

# Ferrocenylium reagents in palladium-catalyzed cross-coupling reactions: asymmetric synthesis of planar chiral 2-aryl oxazolyl and sulfinyl ferrocenes

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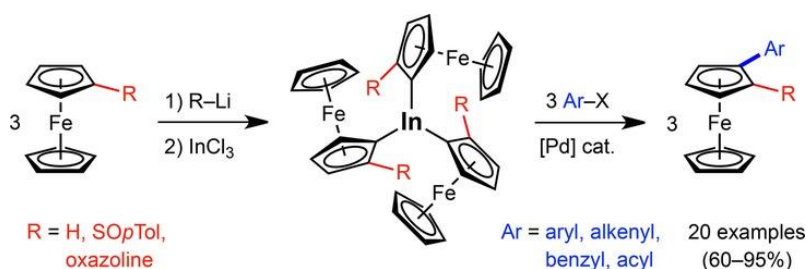
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## Abstract



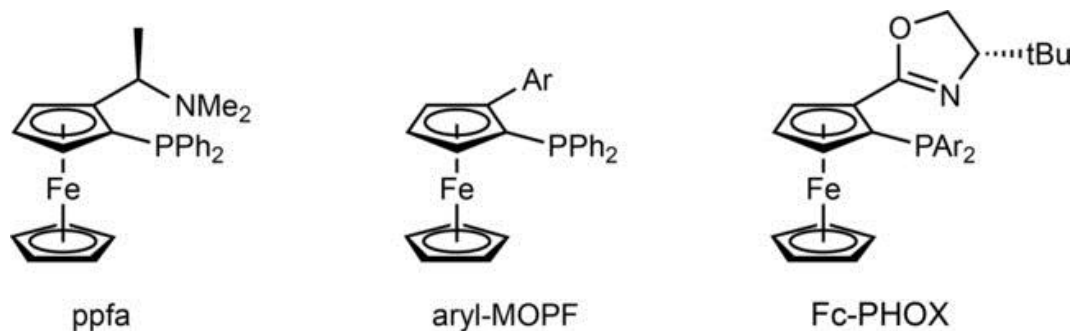
The preparation of ferrocenylium species and palladium-catalyzed cross-coupling reactions for the synthesis of monosubstituted and planar chiral 1,2-disubstituted ferrocenes is described. Triferrocenylium reagents ( $\text{Fc}_3\text{In}$ ) are efficiently prepared in a one-pot

procedure from ferrocenes by lithiation and transmetalation to indium using  $\text{InCl}_3$ . The palladium-catalyzed cross-coupling reactions of  $\text{Fc}_3\text{In}$  (40 mol%) with a variety of organic electrophiles (aryl, heteroaryl, benzyl, alkenyl and acyl halides) in THF at 80 °C overnight provided a wide variety of monosubstituted ferrocenes in good to excellent yields. This methodology allowed the stereoselective synthesis of planar chiral 2-aryl-1-oxazolylferrocenes and 2-aryl-1-sulfinylferrocenes, which are of interest in asymmetric catalysis.

**Keywords:** asymmetric synthesis; cross-coupling; ferrocene ligands; indium; palladium

Ferrocene and derivatives are compounds of great interest in different areas of chemistry due to their fascinating structural and electronic properties.<sup>[1]</sup> The applications of ferrocene derivatives are constantly increasing, especially in organic synthesis,<sup>[2]</sup> materials science<sup>[3]</sup> and medicinal chemistry.<sup>[4]</sup> Ferrocene, for its aromatic character, can be considered a bioisotere of a phenyl ring, and established drugs such as anticancer taxol, or antimalarial artemisinin, have been modified by using ferrocene as a substituent in their core structure.<sup>[5]</sup> On the other hand, the inherent electrochemical properties of the ferrocene unit have led to its introduction in complex structures to provide new molecules with novel nonlinear optical or ferromagnetic properties.<sup>[6]</sup> In addition, the planar chirality of 1,2-disubstituted ferrocenes makes them important ligands in asymmetric catalysis. In this field, chiral ferrocenylyphosphines such as ppfa (*N,N*-dimethyl-1-[2-

(diphenylphosphino)ferrocenyl]ethyl-amine), 2-aryl-monophosphine ferrocenes (aryl-MOPF), or ferrocenyl phosphino-oxazolines (Fc-PHOX) are privileged ferrocene ligands (Figure 1).<sup>[2a,7]</sup> Therefore, the development of efficient methods for the synthesis of functionalized and enantiomerically pure ferrocenes is of great importance.<sup>[2,8]</sup>



**Figure 1.** Privileged ferrocene ligands in asymmetric catalysis.

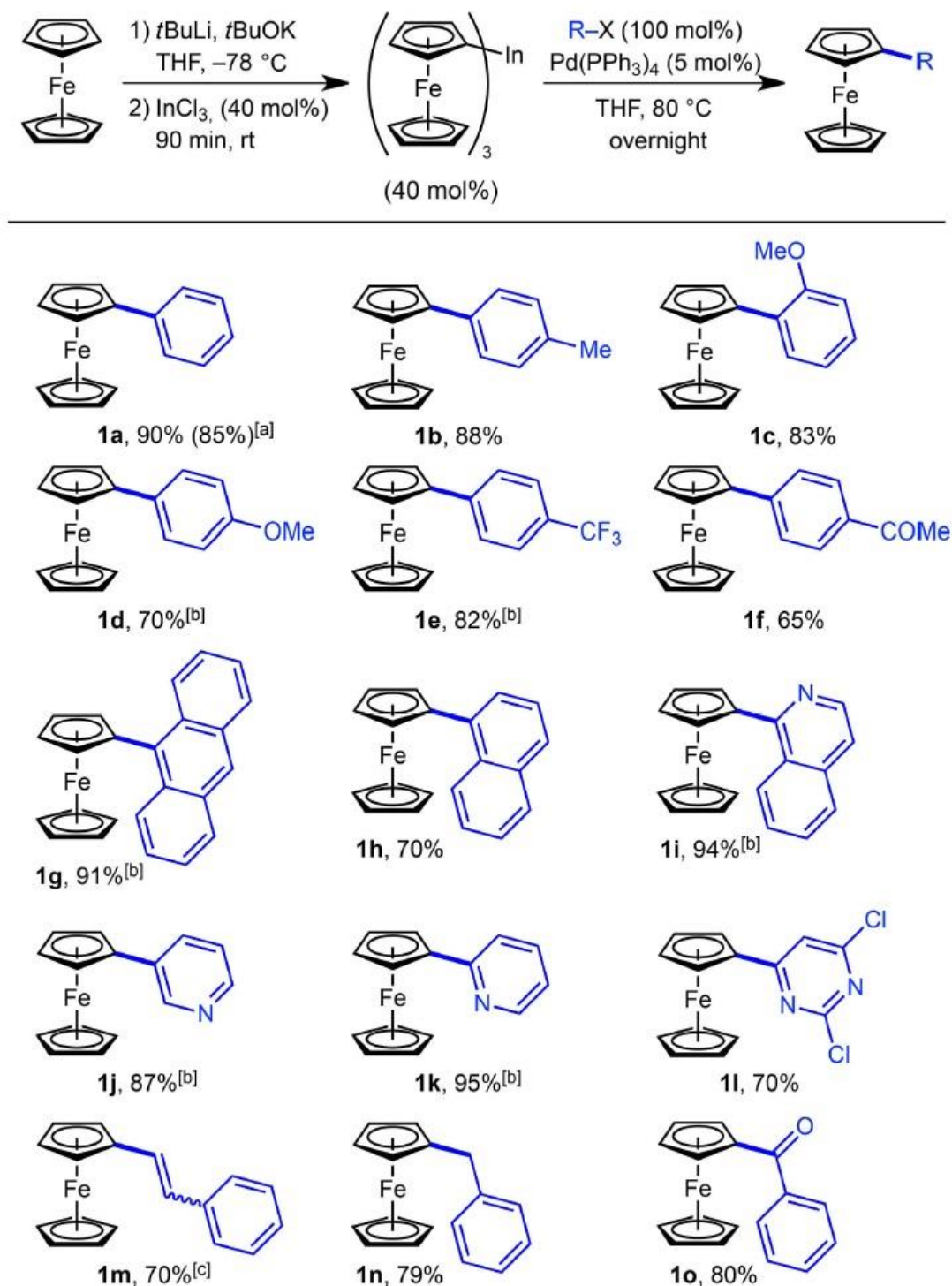
Metal-catalyzed cross-coupling reactions are amongst the most powerful tools available for the construction of new carbon-carbon bonds.<sup>[9]</sup> Although this methodology has already been applied to the synthesis of ferrocenes,<sup>[8c–8g,10]</sup> it often suffers from limitations such as low atom efficiency, the need for harsh reaction conditions or the use of highly toxic compounds. Over the last two decades, triorganoindium compounds (R<sub>3</sub>In), which can be easily prepared from the corresponding organolithium or organic halide, have emerged as alternative reagents in metal-catalyzed reactions.<sup>[11]</sup> The palladium-catalyzed cross-coupling reaction using R<sub>3</sub>In, which was discovered by our group,<sup>[12]</sup> is the most useful reaction of these reagents and its utility in organic synthesis is increasing steadily.<sup>[13]</sup> Besides their high atom efficiency due to the transfer of all three organic groups from indium to the electrophile, R<sub>3</sub>In reagents show excellent selectivity, high versatility and, in general, low toxicity. In this communication we describe the novel preparation of triferrocenylium reagents and their application in palladium-catalyzed cross-coupling reactions for the synthesis of monosubstituted and planar chiral 1,2-disubstituted ferrocenes.

Our investigation started with the one-pot procedure involving lithiation of ferrocene, transmetalation to indium and palladium-catalyzed coupling. It was found that direct lithiation of ferrocene using standard reaction conditions (*t*BuLi/*t*BuOK at –78 °C in THF),<sup>[14]</sup> followed by addition of anhydrous InCl<sub>3</sub> (40 mol%) and coupling with bromobenzene (100 mol%), using Pd(PPh<sub>3</sub>)<sub>4</sub> (5 mol%) as catalyst in THF at 80 °C overnight, gave phenylferrocene (**1 a**) in 90% yield (Table 1). This result supports the formation of the Fc<sub>3</sub>In intermediate and the efficient transfer of the three ferrocene units attached to indium. It should be noted that the coupling reaction is not efficient if indium is not used. Interestingly, the reaction can be monitored by observing the colour of the reaction mixture, which shows the different steps in this chemical transformation.<sup>[15]</sup> The reaction can be performed using palladium(II) complexes such as Pd(dppf)Cl<sub>2</sub> to afford the coupling product in similar yield. The reaction was easily scaled up to gram-scale obtaining a similar yield (85%).

To exploit the scope of this protocol, the palladium-catalyzed coupling reaction using Fc<sub>3</sub>In was evaluated with a variety of organic halides (Table 1). During this research we found that the metallation/transmetalation/coupling works efficiently with aryl halides bearing electron-rich substituents such as 4-bromotoluene, 2-bromoanisole and 4-iodoanisole to give the corresponding phenyl substituted ferrocenes **1 b–d** in high yields (70–88%). Analogously, the cross-coupling using electron-deficient arenes such as 4-trifluoromethyl bromobenzene and 4-bromoacetophenone also afforded the phenylferrocenes **1 e** and **1 f** in

85% and 65% yields, respectively. It is remarkable that the coupling is not sensitive to the nature of the substituent on the phenyl halide and all of the reactions proceeded efficiently at 80 °C overnight. It was observed, however, that in some examples the highest yield was obtained on using Pd(dppf)Cl<sub>2</sub> as the catalyst.

**Table 1.** Pd-catalyzed cross-coupling of Fc<sub>3</sub>In with organic electrophiles.



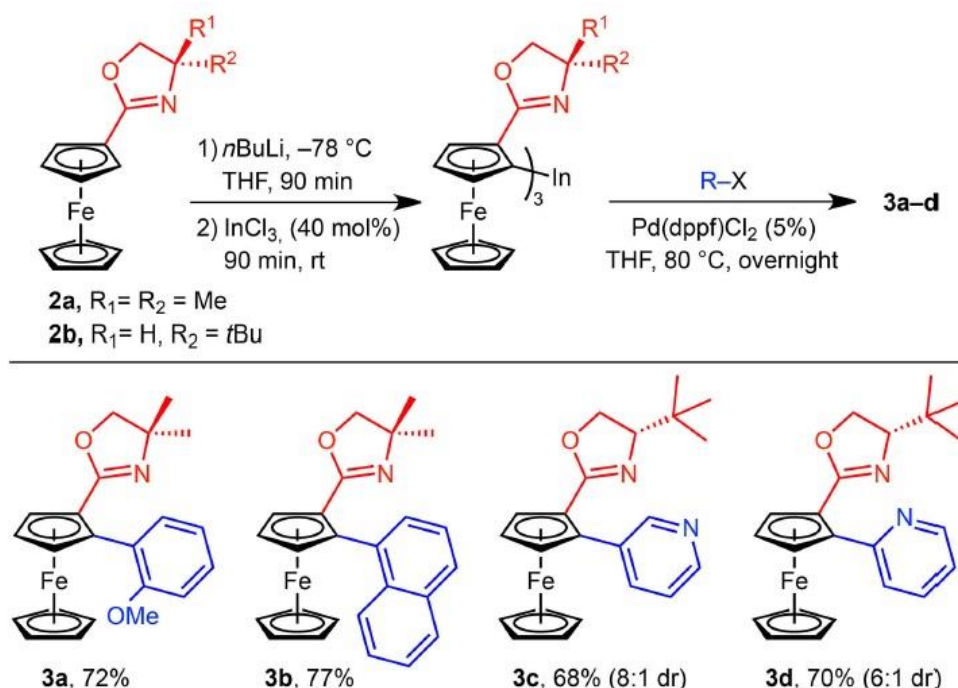
<sup>[a]</sup> In parenthesis, isolated yield at gram-scale. <sup>[b]</sup> Pd(dppf)Cl<sub>2</sub> (5 mol%) used as the catalyst. <sup>[c]</sup> *E*:*Z* 80:20.

The reaction of  $\text{Fc}_3\text{In}$  with bulky electrophiles such as 9-bromoanthracene or 1-bromonaphthalene, which usually require specific reaction conditions (high temperature, excess of the organometallic or additives),<sup>[16]</sup> also gave the corresponding 9-anthranylferrocene (**1 g**) and 1-naphthylferrocene (**1 h**) at 80 °C overnight in high yields (91% and 70%, respectively). Analogously, the coupling with heteroaryl halides allowed the synthesis of interesting substituted ferrocenes bearing nitrogen donor atoms, e. g., 3-pyridylferrocene (**1 j**), 2-pyridylferrocene (**1 k**), 1-isoquinolinylferrocene (**1 i**) and 2,6-dichloro-4-pyrimidylferrocene (**1 l**).<sup>[17]</sup> This study was also extended to organic electrophiles other than aryl halides and these allow further chemical transformations that are useful for the synthesis of new ferrocene derivatives. The cross-coupling of  $\text{Fc}_3\text{In}$  with  $\beta$ -bromostyrene (*E*:*Z*80:20) allowed the introduction of the alkene functionality (**1 m**) and the reaction with benzyl bromide and benzoyl chloride gave the corresponding monosubstituted ferrocenes **1 n** and **1 o** in good yields (70–80%). It is noteworthy that all reactions take place with only 40 mol% of  $\text{Fc}_3\text{In}$  in THF at 80 °C to afford the coupling product in good to excellent yields.

The synthetic utility of ferrocenylindium reagents in palladium-catalyzed cross-coupling reactions was also tested for the stereoselective synthesis of planar chiral 1,2-disubstituted ferrocenes. Ferrocene derivatives that contain a chiral directing group such as an oxazoline,<sup>[18]</sup> or a sulfoxide,<sup>[19]</sup> can be *ortho*-lithiated diastereoselectively under the appropriate conditions. In this study we envisioned that the resulting organolithium species could be transformed into the corresponding triferrocenylindium reagents and used in palladium-catalyzed cross-coupling reactions.

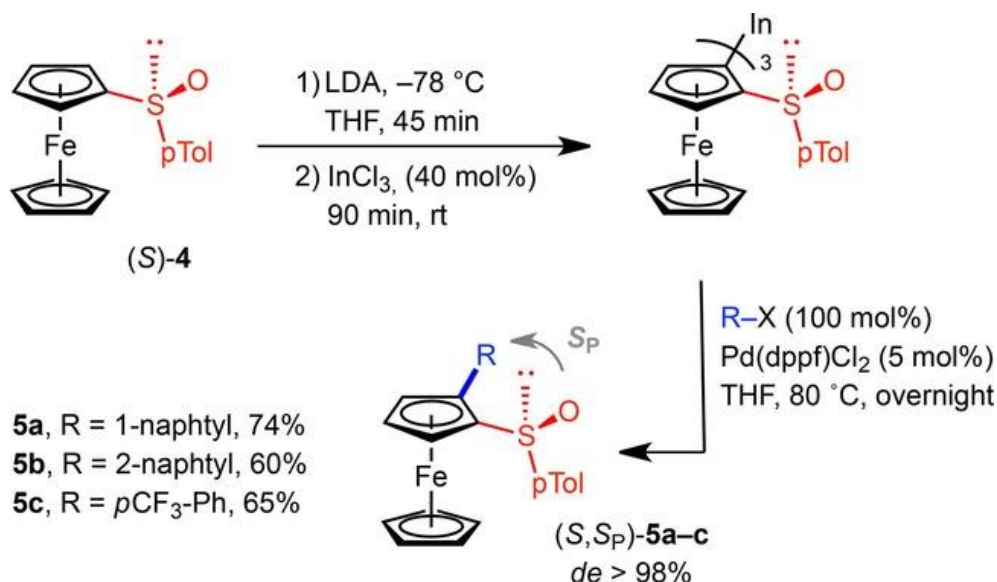
We began by exploring the lithiation/transmetalation/coupling protocol using the achiral ferrocenyl oxazoline **2 a**. As described in the literature, lithiation of **2 a** (100 mol%) with *n*BuLi in THF at –78 °C<sup>[20]</sup> followed by addition of  $\text{InCl}_3$  (40 mol%) and coupling with 2-bromoanisole (100 mol%) in the presence of  $\text{Pd}(\text{dppf})\text{Cl}_2$  (5 mol%) in THF at 80 °C gave the 2-aryl-1-oxazolylferrocene **3 a** in 72% yield (Table 2). Analogously, the reaction using 1-bromonaphthalene afforded the 2-(1-naphthyl)-1-oxazolylferrocene **3 b** in 77% yield. To the best of our knowledge, these results represent the first examples of palladium-catalyzed cross-coupling reactions involving an organometallic ferrocenyloxazoline.

**Table 2.** Synthesis of 2-aryl-1-oxazolylferrocenes.



These encouraging results led us to study the stereoselective synthesis of 2-aryl-1-oxazolyferrocenes. For this purpose, substrates bearing donor atoms such as pyridines were selected as electrophiles. Under the previously developed reaction conditions, lithiation of the enantiomerically pure ferrocenyl oxazoline **2 b** with *n*BuLi, transmetalation with indium and palladium-catalyzed cross-coupling with 3-bromopyridine using Pd(dppf)Cl<sub>2</sub>(5 mol%) in THF under reflux gave (*R<sub>p</sub>*)-2-(3-pyridyl)-1-oxazolyferrocene **3 c** in 68% yield with an 8:1 diastereomeric ratio, as determined by <sup>1</sup>H NMR spectroscopy (Table 2). This *dr* value is equal or slightly higher than that previously reported for the lithiation step, which indicates that the transmetalation-coupling steps take place without loss of diastereoselectivity. The two diastereoisomers were separated by flash column chromatography. The analogous protocol using 2-bromopyridine afforded the chiral (*R<sub>p</sub>*)-2-pyridyl-1-oxazolyferrocene **3 d** in 70% yield (6:1 *dr* by <sup>1</sup>H NMR). Apart from the existing synthetic methods for the preparation of ferrocenyloxazolines,<sup>[7a]</sup> these cross-coupling reactions are the first examples in which oxazolyferrocenyl organometallics have been used for the enantioselective synthesis of 2-pyridyl-1-oxazolyferrocene ligands with planar and central chirality.

Our next objective was the enantioselective synthesis of 2-aryl-1-sulfinylferrocenes using an enantiopure ferrocenyl sulfoxide. The sulfoxide functionality can be used as a chiral *orthometalating* group with high diastereoselectivity and its subsequent conversion allows the stereoselective synthesis of 1,2-disubstituted ferrocenes.<sup>[10d,21]</sup> Accordingly, lithiation of enantiopure *p*-tolyl ferrocenyl sulfoxide (*S*)-**4** using LDA in THF at -78 °C,<sup>[14]</sup> followed by addition of InCl<sub>3</sub> solution (40 mol%) gave the tri(2-sulfinylferrocenyl)indium intermediate (Scheme 2). Palladium-catalyzed cross-coupling with 1-bromonaphthalene using Pd(dppf)Cl<sub>2</sub>(5 mol%) afforded the planar chiral (*S,S<sub>p</sub>*)-2-(1-naphthyl)-1-sulfinylferrocene **5 a** in 74% yield as a single enantiomer (>99:1 by HPLC). Therefore, the lithiation step takes place with high diastereoselectivity and both the transmetalation and coupling steps proceed without affecting the stereoselectivity. In a similar manner, the procedure carried out with 2-bromonaphthalene and 4-trifluoromethylbromobenzene as organic electrophiles gave the enantiomerically rich (*S,S<sub>p</sub>*)-2-aryl-1-sulfinyl ferrocenes **5 b** and **5 c** with high diastereomeric excess (*de* >98%) in 60% and 65% yield, respectively.

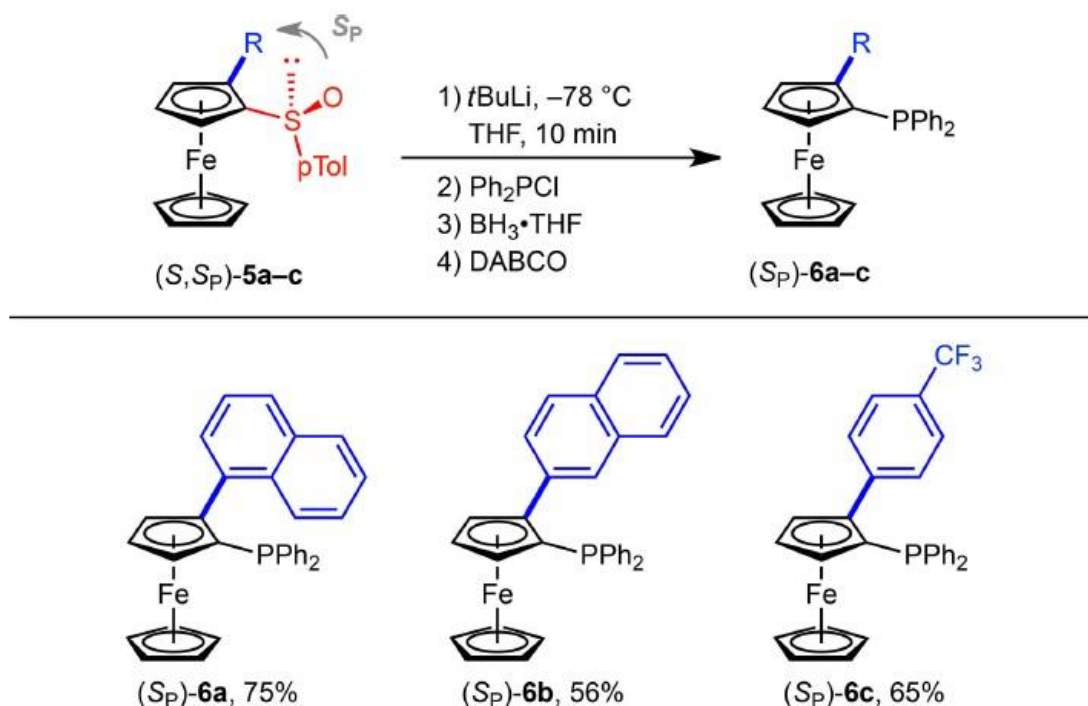


**Scheme 1.** Synthesis of (*S,S<sub>p</sub>*)-2-aryl-1-sulfinylferrocenes.

Finally, and taking advantage of the versatility of the sulfoxide group, the enantiomerically rich (*S,S<sub>p</sub>*)-2-aryl-1-sulfinylferrocenes **5 a-c** were transformed into the corresponding 2-aryl-1-monophosphine ferrocenes.

Following a reported procedure,<sup>[19]</sup> the sulfoxide group was converted into a diphenylphosphine group to give the planar-chiral phosphines ( $S_P$ )-**6 a–c** in good yields (Table 3). The enantiomeric purity of phosphines **6 a–c** was established based on the enantiomeric excess of the chiral sulfoxides **5 a–c** since the transformation is stereospecific.<sup>[19b–19d,21]</sup> It is worth noting that the ( $S_P$ )-2-(1-naphthyl)-diphenylphosphine ferrocene **6 a** exhibits high catalytic activity in the hydrosilylation of styrene.<sup>[21b]</sup> The utility of the novel chiral phosphines **6 b–c** in asymmetric catalysis is still unknown.

**Table 3.** Synthesis of planar chiral ( $S_P$ )-2-aryl-1-diphenylphosphine ferrocenes.



In summary, a practical and efficient procedure for the synthesis of monosubstituted and planar chiral 1,2-disubstituted ferrocenes by palladium-catalyzed cross-coupling reactions using triferrocenyliindium reagents has been developed.  $\text{Fc}_3\text{In}$  reagents can be efficiently prepared from ferrocene and derivatives by lithiation and transmetalation with indium(III).  $\text{Fc}_3\text{In}$  reagents (40 mol%) react with an array of organic electrophiles to provide an interesting range of monosubstituted ferrocenes in good yields under mild reaction conditions. The diastereoselective lithiation, transmetalation to indium and cross-coupling of chiral ( $S$ )-ferrocenyloxazolines led to the synthesis of planar chiral ( $R_P$ )-2-aryl-1-oxazolylferrocenes. Analogously, the coupling reaction in which tri(2-sulfinylferrocenyl)indium was used led to ( $S,S_P$ )-2-aryl-1-sulfinylferrocenes in good yields and with high diastereoselectivity. These compounds were efficiently converted into the corresponding  $N,P$ -2-aryl-1-diphenylphosphine ferrocenes (MOPF), which are of interest in asymmetric catalysis. Further applications of this synthetic method for novel planar chiral ferrocenes are underway.

## Experimental Section

Full experimental details are available in the [Supporting Information](#).

### Preparation of triferrocenyliindium solution (Fc<sub>3</sub>In)

A flame-dried round-bottomed flask under an argon atmosphere, equipped with a Teflon-coated magnetic stirring bar, was charged with ferrocene (1.0 g, 5.375 mmol, 1.0 equiv.). The ferrocene was dissolved in dry THF (40 mL, 0.134 M for ferrocene) and *t*BuOK solution (0.65 mL, 1.0 M in THF, 0.12 equiv.) was added by syringe. The mixture was cooled to  $-78\text{ }^{\circ}\text{C}$ . The resulting yellow solution was treated with *t*BuLi solution (6.3 mL, 1.64 M in pentane, 2.0 equiv.) over 15 minutes by syringe and the resulting orange suspension was stirred at  $-78\text{ }^{\circ}\text{C}$  for 90 min. Then, InCl<sub>3</sub> solution (4.8 mL, 0.45 M in THF, 0.4 equiv.) was added dropwise and the reaction mixture was allowed to warm up to  $0\text{ }^{\circ}\text{C}$  and stirred for 1 h to give triferrocenyliindium (1.79 mmol, 0.034 M in THF) as an orange homogeneous solution, which was immediately used for the cross-coupling step.

### General procedure for the palladium-catalyzed cross-coupling reaction

A flame-dried Schlenk flask under an argon atmosphere, equipped with a Teflon-coated magnetic stirring bar, was charged with the organic halide (1.0 equiv.) and Pd(PPh<sub>3</sub>)<sub>4</sub> (5 mol%) or Pd(dppf)Cl<sub>2</sub> (5 mol%). The mixture was dissolved in dry THF (ca. 0.3 M) and freshly prepared Fc<sub>3</sub>In solution (0.034 M in THF, 0.4 equiv.) was added dropwise by syringe or cannula. The mixture was heated at  $80\text{ }^{\circ}\text{C}$  overnight (16–18 h). The reaction was monitored by TLC and, after completion, quenched by the addition of a few drops of methanol and then tap water. The mixture was extracted with Et<sub>2</sub>O or EtOAc three times and the combined organic phases were washed with brine and dried over anhydrous MgSO<sub>4</sub>. The crude product was obtained by removal of the solvent under reduced pressure and it was purified by flash column chromatography (silica gel) to give the corresponding functionalized ferrocenes (65–95% yield).

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