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Preparation of Fluorinated Tetrahydropyrans and Piperidines using a New Nucleophilic Fluorination Reagent DMPU/HF

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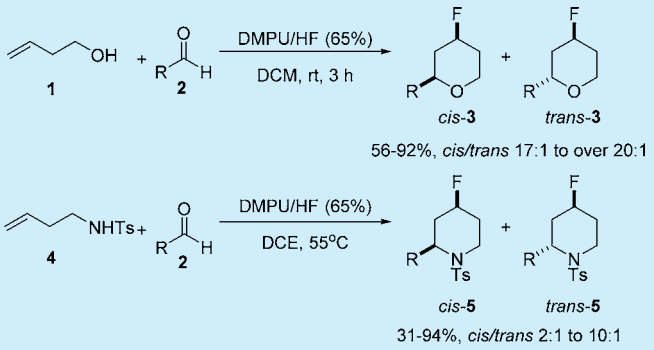
Supporting Information

ABSTRACT: DMPU/HF (HF content 65 wt %/wt) is an ideal nucleophilic fluorination reagent for the diastereoselective synthesis of substituted 4-fluorotetrahydropyrans and 4-fluoropiperidines via a fluoro-Prins reaction. When compared to classical nucleophilic fluorination reagents like pyridine/HF, DMPU/HF gives both higher yields and better diastereoselectivity.



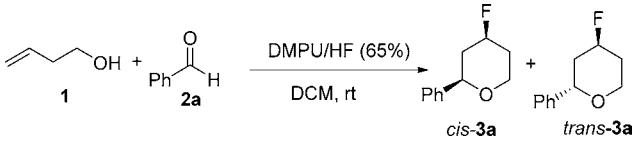
Incorporation of fluorine into organic compounds is known to impart useful and important properties to these compounds.[1,1e] Hydrogen fluoride is regarded as one of the most atom-economical nucleophilic fluorination reagents, but its gaseous state at ambient conditions and toxicity hinder its wider use.[2] In order to ease its manipulation, hydrogen fluoride gas is mixed with amine bases to form complexes such as Olah's reagent (pyridine·9HF) and triethylamine/HF (Et_3N·3HF).[3] However, these amine bases reduce the acidity of the system and may decrease reactivity in reactions that need high acidity. We have recently reported that HF could form acidic stable complexes with potential hydrogen-bond acceptors.[4] Indeed, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) can form a stable complex with up to 11 equiv of HF.[5] This acidic complex has been demonstrated to be an optimal fluorination reagent in the gold-catalyzed mono- and difluorination of alkynes.[5] DMPU/HF can be prepared in 65% yield (wt/wt HF content, mole ratio of DMPU/HF = 1:11.9) or at lower concentrations (e.g., 34%, mole ratio of DMPU/HF = 1:3.3).

Since the DMPU/HF reagent is more acidic than Olah's reagent (pyridine·9HF) or triethylamine HF (Et_3N·3HF), we proposed that its use could be advantageous in fluorination reactions that require a highly acidic medium. Herein, we report an improved diastereoselective synthesis of fluorinated tetrahydropyrans and piperidines using DMPU/HF.

The Prins reaction[6] of a homoallylic alcohol and an aldehyde in the presence of an acid is a well-established synthetic methodology for the preparation of tetrahydropyrans.[7] However, there are only a few reports on the Prins reaction for the synthesis of fluorinated tetrahydropyrans.[8] Most of the reported syntheses of fluorinated tetrahydropyrans utilize a strong Lewis acid, BF_3·OEt_2, as the fluorine source. Hence, they suffer from low yields and especially low diastereoselectivity.[8b] Fuchigami and coworkers reported the synthesis of 4-fluorotetrahydropyrans with HF salts in liquid form, but a large excess of HF was needed (HF as solvent).[8a] Because the Prins reaction requires an acidic medium, the more acidic HF/DMPU system should improve the efficiency of Prins cyclization.

We were pleased to find that the reaction of homoallylic alcohol **1** and benzaldehyde **2a** in the presence of DMPU/HF produced the expected 4-fluorotetrahydropyran **3a** (Table 1).

Table 1. Optimization of the Fluoro-Prins Reaction[a]



entry	solvent	time (h)	conversion (%)	*cis*/*trans*[b]
1	hexane	3	100	17:1
2	toluene	3	100	17:1
3	DCM	3	96	17:1
4[c]	DCM	9	90	17:1
5	DMPU	3	42	10:1
6	THF	9	0	
7	DMF	9	0	

[a]**1** (0.2 mmol), 2 (0.2 mmol), DMPU/HF (2.1 mmol of HF), and solvent (0.5 mL) were mixed in a polyethylene vial and then stirred for 3−9 h at rt. [b]Determined by ^{19}F NMR. [c]34% DMPU−HF.

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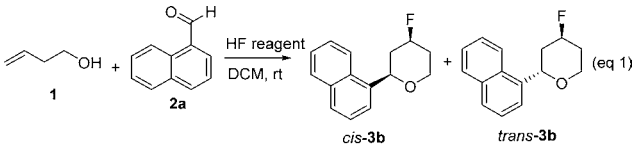
Reactions in a number of nonpolar solvents (hexane, toluene, and DCM) provided high efficiency and excellent diastereoselectivity (Table 1, entries 1−3). A lower concentration of HF in the reaction medium (34% HF/DMPU wt/wt, DMPU/HF = 1:3.3) slowed the reaction, but the diastereoselectivity was maintained (Table 1, entry 4). A complete replacement of solvent by DMPU resulted in a much slower conversion and eroded the diastereomeric ratio (Table 1, entry 5). Reactions were completely shut down in Lewis basic solvents, including THF and DMF (Table 1, entries 6 and 7).

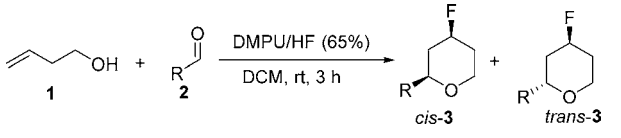
We also compared the reactivity and selectivity of Olah's reagent and HF/DMPU in the Prins reaction of 2-naphthaldehyde eq 1. The more acidic DMPU/HF reagent enabled a faster conversion and much better diastereoselectivity than Olah's reagent.



HF reagent	time	conversion	*cis/trans*
Pyridine/HF (70%)	48 h	95%	4:1
DMPU/HF (65%)	3 h	97%	17:1

To explore the general applicability of our methodology, several aldehydes were subjected to our optimized reaction conditions (Table 2). Aromatic and aliphatic aldehydes gave the

Table 2. Scope of the Fluoro-Prins Reaction[a]



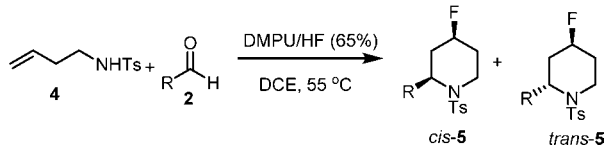
entry	R	3	yield (%)	*cis*-3/*trans*-3[b]
1	C_6H_5−	**3a**	75	17:1
2	2-naphtyl	**3b**	74	>20:1
3	4-ClC_6H_4−	**3c**	87	>20:1
4	4-BrC_6H_4−	**3d**	91	>20:1
5	4-$NO_2C_6H_4$−	**3e**	81	>20:1
6	4-$CF_3C_6H_4$−	**3f**	92	>20:1
7	4-*i*-PrC_6H_4−	**3g**	78	>20:1
8	4-MeC_6H_4−	**3h**	72	>20:1
9	2-$NO_2C_6H_4$−	**3i**	76	>20:1
10	4-OH-3,5-dimethoxy-C_6H_2	**3j**	ro rxn	
11	6-Br-2-OH-3-MeO-C_6H_2	**3k**	56	> 20:1
12	cyclohexyl−	**3l**	88	20:1

[a]**1** (0.2 mmol), **2** (0.2 mmol), and DMPU/HF (2.1 mmol HF) in DCM (0.5 mL) was mixed in a plastic vial and then stirred for 3 h at rt. [b]Determined by ^{19}F NMR.

corresponding fluorinated tetrahydropyrans in good yields and good diastereoselectivity. A more electron-rich aldehyde, such as 4-hydroxy-3,5-dimethoxybenzaldehyde, did not react under these conditions. The same phenomenon was also observed in the $BF_3{\cdot}OEt_2$-mediated Prins cyclization[8b] (Table 2, entry 10).

We also investigated the aza-Prins cyclization of aldehyde and *N*-tosyl homoallyl amine in the presence of our DMPU/HF reagent. As shown in Table 3, the reaction of *N*-tosyl homoallyl amine **4** with aliphatic aldehydes furnished the corresponding fluoropiperidines **5** in excellent yields and good diastereoselectivity after a few hours. Similar to previous literature reports,[9]

Table 3. Scope of the Aza-Prins Fluorocyclization[a]



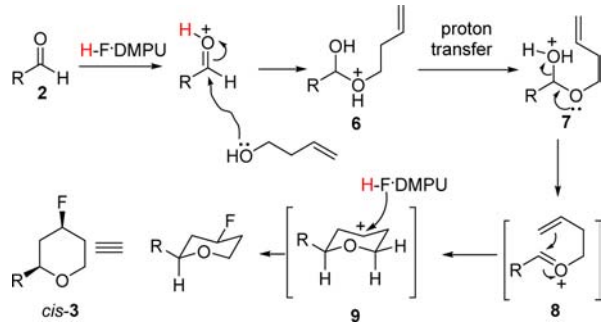
entry	R	time (h)	5	yield (%)	*cis*-5/*trans*-5[b]
1	cyclohexyl−	4	**5a**	100	10:1
2	*n*-C_5H_{11}−	4	**5b**	100	8.5:1
3	Ph−	24	**5c**	96	2:1
4	4-Br-C_6H_4−	24	**5d**	90	2.5:1
5	4-$NO_2C_6H_4$−	24	**5e**	42	2:1
6	4-$MeOC_6H_4$−	48	**5f**	0	

[a]**4** (0.2 mmol), **2** (0.2 mmol), and DMPU/HF (2.1 mmol of HF) in DCE (0.5 mL) was mixed in a polyethylene vial and then stirred at 55 °C. [b]Determined by ^{19}F NMR. [c]Room temperature. [d]Determined by ^{19}F NMR using $PhCF_3$ as internal standard.

this reaction did not proceed well with aryl aldehydes (Table 3, entries 3−5), and longer reaction times were needed in order to achieve a full conversion. The reaction became very sluggish with an electron-rich aromatic aldehyde (e.g., anisaldehyde), and only a trace amount of product was obtained even after an extended reaction time (Table 3, entry 6).

The proposed mechanism of the fluoro-Prins cyclization reaction is shown in Scheme 1. First, HF/DMPU activates the

Scheme 1. Proposed Mechanism for the Fluoro-Prins Cyclization



aldehyde **2**, which then reacts with the homoallylic alcohol. Subsequent elimination of water results in the formation of the intermediate oxonium ion **8** that then cyclizes into carbocation **9**. The nucleophilic fluorine in HF/DMPU quenches intermediate **9** to give the fluorinated product **3**.[10]

In summary, DMPU/HF is a suitable nucleophilic fluorination reagent for the diastereoselective synthesis of substituted 4-fluorotetrahydropyrans and 4-fluoropiperidines via the Prins reaction. When compared to other commonly used nucleophilic fluorination reagents like pyridine/HF, DMPU/HF gives both higher yields and better *cis/trans* selectivity. The experimental procedure is simple and is amenable to scale-up.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01919.

Experimental procedures and analytical data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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