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Enantioselective Prévost and Woodward reactions using chiral hypervalent iodine(III): switchover of stereochemical course of an optically active 1,3-dioxolan-2-yl cation†

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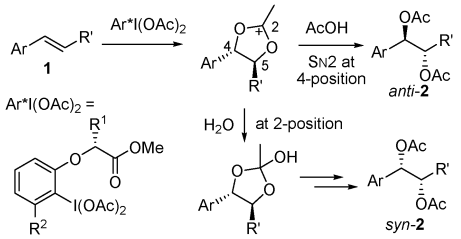
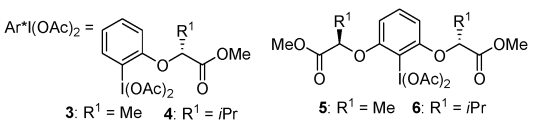
Optically active 1,3-dioxolan-2-yl cation intermediates were generated during enantioselective dioxyacetylation of alkene with chiral hypervalent iodine(III). Regioselective attack of a nucleophile toward the intermediate resulted in reversal of enantioselectivity of the dioxyacetylation.

Reactions involving neighboring group participation have great advantages for powerful stereocontrol and unique stereoselectivity due to a bridged form of the cationic intermediate. The Prévost reaction[1] and the Woodward reaction[2] proceed *via* a 1,3-dioxolan-2-yl cation intermediate[3] in the course of oxidation of alkene with I_2 in the presence of silver carboxylate.[4–6] Regioselective attack of a nucleophile toward the intermediate results in diastereoselective formation of the oxidation products: addition of water at the 2-position of the 1,3-dioxolan-2-yl cation results in retention of configuration of the cation intermediate (Woodward reaction),[2] while S_N2 displacement with carboxylate at the 4- or 5-position results in inversion of configuration (Prévost reaction).[1] To the best of our knowledge asymmetric variants of the Prévost and Woodward reactions have not yet been reported,[6] although optically active 1,3-dioxolan-2-yl cation intermediates play an important role in stereocontrolled transformation of polyoxy-functionalized compounds.[7] Most of the optically active dioxolanyl cation intermediates have been generated from optically active substrates *via* diastereoselective transformation. Thus, direct enantioselective formation of an optically active dioxolanyl cation from an achiral alkene substrate during the asymmetric Prévost and Woodward reactions adds new dimensions to the reaction controlled by a dioxolanyl cation.

Herein we report an asymmetric variant of Prévost and Woodward reactions with use of an optically active hypervalent iodine reagent as shown in Scheme 1. Recent development of chiral hypervalent iodine reagents for asymmetric oxidation[8–11] is



Scheme 1 Enantioselective Prévost and Woodward reactions.



Scheme 2 Optically active hypervalent iodine(III).

favorable for success in enantioselective formation of a dioxolanyl cation. Switchover of stereochemical course of the optically active dioxolanyl cation leads to reversal of enantioselectivity, as well as that of diastereoselectivity.

As optically active hypervalent iodine reagents, we employed the lactate-derived aryl-λ^3-iodane **3–6**, which gave high enantioselectivity in oxylactonization of *o*-alk-1-enylbenzoate.[11a] The structures are given in Scheme 2. Reaction of **1** with the iodine reagents **3–6** was started by injection of boron trifluoride diethyl etherate into a dichloromethane solution containing acetic acid at −80 °C. When the reaction was terminated at −40 °C by addition of water (conditions A), a regioisomeric mixture of the monoacetoxy products **2′** and **2″** was obtained (Table 1). Acetylation of the regioisomeric mixture gave a diacetoxy product *syn*-**2** as a single diastereomer. The enantiomeric purity of the *syn* product was 88–96% ee of (1*S*,2*S*) configuration. Higher enantioselectivity was obtained when the isopropyl substituted reagent **4** was used (entries 2 and 8 in Table 1).

When the reaction was similarly started at −80 °C and the reaction mixture was allowed to warm up to room temperature (conditions B), *anti*-**2** with (1*R*,2*S*) configuration was preferentially obtained as summarized in Table 2. The reaction was carried out in the presence of both acetic acid and trimethylsilyl acetate because the conditions were suitable for selective formation of the *anti* product as examined with an achiral iodane reagent (Table S2 in ESI†). Exclusive formation of the

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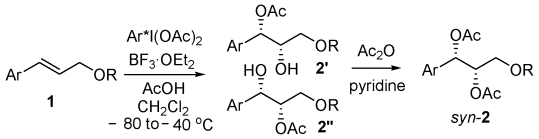
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data for all new compounds, and additional results of the reaction. CCDC 798662. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc10129c

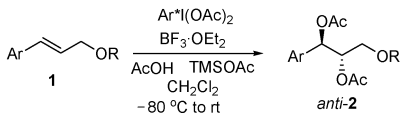
Table 1 Enantioselective formation of the *syn* product under conditions A[a]



Entry	1	Ar*I(OAc)$_2$	2′ : 2″	Yield[b] (%)	*syn* : *anti*	ee[c] (%)
1	**1a**	**3**	6 : 4	55	> 98 : 2	88
2	**1a**	**4**	7 : 3	49	> 98 : 2	95
3	**1a**	**6**	6 : 4	51	> 98 : 2	94
4	**1b**	**3**	6 : 4	48	> 98 : 2	92
5	**1c**	**3**	6 : 4	44	> 98 : 2	89
6	**1d**	**3**	6 : 4	40	98 : 2	88
7	**1e**	**3**	6 : 4	56	> 98 : 2	90
8	**1e**	**4**	7 : 3	63	> 98 : 2	96

[a] **1** = 0.4 mmol, Ar*I(OAc)$_2$ = 0.5 mmol, BF_3·OEt_2 = 0.8 mmol in CH_2Cl_2 (4 mL) and acetic acid (0.2 mL). Reaction was started at −80 °C and terminated at −40 °C. The crude products obtained were treated with acetic anhydride and pyridine. [b] Yield of **2**. [c] ee of *syn*-**2**.

Table 2 Enantioselective formation of the *anti* product under conditions B[a]



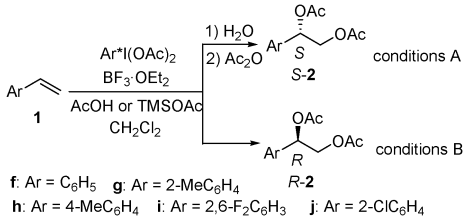
Entry	1	Ar*I(OAc)$_2$	Yield (%) 2	*syn* : *anti*	ee (%) *anti*	ee (%) *syn*
1	**1a**	**3**	70	< 2 : 98[b]	88	88
2	**1a**	**4**	56	< 2 : 98	96	
3	**1a**	**6**	54	< 2 : 98	93	
4	**1c**	**3**	53	< 2 : 98	84	
5	**1d**	**3**	58	18 : 82	88	88
6	**1e**	**3**	47	< 2 : 98	90	
7	**1e**	**4**	55	< 2 : 98	92	

[a] **1** = 0.4 mmol, Ar*I(OAc)$_2$ = 0.5 mmol, BF_3·OEt_2 = 0.8 mmol in CH_2Cl_2 (4 mL), acetic acid (0.2 mL), and trimethylsilyl acetate (0.2 mL). Reaction was started at −80 °C and terminated at rt. [b] The *syn* isomer was not detected by ^{1}H NMR (600 MHz), but GC analysis showed a small amount of the *syn* isomer (*syn*-**2a** : *anti*-**2a** = 1 : 99).

anti product was observed with the exception of the *p*-methyl substrate **1d** (entry 5 in Table 2). The decrease in diastereoselectivity for **1d** may be due to partial contribution from the S_N1 mechanism as discussed below.

Results of the reaction of styrene derivatives are summarized in Table 3. The reaction quenched at low temperature (conditions A) gave the *S* product, while the reaction mixture allowed to warm up to room temperature (conditions B) contained the *R* product. Thus, reversal of enantioselectivity was achieved. The enantioselectivity depends on the aromatic substituent of the styrene substrates. Among the styrene derivatives employed, 2-chlorostyrene (**1j**) gave the highest enantioselectivity (entries 9–11 in Table 3).

Table 3 Switchover of enantioselectivity in the reaction of styrene derivatives[a]

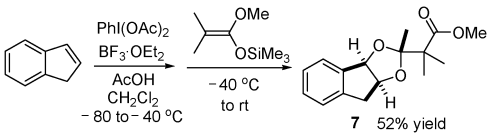


			Conditions A[a]		Conditions B[b]	
Entry	1	Ar*I(OAc)$_2$	Yield (%)	ee (%)	Yield (%)	ee (%)
1	**1f**	**3**	69	64(*S*)	71	72(*R*)
2	**1f**	**4**	59	74(*S*)	82	70(*R*)
3	**1f**	**5**	68	89(*S*)	76	70(*R*)
4	**1g**	**3**	54	34(*S*)	68	16(*R*)
5	**1h**	**3**	35	11(*S*)	50	1(*R*)
6	**1i**	**3**	54	30(*S*)	64	32(*R*)
7	**1i**	**4**	59	40(*S*)		
8	**1i**	**5**	49	60(*S*)		
9	**1j**	**3**	74	88(*S*)	60[c,d]	83(*R*)[c,d]
10	**1j**	**4**	76	92(*S*)	66[c]	85(*R*)[c]
11	**1j**	**5**	53	92(*S*)	81[c]	87(*R*)[c]

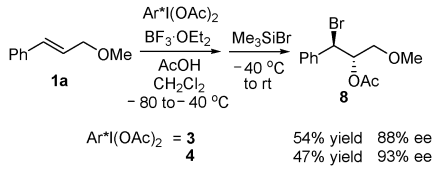
[a] Reaction was started at −80 °C in the presence of AcOH and terminated at −40 °C. The crude products obtained were treated with acetic anhydride and pyridine. [b] Reaction was started at −80 °C in the presence of TMSOAc and terminated at rt, otherwise noted. Results of the reaction in the presence of both AcOH and TMSOAc are given in Table S3 (ESI†). [c] In the presence of AcOH and TMSOAc. [d] The reaction in the presence of only TMSOAc gave **2j** in 64% yield with 84% ee of *R*-**2j**.

The reversal of *syn*/*anti* selectivity (Tables 1 and 2) can be explained by a mechanism involving the 1,3-dioxolan-2-yl cation similar to that proposed for the Prévost and Woodward reactions. That is, addition of water at the 2-position of the 1,3-dioxolan-2-yl cation results in formation of the *syn* product with retention of configuration (Scheme 1). In contrast, the *anti* product must form *via* S_N2 displacement with acetic acid (or acetate). Enantioface-differentiating attack of the iodine reagent may preferentially give the (4*S*,5*S*)-1,3-dioxolan-2-yl cation. The preference of (1*R*,2*S*) configuration of the *anti* product indicates that S_N2 displacement of the cation with acetic acid takes place regioselectively at the benzylic position (the 4-position), where positive charge is localized. If S_N2 at the 5-position was involved in the reaction pathways, ee of the *anti* product should decrease. The S_N2 at the 5-position can be excluded, judging from the comparison of ee values of the *syn* and *anti* products. The S_N1 pathway must give a mixture of the *syn* and *anti* products, and may be involved in the reaction of the *p*-methyl substrate **1d** (entry 5 in Table 2): an electron donating aryl group in **1d** must stabilize the benzylic cation intermediate and facilitate the S_N1 pathway.

The reaction of styrene substrates **1f–j** also can be explained within the framework of the reaction mechanism represented above. The *S*-product is obtained with retention of configuration of the *S*-dioxolanyl cation, and the *R*-product forms *via* inversion of the configuration (S_N2 at the benzyl position). Enantiomeric purity of the *R*-product could decrease if the S_N1 at the benzyl (the 4-) position and S_N2 at the 5-position



Scheme 3 Trapping with ketene silyl acetal.



Scheme 4 Trapping with trimethylsilyl bromide.

took place. These may be major reasons for the decrease in the ee value under conditions B rather than that under conditions A.

The intermediate formation of the dioxolanyl cation was confirmed by trapping reaction with ketene silyl acetal (KSA) as shown in Scheme 3.‡ The reaction was started in the absence of KSA, and the nucleophile was added into the reaction mixture at −40 °C. The trapping product **7** was obtained as a single diastereomer. The structure was determined by nOe observed in ^{1}H NMR spectroscopy, and the diastereoselectivity must be attributed to the steric fence due to the indane moiety during the addition of KSA toward the 1,3-dioxolan-2-yl cation. The 1,3-dioxolanyl framework remains in the trapping product **7** without its ring-opening. This is most convincing evidence for intermediate formation of the 1,3-dioxolan-2-yl cation.

Trimethylsilyl bromide was also employed as a nucleophile for trapping the dioxolanyl cation (Scheme 4). The bromide was introduced at the benzyl position of the trapping product **8**, which has (1*R*,2*S*) configuration. The regio and diastereoselectivities are consistent with the *anti* selectivity observed in the reaction giving the diacetate product **2** (Table 2). The ee value of the bromide **8** is similar to that of the acetate *anti*-**2a** (entries 1 and 2 in Table 2). These results agree well with the reaction pathway involving the optically active dioxolanyl cation, which was trapped by a nucleophile at the benzylic position through the S_N2 mechanism.

Nucleophilic attack of acetate and bromide takes place at the 4-position of the dioxolanyl cation, and addition of water and KSA takes place at the 2-position. Regioselectivity of the nucleophilic attack may be thermodynamically controlled. Nucleophilic addition at the 2-position of the dioxolanyl cation may be kinetically favorable, but addition of acetate and bromide at the 2-position may be reversible. In contrast, addition of H_2O and ketene silyl acetal at the 2-position must be irreversible.

In summary, we demonstrate convenient preparation of an optically active 1,3-dioxolan-2-yl cation, which serves for regio- and stereoselective trapping of several kinds of nucleophile. The selectivity depends on the nature of nucleophile, and contributes to the switchover of stereochemical course of the reaction.

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Notes and references

‡ Dioxyacetylation of indene similarly proceeds, and the results are given in ESI.†

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