A straightforward asymmetric synthesis of 1,2-disubstituted ferrocenylalkyl amines with the unusual (S_{Fc},S) configuration†

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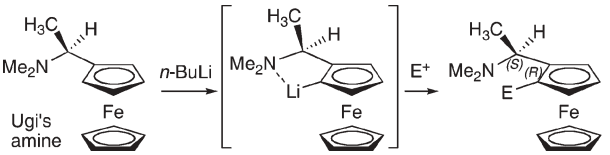
A useful synthesis of rare 1,2-disubstituted ferrocenylalkyl amines with (S_{Fc},S) configuration has been achieved in a sequential one-pot methodology from (*S*)-*p*-tolylsulfinylferrocene.

Due to their properties, particularly those regarding rigidity, ease of derivatization and planar chirality, ferrocenyl compounds have been widely used in asymmetric catalysis.[1] Planar chirality of 1,2-disubstituted ferrocenes is often a decisive factor for exerting control over the absolute configuration and enantiomeric excess.[2] Many of these ferrocenyl ligands were prepared by diastereoselective *ortho*-lithiation of *N*,*N*-dimethyl-1-ferrocenylethylamine (Ugi's amine), followed by introduction of an appropriate electrophile.[3] Consequently, the resulting ferrocenes have both planar and central chirality with (S_{Fc},R) or (R_{Fc},S) configurations (Scheme 1). For the diversity of ligand configuration, there is a need to develop a convenient method for the synthesis of the other diastereoisomer of such compounds.

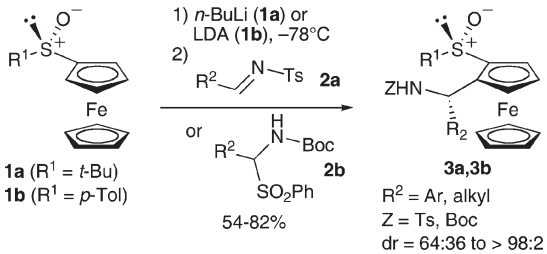


Scheme 1

Indeed, only few reports described the synthesis of ligands with (R_{Fc},R) or (S_{Fc},S) configurations. The main approach involved the introduction of a trimethylsilyl group in the *ortho*-position of Ugi's amine, further difficult metallation on the other *ortho*-position followed by electrophile introduction and then desilylation by treatment with fluoride anion.[4] Recently, a second process was described from (S_{Fc})-α-substituted ferrocenecarbaldehydes[5] in three steps.[6]

Moreover, the use of Ugi's amine as starting material does not allow any variation of substituent of the asymmetric carbon: always a methyl group. On the other hand, the synthesis 1-ferrocenylalkyl- (different from methyl) and 1-ferrocenylaryl-amines derivatives[7] were not very common due to the lack of efficient method[8] for their preparation whereas they were demonstrated to be more effective, as chiral ligands, than the parent methyl-substituted derivatives for some catalytic asymmetric reactions.[9] Only one example to date illustrated this purpose with the synthesis of (R,R_{Fc})-Taniaphos[10] and its use as efficient ligand for asymmetric reactions.[11]

Recently, we have developed the diastereoselective addition of lithiated *tert*-butylsulfinylferrocene **1a** to imines leading to enantiopure 1-ferrocenylalkyl amines **3a** (with various alkyl and aryl groups) having (S_S,S_{Fc},S) configurations (Scheme 2).[12]



Scheme 2

In this context, we argued that the rare 1,2-disubstituted ferrocenes **4** with (S_{Fc},S) configurations (Fig. 1) would be accessible from **3** if the sulfoxide can be replaced by an electrophile. We now wish to report our preliminary results on the synthesis of **3** and their transformation to **4**.

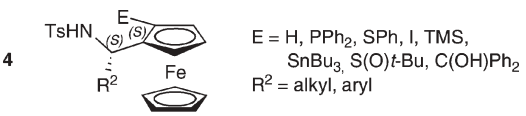


Fig. 1

When (*S*)-*tert*-butylsulfinylferrocene **1a** was submitted to *ortho*-metallation followed by alkyl or aryl imine addition (Table 1), aminosulfoxides **3a** were obtained with complete diastereocontrol when Boc groups were used as electron withdrawing groups on the nitrogen atom (entry 7). In most cases, the dr decreased by the use of *N*-tosyl group (entries 1, 3 and 5). However, we were pleased to find that using sulfoxide **1b**[13] (R^1 = *p*-tolyl) and LDA as a base (1.2 eq., −78 °C, 30 min), complete asymmetric induction was obtained with both *N*-Boc[14] and *N*-Ts series (entries 2, 4 and 8).[15] The expected (S_S,S_{Fc},S) configuration was confirmed by X-ray analysis of **3bb** (Fig. 2).[16]‡ An unusual weak hydrogen bonding

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† Electronic supplementary information (ESI) available: Experimental procedures and characterization for all new compounds described. See DOI: 10.1039/b710109k

Table 1 Diastereoselective *ortho*-lithiation followed by aldimine addition

Entry	Sulfoxide	Base	Imine (R^2, Ts) or sulfone (R^2, Boc)	Product	Isolated yield (%)	dr[a]
1	**1a**	*n*-BuLi	*i*-Pr, Ts	**3aa**	55	90 : 10
2	**1b**	LDA	*i*-Pr, Ts	**3ba**	66	>98 : 2
3	**1a**	*n*-BuLi	Ph, Ts	**3ab**	65	75 : 25
4	**1b**	LDA	Ph, Ts	**3bb**	74	>98 : 2
5	**1a**	*n*-BuLi	*t*-Bu, Ts	**3ac**	54	64 : 36
6	**1b**	LDA	*t*-Bu, Ts	**3bc**	82	84 : 16
7	**1a**	*n*-BuLi	*i*-Pr, Boc	**3ad**	76[b]	>98 : 2
8	**1b**	LDA	*i*-Pr, Boc	**3bd**	58[a,b]	>98 : 2

[a] Determined by ^{1}H NMR on the crude product. [b] Based on sulfone.

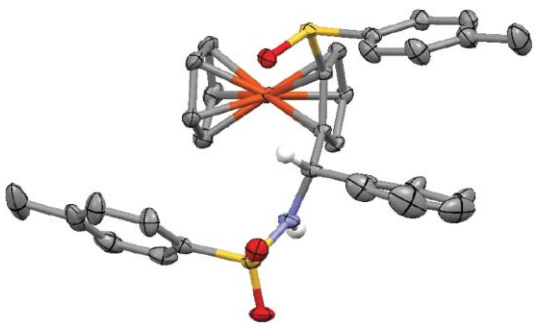


Fig. 2 X-Ray crystal structure of **3bb** (50% thermal ellipsoids). Hydrogen atoms are omitted for clarity except for C*H and NH.

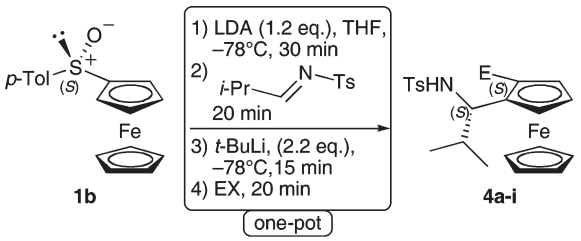
between the C**H* and the sulfinyl oxygen (S(*O*)···C**H*: 2.476 Å; C–H–O angle: 130.3°) was observed.

As a test reaction we next studied the displacement reaction of the *p*-tolylsulfinyl group with *t*-BuLi (−78 °C, 15 min),[17] using first **3ba** (bearing an *N*-tosyl group[18]) in order to synthesize **4a**, an enantiopure analog of Ugi's amine (R^2 = *i*-Pr, E = H).[19] Using 2.1 eq. of base then water as electrophile, **4a** was isolated with 85% yield and er 99 : 1 (enantioselective HPLC). As **3ba** was obtained as a single diastereoisomer, we envisioned to perform the whole sequence in one-pot reaction starting form sulfoxide **1b** (scheme in Table 2). Thus, **4a** was obtained in 49% yield[20] and er 99 : 1, that confirmed no epimerization occurred during all this process.[21]

We explored the scope of the sequential one-pot reaction firstly with chlorodiphenylphosphine as electrophile (Table 2, entry 2). In addition to the expected **4b** (Fig. 3),[22]‡ we were surprised to isolate non phosphinylated **4a** in respectively a 68 : 32 ratio.[23] A protonation reaction of a dilithiated species by diisopropylamine (generated in the first step) could explain this result. To overcome this problem, we decided to carry out the synthesis of **4b** from isolated **3ba** (Scheme 3). Surprisingly, exposure of **3ba** to *t*-BuLi followed by PPh_2Cl allowed the formation of phosphinamidite **5** as a major product and the expected phosphine **4b**, respectively in a 72 : 28 ratio with 90% yield. Monosubstituted ferrocene **4a** or hybrid phosphine-phosphinamidite[24] compound were not detected in the crude product. The amount of **5** can be reduced by using NaH, which deprotonates **3ba** but which does not displace the sulfoxide moiety.[25] Thus an excess of this base (3 eq.) followed (after completed gas evolution) by 1.1 eq. of *t*-BuLi, led to **5** and **4b** in 29 : 71 ratio. A similar result was obtained during the one-pot sequence (51 : 49 ratio).

Using conditions established for **4a**, a variety of electrophiles were next examined. A summary of the results is reported in Table 2. Our expeditious methodology was shown to be

Table 2 Preliminary scope of the sequential one-pot reaction



Entry	EX	E	Compound	Isolated yield (%)
1	H_2O	H	**4a**	49
2	Ph_2PCl	PPh_2	**4b**	41
3	PhSSPh	SPh	**4c**	52
4	TMSCl	TMS	**4d**	51
5	Bu_3SnCl	$SnBu_3$	**4e**	42
6	I_2	I	**4f**	46
7	*t*-BuS(O)S*t*-Bu (*R*)	S(O)*t*-Bu (*R*)	**4g**	43
8	PhCOPh	$C(OH)Ph_2$	**4h**	44
9	PhCHO	CH(OH)Ph	**4i**	41[a]

[a] 53 : 47 inseparable mixture of diastereoisomers.

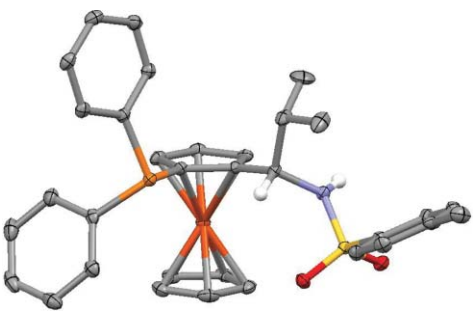
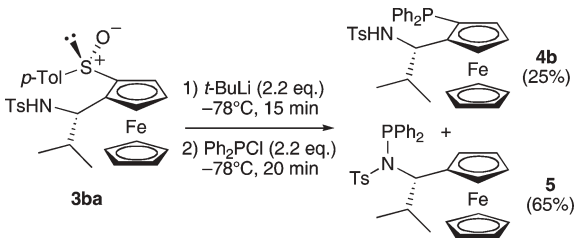


Fig. 3 X-Ray crystal structure of **4b** (50% thermal ellipsoids). Hydrogen atoms are omitted for clarity except for C*H and NH.



Scheme 3

compatible and efficient with various functionalities: sulfide, silane, stannane, halogen, sulfoxide and alcohols (41–52% yield for four steps).[26]

In conclusion, we have established a rapid and convergent methodology for the synthesis of a range of enantiopure ferrocenyl derivatives with the unusual (S_{Fc},S) configurations. The potential use of these new compounds for the preparation of chiral ligands for asymmetric catalysis is currently under investigation in our laboratories. Crucial influence of N–H proton in the ligand could be particularly studied.[27]

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Notes and references

‡ *Crystal data* for **3bb**: $C_{31}H_{29}FeNO_3S_2$, M = 583.54, crystal size 0.54 × 0.31 × 0.27 mm, orthorhombic, space group $P2_12_12_1$, a = 12.2501(3), b = 13.4034(3), c = 16.6923(4) Å, V = 2740.76(10) Å^3, T = 296 K, Z = 4, μ = 0.736 mm^{-1}, 86850 reflections collected, refinement for 8385 reflections and 345 parameters gave GOF = 1.110, R_1 = 0.0346 and wR_2 = 0.0830, absolute structure parameter = 0.002(9). Selected bond lengths (Å) and angles (°): C*–C_{Cp}1.5117(19), S–O 1.5063(12), S–C_{Cp} 1.7573(15), C*–N 1.4707(19); N–C*–C_{Cp} 108.75(12); O–S–C_{Cp}–C_{Cp} −28.6.

Crystal data for **4b**: $C_{33}H_{34}FeNO_2PS$, M = 595.51, crystal size 0.53 × 0.09 × 0.03 mm, monoclinic, space group $C2c$, a = 28.0611(10), b = 10.3417(3), c = 24.2234(9) Å, V = 5768.7(4) Å^3, T = 100 K, Z = 8, μ = 0.682 mm^{-1}, 103330 reflections collected, refinement for 8751 reflections and 488 parameters gave GOF = 1.086, R_1 = 0.0812 and wR_2 = 0.0981. Selected bond lengths (Å) and angles (°): C*–C_{Cp} 1.512(3), C_{Cp}–P 1.820(2), C*–N 1.469(2); P–C_{Cp}–C_{Cp}–C* −5.01.

CCDC 652839 and 652840. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b710109k

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14 We were not able to separate remaining sulfoxide **1b** and adduct **3ba** on silica gel. Thus, the yield was estimated by ^{1}H NMR on the crude product.

15 Except the particular case of *N*-tosylimine (R^2 = *t*-Bu). The dr was however increased (entry 6; 84 : 16 dr) as compared to the use of *tert*-butyl sulfoxide **3a** (entry 5; 64 : 36 dr).

16 Single crystals were obtained from a concentrated solution of AcOEt and by slow diffusion of *n*-heptane.

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20 As the formation of **3ba** was not completed (Table 1, entry 2), the remaining starting material was transformed into ferrocene by action of *t*-BuLi followed by hydrolysis. No other ferrocenic compound has been isolated.

21 While only one equivalent was theoretically sufficient, the best result was obtained using 2.2 eq. of *t*-BuLi.

22 We were able to crystallize only the racemic **4b** from ethanol. Consequently, only the (S,S_{Fc}) enantiomer was represented.

23 **4a**, **4b** and ferrocene were easily separated by column chromatography.

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