Title: Lewis Base Catalyzed Trialkylsilylcyanide Additions to Cyclic 2-Fluoroketones: Nucleophile Directed Access to both *Cis*- and *Trans*- Stereoisomers

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Abstract:

An efficient method for the Lewis base-catalyzed addition of trialkylorganosilanes (TMSCN & TBSCN) to cyclic 2-fluoroketones has been developed producing the TMS- or TBS- protected cyanohydrins in good yield and diastereoselectivity. The Lewis base, solvent, and trialkylorganosilane have a dramatic effect on the reaction time and stereoselectivity for these reactions. TMSCN reacted the fastest using DIPEA as the Lewis base, and favored the *cis* product (up to 22:1), whereas methoxide-catalyzed reactions with TBSCN yielded the *trans* stereoisomer (up to 18:1).

Key Words: Fluorine, Lewis base catalysis, Stereoselective synthesis

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An efficient method for the Lewis base-catalyzed addition of trialkylorganosilanes (TMSCN & TBSCN) to cyclic 2-fluoroketones has been developed producing the TMS- or TBS- protected cyanohydrins in good yield and diastereoselectivity. The Lewis base, solvent, and trialkylorganosilane have a dramatic effect on the reaction time and stereoselectivity for these reactions. TMSCN reacted the fastest using DIPEA as the Lewis base, and favored the *cis* product (up to 22:1), whereas methoxide-catalyzed reactions with TBSCN yielded the *trans* stereoisomer (up to 18:1).

Introduction

Due to the unique properties of the carbon-fluorine bond, fluorinated organic molecules have recently seen increased interest in both the pharmaceutical and agrochemical industries.¹ The increased interest is ostensibly due to the unique properties that fluorine exhibits on biological systems (pKa, hydrogen bonding, lipophilicity, and conformation).^{1,2} Although there is increased demand, the carbon-fluorine bond is not prevalent in nature, and therefore synthetic methodologies must be used for the preparation of these moieties. In order to meet the demand for fluoroorganic molecules, a variety of elegant methods for the strategic substitution of hydrogen with fluorine have emerged.³ Of these recently developed methods, one of the most studied has been the α -fluorination of carbonyls (aldehydes, ketones, & imines).⁴ Although the alpha fluorination has been well studied, methodologies for the derivatization of 2-fluorinated carbonyls have only recently begun to emerge. In an effort to expand on these elegant methods, nucleophilic addition reactions to 2-halogenated (-F and -Cl) carbonyls have been recently developed.⁵ In particular, our laboratory has investigated

the addition of organosilane nucleophiles to 2-fluoroketones in good yield and selectivity.⁶ This letter focuses on our newly-developed Lewis base-catalyzed nucleophilic trialkylsilylcyanide (trimethylsilylcyanide (TMSCN) & *t*-butyldimethylsilylcyanide (TBSCN)) additions to 2-fluoroketones. It was discovered that not only does the Lewis base and solvent greatly enhance the rate of the reaction, but the nucleophile has a significant effect on stereochemical outcome.

Results and Discussion

Previously, we reported a method for the diastereoselective addition of TMSCN to cyclic 2-fluoroketones, producing TMS-protected cyanohydrins in good yields.^{6b} That work proposed that DMF (solvent) activated the organosilane, leading to the increased reactivity of TMSCN. Since this publication, we have begun to investigate both solvent and Lewis base catalysts on reaction time, yield, and diastereoselectivity. To examine the reactivity, reactions were monitored using ¹⁹F NMR. Initially, a variety of deuterated solvents were screened using DIPEA as the Lewis base. DIPEA was chosen as the Lewis base due to its solubility in a wide variety of organic solvents. In this work we show that the reactions proceeded the fastest in CD₃CN > CDCl₃ > C₆D₆ > THF-D₈.⁷ Next, the role of the Lewis base was examined by conducting the reactions in CD₃CN and monitoring reaction progress using ¹⁹F NMR. Based on the seminal work of Denmark and co-workers, a variety of fluoride, alkoxide, amine, and a phosphine Lewis base catalysts were screened.⁸ It was determined that amine and phosphine Lewis base catalysts reacted the fastest with 2-fluoroindanone (DIPEA = Et₃N = *n*-Bu₃P > CH₃O⁺Na > CsF > Ph₃P > DMF), leading to the TMS-protected cyanohydrin in less than ten minutes with minimal effect on the yield and stereoselectivity (Figure 1).⁹ This is a vast

improvement from our previous studies in which reaction times were as long as 96 h when DMF was used as the Lewis base/solvent. The strength of the Lewis catalyst matches observed reactivity match with the exception of Na^+OCH_3 . The reaction with Na^+OCH_3 did not proceed past 90% completion upon extended reaction times. Optimized reaction conditions for the TMSCN addition to 2-fluoroketones favored conducting the reactions in CH_3CN using amine or phosphorous based catalysts.

Figure 1: Effect of the Lewis base catalysis on TMSCN additions to 2-fluoroindanone.

Because of the general instability of alkyl phosphines (easily oxidized), DIPEA was chosen at the optimal Lewis base for substrate studies.

Subsequently, we investigated the role of nucleophile steric effects on the stereochemistry and reactivity of trialkylsilyl cyanide addition to 2-fluoroketones. It was our hypothesis that sterically-bulky trialkylorganosilanes would have a significant impact on the stereochemical outcome of the reaction. To investigate the role of sterics, *t*-butyldimethylsilylcyanide (TBSCN) was chosen as the nucleophile. Although TMSCN has been studied extensively in organic synthesis, less attention has focused on Lewis base mediated TBSCN nucleophilic additions.^{10,11} TBSCN is an attractive alternative to TMSCN, as it is more stable and less susceptible to hydrolysis. To our knowledge, the only mechanistic investigation on Lewis base catalyzed reactions involving sterically demanding organosilanes are recent studies by Zipse and Patschinski in which they examined the TBS- protection of alcohols using amine centered Lewis base catalysts.¹² Initially, the role of solvent on reaction time and selectivity was investigated using DIPEA as the Lewis base (Table 1, Entries 1-5). The reaction proceeds most rapidly using DMF as the solvent, however, a decrease in stereochemistry was observed (Table 1, Entry 3). The rate increase, using DMF as the solvent, correlates with Zipse and Patchinski's investigation of TBS- protection of secondary alcohols.^{12b} Using THF, toluene, and CHCl₃ (Table 1, Entries 1, 2, and 4) led to minimal conversion; however, the stereoselectivity did improve in comparison to DMF (1:8 to 1:3 *cis:trans*). As in the TMSCN studies, CH₃CN proved to be the optimal solvent as the reaction proceeded in 100% conversion and good selectivity in 19 h (Table 1, Entry 5). Next, we investigated the reactivity of TBSCN addition to 2-fluoroindanone in the presence of a variety of oxygen, nitrogen, phosphine, and fluoride centered Lewis base catalysts. The conversion

Table 1:

Reaction Optimization for TBSCN Addition to 2-Fluoroindanone

Entry	Lewis Base	Solvent	Time (h)	Conversion (%) ^a	<i>cis:trans</i> (2:3) ^b
1	DIPEA	THF	22	25	1:7
2	DIPEA	Toluene	24	0	ND
3	DIPEA	DMF	4	100	1:3
4	DIPEA	CHCl ₃	23	57	1:8
5	DIPEA	CH ₃ CN	19	100	1:8
6	NMI	CH ₃ CN	20	100	1:7
7	CsF	CH ₃ CN	23	ND	1:8
8	Et ₃ N	CH ₃ CN	24	100	1:7
9	<i>n</i> -Bu ₃ P	CH ₃ CN	2	100	1:7
10	Ph ₃ P	CH ₃ CN	20	41	1:8
11	<i>i</i> -Pr ₃ P	CH ₃ CN	69	93	1:7
12	CH₃O⁺Na	CH₃CN	1	100	1:9
13	^t BuO ⁺ Na	CH ₃ CN	1	100	1:8

^{a,b}% conversion and *cis:trans* ratios were determined using ¹⁹F NMR.

of starting material to the TBS- protected cyanohydrin was again monitored using ¹⁹F NMR in CD₃CN (Table 1, Entries 6-13). In contrast to TMS-CN additions, where amine and phosphine Lewis base catalysts are favored, alkoxides were optimal for the addition of TBSCN to 2-fluoroindanone (⁻OCH₃=⁻O^tBu > *n*-Bu₃P > DIPEA) (Table 1, Entries 6-13). Both sodium methoxide and sodium *t*-butoxide completely converted 2-fluoroindanone to the TBS-protected cyanohydrin in less than 1 h. This is a vast improvement as previously reported TBSCN addition reactions to ketones require extended reaction times. Fluoride (CsF) was also attempted as a potential Lewis base catalyst, but led to a complex reaction mixture and therefore was not further studied (Table 1, Entry 7). Interestingly, when the

steric bulk of the phosphine Lewis bases were increased (Table 1, Entries 10 & 11), the % conversion was low after extended reaction times although the same trend did not hold for the alkoxides (Table 1, Entries, 12 & 13). Catalyst reactivity matches well with both base strength and the bond dissociation of the Lewis base and silicon.¹³ Based on optimization studies, TBSCN additions were performed in CH₃CN using sodium methoxide (10 mol %).

Next, we investigated the substrate scope of the TBSCN additions to 2-fluoroketones (Table 2). Interestingly, increasing the steric bulk around the silicon center diastereoselectivities reaching 1:18 *cis/trans*. The implementation of electron donating groups led to low conversion due to the poor electrophilicity of the carbonyl (**9b**): however, the reaction producing **9a** led to a high yield. The stereoselectivities and reactivity for these reactions were good for five- and six-membered rings (Table 2, Entries 1-7). However, when the ring size was increased to a seven membered ring or straight chain selectivity and reactivity decreased (Scheme 1). The reaction of 2-fluoropropiophenone (**11**) with TBSCN resulted in 69% yield and a 50:50 mixture of

Table 2:

Substrate scope of TMSCN & TBSCN addition to 2-fluoroketones.

Entry	Cat.	Substrate	Method	Yield	Cis:Trans ^a
1	3a		method 1	85%	20:1
	3b		method 2	81%	1:8
2	4a		method 1	80%	3:1
	4b		method 2	54%	1:6
3	5a		method 1	95%	11:1
	5b		method 2	70%	1:7
4	6a		method 1	88%	7:1
	6b		method 2	80%	1:7
5	7a		method 1	69 %	3:1
	7b		method 2	91%	1:11
6	8a		method 1	83%	22:1
	8b		method 2	95%	1:18
7	9a		method 1	83%	3:1
	9b		method 2	17% ^{b,c}	1:10

^aTrans/cis ratio were determined using ¹⁹F NMR. ^bYield based on ¹⁹F NMR using *o*-fluorotoluene as the internal standard. ^cUnreacted starting material was the major component of this reaction.

diastereomers (**12**). Increasing the ring size to seven carbons (2-fluorocycloheptanone)

(**13**) the reaction led to a complex mixture of products with the major component being

Scheme 1: TBSCN addition to 2-fluoroproioiophenone and 2-fluorocycloheptanone.

unreacted starting material. The reactivity and stereoselectivity decreases as the substrate becomes less planar and more flexibility is possessed by the starting 2-fluoroketone.

Based on this, five & six membered ring systems provided the desired product in highest yield and diastereoselectivity.

Conclusion

The Lewis base catalyzed addition of trialkylorganosilane (TMSCN and TBSCN) nucleophiles to 2-fluoroketones yielding the trialkylsilane protected cyanohydrin was investigated. It was discovered that the chosen nucleophile (TMSCN or TBSCN) has a significant impact on the reaction time and stereoselectivity in the product distribution. In the case of TMSCN additions, DIPEA significantly decreased the reaction time (< 5 min) and the product favored the *cis* stereochemistry. In contrast, using TBSCN as the nucleophile, with a catalytic amount of NaOCH₃, favored the *trans* stereoisomer. Due to the difference in reaction mechanisms, the stereochemical outcome can be predicted based on the chosen Lewis base and trialkylorganosilane nucleophile prior to performing the reaction. Current research is directed toward elucidating the difference in reactivity and stereochemical outcome for these reactions.

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|| Undergraduate contributor

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