

P,O-Ferrocenes in Suzuki–Miyaura C,C Couplings[†]

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S Supporting Information

ABSTRACT: It is generally accepted that efficient Suzuki–Miyaura catalysts contain sterically demanding and strongly Lewis-basic phosphines. Herein we report on the use of chiral *P,O*-ferrocenes in the synthesis of sterically hindered biaryls by the palladium-catalyzed Suzuki–Miyaura coupling. It is apparent that a decrease of the phosphine Tolman cone angle results in a higher catalytic productivity, which is contradictory to what is known as a good Suzuki–Miyaura catalyst. In addition, the *P,O*-ferrocenes were successfully applied for couplings of nonactivated aryl bromides with aromatic boronic acids at catalyst loadings as low as 1 ppm achieving quite high turnover numbers (TONs) of up to 750,000.

KEYWORDS: ferrocene, phosphine, Tolman cone angle, catalysis, Suzuki–Miyaura

The Suzuki–Miyaura coupling is undoubtedly among the most essential catalytic transformations in organic chemistry.^{1–11} In the past decades there have been major efforts to develop efficient catalysts for this reaction.^{12–38} The most common catalysts used today are based on monophosphines, whereby sterically demanding and strongly Lewis-basic phosphines are of highest importance. Kinetic as well as computational investigations have shown that these ligands accelerate the oxidative addition which is believed to be the rate determining step in the Suzuki–Miyaura catalytic cycle.^{39–45}

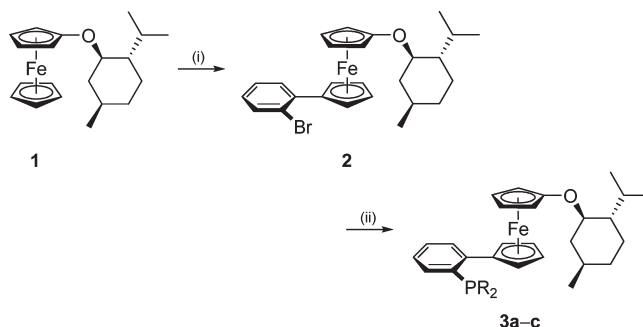
Despite all improvements in the past decades, the synthesis of sterically hindered biaryls by Suzuki–Miyaura coupling is still a challenge. Catalysts that can perform such reactions in an enantioselective manner under mild conditions would enrich natural product synthesis as well as the production of pharmaceuticals.⁴⁶

Previously we reported on the application of planar-chiral *P,O*-ferrocenes of type $\text{Fe}(\eta^5\text{-C}_5\text{H}_5)(\eta^5\text{-C}_5\text{H}_3(\text{OC}_6\text{H}_4\text{-}4\text{-}t\text{-Bu})\text{-2-PR}_2)$ ($\text{R} = \text{Ph}$, 2-tolyl, Cy; Cy = $c\text{-C}_6\text{H}_{11}$) in the coupling of aryl halides and aromatic boronic acids.^{49,50} It has turned out that these phosphines can be regarded as promising ligands for the conversion of hindered substrates; however, we were not able to obtain the ferrocenes in enantiopure form. This prompted us to examine the synthesis and application of *P,O*-ferrocenes starting from enantiopure ferrocenyl alkyl ethers.^{51,52}

RESULTS AND DISCUSSION

The *P,O*-ferrocenes **3a–c** were obtained in a two-step synthesis protocol starting from **1** via lithiation, zincation, and subsequent Negishi coupling with 1-bromo-2-iodobenzene (Scheme 1). Molecule **2** could be converted to the respective ferrocenyl phosphines $\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{OMent})(\eta^5\text{-C}_5\text{H}_4\text{C}_6\text{H}_4\text{-2-PR}_2)$ ($\text{R} = 2\text{-tolyl}$ (**3a**), Ph (**3b**), 2-furyl (**3c**); Ment = (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl⁵²) by halogen-metal exchange and consecutive reaction with ClPR_2 . The identity of **2** and **3a–c** was

Scheme 1. Synthesis of **3a–c**^a



^a(i) 1. *n*-BuLi, *n*-hexane, 25 °C, 12 h; 2. $[\text{Zn}(\text{thf})_2\text{Cl}_2]$, 1-bromo-2-iodobenzene, $[\text{Pd}(\text{PPh}_3)_4]$, thf, 70 °C, 60 h (52%). (ii) 1. *n*-BuLi, thf, –78 °C, 1 h; 2. ClPR_2 (33–45%).

confirmed by state-of-the-art analytical methods (Supporting Information).

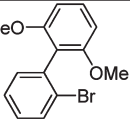
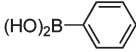
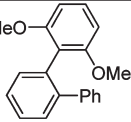
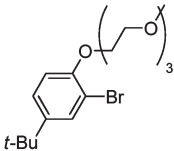
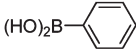
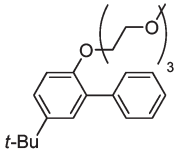
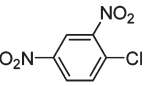
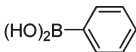
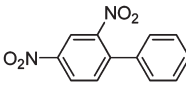

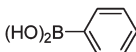
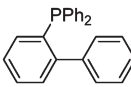
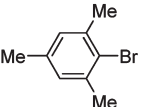
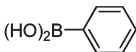
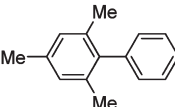
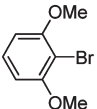
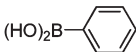
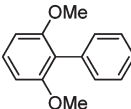
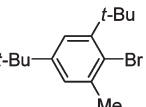
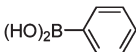
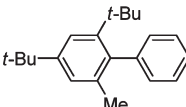
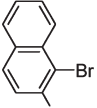
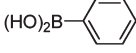
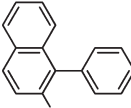
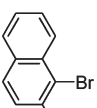
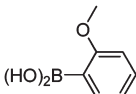
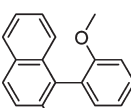
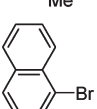
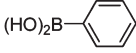
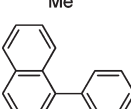
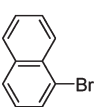
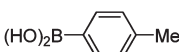
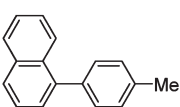
P,O-Ferrocenes **3a–c** were applied in the palladium mediated Suzuki–Miyaura coupling of aryl halides with aromatic boronic acids in situ generating the catalytic active species by applying stoichiometric mixtures of $[\text{Pd}_2(\text{dba})_3]$ and **3a–c** (dba = dibenzylideneacetone). Table 1 shows the catalytic transformation of sterically hindered aryl halides with aromatic boronic acids. It becomes clear that **3b** allows the conversion of nonactivated (entries 1, 5, 7, 8, 11) and deactivated (entries 2, 6, 10) aryl bromides as well as activated aryl chlorides (entry 3) at 50 °C and 0.1 mol % $[\text{Pd}]$. The catalyst tolerates steric hindrance at the aryl halide component; the introduction of bulky ortho substituents (e.g., alkyl or aryl moieties, ethylene glycol chains, or nitro

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Table 1. Conversion of Sterically Hindered Aryl Halides^a

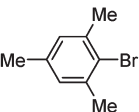
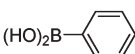
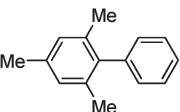
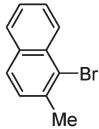
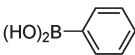
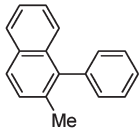
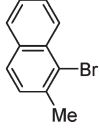
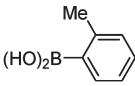
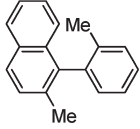

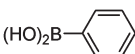
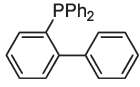

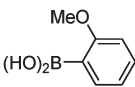
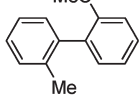
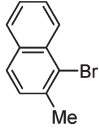
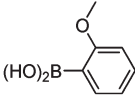
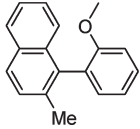
Entry	Aryl halide	Boronic acid	Product	Yield / %
1				97
2				98
3				96
4				20 ^b
5				94 ^c
6				99
7				98
8				90 ^c
9				39 ^b
10				99
11				99

^a Reaction conditions: aryl halide (1.0 equiv), boronic acid (1.5 equiv), K₃PO₄ (3.0 equiv), toluene (2 mL · mmol⁻¹ halide), [Pd₂(dba)₃]/**3b**, 0.1 mol % [Pd], 50 °C, 24 h. Reaction times were not minimized. ^b 100 °C reaction temperature. ^c 6 h reaction time.

groups) or the use of 1-naphthyl and 9-anthracenyl derivatives, respectively, has no significant impact on the yield of the cross-coupling. However, extremely hindered ortho PPh₂-substituted bromobenzene (Table 1, entry 4) could not be coupled smoothly.⁵³ Noteworthy is the coupling of 2-bromo-1,5-di-*tert*-


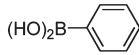
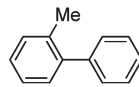

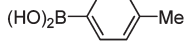
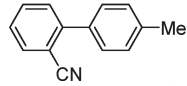
butyl-3-methylbenzene with phenyl boronic acid in almost quantitative yield applying the conditions mentioned above (Table 1, entry 7). When commercially SPhos is applied in this reaction a higher reaction temperature (110 °C vs 50 °C (**3b**)) along with a higher catalyst loading (10 mol % vs 0.1 mol % (**3b**))

Table 2. Influence of the Ligand Structure of 3a–c on the Yield of Suzuki–Miyaura Couplings^a

Entry	Aryl halide	Boronic acid	Product	Yield / %		
				3a	3b	3c
1				20 ^b	94 ^b	n.d.
2				47 ^b	90 ^b	n.d.
3				< 10	< 10	40
4				n.d.	20	50
5				n.d.	22	84
6				n.d.	39	93

^a Reaction conditions: aryl halide (1.0 equiv), boronic acid (1.5 equiv), K₃PO₄ (3.0 equiv), toluene (2 mL · mmol⁻¹ halide), [Pd₂(dba)₃]/3a–c, 0.1 mol % [Pd], 100 °C, 24 h. Reaction times were not minimized. Note: n.d., not determined. ^b 50 °C reaction temperature, 6 h reaction time.

Table 3. Comparison of 3b and 3d in Suzuki–Miyaura Couplings^a

Entry	Aryl halide	Boronic acid	Product	Yield / %	
				3b	3d
1				99	15
2				98 ^b	61 ^b

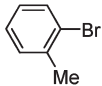
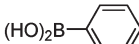
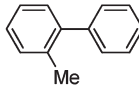
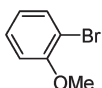
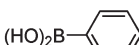
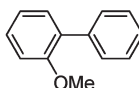
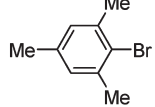

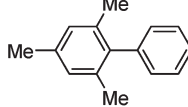
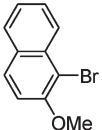

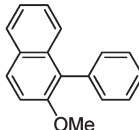
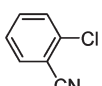
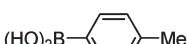
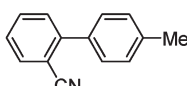
^a Reaction conditions: aryl halide (1.0 equiv), boronic acid (1.5 equiv), K₃PO₄ (3.0 equiv), toluene (2 mL · mmol⁻¹ halide), [Pd₂(dba)₃]/3b,d, 0.01 mol % [Pd], 25 °C, 24 h. Reaction times were not minimized. ^b 50 °C reaction temperature, [Pd₂(dba)₃]/3a,d, 0.1 mol % [Pd].

is required to obtain the respective biphenyl in approximately the same yield.¹³

The main issue of the presented catalysts is the quite low tolerance toward ortho substituents at the boronic acid (entries 8 vs 9). An increase of reaction temperature, reaction time, and catalyst loading did not significantly affect this behavior. To overcome this problem we investigated the influence of the structure of the phosphines (comparison of 3a (R = 2-tolyl), 3b (R = Ph) and 3c (R = 2-furyl)) on the yield of selected cross-coupling reactions (Table 2). Obviously the productivity of the respective catalysts increases with decreasing steric demand of the phosphine (the Tolman cone angle decreases in the series 3a > 3b > 3c)⁵⁴ and hence, an increase of steric

hindrance of the substrates can be compensated by the use of ligands with smaller Tolman cone angles. Consequently the least Lewis-basic and least sterically demanding phosphine in this series is the best catalyst under the conditions applied, which is in direct contradiction to what is meant to be a good Suzuki–Miyaura catalyst (vide supra). Recently, Kwong et al. reported one example, where the substitution of a PCy₂ by a PPh₂ moiety exceedingly increased the catalytic productivity for the coupling of 2,6-dimethylchlorobenzene and mesityl boronic acid.³⁰ Already some time ago the group of Fu notified that the use of PCy₃ instead of Pt-Bu₃ as supporting ligand may be advantageous for the synthesis of sterically hindered biaryls.⁵⁷ In concluding, to overcome one of the last challenges of the

Table 4. Suzuki–Miyaura Couplings at Low Catalyst Loadings^a

Entry	Aryl halide	Boronic acid	Product	[Pd] / mol-%	T / °C	Yield / %
1				0.01 0.001 0.0001	25 50 100	99 98 75
2				0.001	100	65
3				0.001	100	59
4				0.001	100	28
5				0.01 0.001	100 100	98 9

^a Reaction conditions: aryl halide (1.0 equiv), boronic acid (1.5 equiv), K₃PO₄ (3.0 equiv), toluene (2 mL · mmol⁻¹ halide), [Pd₂(dba)₃]/**3b**, 24 h. Reaction times were not minimized.

Suzuki–Miyaura coupling, the efficient synthesis of sterically hindered biaryls, it is necessary to abandon the idea that a promising phosphine should have inevitably a wide Tolman cone angle.

A comparison of Fe(η^5 -C₅H₄OMent)(η^5 -C₅H₄C₆H₄-2-PPh₂) (**3b**) with FcC₆H₄-2-PPh₂ (**3d**)⁵⁸ (Fc = Fe(η^5 -C₅H₅)(η^5 -C₅H₄)) is shown in Table 3 proving that the introduction of an alkoxy moiety at the second cyclopentadienyl ligand significantly enhances the catalytic activity in the Suzuki–Miyaura reaction. Obviously there is an interaction between the palladium atom and the alkoxy moiety which could be shown in structurally related compounds.^{59–62} This observation prompted us to investigate whether this interaction stabilizes the catalytic active species allowing a decrease of the catalyst loading. Table 4 shows the results of these investigations. It is possible to achieve a turnover number (TON) of 750,000 (entry 1, catalyst concentration 0.0001 mol % = 1 ppm [Pd]) for the coupling of 2-bromotoluene and a TON of almost 10,000 for the conversion of 2-chlorobenzonitrile (entry 5). These results represent a significant improvement compared to *P*,*O*-ferrocenes previously described in the literature,⁵¹ although examples are known showing higher TONs.⁶³

Furthermore, it should be examined whether the interaction between palladium and the menthoxy moiety enables the catalyst to couple biphenyls in an atropselective manner. The coupling of 1-bromo-2-methylnaphthalene and 2-methoxyphenyl boronic acid with [Pd₂(dba)₃]/**3c** as catalyst was chosen as test reaction (Table 2, entry 6), providing the respective biphenyl in only 2–7% *ee*. Obviously the aforementioned interaction is not strong enough, at least during the reductive elimination,⁶⁶ to induce a noteworthy enantiomeric excess.

CONCLUSION

Within this study the synthesis of chiral *P*,*O*-ferrocenes and their use as supporting ligands in Suzuki–Miyaura C,C

couplings is reported. The phosphines allow the conversion of aryl halides independently of the presence of sterically demanding ortho substituents in an efficient way, however, being rather intolerant toward ortho substitution of the boronic acid. The influence of the ligand structure on the productivity of the coupling of sterically hindered substrates has been determined revealing that the phosphine exhibiting the smallest Tolman cone angle shows the highest performance, which is in direct contradiction to what is meant to be a good Suzuki–Miyaura catalyst. While the comparison between a here presented *P*,*O*-ferrocene and its achiral analogue showed a significant improvement of the catalytic behavior indicating an interaction between palladium and the menthoxy moiety, the application in an atropselective Suzuki–Miyaura coupling failed so far. In addition the *P*,*O*-ferrocenes were successfully applied for couplings being conducted at low catalyst loadings achieving TONs of up to 750,000 for the conversion of non-activated aryl bromides.

ASSOCIATED CONTENT

S Supporting Information. Text and figures giving full experimental and spectroscopic details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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DEDICATION

[†]Dedicated to Professor Gernot Frenking on the occasion of his 65th birthday.

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