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Titanium-Catalyzed Stereoselective Geminal Heterodihalogenation of β-Ketoesters

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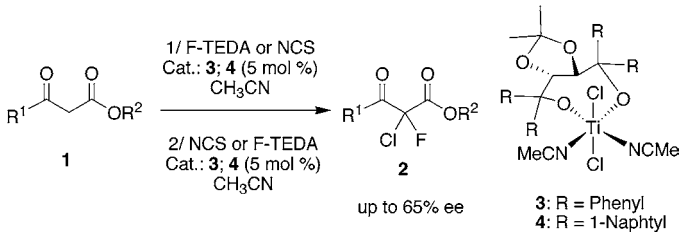
ABSTRACT



β-Ketoesters can be effectively monofluorinated with F-TEDA using $CpTiCl_3$ as a catalyst. With the use of this catalyst, the extent of the competing difluorination does not reach 10%. [$TiCl_2$(TADDOLato)] complexes catalyze the one-pot enantioselective heterodihalogenation of β-ketoesters with F-TEDA and NCS to afford α-chloro-α-fluoro-β-ketoesters in moderate to good yields. The sequence of addition of the halogenating agents determines the sense of chiral induction.

Fluorine-containing organic molecules are becoming increasingly important in medicinal chemistry and as crop protection agents.[1] Besides the fluorination of aromatic groups and the introduction of perfluoroalkyl chains, the development of synthetic methods in this area has addressed also stereoselective C−F bond-forming reactions.[2] In this context, chiral enantiopure fluorinating reagents[3] or chiral starting materials[4] have been used. Recently, we reported the first asymmetric electrophilic fluorination of β-ketoesters with the commercially available fluorinating agent F-TEDA (also called Selectfluor; 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo-[2,2,2]octane bis(tetrafluoroborate)), catalyzed by a [$TiCl_2$-(TADDOLato)] complex, giving enantioselectivities of up to 90% ee.[5]

We also reported the analogous chlorination and bromination reactions.[6] More recently, Sodeoka has shown that Pd(II) complexes bearing axial-chiral diphosphines catalyze

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similar fluorinations with NFSI.[7] This latter reagent has been used successfully also in fluorinations carried out under conditions of asymmetric phase-transfer catalysis.[8]

Very few methods for the preparation of α-chloro-α-fluoro-β-ketoesters are known.[9] For example, Chambers reported the direct fluorination of ethyl-2-chloro acetoacetate using fluorine in the presence of formic acid.[9b] The same starting material was fluorinated using *N*-fluorobis[(trifluoromethyl)sulfonyl]-imide as reported by DesMarteau.[9d] To the best of our knowledge, no catalytic stereoselective reaction leading to α-chloro-α-fluoro-β-ketoesters has ever been described in the literature. A collateral problem is related to the selectivity toward monohalogenation of active methylene compounds, which is still quite challenging.[10]

In the first stage of our work, we investigated the reaction of the α-unsubstituted β-ketoesters depicted in Figure 1 with

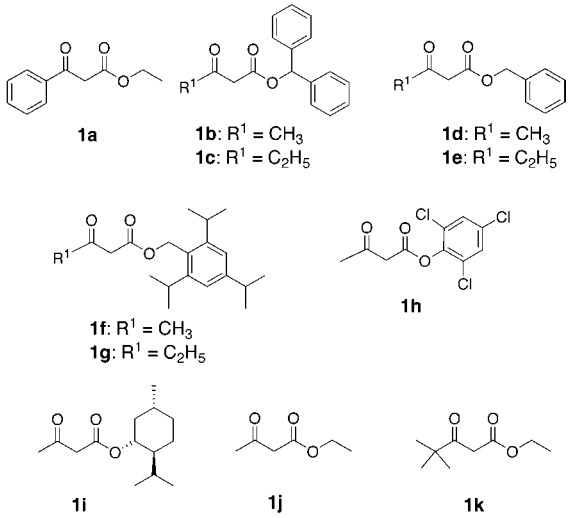
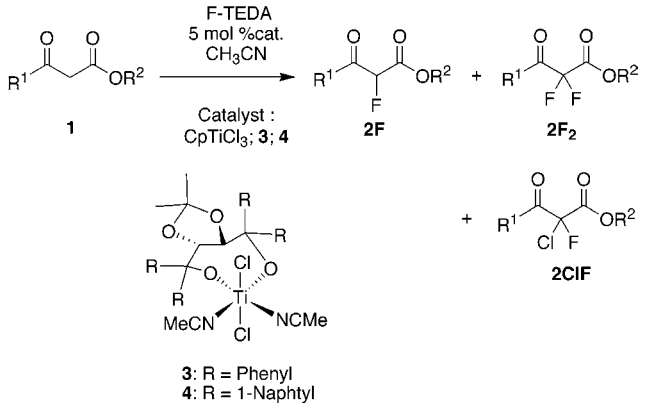


Figure 1. β-Ketoesters as substrates for catalytic halogenation reactions used in this study.

1 equiv of F-TEDA in acetonitrile and in the presence of 5 mol % titanium catalyst ($TiCl_4$, $CpTiCl_3$, (*R*,*R*)-**3**, or (*R*,*R*)-**4**; see Scheme 1 and Table 1).

These reactions generally lead to the formation of mixtures of the monofluorinated and difluorinated products **2F** and **2F$_2$**, respectively, often accompanied by a small amount of the chlorofluorinated derivative **2ClF**, the latter arising from

Scheme 1. Mono- and Difluorination of β-Ketoesters



the incorporation of chlorine from the catalyst, as previously reported.[6]

Inspection of the results collected in Table 1 clearly indicates that the simple organometallic complex $CpTiCl_3$ constitutes an excellent catalyst, affording the highest degree of chemoselection.[11] Product ratios reach a value of 32:1 (β-ketoester **1h**) in favor of the monofluorinated derivative, as determined by ^{19}F NMR of the crude reaction mixtures. Surprisingly, chemoselectivity is much lower when using the more sophisticated chiral catalysts **3** and **4**, with a minimum extent of difluorination of ca. 10−12%. Also, the mono-

Table 1. Monofluorination of β-Ketoesters

substrate	catalyst	yield[a]	ratio **2F**/**2F$_2$**[b]	δ ^{19}F (ppm)[c]
1a	$TiCl_4$		6:1	−190.7/−108.8
1a	$CpTiCl_3$	80%	20:1	
1a	**4**		8.3:1	
1b	$CpTiCl_3$	66%	11:1	−193.2/−113.9
1b	**3**		8:1	
1b	**4**		6:1	
1c	$CpTiCl_3$	88%	15:1	−195.7/−114.3
1b	**4**		10:1	
1d	$CpTiCl_3$	39%	18:1	−193.6/−113.9
1d	**4**		4.4:1	
1e	$CpTiCl_3$	71%	30:1	−196.0/−114.5
1e	**4**		6.5:1	
1f	$CpTiCl_3$	51%	30:1	−193.0/−113.4
1f	**4**		8:1	
1g	$CpTiCl_3$	67%	21:1	−196.0/−114.4
1g	**4**		7.8:1	
1h	$CpTiCl_3$	n.d.	32:1	−193.6/−113.3
1h	**4**		9:1	
1i	$CpTiCl_3$	68%	10.7:1	−192.8; −193.1/−114.1
1i	**4**		5.7:1	
1j	$CpTiCl_3$	n.d.	20:1	−194.6/−114.5
1j	**4**		4.7:1	
1k	$CpTiCl_3$	66%	21:1	−191.0/−108.7

[a] After column chromatographic purification. [b] Ratios of mono- and difluorinated products, as determined by ^{19}F NMR. [b] ^{19}F NMR measured in $CDCl_3$, relative to $CFCl_3$.

(7) Hamashima, Y.; Yagi, K.; Takano, H.; Tamás, L.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 14530−14531.

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(10) (a) Umemoto, T.; Fukami, S.; Tomizawa, G.; Harasawa, K.; Kawada, K.; Tomita, K. *J. Am. Chem. Soc.* **1990**, *112*, 8563−8575. (b) Davis, F. A.; Han, W.; Murphy, C. K. *J. Org. Chem.* **1995**, *60*, 4730−4737. (c) Umemoto, T.; Nagayoshi, M.; Adachi, K.; Tomizawa, G. *J. Org. Chem.* **1998**, *63*, 3379−3385. (d) Poss, A. J.; Shia, G. A. *Tetrahedron Lett.* **1999**, *40*, 2673−2676.

halogenated products obtained using the chiral catalysts did not display any appreciable level of enantiomeric enrichment, obviously because of the dual enolization/racemization activity of the Ti complexes.

One of the racemic products obtained with catalyst **4** could be isolated in crystalline form and subjected to an X-ray structural study.[12] An ORTEP view of this compound is shown in Figure 2. In the solid state, the compound is not

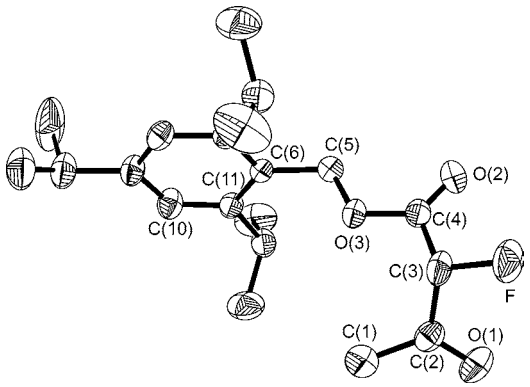

Figure 2. ORTEP view (30% probability ellipsoids) of **2fF** (hydrogen atoms are omitted for clarity).

enolized and the C−F distance of 1.367(3) Å reflects typical values.[13] It is, however, noteworthy that both carbonyl groups assume a nearly syn planar orientation with respect to the C−F bond, as illustrated by the torsion angles O2−C4−C3−F and O1−C2−C3−F of 8.9 and 15.2°, respectively.[14]

We next turned our attention to the selective catalytic heterodihalogenation of β-ketoesters to form α-chloro-α-fluoro-β-ketoesters by changing the sequence of addition of the halogenating agents (Scheme 2). Thus, in the first protocol (F → Cl), a fluorination reaction with F-TEDA in the presence of a catalytic amount of one of the two titanium complexes **3** and **4** was performed. The intermediate was then enantioselectively chlorinated by NCS. In the second protocol (Cl → F) the halogenation sequence was inverted.[15]

(11) For a recent example of monobrominations catalyzed by $Mg(ClO_4)_2$, see: Yang, D.; Yan, Y.-L.; Lui, B. *J. Org. Chem.* **2002**, *67*, 7429−7431.

(12) Crystallographic data for the structure reported in this paper have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 195249. Copies of the data can be obtained free of charge upon application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax, (+44) 1223 762910; e-mail, deposit@ccdc.cam.ac.uk).

(13) Orpen, A. G.; Brammer, L.; Allen, F. H. Kennard, O. Watson, D. G. Taylor, R. In *Structure Correlation*; Bürgi, H.-B., Dunitz, J., Eds.; VCH: Weinheim, Germany, 1994; Vol. 2, Appendix A, p 751.

(14) For a recent paper discussing conformational effects due to fluorine, see: Briggs, C. R. S.; O'Hagan, D.; Howard, J. A. K.; Yufit, D. S. *J. Fluorine Chem.* **2003**, *119*, 9−13.

(15) **General Procedure: F → Cl Sequence.** F-TEDA (0.28 mmol) was added to a solution of β-ketoester (0.25 mmol) and the titanium complex (0.0125 mmol) in CH_3CN (3 mL) at room temperature. The completion of the first halogenation reaction was monitored by ^1H NMR. A second portion of the catalyst (0.0125 mmol) and NCS (0.28 mmol) were then added, and the reaction mixture was stirred until complete conversion. After the addition of MTBE, the mixture was filtered, the liquid phase concentrated, and the residue chromatographed on silica to afford the product in an analytically pure form as an oily material.

Scheme 2. Consecutive Halogenations of β-Ketoesters

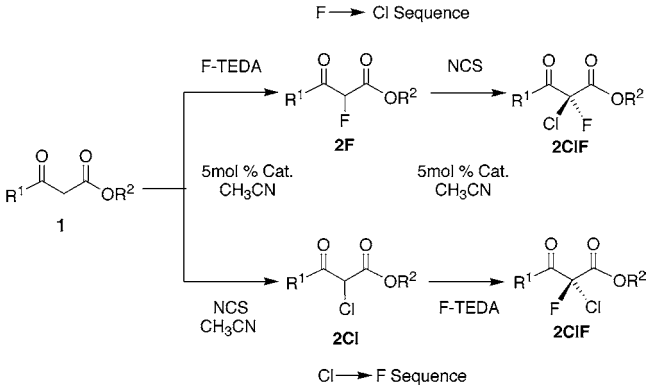

Table 2 summarizes the results obtained in these one-pot experiments, which gave invariably quantitative conversions.

Table 2. Catalytic Enantioselective Heterodihalogenation[a]

substrate	catalyst/ sequence	yield[b]	selectivity (ee)	analysis
1a	**4**/F → Cl	80%	32%	14.84/**18.13**[d]
1a	**4**/Cl → F	53%	33%	**14.84**/18.13[d]
1d	**3**/F → Cl	nd	44%	**89.4**/91.0[e]
1d	**3**/Cl → F	nd	32%	89.4/**91.0**[e]
1d	**4**/F → Cl	nd	35% (49%[c])	**89.4**/91.0[e]
1d	**4**/Cl → F	nd	52% (51%[c])	89.4/**91.0**[e]
1e	**4**/F → Cl	65%	65% (45%[c])	124.2/**127.9**[e]
1e	**4**/Cl → F	60%	57% (55%[c])	**124.2**/128.9[e]
1i	**4**/F → Cl	45%	∼4% de	−**123.0**/−123.1[f]
1i	**4**/Cl → F	nd	59% de	−123.0/−**123.1**[f]
1j	**4**/F → Cl	nd	24%	**23.7**/25.0[e]
1j	**4**/Cl → F	nd	25.5%	23.7/**25.0**[e]

[a] Reaction conditions: 0.25 mmol of substrate in CH_3CN, 5 mol % catalyst. Quantitative conversions (NMR and TLC). [b] Yields are given for compounds isolated after column chromatography. [c] Reactions carried out with the isolated monohalogenated products **2dCl**, **2dF**, and **2eCl**, **2eF**, respectively. [d] Determined by chiral HPLC analysis on a Daicel Chiralcel OJ 25 cm column. Retention times in min of minor/**major** enantiomer. See Supporting Information for details. [e] Determined by chiral GC on a Supelco β-dex column. Retention times in min of minor/**major** enantiomer. See Supporting Information for details. [f] ^{19}F NMR chemical shifts minor/**major** diastereoisomers.

Enantioselectivities were as high as 65% ee in the case of substrate **1e**, using catalyst **4**. In the case of the menthyl ester **1i** a diastereoselectivity up to 59% de was observed. It is interesting to note that the reaction of the isolated monohalogenation intermediate does not afford the same selectivity as the one-pot procedure. The reasons for the observed deviation are not apparent. Despite full consumption of the β-ketoesters in all dihalogenation experiments, the isolation of the pure chlorofluoro products turned out to be difficult. Thus, the isolated yields were only moderate (45−65% and in one case up to 80%). Two main factors are responsible for this: (1) the relatively low chemoselectivity of the chiral catalysts **3** or **4**, affording in the first step the dichloro or difluoro derivative as contaminating byproducts, respectively,

and (2) the very similar chromatographic behavior of main- and byproducts, leading to relatively large losses of material when working on a small scale (0.25 mmol of β-ketoester).

Although the selectivities are not very high in absolute terms, the most important finding of this study is that *the sequence of addition of the halogenating agents determines the sense of chiral induction*. In other words, given one enantiomeric form of the catalyst, it is possible to form either enantiomer of the product preferentially just by choosing the order of the two halogenation steps in this one-pot tandem process. This is a very rare observation in asymmetric catalysis.[16] It is, however, easily explained by assuming that the first halogen is introduced in a nonstereoselective manner (vide supra) and that the overall stereochemical outcome is solely determined by the second halogenation step. Given that for the catalysts derived from (*R*,*R*)-TADDOLs the major product enantiomer is formed via *Si*-side attack of the halogenating agent onto the coordinated enolate,[5c] we assign the absolute configuration (*S*)- to the preferred enantiomer obtained via the F → Cl sequence (and (*R*)- for the Cl → F sequence).

We are currently trying to improve the stereoselectivity of this unique double-halogenation reaction, as well as investigating the reactivity and potential use as chiral building blocks of these dihalocompounds.

Supporting Information Available: Experimental conditions and spectroscopic and analytical characterization of β-ketoesters and mono- and dihalogenated β-ketoesters. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) A comparable situation was reported for the enantioselective double alkylation of aldimine Schiff bases derived from glycine under phase-transfer catalytic conditions. See: Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228−5229. We thank one of the reviewers for drawing our attention to this.