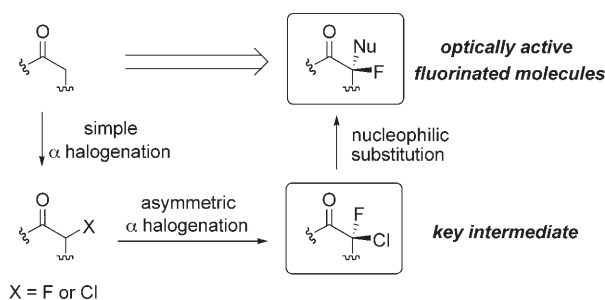


Stereoselective Synthesis of α,α -Chlorofluoro Carbonyl Compounds Leading to the Construction of Fluorinated Chiral Quaternary Carbon Centers**

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The preparation of fluorine-containing organic molecules has attracted considerable attention in the field of pharmaceutical and agricultural chemistry.^[1] One of the most challenging synthetic operations used to access these molecules is the stereoselective construction of a fluorinated chiral carbon center.^[2] Various stereoselective electrophilic fluorination reagents have been developed for this purpose.^[3] Following a study by Hintermann and Togni,^[4a] efficient catalytic asymmetric fluorination reactions of β -ketoesters have been reported.^[4b,e] Organocatalytic enantioselective α -fluorination reactions of aldehydes have also been successfully realized.^[5] Although the field of asymmetric α -fluorination is progressing steadily, a flexible route for the stereoselective construction of fluorinated quaternary carbon centers is still required. We propose the synthesis of optically active α,α -chlorofluoro carbonyl compounds, which can be stereoselectively converted into various chiral molecules with a fluorinated quaternary carbon by nucleophilic substitution (Scheme 1). Surprisingly little attention has been given to the synthesis of optically active α,α -chlorofluoro carbonyl compounds^[6] or their selective transformation.^[7] Herein, we disclose the first enantioselective synthesis of α,α -chlorofluoro carbonyl compounds from simple aldehydes or ketones, and their subsequent transformation into a variety of optically active molecules in which the fluorinated quaternary carbon center is adjacent to the carbonyl group.

Our initial studies focused on the organocatalytic asymmetric synthesis of α,α -chlorofluoro aldehydes. According to our synthetic plan (Scheme 1), simple α fluorination or chlorination of carbonyl compounds would be followed by



Scheme 1. Methodology for the selective construction of fluorinated chiral quaternary carbon centers. Nu = nucleophile.

asymmetric α halogenation, which introduces another halogen substituent (Cl or F), and would provide optically active α,α -chlorofluoro carbonyl compounds. We chose α -chloroaldehydes **1** as precursors because they can be easily synthesized from simple aldehydes.^[8] As summarized in Table 1, various α,α -chlorofluoro aldehydes **3** were successfully synthesized with high enantioselectivity (e.r. values ranging from 91:9 to > 99:1) from racemic α -chloroaldehydes (*rac*-**1**) and *N*-fluorosuccinimide (NFSI) in the presence of organocatalyst **2**, which was developed by Jørgensen et al.^[5b] A lower reaction temperature slightly increased the enantioselectivity of the reaction (Table 1, compare entries 1 and 3 to entries 2 and 4). Although the fluorination of sterically hindered aldehyde required higher temperature (25 °C), the product **4d** was obtained in high yield and with an excellent enantioselectivity (e.r. > 99:1; Table 1, entry 6).

Next, the enantioenriched α,α -chlorofluoro aldehydes **3** were successfully transformed into unsymmetrical α,α -chlorofluoro ketones. Thus, in situ treatment of **3a** or **3b** with a Grignard reagent followed by oxidation using the Dess–Martin reagent afforded the corresponding α,α -chlorofluoro ketones **5** and **6**, respectively, without loss of optical purity (Scheme 2); this result clearly expands the range of accessible α,α -chlorofluoro carbonyl compounds.

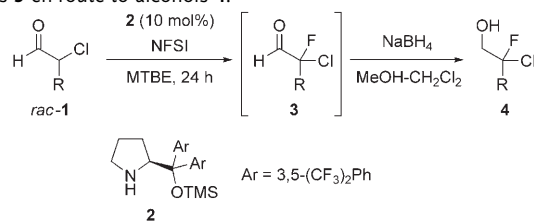
After using organocatalysis for the successful synthesis of enantioenriched α,α -chlorofluoro carbonyl compounds, we turned our attention to the direct synthesis of α,α -chlorofluoro ketones from α -unsubstituted ketones. There are few reports on the enantioselective α halogenation of simple ketones.^[9,10] We have previously reported the asymmetric chlorination of silyl enolates, which is mediated by zirconium(IV) chloride and chiral α,α -dichloromalonate,^[9] and presently this may be the best system for the asymmetric α halogenation of highly substituted ketones. We initially synthesized racemic α,α -chlorofluoro-1-tetralone (**8**) by the

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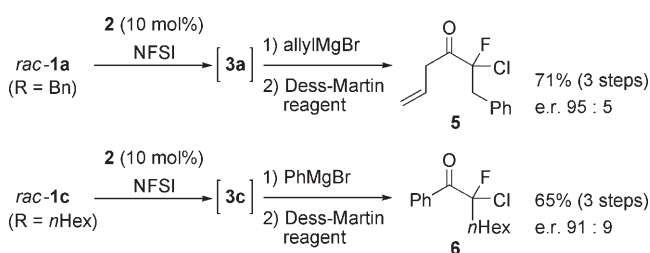
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Table 1: Organocatalytic asymmetric synthesis of α,α -chlorofluoro aldehydes **3** en route to alcohols **4**.^[a]



Entry	Product	T [°C]	Yield [%] ^[b]	e.r. ^[c]
1 ^[d]		25	88	94:6
2		0	85	96:4
3 ^[d]		25	75	94:6
4		0	62	96:4
5		0	81	91:9
6 ^[e]		25	86 ^[f]	> 99:1 ^[f]
7		0	< 5 ^[g]	n.d. ^[h]

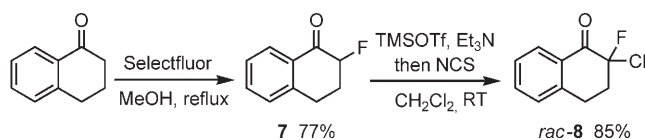
[a] All reactions were carried out using 3 equivalents of racemic α -chloroaldehyde (*rac*-1) and 10 mol% of catalyst **2** with respect to NFSI in MTBE (methyl *tert*-butyl ether; 0.25 M) unless otherwise noted. [b] Yields of isolated product **4**. [c] Enantiomeric ratios of alcohols **4** were determined by HPLC on a chiral stationary phase or by GC analysis. [d] Reaction time was 12 h. [e] Reaction time was 30 h with 30 mol% of **2**. [f] Yield of the isolated product and enantiomeric ratio were determined after conversion of the product into the 3,5-dinitrobenzoate owing to the volatility of **4d**. [g] Determined by ¹H NMR spectroscopy of the crude product. [h] n.d. = not determined.



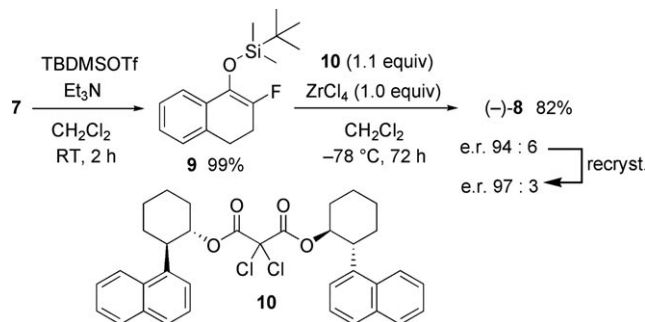
Scheme 2. Asymmetric synthesis of α,α -chlorofluoro ketones by using organocatalysis. Bn = benzyl, *n*Hex = *n*-hexyl.

electrophilic chlorination of a fluorinated silyl enolate.^[11] Fortunately, **8** could also be obtained from α -fluoro-1-tetralone (**7**)^[12] by treatment with *N*-chlorosuccinimide (NCS) following the formation of silyl enolate in situ (Scheme 3). Notably, **8** was stable when left at room temperature for one month.

Following the racemic synthesis of **8**, we then proceeded with its enantioselective preparation using chiral α,α -dichloromalonate by using a method developed earlier.^[9] The best result was obtained by the reaction of *tert*-butyldimethylsilyl enolate (**9**) with chiral α,α -dichloromalonate (**10**) to give (–)-**8** in 82% yield with an e.r. of 94:6 (Scheme 4). A single recrystallization from *n*-hexane/2-propanol (9:1) gave crystals of (–)-**8** in 65% yield with a lower enantiopurity, while the mother liquor had an e.r. of 97:3.

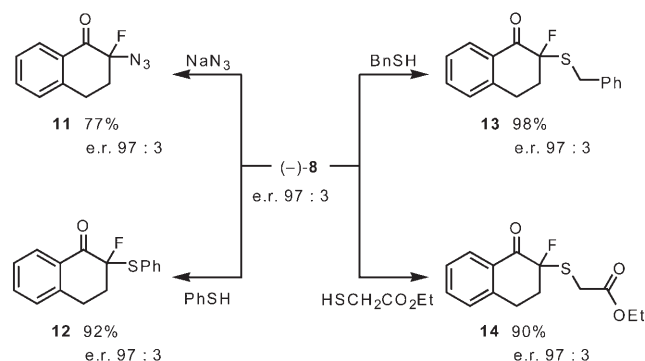


Scheme 3. Racemic synthesis of α,α -chlorofluoro-1-tetralone (**8**). NCS = *N*-chlorosuccinimide, Selectfluor = 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bistetrafluoroborate, TMS = trimethylsilyl.



Scheme 4. Asymmetric synthesis of (–)-**8**. TBDMS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl.

With a successful asymmetric synthesis of α,α -chlorofluoro carbonyl compounds in hand, we tried the nucleophilic substitution reaction of (–)-**8**. Sodium azide or thiols worked very well as nucleophiles to afford the corresponding substituted products **11**–**14** in high yields (Scheme 5). Notably, the reactions proceeded without loss of optical purity. This means that the reactions proceed in a rigorous S_N2 fashion.



Scheme 5. S_N2 reactions of (–)-**8**.

In summary, we have described the enantioselective synthesis of α,α -chlorofluoro aldehydes and ketones from simple carbonyl compounds. These compounds can be converted into various optically active molecules having fluorinated chiral quaternary carbon centers by using nucleophilic substitution. We believe that the present methodology allows access to a new class of fluorinated chiral organic molecules.

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