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Convenient Access to New Chiral Ferroceno-(iso)quinolines

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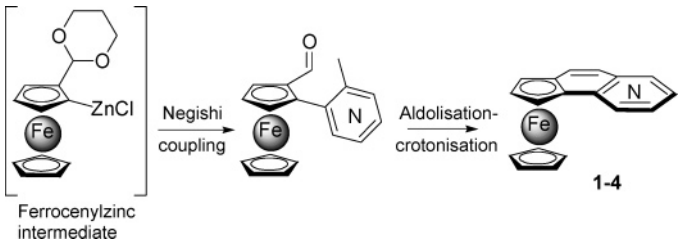

New chiral pyridine derivatives possessing the planar chirality of the ferrocene have been prepared by means of an aldolization−crotonization reaction. This very simple reaction has been applied to the synthesis of isomers **1**−**4** that differ in the position of the nitrogen atom on the pyridine ring. Following the same procedure, asymmetric synthesis of **1** has been achieved using an enantiopure ferrocenylzinc intermediate. This method has also allowed the preparation of a chiral analogue of 2,2′-bipyridine.

In the growing interest of organocatalysis, chiral pyridine derivatives are attracting much attention due to their reactivity as a base or as a nucleophile.[1] Moreover, these compounds can be easily transformed into bipyridines and terpyridines to afford good ligands for asymmetric homogeneous catalysis[2] and material science.[3] As a part of our research program aiming at the synthesis of new functional pyridine-containing polycyclic ligands, we were interested in the easy asymmetric synthesis and functionalization of new chiral pyridine derivatives possessing the planar chirality of the ferrocene. The chemistry of ferrocene-based planar-chiral pyridines and bipyridines is limited to the work by Fu and co-workers, who developed effective enantioselective catalysts for several reaction classes.[4] In our approach, the ferrocene and the pyridine moieties are included in a planar system obtained in a final ring-closure step (Figure 1). The central ring can be crucial in asymmetric reactions, allowing a π-stacking between the pyridine

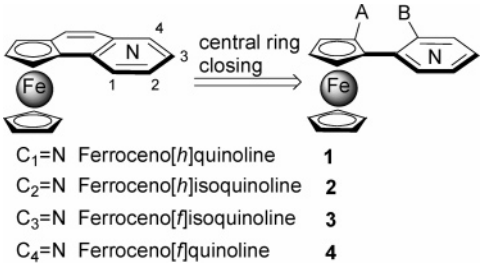

FIGURE 1. Target molecules **1**−**4**.

core and an aromatic ring placed on the other Cp ring, leading to a complete shielding of the bottom face. A careful tuning of A and B substituents as well as of the position of the nitrogen atom could allow the synthesis of all isomers **1**−**4**.

According to a previous work concerning the Negishi coupling of a ferrocenylzinc complex with aryl bromides,[5] we first decided to use this methodology to bring together the ferrocene and the pyridine moieties. After lithiation of ferrocenylacetal **5** with *sec*-BuLi,[6] the generated ortholithiated species was transmetalated with $ZnCl_2$ and cross-coupled with 2-bromopyridine-3-carbaldehyde[7] and 3-bromo-2-chloropyridine in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$ to afford aldehydes **6** and **7** in good yields (Scheme 1). These two compounds were then used to test different strategies for performing the intramolecular cyclization.

The formation of ferroceno[*h*]quinoline **1**[8] was easily obtained by a McMurry reaction[9] of **6** using the Ti/Zn system. Despite the good yield, the use of a large excess of $TiCl_4$ and Zn is a limiting factor for the reaction scale-up. Alternatively, **1** can be obtained by a second procedure based on a recent work describing the preparation of phenanthrenes by ring-closing metathesis.[10] Compound **6** was first transformed to bisalkene **8**, which upon treatment with a catalytic amount of the second-generation Grubbs catalyst in refluxing toluene furnished **1**. In these conditions the lifetime of the catalyst is very short and the conversion did not exceed 80% even after longer reaction times. The use of milder conditions such as refluxing dichloromethane led to only 6% conversion after 5 h. Nevertheless, the combined yield of 46% for the two steps leading to **1** prompted us to give up this second strategy. On the other hand, ferroceno[*f*]quinoline **4** was prepared starting from **7** by an intramolecular Heck reaction. Compound **7** was first transformed by a Wittig reaction to give **10**, which was cyclized using Fu conditions[11] to afford the desired compound in good yield. Unfortunately, **4** was accompanied with the nonseparable

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(2) Chelucci, G.; Thummel, R. P. *Chem. Rev.* **2002**, *102*, 3129−3170.

(3) Kaes, C.; Katz, A.; Hosseini, M. W. *Chem. Rev.* **2000**, *100*, 3553−3590.

(4) For recent reviews about pyridines see: (a) Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542−547. (b) Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412−420. For the only example about bipyridines see: (c) Rios, R.; Liang, J.; Lo, M. M.-C.; Fu, G. C. *Chem. Commun.* **2000**, 377−378.

(5) (a) Mamane, V.; Ledoux-Rak, I.; Deveau, S.; Zyss, J.; Riant, O. *Synthesis* **2003**, 455−467. (b) Mamane, V.; Riant, O. *Tetrahedron* **2001**, *57*, 2555−2561.

(6) Steffen, W.; Laskoski, M.; Collins, G.; Bunz, U. H. F. *J. Organomet. Chem.* **2001**, *630*, 132−138.

(7) Numata, A.; Kondo, Y.; Sakamoto, T. *Synthesis* **1999**, 306−311.

(8) The nomenclature is given by analogy with the one used for benzoquinoline and -isoquinoline.

(9) McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513−1524.

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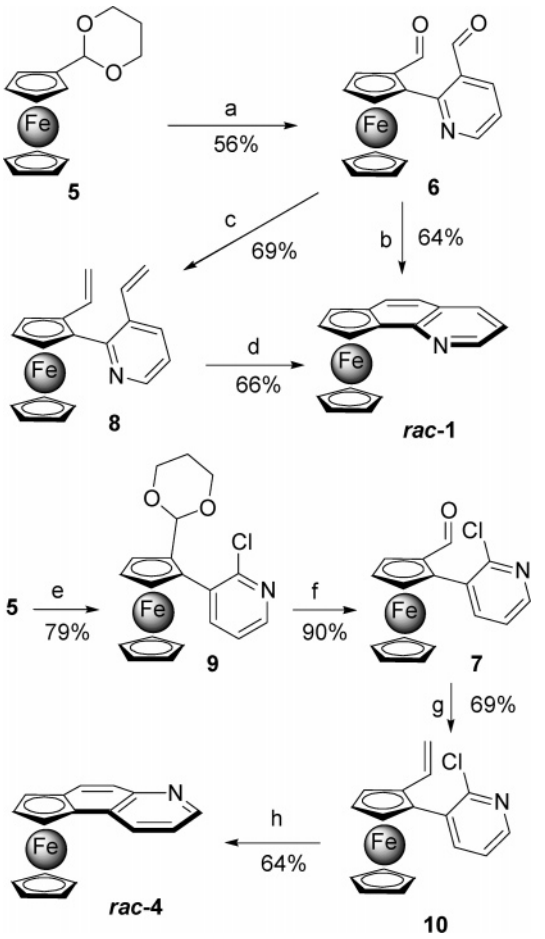
SCHEME 1. Synthetic Study of the Intramolecular Cyclization[a]

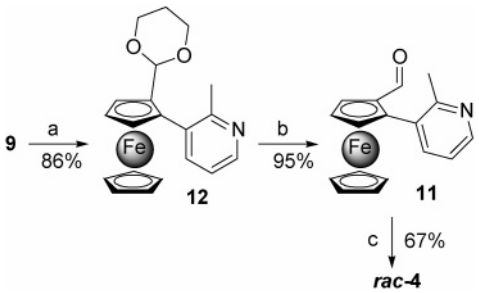


[a] Reagents and conditions: (a) (i) *sec*-BuLi, THF, −78 to −10 °C, 1 h; (ii) $ZnCl_2$, THF, −78 °C to rt, 1 h; (iii) 2-bromopyridine-3-carbaldehyde (1 equiv), $PdCl_2(PPh_3)_2$ (5 mol %), THF, rt, 10 h; (iv) *p*-TSA (1 equiv), THF, H_2O, rt, 2 h. (b) $TiCl_4$ (5 equiv), Zn (10 equiv), pyridine (5 equiv), THF, reflux. (c) $Ph_3P{=}CH_2$ (3 equiv), THF, −40 °C to rt. (d) Grubbs second-generation (20 mol %), toluene, reflux, 30 min. (e) *sec*-BuLi; (ii) $ZnCl_2$; (iii) 3-bromo-2-chloropyridine (1 equiv), $PdCl_2(PPh_3)_2$ (5 mol %), THF, rt, 10 h. (f) *p*-TSA (1 equiv), THF, H_2O, rt, 2 h. (g) $PPh_3P{=}CH_2$ (1.5 equiv), THF, −40 °C to rt, 3 h. (h) $Pd_2(dba)_3$ (1.5 mol %), P(*t*-Bu)$_3$ (6 mol %), Cy_2NMe (1.1 equiv), dioxane, 120 °C, 20 h.

exo isomer resulting from the attack at the more subtituted position of the alkene.

In our research of the best method allowing the easy synthesis of all isomers **1**−**4**, we then focused on the use of commercial or easily available pyridine derivatives. These characteristics were fulfilled by the picoline derivatives due to the facile deprotonation of the methyl group and the possible cyclization with an internal aldehyde as described by de Koning and co-workers.[12] This group used 4 equiv of *t*-BuOK in DMF at 80 °C under irradiation for 10 min to perform this reaction. To valid this strategy, compound **11** was prepared by Kumada coupling[13] of **9** with MeMgBr in the presence of

SCHEME 2. Synthesis of 4 Using the Aldolization−Crotonization Reaction[a]



[a] Reagents and conditions: (a) MeMgBr (3 equiv), $NiCl_2$(dppp) (20 mol %), Et_2O, rt, 20 h. (b) *p*-TSA (1 equiv), THF, H_2O, rt, 2 h. (c) *t*-BuOK (2 equiv), DMF, rt, 2 h.

$NiCl_2$(dppp) as the catalyst followed by the deprotection of the acetal. We found that only 2 equiv of *t*-BuOK in DMF at room temperature for 2 h was necessary to achieve the cyclization of **11** to **4** in good yield (Scheme 2).

Having an easy and efficient method for the cyclization reaction, our next goal was the synthesis of the other isomers, **1**−**3**, using the same methodology. For this purpose disubstituted pyridines **13**−**16** were chosen to perform the Negishi coupling with acetal **5** (Figure 2).

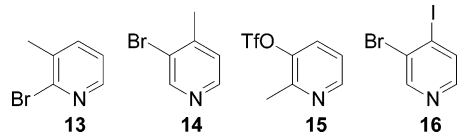


FIGURE 2. Pyridines involved in the Negishi cross-coupling of **5**.

Compounds **13** and **14** are commercially available, and compounds **15**[14] and **16**[15] have been obtained in one step using known procedures. Triflate **15** was expected to generate directly compound **11** by a Negishi coupling, avoiding the long sequence depicted in Scheme 2. In compound **16** the bromine atom was placed to be exchanged later by a methyl group.

As previously described for the synthesis of **6** and **7**, the zinc complex generated from **5** was coupled with **13** and **14** to afford, after hydrolysis of the acetal groups, **17**[16] and **18** in good yields. Following the procedures described by Knochel,[17] compounds **15** and **16** were coupled with **5** to yield **11** and **19**. Compound **19** was then transformed into **20** by a Stille coupling[18] using Me_4Sn followed by hydrolysis of the acetal. Compounds **17**, **18**, and **20** were cyclized using the same procedure described for **11** (Scheme 2) to furnish **1**−**3** in moderate to excellent yields (Scheme 3).

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(15) Baxter, P. N. W. *Chem. Eur. J.* **2003**, *9*, 2531−2541.

(16) Compounds **6**, **17**, **(R)-17**, and **24** are very unstable and were cyclized directly after the deprotection step.

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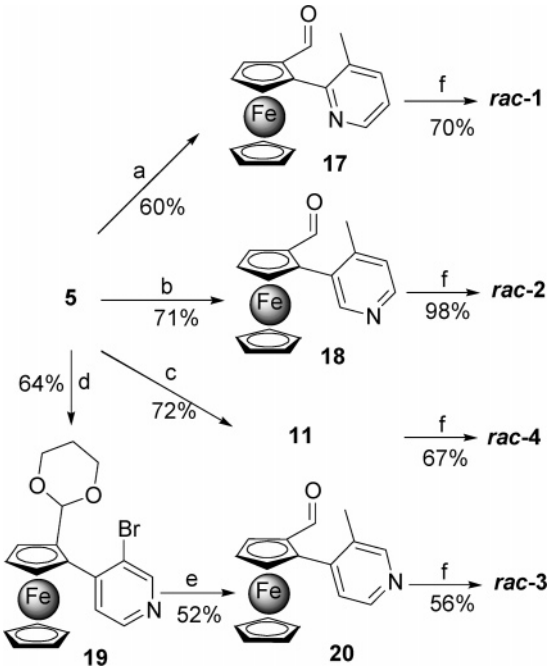
(18) For a recent review see: Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704−4734.

SCHEME 3. Synthesis of All Isomers 1−4[a]

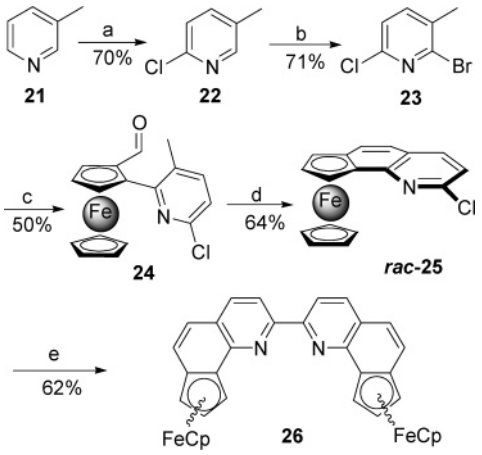


[a] Reagents and conditions: (a) (i) *sec*-BuLi; (ii) $ZnCl_2$; (iii) **13** (1 equiv), $PdCl_2(PPh_3)_2$ (5 mol %), THF, rt, 10 h; (iv) *p*-TSA (1 equiv), THF, H_2O, rt, 2 h. (b) (i) *sec*-BuLi; (ii) $ZnCl_2$; (iii) **14** (1 equiv), $PdCl_2(PPh_3)_2$ (5 mol %), THF, rt, 10 h; (iv) *p*-TSA (1 equiv), THF, H_2O, rt, 2 h. (c) (i) *sec*-BuLi; (ii) $ZnCl_2$; (iii) **15** (0.5 equiv), $Pd_2(dba)_3$ (5 mol %), dppf (5 mol %), THF, 65 °C, 10 h; (iv) *p*-TSA (1 equiv), THF, H_2O, rt, 2 h. (d) (i) *sec*-BuLi; (ii) $ZnCl_2$; (iii) **16** (1 equiv), $Pd_2(dba)_3$ (2.5 mol %), P(2-furyl)$_3$, THF, rt, 10 h. (e) (i) Me_4Sn (2 equiv), $Pd(PPh_3)_4$ (5 mol %), DMF, 100 °C, 20 h; (ii) *p*-TSA (1 equiv), THF, H_2O, rt, 2 h. (f) *t*-BuOK (2 equiv, 1 equiv in the case of **18**), DMF, rt, 2 h.

One other advantage for using picolines as starting material for this synthesis was the expertise of our laboratory in the functionalization of such compounds using the superbase *n*-BuLi-LiDMAE (lithium dimethylaminoethoxide).[19] This method allowed us to introduce successively a chlorine and a bromine atom in the 2- and 6-positions of 3-picoline **21** (Scheme 4). The resulting compound **23** was then used to synthesize in three steps one analogue of 2,2′-bipyridine. The Negishi protocol between **23** and **5** followed by deprotection of the acetal furnished **24**, which was cyclized to yield **25**. Homocoupling of **25** in the presence of a nickel complex[20] allowed the formation of both diastereoisomers of **26**, the *meso* and the *dl*, in a 1:1 mixture, as shown by ^{1}H NMR analysis.[21]

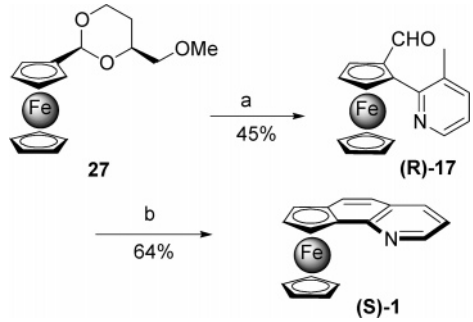
To prove the viability of this method for the asymmetric synthesis of these new ferrocenylpyridine derivatives, we performed the synthesis of **(S)-1** (Scheme 5).[22] Following the procedure used previously, **27** was ortholithiated diastereoselectively,[23] transmetalated with $ZnCl_2$,

SCHEME 4. Synthesis of a 2,2′-Bipyridine Analogue[a]



[a] Reagents and conditions: (a) (i) *n*-BuLi-LiDMAE (3 equiv), hexane, 0 °C, 1 h; (ii) C_2Cl_6 (3.5 equiv), THF, −78 °C, 1 h. (b) (i) *n*-BuLi−LiDMAE (3 equiv), hexane, 0 °C, 1 h; (ii) CBr_4 (3.5 equiv), THF, −78 °C, 1 h. (c) (i) **5** (1 equiv), *sec*-BuLi; (ii) $ZnCl_2$; (iii) **23** (1 equiv), $PdCl_2(PPh_3)_2$ (5 mol %), THF, rt, 10 h; (iv) *p*-TSA (1 equiv), THF, H_2O, rt, 2 h. (d) *t*-BuOK (2 equiv), DMF, rt, 2 h. (e) $NiCl_2 \cdot 6H_2O$ (1 equiv), PPh_3 (4 equiv), Zn (1 equiv), DMF, 50 °C, 3 h.

SCHEME 5. Asymmetric Synthesis of 1[a]



[a] Reagents and conditions: (a) (i) *t*-BuLi, Et_2O, −78 °C to rt, 1 h; (ii) $ZnCl_2$, THF, −78 °C to rt, 1 h; (iii) **13** (1 equiv), $PdCl_2(PPh_3)_2$ (5 mol %), THF, rt, 10 h; (iv) *p*-TSA (1 equiv), THF, H_2O, rt, 2 h. (b) *t*-BuOK (2 equiv), DMF, rt, 2 h.

and coupled with **13** to furnish **(R)-17**, which was cyclized in the presence of *t*-BuOK to give **(S)-1** in moderate yield.

In conclusion, the present study reveals an easy access to all isomers of the chiral ferroceno-(iso)quinolines. The synthetic protocol described in this paper is simple and convenient and has been applied to the asymmetric synthesis of ferroceno[*h*]quinoline **1** and to the synthesis of the bipyridine analogue **26**. The functionalization of these new molecules as well as the activity of the enantiopure forms in asymmetric synthesis and catalysis is in progress in our laboratory.

Experimental Section

Representative Procedure for the Negishi Cross-Coupling Reaction. Preparation of 2-(3-Methylpyridin-2-yl)-ferrocenecarbaldehyde (17). To a solution of **5** (816 mg, 3.0

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(21) One diastereoisomer has been isolated by chromatography on silica gel and characterized.

(22) The stereochemistry is given according to the Schlögl rule: Schlögl, K. *Top. Stereochem.* **1967**, *1*, 39−93.

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mmol) in dry THF (12 mL) at −78 °C under nitrogen was added slowly a solution of *sec*-BuLi (1.4 M in cyclohexane, 2.4 mL, 3.3 mmol). After 20 min the temperature was raised to −10 °C for 1 h. The orange solution was cooled to −78 °C, a solution of freshly dried $ZnCl_2$ in THF (0.5 M, 7.2 mL, 3.6 mmol) was added slowly, the temperature was raised to room temperature, and the reaction mixture was stirred for 1 h. To the orange suspension were successively added pyridine **13** (340 μL, 3 mmol) and $PdCl_2(PPh_3)_2$ (105 mg, 0.15 mmol), and the mixture was stirred at room temperature overnigt to give a red-brown solution. Brine was added, and the mixture was extracted with ethyl acetate, dried over $MgSO_4$, and concentrated. The residue was dissolved in THF (15 mL) water (0.75 mL) and *p*-TSA (570 mg, 3 mmol) were added, and the mixture was stirred at room temperature for 2 h under exclusion of light. A saturated solution of sodium hydrogencarbonate was added, and the mixture was extracted with ethyl acetate, dried over $MgSO_4$, and concentrated. The residue was purified by chromatography on silica gel (hexanes/ethyl acetate, 7:3) to afford compound **17** as a red-orange syrup (550 mg, 60%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.34 (s, 3H), 4.35 (s, 5H), 4.74 (s, 1H), 4.84 (s, 1H), 5.03 (s, 1H), 7.13 (br s, 1H), 7.45 (br s, 1H), 8.48 (br s, 1H), 10.21 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.0, 67.6, 71.1, 71.6, 75.1, 78.3, 91.0, 112.8, 121.6, 132.1, 137.7, 146.5, 194.5; MS (EI) *m/z* 305 (M^+, 79), 277 (100), 212 (79), 184 (23), 154 (34), 121 (18), 56 (33).

Representative Procedure for the Aldolization−Crotonization Reaction. Preparation of Ferroceno[*h*]quinoline (1). To a solution of compound **17** (305 mg, 1 mmol) in dry DMF (2 mL) under nitrogen was slowly added at room temperature a solution of *t*-BuOK (224 mg, 2 mmol) in DMF (4 mL), and the red mixture was stirred for 2 h. The reaction mixture was quenched by addition of water and extracted with dichloromethane. After drying over magnesium sulfate and concentration, the residue was purified by chromatography on silica gel (hexanes/ethyl acetate, 9:1) to afford **1** as a red solid (200 mg, 70%): mp 98−100 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.79 (s, 5H), 4.35 (s, 1H), 4.90 (s, 1H), 5.64 (s, 1H), 7.08 (d, J = 9.2 Hz, 1H), 7.34 (dd, J = 7.6, 2.4 Hz, 1H), 7.47 (d, J = 9 Hz, 1H), 7.89 (d, J = 7.8 Hz, 1H), 8.75 (d, J = 4.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 63.0, 64.9, 69.2, 70.4, 71.3, 85.5, 120.3, 121.7, 123.4, 127.1, 129.1, 135.2, 148.0. MS (EI) *m/z* 287 (M^+, 100), 166 (9), 121 (30), 56 (15). Anal. Calcd for $C_{17}H_{13}FeN$ (287.14): C, 71.11; H, 4.56; N, 4.88. Found: C, 70.91; H, 4.59; N, 4.81.

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Supporting Information Available: Experimental procedures and spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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