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Brook/Elimination/Aldol Reaction Sequence for the Direct One-Pot Preparation of Difluorinated Aldols from (Trifluoromethyl)-trimethylsilane and Acylsilanes

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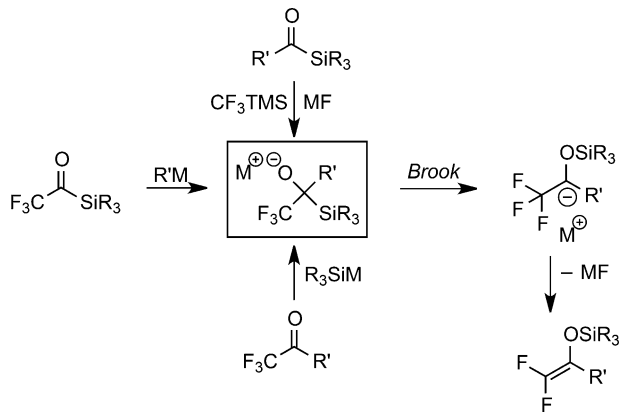
Abstract: A methodology allowing the one-pot preparation of difluorinated aldols directly from Ruppert–Prakash reagent, acyltrimethylsilanes and aldehydes is reported. The process, initiated by a catalytic amount of an ammonium salt, involves the addition of (trifluoromethyl)trimethylsilane to the acylsilane, followed by a Brook rearrangement and elimination of a fluoride anion that promotes the subsequent aldol reaction. An efficient racemic reaction catalyzed by tetrabutylammonium difluorotriphenylsilicate is described, as well as our first efforts towards an asymmetric version.

Keywords: aldol reaction; Brook rearrangement; fluorine; organocatalysis

While long ignored by organic and medicinal chemists, fluorinated molecules have increasingly attracted their attention since half a century. The ever-growing number of fluorinated drugs and agrochemicals released on the market every year reflects this situation.[1] This popularity arises from the unique properties of the fluorine atom and of the C–F bond. The fluorine atom is the second smallest (van der Waals radius is 1.47 Å) of the periodic table and exhibits the strongest electronegativity (4.0 on the Pauling scale). The C–F bond is consequently short (1.35 Å) and has a very high dissociation energy of 105.4 kcal mol^{-1}.[2] Thanks to these properties, the introduction of fluorine onto a bioactive molecule has often major consequences on its pharmacodynamic or pharmacokinetic properties. Indeed, the presence of a fluorine atom or a fluorinated group in the appropriate position can improve the binding of a molecule with a receptor, increase its lipophilicity, modulate its pK_a or inhibit its metabolic degradation.[3] The number of fluorinated drugs has consequently increased, as well as the need for methodologies that enable the efficient preparation of fluorinated synthons. Great achievements in the fields of fluorination and trifluoromethylation reactions have been realized over the past twenty years.[4] The use of reactive fluorinated building blocks, such as fluoroenol ethers or fluoroenolates, is nevertheless a nice alternative.[5] Indeed, this approach allows an access to fluoro- or difluoromethylene-containing molecules without the limitations of direct fluorination reactions. Moreover, the second functional group which is generally introduced through such reactions might serve for further synthetic elaboration. Aldol reactions with difluoroenolates are highly representative of this strategy since a difluoromethylene group and a carbonyl function can be introduced in a single step. The preparation of α,α-difluoro-β-hydroxy ketones or esters through either Mukaiyama aldol or Reformatsky-like reactions is well documented.[6,7] However, Mukaiyama reactions are often hampered by the poor stability of trimethylsilyl fluoroenol ethers, while Reformatsky reactions suffer from the drawbacks associated with the use of stoichiometric amounts of organometallic reagents (basic and strictly anhydrous conditions, metallic wastes, …). In this context, the trifluoroacetate release strategy initially developed by Colby and Wolf, which enables the mild *in situ* generation of a difluoroenolate from a stable precursor, was a very interesting approach.[8] We were on our part intrigued by the long known Brook rearrangement/fluoride elimination process, which proved highly helpful for the preparation of difluoroenoxysilanes (Scheme 1).[9]



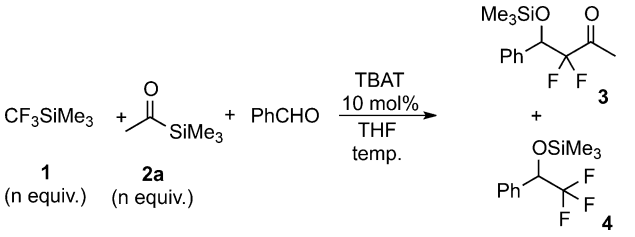
Scheme 1. Brook/elimination sequence.

This sequence was appealing since it allowed a mild *in situ* generation of a difluoroenoxysilane, while generating a fluoride anion as the sole by-product. We thus envisioned that such a process could be applied to a one-pot/one-catalyst aldol reaction directly from acylsilanes. We wish to report herein our efforts in this area that led to the development of a Brook rearrangement/fluoride elimination/aldol reaction sequence.

Inspired by our results in the development of a similar sequence leading to monofluorinated aldols from β,β-difluoro-α-(trimethylsilyl) alcohols,[10] we focused our interest on the nice approach reported by Portella for the preparation of difluoroenoxysilanes. This difluorotriphenylstannate-promoted addition of (trifluoromethyl)trimethylsilane to acylsilanes was the starting point of our study. We followed the simple reasoning that the fluoride anion that is generated in the process could itself act as a catalyst for the aldol reaction. Indeed, Portella's methodology was apparently willingly restricted to the preparation of difluoroenoxysilanes, even if the latter were afterwards subjected to a Lewis acid-promoted Mukiyama aldol reaction.[11] We thus investigated a one-pot reaction between (trifluoromethyl)trimethylsilane, acetyltrimethylsilane and benzaldehyde that was expected to directly afford the corresponding difluorinated aldol.

We first studied this reaction using tetrabutylammonium difluorotriphenylsilicate (TBAT) as the catalyst, a commercially available, silicate version of the catalyst used by Portella.[9c] In a first attempt, an equimolar mixture of the three reagents was subjected to 10 mol% of TBAT in THF at −40 °C. After three hours of reaction and complete consumption of benzaldehyde according to TLC monitoring, a 51:49 mixture of the expected aldol **3** and trifluoromethyl carbinol **4** was obtained (Table 1, entry 1). Although unsatisfactory, this result was nonetheless encouraging. Indeed, we were initially worried about the relative reactivities of acetyltrimethylsilane and benzaldehyde. Since the aldol and the trifluoromethyl carbinol were

Table 1. Optimization of the one-pot Brook rearrangement/fluoride elimination/aldol reaction sequence.



1 (n equiv.) 2a (n equiv.)

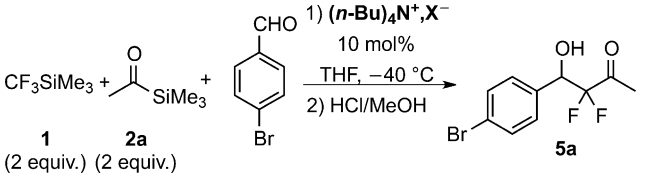
Entry	n	Temp.	Method[a]	**3**:**4**:PhCHO[b]
1	1	−40 °C	A	51:49:0
2	1	−40 °C	B	6:12:82
3	2	−40 °C	A	56:44:0
4	2	−40 °C	B	100:0:0
5	2	−60 °C	B	66:34:0

[a] Method A: the PhCHO is introduced at once. Method B: a THF solution of PhCHO is added in 15 min with a syringe pump.
[b] Measured by ^{1}H NMR of the crude mixture.

obtained in the same amount, a simple optimization of the reaction procedure was expected to solve this issue. Disappointingly, the addition of benzaldehyde in 15 min using a syringe pump to a THF solution of CF_3TMS and CH_3COTMS led to a very poor conversion of benzaldehyde (Table 1, entry 2). A result similar to entry 1 was obtained when using an excess of (trifluoromethyl)trimethylsilane reagent and acetyltrimethysilane (Table 1, entry 3). Combining the slow addition of benzaldehyde with the use of an excess of difluoroenoxysilane precursors eventually allowed a full conversion of benzaldehyde and a total selectivity in favour of the aldol product (Table 1, entry 4). Lowering the temperature at −60 °C was deleterious since trifluoromethyl carbinol was again detected in the reaction mixture, whatever the rate of addition of the benzaldehyde solution (Table 1, entry 5).

Based on the conditions devised in Table 1, entry 4, a quick survey of onium pair catalysts was conducted (Table 2). *para*-Bromobenzaldehyde was used as the electrophile and an acidic cleavage of the trimethylsilyl ether was performed after the reaction. This study was meant to assess the influence of the nature of the Lewis base on the course of the reaction. The efficiency of TBAT as a catalyst was confirmed since **5a** could be isolated in 62% yield after deprotection of the intermediate trimethylsilyl ether (Table 2, entry 1). In contrast, the use of tetrabutylammonium fluoride (TBAF) led to a complex mixture, from which only small amounts of trifluoromethylated product **3** and of its corresponding free alcohol could be identified (Table 2, entry 2). This result was not surprising since Portella had demonstrated that TBAF was not an appropriate promoter for the difluoroenoxysilane generation and led to many side-pro-

Table 2. Catalyst survey.



Entry	X^-	Yield[a]
1	$Ph_3SiF_2^-$	62%
2	F^-	nd
3[b]	$(p\text{-MeO})C_6H_4O^-$	16%
4	AcO^-	54%

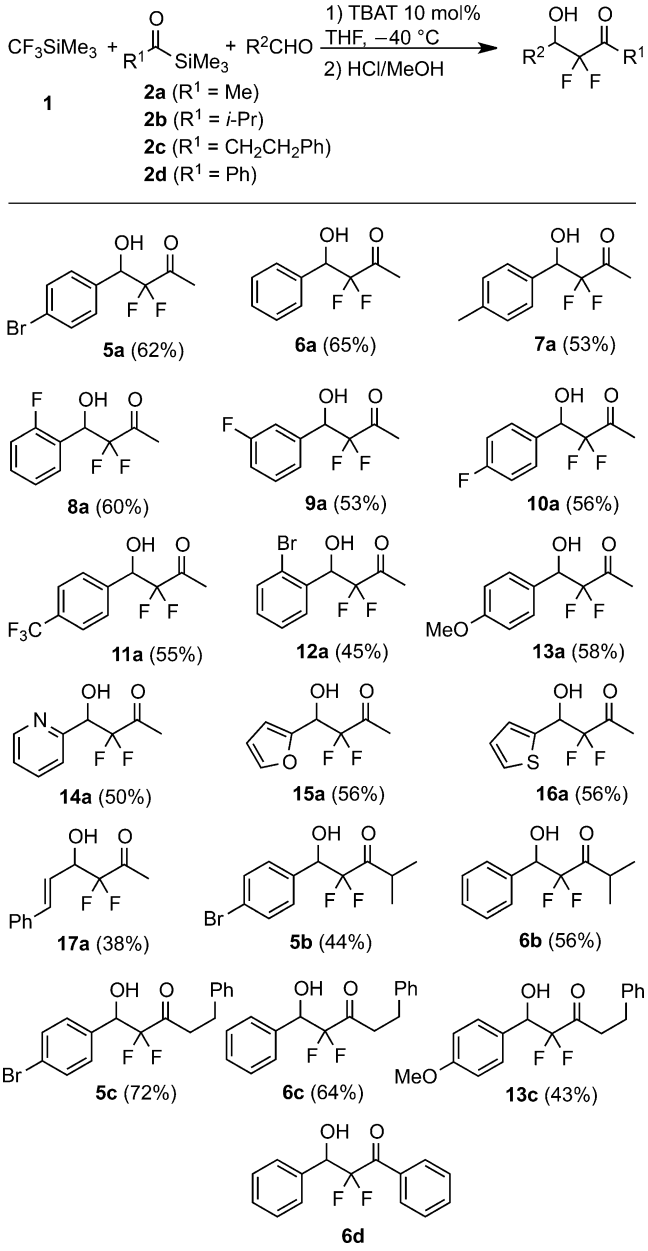
[a] The reaction is performed using method B: a THF solution of PhCHO is added in 15 min with a syringe pump.
[b] The catalyst was prepared in *situ* by anion metathesis from $(n\text{-Bu})_4N^+,Br^-$ and $(p\text{-MeO})C_6H_4ONa$ in THF for 1 h.

ducts.[9c] Disappointingly, the use of tetrabutylammonium (*para*-methoxy)phenoxide led to a low 16% isolated yield of **5a**. The crude mixture was mainly constituted of unreacted aldehyde and its trifluoromethylation product (Table 2, entry 3). In contrast, tetrabutylammonium acetate appeared as an efficient promoter since the same reaction led this time to a 54% yield of **5a**, with no traces of unreacted aldehyde or of trifluoromethylcarbinol (Table 2, entry 4).

The scope of the reaction was next examined using TBAT as the catalyst under the optimized conditions (Scheme 2).

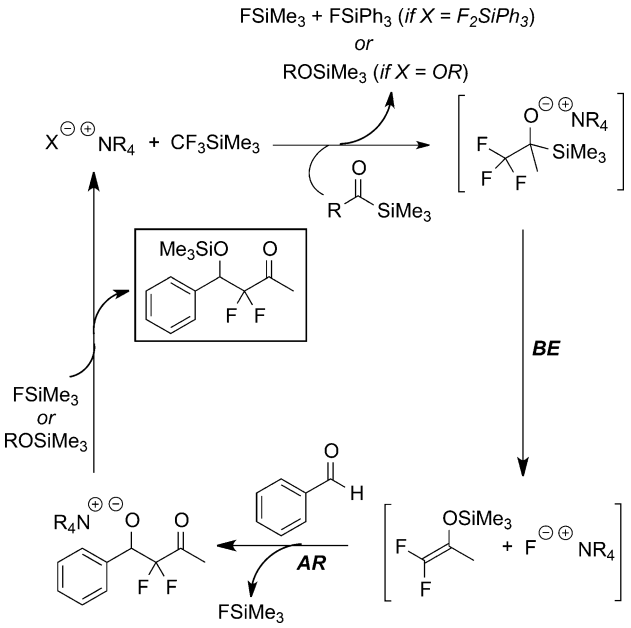
The compounds were obtained in overall yields ranging from 38 to 72%. One should keep in mind that these yields reflect a four-step process (addition of CF_3TMS to the acylsilane, Brook/elimination sequence, aldol reaction and deprotection) with, therefore, an average yield of 79–92% for each step. Our one-pot sequence is thus fairly efficient and nicely competes with Portella's sequential method.[11] Aromatic aldehydes appeared as suitable substrates for this reaction, albeit the yield decreased using cinnamaldehyde (38%). Moreover, only a complex mixture was obtained from isobutyraldehyde. Other acylsilanes (i-$PrCOSiMe_3$ and $PhCH_2CH_2COSiMe_3$) were successfully used (products **5b**, **6b**, **5c**, **6c** and **13c**). Disappointingly, product **6d**, resulting from the reaction with benzoyltrimethylsilane and benzaldehyde, could never be obtained as a pure sample, despite a good conversion. Unexpectedly, this aldol was, in our hands, moderately stable and always underwent degradation during purifications.

The mechanism and the catalytic cycle of the reaction are depicted on Scheme 3. As mentioned above, the addition of (trifluoromethyl)trimethylsilane to the acylsilane is triggered by the catalyst and is followed by the Brook rearrangement/elimination sequence.



Scheme 2. Scope of the one-pot aldol reaction.

The latter affords the difluoroenoxysilane as well as an ammonium fluoride that can promote the aldol reaction. Two pathways are possible for closing the cycle, depending on the initial catalyst. If the latter is TBAT, the resulting ammonium alkoxide might be silylated with TMSF to release the product and an ammonium fluoride that can catalyze the first step.[12] If the reaction is catalyzed by tetrabutylammonium acetate or aryloxide, silylation of the ammonium alkoxide by the $ROSiMe_3$ species produced in the first step can occur and regenerate the catalyst.[13] In both cases, the possibility that the ammonium alkoxide resulting from the aldol reaction would itself catalyze



Scheme 3. Postulated catalytic cycle (BE = Brook rearrangement/elimination; AR = aldol reaction).

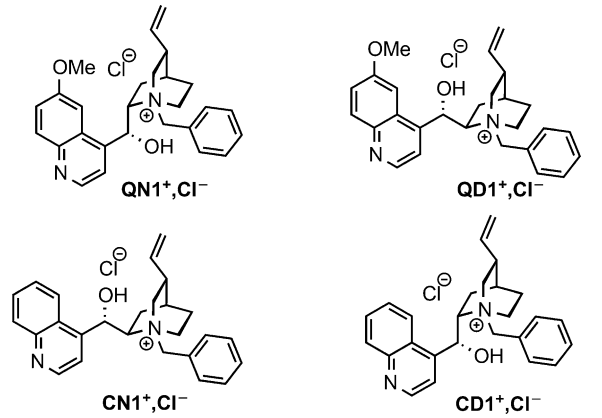


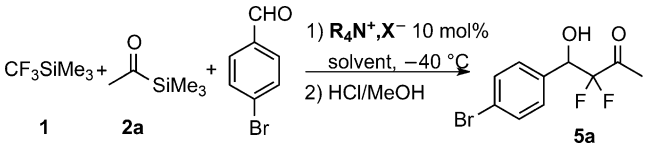
Figure 1. Chiral ammonium salts tested during the survey.

the addition of the Ruppert reagent cannot be ruled out.[10]

We afterwards decided to explore the possibilities of developing an asymmetric version of this reaction. Indeed, although meaningless for the enoxysilane generation, the use of a chiral ammonium cation would allow us to induce enantioselectivity during the aldol reaction. An efficient asymmetric version of our reaction would provide an access to enantioenriched difluoro aldols derived from aliphatic ketones, while the advanced literature methods are limited to aromatic difluoroenolates.[8h] Cooperative chiral ion pairing catalysis, i.e., processes involving the active participation of the anionic and cationic parts in the catalytic cycle, has proved to be an efficient approach in terms of reaction scope and stereoselectivity.[14] As such, chiral ammonium fluorides have been extensively studied as organocatalysts in which the ammonium part is able to bring chiral information and stabilize the development of a negative charge, while the fluoride part acts as a (Lewis or Brønsted) base that activates a pro-nucleophile.[15] However, the handling and storage of ammonium fluoride catalysts is often difficult due to their hygroscopic character. Moreover, TBAF failed to promote our racemic reaction, ruling out the use of chiral ammonium fluorides (Table 2). The use of a less basic, softer anion such as hydrogen bifluoride, acetate or phenoxide is often a nice alternative to produce chiral catalysts that are more stable and more easily handled.[16,17] Regarding our one-pot reaction, tetrabutylammonium acetate and, to a much smaller extent, (*para*-methoxy)phenoxide appeared as efficient catalysts for the racemic reaction. Starting from a small family of *N*-benzylammonium chlorides derived from *Cinchona* alkaloids (Figure 1), several acetate and phenoxide salts were thus prepared and tested as catalysts in our reaction. They were generated *in situ* from the corresponding chloride salts, through an anion metathesis reaction with sodium acetate or with the corresponding sodium phenoxide.[16c] Our first goal was to determine the appropriate counter-anion, using commercially available **QN1$^+$,Cl$^-$** as the standard pre-catalyst (Table 3). Surprisingly, using the acetate counter-ion was in this case unproductive (Table 3, entries 1 and 2). We thus turned back to ammonium phenoxides and the use of **QN1$^+$,(*p*-CF$_3$)C$_6$H$_4$O$^-$** as the catalyst allowed the formation of **13a** in average yield and low enantioselectivity (Table 3, entry 3). We then tried to slightly modulate the basicity of this anion (Table 3, entries 4 and 5), which has a slight, but sensitive influence on the reactivity. The use of a simple phenoxide brought no improvement, while the more basic (*p*-MeO)C$_6$H$_4$O$^-$ led to a moderate yield and a slighty higher *ee*. The latter was retained for the rest of the study. A quick solvent survey demonstrated that apolar or non-basic solvents were inappropriate (Table 3, entries 6 and 7). However, the use of a strongly polar solvent such as DMF resulted in a complete erosion of the enantioselectivity (Table 3, entry 8). Finally, *N*-benzylquinidinium, cinchoninium and cinchonidinium were also tested under the standard conditions and a modest 24% *ee* was obtained in the best case (Table 3, entries 9–11).[18] The feasibility of such an asymmetric one-pot/one-catalyst aldol reaction has, however, been demonstrated and an extensive screening of onium pair catalysts has now to be performed.

In summary, a one-pot preparation of difluorinated aldols directly from (trifluoromethyl)trimethylsilane, acyltrimethylsilanes and aldehydes was developed. The process is promoted by a catalytic amount of an ammonium salt and generates TMSF as the sole by-

Table 3. Preliminary study for an asymmetric version of the one-pot Brook/elimination/aldol reaction sequence.



1 2a 5a

Entry	X^{-}[a]	R_4N^+	Solvent	Yield [%]	*ee*[c] [%]
1	AcO^-	QN1$^+$	THF	–	–
2[b]	AcO^-	QN1$^+$	THF	–	–
3	$(p\text{-}CF_3)C_6H_4O^-$	QN1$^+$	THF	49	10
4	$C_6H_5O^-$	QN1$^+$	THF	38	12
5	$(p\text{-MeO})C_6H_4O^-$	QN1$^+$	THF	40	16
6	$(p\text{-MeO})C_6H_4O^-$	QN1$^+$	$PhCH_3$	–	–
7	$(p\text{-MeO})C_6H_4O^-$	QN1$^+$	CH_2Cl_2	–	–
8	$(p\text{-MeO})C_6H_4O^-$	QN1$^+$	DMF	52	2[d]
9	***(p-MeO)C$_6$H$_4$O$^-$***	***QD1$^+$***	***THF***	***42***	***24[d]***
10	$(p\text{-MeO})C_6H_4O^-$	CN1$^+$	THF	20	6[d]
11	$(p\text{-MeO})C_6H_4O^-$	CD1$^+$	THF	54	12

[a] The catalyst was prepared *in situ* by anion metathesis from **R_4N^+,Cl^-** and NaX in THF for 1 h, unless otherwise indicated.
[b] The catalyst was prepared and isolated prior to reaction by anion metathesis from **QN1$^+$,Cl^-** and AcOAg in CH_2Cl_2.[19]
[c] Measured prior to any chromatographic purification by chiral HPLC using a Daicel Chiralpak® IB column.
[d] The enantioselectivity is reversed compared to the other entries.

product. The anionic part of the ammonium salt has to be carefully chosen so that it efficiently activates (trifluoromethyl)trimethylsilane. An efficient racemic reaction was devised, using commercially available TBAT as the catalyst, leading directly to difluorinated aldols in good overall yield. Compared to the previous sequential methods (preparation of the difluoroenoxysilane followed by Mukaiyama aldol reaction), this one-pot/one-catalyst method is fairly efficient. Despite the fact that acylsilanes are not always easily accessible, this approach allows the preparation of difluoro aldols derived from aliphatic ketones, which is rarely the case for classical methods.[6,8] A preliminary study of an asymmetric version is also reported, with a first result (42% yield, 24% *ee*) that is of course unsatisfactory. If asymmetric catalysis appears possible for this reaction, the determination of an efficient chiral ion pair is still under investigation in our laboratory and results in this area will be reported in due course.

Experimental Section

General Procedure for the TBAT-Catalyzed Brook Rearrangement/Fluoride Elimination/Aldol Reaction Sequence

To a solution of CF_3TMS (296 μL, 2 mmol, 2 equiv.) in THF (2 mL) at −40 °C were added acylsilane (2 mmol, 2 equiv.) and TBAT (54 mg, 0.1 mmol, 0.1 equiv.). To this mixture was added over a period of 15 min a solution of aldehyde (1 mmol, 1 equiv.) in THF (1 mL). The solution was stirred for 1 h 30 min at −40 °C and then a saturated aqueous solution of NH_4Cl was added. The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was then diluted in MeOH (2 mL) and a solution of 10% aqueous HCl (5 mL) was added at 0 °C. The solution was stirred for 10 min at this temperature and neutralized with a saturated solution of $NaHCO_3$. The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by flash column chromatography (pentane/Et_2O 90:10) to give the expected difluorinated aldol.

Acknowledgements

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