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Chelation-Controlled Diastereoselective Reduction of α-Fluoroketones

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The replacement of hydrogen or heteroatoms with fluorine can provide an enormous impact on the biological activity of substrates.[1] There is currently great demand for the development of new synthetic methodologies to obtain optically active pure isomers of fluorine-containing substrates, and in particular, stereoselective approaches to α-fluoro alcohols are important in numerous drug targets.[2] In recent decades, considerable progress has been made in controlling the stereochemistry of newly formed chiral centers by aid of interactions between carbonyls and polar neighboring groups (e.g., alkoxy, amine, etc.) with Lewis acids (LA) through chelation.[3] While there are a number of approaches to the stereoselective synthesis of α-fluoro alcohols, to the best of our knowledge, none utilize chelation with Lewis acids to control stereoselectivity.[4,5] To examine the use of chelation control, a series of α-fluoroketones were synthesized and reduced with common reductants in the presence of $TiCl_4$ and $Ti(O^iPr)_4$. The data described herein show two important features: (1) The identity of the Ti-based Lewis acid has a large impact on the diastereoselectivity of reduction, and (2) NMR (^1H, ^{13}C, ^{19}F) data are consistent with the presence of chelation between $TiCl_4$ and α-fluoroketones under conditions utilized in synthetic studies.

Salts of titanium(IV) are known to be effective Lewis acids for chelation-controlled reactions of α- and β-alkoxyketones,[3] and since fluorine is a relatively hard, electron-rich atom, analogous approaches should work for α- and β-fluoroketones. A mechanistic pathway for chelation-controlled reduction of α-fluoroketones requires a relatively strong interaction between Ti-based Lewis acids and fluorine. Examination of the bond strengths of diatomic titanium−fluorides (Ti−F, 136 ± 8 kcal/mol) shows that there is a strong interaction between fluorine and titanium.[6] Further evidence supporting the interaction of Lewis acids with fluoro substituents is found in the recent work of Hessen and co-workers who have shown that the titanocene cation has a high affinity for fluorine.[7] Another potential advantage of using Ti(IV) Lewis acids is their solubility in a range of organic solvents.

To examine the concept of chelation control in detail, α-fluoropropiophenone was prepared using standard methods. Reductions were examined in CH_2Cl_2 and Et_2O using the mild reductants $NaBH_4$ and $LiBH_4$ in the presence and absence of $TiCl_4$ and $Ti(O^iPr)_4$. When the Lewis acids were used, they were premixed with substrate for 15 min at −78 °C before addition of reductant. Diastereomers were determined by ^1H and ^{19}F NMR coupling constants, and the selectivity was determined by GC. The results of these experiments are shown in Table 1. In the absence of a Lewis acid, $NaBH_4$ provides the *anti* diastereomer predominantly, whereas $LiBH_4$ provides the *syn* isomer, but overall, the selectivity was modest. The addition of $TiCl_4$ produced the *syn* diastereomer regardless of the solvent or reductant used, and the selectivity is higher in the presence of this Lewis acid with higher diastereoselectivities in Et_2O.[8] In particular, the combination of $TiCl_4$ with $LiBH_4$ in Et_2O produces very high *syn* selectivity of 24:1. Conversely, the addition of $Ti(O^iPr)_4$ to the substrate prior to reduction by $LiBH_4$ provides the *anti* diastereomer predominantly.

Table 1. Data for Reduction of α-Fluoropropiophenone in the Presence and Absence of Ti-Based Lewis Acids[a]

entry	Lewis acid	reducing agent	solvent	*syn*:*anti*	yield (%)
1	none	$NaBH_4$	Et_2O	1:2	q[b]
2	none	$NaBH_4$	CH_2Cl_2	1:4	q[c]
3	none	$LiBH_4$	Et_2O	3:1	q[b]
4	none	$LiBH_4$	CH_2Cl_2	2:1	q[c]
5	$TiCl_4$	$NaBH_4$	Et_2O	9:1	88[b]
6	$TiCl_4$	$NaBH_4$	CH_2Cl_2	6:1	83[c]
7	$TiCl_4$	$LiBH_4$	Et_2O	24:1	96[b]
8	$TiCl_4$	$LiBH_4$	CH_2Cl_2	7:1	76[d]
9	$Ti(O^iPr)_4$	$LiBH_4$	Et_2O	1:3	99[b]
10	$Ti(O^iPr)_4$	$LiBH_4$	CH_2Cl_2	1:2	98[c]

[a] Experimental conditions: 1 equiv of substrate is treated with 1.25−2.5 equiv of LA at −78 °C; 2 equiv of metal hydrides with respect to substrate is used. [b] Reaction time = 6 h. [c] Reaction time = 7 h. [d] Reaction time = 4 h.

The stereochemical results of the reactions shown in Table 1 can be explained using Cram's chelation[9] and the Felkin−Ahn[10] models. In the absence of chelation, the dipoles of the carbonyl and C−F bond align to minimize repulsion.[11] Attack on this conformation by reductant would be expected to provide the *anti* product predominantly. Conversely, the presence of a Lewis acid capable of interacting with the carbonyl oxygen and fluorine would provide a chelated intermediate, and attack on the less hindered side of this conformation would lead to the *syn* fluoro alcohol. The *anti* product reduction is observed when $NaBH_4$ is used alone or when $Ti(O^iPr)_4$ is used as the LA in concert with $LiBH_4$, indicating that the Na^+ or the sterically encumbered LA are incapable of providing a chelated intermediate. When $LiBH_4$ is used alone or when $TiCl_4$ is used as the LA with either reductant, the *syn* diastereomer is the major product, a finding consistent with chelation.

To examine the likelihood of chelation in detail, NMR experiments were initiated to explore the influence of the Ti-based Lewis acid on α-fluoropropiophenone. The seminal work of Keck has shown the utility of this approach in exploring the extent of chelation in β-alkoxyketones.[12] Figure 1 contains the ^1H, ^{13}C, and ^{19}F NMR spectra of α-fluoropropiophenone in the presence and absence of 1.25 equiv of Ti(IV)-based Lewis acids in CD_2Cl_2 at −78 °C. Further addition of up to 2.5 equiv of Lewis acid showed no change in the NMR spectrum. In the absence of LA, the proton signals of $-CH_3$ and $-CHF-$ appear at δ 1.58 (dd, $J_{HH} = 6.7$ Hz, $J_{HF} = 24.4$ Hz) and δ 5.96 (dq, $J_{HH} = 6.7$ Hz, $J_{HF} = 49.0$ Hz) (Figure 1A), respectively. A significant downfield shift of the corresponding proton signals to δ 2.15 (dd, $J_{HH} = 6.4$ Hz, $J_{HF} = 28.8$ Hz, CH_3) and δ 6.82 (bdd, $J_{HH} = 5.8$ Hz, $J_{HF} = 50.4$ Hz,

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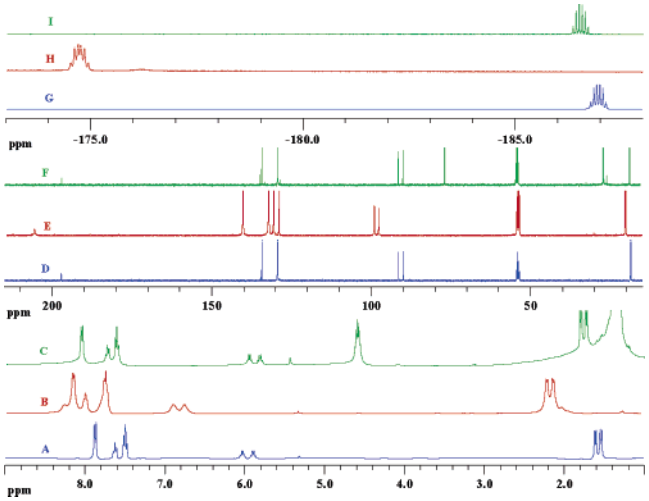

Figure 1. All spectra are recorded at −78 °C in CD_2Cl_2.^{1}H, ^{13}C, and ^{19}F NMR spectra of 2-fluoropropiophenone are shown in A, D, and G, respectively. Spectra B, E, H and C, F, I are the ^{1}H, ^{13}C, and ^{19}F NMR spectra of 2-fluoropropiophenone−$TiCl_4$ complex and 2-fluoropropiophenone−$Ti(O^iPr)_4$ complex, respectively. In all ^{1}H NMR spectra, the peak at δ 5.32 is due to trace amounts of $CHDCl_2$ in CD_2Cl_2, whereas the additional peaks at δ 1.41 and 4.67 in spectrum C are due to isopropoxide. In all ^{13}C NMR spectra, the peak at δ 54.0 is due to CD_2Cl_2, and the peaks at δ 76.59 and 26.71 in spectrum F are due to isopropoxide. The peak at δ 25.54 in F is due to 2-propanol impurity.

C*H*F) are observed when ^{1}H NMR is recorded in the presence of $TiCl_4$ under similar conditions (Figure 1B).

In the presence of $TiCl_4$, the ^{13}C spectrum shows that the carbonyl carbon, CH_3CFH- and CH_3 appear at δ 205.8 (bs), δ 98.36 (d), and δ 20.12 (d) (Figure 1E), whereas the respective ^{13}C signals of α-fluoropropiophenone in the absence of Lewis acid appear at δ 196.17 (d), δ 90.93 (d), and δ18.11 (d) (Figure 1D). Addition of $TiCl_4$ also results in a downfield shift of the aromatic ^{13}C signals [δ 129.0, 130.7, 132.23, 140.33] with respect to original aromatic ^{13}C signals [δ 129.0, 129.12, 134.07, 134.47]. In addition, ^{19}F NMR spectra of α-fluoropropiophenone in the presence and absence of $TiCl_4$ display the ^{19}F signal at δ −174.82 (m) and δ −187.0 (m), respectively. Interaction of Ti with the fluorine and the carbonyl, as shown by the concomitant shift of the ^{19}F signal and ^{13}C, provides compelling evidence for the formation of $TiCl_4$−α-fluoropropiophenone chelate. Furthermore, the ^{1}H and ^{13}C $\Delta\delta$ values for the CH_2 of propiophenone in the presence and absence of $TiCl_4$ (where chelation is not possible) were 0.46 and 0.93 ppm, respectively, whereas the corresponding ^{1}H and ^{13}C $\Delta\delta$ values for the −CHF α-fluoropropiophenone were 0.86 and 7.43 ppm, further supporting the intermediacy of a chelated intermediate.

In further studies, ^{1}H and ^{13}C NMR spectra of α-fluoropropiophenone obtained in the presence of $Ti(O^iPr)_4$ (Figure 1C,F) do not show significant downfield shifts of aliphatic proton and carbon signals (Figure 1A,D). While the $Ti(O^iPr)_4$ is bulkier than $TiCl_4$, the Lewis acidity of alkoxytitanium reagents decreases drastically as chlorides are replaced by alkoxides in the series from $TiCl_4$ to $Ti(O^iPr)_4$, suggesting that the latter might be incapable of chelation.[13]

Taken together, these experiments show the following. (1) The identity of the counterion on the reductant and the Ti-based Lewis acid alters the diastereoselectivity of reduction of α-fluoropropiophenone. (2) NMR data are consistent with chelation between $TiCl_4$ and α-fluoropropiophenone. For this approach to be useful, it should be applicable to a range of α-fluoroketones. To initially examine the generality of this protocol, a series of α-fluoroketones were reduced using $LiBH_4$ in the presence and absence of $TiCl_4$ (Table 2). In each case, pretreatment with $TiCl_4$ substantially increased the diastereoselectivity of the reduction, providing a selectivity consistent with chelation. Detailed mechanistic studies on the use of other Lewis acids and the role of solvent on the diastereoselectivity of reductions and bond-forming reactions are currently being examined. The results of these studies will be reported in due course.

Table 2. Reduction of α-Fluoroketones by $LiBH_4$ in Et_2O in the Presence of $TiCl_4$[a]

entry	substrate	LA	*syn*:*anti*	yield (%)
1	α-fluorotetralone	none	8:1	q
2	α-fluorotetralone	$TiCl_4$	27:1	q
3	α-fluoroindanone	none	3:1	98
4	α-fluoroindanone	$TiCl_4$	32:1	87
5	3-fluoro-2-butanone	none	1:1	91
6	3-fluoro-2-butanone	$TiCl_4$	5:1	85
7	3-fluoro-2-octanone	none	1:1	93
8	3-fluoro-2-octanone	$TiCl_4$	6:1	88
9	4-fluoro-5-nonanone	none	2:1	96
10	4-fluoro-5-nonanone	$TiCl_4$	5:1	89

[a] Experimental conditions: 1 equiv of substrate is treated with 1.25−2.5 equiv of LA at −78 °C, followed by addition of 2 equiv of $LiBH_4$. Reaction times were 5−7 h.

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Supporting Information Available: General experimental conditions, synthetic procedures, and spectral data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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