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Brønsted Acid-Mediated Stereoselective Cascade Construction of Functionalized Tetrahydropyrans from 2-(Arylmethylene)cyclopropylcarbinols and Aldehydes

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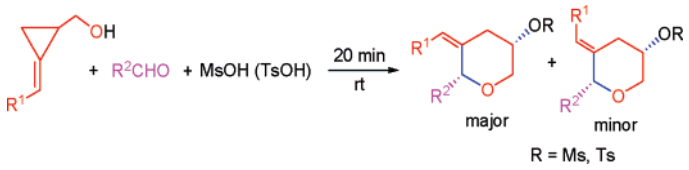
ABSTRACT



(*E*)- and (*Z*)-2-(Arylmethylene)cyclopropylcarbinols 1 could be converted to the corresponding tetrahydropyrans 2 and 3 stereoselectively in the presence of Brønsted acids MsOH or TsOH under mild conditions. A plausible Prins-type reaction mechanism has been proposed.

Methylenecyclopropanes (MCPs) are highly strained but readily accessible molecules that serve as useful building blocks in organic synthesis.[1] MCPs undergo a variety of ring-opening/cycloaddition reactions in the presence of transition metals or Lewis acids because the relief of ring strain can provide a powerful thermodynamic driving force.[2,3] Thus far, a number of interesting cycloadditions of MCPs have been explored. For example, Yamamoto et al. reported cycloaddition reactions of MCPs with aldehydes and imines, using a palladium catalyst, that afforded the corresponding tetrahydrofuran and pyrrolidine skeletons in good yields.[4] In addition, we and others have developed a number of heterocycle-forming reactions from MCPs and aldehydes or imines in the presence of Lewis or Brønsted acids.[5,6] Moreover, we found that 2-(arylmethylene)cyclopropylcarbinols **1**, methylenecyclopropanes bearing an additional hydroxymethyl group, could undergo a number of similar

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reactions under mild conditions.[7] Herein, we wish to report a highly efficient Brønsted acid-mediated cascade reaction of **1** with aldehydes that stereoselectively produces functionalized tetrahydropyrans **2** and **3** in good to high yields under mild conditions.

Initial examinations using (*E*)-2-(phenylmethylene)cyclopropylcarbinol (**1a**) and benzaldehyde as the substrates in the presence of methanesulfonic acid (MsOH) were aimed at determining the optimal conditions, and the results of these experiments are summarized in Table 1. In the presence of

Table 1. Optimization of the Reaction Conditions

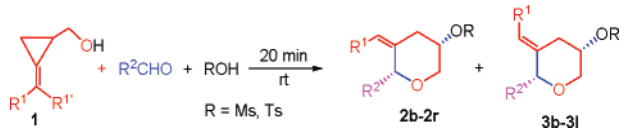
entry[a]	Brønsted acid	solvent	temp (°C)	time (min)	2a/3a	yield[b] (%)
1[c]	MsOH (1.2 equiv)	DCE	rt	20	12:1	46
2[d]	MsOH (1.2 equiv)	DCE	rt	20	12:1	74
3[d,e]	MsOH (1.2 equiv)	DCE	rt	20	12:1	52
4[d,f]	MsOH (1.2 equiv)	DCE	rt	20	12:1	41
5[d]	MsOH (1.4 equiv)	DCE	rt	20	12:1	78
6[d]	MsOH (1.4 equiv)	DCE	rt	20	12:1	48
7[d]	MsOH (1.4 equiv)	C_6H_5Me	rt	20	12:1	16
8[d]	MsOH (1.4 equiv)	THF	60	120		
9[d]	MsOH (1.4 equiv)	EtOEt	rt	20	12:1	47
10[d]	**MsOH (1.4 equiv)**	**DCM**	**rt**	**20**	**12:1**	**85**

[a] All reactions were carried out with **1a** (0.30 mmol), benzaldehyde (0.36 mmol), and MsOH in 1 mL of solvent. [b] Isolated yields based on **1a**. [c] MsOH was dropped into a solution of **1a** and benzaldehyde. [d] In these cases of entries 2−10, **1a** was added into a solution of MsOH and benzaldehyde. [e] MS **4A** (20 mg) was added. [f] H_2O (1.0 equiv) was added.

MsOH the reactions proceeded smoothly to afford isomers **2a** and **3a**, as single diastereoisomers with *syn*-configuration, within a short time and with **2a** being the major product in all cases at 20 °C. We found that the addition sequence of starting materials had a significant effect on this transformation. The addition of **1a** to the solution of MsOH (1.2 equiv) and benzaldehyde produced **2a** and **3a** in higher yields than did the addition of MsOH (1.2 equiv) to a solution of **1a** and benzaldehyde in 1,2-dichloroethane (DCE) (Table 1, entries 1 and 2). The addition of molecular sieves or water did not improve the yields of **2a** and **3a** (Table 1, entries 3 and 4). However, in the presence of 1.4 equiv of MsOH under identical conditions, **2a** and **3a** were produced in 78% total yield (Table 1, entry 5). Solvent effects have been examined with MsOH (1.4 equiv) at room temperature in acetonitrile, toluene, THF, ethyl ether, and dichloromethane (DCM). In THF no reaction occurred, even at 60 °C (Table 1, entry 8). We found that DCM is the solvent of choice (Table 1, entries 5−10). Therefore, the optimized reaction conditions are to carry out the reaction in DCM at room temperature using MsOH (1.4 equiv) as a mediator (Table 1, entry 10). Other Brønsted acids, such as trifluoroacetic acid (TFA), benzoic acid, acetic acid, benzylphosphonic acid, and *O*,*O*′-diethyl dithiophosphate did not promote this reaction under otherwise identical conditions, presumably owing to their weaker acidities.

Under these optimal reaction conditions, we next carried out this heterocycle-forming reaction using a variety of starting materials **1** and aldehydes. The results are summarized in Table 2. As can be seen from Table 2, the

Table 2. Construction of Tetrahydropyrans from **1** and Aldehydes



entry[a]	$R^1/R^{1'}$	R^2	acid	2/3	yield[b] (%)
1	C_6H_5/H	4-MeC_6H_4	MsO	**2b/3b** (9:1)	93
2	C_6H_5/H	4-ClC_6H_4	MsO	**2c/3c** (12:1)	80
3	C_6H_5/H	4-BrC_6H_4	MsO	**2d/3d** (16:1)	84
4	C_6H_5/H	4-FC_6H_4	MsO	**2e/3e** (10:1)	86
5	4-ClC_6H_4/H	C_6H_5	MsO	**2f/3f** (20:1)	91
6	4-BrC_6H_4/H	C_6H_5	MsO	**2g/3g** (14:1)	88
7	4-MeC_6H_4/H	C_6H_5	MsO	**2h/3h** (15:1)	81
8[c]	4-$MeOC_6H_4$/H	C_6H_5	MsO	**2i**	57
9	4-FC_6H_4/H	C_6H_5	MsO	**2j/3j** (16:1)	95
10	4-FC_6H_4/H	4-ClC_6H_4	MsO	**2k/3k** (13:1)	84
11	4-ClC_6H_4/H	4-ClC_6H_4	MsO	**2l/3l** (11:1)	85
12[c,d]	C_6H_5/H	C_6H_5	TsO	**2m**	76
13[c,d]	4-FC_6H_4/H	C_6H_5	TsO	**2n**	70
14[c]	3-FC_6H_4/H	C_6H_5	MsO	**2o**	42
15[c]	2-BrC_6H_4/H	C_6H_5	MsO	**2p**	51
16[c]	C_6H_5/H	Me	MsO	**2q**	70
17[c]	C_6H_5/H	$C_6H_5(CH_2)_2$	MsO	**2r**	67
18	H/C_6H_5	C_6H_5	MsO	**2a/3a** (12:1)	80

[a] All reactions were carried out with **1** (0.30 mmol), aldehydes (0.36 mmol), and acids (0.42 mmol) in 1.0 mL of DCM under optimized conditions unless otherwise noted. [b] Isolated yields based on **1**. [c] In these cases, traces of **3** were formed on the basis of TLC plates. [d] Carried out at 40 °C for 10 h.

corresponding tetrahydropyrans **2** and **3** were obtained in moderate to high total yields and high isomeric selectivities (**2**/**3** > 9/1), and in some cases tetrahydropyrans **2** were produced almost exclusively, with only a trace of **3** formed within 20 min (Table 2). Substituents on the aromatic ring of **1** have modest influence on the reaction. Adding a strongly electron-donating group, such as methoxy group, on the aromatic ring of **1** afforded the corresponding tetrahydropyran **2i** in somewhat low yield (57%) along with trace of **3i** (Table 2, entry 8). Using toluenesulfonic acid (TsOH) as a Brønsted acid, the corresponding tetrahydropyrans **2m** and

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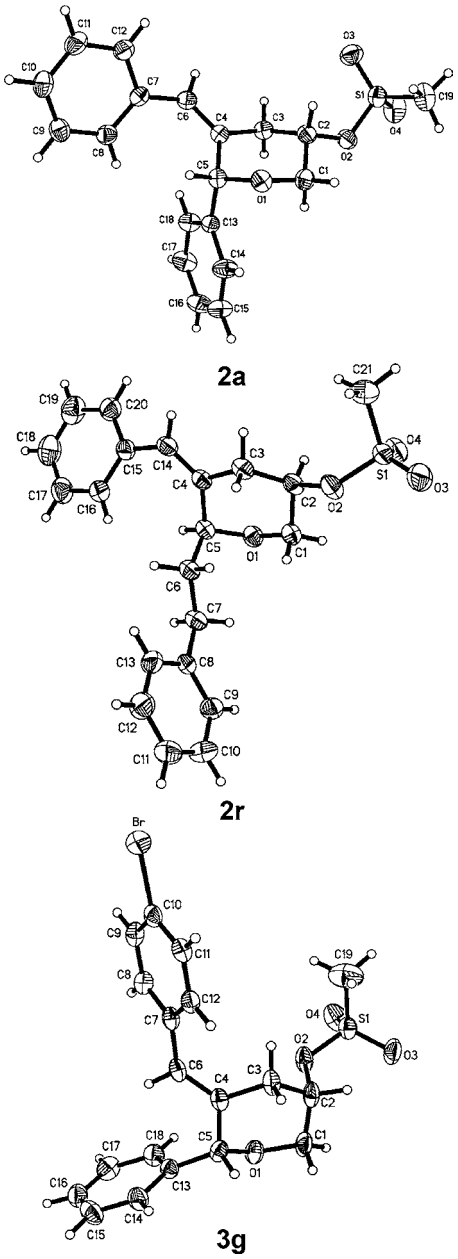
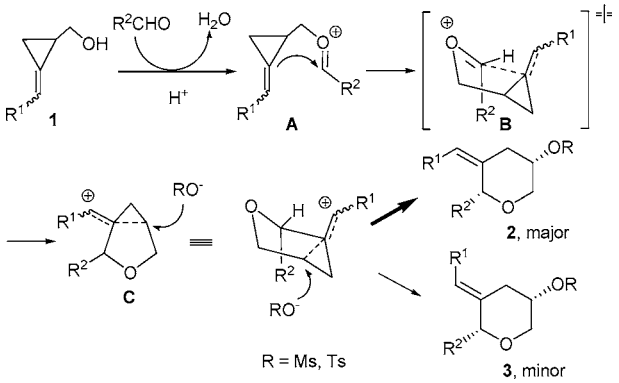


Figure 1. ORTEP Drawing of **2a**, **2r**, and **3g**

2n were obtained in good yields along with traces of their isomers (Table 2, entries 12 and 13). The presence of electron-withdrawing groups, such as fluoro- and bromo-substituents, at the 2- or 3-position of benzene ring of **1** gave the corresponding tetrahydropyrans **2** in moderate yields (Table 2, entries 14 and 15). Substituents on the aryl aldehydes did not significantly affect the reaction (Table 2, entries 1−9). Aliphatic aldehydes also reacted with **1** smoothly to afford the corresponding tetrahydropyrans **2** with the same stereochemistry as those of aryl aldehydes, although in somewhat lower yields (Table 2, entries 16 and 17). In addition, using (*Z*)-2-(phenylmethylene)cyclopropylcarbinol as a substrate to react with benzaldehyde under the standard conditions, **2a** and **3a** were also formed in 72% and 6% yields, respectively, which is the same as that of **1a** (Table 2, entry 18). Product structures were determined by ^{1}H and ^{13}C NMR spectroscopic data, HRMS, and microanalysis. Furthermore, the X-ray crystal structures of **2a**, **2r**, and **3g** were determined (see Figure 1), and their CIF data is presented in the Supporting Information.[8]

A plausible mechanism based on a Prins-type reaction is outlined in Scheme 1.[9] In the presence of a Brønsted acid, **1**

Scheme 1. Plausible Mechanism for the Construction of Tetrahydropyrans from **1** and Aldehydes



reacts with the aldehyde to produce intermediate **A**, which undergoes intramolecular nucleophilic attack to afford intermediate **C** via transition state **B**. Intermediate **C** is trapped by the counterion from the opposite direction of the R^1 group to provide products **2** and **3**.

Under the standard conditions, optically active (*S*)-**1g** with 61% ee could be transformed into the corresponding optically active **2g** and **3g** in 88% total yield without loss of enantioselectivity (Supporting Information), indicating the complete chirality inversion in intermediate **C** (Scheme 2).

In addition, upon treatment with methylmagnesium bromide, **2a** can be easily demesylated to afford compound **4a**

(8) The crystal data of compound **2a** have been deposited in CCDC with number 610599. Empirical formula, $C_{19}H_{20}O_4S$; formula weight, 344.41; crystal color; habit, colorless, prismatic; crystal dystem, monoclinic; lattice type, primitive. Lattice parameters: a = 5.4291(10) Å, b = 30.429(6) Å, c = 10.873(2) Å, α = 90°, β = 99.416(3)°, γ = 90°, V = 1772.0(6) Å^3. Space group, $P2(1)/c$; Z = 4; D_{calcd} = 1.291 g/cm^3; F_{000} = 728. Diffractometer, Rigaku AFC7R; residuals R, R_w, 0.0486, 0.1014. The crystal data of compound **2r** have been deposited in CCDC with number 622269. Empirical formula, $C_{21}H_{24}O_4S$; formula weight, 372.46; crystal color; habit, colorless, prismatic; crystal system, monoclinic; lattice type, primitive. Lattice Parameters: a = 9.738(16) Å, b = 10.632(18) Å, c = 19.29(3) Å, α = 90°, β = 103.06(3)°, γ = 90°, V = 1946(6) Å^3. Space group, $P2(1)/n$; Z = 4; D_{calcd} = 1.271 g/cm^3; F_{000} = 792. Diffractometer, Rigaku AFC7R; residuals R, R_w, 0.0674, 0.1526. The crystal data of compound **3g** have been deposited in CCDC with number 620556. Empirical formula, $C_{19}H_{21}BrO_5S$; formula weight, 441.33; crystal color; habit, colorless, prismatic; crystal system, triclinic; lattice type, primitive. Lattice Parameters: a = 5.7054(17) Å, b = 10.466(3) Å, c = 17.168(5) Å, α = 80.479(5)°, β = 83.302(5)°, γ = 79.666(6)°, V = 990.6(5) Å^3. Space group, $\bar{P}1$; Z = 2; D_{calcd} = 1.480 g/cm^3; F_{000} = 452. Diffractometer, Rigaku AFC7R; residuals R, R_w, 0.0730, 0.1809.

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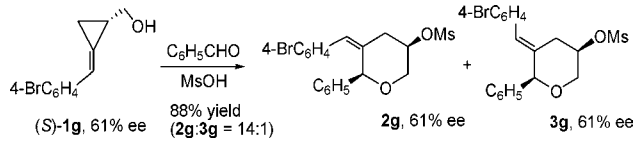
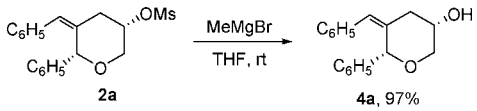
Scheme 2. Complete Chirality Transfer



with retention of stereochemistry in quantitative yield, affording the possibility for further transformation (Scheme 3).[10]

Scheme 3. Demesylation of **2a**



Functionalized pyrans are a common structural motif found in many natural products and bioactive compounds and over the years, there have been many elegant methodologies developed for the synthesis of such heterocycles.[11] The synthetic method we present here takes great advantage over many of these in that it is a metal-free and mild process.

In conclusion, we have found an interesting procedure where 2-(arylmethylene)cyclopropylcarbinols react with aldehydes to provide stereo- and regioselectively terahydropyrans mediated by Brønsted acid. A plausible reaction mechanism has been proposed that is based on a Prins-type reaction pathway. Using this procedure, a series of tetrahydropyrans were obtained selectively, with easily available reagents under mild conditions, in moderate to good yields. Further studies regarding the mechanistic details and scope of this process are in progress.

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Supporting Information Available: Spectroscopic data of all the new compounds, the detailed descriptions of experimental procedures, and X-ray data for compounds **2a**, **2r**, and **3g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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