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Highly Efficient Diastereoselective Reduction of α-Fluoroimines

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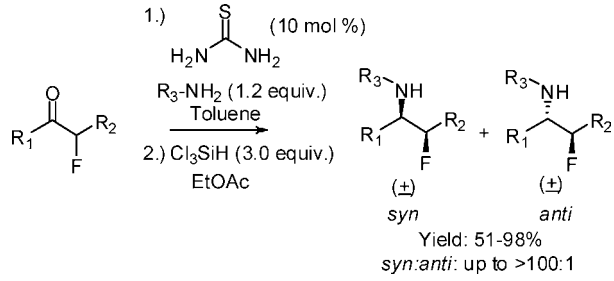
ABSTRACT



A highly selective reduction of α-fluoroimines to the corresponding *β*-fluoroamines has been developed utilizing trichlorosilane as the reductant. The key aspect of this reaction is the ability of fluorine and nitrogen to activate organosilanes leading to high diastereoselectivity (>100:1) in the product distribution. This new method provides a new avenue for the diastereoselective synthesis of *β*-fluorinated amines in good yields and selectivity.

Interest in fluorinated drug candidates has increased dramatically over the past two decades. The introduction of fluorine to a molecule can have a profound influence on its biological activity altering properties including acidity, metabolic stability, and binding affinity.[1] Although many fluorinated drug candidates have emerged with approximately 150 candidates in phase II and III clinical trials, methods for their preparation are still lacking.[2] Current methods for the introduction of fluorine generally rely on nucleophilic (DAST) or electrophilic fluorinating agents (Selectfluor or Accufluor).[3] Additionally, Jorgenson and MacMillan recently reported the asymmetric synthesis of α-fluoroalcohols utilizing organocatalysts based on proline and imidazolidinone.[4,5] Lindsley expanded on this methodology by utilizing MacMillan's imidazolidinone catalyst for the asymmetric synthesis of *β*-fluoroamines.[6] Although such methods are beginning to emerge for the stereoselective introduction of fluorine, methods for the derivitization of these substrates remain limited.[7] Motivated by the current interest in fluorinated drug candidates and the lack of synthetic methodology, we initiated an investigation into the diastereoselective reduction of α-fluoroimines to the corresponding *β*-fluoroamine in high yield and stereoselectivity. Our approach was to utilize Lewis acid/base activation to mimic chelation control, thus enhancing selectivity in the product distribution.[8,9] Denmark and co-workers have pioneered the area of Lewis base catalysis utilizing organosilanes and a variety of catalysts.[10] Our hypothesis in using Lewis acid/base activa-

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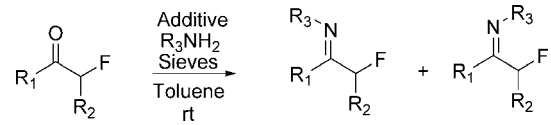
Table 1. Effect of Molecular Additives on Rate of Imine Formation



entry	α-fluoroketone	amine	additive	reaction time (h)	conversion[a] (%)
1	α-fluorocyclohexanone	*p*-anisidine	no additive	24	100
2	α-fluorocyclohexanone	*p*-anisidine	Amberlyst-15	24	100
3	α-fluorocyclohexanone	*p*-anisidine	thiourea (10 mol %)	4	100
4	α-fluoroindanone	benzylamine	no additive	48	50
5	α-fluoroindanone	benzylamine	Amberlyst-15	15	85
6	α-fluoroindanone	benzylamine	thiourea (10 mol %)	12	100

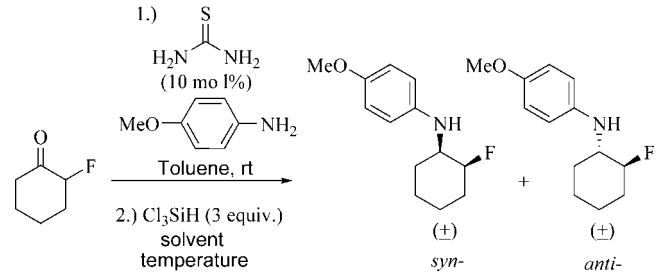
[a] Imine conversion was determined by both GC and ^{19}F NMR.

tion was based on the strong affinity of fluorine and nitrogen for silicon, forming an ordered transition state, leading to high diastereoselectivity in the product distribution.[11] Our method design was to use α-fluoroimine substrates (Lewis base) to activate trichlorosilane (Cl_3SiH) (Lewis acid), increasing its potency as a reductant, and allowing the production of *β*-fluoroamines in high yield and stereoselectivity.[12]

Our initial approach was to perform this reaction in a sequential method without the purification of the intermediate imine, as α-fluoroimines are generally difficult to purify due to their decomposition upon heating or standard flash chromatography. In designing our method, an attempt to accelerate the imine formation was required. We investigated a variety of molecular additives and found that a catalytic amount of thiourea (10 mol %) in toluene greatly decreased the reaction time for the formation of the α-fluoroimine (Table 1).[13,14] In the case of α-fluorocyclohexanone and *p*-anisidine, the reaction time decreased from 24 to 4 h upon the addition of thiourea (Table 1, entry 3).

With an efficient method for the preparation of the imines in hand, we began to investigate the reaction parameters (solvent and temperature) for the diastereoselective reduction of the imine derived from α-fluorocyclohexanone and *p*-anisidine utilizing Cl_3SiH. These studies showed that THF and EtOAc provided the best diastereoselectivity (17:1 *syn*:*anti*) in the reduction of the model imine at 0 °C (Table 2, entries 3 and 7).[15] EtOAc was chosen as the optimal solvent due to its advantageous properties to industrial scale synthesis in comparison to THF, as well as the modest increase in product yield (57% to 73%). Next, we examined the effect of temperature on the selectivity and yield utilizing EtOAc

Table 2. Reaction Optimization for the Reduction of α-Fluoroimines[a,b]



entry	solvent	temp (°C)	yield (%)	*syn*:*anti*
1	CH_2Cl_2	0	80	6:1
2	CH_3CN	0	77	11:1
3	THF	0	57	17:1
4	toluene	0	82	4:1
5[c]	acetone	0	0	N/A
6[c]	DMSO	0	0	N/A
7	EtOAc	0	73	17:1
8	EtOAc	−10	81	20:1
9	EtOAc	−78	80	24:1

[a] All reductions were performed on a 0.3 mmol scale. [b] All reactions were initiated at the indicated temperature, allowed to slowly warm to room temperature, and then stirred for 12 h. [c] Starting α-fluoroketone was recovered.

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(12) For reductions of imines utilizing Cl_3SiH see: (a) Zhou, L.; Wang, Z.; Wei, S.; Sun J. *J. Chem. Soc., Chem. Commun.* **2007**, *28*, 2977–2979. (b) Blackwell, J. M.; Sonmor, E. R.; Scoccitti, T.; Piers, W. R. *Org. Lett.* **2000**, *2*, 3921–3923. (c) Onomura, O.; Kouchi, Y.; Iwasaki, F.; Matsumura, Y. *Tetrahedron Lett.* **2006**, *47*, 3751–3754. (d) Guizzetti, S.; Benaglia, M.; Rossi, S. *Org. Lett.* **2009**, *11*, 2928–2931. (e) Wang, C.; Wu, Z.; Zhou, L.; Sun, T. *Chem.—Eur. J.* **2008**, *29*, 8789–8792. (f) Zheng, H.; Deng, J.; Lin, W.; Zhang, X. *Tetrahedron Lett.* **2007**, *45*, 7934–7937. (g) Wang, Z.; Ye, X.; Wei, S.; Zhang, A.; Sun, J. *Org. Lett.* **2006**, *8*, 999–1001. (h) Malkov, A. V.; Stewart Liddon, A. J. P.; Ramirez-Lopex, P.; Bendova, L.; Haigh, D.; Kocovsky, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 1432–1435. (i) Giuzzetti, S.; Benaglia, M.; Rossi, S. *Org. Lett.* **2009**, *11*, 2928–2931. (j) Malkov, A. V.; Figlus, M.; Kocovsky, P. *J. Org. Chem.* **2008**, *73*, 3985–3995. (k) Malkov, A. V.; Figlus, M.; Stoncius, S.; Kocovsky, P. *J. Org. Chem.* **2007**, *72*, 1315–1325. (l) Malkov, A. V.; Vrankova, K.; Stoncius, S.; Kocovsky, P. *J. Org. Chem.* **2009**, *74*, 5839–5849.

Table 3. Examining the Substrate Scope for the Diastereselective Reduction of α-Fluoroimines

entry	α-fluoroketone	amine	imine conversion[a] (%)	yield[b] (%)	*syn*:*anti*[c]
1	α-fluorocyclohexanone	*p*-anisidine	100	78	24:1
2	α-fluorocyclohexanone	benzylamine	100	98	14:1
3	α-fluorocyclohexanone	cyclohexylamine	100	51	11:1
4	α-fluorocyclohexanone	hexylamine	100	68	12:1
5	α-fluorocyclohexanone	*p*-chloroaniline	0	ND	ND
6	α-fluorocyclohexanone	aniline	25	ND	ND
7	α-fluoroindanone	*p*-anisidine	100	88	>100:1
8	α-fluoroindanone	benzylamine	100	80	>100:1
9	α-fluoroindanone	hexylamine	100	57	78:1
10	α-fluoroindanone	*p*-chloroaniline	10	ND	ND
11	α-fluoropropiophenone	*p*-anisidine	75	51	19:1
12	α-fluoropropiophenone	benzylamine	91	68	5:1
13	α-fluoropropiophenone	hexylamine	100	51[d]	4:1

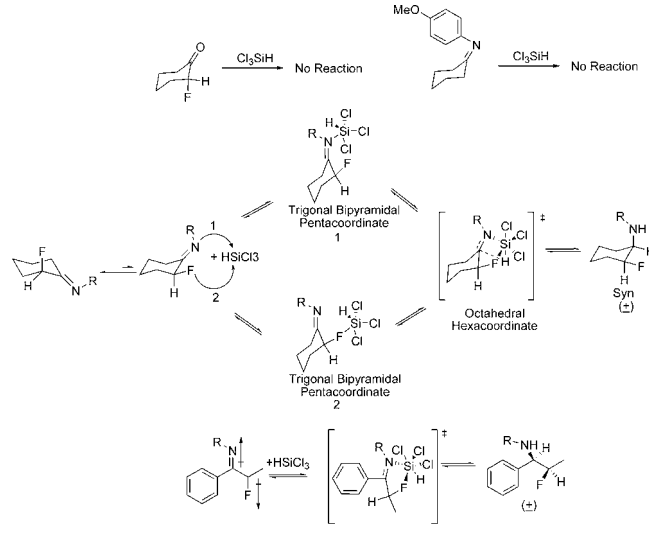
[a] Imine conversion was determined with GC. [b] Yield is based on purifed yield after chromatography. [c] Diastereoselectivity was determined by integration of the ^{19}F NMR and in select cases confirmed by GC. [d] Crude yield in 98% purity based on ^{1}H and ^{19}F NMR. Product decomposed upon attempted purification procedures.

as the solvent of choice. As the temperature was lowered from 0 to −78 °C, the diastereoselectivity increased from 17:1 to 24:1 *syn*:*anti* with comparable yields (Table 2, entries 7 and 9). On the basis of these results, optimal reaction conditions favored the reduction of α-fluoroimines in EtOAc at −78 °C.

The substrate scope of the reduction was then investigated. We discovered that the yield of the two-step process ((1) imine formation followed by (2) reduction of the imine) was highly dependent upon the formation of the imine. Electronic effects played an important role in the formation of the imine, as electron-poor, weakly nucleophilic amines led to minimal imine formation (Table 3, entries 5, 6, and 10). Due to the difficulty of forming these imines under these conditions, we focused our attention on amines with electron-donating substituents to foster complete conversion. The reaction proceeded well for a variety of amines, including acyclic (Table 3, entries 2, 4, 8, 9, 12, and 13), cyclic (Table 3, entry 3), aromatic (Table 3, entries 1, 7, and 11), as well as acyclic (Table 3 entries 11−13) and cyclic α-fluoroketones (Table 3, entries 1−10). Diastereoselectivities ranged from 4:1 to >100:1 *syn*:*anti*. These substrate studies showed that the reduction of α-fluoroimines proceeds in high yield and selectivity accommodating a variety of amines with the preparation of the subsequent α-fluoroimine being the limiting factor of the two-step process.

A preliminary mechanistic investigation of this reaction found that the absence of fluorine or nitrogen in the substrate was sufficient to prevent the reduction of the imine or α-fluoroketone (Scheme 1). As illustrated in Scheme 1, neither the imine derived from cyclohexanone and *p*-anisidine nor α-fluorocyclohexanone produced any of the desired reduction products upon the treatment with Cl_3SiH under the conditions described above. However, the reduction of the corresponding α-fluoroimines proceeds well in good yield and diastereoselectivity favoring the *syn*-diastereomer. On the basis of these results, it is imperative that the presence of the fluorine and nitrogen are both required for the reduction to occur.[16] Our proposed mechanism involves an initial activation of Cl_3SiH (Lewis acid) by fluorine or nitrogen (Lewis base), forming a pentacoordinate trigonal bypyramidal silicon.[17] Following the interaction of the fluorine or nitrogen with silicon, the reaction proceeds

Scheme 1. Preliminary Mechanistic Insights for the Reduction of α-Fluoroimines



(13) Thiourea derivatives have been utilized extensively as organocatalysts for the activation of ketones and imines. For a recent review see: Jacobsen, E. N.; Taylor, M. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520–1543.

(14) For thiourea activation see: (a) Menche, D.; Arikan, F. *Synlett* **2006**, *6*, 841–844. (b) Menche, D.; Hassfeld, J.; Menche, G.; Ritter, A.; Rudolph, S. *Org. Lett.* **2008**, *8*, 740–744.

(15) The *syn*/*anti* stereochemistry was determined by ^{19}F NMR and ^{1}H NMR. The ^{19}F NMR signal for the *syn* stereoisomer appears upfield in comparison to that of the *anti* stereoisomer. For examples of stereochemical assignment of *β*-fluoroamines see: (a) Fan, R.; Zhou, Y.; Zhang, W.; Hou, X.; Dai, L. *J. Org. Chem.* **2004**, *69*, 335–338. (b) Alvernhe, G. M.; Ennakoua, C. M.; Lacombe, S. M.; Laurent, A. J. *J. Org. Chem.* **1981**, *46*, 4938–4948. (c) Wade, T. N. *J. Org. Chem.* **1980**, *45*, 5328–5333. (d) Avernhe, G. M.; Lacombe, S. M.; Laurent, A. J. *Tetrahedron Lett.* **1980**, *21*, 289. (e) Toulgui, C.; Chaabouni, M. M.; Baklouti, A. *J. Fluorine Chem.* **1990**, *46*, 385–391.

through a highly ordered transition state featuring a five-member ring between the octahedral silicon, fluorine, and nitrogen atoms.[18,19] In this transition state, the donation of electron density from the fluorine and nitrogen to the silicon produces an electron-rich silicon, which is now primed to deliver a hydride to reduce the imine to the corresponding β-fluoroamine in high diastereoselectivity. The high *syn*:*anti* ratio is consistent with the transition state being under chelation control (Scheme 1). The role of chelation is supported by computational studies conducted by Paddon-Row involving nucleophilic addition to acyclic α-fluorinated aldehydes.[20] On the basis of these computational studies in the absence of metal chelation, the nitrogen and fluorine will be antiperiplanar due to electron repulsion of the lone pairs, and thus yield the *anti*-diastereomer.[20] Our results for the reduction of α-fluorinated imines (Scheme 1) display a preference for the *syn*- *dia*stereomer (Table 3, entries 1−13) as the major product further suggesting the role of chelation in the transition state leading to the observed *syn*-stereoselectivity.

(16) For examples of nitrogen and fluorine interaction with silicon see: (a) Nakash, M.; Gut, D.; Goldvaser, M. *Inorg. Chem.* **2005**, *44*, 1023–1030. (b) Yamamura, M.; Kano, N.; Kawashima, T.; Matsumoto, T.; Harada, J.; Ogawa, K. *J. Org. Chem.* **2008**, *73*, 8244–8249.

(17) For mechanistic insights in the Lewis acid/base activation for allylsilane additions see: (a) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2000**, *122*, 12021–12022. (b) Denmark, S. E.; Fu, J.; Coe, D. M.; Su, X.; Pratt, N. E.; Gridel, B. D. *J. Org. Chem.* **2006**, 1513–1522.

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We are currently conducting NMR studies to investigate the interaction of fluorine, ketones, and imines with a variety of organosilanes to begin to deduce the affinity of nitrogen and fluorine for silicon, and to monitor the coordination events around silicon. These results will be presented in due course.

In conclusion, we have developed a new methodology for the reduction of α-fluoroimines in high yield and diastereoselectivity. This new methodology is based on the activation of organosilanes by fluorinated substrates, which results in highly ordered transition states and enhanced reducing reactivity. This approach is especially applicable for industrial-scale synthesis because the reaction is sequential and eliminates the use of highly volatile ethereal solvents that are generally used in transition metal based chelation control synthesis.

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Supporting Information Available: Experimental procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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