



1,2-*P,O*-FERROCENES IN SUZUKI-MIYAUURA C,C COUPLINGS

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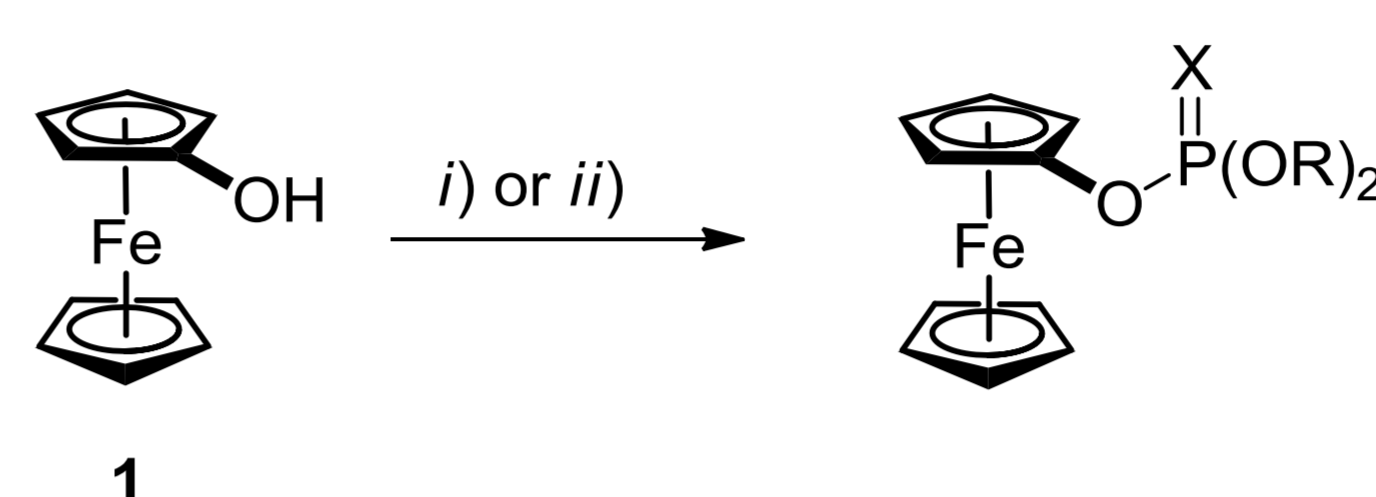
Introduction

Since its first synthesis, ferrocene has emerged as one of the most important organometallic structural motifs. Industrial and academic applications are well known and range from fuel additives to ferrocene-based highly-active and efficient ligands for homogeneous catalysis.^[1] In particular, oxygen functionalized ferrocenes are rarely examined. Recent investigations already explored a pathway for the synthesis of ferrocenyl-aryl ethers and their suitability in *ortho*-directed

metalations. However, unwanted side reactions result in the formation of 1,1'-substituted ferrocenes and require elaborate column chromatographic purification.^[2] As an option, the intramolecular phospho-Fries rearrangement enhances the formation of *ortho*-substituted products, which is a well known synthesis strategy for phenyl-based compounds.^[3]

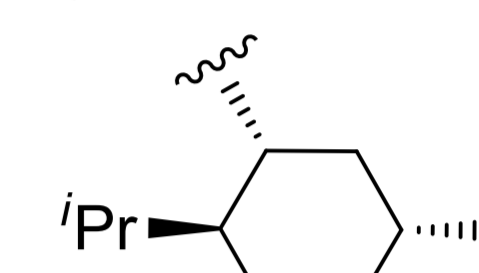
Synthesis of Ferrocene-O-P Compounds

Suitable starting materials for anionic Fries rearrangements in general require electron withdrawing substituents to ensure *ortho*-lithiation and intramolecular attack. Starting from ferrocene, ferrocenol (**1**) can be synthesized in a four steps synthesis.^[4] Treatment with chloro phosphorous compounds in the presence of a base yields the Fc-O-P compounds **2a-c**.^[5] Electronically modified derivatives are easily accessible, starting from the P(III) compounds by adding either sulfur or borane-thf adduct. The obtained compounds are stable towards air and moisture. Furthermore, introduction of chiral alkyl substituents can easily be achieved by using the respective chlorophosphates and reaction with FcOLi, which yields the chiral ferrocenyl phosphates **2d,e**.^[5]

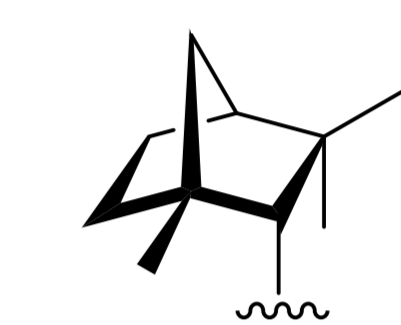


2a 90 % X = O, R = Et
2b 31 % X = S, R = Et
2c 76 % X = BH₃, R = Et

2d 91 % X = O, R =

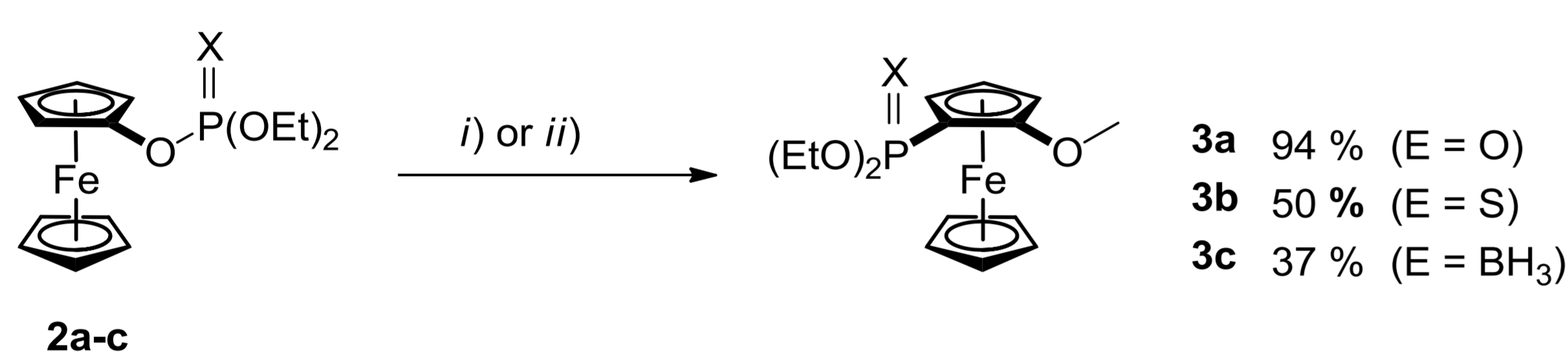


2e 83 % X = O R =



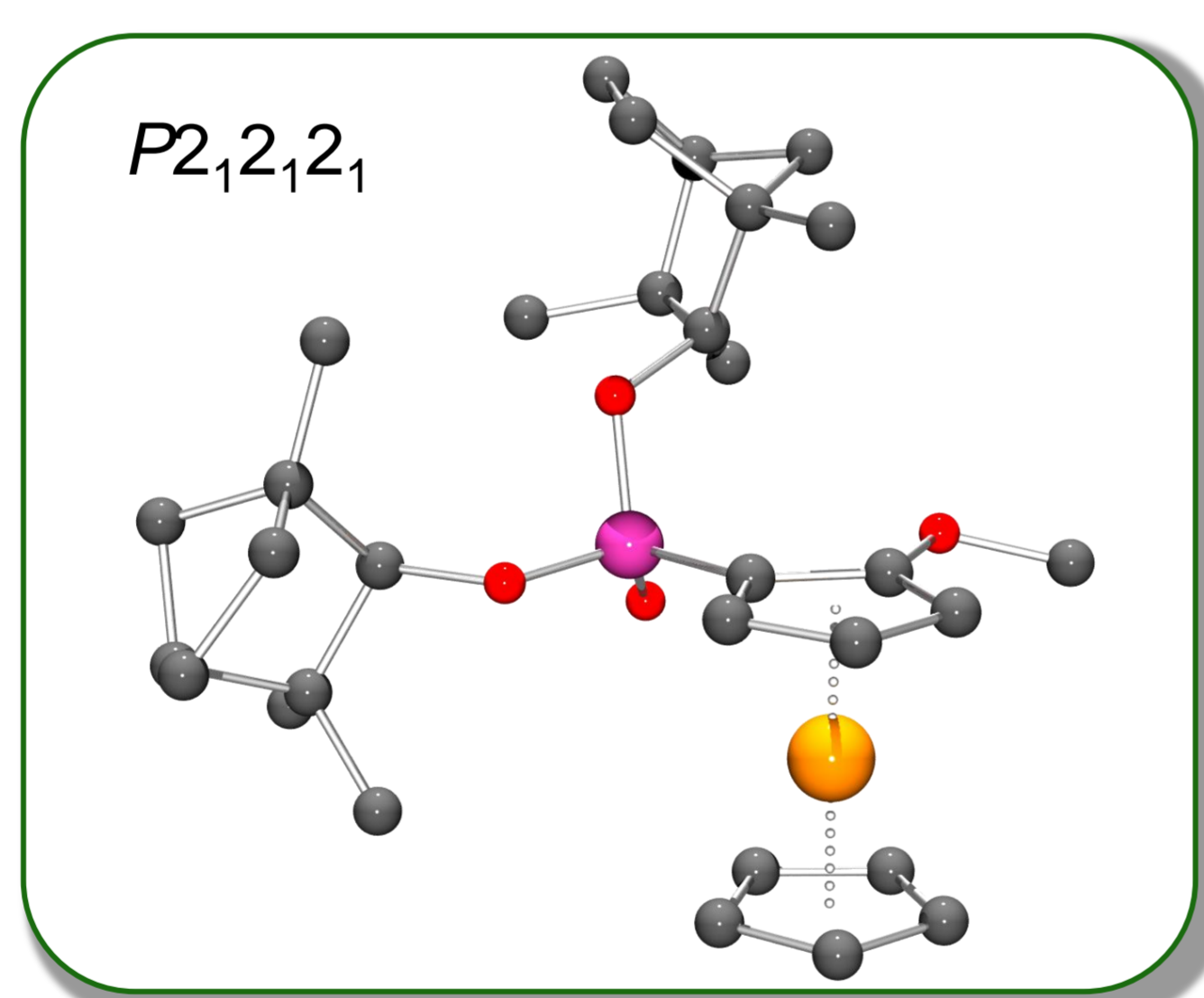
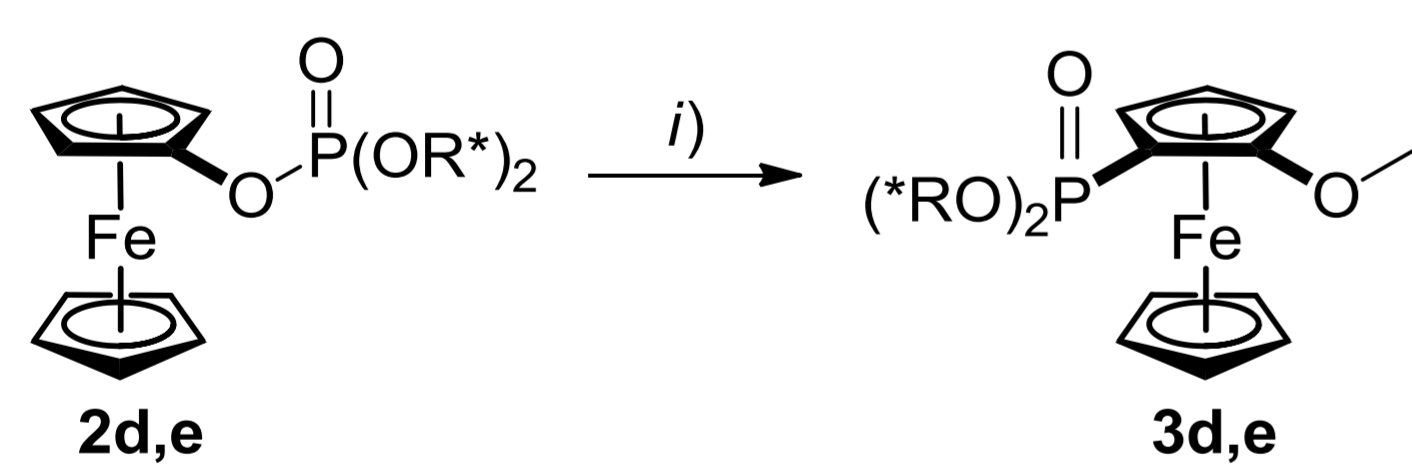
Scheme 1. i) (R = Et, X = O) NEt₃, CH₂Cl₂, -30 °C, ClP(O)(OEt)₂, (R = Et, X = S, BH₃) NEt₃, CH₂Cl₂, -30 °C, ClP(OEt)₂, S₈/BH₃-thf. ii) (R ≠ Et), BuLi, thf, -30 °C, ClP(O)(OR)₂.

Anionic Phospho-Fries Rearrangement



Scheme 2. i) **2a-c**: LDA, -30 °C, 4 h, thf, Me₂SO₄. ii) **2b**: ^tBuLi, -30 °C, 4 h, Me₂SO₄.

The anionic Phospho-Fries rearrangement is induced by lithiation in *ortho* position of the ferrocenyl oxygen. The *ortho*-directing effect of the O-P substituents enables selective deprotonation in the desired position. The usage of non-nucleophilic bases is essential to avoid nucleophilic attack at the phosphorous atom. Esters **2a-c** rearrange at -30 °C to the respective Phospho-Fries products **3a-c** within a strict temperature regime.^[5] The addition of an electrophile protects the OH-functionality, which is sensitive to oxidation. However, for **2d,e** bearing sterically more demanding chiral alkyl substituents higher temperatures are required for the lithiation. Thus, the reaction conditions can be simplified by stirring at ambient temperature and using hexane as the solvent to avoid the ether cleavage.



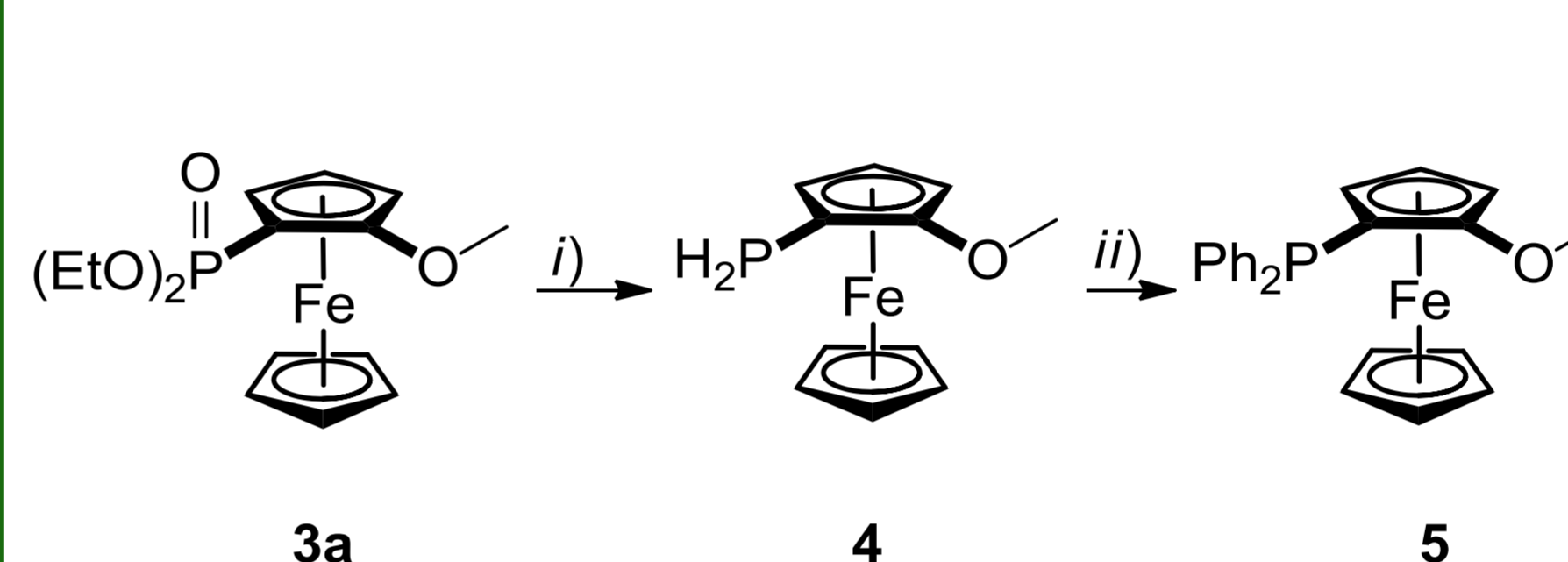
	R*	Base	Amine	de	Yield ^[a]
d	(1 <i>R</i>)-Menthyl	LDA	TMEDA	0.29	99 %
		LDA	(-)-Sparteine	0.40	99 %
		LiTMP	(-)-Sparteine	0.00	99 %
e	(1 <i>R</i>)- α -Fenchyl	LDA	TMEDA	0.72	29 %
		LDA	(-)-Sparteine	0.58	79 %
		LTMP	TMEDA	0.80	65 %

Scheme 3. i) base, amine, hexane, 25 °C, 14 h, Me₂SO₄, 60 °C, 1 h. [a] Isolated yields based on **2**. Top right: *Ball-and-Stick* model of the molecular structure of **3e** in the solid state. All hydrogen atoms have been omitted for clarity. (LDA = Lithium diisopropylamide, LTMP = Lithium 2,2,6,6-tetramethylpiperide, TMEDA = Tetramethylethylenediamine.)

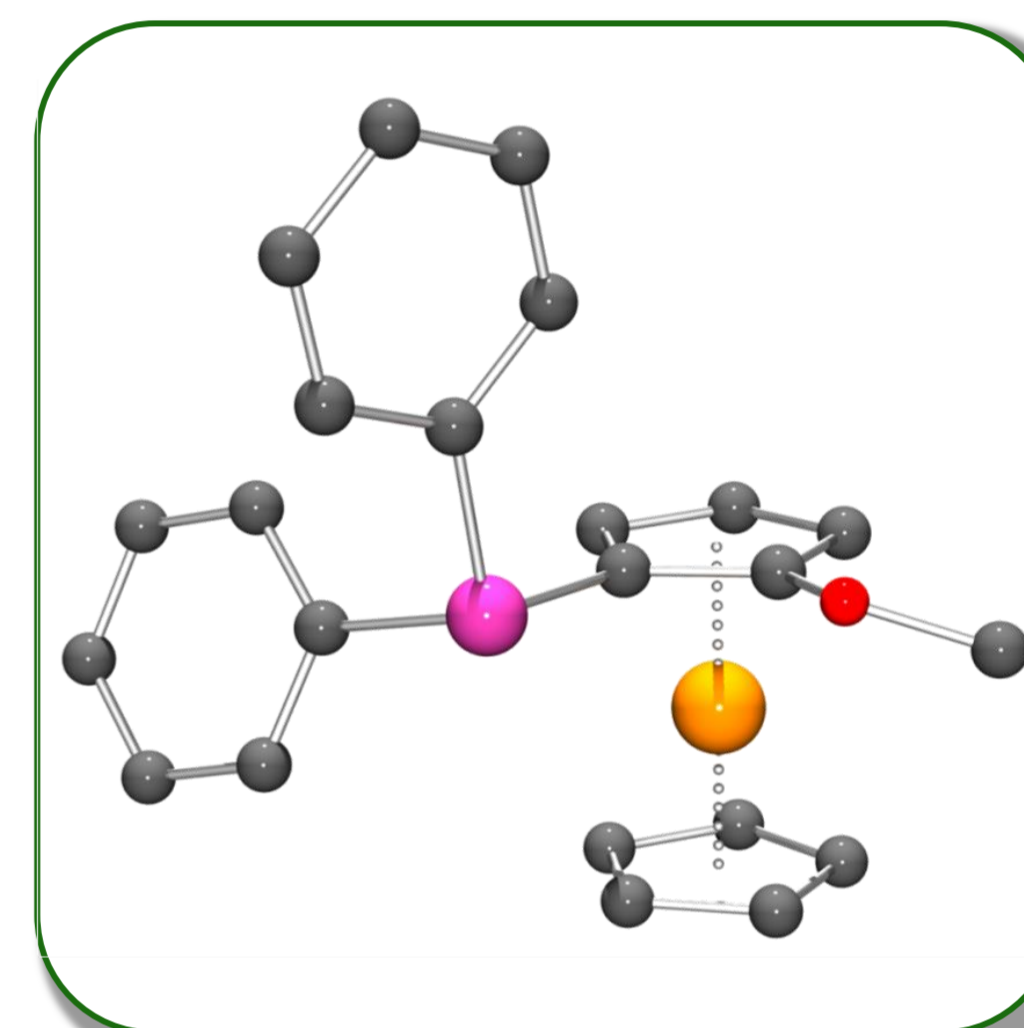
Summary

The successful synthesis of 1,2-*P,O*-substituted ferrocenes via the anionic Phospho-Fries rearrangement enables a new synthesis pathway starting from easily accessible ferrocenyl phosphates. The rearrangement products can be converted to phosphane **5**, which is suitable as a supporting ligand in C,C cross-coupling reactions for the synthesis of hindered biaryls under mild conditions. Running the anionic Phospho-Fries rearrangement stereoselectively should result in a planar chiral phosphane **5** and thus, should result in the formation of enantioenriched biaryls, which is currently in progress. A further functionalization at the oxygen moiety is planned to increase the catalytic activity.

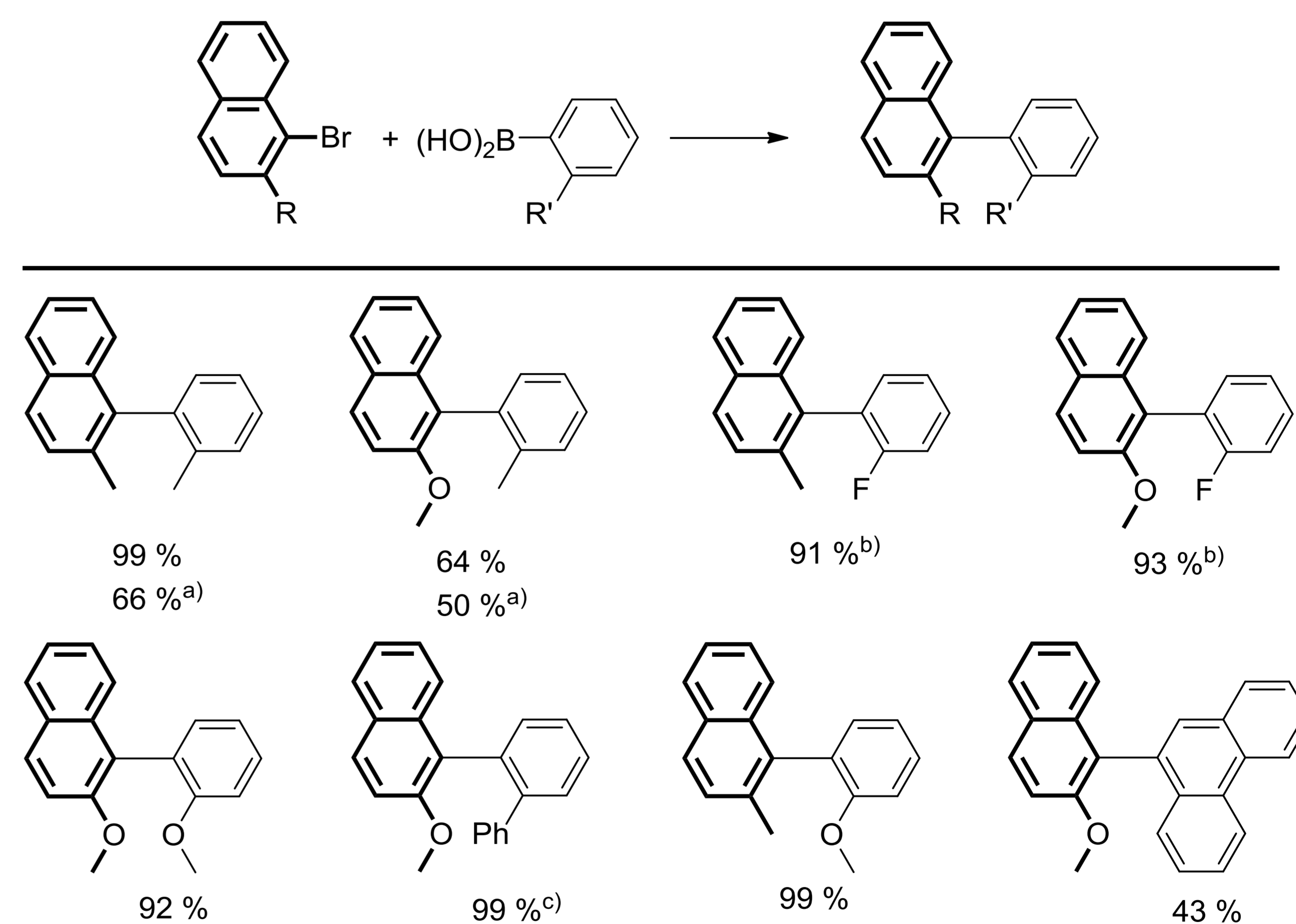
P,O-Ferrocenes in the Suzuki-Miyaura Reaction



Scheme 4. i) LiAlH₄, TMSCl, thf, 45 °C, quant. ii) 2 eq K₃PO₄, 2 PhI, 2 mol% [Pd(dppf)Cl₂], toluene, 110 °C, 14 h, 50 % (based on **4**). Right: *Ball-and-Stick* model of the molecular structure of **5** in the solid state. H atoms have been omitted for clarity.



Phosphonate **3a** was converted to phosphine **4** by reduction using LiAlH₄/Me₃SiCl^[6a] in the absence of oxygen. The subsequent Stelzer reaction^[6b] allows the C-P bond formation and produces **5** in moderate yields. Compound **5** was tested as a supporting ligand in C,C cross-coupling reactions for the synthesis of hindered biaryls bearing three *ortho*-substituents. The obtained activated and de-activated biaryls are racemic mixtures of the axial chiral compounds.



Scheme 5. [Pd₂(dba)₃] (0.25 mol%), **5** (1 mol%), K₃PO₄ x H₂O, toluene, 70 °C, 24 h. a) 50 °C. b) K₃PO₄ x 3 H₂O. c) 100 °C.

References and Acknowledgement

- [1] *Ferrocenes: Ligands, Materials and Biomolecules*, John Wiley & Sons Ltd., Chichester, 2008.
- [2] (a) M. R. an der Heiden, G. D. Frey, H. Plenio, *Organometallics* **2004**, *23*, 3548.
(b) D. Schaarschmidt, H. Lang, *Eur. J. Inorg. Chem.* **2010**, 4811.
- [3] C. M. Taylor, A. J. Watson, *Curr. Org. Chem.* **2004**, *8*, 623.
- [4] D. Guillauneux, H. B. Kagan, *J. Org. Chem.* **1995**, *60*, 2502. A. N. Nesmejanow, W. A. Ssasonowa, V. N. Drosd, *Chem. Ber.* **1960**, *93*, 2717.
- [5] M. Korb, D. Schaarschmidt, H. Lang, *Organometallics* **2014**, *33*, 2099–2108.
[6] (a) J. Andrieu, M. Azouri, *Inorg. Chim. Acta* **2007**, *360*, 131–135. (b) O. Herd, A. Heßler, M. Hingst, M. Trepper, O. Stelzer, *J. Organomet. Chem.* **1996**, *522*, 69.

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