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Chiral ferrocenyl ligands with bidentate pyridine donors. Synthesis and application in Pd-catalyzed asymmetric allylic alkylation of 1,3-diphenylpropenyl-1-esters

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ABSTRACT

A synthetic procedure relying on the Friedländer condensation of enantiopure α-amino ferrocenecarboxaldeyde has been devised for the regio-designed elaboration of a pyridine nucleus fused onto the ferrocene scaffold. Three novel bidentate ligands with different pyridine nitrogen donors featuring the [3,2-*b*]ferrocenopyridine fragment **a** as the sole chirogenic element have been prepared in enantiopure form through a multi step route involving the diastereoselective deprotonation of a chiral acetal of ferrocenecarboxaldehyde in the stereodetermining step. The ligands were assessed in the Pd-catalyzed allylic alkylation of 1,3-diphenyl-2-propenyl esters with good stereoselectivity.

1. Introduction

Planar chirality in chiral ligands with pyridine nitrogen donors is quite rare and there are a few examples of such a kind of derivatives in the current literature. The cyclophane bipyridine **1** and the related pyridyl quinolinophane **2** (Fig. 1) were isolated in low yield at the end of an elaborate synthetic procedure involving enantiomeric resolution.[1a] Both ligands were tested in Cu-catalyzed asymmetric cyclopropanation of styrene and in Ir-catalyzed asymmetric H-transfer reduction of acetophenone with modest results (25–30% ee).[1b] A similar quinolinophane template was used as the stereogenic scaffold of N,O- and P,N-bidentate ligands **3**.[2] Ligand **3a** gave excellent ee's (99%) in the diethylzinc addition to aldehydes[2a] while the corresponding P,N-derivatives were much less efficient in the Pd-catalyzed allylic alkylation.[2b]

The large majority of ligands featuring a stereogenic plane as the chiral element contain in their structure a ferrocene unit which has been properly elaborated as to become the source of chirality of the molecule. The combinations of donors appended onto the ferrocene template for meeting this purpose are the most varied, phosphorus derivatives being the most popular choice.[3] Less frequent is the case where these ligands feature only nitrogen atoms as donor centers and even rarer are the chiral ferrocenylpyridines with the nitrogen atom directly linked onto the cyclopentadienyl ring. The efficiency of ferroceno-condensed planar-chiral pyridine ligands in asymmetric catalysis has been first pointed out by Fu several years ago when he showed that the DMAP-surrogate **4a**

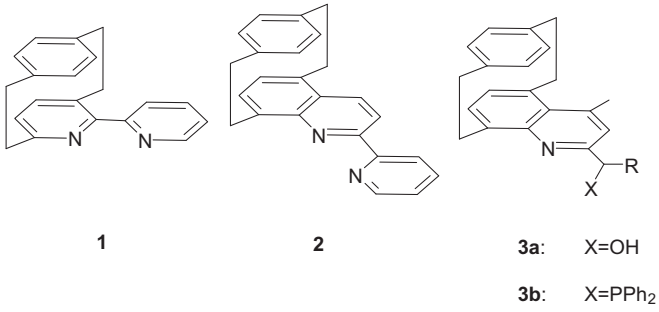

Figure 1.

and the relevant *N*-oxide **4b** (Fig. 2) are effective chiral inducers enabling ee's higher than 90% in a range of asymmetric reactions.[4]

A few years later, the same group reported the synthesis of the C_2-symmetrical chiral ferrocenyl bipyridine **4c** which was assessed in the Cu-catalyzed cyclopropanation of styrene with very good results (94% ee).[5a] To the best of our knowledge, this is the sole bidentate pyridine nitrogen ligand obtained in enantiopure form whose planar chirality comes from a stereogenic ferrocenyl framework. The relatively similar 2,2′-biquinoline **4d**[5b] has been obtained but only in racemic form along with the *meso* diastereoisomer.

Pursuing our long standing interest in chiral pyridine ligands,[6] some time ago we thought it worthwhile to expand the structural diversity of ligands of this type with planar chirality. To this purpose, we set out to design a synthetic strategy which could pave the way to a modular procedure useful for the stereoselective preparation of a library of pyridine ligands featuring the [3,2-*b*]ferrocenopyridine

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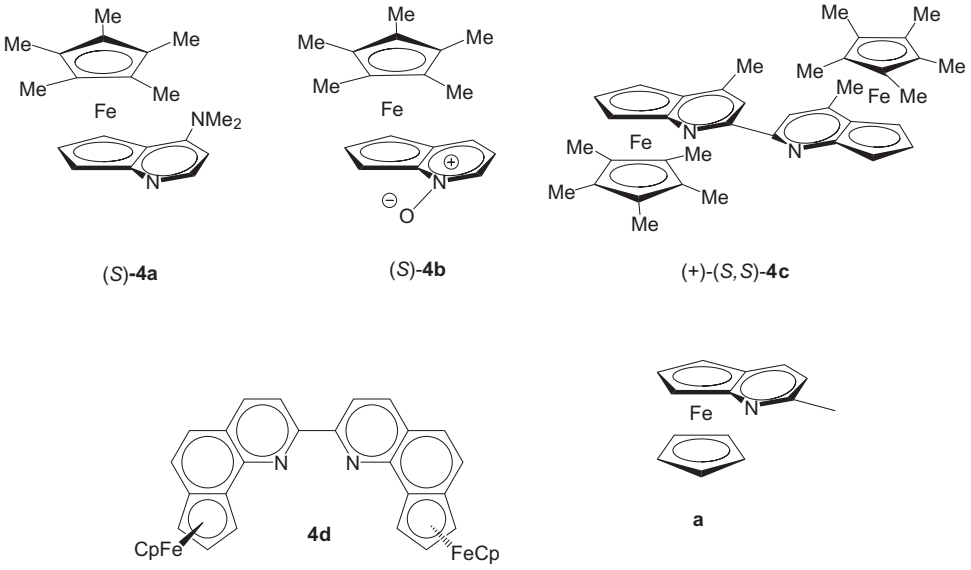


Figure 2.

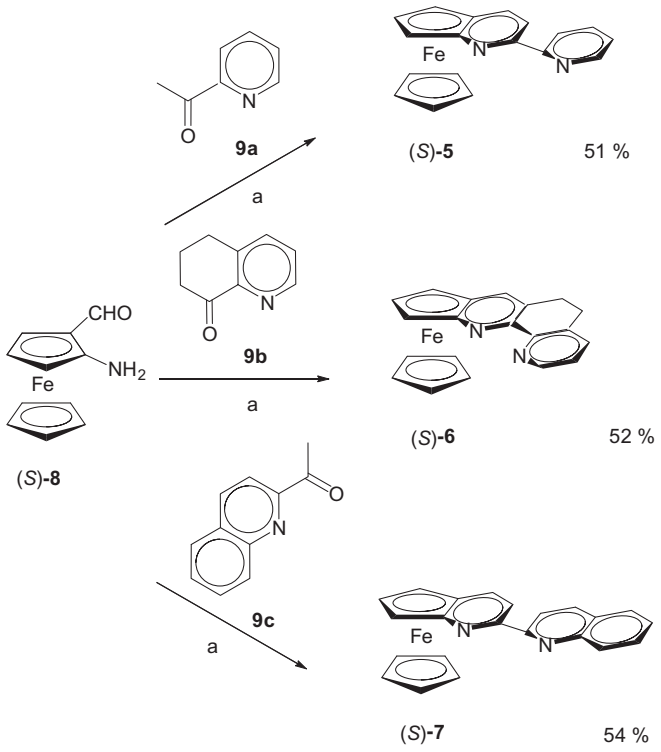
fragment **a** as the common chirogenic element. Herein we report on the synthesis of the first three ligands of this category and on their application in the Pd-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl esters.

2. Results and discussion

2.1. Preparation of ligands

The main goal of this investigation resided in establishing a straightforward procedure for the preparation in enantiopure form of the planar-chiral tag **a** distinctive of this category of ligands. At the same time the synthetic procedure had to meet the request of making readily accessible a library of bidentate ligands of modular diversity featuring a second pyridine donor in a predetermined position suitable for supporting the chelate binding of the ligand to a metal center. Among the synthetic strategies amenable for elaborating a fused pyridine ring onto one cyclopentadienyl fragment of the ferrocene template, the Friedländer condensation[7] was deemed the best suited tool for the synthesis of the targeted ligands **5**, **6**, and **7** with the desired directional control. From our previous experience in the field,[8] this condensation provides good yields of the desired pyridine derivatives under reasonably mild conditions and allows to introduce a wide structural diversity. We were reasonably confident that such operative conditions might be compatible with the utilization of an enantiopure 1,2-disubstituted ferrocene with a stereogenic plane as the chiral synthon while tolerating the presence of different structural decorations in the condensation partner. Retrosynthetic analysis of the Friedländer condensation led us to single out the enantiopure α-amino ferrocenecarboxaldeyde **8** as a common chiral intermediate providing the stereogenic plane and the pyridylketones **9a**–**c** as the suitable partners for the preparation of our targets (Scheme 1).

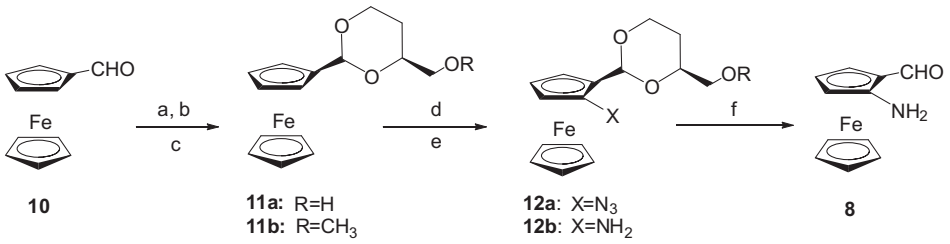
The asymmetric synthesis of enantiopure 1,2-disubstituted ferrocenes is most frequently accomplished according to two basic strategies both relying on heteroatom-assisted diastereoselective deprotonation.[9] In the first one, diastereoselectivity is achieved due to the presence on the ferrocenyl template of a chiral substituent aiding the recognition of the diastereotopic vicinal proton to be selectively extracted by the base. Extensive use of temporary chiral auxiliaries such as acetals, oxazolines, amines, and sulfoxides has been exploited more or less successfully in this task. The second approach is best suited for ferrocenes substituted with an achiral *ortho*-directing group and relies on an external source of chirality such as (−)-sparteine[10] that can promote the formation of diastereomeric complexes at the level of the lithiated ferrocene.



Scheme 1. Reagents and conditions: (a) KOH, EtOH, 25 °C, 4–12 h.

Notably, the preparation of our key intermediate **8** was reported for the first time several years ago by Kagan et al. according to the reaction sequence in Scheme 2.[11]

In that seminal paper, the installation of the amino group on the vicinal carbon of ferrocenecarboxaldeyde was achieved with complete diastereoselectivity through a six-step synthetic route. Key steps of that synthesis were the heteroatom-assisted deprotonation of a temporary chiral acetal and the quenching of the relevant



Scheme 2. Reagents and conditions: (a) trimethylorthoformate, H^+, MeOH, 80 °C, 3 h; 96%; (b) (*S*)-(−)-1,2,4-butanetriol, H^+, $CHCl_3$, 4 Å molecular sieves, 25 °C, 12 h; 97% **11a**; (c) NaH, CH_3I, THF, 25 °C, 12 h; 99% **11b**; (d) *t*-BuLi, Et_2O, −78 °C, $TosN_3$, THF, 25 °C; 75–85% **12a**; (e) $NaBH_4$, Bu_4NHSO_4, CH_2Cl_2, H_2O, 25 °C, 12 h; 74% **12b**; (f) HCl 10%, CH_2Cl_2, 25 °C, 30 min; 97%.

mixed cyanocuprate with *N*,*O*-bis(trimethylsilyl)hydroxylamine, an electrophilic source of nitrogen. The α-aminoaldehyde **8** was eventually obtained via the intermediate amino acetal **12b** by hydrolytic work up.

The advantage of using a chiral acetal as the *ortho*-directing group is immediately apparent in our case since the required formyl group can be regenerated under very mild conditions that are compatible with the presence of the delicate combination of functionalities displayed by **8**. Thus, transacetalization of the dimethyl acetal of ferrocenecarboxaldehyde **10** with (*S*)-(−)-1,2,4-butanetriol, either commercially available or prepared from (*S*)-malic acid,[12] gave the chiral 1,3-dioxane **11a** (90% yield) in perfect agreement with the literature. Methylation of the free hydroxyl group was then performed using NaH and CH_3I in THF to give the desired acetal **11b** (99% yield). The following step was the most critical of the entire sequence. In our hands the methodology devised by Kagan gave low and erratic yields never higher than 30%. In spite of our numerous attempts the yields of this reaction could not be stabilized at a satisfactory level and this forced us to search for a more performant and reliable electrophilic source of nitrogen. Many efforts have been spent to solve this problem and a wide range of nitrogen reagents (diazonium salts, diphenyl phosphoryl azide, diethyl azodicarboxylate, etc.) have been screened for this purpose. At the end of this study tosylazide resulted as the best reagent for the introduction of an amino group synthon onto the *ortho*-position. Thus, treating the lithiated acetal with tosylazide at −78 °C and further stirring at room temperature overnight lead to the formation of the azidoacetal **12a**. From ^1H NMR the azido derivative accounts for 75–85% of the crude product and is obtained as a single diastereomer. The introduction of the azido group was confirmed by the presence of a strong band at 2127 cm^{-1} in the IR spectrum of a sample of **12a** purified by flash chromatography.

Due to its poor stability the crude azido acetal **12a** was directly subjected to reduction with $NaBH_4$ in biphasic conditions to provide the corresponding amino derivative **12b** in 70–75% isolated yield after flash chromatography. Removal of the acetal protection was quantitatively obtained by stirring a dichloromethane solution of **12b** with dilute hydrochloric acid for 30 min at room temperature. Neutralization of the aqueous solution gave the desired amino aldehyde **8** pure enough as to be used straight in the Friedländer condensation. This last step was performed by stirring overnight at room temperature an ethanolic solution of the aminoaldehyde with the suitable enolizable pyridyl ketone **9** in the presence of potassium hydroxide as a condensing agent. Under these conditions the aminoaldehyde undergoes some decomposition and a 50% molar excess was found appropriate in order to counterbalance its poor stability. With this trick the targeted ligands **5** and **6** could be obtained after chromatographic purification in isolated yield as high as 50–55%. For the Friedländer synthesis of ligand **7**, the required partner was 2-acetylquinoline **9c**.[13] Keeping strictly to the Friedländer chemistry we elaborated a straightforward route for its preparation from 2-aminobenzaldehyde and 2,3-butanedione. The condensation of these two reagents was best accomplished under acid rather than under basic catalysis.[14] Thus, refluxing overnight a THF solution containing a 5:1 mixture of diketone and aminoaldehyde in the presence of 5% sulfamic acid gave in one step the desired ketone in 36% isolated yield after chromatographic purification. This preparation is straightforward and compares favorably with the multistep procedures reported in the literature.

2.2. Palladium-catalyzed allylic alkylation

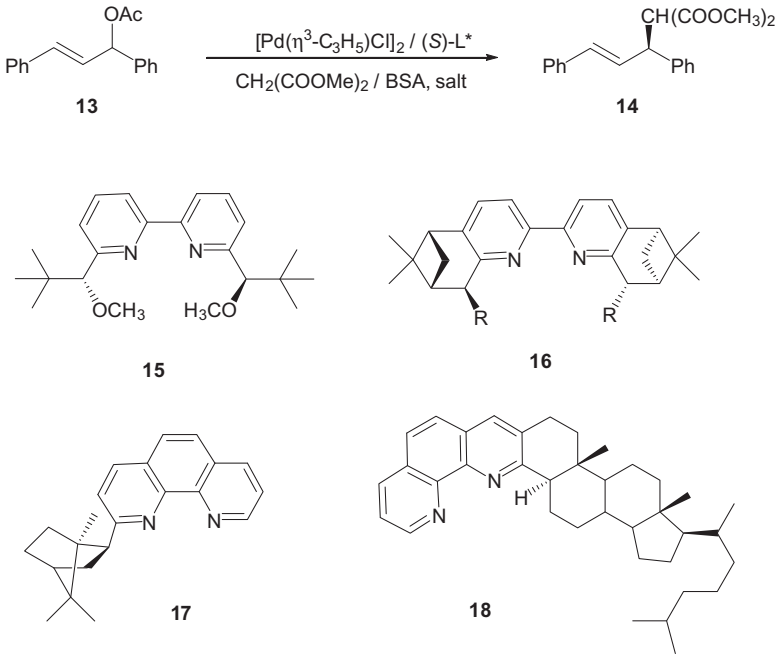
The utility of chiral bidentate pyridine donors in metal-catalyzed enantioselective catalysis is well established and their efficiency has been expressed in a wide number of reactions centered on a variety of different metals.[15] For screening the potential of ligands **5**, **6**, and **7** as chiral inducers we selected two benchmark asymmetric reactions: the Cu-catalyzed cyclopropanation of styrene by diazoacetate and the Pd-catalyzed allylic alkylation of racemic 1,3-diphenyl-2-propenyl acetate **13** with dimethyl malonate anion. In the first process C_2-symmetrical bipyridines such as **4c**, **15**, and **16**[16] consistently outperform the analogue phenanthrolines and the C_1-symmetric counterparts providing ee's in the range of 90% ee. In the Pd-catalyzed allylic alkylation the opposite trend is usually observed. In this reaction phenanthrolines such as **17** and **18**[17] are comparably better chiral inducers than bipyridines and C_1-symmetry is apparently better suited for high ee's to be attained.

When ligands **5** and **6** were tested in the first reaction very low catalytic activities and negligible ee's were observed. The results obtained in the second asymmetric process were more gratifying and are detailed below. The active catalyst was generated in situ from $[PdCl(\eta^3\text{-}C_3H_5)]_2$ and the appropriate chiral ligand (Scheme 3) while the nucleophile was generated by the combined action of BSA with a catalytic amount of an inorganic base.

The first set of results shown with ligands **5** and **6** are reported in Tables 1 and 2.

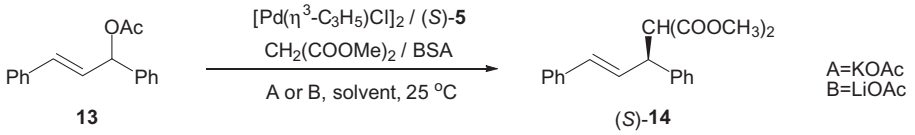
For gaining an insight in the coordination mode of our ligands during the catalytic reaction, the effect of the variation of the Pd/ligand (*S*)-**5** ratio was checked first. In dichloromethane reducing the ratio of the Pd/ligand from 1:2 to 1:1 had no effect on rate and stereoselectivity of the reaction. A further decrease of the relative amount of ligand to 0.25 brought about only a modest drop of rate and selectivity (Table 1, entries 1–3). This was taken as an indication that in this range of concentrations a chelate Pd-complex is the operating catalyst. Addition of $AgPF_6$ aiming at removing the potential interference of the chloride anion[18] had a negative effect on the catalytic activity which was almost suppressed.

Conversion and stereoselectivity of the reaction were strongly dependent on the solvent and on the operative conditions and the reaction times required for a complete conversion to be achieved were quite different. With both ligands **5** and **6**



Scheme 3.

Table 1
Allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate in the presence of Pd/(*S*)-**5**



Entry	Solvent	Time	Conv. (%)	ee (%)
AcOK				
1	CH_2Cl_2	5 min	100	51 (*S*)
2[a]	CH_2Cl_2	5 min	100	50 (*S*)
3[b]	CH_2Cl_2	20 min	100	45 (*S*)
4	$CHCl_3$	48 h	50	49 (*S*)
5[a]	THF	78 h	40	37 (*S*)
6	THF	4 h	100	47 (*S*)
7[a]	Toluene	15 min	100	50 (*S*)
8	Toluene	10 min	100	47 (*S*)
AcOLi				
9[a]	CH_2Cl_2	45 h	90	58 (*S*)
10[a]	$CHCl_3$	45 h	25	64 (*S*)
11	$CHCl_3$	48 h	50	66 (*S*)
12[c]	$CHCl_3$	45 h	22	75 (*S*)
13	THF	32 h	98	52 (*S*)
14[a]	Toluene	30 min	100	52 (*S*)

$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ 0.005 mmol, (*S*)-**5** 0.02 mmol, substrate 0.2 mmol, dimethyl malonate 0.6 mmol, BSA 0.6 mmol, acetate salt 0.006 mmol, room temperature.
[a] Ratio Pd/L = 1:1.
[b] Ratio Pd/L = 1:0.25.
[c] Temperature = 0 °C.

chlorinated solvents performed slightly better than oxygenated ones or hydrocarbons (Tables 1 and 2), the difference being more pronounced with lithium acetate as a base. With this base, a dramatic decrease of the reaction rate accompanied by a moderate increase of the stereoselectivity was observed in dichloromethane and THF (Table 1, compare entries 2 and 9 and entries 6 and 13; Table 2, compare entries 1 and 5 and entries 3 and 8).

The reaction was even slower in chloroform but this solvent turned out to be consistently more effective than dichloromethane in terms of selectivity (Table 1, compare entries 9 and 10; Table 2, compare entries 5 and 6). A definite improvement of the enantioselectivity of the reaction was obtained by lowering the temperature to 0 °C (Table 1, compare entries 11 and 12; Table 2, compare entries 6 and 7). When the reaction was performed at this temperature in chloroform, 75% ee was scored with the bipyridine derivative **5** (Table 1, entry 12) and 68% ee with the dihydrophenanthroline ligand **6** (Table 2, entry 7). This result follows in keeping with the general trend observed in this study where the dihydrophenanthroline derivative was consistently outperformed by the bipyridine ligand.

Table 2
Allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate in the presence of in situ-generated Pd/(*S*)-**6**

Entry	Solvent	Time	Conv. (%)	ee (%)
AcOK				
1	CH_2Cl_2	45 min	100	40 (*S*)
2[a]	CH_2Cl_2	45 min	100	46 (*S*)
3	THF	45 min	100	42 (*S*)
4	Toluene	1.2 h	100	52 (*S*)
AcOLi				
5	CH_2Cl_2	45 h	54	53 (*S*)
6[a]	$CHCl_3$	45 h	25	59 (*S*)
7[b]	$CHCl_3$	48 h	50	68 (*S*)
8	THF	32 h	44	49 (*S*)
9	Toluene	2 h	100	40 (*S*)

$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ 0.005 mmol, (*S*)-**6** 0.02 mmol, substrate 0.2 mmol, dimethyl malonate 0.6 mmol, BSA 0.6 mmol, acetate salt 0.006 mmol, room temperature.
[a] Ratio Pd/L = 1:1.
[b] Temperature = 0 °C.

In the presence of both potassium and lithium acetate the complex obtained from the quinolyl derivative (*S*)-**7** displayed a good catalytic activity. Quantitative conversions were obtained within 2–3 h in dichloromethane with KOAc and, more surprisingly, even with LiOAc in chloroform but the stereoselectivities for (*S*)-**14** were quite low, 12% and 22%, respectively. When this ligand was used in THF the catalytic activity collapsed (9% conversion after 48 h).

The remarkable differences observed with potassium and lithium acetate prompted us to explore in more detail the influence of the salt on the enantioselectivity and the conversion when the reaction is run in chloroform (Table 3). As it is apparent from Table 3, the reaction is pretty sensitive both to the cationic and the anionic components of the base. The effect of the anion is just moderate and acetate is generally a better suited base than carbonate, enabling higher ee's to be obtained. On the contrary, the nature of the alkaline cation has a profound influence on the reaction rate which spans over two order magnitude when moving from the most to the least efficient salt sodium (entry 5) and cesium acetate (entry 7), respectively. Even if of some significance, the fluctuations of stereoselectivity induced by the different cations are in a more restricted range. The best ee's of this set were obtained with CH_3COOLi (Table 3, entries 3 and 9), however, with incomplete conversion even after a prolonged reaction time. In the presence of other alkaline cations the selectivity was slightly lower.

Notably, complete conversions were observed only with CH_3COONa and Na_2CO_3 for (*S*)-**5** (Table 3, entries 5 and 6) and with CH_3COOK for (*S*)-**6** (Table 3, entry 8).

On the contrary, ligand (*S*)-**7** gave complete conversion with both CH_3COOLi and CH_3COOK, but with very low enantiomeric excess.

The influence of the leaving group of the substrate has been inspected by exchanging the acetate ester of **13** with the methoxycarbonate of **19**. This variation did not substantially alter the stereoselectivity, as almost identical ee's were obtained with both the esters (Table 4).

3. Conclusions

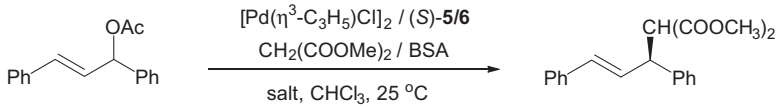
In the course of this investigation we have elaborated and validated a practical procedure useful for the modular synthesis of ferroceno-condensed planar-chiral pyridine ligands featuring as the unique chiral element a stereogenic plane arising from the ferrocene scaffold. This methodology has been successfully exploited in the preparation of one pyridine, one quinoline, and one phenanthroline ligand, **5**, **6**, and **7**, respectively, using enantiopure 2-aminoferrocenecarboxaldeyde (*S*)-**8** as the common chiral synthon for all these derivatives. These C_1-symmetry bidentate ligands have been assessed in the palladium-catalyzed alkylation of *rac*-1,3-diphenyl-2-propenyl esters **13** and **19** with dimethyl malonate. The outcome of the reaction is strongly dependent on the solvent, the temperature, and the nature of the cation of the salt used as a basic promoter. Under optimized conditions both ligands **5** and **6** gave similar stereoselectivities of (*S*)-alkylated product **14**, the top value being 75% ee. In the same reaction ligand **7** produced an active catalyst that led to 100% conversions, but with very low enantiomeric excess (22%).

4. Experimental section

4.1. General

Nuclear magnetic resonance spectra were obtained on a Varian VXR-5000 spectrometer at 300 MHz for ^1H, 121.42 MHz for ^{31}P and 75 MHz for ^{13}C. Chemical shifts were reported in ppm downfield from internal Me_4Si in $CDCl_3$ for ^1H and ^{13}C and from H_3PO_4 for ^{31}P NMR. Optical rotations were measured on a Jasco P-1010 polarimeter. Melting points were obtained with a Buchi 530 melting point apparatus. For column chromatography silica gel

Table 3
Allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate in the presence of in situ-generated Pd/(*S*)-**5** or Pd/(*S*)-**6**: effect of salt

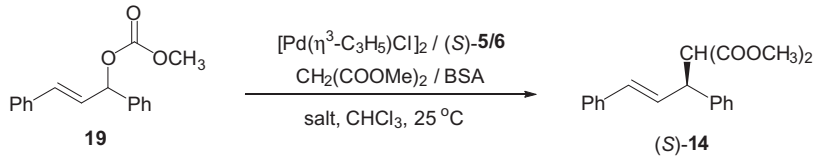


13 (*S*)-**14**

Entry	Ligand	Salt	Time (h)	Conv. (%)	ee (%)
1	(*S*)-**5**	KOAc	48	50	49 (*S*)
2	(*S*)-**5**	K_2CO_3	48	84	54 (*S*)
3	(*S*)-**5**	LiOAc	48	50	66 (*S*)
4	(*S*)-**5**	Li_2CO_3	48	68	59 (*S*)
5	(*S*)-**5**	NaOAc	1.5	100	60 (*S*)
6	(*S*)-**5**	Na_2CO_3	1.5	100	56 (*S*)
7	(*S*)-**5**	Cs_2CO_3	48	32	52 (*S*)
8	(*S*)-**6**	KOAc	8	100	43 (*S*)
9	(*S*)-**6**	LiOAc	36	50	59 (*S*)
10	(*S*)-**6**	Li_2CO_3	48	45	51 (*S*)

General experimental conditions $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ 0.005 mmol, (*S*)-**5** /**6** 0.02 mmol, substrate 0.2 mmol, dimethyl malonate 0.6 mmol, BSA 0.6 mmol, salt 0.006 mmol, room temperature, $CHCl_3$ 2 ml.

Table 4
Allylic alkylation of 1,3-diphenylprop-2-enyl carbonate in the presence of in situ-generated Pd/(*S*)-**5** or Pd/(*S*)-**6**: effect of the salt



Entry	Ligand	Salt	Conv. (%)	ee (%)
1	(*S*)-**5**	KOAc	64	57 (*S*)
2	(*S*)-**5**	K_2CO_3	64	54 (*S*)
3[a]	(*S*)-**5**	LiOAc	100	68 (*S*)
4	(*S*)-**6**	LiOAc	71	56 (*S*)

General experimental conditions $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ 0.005 mmol, (*S*)-**5**/**6** 0.02 mmol, substrate 0.2 mmol, dimethyl malonate 0.6 mmol, BSA 0.6 mmol, salt 0.006 mmol, $CHCl_3$ 2 ml, 48 h.
[a] Time: 7 h.

(230–400 mesh, Merk 60) and neutral Al_2O_3 (70–230 mesh, Merck) were used, according to the literature. All commercial reagents were used without further purification and solvents were distilled after refluxing under nitrogen or argon and stored under an inert atmosphere until used. (2*S*,4*S*)-4-(Methoxymethyl)-2-ferrocenyl-1,3-dioxane **11b** was prepared as reported in the literature.[11]

4.2. Synthesis of (2*S*,4*S*,S_{Fc})-4-(methoxymethyl)-2-(α-azidoferrocenyl)-1,3-dioxane 12a

(2*S*,4*S*)-4-(Methoxymethyl)-2-ferrocenyl-1,3-dioxane **11b** (4.39 g, 13.88 mmol) was dissolved in ether (72 ml, 5–10 ml of ether per 2 mmol of acetal) and stirred at −78 °C for 30 min under argon. *t*-BuLi (1.1 equiv as a 1.5 M solution, 13.9 ml, 20.82 mmol) was added dropwise, yielding after a few minutes a bright yellow precipitate. After 30 min of stirring at −78 °C, the mixture was allowed to warm up to room temperature and stirring was continued until a bright orange precipitate of lithiated acetal gradually formed. The mixture was cooled again to −78 °C and at this temperature a solution of anhydrous tosylazide (3.55 g, 18.01 mmol) in THF (36 ml) was added through cannula. The mixture was warmed up to room temperature and left stirring overnight resulting in a bright red solution. The reaction was quenched with water and the solvent was removed under reduced pressure. The resulting slurry was diluted with water and extracted three times with dichloromethane. The combined organic phases were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give crude **12a** as a dark oil (5.3 g). NMR analysis of this product showed the presence of the desired product **12a** (75–85%) impure of starting material **11b** and excess of tosylazide. The crude compound can be used as such in the next step. A sample purified by flash chromatography showed in the IR spectrum (KBr) an intense stretching band at 2127 cm^{-1} diagnostic for the presence of the azido group. ^1H NMR ($CDCl_3$) δ 5.47 (s, br, 1H), 4.30 (m, 2H), 4.28 (s, 5H), 4.20–4.17 (m, 2H), 4.10–3.96 (m, 2H), 3.54 (m, 2H), 3.82 (s, 3H), 1.82 (m, 1H), 1.51 (m, 1H).

4.3. Synthesis of (2*S*,4*S*,S_{Fc})-4-(methoxymethyl)-2-(α-aminoferrocenyl)-1,3-dioxane 12b

At first, $NaBH_4$ (2.14 g, 56.56 mmol) in distilled H_2O (14 ml) was added to the mixture of (2*S*,4*S*,S_{Fc})-4-(methoxymethyl)-2-(α-azidoferrocenyl)-1,3-dioxane **12a** (5.5 g,14.14 mmol) in CH_2Cl_2 (23 ml) and Bu_4NHSO_4 (1.92 g, 5.65 mmol) at room temperature under argon. The resulting two-phase solution was vigorously stirred at room temperature overnight. The reaction was monitored by TLC on silica gel (Et_2O/AcOEt/Et_3N = 4:1:0.1). The reaction mixture was then diluted with equal volume of brine (36 ml), extracted three times with dichloromethane, dried (Na_2SO_4), filtered and the solvent was evaporated. The crude was analyzed by ^1H NMR. The analysis showed the presence of the desired product **12b**, some unreacted starting material **12a**, and a trace of the parent acetal **11b**. The pure product **12b** (3.8 g, 74%) was isolated after flash chromatography on silica gel (AcOEt:Et_2O:Et_3N = 1:4:0.1). ^1H NMR ($CDCl_3$) δ 5.40 (s, br, 1H), 4.22 (m, 2H), 4.13 (s, 5H), 4.04 (m, 1H), 3.91 (m, 2H), 3.81 (s, br, 1H), 3.52 (m, 2H), 3.45 (s, 3H), 3.03 (m, br, 2H), 1.83 (m, 1H), 1.51 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 101.1, 76.2, 75.8, 73.2, 69.8, 66.7, 63.2, 62.1, 59.6, 58.5, 28.1. IR (KBr) cm^{-1} 3422, 3343.

4.4. Synthesis of (*S*)-α-aminoferrocenecarboxaldehyde 8

At first, 10% HCl (17 ml) was added to a solution of (2*S*,4*S*,S_{Fc})-4-(methoxymethyl)-2-(α-aminoferrocenyl)-1,3-dioxane **12b** (0.3 g, 0.9 mmol) in CH_2Cl_2 (17 ml) in a separatory funnel and shaken vigorously. The organic layer, initially light yellow, becomes immediately colorless while the aqueous phase becomes dark red, indicating the almost instantaneous deprotection. The aqueous phase was separated, made alkaline with NaOH 10%, and extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The resulting red-colored product **8** (0.2 g, 97%) was used directly in the next step without further purification. ^1H NMR ($CDCl_3$) δ 9.99 (s, 1H), 4.41 (m, 1H), 4.33 (m, 1H), 4.20 (m, 1H), 4.16 (s, 5H), 3.83 (br s, 2H), identical with the data reported by Kagan.[11]

4.5. Synthesis of (*S*)-6-(2′-pyridyl)[3,2-*b*]ferrocenopyridine 5

Saturated ethanolic KOH (1.78 ml) was added to a suspension of ferrocenyl amino aldehyde **8** (0.5 g, 2.18 mmol) and 2-acetylpyridine **9a** (0.15 g, 1.75 mmol) in absolute ethanol (40 ml) under argon. The mixture was stirred for 12 h at room temperature. Then the reaction was quenched with water and the solvent was evaporated. The resulting slurry was diluted with water and extracted three times with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on neutral alumina with EtOAc yielding **5** (0.35 g, 51%) as a green solid. ^1H NMR ($CDCl_3$) δ 8.69 (d, 1H, *J* = 4.8 Hz), 8.47 (d, 1H, *J* = 8.1 Hz), 8.28 (d, 1H, *J* = 9.3 Hz), 7.96 (d, 1H, *J* = 9.0 Hz), 7.84 (t, 1H, *J* = 6.9 Hz), 7.35 (t, 1H, *J* = 6.0 Hz), 5.46 (s, 1H), 4.95 (s, 1H), 4.26 (s, 1H), 3.90 (s, 5H). ^{13}C NMR ($CDCl_3$): δ 159.5, 157.2, 149.3, 141.8, 137.1, 124.1, 121.9, 116.8, 108.9, 80.8, 71.7, 68.9, 63.8, 60.1. Anal. Calcd for $C_{18}H_{14}FeN_2$: C, 68.82; H, 4.49; N, 8.92. Found: C, 68.70; H, 4.65; N, 9.14.

4.6. Synthesis of (*S*)-[2,3-*b*]-ferrocenyl-5,6-dihydrophenantroline 6

Saturated ethanolic KOH (2.86 ml) was added to the solution of ferrocenyl amino aldehyde **8** (0.8 g, 3.49 mmol) and 6,7-dihydro-5*H*-quinolin-8-one **9b** (0.32 g, 2.8 mmol) in absolute ethanol (55 ml) under argon. The mixture was stirred for 12 h at room temperature. Then the reaction was quenched with water and the solvent was evaporated. The resulting slurry was diluted with water and extracted three times with CH_2Cl_2. The combined organic phases were dried over (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on neutral alumina with EtOAc yielding 0.62 g of the expected product **6** (52%). ^{1}H NMR ($CDCl_3$) δ 8.78 (d, 1H, J = 4.2 Hz), 7.94 (s, 1H), 7.57 (d, 1H, J = 7.5 Hz), 7.28 (s, 1H), 5.58 (s, 1H), 4.90 (s, 1H), 4.22 (s, 1H), 3.89 (s, 5H), 2.96 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 155.6, 152.4, 149.5, 137.3, 136.3, 134.9, 128.4, 123.8, 108.9, 81.2, 71.5, 68.7, 64.4, 59.3, 29.9, 28.6. Anal. Calcd for $C_{20}H_{16}FeN_2$: C, 70.61; H, 4.74; N, 8.23. Found: C, 70.42; H, 4.65; N, 8.14.

4.7. Synthesis of 2-acetylquinoline 9c

At first, 5% sulfamic acid (0.02 g, 0.21 mmol) was added to a solution of 2-aminobenzaldehyde (0.5 g, 4.13 mmol) and 2,3-butanedione (1.78 g, 20.65 mmol) in THF (15 ml) under argon. The mixture was refluxed overnight, then the reaction was quenched with aqueous sodium bicarbonate and the solvent was evaporated. The resulting slurry was taken up with water and extracted three times with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on neutral alumina (petroleum ether/EtOAc = 8:2) to give the expected product **9c** (0.25 g, 36%). ^{1}H NMR ($CDCl_3$): δ 8.25–8.18 (m, 2H), 8.12 (d, 1H, J = 6 Hz), 7.85 (d, 1H, J = 6 Hz), 7.77 (t, 1H, J = 6 Hz), 7.63 (t, 1H, J = 6 Hz), 2.87 (s, 3H). Anal. Calcd for $C_{20}H_{16}FeN_2$: C, 70.61; H, 4.74; N, 8.23. Found: C, 70.70; H, 4.65; N, 8.04.

4.8. Synthesis of (*S*)-6-(2′-quinolinyl)[3,2-*b*]ferrocenopyridine 7

Saturated ethanolic KOH (0.8 ml) was added to a solution of ferrocenyl amino aldehyde **8** (0.21 g, 0.9 mmol) and 2-acetylquinoline **9c** (0.15 g, 0.88 mmol) in absolute ethanol (17 ml) under argon. The mixture was stirred for 3 h at room temperature. Then the reaction was quenched with water and the solvent was evaporated. The resulting slurry was taken up with water and extracted three times with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on neutral alumina (Et_2O) yielding 0.18 g of the expected product **7** (54%). ^{1}H NMR ($CDCl_3$): δ 8.69 (d, 1H, J = 9 Hz), 8.31–8.27 (m, 3H), 8.19 (d, 1H, J = 6 Hz), 7.87 (d, 1H, J = 6 Hz), 7.75 (t, 1H, J = 7.5 Hz), 7.58 (d, 1H, J = 15 Hz), 5.49 (s, 1H), 4.98 (s, 1H), 4.30 (s, 1H), 3.92 (s, 5H). ^{13}C NMR ($CDCl_3$): δ 159.4, 156.7, 148.0, 141.5, 136.7, 130.1, 129.7, 128.5, 127.9, 127.1, 119.6, 117.0, 108.7, 80.9, 71.8, 68.8, 63.8, 60.2. Anal. Calcd for $C_{22}H_{16}FeN_2$: C, 72.55; H, 4.43; N, 7.69. Found: C, 72.77; H, 4.31; N, 7.95.

4.9. General procedure for allylic alkylation

A mixture of ligand (0.01–0.02 mmol) and $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.83 mg, 0.005 mmol) in THF (1 ml) was stirred at room temperature for 30 min. The resulting solution was added with a solution of *rac*-1,3-diphenyl-2-propenyl acetate **13** (0.2 mmol, 50.5 mg) in THF (1 ml), followed by dimethyl malonate (0.6 mmol, 79 mg), BSA (0.6 mmol, 122 mg) and a small amount of potassium acetate (or other salt). The mixture was stirred at the given temperature, while observing the conversion by tlc (silica, Et_2O/petroleum ether = 1:3). After the reaction was complete, the mixture was diluted with dichloromethane and washed with saturated aqueous ammonium chloride solution. The organic phase was dried (Na_2SO_4) and filtered and the solvent was evaporated under reduced pressure. Conversion was determined by NMR on this residue. The crude product was purified by column chromatography on silica gel (Et_2O/petroleum ether = 1:3) to give **14**. Ee's of the product were determined from the integrals of the methoxy groups of (1,3-diphenylprop-2-enyl)malonate, as split by the chiral shift reagent europium(III) tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorate]. The absolute configuration was assigned by comparison of the sign of the measured value of the specific rotation with the published data.

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