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Brook/Elimination/Aldol Reaction (BEAR) Sequence for the Direct Preparation of Fluorinated Aldols from β,β-Difluoro-α-(trimethylsilyl)alcohols

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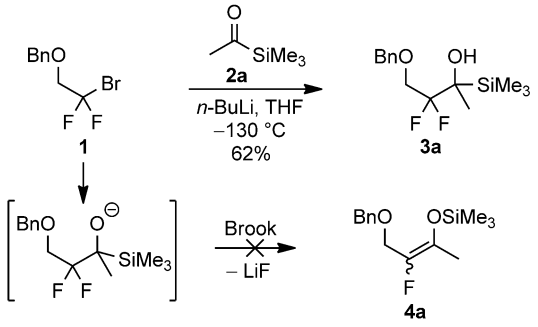
Abstract: A methodology allowing the preparation of aldols featuring a fluorinated stereogenic center is reported. The corresponding fluoroenolates are formed *in situ* from stable β,β-difluoro-α-(trimethylsilyl)alcohols, through a base-mediated process involving a Brook rearrangement followed by a fluoride elimination, and are directly added to aromatic aldehydes. Two different sets of conditions were disclosed. The first one involves the stoichiometric addition of potassium *tert*-butoxide (*t*-BuOK) while the second is based on the use of a catalytic amount of an ammonium phenoxide. The latter opens the way for a catalytic and asymmetric version of this Brook/elimination/aldol reaction (BEAR) sequence.

Keywords: aldol reaction; Brook rearrangement; fluorine; organocatalysis; stereogenic centers

Since the disclosure of fluorouracil and of fluorinated corticosteroids in the 1950s, the presence of fluorine atoms in bioactive molecules has considerably increased, with a strong acceleration during the last twenty years.[1,2] Up to 20% of the drugs and 30% of the agrochemicals launched every year since 2000 feature a fluorinated group in their structure, and the proportion is even higher for top-selling drugs.[3] The singular properties of the fluorine atom and of the C–F bond often allow interesting modulations of the behaviour of these molecules, which go from a higher metabolic stability to an increased activity.[4] The development of synthetic methodologies for the preparation of fluorinated organic molecules has thus become a major goal in modern organic chemistry. The investigation of direct electrophilic or nucleophilic fluorination as well as difluoromethylation and trifluoromethylation reactions is still a privileged research field.[5] However, the use of reactive, partially fluorinated building blocks often offers interesting alternatives with a higher flexibility and a greater molecular diversity. Fluorinated enol ethers and enolates are representative of this strategy since they allow the introduction of a fluorinated carbonyl moiety through an aldol reaction.[6] The efficiency of aldol or Reformatsky reactions to provide monofluorinated aldols has been demonstrated.[7] However, there are only few examples of aldol reactions providing monofluorinated adducts featuring a tetrasubstituted stereogenic center.[8,9] Moreover, among all these examples, direct aldol reactions often require the use of strong bases while Mukaiyama aldol reactions involve poorly stable fluorinated silyl enol ethers. We wish to present herein a new methodology allowing the preparation of new aldols featuring a fluorinated tetrasubstituted stereogenic center, and proceeding through the mild *in situ* generation of the enolate from a stable precursor.[10,11]

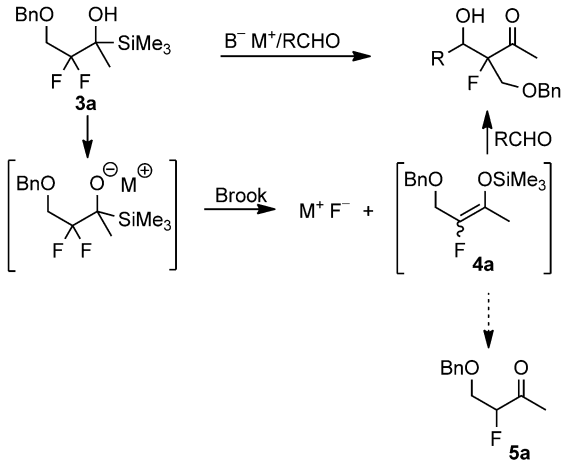
While studying for other purposes the addition of difluoromethyllithium compounds onto electrophiles, we were intrigued by the results obtained in the reaction between **1** and acetyltrimethylsilane **2a**.[12] Indeed, we expected that such an addition would lead directly to the corresponding monofluorinated silyl enol ether **4a** through the well known Brook rearrangement/elimination sequence (Scheme 1), even at the low temperatures required by the poor stability of the anion.[13] To our surprise, the addition of the anion derived from **1** to acetyltrimethylsilane **2a** yielded α-(trimethylsilyl)alcohol **3a** in 62% yield



Scheme 1. Preparation of α-(trimethylsilyl)carbinol **3a**.

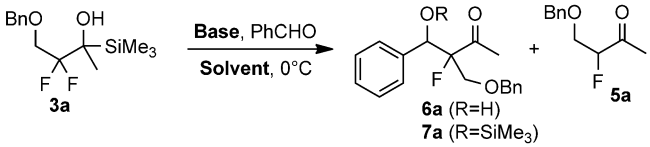
(Scheme 1).[14] The product was stable and could be purified by column chromatography over silica gel.

This result was seen as an opportunity to use β,β-difluoro-α-(trimethylsilyl)alcohol **3a** as a stable surrogate to the labile trimethylsilylenol ether **4a**. Our goal was to release, under mild reaction conditions, the corresponding enolate from **3a** and make it readily react with aldehydes to afford the corresponding aldol products. We indeed envisioned a one-pot process in which a moderately strong base M^+B^- would trigger the Brook/elimination sequence to deliver the corresponding enol ether, as well as a fluoride source M^+F^- that could itself promote the aldol reaction (Scheme 2).



Scheme 2. Envisioned one-pot Brook/elimination/aldol reaction (BEAR) sequence.

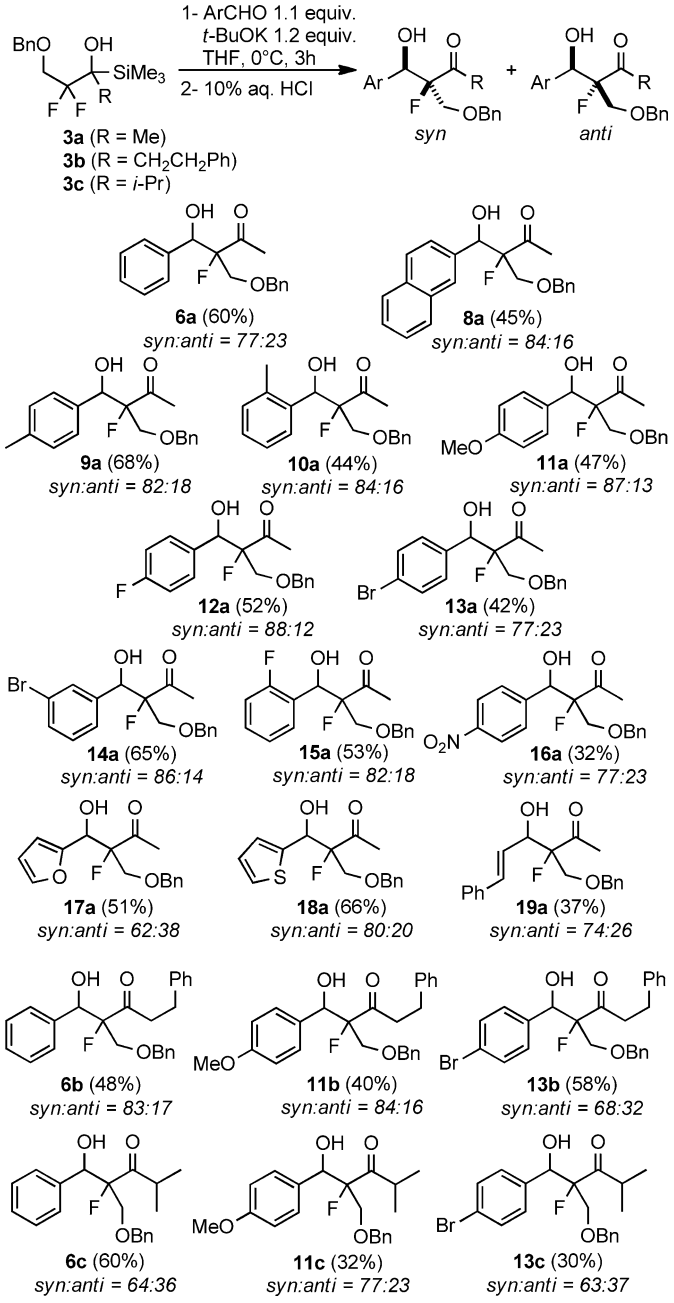
The reaction was first investigated using *t*-BuOK as a promoter and the crucial role of the solvent was immediately unveiled. Indeed, the reaction was complete in 3 h at 0 °C in THF, leading to the expected compound as a mixture of the free alcohol **6a** and of the TMS ether **7a** (Scheme 3). In contrast, the reaction failed in all other solvents, either producing only the fluoro ketone **5a** (toluene, Et_2O, MeCN) or leading to complete degradation (DMF). Similarly, other alkoxide bases (*i*-PrOMgBr or *t*-BuOLi) failed to produce the desired compound. Finally, the optimized conditions led, after desilylation with an aqueous solution of HCl, to aldol **6a** in 60% yield (Scheme 4).



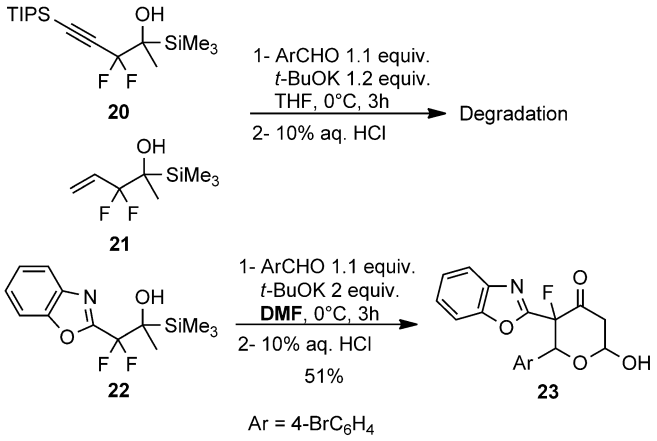
Scheme 3. Investigation of the BEAR sequence.

Based on these conditions, the scope of the reaction starting from **3a** was examined with various aldehydes (Scheme 4). The yields are in the 45–65% range for most examples, with occasional drops below these values for three examples, and reflect an efficient three elementary step process (75–85% as average yield for each step). Indeed, one should keep in mind that the reaction involves a Brook/elimination sequence, a fluoride-promoted aldol reaction and a final deprotection. The method was on the other hand ineffective with aliphatic aldehydes, since pivalaldehyde and isobutyraldehyde only led to degradation products. Compounds **6–19** were isolated as unseparable mixtures of diastereomers. The diastereomeric ratios ranged from 62:38 to 88:12, with a majority of examples around 80:20. This diastereoselectivity should be examined in light of the few reported reactions furnishing tetrasubstituted fluorinated aldols. Our results either favourably compare to or are in the same range as the diastereoselectivity reported for most of these reactions.[8] α-(Trimethylsilyl)carbinols **3b** an **3c**, which were prepared similarly to **3a**, were also used as starting materials in this reaction with comparable results. Finally, it should be mentioned that products **6–19** represent a novel class of polyfunctional fluorine-containing compounds of pharmaceutical importance.

The crystallization of the major diastereomer of **14a** made possible the determination of its relative configuration. The X-ray diffraction study indicated a *syn* relationship between the hydroxy group and the fluorine atom.[15] The ^{1}H NMR analysis of *syn*-**14a** revealed that the chemical shift of the methyl group was substantially higher than that for *anti*-**14a** (2.25 ppm *vs.* 1.99 ppm). All ^{1}H NMR spectra for compounds **6a–19a** followed the same pattern, with a chemical shift of the methyl group around 2.2–2.3 ppm for the major diastereomer and around 1.9–2.0 ppm for the minor one. The *syn* relative configuration was therefore assigned to all the major diasteromers of compounds **6a** and **8a–19a**. By analogy, and due to similar NMR data, the *syn* configuration was also assumed for the major diastereomer of compounds **6b–c**, **11b–c**, **13b–c**.



Scheme 4. Scope of the *t*-BuOK-mediated BEAR sequence.



Scheme 5. *t*-BuOK-mediated BEAR sequence with other substrates.

Two other substrates, arising from bromides other than **1**, were also tested. α-(Trimethylsilyl)carbinols **20** and **21** were indeed prepared in a similar manner from the corresponding bromides.[16] These two compounds were chosen for their ability to generate an extended enolate that might lead to interesting aldolization regioselectivity outcomes. Unfortunately, the *t*-BuOK-mediated BEAR sequence applied to **20** and **21** only led to unidentified degradation products, despite a full conversion of the substrates (Scheme 5). On the other hand, benzoxazole-derived compound **22**, also prepared from the known corresponding bromide,[17] led to an unexpected result. Although this substrate was unreactive in THF, the reaction in DMF provided lactol **23** in 51% yield (unoptimized) and as a 1:1 mixture of diastereomers. Lactol **23** probably arose from an additional base-promoted condensation to DMF and a subsequent cyclization. This five elementary step sequence is an interesting result that certainly deserves further investigation.

Our next step was to develop a catalytic process for this reaction, which ideally could open the way for an asymmetric version. Indeed, it should be possible to introduce the base in a substoichiometric amount due to the *in situ* generation during the process of the fluoride catalyst required for the aldol reaction. However, this will be possible only if the alkoxide resulting from the aldol reaction is able to initiate the Brook rearrangement or regenerate the base and thus close the catalytic cycle. Regarding a future enantioselective version, and considering the mechanism of the reaction, the chiral control element could only be placed on the enolate counter-cation, which leaves only two possibilities: the use of a metal complexed by a chiral ligand or the use of a chiral organic cation such as an ammonium.[18]

We started this study by checking if our initial promoter could be used as a catalyst. This was clearly not the case since the use of 10 mol% of *t*-BuOK only led to traces of the expected product (conversion $<10\%$), proving that the resulting alkoxide **6′a** could not act as a base or regenerate one (Table 1, entry 1). One way to circumvent this problem would be the use an additive that could release a base upon reaction with **6′a**, strong enough to deprotonate **3a** and thus reinitiate the cycle. We thus turned our attention to the work of Levacher who designed a catalytic system for the direct vinylogous aldol reaction of (5*H*)-furan-2-ones.[19] This system is based on the use of an ammonium phenoxide as a catalyst and of *N,O*-bis(trimethylsilyl)acetamide (BSA) as a stoichiometric addi-

Table 1. Development of a catalytic process for the BEAR sequence.

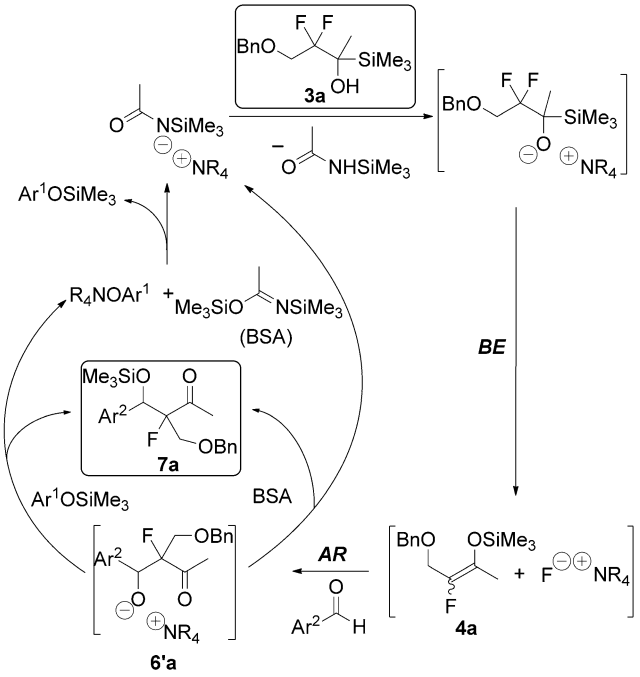
Entry	Cat.	Additive	Temp. [°C]	Yield [%]
1	*t*-BuOK	–	0	n.d.[a]
2	*t*-BuOK	BSA	0	n.d[b]
3	*t*-BuOK	BSA	−40	n.d[b]
4	(*rac*-BINAP)CuF	BSA	−40	18[b]
5	4-$MeOC_6H_4O^-$ (*n*-Bu)$_4N^+$	BSA	−40	63[b]

[a] Conversion < 10%.
[b] Conversion = 100%

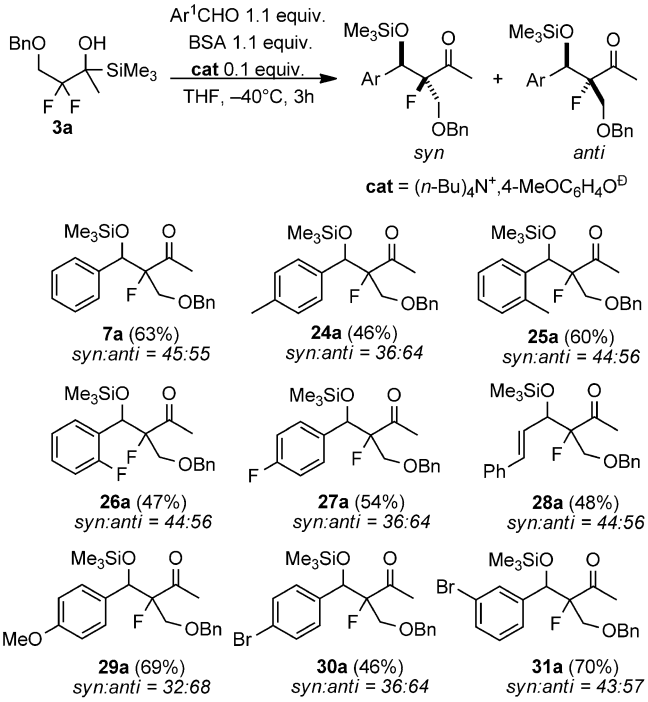
tive, which simultaneously acts as a silylation agent and as a Brønsted pro-base. In our hands, BSA was equally efficient as, in the presence of 1 equivalent of this reagent and using *t*-BuOK as the catalyst, silylated aldol **7** was obtained with full conversion (Table 1, entry 2). Not surprisingly, the reaction using only BSA failed, proving that the introduction of a base is necessary to initiate the reaction. The temperature could be lowered to −40 °C without reducing the conversion or slowing down too much the reaction (Table 1, entry 3). The next step was to identify an ion pair or a metal salt able to initiate the reaction and ultimately deliver a chiral enolate. A tetrabutylammonium phenoxide was of course tested, as well as a racemic copper(I) fluoride-BINAP complex previously used in Mukaiyama vinylogous aldol reactions (Table 1, entry 4).[20] Although the latter led to a low 18% yield, the catalytic system reported by Levacher provided **7** in 63% yield, a result similar to the reaction mediated by stoichiometric *t*-BuOK (Table 1, entry 5). The postulated catalytic cycle, similar to the one proposed by Levacher, is displayed in Scheme 6.[19]

These catalytic conditions were next tested on other aromatic aldehydes in order to assess their generality (Scheme 7). The products were isolated as their TMS ethers and yields were in most cases comparable to the stoichiometric reaction. The diastereoselectivity was, however, lower and reversed, ranging from 45:55 to 36:64 in favour of the *anti* diasteromer. The configuration of the major diastereomer was assigned on the basis of the ^{1}H NMR spectrum after conversion of the TMS ether to the free alcohol and comparison with the former products.

The diastereoselectivity of both *t*-BuOK-mediated and ammonium aryloxide-catalyzed reactions raises questions about their respective mechanisms. In the first case, the coordinating potassium counter-cation



Scheme 6. Catalytic cycle.



Scheme 7. Scope of the catalytic BEAR sequence.

might allow a closed, Zimmerman–Traxler-type transition state that should reflect the geometry of the intermediate silyl enol ether. In contrast, the ammonium counter-cation is not likely to allow any coordination with the aldehyde and the catalyzed reaction

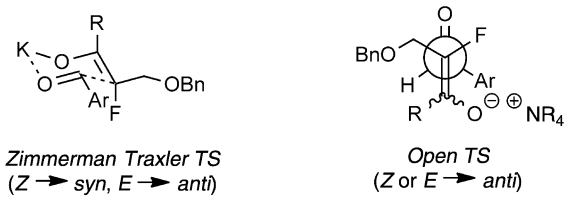
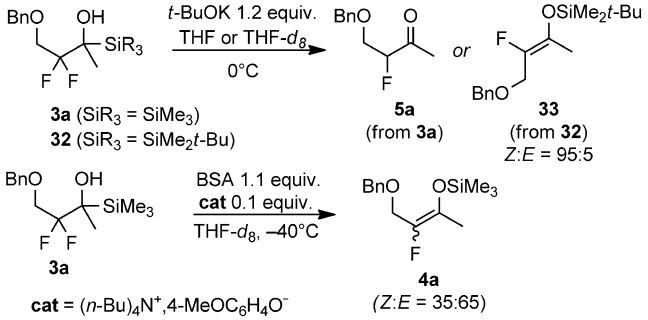


Figure 1. Transition states for the aldol reactions.

should proceed through an open transition state (Figure 1).

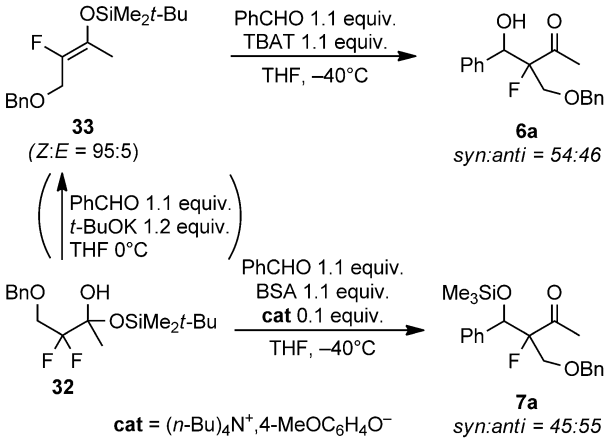
Our first task was thus to assess the *E*/*Z* ratio of the intermediate silyl enol ethers for both reactions. Unfortunately, the reaction of **3a** with *t*-BuOK in the absence of aldehyde did not allow us to isolate **4a**. Only ketone **5a** could be observed, even by direct NMR analysis of the reaction medium when the reaction was performed in THF-d_8 (Scheme 8). We thus



Scheme 8. Investigations on the intermediate silyl enol ethers.

moved to the more stable TBDMS derivative and **33** was eventually detected after the reaction of **32** with *t*-BuOK, and isolated as a 95:5 mixture of isomers (Scheme 8).[21] NOESY and HOESY experiments showed that the *Z* isomer (^{19}F NMR, $\delta = -137.6$ ppm) was the major one (^{19}F NMR, $\delta = -151.8$ ppm for the *E* isomer).[22] Regarding the ammonium aryloxide-catalyzed reaction, the presence of highly reactive trimethylsilylating agent BSA allows the observation of **4a** in the reaction mixture, as the sole product and as a 35:65 mixture of isomers (Scheme 8). Although **4a** was still too labile to perform conclusive NOESY experiments, the ^{19}F NMR chemical shifts of the two isomers of **4a** were almost identical to that of **33** (−138.6 ppm and −152.1 ppm for **4a**). Based on this analogy, the *E* configuration was assigned to the major isomer of **4a**.

Drawing conclusions on the diastereoselectivity of each reaction from these results is, at best, speculative. The *syn* selectivity of the *t*-BuOK-mediated BEAR sequence and the *Z*-selectivity observed in the generation of the TBS enol ether **32** are consistent with a closed transtion state. In contrast, the weak *anti*-selectivity of the catalyzed reaction probably arises from a poorly selective open transition state, a model that is more credible in this situation, and should not depend on the configuration of the enoxysilane. The results obtained in the reaction of *Z*-**33** with benzaldehyde in the presence of TBAT supports this hypothesis since aldol **6a** was this time obtained with almost no selectivity (Scheme 9). As expected, the ammonium aryloxide-catalyzed BEAR sequence starting from **32** produced aldol **7a** in a 40:60 *syn*:*anti* ratio, almost the same as from **3a** (Scheme 9). Finally, it should be mentioned that the reaction **32** with *t*-BuOK in the presence benzaldehyde afforded only enol ether **33**, with no traces of **6a**.



Scheme 9. Control experiments.

In conclusion, we have reported a methodology allowing the preparation of unprecedented aldols featuring a fluorinated tetrasubstituted stereogenic center. The corresponding fluoroenolates are formed *in situ* from stable β,β-difluoro-α-(trimethylsilyl)alcohols, through a base-mediated Brook rearrangement/elimination sequence and then added to aromatic aldehydes *via* a fluoride-mediated aldol reaction. Two sets of conditions were disclosed for this original one-pot BEAR sequence that avoids the isolation of poorly stable fluorinated enoxysilanes. The first one involves the stoichiometric addition of *t*-BuOK at 0 °C, which yielded aldols in fair yield and diastereoselectivity. A catalytic process was next devised using an ammonium phenoxide as catalyst and BSA as a silylating agent and relay base. Although the latter conditions open the way for an asymmetric version, some improvement must be brought to the reaction, especially to its diastereoselectivity, to obtain a synthetically useful enantioselective methodology. Results in this area will be reported in due course.

Experimental Section

General Procedure for the *t*-BuOK-Mediated BEAR Sequence

Under an argon atmosphere, *t*-BuOK (0.36 mmol, 1.2 equiv.) was added to a solution of α-trimethylsilylcarbinol **3** (0.3 mmol, 1 equiv.) and aldehyde (0.33 mmol, 1.1 equiv.) in dry THF (2 mL) at 0 °C. The solution was stirred at this temperature for 3 h and a saturated solution of NH_4Cl was then added. The aqueous layer was extracted with Et_2O and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was then diluted in THF (2 mL) and a 10% aqueous HCl solution (5 mL) was added. The solution was stirred for 1 h and neutralized with a saturated aqueous $NaHCO_3$ solution. 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 (80:20 petroleum ether/diethyl ether) to afford the expected fluorinated aldol as an inseparable mixture of *syn* and *anti* diasteromers.

Acknowledgements

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