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Palladium Complexes of Planar Chiral Ferrocenyl Phosphine-NHC Ligands: New Catalysts for the Asymmetric Suzuki−Miyaura Reaction

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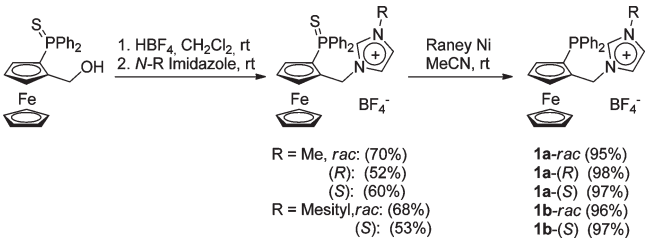
Summary: Air-stable neutral and cationic palladium complexes bearing chiral phosphine-N-heterocyclic carbene ligands with planar chirality only have been prepared in moderate to good yields and characterized by NMR and X-ray diffraction studies. They are shown to catalyze the asymmetric coupling of aryl bromides with arylboronic acids in good yields and moderate enantioselectivities (up to 42% ee) with low catalyst loadings (0.1−0.5 mol %).

N-heterocyclic carbenes (NHCs) have received a great deal of attention recently and are now considered as ligands of choice for various catalytic reactions,[1] among which are Suzuki−Miyaura reactions using aryl bromides and less reactive aryl chlorides.[2] They have several advantages over phosphines, such as air and thermal stability of the resulting complexes. We have focused our attention on the synthesis of functionalized NHC ligands, with the aim to produce robust and yet highly active catalysts.[3] The combination of a phosphine and a NHC allows access to stable chelate complexes with interesting electronic properties that have been successfully used in catalysis.[4] Among C−C cross-coupling reactions, the Suzuki−Miyaura reaction has become one of the most appealing, due to its tolerance to functional groups and the low toxicity of its byproducts.[5] Although axially chiral biaryls are present in numerous natural products and constitute an important class of ligands for asymmetric catalysis, there are few reports to date of asymmetric Suzuki−Miyaura reactions.[6] One of the challenges remains to find catalysts that are able to induce high levels of enantioselectivities at low loadings. Surprisingly, NHC ligands have never been used so far in the asymmetric version of the Suzuki−Miyaura reaction. We report here the first example, using a chiral palladium-NHC complex with planar chirality only.

Scheme 1. Synthesis of Racemic and Enantiopure Ferrocenyl Phosphine-Imidazolium Salts 1a,b



We presented recently the synthesis of achiral and racemic ferrocenyl phosphine-NHC ligands and showed their efficiency in the rhodium-catalyzed hydrosilylation of ketones.[3c,d] Here we describe for the first time the synthesis of such ligands in their enantiopure form, as well as their palladium complexes. Building on our experience in the preparation of enantiopure ferrocenyl ligands,[7] we obtained enantiopure (*R*)- and (*S*)-ferrocenyl phosphine-imidazolium salts **1a**,**b** in

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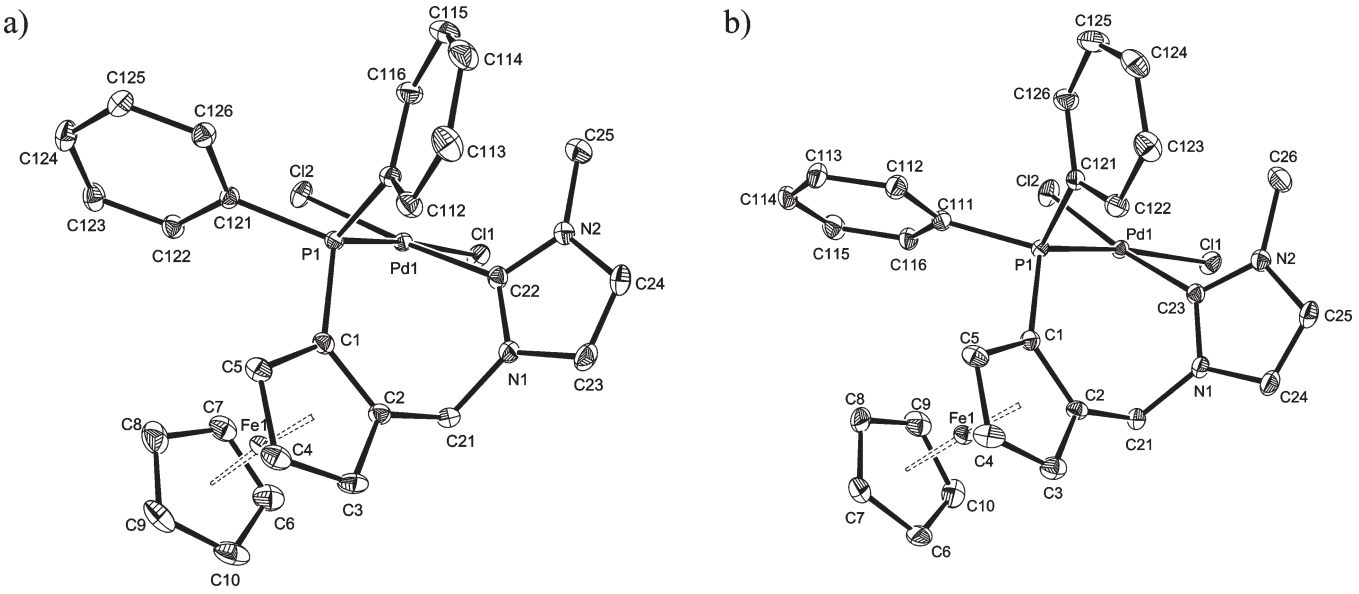
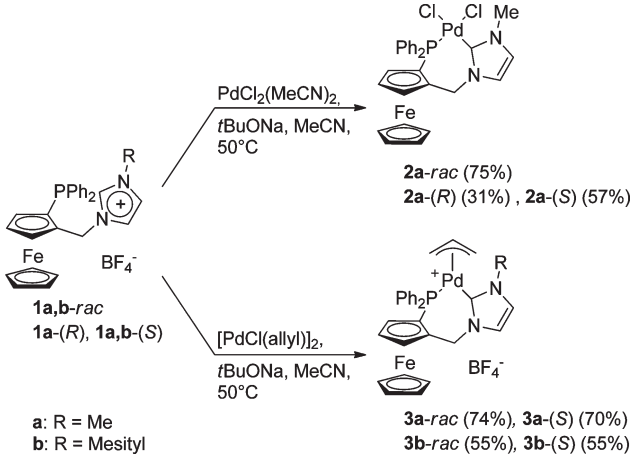


Figure 1. ORTEP representations of complexes **2a**-*rac* (left) and **2a**-(*R*) (right). Ellipsoids are shown at the 30% level. All hydrogens are omitted for clarity. Selected bond distances (Å) and angles (deg) are as follows. **2a**-*rac*: C(22)−Pd(1) = 1.991(3), P(1)−Pd(1) = 2.2444(8), Cl(1)−Pd(1) = 2.3614(9), Cl(2)−Pd(1) = 2.3397(8); C(22)−Pd(1)−P(1) = 84.95(9), C(22)−Pd(1)−Cl(1) = 88.24(9), P(1)−Pd(1)−Cl(2) = 95.06(3). **2a**-(*R*): C(23)−Pd(1) = 1.976(3), P(1)−Pd(1) = 2.2472(10), Cl(1)−Pd(1) = 2.3665(9), Cl(2)−Pd(1) = 2.3481(9); C(23)−Pd(1)−P(1) = 86.61(10), C(23)−Pd(1)−Cl(1) = 83.61(10), P(1)−Pd(1)−Cl(2) = 98.97(3).

Scheme 2. Synthesis of Neutral and Cationic Palladium(II) Complexes



good yields (Scheme 1). Both racemic and enantiopure imidazolium salts were prepared by reaction of the racemic and enantiopure ferrocenyl alcohol, respectively, with HBF_4, immediately followed by the N-substituted imidazole. The phosphine was then cleanly deprotected with an excess of Raney nickel in MeCN.

Two different precursors were used to prepare palladium complexes: $PdCl_2(MeCN)_2$ led to the neutral complexes **2a**-*rac,* **2a**-(*R*), and **2a**-(*S*), while $[Pd(allyl)Cl]_2$ gave the cationic complexes **3a**,**b**-*rac* and **3a**,**b**-(*S*) in moderate to good yields (Scheme 2). Oddly enough, all our attempts to synthesize the neutral complex bearing a bulky mesityl group on the NHC unit (**2b**) failed. $PdCl_2(PhCN)_2$ was tested under similar conditions but also failed to give the expected product. We finally treated the allyl complex **3b**-*rac* in CH_2Cl_2 with a solution of aqueous HCl and obtained again an intractable mixture. All complexes, even those possessing an allyl moiety, are air-stable and can be purified by column chromatography on silica gel.

NMR data of the allylic compounds indicated the presence of two species in a 55:45 (**3a**) or 75:25 (**3b**) ratio, which we can attribute to exo and endo configurational isomers. This refers to the position of the allyl group relative to the ferrocene, as described by Togni et al. for similar complexes.[4g] Unfortunately, the NMR data did not allow us to determine the configuration of the major isomer. The structures of complexes **2a**-*rac*, **2a**-(*R*), **3a**-*rac*, and **3b**-*rac* were confirmed by crystallographic methods (Figures 1 and 2). The structures of both **3a**-*rac* and **3b**-*rac* display the endo isomer, with the central C−H of the allyl group pointing toward the ferrocenyl moiety. The allyl group of complex **3a** is disordered, which is not uncommon for this type of complex.[4g,8] The bond lengths and angles are all within the expected range, either for neutral or for cationic complexes, with a square-planar or slightly distorted square-planar geometry. $Pd-C_{NHC}$ and Pd−P distances are longer in the cationic complexes **3**. In the neutral complex **2a**, surprisingly, the Pd−Cl bond trans to the NHC is slightly but significantly shorter than the Pd−Cl bond trans to the phosphine. We would have expected the opposite, since the NHC should be more donating and exert a higher trans influence. However, this has already been observed for a similar complex.[9] Finally, a noticeable difference is observed in the bond angles between allyl complexes **3a** and **3b**. Indeed, the $C_{NHC}-Pd-P$ angle is 88.52(11)° in **3a**, which bears a methyl substituent on the imidazol-2-ylidene part, whereas it reaches 102.06(8)° in the case of **3b**, possessing a bulkier mesityl group.

Preliminary catalytic tests were carried out with racemic complexes, in order to evaluate their activity in the Suzuki−Miyaura coupling reaction between aryl bromides and phenylboronic acid (Table 1).

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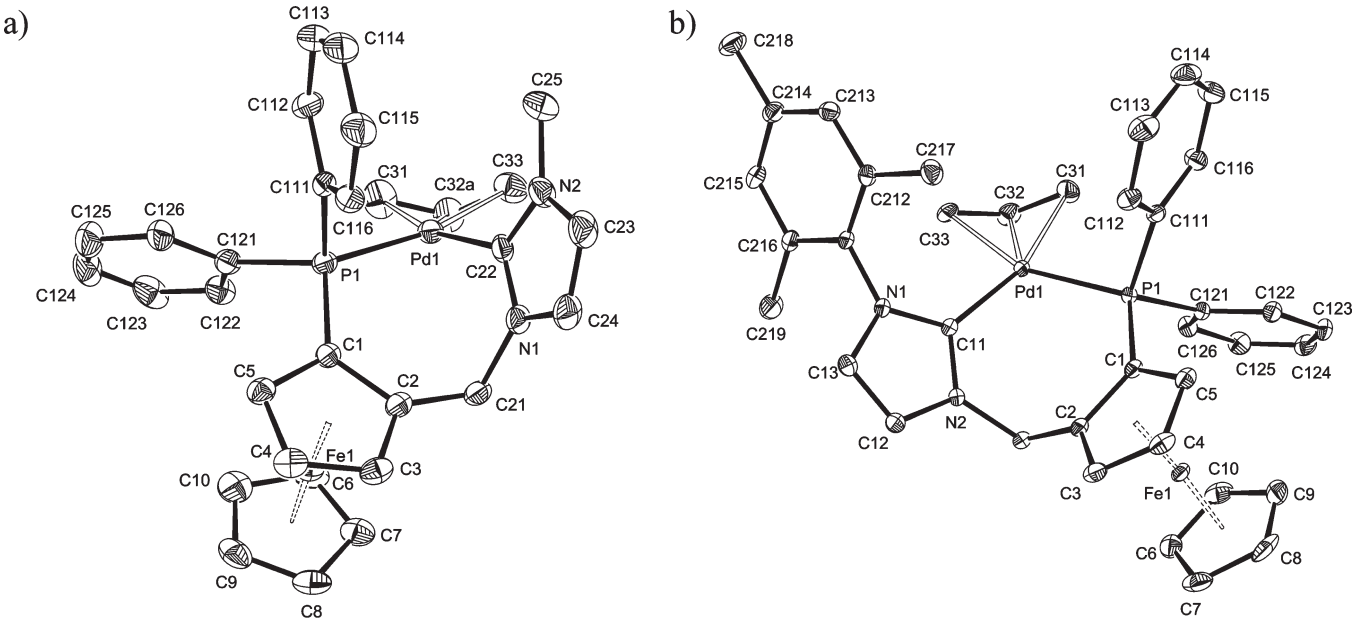
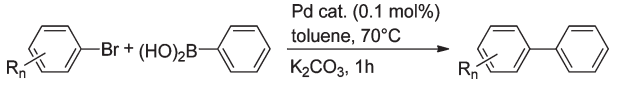


Figure 2. ORTEP representations of cations in complexes **3a**-*rac* (left) and **3b**-*rac* (right). Ellipsoids are shown at the 30% level. All hydrogens are omitted for clarity. Selected bond distances (Å) and angles (deg) are as follows. **3a**-*rac*: C(22)−Pd(1) = 2.050(4), P(1)−Pd(1) = 2.2964(11), C(31)−Pd(1) = 2.173(5), C(32)−Pd(1) = 2.173(6), C(33)−Pd(1) = 2.186(5), C(31)−C(32) = 1.320(8), C(32)−C(33) = 1.408(8); C(22)−Pd(1)−P(1) = 88.52(11), C(22)−Pd(1)−C(33) = 99.98(18), P(1)−Pd(1)−C(31) = 102.99(16). **3b**-*rac*: C(11)−Pd(1) = 2.054(3), P(1)−Pd(1) = 2.3128(7), C(31)−Pd(1) = 2.157(2), C(32)−Pd(1) = 2.167(2), C(33)−Pd(1) = 2.1744(17), C(31)−C(32) = 1.394(5), C(32)−C(33) = 1.375(5); C(11)−Pd(1)−P(1) = 102.06(8), C(11)−Pd(1)−C(33) = 97.48(9), P(1)−Pd(1)−C(31) = 92.32(7).

Table 1. Suzuki−Miyaura Reaction between Aryl Bromides and Phenylboronic Acid[a]



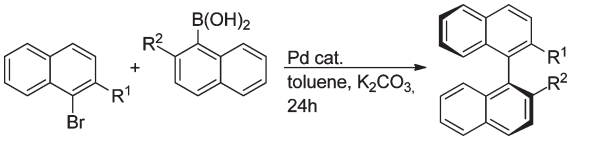
entry	cat.	R_n	yield (%)[b]
1	**2a**-*rac*	4-OMe	83
2	**3a**-*rac*	4-OMe	51
3	**3b**-*rac*	4-OMe	42
4	**2a**-*rac*	2-Me	87
5	**2a**-*rac*	2,4,6-Me_3	40

[a] Reagents and conditions: aryl bromide (1.0 equiv), phenylboronic acid (1.2 equiv), Pd cat. (0.1 mol %), K_2CO_3 (2.4 equiv), toluene, 70 °C, 1 h. [b] GC yield.

After optimization of the reaction conditions with 4-bromoanisole, toluene and K_2CO_3 were chosen respectively as the best solvent and base. Complex **2a**-*rac* was found to give the best results, with 83% yield (entry 1) after 1 h at 70 °C and a low catalyst loading (0.1 mol %). The cationic allyl complexes **3a**-*rac* and **3b**-*rac* were less active, giving respectively 51% and 42% of product (entries 2 and 3) under the same conditions. The introduction of an ortho substituent did not lower the yield with **2a**-*rac*: 87% was obtained with 2-bromotoluene (entry 4). Finally, sterically crowded 2-bromomesitylene was successfully coupled to phenylboronic acid under these conditions (entry 5), which prompted us to turn to naphthyl derivatives (Table 2).

Complex **2a**-(*R*) successfully catalyzed the coupling of naphthyl bromides to naphthylboronic acid under these conditions. Reaction times were not optimized and were extended to 24 h to maximize conversions. Enantioselectivities obtained initially were modest, and we did not observe any substantial improvement when the temperature was lowered (Table 2, entries 1−3 and 4−7). Reducing the temperature to 40 °C allowed us to reach a 42% ee for R^1 = Me (entry 4). The same level of enantioselectivity was observed when the reaction was stopped after 8 h instead of 24 h (entry 5),

Table 2. Asymmetric Suzuki−Miyaura Reaction between Naphthyl Bromides and Naphthylboronic Acids[a]



entry	Pd cat. (mol %)	R^1	R^2	T (°C)	yield (%)[b]	ee (%)[c]
1	**2a**-(*R*) (0.1)	Me	H	70	89	38
2	**2a**-(*R*) (0.1)	OMe	H	70	86	33
3	**2a**-(*R*) (0.1)	OEt	H	70	89	30
4	**2a**-(*R*) (0.5)	Me	H	40	88	42
5	**2a**-(*R*) (0.5)	Me	H	40	57[d]	39[d]
6	**2a**-(*R*) (0.5)	OMe	H	40	93	33
7	**2a**-(*R*) (0.5)	OEt	H	40	92	24
8	**2a**-(*S*) (0.5)	Me	H	40	88	40
9	**2a**-(*S*) (0.5)	OMe	H	40	95	35
10	**2a**-(*S*) (0.5)	OEt	H	40	95	23
11	**2a**-(*S*) (0.5)	H	Me	40	0	
12	**3a**-(*S*) (0.5)	Me	H	40	0	
13	**3a**-(*S*) (0.5)	OMe	H	40	30	28
14	**3a**-(*S*) (0.5)	OEt	H	40	14	10
15	**3b**-(*S*) (0.5)	Me	H	40	86	19
16	**3b**-(*S*) (0.5)	OMe	H	40	82	< 2
17	**3b**-(*S*) (0.5)	OEt	H	40	0	

[a] Reagents and conditions: naphthyl bromide (1.0 equiv), boronic acid (1.2 equiv), Pd cat., K_2CO_3 (2.4 equiv), toluene, 24 h. [b] Isolated yield. [c] Determined by HPLC with a Chiracel-OJ column. [d] Reaction stopped after 8 h.

which means we probably have the same catalytic species throughout the reaction. As expected, similar levels of enantioselectivities were observed with the opposite enantiomer **2a**-(*S*) (entries 8−10). However, no product was obtained when the methyl substituent was introduced ortho to the boronic acid instead of to the bromide (entry 11). The allyl palladium complexes **3a**-(*S*) and **3b**-(*S*) gave surprising results. Indeed, complex **3a**-(*S*), bearing a methyl substituent on the nitrogen atom of the imidazol-2-ylidene, gave the expected binaphthyls in very low yields (entries 12−14), no product being observed in the case of methyl-substituted naphthyl bromide (entry 12). The catalyst seemed to decompose in the course of the reaction, giving a black precipitate in the reaction medium. Complex **3b**-(*S*), bearing a bulkier mesityl substituent on nitrogen, reacted with methyl- and methoxy-substituted naphthyl bromides (entries 15 and 16) but again decomposed in the course of the reaction in the presence of ethoxy-substituted naphthyl bromide (entry 17). Moreover, ee's observed with this catalyst are very low. Our first hypothesis was that steric crowding near the palladium was probably too important in the case of **3b** and became detrimental to the reaction. However, X-ray structures indicated important variations in the C_{NHC}−Pd−P angles between **3b**-*rac* (102.06(8)°) and other complexes (84.95(9)° for **2a**-*rac* to 88.52(11)° for **3a**-*rac*) that could account for the differences in reactivity.

In conclusion, new palladium(II) complexes bearing planar chiral ferrocenyl phosphine-NHC ligands showed very good activities in the Suzuki−Miyaura reaction of aryl bromides with arylboronic acids. Although enantioselectivities are moderate, this is the first example of asymmetric Suzuki−Miyaura reactions with complexes bearing N-heterocyclic carbene ligands. Future studies include the use of other planar chiral NHC ligands in order to improve enantioselectivities.

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Supporting Information Available: A scheme summarizing the preparation of racemic and enantiopure 1,2-disubstituted ferrocenyl alcohols, text and figures giving full experimental details and spectroscopic data for the preparation of all new compounds, figures giving NMR spectra, and CIF files giving crystallographic information. This material is available free of charge via the Internet at http://pubs.acs.org.