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Axial-selectivity in Prins Cyclization Reaction: Synthesis of 4-Iodotetrahydropyrans

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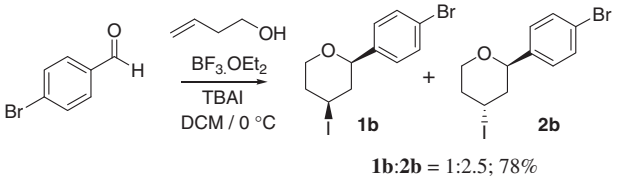
Trimethylsilyl triflate and tetrabutylammonium iodide (TBAI) effectively mediate the Prins cyclization of homoallylic alcohols and aldehydes to give 4-iodotetrahydropyrans with axial selectivity and good yields.

The Prins cyclization is an important reaction for carbon–carbon and carbon–heteroatom bond formation and it has long been used for the synthesis of highly substituted tetrahydropyrans with high stereoselectivity.[1] The main advantage of Prins cyclization is its all-*cis* selectivity. The tetrahydropyran unit is found in many natural and biologically active compounds.[2] Therefore, efficient and selective synthesis of tetrahydropyran is of great importance in organic synthesis. Recently, several groups have reported the highly selective synthesis of all-*cis* 4-substituted tetrahydropyrans with good yields.[2] Among these, 4-halotetrahydropyrans are important in organic synthesis because they can be transformed into other substituted tetrahydropyrans.[2g,3] Generally, 4-halotetrahydropyrans are prepared using Lewis acids such as $SnCl_4$,[4] $SnBr_4$,[5] TMSBr,[2a–2c] $TiCl_4$,[6] $TiBr_4$,[7] TiF_4,[8] $InCl_3$,[9] $AlCl_3$,[10] $FeCl_3$,[3b] $ZrCl_4$,[11] $BF_3{\cdot}OEt_2$,[12] $NbCl_4$,[13] $BiCl_3$,[14] TMSI,[15] $CeCl_3$,[16] and others.[17] The halo function in all these reactions is placed in equatorial position. This is in accordance to the Alder model.[18] There are limited methods for the synthesis of 4-axial halotetrahydropyrans. There are a few methods where axial-4-halo-substituted tetrahydropyrans are side products or 1:1 mixture with equatorial products.[12,17b] Rychnovsky and co-workers have reported an axial-selective Prins cyclization reaction by solvolysis of α-bromo ethers promoted by TMSBr in high diastereoselectivity and very good yields.[19] Here, we now report an axial selective Prins cyclization reaction for the synthesis of 4-iodotetrahydropyran from homoallylic alcohols and aldehydes promoted by TMSOTf and tetrabutylammonium iodide (TBAI). In continuation of our interest in $BF_3{\cdot}OEt_2$-mediated tetrahydropyran synthesis,[20] we were in search of a halogenating agent, other than Lewis acid, for the synthesis of 4-halotetrahydropyrans. Considering tetrabutylammonium iodide as such type of iodinating agent, 4-bromobenzaldehyde and homoallylic alcohol were treated with tetrabutylammonium iodide under Prins cyclization conditions. To our surprise, a diastereomeric mixture **1b** and **2b** with an equatorial to axial ratio 1:2.5 was obtained in 78% yield (Scheme 1). The result is in contrast to the usual Prins cyclization reaction.

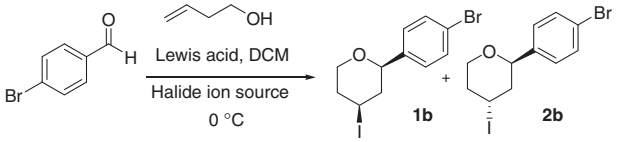


1b:**2b** = 1:2.5; 78%

Scheme 1. Synthesis of 4-iodotetrahydropyran.

With the result in hand, the reaction was investigated using different Lewis acids and is summarized in Table 1. Reaction of 4-bromobenzaldehyde and homoallylic alcohol with $BF_3{\cdot}OEt_2$/NaI and TMSCl/NaI gave a 1:1 mixture of axial and equatorial isomers with 46% and 91% yield, respectively (Entries 1 and 4). The reaction with TMSI along with catalytic amount of 2,6-lutidine gave a 3:2 mixture of equatorial and axial products (Entry 3) which was in contrast to the results reported by Rychnovsky.[19] On the other hand, $BF_3{\cdot}OEt_2$/TBAI and TMSCl/TBAI gave mixtures with ratios 1:2.5 and 1:2 in 78% and 62% yield, respectively (Entries 2 and 5). It was observed that systems like $InCl_3$/TBAI, $Sc(OTf)_3$/TBAI, and $In(OTf)_3$/TBAI were not suitable for this reaction (Entries 6–8). The reaction with one equivalent of TMSOTf produced a single diastereomer **2b** with 76% yield, which was confirmed by ^{1}H NMR of crude product (Entry 10). The same reaction with catalytic amount of TMSOTf gave only 18% yield (Entry 9). Replacement of TBAI with iodine (Entry 11) also gave a mixture (1:1) of products. The scope of the reaction was further studied with varieties of aldehydes and homoallylic alcohols under the same reaction conditions (Table 2). Both aliphatic and aromatic aldehydes gave axial selective products with high yields and diastereoselectivity. Simple aromatic aldehydes, benzaldehyde and aldehydes having electron-donating substituents on an aromatic ring, such as 4-methoxybenzaldehyde, gave equatorial and axial diastereomers **5** and **6** with a ratio of 1:1 and 1:2, respectively (Figure 1). This is due to the stabilization of oxocarbenium ion by phenyl and methoxy groups, which leads to oxina-Cope rearrangement. Similarly, reaction with bro-

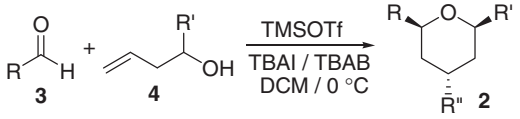
Table 1. Prins cyclization in different conditions



Entry	Lewis acid (equiv)	Iodide ion source	Ratio of (**1b**:**2b**)	Yield[a]/%
1	$BF_3{\cdot}OEt_2$ (1)	NaI	1:1	46
2	$BF_3{\cdot}OEt_2$ (1)	TBAI	1:2.5	78
3	TMSI (1)/2,6-Lutidine	—	3:2	82
4	TMSCl (1)	NaI	1:1	91
5	TMSCl (1)	TBAI	1:2	62
6	$InCl_3$ (1.0)	TBAI	NR	—
7	$Sc(OTf)_3$ (1.0)	TBAI	NR	—
8	$In(OTf)_3$ (1.0)	TBAI	NR	—
9	TMSOTf (0.1)	TBAI	0:1	18
10	TMSOTf (1)	TBAI	0:1	76
11	TMSOTf (1)	I_2	1:1	50

[a]Yields refer to isolated yield. The compounds are characterized by IR, ^{1}H and ^{13}C NMR, and mass spectrometry.

Table 2. Synthesis of axial-4-bromo- and iodotetrahydropyran



Entry	Aldehyde **3** R =	Alcohol **4** R′ =	TBAI/ TBAB	Time/h	Product **2**	Yield[a] /%
1	4-NO_2–C_6H_4	H	TBAI	0.5	**2a**	78
2	4-Br–C_6H_4	H	TBAI	0.5	**2b**	76
3	3-NO_2–C_6H_4	H	TBAI	0.5	**2c**	76
4	4-MeO_2C–C_6H_4	H	TBAI	0.5	**2d**	85
5	C_6H_5–CH_2	H	TBAI	0.5	**2e**	78
6	*n*-C_6H_{13}	H	TBAI	0.5	**2f**	83
7	c-C_6H_{11}	H	TBAI	0.5	**2g**	82
8	*n*-C_3H_7	*n*-C_3H_7	TBAI	0.5	**2h**	80
9	*n*-C_2H_5	C_6H_5–CH_2	TBAI	0.5	**2i**	74
10	4-Cl–C_6H_4	C_6H_5–CH_2	TBAI	2	**2j**	86
11	c-C_6H_{11}	H	TBAB	2	**2k**	65
12	$(CH_3)_2CHCH_2$	H	TBAB	2	**2l**	70
13	*n*-C_2H_5	C_6H_5–CH_2	TBAB	2	**2m**	58
14	c-C_6H_{11}	cyclo-C_6H_{11}	TBAB	2	**2n**	60

[a]Yields refer to isolated yield. Compounds are characterized by IR, ^{1}H and ^{13}C NMR, and mass spectrometry.[23]

minating agent, tetrabutylammonium bromide (TBAB) also yielded axial-4-bromotetrahydropyrans. The TBAB was found to be less reactive than the TBAI and gave low yields. The stereoselectivity and stereochemistry of the compounds were

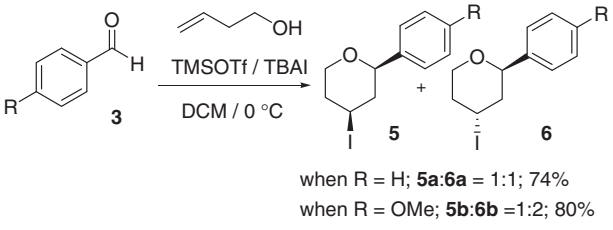


Figure 1. Prins cyclization with benzaldehyde and 4-methoxybenzaldehyde.

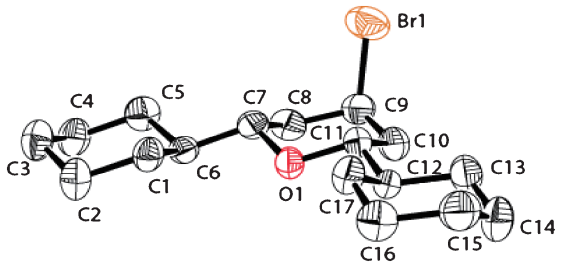


Figure 2. ORTEP diagram of 4-bromo-2,6-dicyclohexyltetrahydro-2*H*-pyran (**2n**).

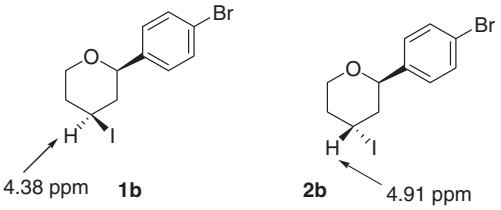


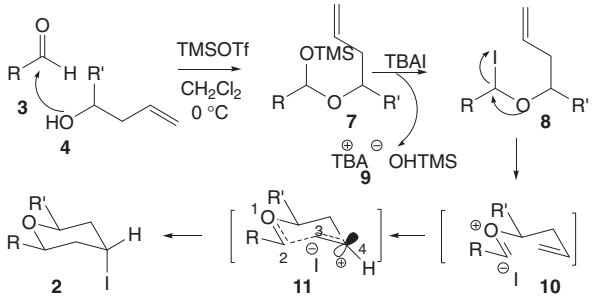
Figure 3. Chemical shift values (ppm) of axial and equatorial protons of **1b** and **2b**.

determined from crude ^{1}H NMR and single-crystal X-ray crystallographic analysis (Figure 2).[21] The axial position of the halide group at the 4-position was determined by comparison with equatorial products. It is known that reaction of aldehydes with homoallylic alcohols in the presence of iodine gives equatorial iodinated products.[17c]

It was observed that the equatorial proton of **2b** attached to the axial iodide resonates at 4.91 ppm and in the case of axial proton of equatorially substituted iodide resonates at 4.38 ppm (Figure 3). This is in agreement with the fact that the equatorial proton resonates at lower field than the axial proton.[17c,22]

The mechanism of formation of axial-selective Prins cyclization is proposed as shown in Scheme 2. The reaction of aldehyde **3** with alcohol **4** in the presence of TMSOTf gives acetal **7**, which after reaction with TBAI gives species **8**. The species **8** decomposes to provide oxocarbenium ion **10**, which then forms an intimate ion pair **11** with iodide ion. The Prins cyclization of favored chair intermediate **11** and simultaneous addition of proximate iodide ion produces the desired axial product **2**.

In conclusion, we have developed an axial selective Prins cyclization reaction with high diastereoselectivity and good yields. The 4-axial halo-substituted products would be an important synthetic intermediate for the synthesis of 4-equatorial-substituted tetrahydropyrans by substitution reaction.



Scheme 2. Proposed mechanism of the reaction.

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