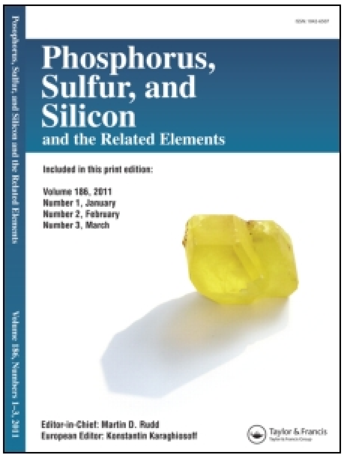

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Synthesis and Chemistry of New Central and Planar Chiral Sulfur-Containing Ferrocenyl Compounds

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Enantiomerically pure 2-hydroxyalkyl, 2-aminoalkyl and 2-iminoalkyl ferrocenyl p-*tolylsulfides are easily prepared in good yields and with complete diastereocontrol from (*S*)-(2-*p-*tolylthio)ferrocencarboxyaldehyde. 2-Iminoalkyl ferrocenyl derivatives can be used as ligands in asymmetric catalysis and as starting materials for asymmetric Staudinger reaction.*

Keywords β-lactams; palladium allylic substitution; sulfur-containing planar chiral ferrocene derivatives

Since the discovery of ferrocene in 1951,[1] its chemistry has been intensively investigated.[2] In particular the use of ferrocenyl ligands in organic catalysis still continues to grow. As a part of our ongoing interest in sulfur-containing compounds[3] and in molecules bearing the ferrocene moiety,[4] we have recently synthesised enantiomerically pure β-hydroxyalkyl, β-aminoalkyl, and β-iminoalkyl ferrocenyl sulfides starting from mercaptoferrocene. These derivatives, having only the central chirality, were successfully employed as ligands in palladium-catalyzed allylic substitution with asymmetric induction up to 99%.[5]

More recently we used (S_{Fc})-(2-*p*-tolylthio) ferrocencarboxyaldehyde **1** as the key compound for the synthesis of new sulfur-containing ferrocenyl derivatives, such as 2-(hydroxyalkyl)- **2**, 2-(aminoalkyl)-ferrocenyl *p*-tolylsulfides **3** with planar and central chirality,

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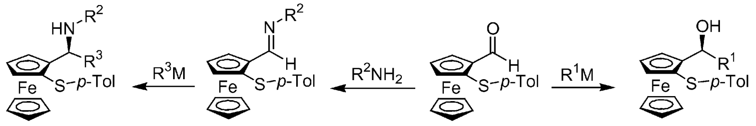


3a: R^2 = Ts, R^3 = Me
3b: R^2 = Ts, R^3 = $CH{=}CH_2$
3c: R^2 = Ts, R^3 = Ph

4a: R^2 = *p*-$Me_2NC_6H_4$
4b: R^2 = *p*-$MeOC_6H_4$
4c: R^2 = *o*-ClC_6H_4
4d: R^2 = Mes
4e: R^2 = CH_2Ph
4f: R^2 = (*R*) $CH(CH_3)Ph$
4g: R^2 = Ts

(S_{Fc})-**1**

2a: R^1 = Me
2b: R^1 = $CH{=}CH_2$
2c: R^1 = Ph
2d: R^1 = *n*-Bu
2e: R^1 = CH_2-$CH{=}CH_2$
2f: R^1 = CN

SCHEME 1

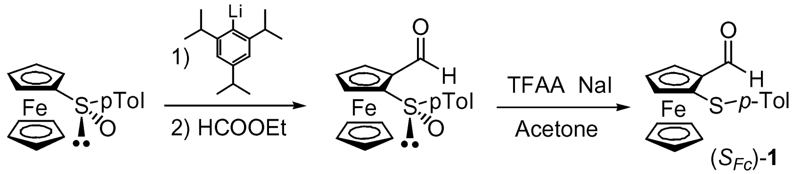
and 2-(iminoalkyl)-ferrocenyl *p*-tolylsulfides **4** with planar chirality (Scheme 1).[6]

For the synthesis of aldehyde (S_{Fc})-**1** beside the Kagan strategy,[7] we developed an alternative procedure based on the diastereoselective ortho-lithiation of (S_{Fc})-ferrocenyl-p-tolyl sulfoxide with 2,4,6-triisopropylphenyl lithium followed by electrophilic trapping with ethylformiate and reduction of the sulfoxide with sodium iodide and trifluoroacetic anhydride in acetone.[6]

The reaction of aldehyde (S_{Fc})-**1** with organometallic derivatives, namely Grignard reagents, organolithium derivatives, tetraallyltin in the presence of $Sc(OTf)_3$, diethylaluminium cyanide and trimethylsilylcyanide, afforded in high yields and high distereoselectivity the secondary alcohols **2** with the (*S*) configuration at the newly formed stereocenter.

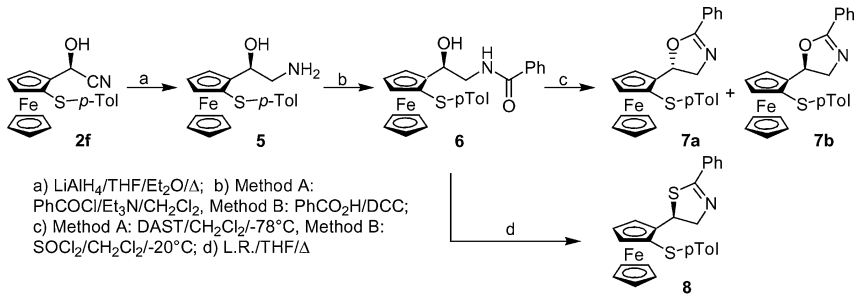
Of particular interest is the preparation of the first ferrocenyl cyanohydrin **2f** containing both the central (*S*) and the planar (S_{Fc}) chirality. From **2f**, the *β*-amino alcohol **5** was obtained using $LiAlH_4$ (Scheme 2) in refluxing THF/Et_2O. The *β*-hydroxyamide **6** was cyclodehydrated in acid condition (DAST or $SOCl_2$) and afforded a mixture of two diastereomeric oxazolines **7a** and **7b** (Scheme 3).[8]

The lack of stereoselectivity in the cyclization step can be ascribed to a partial epimerization of the firstly formed oxazoline (*S*)-**7b** to the



(S_{Fc})-**1**

SCHEME 2



SCHEME 3

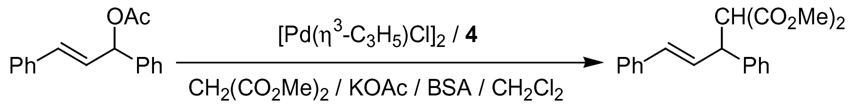
more stable (*R*) form, because of the acidity of the reaction conditions, with the intermediacy of a ferrocenyl alkyl cation.[9] Treatment of **6** with Lawesson reagent in boiling tetrahydrofuran (THF) yielded the ferrocenyl thiazoline **8** with retention of configuration.[8]

Planar chiral ferrocenyl imines **4** (Scheme 1) are of particular interest in diastereoselective asymmetric addition of organometallic reagents, in asymmetric Staudinger reactions leading to β-lactams, and as ligands. For this reason, a variety of imines, prepared in excellent yields, were tested as ligands in palladium-catalyzed allylic substitution of 1,3-diphenylprop-2-enyl acetate with dimethylmalonate (Table 1).

The results in term of ee are in some cases good and it is possible to observe the beneficial effect on the asymmetric induction of electron-donating substituents in the *para*- position of the aromatic ring.

The imine **4g** (R^2 = Ts) reacted with tetraallyltin in the presence of Sc(OTf)$_3$ and with Grignard reagents in the presence of a Lewis acid

TABLE I

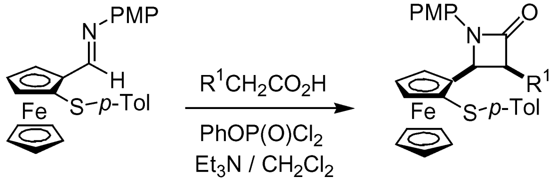


Entry	Imine 4	ee (%)	Absolute configuration
1	**a**	72	*R*
2	**b**	70*	*R*
3	**c**	32	*R*
4	**d**	15	*S*
5	**e**	60	*R*
6	**f**	60	*R*

*76 at O°C.

(LiCl, $MgBr_2$) affording the (*S*)-2-aminoalkyl ferrocenyl *p*-tolylsulfides **3** in high yields and excellent diastereoselectivity (de > 98%) (Scheme 1).

In the past we described the synthesis of 3-ferrocenyl substituted *cis*-β-lactams by Staudinger reaction of ferrocenyl acetic acid and achiral or chiral imines.[10] The one-pot reaction of substituted acetic acids and planar chiral ferrocenyl imines **4** in the presence of phenyldichlorophosphate and triethylamine, afforded 4-ferrocenyl substituted β-lactams **9** as single diastereoisomer (Scheme 4).



4b

9a: R^1 = OPh 52%
9b: R^1 = OAc 43%
9c: R^1 = OBn 76%
9d: R^1 = ONpht 63%

SCHEME 4

The *cis* stereochemistry of the obtained products was established on the basis of the coupling constant values of the signal corresponding to the C_3 and C_4 protons.

Studies on the stability of 4-ferrocenyl substituted β-lactams in comparison with 3-ferrocenyl substituted derivatives as well as biological and synthetic applications of these molecules are under investigation in our laboratory.

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