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Synthesis of Chiral Ferrocenylazines. Negishi Cross-Coupling or S_N^H Reactions?

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Abstract—Preparation of new hetaryl-containing planar chiral ferrocene by a nucleophilic substitution of hydrogen in azines was performed using a lithium derivative of (*S*)-ferrocenyl-p-tolylsulfoxide as s nucleophilic reagent

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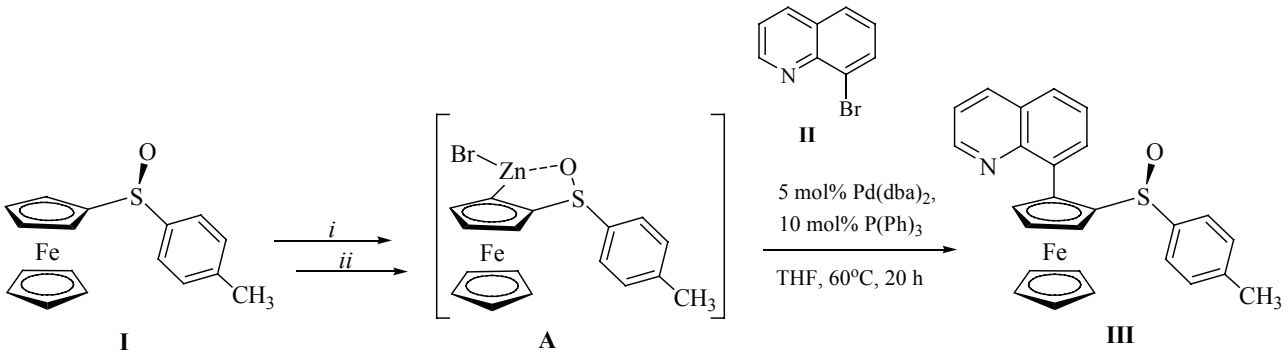
Planar chiral ferrocene derivatives are extensively used as ligands in versatile reactions of asymmetric synthesis [1–10]. An important place among the ligands of the ferroce series belongs to heterocyclic derivatives capable of forming complexes with metals and also with charged and neutral molecules [1, 11].

Quite a number [12–17] of compounds is known containing chiral groups, among them sulfoxide **I** (Scheme 1) [18]. The presence in the ferrocene structure of directing the 1,2-lithiation chiral moieties plays a decisive role in attaining both regio- and diastereoselectivity owing to the formation of cyclic structures in the intermediate metal derivatives (Complex Induced Proximity Effect, CIPE) [19, 20] due to the coordination of the lithium atom by the lone electron pair in the directing group, and to the spatial orientation of the substituent at the asymmetric center of the side chain of the ferrocene scaffold (compound **B**, Scheme 2).

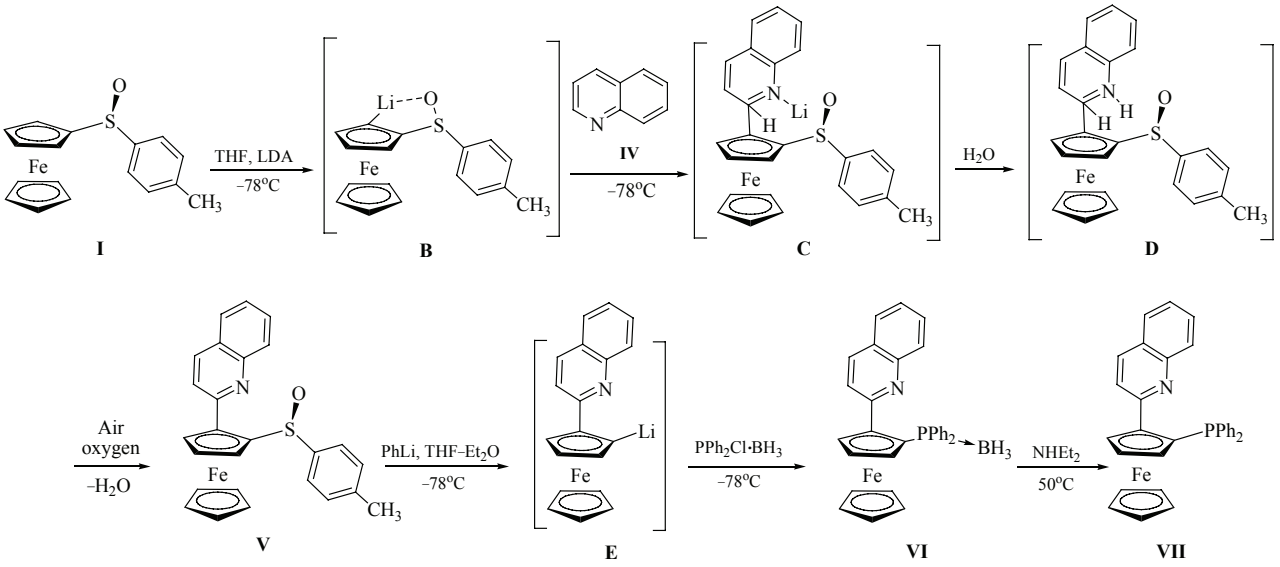
In most cases hetarylferrocenes, also the optically active ones, are prepared by cross-coupling catalyzed with transition metals [1, 11, 16]. At the same time the direct C–C and C–X couplings (X = N, O, S, P) are known of nucleophilic reagents with azines, the reactions of direct nucleophilic aromatic substitution of hydrogen (S_N^H reaction) providing the possibility to functionalize the bonds C_{sp^2}–H in (hetero)arenes [21, 22]. We formerly showed the efficiency of the S_N^H reaction in the direct coupling of lithium derivatives of ferrocene and cymantrene with

Scheme 1.



(*i*) LDA, THF, –78°C, 30 min; (*ii*) $ZnBr_2$, THF, –78°C, 60 min.

Scheme 2.



azines [23–25]. To the best of our knowledge the S_N^H reaction was not used as the key stage in the synthesis of chiral *P,N*-ligands.

In this report we show by an example of (quinolin-2-yl)-containing ferrocene *P,N*-ligand that the S_N^H procedure can be applied to the preparation of planar chiral compounds**.**

In [18] (Scheme 1) a five-stage synthesis was described of a ligand (S_{Fc},*S*)-[2-(quinolin-8-yl)ferrocene-1-yl]-*p*-tolylsulfoxide **(III)** using as the initial reagent sulfoxide **I** [26] that was subjected to lithiation (*i*), then to transmetallation into Zn-derivative **A** (*ii*), and to palladium-catalyzed cross-coupling with 8-bromoquinoline by Negishi reaction to obtain finally compound **III**, whose *p*-tolyl sulfoxide group was replaced by a diphenylphosphine residue.

We showed that the application of the S_N^H procedure made it possible to introduce directly a quinoline residue into compound **B** (Scheme 2). This approach has a number of advantages: It permits avoiding the use of quinoline haloderivatives, does not require the application of palladium salts and of the accompanying ligands, reduces the number of stages. The overall yield with respect to compound **I** along our protocol reached 50.4% **(**28.5% [18]**).**

Compound **B** readily enters into the direct coupling reaction with quinoline (**IV**) affording the corresponding planar chiral derivative **V** at –78°C within 30 min. It is presumable that the formation of compound **V** proceeds according to the scheme generally accepted for the S_N^H reaction [21, 22]: the addition of the lithium derivative **B** to the azine with the formation of σ^H-adducts **C,** their hydrolysis to dihydrocompounds **D**, and fast spontaneous aromatization of dihydroazines **D** to the reaction products **V** under the oxidative action of the air oxygen (Scheme 2).

Sulfoxide **I** we prepared by an improved method reacting ferrocenelithium with (*S*)-(–)-menthyl-*p*-tolylsulfinate at –78°C. The process proceeds stereoselectively with the formation of *S*-isomer in a good yield (80%).

The exchange of the functional group sulfoxide–lithium in hetarylsulfoxide **V** and the subsequent introduction of the diphenylphosphine fragment afforded a *P,N*-ligand, (S_{Fc},*S*)-[2-(quinolin-2-yl)-ferrocene-1-yl] diphenylphosphine (**VII**). Thus at –78°C in anhydrous THF PhLi reacts with derivative **V** giving within 10 min 1-lithium-2-hetarylferrocene **E** that with $PPh_2Cl{\cdot}BH_3$ furnishes a stable against the air and moisture borane complex **VI** (Scheme 2). Complex **VI** was subjected to column chromatography on SiO_2. The removal of the borane protection occurs readily at heating compound **VI** in diethylamine in a quantative yield [27]. Compound **VI** was isolated in 72% yield. The *de* value for compounds **V, VI** was >99%.

The assumed structure of 1,2-disubstituted hetarylferrocenes is in agreement with the data of ^1H and ^{13}C NMR, IR, and mass spectra; the composition is

consistent with the elemental analysis data. The optical purity of the derivatives was determined by HPLC on a column with an optically active adsorbent Chiralcel OD-H.

Hence the S_N^H procedure that we applied for the first time to the synthesis of chiral ensembles ferrocene–azine made it possible to simplify their synthesis. We believe that the above described metal noncatalyzed S_N^H cross-coupling possesses a general character.

EXPERIMENTAL

^{1}H (400 MHz), ^{13}C (100 MHz), and ^{31}P (162 MHz) NMR spectra were registered on a spectrometer Bruker Avance II (400 MHz) from solutions in $CDCl_3$. Chemical shifts are reported from internal reference $SiMe_4$. The assignment of ^{1}H and ^{13}C signals was performed with the help of a combination of 2D heteronuclear experiments ^{1}H–^{13}C HSQC and ^{1}H–^{13}C HMBC. IR spectra were recorded on an IR Fourier spectrophotometer Bruker Alpha equipped with a device for measuring incomplete internal reflection. Mass spectra were taken on an instrument MicrOTOF-Q II Bruker Daltonics. Elemental analysis was carried out on an analyzer Perkin Elmer 2400-II, HPLC analysis, on a chromatograph Merck Hitachi (column DIACEL Chiralcel OD-H). The rotation angles were measured on a spectrophotopolarimeter Perkin Elmer 343 Plus. The solvents were purified and dried by standard procedures. In the study were used commercial reagents quinoline, (*S*)-(–)-menthyl *p*-tolylsulfinate, BuLi, LDA, PhLi, THF purchased from Sigma-Aldrich, all other reagents and solvents were obtained from Khimreaktivsnab. Bromoferrocene [28], $Ph_2PCl{\cdot}BH_3$ [18] were synthesized by published methods. The properties of compounds coincide with the published data [18, 28].

(*S*)-Ferrocenyl-*p*-tolylsulfoxide (I). To a solution of 0.265 g (1 mmol) of bromoferrocene in 6 ml of THF under an argon atmosphere at room temperature was added 0.63 ml (1 mmol) of 1.6 M solution of BuLi in hexane, and the mixture was kept for 20 min. Then to the reaction mixture was added 0.325 g (1.1 mmol) of (*1R*,*2S*,*5R*)-(–)-menthyl-(*S*)-*p*-toluenesulfinate in 15 ml THF, the mixture was cooled to –78°C and maintained for 30 min. The reaction products were isolated by column chromatography, eluent hexane–ethyl acetate, 7:3 (R_f 0.3). Yield 0.217 g (67%), yellow powder. The properties of compound **I** are consistent with the published data [26].

(S_{Fc},*S*)-[2-(Quinolin-2-yl)ferrocen-1-yl]-*p*-tolylsulfoxide (V). To a solution of 0.324 g (1 mmol) of sulfoxide **I** in 5 ml of THF under an argon atmosphere at –78°C was added 0.55 ml (1.1 mmol) of 2 M of LDA solution in THF. After 40 min of vigorous stirring was added a solution of 0.26 ml (2.0 mmol) of quinoline (**IV**) in 7 ml of THF. The reaction mixture was stirred for 30 min at –78°C, then it was gradually warmed to room temperature. The solution was concentrated at a reduced pressure. The residue obtained was chromatographed on SiO_2, eluent hexane–ethyl acetate, 8:2 (R_f 0.2). Yield 0.316 g (70%), dark red crystals, mp 104°C, $[\alpha]_D$ +188.08° (*c* 0.1 $CHCl_3$). IR spectrum, ν, cm^{-1}: 2920, 2850, 1597, 1041, 1004. ^{1}H NMR spectrum, δ, ppm: 2.37 s (3H, CH_3), 4.18 s (5H, Cp), 4.39 br.s (1H, C_5H_3), 4.57 br.s (1H, C_5H_3), 5.25 br.s (1H, C_5H_3), 7.26 t (2H, C_6H_4, *J* 7.4 Hz), 7.51 t (1H, H$^{4'}$, *J* 7.0 Hz), 7.68 d (1H, H$^{7'}$, *J* 8.0 Hz), 7.71 d (2H, C_6H_4, *J* 4.0 Hz), 7.78 d (1H, H$^{6'}$, *J* 7.8 Hz), 8.09 s (2H, H$^{5'}$, H$^{8'}$), 8.12 d (1H, H$^{3'}$, *J* 8.68 Hz). ^{13}C NMR spectrum, δ, ppm: 21.50 (CH_3), 70.38 (C_5H_3), 71.49 (Cp), 71.85 (C_5H_3), 72.62 (C_5H_3), 85.37 (C–Cp), 94.54 (C–Cp), 121.53 (C_6H_4), 125.62 (C^{8}), 125.71 (C^{7}), 126.99 (C^{4}), 127.53 (C^{6}), 129.33, 129.48 (C_6H_4), 129.53 (C^{5}), 135.71 (C^{3}), 140.95 (C^{8a}), 141.42 (C_6H_4), 148.05 (C^{4a}), 157.26 (C^{2}). Mass spectrum, *m/z* ($I_{rel.}$, %): 452.07 (100) $[M + H]^+$. Found, %: C 68.52; H 4.98; N 2.99. $C_{26}H_{21}FeNOS$. Calculated, %: C 69.18; H 4.66; N 3.10. *M* 451.36.

(S_{Fc},*S*)-[2-(Quinolin-2-yl)ferrocene-1-yl] diphenylphosphine·BH_3 (VI). To a solution of 0.451 g (1 mmol) of quinolinylferrocenyl *p*-tolyl sulfoxide (**V**) in 5 ml of THF under an argon atmosphere at –78°C was added 1.1 ml (2.0 mmol) of 1.8 M solution of PhLi in dibutyl ether. After 10 min of vigorous stirring at –78°C was added 3.0 mmol of $Ph_2PCl{\cdot}BH_3$. The reaction mixture was kept for 5 min at –78°C, then it was gradually warmed to room temperature. On the completion of the reaction was added 0.5 ml of water and 0.15 ml of triethylamine, and the mixture was stirred for 5 min. The solution was concentrated at a reduced pressure. The residue obtained was chromatographed on SiO_2, eluent hexane–ethyl acetate, 8 : 2 (R_f 0.4). Yield 0.368 g (72%), dark red crystals, mp 142°C, $[\alpha]_D$ +305° (*c* 0.1 $CHCl_3$). IR spectrum, ν, cm^{-1}: 2963, 2380, 2343, 1099, 1056, 1016, 797. ^{1}H NMR spectrum, δ, ppm: 1.25 s (3H, BH_3), 3.93 s (1H, C_5H_3), 4.49 s (5H, CpH), 4.59 s (1H, C_5H_3), 5.12 s (1H, C_5H_3), 7.28–7.32 m (2H, Ph), 7.38–7.53 m (5H, Ph), 7.56–7.65 m (3H, Ph), 7.67 s (1H, H$^{4'}$), 7.70 d (2H, H$^{6'}$, H$^{7'}$, *J* 4.0 Hz), 7.72 s (1H, H$^{5'}$), 7.74 s (1H, H$^{8'}$), 7.94 d (1H, H$^{3'}$, *J* 8.0 Hz). ^{13}C NMR spectrum, δ, ppm: 71.42 (C_5H_3), 71.58 (C_5H_3), 73.78 (Cp), 76.84 (C_5H_3),

89.88 (C–Cp), 89.96 (C–Cp), 120.71 (C^4), 125.92, 126.69, 127.30, 128.01, 128.11, 128.21 (Ph), 128.30 (C^8), 128.97 (C^{8a}), 129.39 (C^6), 131.40 (C^5), 132.81, 132.90 (Ph) 133.40 (C^7), 135.34 (C^3), 147.18 (C^{4a}), 156.17 (C^2). ^{31}P NMR spectrum, δ, ppm: 29.85 (PPh_2). Mass spectrum, *m/z* ($I_{отн.}$, %): 512.13 (25) $[M + H]^+$, 498.1 (100) $[M + H - BH_3]^+$. Found, %: C 72.47; H 5.60; N 2.49. $C_{31}H_{27}BFeNP$. Calculated, %: C 72.80; H 5.28; N 2.74. *M* 511.18.

(S_{Fc},*S*)-[2-(Quinolin-2-yl)ferrocene-1-yl]diphenylphosphine (VII). In 2 ml of diethylamine was dissolved 0.01 g (0.02 mmol) of borane complex **VI**, and the solution was heated at 50°C for 30 min. The solvent was distilled off at a reduced pressure. The procedure was repeated 4 times. Yield 0.010 g (99%), dark red crystals. ^{1}H NMR spectrum, δ, ppm: 3.83 s (1H, C_5H_3), 4.10 s (5H, CpH), 4.53 s (1H, C_5H_3), 5.20 s (1H, C_5H_3), 7.23–7.41 m (6H, Ph), 7.51–7.71 m (7H, $H^{4'}$, $H^{5'}$, $H^{7'}$, Ph), 7.80 d (1H, $H^{6'}$, *J* 8.0 Hz), 7.92 d (1H, $H^{8'}$, *J* 8.0 Hz), 8.03 d (1H, $H^{3'}$, *J* 8.0 Hz). ^{31}P NMR spectrum, δ, ppm: 17.59 (PPh_2).

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REFERENCES

1. Togni, A. and Hayashi, T., *Ferrocenes: Homogeneous Catalysis – Organic Synthesis – Materials*, Science VCH, Weinheim, 1995.
2. Burckhardt, U., Baumann, M., Trabesinger, G., Gramlich, V., and Togni, A., *Organometallics*, 1997, vol. 16, p. 5252.
3. Evans, D.A., Campos, K.R., Tedrow, J.S., Michael, F.E., and Gagne, M.R. *J. Am. Chem. Soc.,* 2000, p. 122, p. 7905.
4. Hu, X.-P., Chen, H.-L., and Zheng, Z. *Adv. Synth. Catal.,* 2005, vol. 347, p. 541.
5. Cheung, H.Y., Yu, W.-Y., Au-Yeung, T.T.L., and Zhou, Z., Chan, A.S.C. *Adv. Synth. Catal*., 2009, vol. 351, p. 1412.
6. Fukuzawa, S., Oki, H., Hosaka, M., Sugasawa, J., and Kikuchi, S. *Org. Lett., 20*07, 9, p. 5557.
7. Wang, D.-Y., Hu, X.-P., Hou, C.-J., Deng, J., Yu, S.-B., Duan, Z.-C., Huang, J.-D., and Zheng, Z., *Org. Lett.,* 2009, vol. 11, p. 3226.
8. Schnyder, A., Togni, A., and Wiesli, U.*, Organometallics.,* 1997, vol. 16, p. 255.
9. Oura, I., Shimizu, K., Ogata, K., and Fukuzawa, S., *Org. Lett.,* 2010, vol. 12, p. 1752.
10. Zhang, C., Yu, S.-B., Hu, X.-P., Wang, D.-Y., and Zheng, Z., *Org. Lett.,* 2010, vol. 12, p. 5542.
11. Utepova, I.A., Chupakhin, O.N., and Charushin, V.N., *Heterocycles*, 2008, vol. 76, p. 39.
12. Gokel, G.W., Marquarding, D., and Ugi, I.K., *J. Org. Chem.,* 1972, vol. 37, p. 3052.
13. Kloetzing, R.J., Lotz, M., and Knochel, P., *Tetrahedron: Asymmetry,* 2003, vol. 14, p. 255.
14. McManus, H.A. and Guiry, P.J., *Chem. Rev*., 2004, vol. 104, p. 4151.
15. Sutcliffe, O.B. and Bryce, M.R., *Tetrahedron: Asymmetry*., 2003, vol. 14, p. 2297.
16. Atkinson, R.C.J., Gibson, V.C., and Long, N.J., *Chem. Soc. Rev*., 2004, vol. 33, p. 313.
17. Peters, R. and Fischer, D.F., *Org. Lett.,* 2005, vol. 7, p. 4137.
18. Kloetzing, R.J. and Knochel, P., *Tetrahedron: Asymmetry,* 2006, 17, p. 116.
19. Whisler, M.C., MacNeil, S., Snieckus, V., and Beak, P., *Angew. Chem., Int. Ed.,* 2004, vol. 43, p. 2206.
20. Schlosser, M. and Mongin, F., *Chem. Soc. Rev.,* 2007, vol. 36, p. 1161.
21. Chupakhin, O.N., Charushin, V.N., and van der Plas, H., *Nucleophilic Aromatic Substitution of Hydrogen*, San Diego–New York: Academic Press, 1994, p. 367.
22. Makosza, M., *Synthesis*, 2011, vol. 15, p. 2341.
23. Chupakhin, O.N., Utepova, I.A., Kovalev, I.S., Rusinov, V.L., and Starikova, Z.A., *Eur. J. Org. Chem.,* 2007, vol. 5, p. 857.
24. Utepova, I.A., Lakhina, A.E., Varaksin, M.V., Kovalev, I.S., Rusinov, V.L., Slepukhin, P.A., Kodess, M.I., and Chupakhin, O.N., *Russ. Chem. Bull., Int. Ed..,* 2008, vol. 57, p. 2156.
25. Utepova, I.A., Musikhina, A.A., Chupakhin, O.N., and Slepukhin, P.A., *Organometallics, 20*11, vol. 30, p. 3047.
26. Guillaneux, D. and Kagan, H.B., *J. Org. Chem.,* 1995, vol. 60, p. 2502.
27. Imamoto, T., Kusumoto, T., Suzuki, N., and Sato, K., *J. Am. Chem. Soc.,* 1985, vol. 107, p. 5301.
28. Drouin, B.J., Lavaty, T.G., Cassak, P.A., and Kukolich S.G., *J. Chem. Phys.,* 1997, vol. 107, p. 6541.