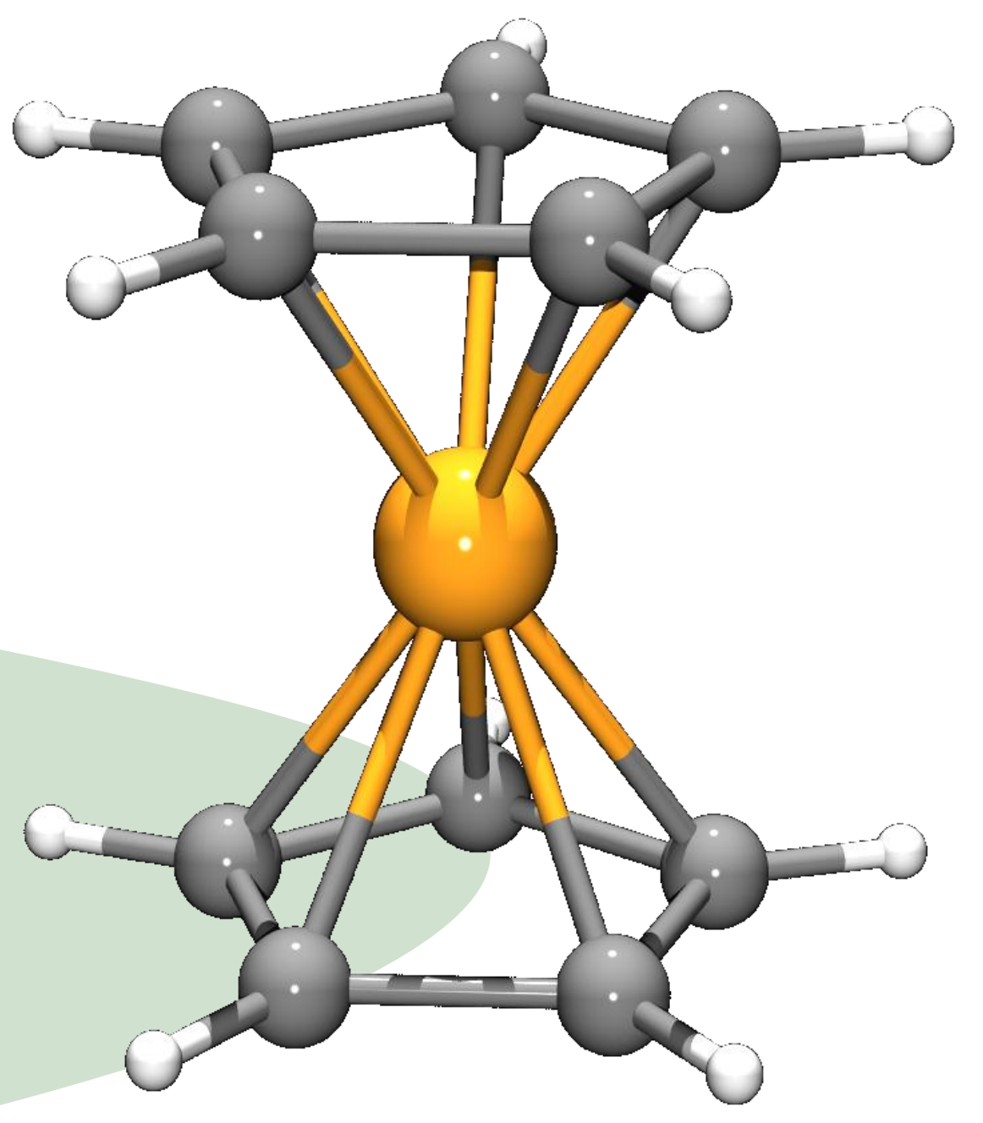
The versatile Chemistry of Ferrocenyl Alkyl Ethers



Dieter Schaarschmidt, Heinrich Lang*

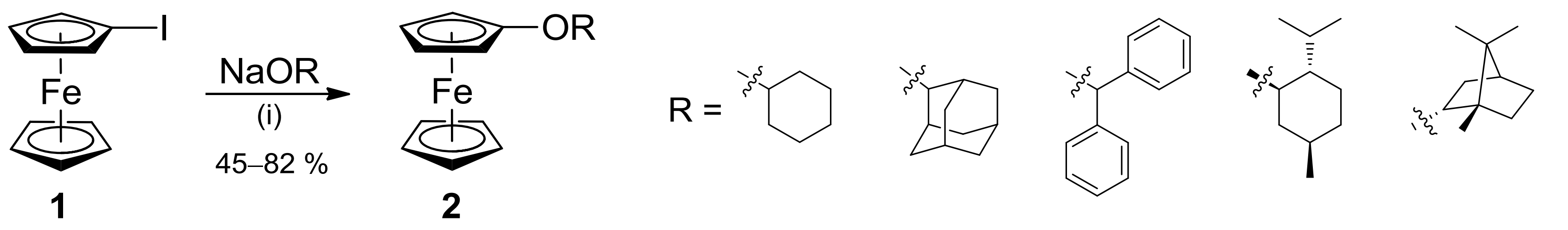
Chemnitz University of Technology, Department of Chemistry,
Chair of Inorganic Chemistry, Straße der Nationen 62, 09111 Chemnitz, Germany.
heinrich.lang@chemie.tu-chemnitz.de

Introduction

In the last decades ferrocene has emerged as an essential motif in organometallic chemistry. It has found numerous applications in academia and industry; the spectrum ranges from its use as backbone for highly selective and efficient ligands in asymmetric homogeneous catalysis to fuel additives for diesel engines. [1] The field of oxygen-substituted ferrocenes is one aspect that is still not fully developed. Recently, a straightforward synthesis methodology for ferrocenyl aryl ethers has been reported. [2a] The reactions chemistry of these ferrocenes utilizing the *ortho*-directing effect of the aryl ether has been discussed in detail, however, the thus available planar-chiral ferrocenes could not be obtained in enantiopure form. [2b] This prompted us to study the reaction chemistry of chiral, enantiopure ferrocenyl alkyl ethers, where reasonably *ortho*-directed functionalizations can be performed in a diastereoselective manner.

Synthesis of Ferrocenyl Alkyl Ethers

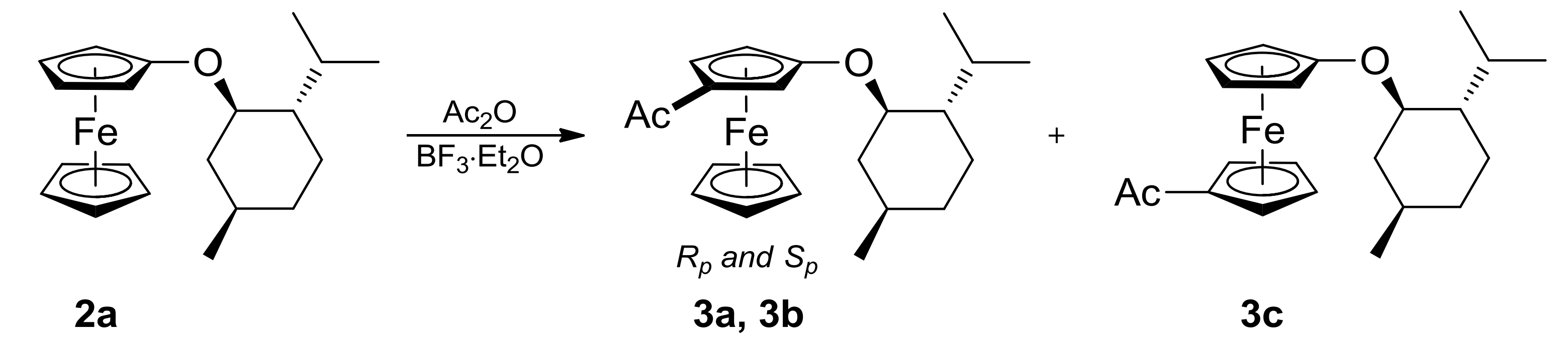
Ferrocenyl alkyl ethers are accessible exerting a copper mediated Ullman-type coupling of iodoferrocene and an alcoholate NaOR (Scheme 1). Secondary alcoholates show a higher reactivity than primary ones, tertiary alcoholates are almost unreactive. Applying chiral alcohols in this coupling results in full retention of configuration. Noteworthy, ferrocenyl alkyl ethers derived from secondary alkyl derivatives cannot be synthesized using the Williamson etherification of ferrocenol. [3]



Scheme 1. Synthesis of ferrocenyl alkyl ethers. (i) 1. CuI, 2,2'-bipyridine, *N*-methyl-2-pyrrolidone, 70 °C, 18 h.

Electrophilic Aromatic Substitution

As common for electron-rich aromatic compounds, ferrocene can easily be reacted in terms of a Friedel-Crafts-Acylation. When menthoxyferrocene (**2a**) is treated with Ac_2O in presence of a Lewis acid, *e. g.* BF_3, three monoacylated ferrocenes are isolated in a ratio of 1:1:2 (**3a**:**3b**:**3c**) (Scheme 2). This acylation proceeds regarding the formation of the two diastereomeric 1,3-disubstituted ferrocenes (**3a**, **3b**) without diastereoselectivity.

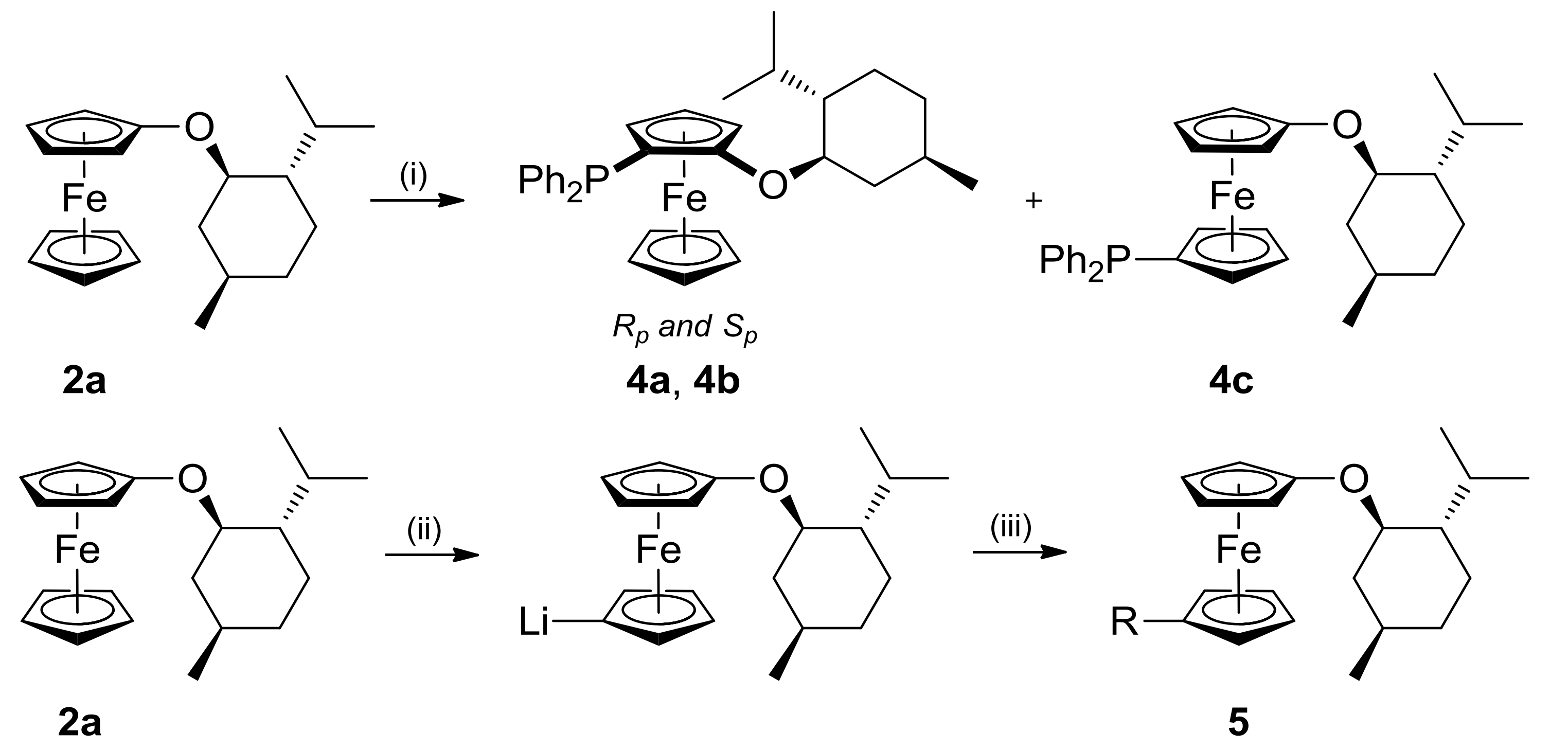


Scheme 2. Acylation of menthoxyferrocene.

Monolithiation

Ortho-directed lithiation and subsequent functionalization with appropriate electrophiles is most commonly used for the synthesis of planar-chiral 1,2-disubstituted ferrocenes. For this reason a standard lithiation protocol was applied on **2a**; the lithiated species were converted into the corresponding phosphines by treatment with $ClPPh_2$ (Scheme 3, top). Just like the electrophilic aromatic substitution, three ferrocenes are formed in a ratio of 4:3:1 (**4a**:**4b**:**4c**). However, **4a** and **4b** (14 % *de*) exhibit a 1,2-substitution pattern.

In contrast, ferrocenyl aryl ethers are under the same conditions firstly substituted at the substituted cyclopentadienyl, indicating a stronger *ortho*-directing influence of the aryl ether moiety. [2b]

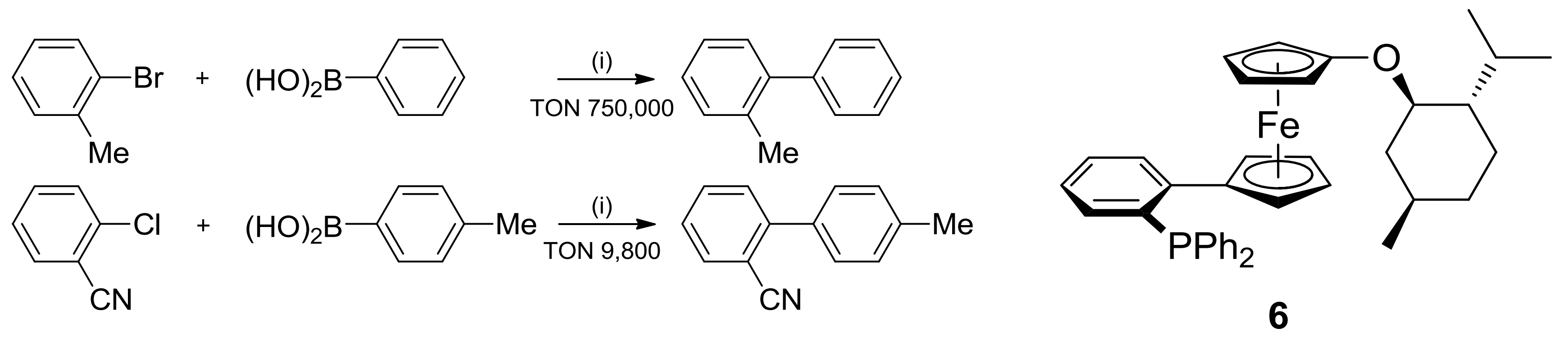


Scheme 3. Functionalization of **2a** *via* lithiation. (i) 1. *n*-BuLi/tmeda, *n*-hexane, 25 °C, 12 h; 2. $ClPPh_2$, – 78 °C, 1 h. (ii) *n*-BuLi, *n*-hexane, 25 °C, 12 h. (iii) electrophile, – 78 °C, 1 h (R = $SnBu_3$ (57 %), CPh_2OH (36 %)) or $[Zn(thf)_2Cl_2]$, aryl iodide, $[Pd(PPh_3)_4]$, thf, 70 °C, 60 h (Ph (27 %), C_6H_4-2-Br (52 %)).

Omitting tmeda ((tmeda = *N*,*N*,*N*',*N*'-tetramethylethylenediamine) in the lithiation of **2a** results in the selective deprotonation in 1'-position. In this manner 1,1'-disubstituted ferrocenes **5** are easily accessible either by treatment with an electrophile or cross-coupling reactions (*e. g.* Negishi *C,C* couplings). (Schema 3, bottom)

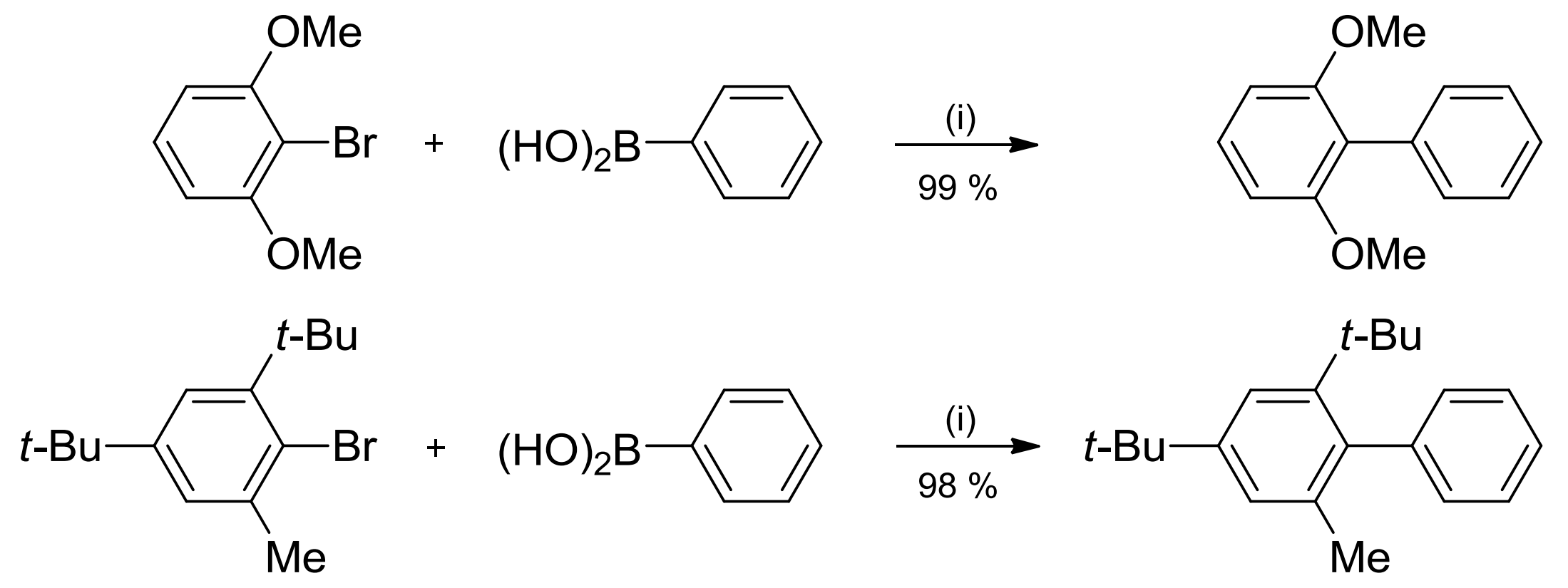
P,O-Ferrocenes in Suzuki-Miyaura *C,C* Couplings

P,O-Ferrocene **6** was synthesized starting from 1,1'-disubstituted **5a** *via* halogen-metal-exchange and consecutive reaction with $ClPPh_2$. This phosphine was applied in palladium mediated Suzuki-Miyaura coupling of aryl halides with aromatic boronic acids *in situ* generating the catalytic active species by applying stoichiometric mixtures of $[Pd_2(dba)_3]$ and **6** (dba = dibenzylideneacetone). [4] The alkyloxy moiety stabilizes the catalytic active species and therefore allows coupling reactions to be conducted at low catalyst levels. Bromo- and activated chloroarenes can be converted into the respective biaryls with catalyst loadings of 1–100 ppm, thus turn over numbers of up to 750,000 can be achieved (Scheme 4).



Scheme 4. Suzuki-Miyaura couplings at low catalyst levels.
(i) aryl halide (1.0 mmol), boronic acid (1.5 mmol), K_3PO_4 (3.0 mmol), toluene (2 mL), $[Pd_2(dba)_3]$/**6**, 24 h.

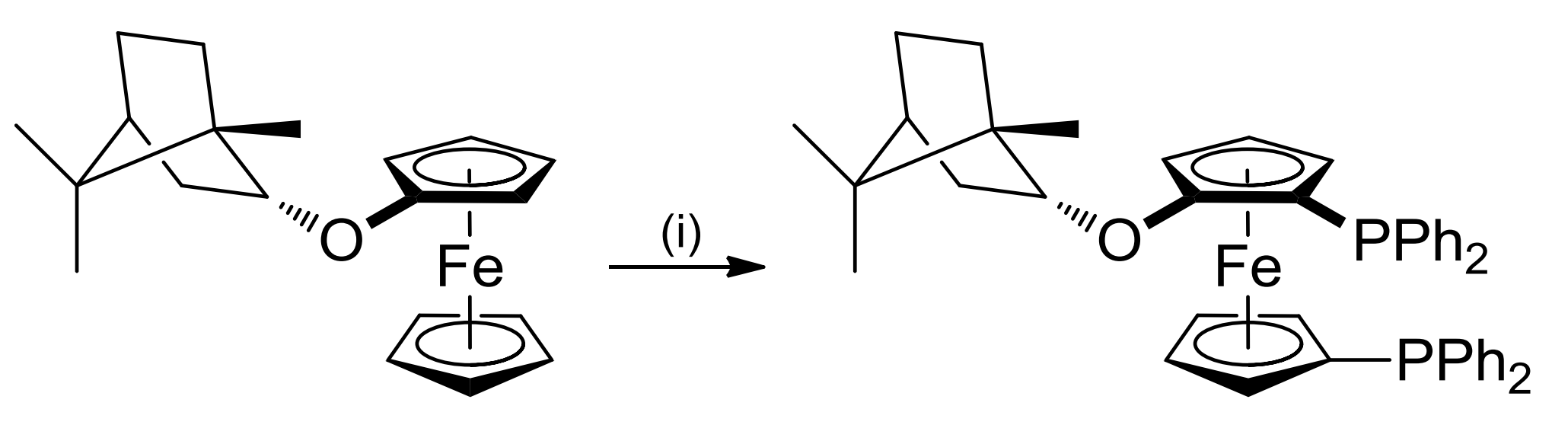
P,O-Ferrocene **6** allows the conversion of sterically hindered aryl halides at mild reaction conditions (0.1 mol-% catalyst, 50 °C). The introduction of bulky *ortho* substituents has no significant impact on the yield of the cross-coupling (Scheme 5).



Scheme 5. Conversion of sterically hindered aryl halides.
(i) aryl halide (1.0 mmol), boronic acid (1.5 mmol), K_3PO_4 (3.0 mmol), toluene (2 mL), 0.05 mol-% $[Pd_2(dba)_3]$, 0.2 mol-% **6**, 50 °C, 24 h.

Dilithiation

A two-fold lithiation is undoubtedly widespread in ferrocene chemistry, there is in general no need for directing functionalities to achieve good yields in this transformation. [1] However, in case of the chiral ethers **2**, the lithiation at the substituted cyclopentadienyl has to proceed with high diastereoselectivity in order to obtain a spectroscopic pure product. This happens when borneoxyferrocene (**2b**) is converted into diphosphine (R_p)-**7**. This diastereomer is isolated in > 95 % *de* after single recrystallization from *n*-pentane (Scheme 6, Figure 1).



2b (R_p)-**7**

Scheme 6. Difunctionalization of borneoxyferrocene.
(i) 1. *n*-BuLi/(–)-sparteine, *n*-hexane, 25 °C, 12 h; 2. $ClPPh_2$, – 78 °C, 1 h (42 %).

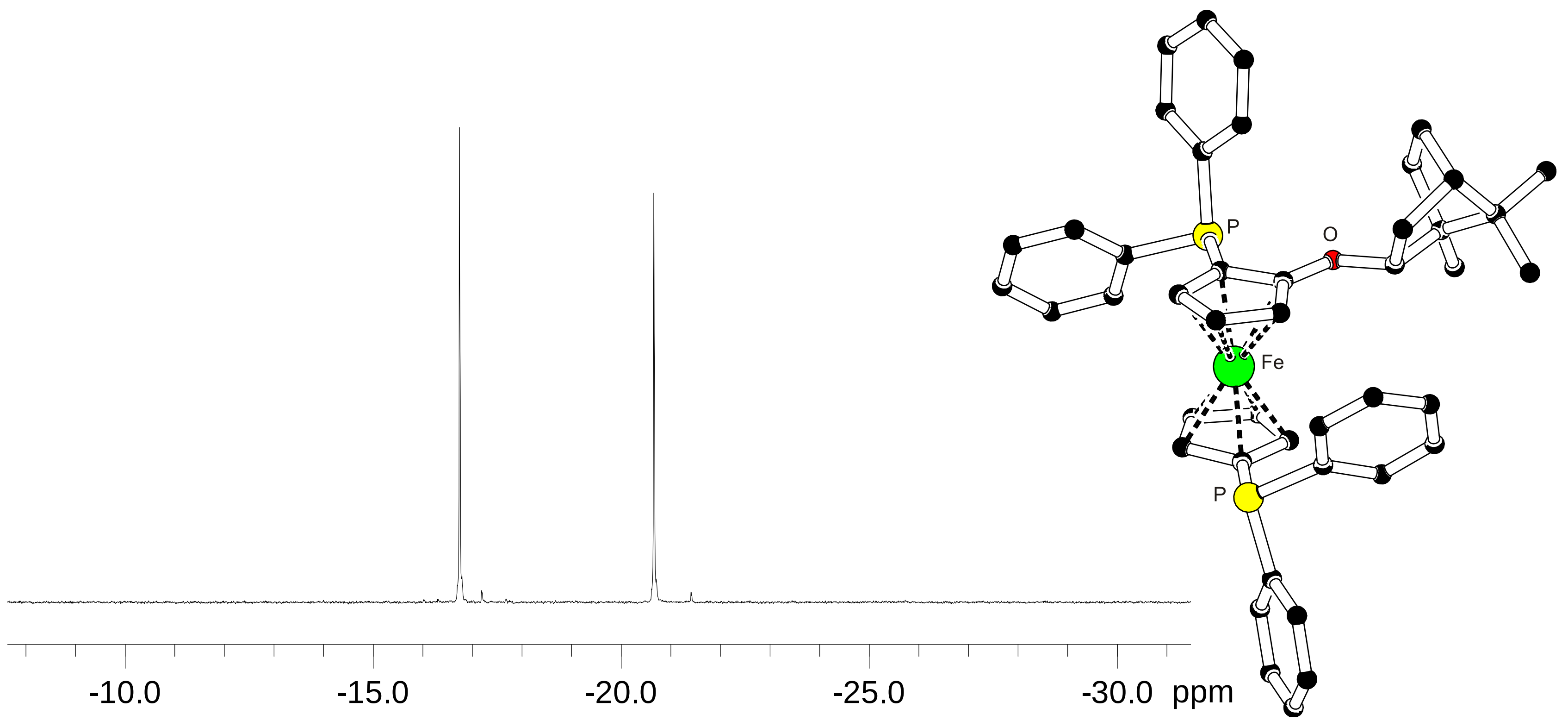


Figure 1. $^{31}P\{^1H\}$ nmr spectrum (202.5 MHz, $CDCl_3$, 25 °C) and molecular structure of (R_p)-**7**.

Conclusion

Ferrocenyl alkyl ethers are accessible by an Ullman-type coupling of iodoferrocene and an acoholate in good yields; chiral, enantiopure alcohols provide chiral, enantiopure ether with full retention of configuration. These ferrocenes can selectively be functionalized at the unsubstituted cyclopentadienyl *via* lithiation and subsequent reaction with an electrophile. In addition, two-fold lithiation results in the formation of planar-chiral ferrocenes with high diastereoselectivity.

P,O-Ferrocenes derived from ferrocenyl alkyl ethers have been applied to Suzuki-Miyaura *C,C* couplings. High catalytic activity is observed even at catalyst levels as low as 1 ppm, furthermore, sterically hindered aryl halides can be converted at mild reaction conditions.

References and Acknowledgement

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