Enantioselective chlorination and fluorination of β-keto phosphonates catalyzed by chiral Lewis acids†

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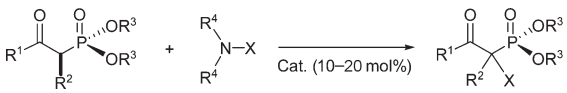
The direct chiral Lewis acidic enantioselective chlorination and fluorination of β-keto phosphonates is presented; the chlorination proceeds in high yields and with up to 94% ee using NCS as the chloro source, while the fluorination with $(PhSO_2)_2NF$ (NFSI) gives the optically active α-fluoro-β-keto phosphonates in moderate to good yields and with up to 91% ee.

The stereoselective introduction of halogens into compounds of biological importance, such as amino acids and their derivatives as well as other bioactive compounds, might have beneficial properties in terms of *e.g.* enhanced chemical stability, increased intrinsic activity and improved metabolic stability.[1] Furthermore, organic compounds having the C–X (X = halogen) bond attached to a chiral stereocenter are of great importance as versatile synthetic intermediates.

The importance of these optically active organic compounds having C–X bonds has led to an increased interest in the development of stereocontrolled syntheses of these compounds.[1a] For the formation of a stereogenic C–F centre using a catalytic enantioselective electrophilic halogenation approach, the focus has been mainly on 1,3-dicarbonyl compounds.[2] The catalytic enantioselective electrophilic chlorination and bromination have also been developed for 1,3-dicarbonyl compounds such as β-keto esters using chiral Lewis acids as catalysts,[3] and cinchona alkaloids are excellent catalysts for the tandem halogenation/esterification of acyl halides leading to optically active versatile α-haloesters.[4] Very recently the direct organocatalytic α-chlorination of aldehydes[5a,b] and ketones[5c] giving the corresponding optically active α-chloro carbonyl compounds with very high enantiomeric excesses was presented.

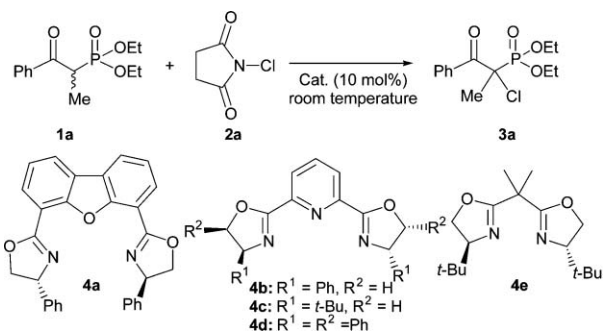
The interest in the biological activity of phosphonic acids and related compounds has grown tremendously in recent years. Phosphonates have been considered in many instances as analogues of naturally occurring phosphates, with enhanced metabolic stability.[6] The tetrahedral phosphonic acid moiety can also in some cases replace a planar and less bulky carboxylic acid, and *e.g.* optically active α-amino phosphonic acids have been widely used as surrogates of α-amino acids, both as single units, or incorporated into peptides in an attempt to mimic the tetrahedral transition state of enzyme-mediated peptide hydrolysis.[7]

In this paper we will present the first catalytic enantioselective chlorination and fluorination of β-keto phosphonates using *N*-chlorosuccinimide (NCS) and *N*-fluorobenzenesulfonimide (NFSI) as the chlorination and fluorination reagents, respectively, leading to the corresponding optically active α-chloro/α-fluoro β-keto phosphonates in high enantiomeric excesses [eqn. (1)].[8] α-Halogenated phosphonates are potentially better "isosteric and isopolar" mimics of phosphates than the corresponding simple phosphonates bearing a methylene group.[9] Parameters that favor α-fluorophosphonates in particular are reduced pK_{a2}, increased polarity and the possibility for C–F···H–X hydrogen bonding.[9d,10]



(1)

We started our investigation by screening ligands and Lewis acids as catalysts for the enantioselective chlorination of (1-methyl-2-oxo-2-phenyl-ethyl)phosphonic acid diethyl ester **1a** with NCS **2a**. The screening revealed that the tridentate ligands (*R,R*)-4,5-dibenzofurandiyl-2,2′-bis(4-phenyloxazoline) (Ph-DBFOX)[11] **4a** and phenyl-substituted 2,6-bis(oxazolinyl)-pyridines (PyBOX)[12] **4b,d** were the best ligands of those investigated. In combination with Zn(II), Sc(III) and Cu(II), the optically active (1-chloro-1-methyl-2-oxo-2-phenyl-ethyl)phosphonic acid diethyl ester **3a** [eq. (2)] could be obtained in high yield and enantiomeric excess. Table 1 shows some representative screening results.



(2)

Table 1 Catalytic enantioselective chlorination of (1-methyl-2-oxo-2-phenyl-ethyl)phosphonic acid diethyl ester **1a** with NCS **2a** catalyzed by different chiral ligands and Lewis acids in CH_2Cl_2 at room temperature

Entry	Ligand	Lewis acid	Reac. time (h)	Conv. (%)	Ee[a] (%)
1	**4a**	$Zn(OTf)_2$	20	>95	74
2	**4a**	$Zn(SbF_6)_2$	20	>95	92
3	**4b**	$Sc(OTf)_3$	1	>95	75
4	**4b**	$Zn(OTf)_2$	20	25	Rac.
5	**4c**	$Sc(OTf)_3$	5	95	Rac.
6	**4d**	$Sc(OTf)_3$	20[b]	>95	91[c]
7	**4e**	$Zn(OTf)_2$	20	>95	45
8	**4e**	$Cu(OTf)_2$	20	>95	64

[a] Enantiomeric excess measured by chiral stationary phase HPLC. [b] Reaction temperature 0 °C. [c] THF was used as the solvent.

† Electronic Supplementary Information (ESI) available: experimental section. See http://www.rsc.org/suppdata/cc/b4/b415568h/

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Table 2 Catalytic enantioselective chlorination and fluorination of β-keto phosphonates **1a–f** with NCS **2a** and NFSI **2b**, catalyzed by Ph-DBFOX-Zn$(SbF_6)_2$ and Ph-DBFOX-Zn$(ClO_4)_2$ respectively, in CH_2Cl_2 at room temperature

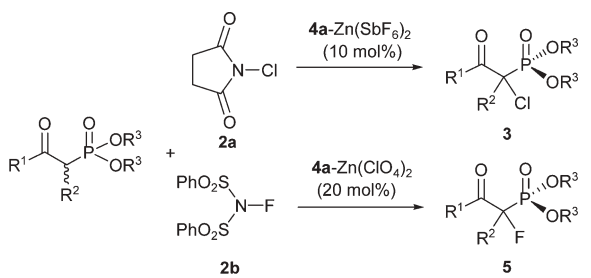
				Chlorination (**2a**)		Fluorination (**2b**)	
Entry	R^1	R^2	R^3	Yield[a] (%)	Ee[b] (%)	Yield[a] (%)	Ee[b] (%)
1	Ph	Me	Et	**3a** – 98	92	**5a** – 59 (86)[c]	89 (88)[c]
2	Ph	Me	Me	**3b** – 97	78	**5b** – 46 (77)[c]	70 (70)[c]
3	Ph	Allyl	Et	**3c** – 93	92	**5c** – 41 (91)[c]	91 (90)[c]
4	2-Np	Me	Et	**3d** – 97	93	**5d** – 71	89
5	Me	Me	Et	**3e** – 80	94	—	—
6	$-(CH_2)_3-$		Et	**3f** – 40	80	**5f** – 38	91

[a] Isolated yield. [b] Enantiomeric excess measured by chiral stationary phase HPLC or GC. [c] Results in brackets refer to reaction performed at reflux temperature.

A number of different combinations of chiral ligands and Lewis acids can catalyze the chlorination of (1-methyl-2-oxo-2-phenyl-ethyl)phosphonic acid diethyl ester **1a** by NCS. From the results presented in Table 1 it appears that both the Ph-DBFOX **4a** and PyBOX ligands **4b,d** in combination with Zn$(SbF_6)_2$ and Sc$(OTf)_3$, gave the optically active (1-chloro-1-methyl-2-oxo-2-phenyl-ethyl)-phosphonic acid diethyl ester **3a** in up to 92% ee (entries 2, 3, 6). The influence of the substituents at the chiral centers in the PyBOX ligands on the enantioselectivity should be noted. The PyBOX ligand **4b** with two phenyl substituents and Sc$(OTf)_3$ as the Lewis acid gave **3a** with 75% ee (entry 3), while PyBOX **4c** with two *tert*-butyl substituents provided **3a** as a racemate (entry 5). The introduction of two stereogenic centers in the PyBOX ligand (**4d**) improved the enantioselectivity to 91% ee at 0 °C (entry 6). The use of the bidentate chiral bisoxazoline ligand **4e** and Zn$(OTf)_2$ or Cu$(OTf)_2$ as the Lewis acids, gave also **3a** with high conversion; however, the enantioselectivity was only moderate (entries 7, 8) compared to the tridentate ligands.

As shown in Table 2 we have extended the catalytic enantioselective chlorination to a series of β-keto phosphonates **1a–f**, and, furthermore, we will show that the catalytic system can also be applied for the enantioselective fluorination of the same substrates (Scheme 1).

The Ph-DBFOX-Zn$(SbF_6)_2$ is an effective catalyst for the enantioselective chlorination. The acyclic β-keto phosphonates having both aromatic and alkyl substituents in the β-position (**1a–e**) are converted into the corresponding optically active α-chloro β-keto phosphonates **3a–e** in high yields and enantioselectivities. The enantioselectivity is slightly dependent on the ester substituent, (1-methyl-2-oxo-2-phenyl-ethyl)phosphonic acid diethyl ester **1a** gives 92% ee of **3a** (entry 1), while the similar methyl ester (**3b**) is formed with 78% ee (entry 2). For the β-keto phosphonates having an allyl substituent in the α-position (entry 3), as well as an aryl or a methyl substituent at the β-position (entries 4, 5), excellent enantioselectivities of **3c–e** – 92–94% ee are obtained. The cyclic β-keto phosphonate **1f** can also be chlorinated in the α-position with the same good enantioselectivity, however, the yield is lower compared to the acyclic substrates (entry 6).



Scheme 1 Catalytic enantioselective chlorination and fluorination of β-keto phosphonates.

The catalytic enantioselective fluorination of the β-keto phosphonates **1a–f** by NFSI **2b** using a Ph-DBFOX-Zn(II) catalyst also proceeds well (Table 2). Noteworthy, for the fluorination reaction a more simply prepared catalyst formed by a combination of $Zn(ClO_4)_2 \cdot 6H_2O$ and Ph-DBFOX (**4a**) in the presence of 4Å molecular sieves could be used with comparable results. The yields obtained when the reaction is performed at room temperature are slightly lower compared to the chlorination reactions. However, the enantiomeric excesses of the α-fluoro β-keto phosphonates **5a–d,f** are as high as for the α-chloro β-keto phosphonates. For the acyclic α-fluoro β-keto phosphonates (**5a–d**), the enantioselectivities are in the range of 70–91% ee (entries 1–4), while the cyclic β-keto phosphonate **1f** gives the fluorinated product **5f** in 91% ee (entry 6). The yields of the optically active α-fluoro-β-keto phosphonates (**5a–c**) could be improved significantly to 86%, 77% and 91%, respectively, simply by performing the reaction at reflux in CH_2Cl_2, without affecting the enantioselectivities (entries 1–3).

In summary, we have developed the first catalytic enantioselective chlorination and fluorination of β-keto phosphonates. This reaction proceeds well for both acyclic and cyclic β-keto phosphonates giving the corresponding optically active α-chloro and α-fluoro β-keto phosphonates, respectively, in high yields and enantioselectivities using a (*R,R*)-4,5-dibenzofurandiyl-2,2′-bis(4-phenyloxazoline)-Zn(II) catalyst.

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