Enantioselective Fluorination

Direct Asymmetric α-Fluorination of Aldehydes**

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Organic molecules containing fluorine have attracted much attention because they show distinctive characteristics in comparison with their parent compounds owing to the unique C–F bond.[1] Substitution of hydrogen by fluorine is often considered isosteric and the high C–F bond strength generally protects fluorine from metabolic transformations. In addition, as fluorine has the ability to function as a hydrogen bond acceptor, fluorine-substituted bioactive compounds are useful analogues and probes of hydrogen bonding characteristics. The selective formation of carbon-fluorine bonds under mild conditions is thus a highly desirable methodology, especially in medicinal chemistry.[2] Previous approaches toward asymmetric fluorination relied on stoichiometric amounts of chiral fluorinating reagents[3] or chiral auxiliaries.[4] More recently, the catalytic asymmetric fluorination of β-keto esters with titanium and palladium as Lewis acids was reported.[5]

α-Fluoro aldehydes have been characterized as unstable compounds that generally decompose upon purification. As a result, their syntheses have been very limited. Synthesis of α-fluoro aldehydes was first reported by Middleton and Bingham, who treated silyl enol ethers with trifluoromethyl hypofluorite (CF_3OF).[6] Subsequently, enolate methodologies that use commercially available electrophilic fluorinating reagents such as NFSi (*N*-fluorobenzenesulfonamide; **5**) and Selectfluor (F-TEDA-BF_4 or 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate); **3**) have

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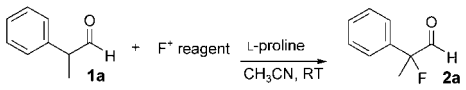
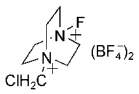
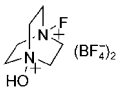
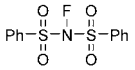
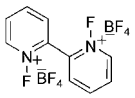
been employed to produce α-fluoro carbonyls.[7] Although there is an extensive body of research on the α-fluorination of carbonyls, there are no examples of direct asymmetric fluorinations of aldehydes. Herein, we report the first examples of direct α-fluorinations with asymmetric induction.

Proline and its analogues have been found to be excellent catalysts in asymmetric aldol,[8] Mannich,[9] and α-chlorination[10] reactions of carbonyls. Our early work in fluorine chemistry focused on the use of α-fluoro carbonyl compounds as nucleophiles in reactions catalyzed by enzymes,[11] catalytic antibodies,[12] and organocatalysts[13] in asymmetric aldol reactions and, in one case, the Mannich reaction.[14] The asymmetric α-fluorination of aldehydes is based on the same principles of organocatalysis that we used in our first Michael, aldol, and Mannich catalytic asymmetric aldehyde addition reactions.[15]Initial screening of electrophilic fluorinating reagents was done with L-proline and 2-phenylpropionaldehyde (**1a**) in acetonitrile at room temperature (Table 1).

Table 1: Comparison of N–F reagents for direct α-fluorination of aldehydes.[a]



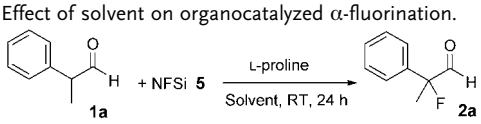
Entry	N–F Reagent		*t*	Yield [%][b]	*ee* [%][c]
1		**3**	24 h	87	4
2		**4**	24 h	90	0
3		**5**	24 h	87	25
4		**6**	5 d	NR	–
5		**7**	5 d	7	12

[a] N–F reagent (1.2 equiv) was added to a mixture of aldehyde and catalyst at ambient temperature. [b] All isolated yields determined after aqueous workup. [c] Enantiomeric excess determined by chiral GLC analysis (Bodman γ-TA).

2-Phenylpropionaldehyde was chosen for screening because of its excellent reactivity and because the product is unable to racemize, as it has no proton alpha to the aldehyde. It was found that NFSi (**5**) was the only fluorinating reagent to provide any enantioselectivity in a reasonable time period. Commercially available fluorinating reagents Selectfluor (**3**) and Accufluor (**4**) were employed, but afforded 4 and 0% *ee* respectively. The pyridinium fluoride reagents **6** and **7** were minimally reactive, and thus gave very low yields. Therefore, NFSi (**5**) was used for subsequent reactions.

Following this selection of an electrophilic fluorinating reagent, a solvent screen was undertaken. Acetonitrile is a standard reaction solvent used in electrophilic fluorination. Acetonitrile (Table 2, entry 1, 87% conversion, 25% *ee*) was adequate, but tetrahydrofuran, dimethylformamide (DMF), 1,4-dioxane, and methanol all provided the product in higher yield. Interestingly, THF afforded both the best selectivity and highest chemical yield (Table 2, entry 4, 94% conversion, 28% *ee*). DMSO has a mildly exothermic reaction with NFSi, possibly explaining the poor aldehyde fluorination in this medium.

Table 2: Effect of solvent on organocatalyzed α-fluorination.



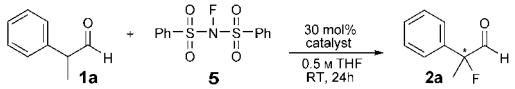
Entry	Solvent	Conversion [%][a]	*ee* [%][b]
1	CH_3CN	87	25
2	DMF	92	20
3	DMSO	30	22
4	THF	94	28
5	1,4-dioxane	93	25
6	CH_2Cl_2	32	18
7	NMP[c]	87	19
8	Et_2O	10	20
9	toluene	9	15
10	MeOH	93	5
11	EtOH	76	15
12	C_6H_{14}	8	17
13	H_2O	NR	NR
14	[bmim]PF_6[d]	39	26
15	[bmim]BF_4[d]	56	19

[a] Conversion measured by ^{1}H NMR spectroscopy of the crude reaction mixture and correlated to GC, owing to high volatility of products. [b] Enantiomeric excess determined by chiral GLC analysis (Bodman γ-TA). [c] NMP = *N*-methylpyrrolidinone. [d] BMIM = 1-butyl-3-methylimidizolium.

It is important to note that α-fluorinated aldehydes are generally not stable under column purification or distillation conditions, and that the addition of an α-fluorine significantly increases the volatility relative to that of the starting aldehyde.[16] These characteristics of α-fluorinated aldehydes make them difficult substrates to manipulate. To optimize the fluorination reaction with branched aldehydes, **1a** was subjected to a catalyst screen with NFSi as the electrophilic fluorinating reagent and THF as a standard solvent (Table 3). The silylated L-prolinol derivative **9c**, with the sterically demanding triisopropylsilyl (TIPS) group, provided the highest enantioselectivity (44% *ee*, 90% yield), although the reaction yield was much improved with the proline-derived tetrazole catalyst **11** (38% *ee*, 98% yield).

We next examined the organocatalytic asymmetric fluorination of straight-chain aldehydes. These aldehydes are prone to self-react under organocatalysis to yield self-aldol products. Decyl aldehyde (**1b**), which is slow to form the self-aldol product and which has a high boiling point, was chosen as a general aldehyde for reaction optimization (Table 4). The initial fluorination reactions of decyl aldehyde were monitored by ^{1}H NMR and ^{19}F NMR spectroscopy in $CDCl_3$, CD_3CN and [D_7]DMF. All reactions reached completion after approximately 30 minutes. Also, after initial α-fluoro decyl

Table 3: Screening of catalysts for direct enantioselective α-fluorination of 2-phenylpropionaldehyde.

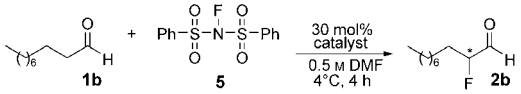


1a + **5** → **2a**

Entry	Catalyst	Yield [%][a]	*ee* [%][b]
1	**8a** R = OH	94	28
	8b R = O*t*Bu	90[c]	13
	8c R = morpholine	63	8
	8d R = OBn	75	28
2	**9a** R = H	70	24
	9b R = Me	83	24
	9c R = TIPS	90	44
3	**10a** R^1,R^2 = H	99	12
	10b R^1 = H, R^2 = *n*Bu	30	12
	10c R^1,R^2 = pyrrolidine	84	12
	10d R^1,R^2 = pyrrolidine, TFA	85	16
	10e R^1,R^2 = morpholine	66	16
	10f R^1 = H, R^2 = Ph	88	0
4	**11**	98	38
5	**12a** R = H	70	0
	12c R = CH_3	75	28
6	**13a** R = OH	93	22
	13b R = O*t*Bu	65	27
7	**14a**	77	16
8	**15**	34[c]	24
9	**16a** R = CH_3	19[c]	18
	16b R = CH_2OCH_3	42[c]	14
10	pyrrolidine	84	0
11	no catalyst	0[c]	0

[a] Yield measured by ^{1}H NMR spectroscopy of the crude reaction mixture and correlated to GC, owing to high volatility of products. [b] Enantiomeric excess determined by chiral GLC analysis (Bodman γ-TA). [c] Reactions continued for 48 h before workup and analysis.

Table 4: Catalyst screening for direct enantioselective α-fluorination of linear aldehydes.



1b + **5** → **2b**

Entry	Catalyst	Conversion [%][a]	*ee* [%][b]
1	**8a** R = OH	29	29
	8e R = NH_2	50	22
2	**9b** R = Me	30	32
	9c R = TIPS	30	37
3	**11**	32	30
4	**13b** R = CH_3	trace	–
5	**14a** R^1 = H, R^2 = *t*Bu	65	76
	14b R^1,R^2 = CH_3	30	88
6	**15**	9	50
7	**16b** R = CH_2OCH_3	21	46[c]
8	pyrrolidine	71[d]	0
9	no catalyst	0	0

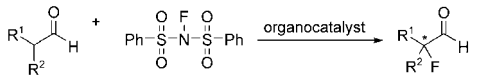
[a] Yield measured by ^{1}H NMR spectroscopy of the crude reaction mixture and correlated to GC, owing to high volatility of products. [b] Enantiomeric excess determined by chiral GLC analysis (Bodman γ-TA). [c] Opposite enantiomer from that obtained with other catalysts. [d] Stoichiometric amount of pyrrolidine.

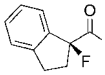
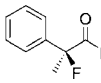
aldehyde formation (^{19}F NMR (CD_3CN): $\delta = -200.2$ ppm) the $CDCl_3$ and CD_3CN reactions showed steady formation of α,α-difluoro product (^{19}F NMR (CD_3CN): $\delta = -115.2$ ppm).[17] Subsequent reactions with THF also gave the α,α-difluoro product. Therefore, DMF, which inhibited formation of the α,α-difluoro product, was employed throughout the catalyst screening with linear aldehydes.

Interestingly, imidazolidinone catalysts **14a** and **14b** (Table 4, entry 5) provided the desired product with the highest enantioselectivities. Catalyst **14a** was used in a sub-stoichiometric amount, yet in repeated reactions would not progress beyond 65% completion. The highest optical purity was obtained with catalyst **14b** (30% conversion, 88% *ee*). Use of the hydrochloric, trifluoroacetic or 5-methyltetrazole salts of **14a** and **14b** resulted in diminished enantioselectivity and no enhancement in turnover. Lowering the reaction temperature to −20°C inhibited the reactivity greatly, without increasing the enantioselectivity. Conversely, raising the temperature to room temperature resulted in an increased formation of side products, presumably self-aldol products.

To determine the scope of the reaction, we subjected a series of aldehydes to the optimized conditions (Table 5). Generally, **14b** catalyzed the direct asymmetric α-fluorination of linear aldehydes with good to excellent yields (Table 5, entries 1–6) and with enantioselectivities ranging from 86% for 2-fluoro-1-octanal (**2e**) (Table 5, entry 4) to 96% for 2-fluoro-isovaleraldehyde (**2c**) (Table 5, entry 1). Linear aldehydes were transformed with the highest enantioselectivity when reacted with equimolar imidazolidinone **14b** as a chiral promoter at 4°C in DMF. The absolute stereochemistry was confirmed for several compounds: **2e** was reduced to 2-fluoro-1-octanol with sodium borohydride,[18] 2-fluoro-2-phenylpropionaldehyde (**2a**) was oxidized to the corresponding carboxylic acid,[19] and (*S*)-(−)-2-fluoro-isovaleraldehyde (**2c**) is known in the literature.[20] In each case, the optical rotation of the compounds prepared compared favorably with the literature values reported. These results are all consistent with the assignment of an *S* configuration to the fluorinated aldehydes and are in agreement with a *Si*-face approach of the electrophile. The *Re* face of the enamine is shielded by the sterically demanding benzyl and 2,2-dimethyl substituents of

Table 5: Direct organocatalytic enantioselective α-fluorination of aldehydes.[a]



Entry	Aldehyde		Catalyst	*t* [h]	Yield [%][b]	*ee* [%][c]
1		**2c**	**14b**	2	74[d]	96
2		**2b**	**14b**	3	90	88
3		**2d**	**14b**	3	59	93
4		**2e**	**14b**	3	94	86
5		**2f**	**14b**	3	40[d]	92
6		**2g**	**14b**	2	97	88
7		**2h**	**9c**	6	98	66
			11	2	98	55
			8a	24	93	44
8		**2a**	**9c**	6	92	40
			11	2	99	45
			8a	24	93	28

[a] Reaction conditions for linear aldehydes (entries 1–6): 4 °C in DMF with stoichiometric amounts of chiral promoter **14b**; branched aldehydes (entries 7 and 8): room temperature in THF with 30 mol% catalyst. [b] Yield measured by ^{1}H NMR spectroscopy of the crude reaction mixture and correlated to GC, owing to high volatility of products. [c] Enantiomeric excess determined by chiral GLC analysis (Bodman γ-TA). [d] Yield and enantiomeric excess determined by chiral HPLC of the corresponding hydrazone derivative with Daicel CHIRALCEL OD-R.

the catalysts. Similar models have been proposed with sterically demanding enamine catalysts.[21]

Our methodology was extended to branched aldehydes **2h** and **2a** (Table 5, entries 7 and 8) to show the broad scope of this reaction. With L-proline (**8a**), silylated prolinol derivative **9c**, and proline-derived tetrazole **11** as catalysts for the formation of chiral quaternary α-fluoro aldehydes, excellent yields of up to 98% were attained, albeit with moderate enantioselectivities of up to 66%. Reactions of branched aldehydes were carried out at room temperature in THF with 30 mol% catalyst. The reaction rate was greatly enhanced when **11** was used with branched aldehyde substrates, although **9c** provided products with higher enantioselectivity. Catalyst **8a** gave excellent yields, but had diminished enantioselectivity and slow reaction times.

In summary, we have developed an organocatalytic α-fluorination reaction for branched aldehydes that delivers optically active quaternary α-fluoroaldehydes in high yield and with moderate enantioselectivity. In conjunction, we have developed a highly enantioselective direct mono α-fluorination reaction of linear aldehydes employing imidazolidinones as chiral promoters. The chiral α-fluoroaldehydes that can now be readily prepared are versatile synthons and should find considerable utility. This new methodology complements our previous studies in fluorine chemistry that used fluorine-containing ketones as nucleophiles in enamine-based addition reactions, and extends the chemistry of aldehydes in a significant way.[22]

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[22] Note added in proof (April 26, 2005): Since our submission of this study, Enders and Hüttl reported results concerning L-proline/Selectfluor transformations related to our results (Table 1, entry 1); see: D. Enders, M. R. M. Hüttl, *Synlett* **2005**, 991 – 993.

