodosylbenzene in the presence of $BF_3{\cdot}OEt_2$ stereospecifically gave *cis*-3-acyloxy-2-(triethylsilyl)tetrahydrofurans **2** (Scheme 1).[8a] The ^{18}O-tracer experiments suggested that the tetrahydrofuranylation proceeded via a 1,3-dioxan-2-yl cation intermediate.[8] In this Letter, we will discuss that the simple but-3-enyl carboxylates without the 4-silyl group are efficient substrates for the tetrahydrofuranylation. Optically active hypervalent iodine(III) reagents derived from lactic acid were prepared and used for an enantiodifferentiating variant of the tetrahydrofuranylation.

Reaction of but-3-enyl benzoate (**1c**) with iodosylbenzene in the presence of $BF_3{\cdot}OEt_2$ in dichloromethane exclusively gave 3-benzoyloxytetrahydrofuran (**2c**) in 58% yield. In this reaction, no 3-oxobutyl benzoate (**3c**) was obtained in contrast to the formation of ketone **3b** as a major product in the reaction of the silyl-substituted substrates **1b**.[8a] The reaction of 3-methylbut-3-enyl benzoate



(*E*)-**1a**: R^1 = Me, R^2 = H, R^3 = $SiEt_3$
(*E*)-**1b**: R^1 = Ph, R^2 = H, R^3 = $SiEt_3$
1c: R^1 = Ph, R^2 = R^3 = H
1d: R^1 = Ph, R^2 = Me, R^3 = H

2 **3**

Scheme 1. Reaction of but-3-enyl carboxylate **1** with iodosylbenzene.

Keywords: Asymmetric synthesis; Neighboring group participation; Iodosylbenzene; Hypervalent iodine.
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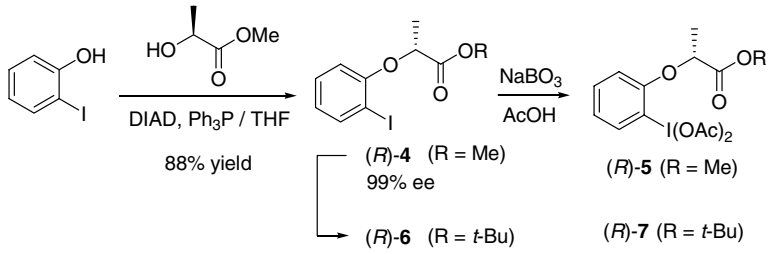
(**1d**) also gave 3-benzoyloxy-3-methyltetrahydrofuran (**2d**) in 52% yield. These two substrates **1c** and **1d** as well as the silyl-substituted substrates **1a** and **1b** were employed for enantiodifferentiating tetrahydrofuranylation.

Optically active hypervalent iodine(III) reagents **5** and **7** were prepared by the Mitsunobu reaction of 2-iodophenol with optically active methyl lactate followed by oxidation with sodium perborate in acetic acid, as shown in Scheme 2. The Mitsunobu reaction of phenols with lactate proceeds with the inversion of the stereogenic center of lactate.[9] The inversion of stereochemistry was confirmed by X-ray crystallographic analysis of **5**.[10] *tert*-Butyl ester **6** was prepared by the ester-exchange reaction of **4** via the acid chloride. Chiral GC analyses indicated that iodoarenes **4** and **6** had the stereochemical purity of 99% ee. (Diacetoxyiodo)arenes **5** and **7** were obtained as a colorless solid.

Tetrahydrofuranylation of **1** was carried out using the optically active hypervalent iodine(III) reagents **5** and **7**. Yields and enantiomeric ratios are summarized in Table 1. The reactions of (*E*)-**1a** and **1b** stereospecifically gave *cis*-tetrahydrofuran products, *cis*-**2** [(2*R**,3*R**)-**2**], together with a small amount of ketone **3**. The product distributions are similar to those obtained in the reaction with achiral iodosylbenzene.[8a] Diastereomeric tetrahydrofuran *trans*-**2** [(2*R**,3*S**)-**2**] was selectively obtained in the reaction of (*Z*)-**1b** (entry 9). Chiral HPLC analyses were carried out for the determination of enantiomeric ratio of *cis*-**2b**, *trans*-**2b**, **2c**, and **2d**. Gas chromatography was also employed for chiral analyses of *cis*-**2a** and *cis*-**2b**. Accuracies of the chiral chromatographic analyses were confirmed as follows: (1) The reactions with (*S*)-**5** gave antipodal enantiomeric ratios of **2** (*cis*-**2b** and **2c**) obtained from the reaction with (*R*)-**5** (entries 7 and 11). (2) The enantiomeric ratios determined by chiral chromatography agreed well with the diastereomeric ratios of the Mosher esters derived from **2** (*cis*-**2a**, *cis*-**2b**, and *trans*-**2b**) as shown in Supplementary data.

The reaction of (*E*)-**1a** with (*R*)-**5** gave (2*S*,3*S*)-**2a** as a major enantiomer of *cis*-**2a** [(2*R**,3*R**)-**2a**] in the range of 42–58% ee (entries 1–3). Preferential formation



Scheme 2. Preparation of optically active hypervalent iodine(III) reagents, **5** and **7**.

Table 1. Enantioselective reactions of **1** with optically active iodine(III) reagents[a]

Entry	Sub.	Reagent	Yield (%)		(3*S*)-**2**/(3*R*)-**2**[b] (ee)
			2	**3**	
1[c]	(*E*)-**1a**	(*R*)-**5**	44[d]	16	71/29 (42)[d]
2	(*E*)-**1a**	(*R*)-**5**	58[d]	5	75/25 (50)[d]
3	(*E*)-**1a**	(*R*)-**5**[e]	56[d]	0	79/21 (58)[d]
4	(*E*)-**1a**	(*R*)-**7**	48[d]	0	73/27 (46)[d]
5	(*E*)-**1b**	(*R*)-**5**	24[d]	23	82/18 (64)[d]
6	(*E*)-**1b**	(*R*)-**5**[e]	45[d]	7	82/18 (64)[d]
7	(*E*)-**1b**	(*S*)-**5**[e]	59[d]	0	18/82 (64)[d]
8	(*E*)-**1b**	(*R*)-**7**	16[d]	21	82/18 (64)[d]
9	(*Z*)-**1b**[f]	(*R*)-**5**[e]	38 (trans)[g]	0	60/40 (20)[g]
10	**1c**	(*R*)-**5**	53	0	73/27 (46)
11	**1c**	(*S*)-**5**	60	0	27/73 (46)
12	**1c**	(*R*)-**5**[e]	48	0	63/37 (26)
13	**1c**	(*R*)-**7**	48	0	79/21 (58)
14	**1d**	(*R*)-**5**	22	—	50/50 (0)
15	**1d**	(*R*)-**5**[e]	73	—	56/44 (12)[h]

[a] The reaction was typically carried out in dichloromethane (2 mL) containing 1% (v/v) water at −78 °C in the presence of **1** (0.44 mmol), **5** or **7** (0.53 mmol), and $BF_3{\cdot}OEt_2$ (0.57 mmol) for 3 h.

[b] Enantiomeric ratios were determined by chiral GC and HPLC. Details are given in Supplementary data. The values in parentheses are the enantiomeric excess (ee) of **2**.

[c] The reaction was carried out at −40 °C.

[d] Values for (2*R**,3*R**)-3-benzoyloxy-2-(triethylsilyl)tetrahydrofuran (*cis*-**2**, (2*R**,3*R**)-**2**). No trans isomer was obtained. (3*S*)-**2** means (2*S*,3*S*)-**2**.

[e] Reagent **5** was treated with *p*-TsOH before the reaction with **1**.

[f] The sample is a 6:4 mixture of (*Z*)-**1b** and 3-(triethylsilyl)but-3-enyl benzoate. The yield is based on (*Z*)-**1b**.

[g] Values for (2*R**,3*S**)-3-benzoyloxy-2-(triethylsilyl)tetrahydrofuran (*trans*-**2**, (2*R**,3*S**)-**2**). (3*S*)-**2** means (2*R*,3*S*)-**2**.

[h] Absolute stereochemistry of **2d** was not determined.

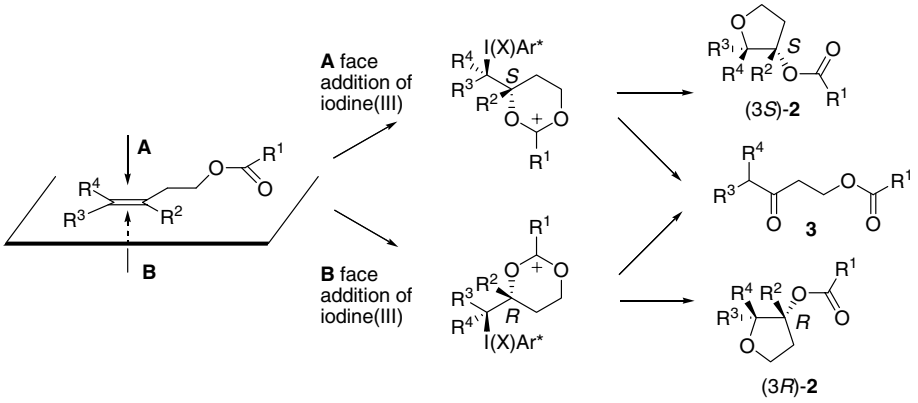
of (2*S*,3*S*)-**2** was also observed for the reaction of (*E*)-**1b**, in which higher enantiomeric ratio of *cis*-**2b** [(2*R**,3*R**)-**2b**] was provided (entries 5–7) than the reaction of (*E*)-**1a**. For the reaction of (*Z*)-**1b**, the major enantiomer of *trans*-**2b** [(2*R**,3*S**)-**2b**] has 3*S*-configuration [(2*R*,3*S*)-**2b**] as well (entry 9), and the enantiomeric ratio became lower than that of *cis*-**2b** in the reaction of (*E*)-**1b**. The reaction of **1c** also gave 3*S*-tetrahydrofuran product (*S*)-**2c** in 26–46% enantiomeric excess (entries 10–12). On the other hand, the reaction of **1d**, which has a methyl substituent at the 3-position, gave **2d** with a poor enantiomeric ratio (entries 14 and 15). The reactions of (*E*)-**1a** and **1b** with *tert*-butyl reagent (*R*)-**7** resulted in a similar (slightly lower) selectivity (entries 4 and 8) in comparison with the reaction with **5**. For the reaction of **1c**, a slightly higher selectivity was obtained with *tert*-butyl reagent **7** (entry 13) than with methyl derivative **5**. It is noteworthy that the major enantiomers have the 3*S*-configuration for the reactions of (*E*)-**1a**, (*E*)-**1b**, (*Z*)-**1b**, and **1c** with (*R*)-**5** and **7**.

The mechanism for the tetrahydrofuranylation was discussed in the previous Letter[8a] as follows: The internal acyloxy group may nucleophilically participate in an *anti* fashion to the electrophilic addition of the iodine(III) reagent toward the substrates (Scheme 3). The 1,3-dioxan-2-yl cation intermediate obtained may be hydrolyzed, and intramolecular re-cyclization giving tetrahydrofuran may be accompanied by the departure of the aryliodonio group. These are consistent with the stereospecific tetrahydrofuranylation; *cis*- and *trans*-**2** were selectively obtained from (*E*)- and (*Z*)-**1**, respectively.

According to the mechanism, the enantiomeric excess of the tetrahydrofuran products may conceivably be affected by the three steps as follows: (1) Stereoface-differentiating addition of iodine(III) toward the olefin moiety of the substrate is one of the key steps for the enantioselective reaction. The 3*S*-tetrahydrofuran product (3*S*)-**2** must form via the electrophilic addition of iodine(III) toward the A-face of substrate **1** as shown in Scheme 3. (2) Internal nucleophilic addition of the acyloxy group can be involved in the stereo-determining steps. The nucleophilic addition concerted with the electrophilic addition of iodine(III) meets the requirement for its involvement in the stereo-determining steps. An alternative conceivable mechanism is the reversible addition of iodine(III) followed by the nucleophilic attack of the acyloxy group. (3) Decomposition steps of the 1,3-dioxan-2-yl cation intermediate might affect the enantiomer ratio of the tetrahydrofuran product, if it proceeded in a diastereoselective manner. The ketone product **3** forms as a side product in the reaction of **1a** and **1b** via the 1,3-dioxan-2-yl cation intermediate.

Among these three steps, the electrophilic addition of iodine(III) is the most important for the enantioselectivity, judging from the stereoselectivity depending on the steric effects owing to the substituents at the carbon–carbon double bond of the substrates; the reactions of (*Z*)-substrate (*Z*)-**1b**, and 3-methyl substituted substrate **1d** resulted in a lower selectivity than those of (*E*)-**1a**, (*E*)-**1b**, and **1c**. The enantiomeric ratio of the products was also affected by the kind of the acyloxy groups of (*E*)-**1a** and (*E*)-**1b** substrates, but the effect was smaller than the substituents at the olefin. This suggests that the nucleophilic participation of the acyloxy group may be involved in the stereo-determining steps.[11] The enantiomeric ratios of **2** were independent of the product distribution of **2**/**3** in the reaction of (*E*)-**1b** (entries 5–7). Thus, there was no evidence for the contribution of the diastereoselective decomposition of the 1,3-dioxan-2-yl cation intermediate to the enantiomeric ratio of the products.

Product distributions including ee of **2** and the ratio of **2**/**3** were slightly affected by the treatment of **5** with *p*-TsOH (entries 3, 6, 9, 12, and 15). Such treatments may cause exchange of the ligands of the hypervalent iodine(III) from diacetoxy to hydroxy and tosyloxy groups as reported.[7b,c] For the X-ray crystallographic analysis of a (hydroxy(tosyloxy)iodo)arene, the iodine interacts with the oxy side chain of the aryl group in contrast to no interaction in the corresponding diacetoxyiodo complex.[7b,c] The interaction may affect the stereodifferentiation in the tetrahydrofuranylation reactions, and the *p*-TsOH treatment induces a change in the enantiomeric ratio of the tetrahydrofuran products, if the effects of ligands were maintained after the iodine(III) was activated by $BF_3{\cdot}OEt_2$. The lactate moiety of **5** possibly interacts with the iodine when the diacetoxy reagent is activated by $BF_3{\cdot}OEt_2$ during the



Scheme 3. Stereodifferentiation in the tetrahydrofuranylation.

reaction. The *p*-TsOH treatment resulted in a slight increase of ee in the reactions of **1a** and **1d**, no change of ee in the reaction of **1b**, and a decrease of ee in the reaction of **1c**. Thus, effects of *p*-TsOH on the enantioselectivity are not straightforward. It is noteworthy that the *p*-TsOH treatment increased the fraction of the tetrahydrofuran product **2** versus the ketone **3** as observed for the reactions in the presence of water.[8a]

No side product **3** was obtained in the reactions of **1d** and **1c** in comparison with noticeable formation of **3** in the cases of the silyl-substituted substrates **1a** and **1b**. Ketone **3** may form via 1,2-elimination of the 1,3-dioxanyl intermediates according to the mechanism reported.[8a] Judging from the results of the reactions, the steric effect of the silyl substituent may control the conformation of the intermediate ready for the 1,2-elimination.

In summary, lactic acid-derived optically active hypervalent iodine(III) reagents were prepared and employed for the tetrahydrofuranylation of acyloxybutenes. The enantiomeric ratio of the tetrahydrofuran products was related to the structure of acyloxyalkene substrates. This is consistent with a mechanism where the stereoselectivity was controlled by the electrophilic addition of the iodine(III) and by the nucleophilic addition of the internal acyloxy group toward the olefin.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.10.015.

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10. CCDC 658662 contains the Supplementary crystallographic data for this Letter. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.
11. Reactions of (*E*)- and (*Z*)-**1b** with (*R*)-**5** gave (2*S*,3*S*)-**2b** and (2*R*,3*S*)-**2b**, respectively, as a major enantiomer. These two 3*S*-tetrahydrofuran products must form via the A-face addition of the iodine(III) and the B-face addition of the acyloxy group. The preferential formation of the 3*S*-products indicates that the stereoface-selectivity is tightly controlled by the acyloxyethyl substituent rather than by the triethylsilyl group at the R^3 and R^4 positions. These results are also consistent with the involvement of the acyloxy participation in the stereo-determining steps.