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Phosphine/N-heterocyclic carbene palladium complex for Suzuki-Miyaura cross-coupling reactions: The role of water on activity

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Abstract: A new bidendate ferrocenyl phosphine/N-heterocyclic carbene (NHC) palladium complex *rac-6*, bearing a functionalized pendant arm for further grafting on a solid surface, has been synthesized in good yields and fully characterized. The molecular structure of proligand *rac-4-BF₄* and complex *rac-6* were obtained by X-ray diffraction on single crystals. Kinetic studies demonstrated the good activity and stability of *rac-6* in the Suzuki-Miyaura coupling of aryl bromides with arylboronic acids. The catalyst proved also to be active for the coupling of more challenging, bulky substrates such as 1-bromo-2-methylnaphthalene and naphthylboronic acid at relatively mild temperatures (40-70°C) and low loadings (0.1-0.5 mol%). Experiments carried out with various amounts of water highlighted the role of water on both activity and mechanism.

1. Introduction

The price and rarity of late transition metals, as well as the societal demand for a more sustainable use of resources, has boosted the research effort toward more efficient, less energy-intensive processes, producing less waste. Homogeneous catalysis complies with a few of the twelve principles of green chemistry, however it is often complicated or even impossible to recover the catalyst after reaction. To circumvent this problem, several approaches have been proposed [1-3], among which grafting of the catalyst onto inorganic solid support [4-7] or magnetic nanoparticles [8-10], inclusion in polymeric structures [11-16], micelles [17], etc. Our team has been interested for some years in the development of supported catalysts for recycling purposes [18], either by grafting on solids [19] or by incorporation in core-shell polymeric nanospheres.[20-22] Although the supported approach has certain general limitations – catalyst leaching, loss of activity compared to homogeneous systems, cost of grafting [1] – , we think that there is still room for improvement in terms of catalytic systems and even positive effects of confinement can be expected on stereoselectivity.[23] The asymmetric Suzuki-Miyaura (S.-M.) coupling of aryl halides with arylboronic acids is still an ongoing challenge since the coupling of the two bulky components in an enantioselective manner requires high activity to circumvent the steric hindrance while providing the high geometry control of the diaryl intermediate needed for selectivity.[24-27] We developed chiral palladium complexes bearing bidentate phosphine/N-heterocyclic carbene (NHC) ligands that are highly active for the S.-M. coupling of naphthyl bromides with naphthylboronic acid at low (0.1-0.5 mol%) catalyst loadings (Figure 1).[28,29]

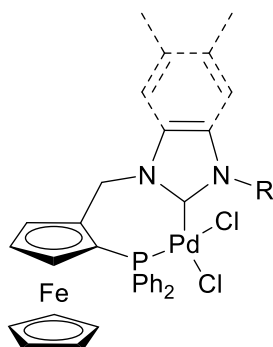


Figure 1. Chiral palladium complexes bearing phosphine/N-heterocyclic carbene ligands for asymmetric Suzuki-Miyaura reactions (ref. [28,29]).

The complexes did not show any sign of decomposition or formation of palladium black at the end of the reactions. However, the enantioselectivities remained moderate (up to 46% e.e). This reaction is known to be very dependent on the nature of the substituents carried by the carbons at the α position to the C-C bond to be formed.[30] We can thus expect an enantioselectivity improvement by exploring new substrates. Moreover, the structure of the complexes suggests that we can easily modulate the catalyst activity and selectivity by modifying the nature of the phosphine substituents (aryls, alkyls), the nature of the NHC or by introducing new chiral centers on the R fragment (Figure 1).

We thus envisaged that the grafting of these complexes on various supports would allow us to 1/ evaluate the activity and stability of the catalyst over time and cycles, and 2/ measure the influence of grafting or confinement in porous solids on enantioselectivity, according to the nature of the support, in order to develop efficient continuous applications. Indeed, the stability of supported palladium complexes used in the Suzuki-Miyaura reaction is often compromised by the high temperatures applied and the decomposition of the complexes to form non-supported palladium nanoparticles (NPs).[1, 31-33] On the other hand, the nature of the support is known to have a non-negligible influence on activity and enantioselectivity.[3,23] The latter is not necessarily a negative one, since the confinement can help to create a pocket that can induce higher stereoselectivities (e.g. with mesoporous silica NPs).[23] Therefore, such investigations necessitate preliminary kinetic studies in homogeneous solution for comparison purposes, and so as to validate the future grafting strategy and to optimize catalytic conditions. This paper describes the synthesis of a functionalized catalyst. Its catalytic activity in the Suzuki-Miyaura coupling will be compared to previously published results [28,29] in order to assess the influence of the functionalized grafted arm and the catalyst robustness. The study has been carried out exclusively with racemic ligands, as their synthesis requires a smaller number of steps compared to enantiomerically pure ones; the latter are easily accessible via previously reported procedures.

2. Experimental procedures

2.1 General Considerations

All manipulations were performed under an inert atmosphere of dry argon by using vacuum line and Schlenk tube techniques. Solvents for syntheses were dried and degassed by standard methods before use. 1D- and 2D-NMR spectra were recorded with a Bruker Avance400 spectrometer. ^1H and ^{13}C chemical shifts (δ) are given in ppm (the residual peak of deuterated solvent was used as reference). ^{31}P Chemical shifts are reported in ppm. Peaks are labelled as singlet (s), doublet (d), triplet (t), multiplet (m) and broad (br). The proton and carbon assignments were confirmed by 2D experiments (^1H - ^1H COSY, ^1H - ^{13}C HMQC and ^1H - ^{13}C HMBC). MS spectra were recorded on a Waters Xevo G2 Q TOF instrument. Thermogravimetric analyses (TGA) were realized with a TA instrument (TGA55 – Discovery series) using aluminum crucibles. 30 mg sample were heated from 25°C to 350°C at 15°C/min rate. Gas chromatographic analyses were carried out with a Perkin Elmer Clarus 480 instrument using a COL-Velocity-1 column. Commercial chemicals were purchased from Acros, Aldrich, Alfa Aesar, or Fluka and used as received.

Abbreviations: Cp^{A} = cyclopentadienyl ring with PPh_2 and NHC substituents; Cp^{B} = unsubstituted cyclopentadienyl ring; Fc = ferrocenyl; Im = imidazolyl; C_q = quaternary carbon.

2.2 Synthesis and characterizations

2.2.1 Ferrocenyl thiophosphine-imidazolium salt (*rac*-4-BF₄). Ferrocenyl thiophosphine-alcohol **1** (100 mg, 0.23 mmol) was dissolved in dry, degassed CH_2Cl_2 (10 mL). $\text{HBF}_4 \cdot \text{OEt}_2$ (48 μL , 54% wt. in Et_2O , 0.35 mmol) was added in one portion and, after 1 min, a solution of imidazole **3** (147 mg, 0.69 mmol) in CH_2Cl_2 (1 mL) was added in one portion. After five minutes, the solution was transferred to a separating funnel and washed with sat. aq. NaHCO_3 . The organic phase was dried (Na_2SO_4), filtered and concentrated to ca. 2 mL. Excess pentane was added, the yellow precipitate was filtered on Celite® and rinsed with pentane. The yellow solid was finally purified by flash column chromatography on silicagel (eluent: CH_2Cl_2 /acetone 9/1). The product was obtained as an orange solid (90 mg, 61% yield). ^1H NMR (acetone-*d*₆, 400 MHz, 298K): δ 8.63 (1H, app. s, NCHN), 7.89-7.83 (2H, m, CH PPh_2), 7.70-7.56 (4H, m, CH PPh_2), 7.44-7.40 (5H, m, CH PPh_2 + NCH=CH), 7.30 (1H, app. s, NCH=CH), 6.49 (1H, d, AB system, J_{HH} = 14.3 Hz, CH_2Fc), 5.35 (1H, d, AB system, J_{HH} = 14.3 Hz, CH_2Fc), 5.17 (1H, app. s, CH Cp^{A}), 4.66 (1H, app. s, CH Cp^{A}), 4.46 (5H, s, CH Cp^{B}), 4.14-4.08 (1H, m, CH_2Im^+),

4.02-3.95 (1H, m, CH₂Im⁺), 3.96 (1H, m, CH Cp^A), 3.90-3.87 (2H, m, CH₂OSi(CH₃)₂C(CH₃)₃), 0.86 (9H, s, CH₂OSi(CH₃)₂C(CH₃)₃), 0.03+0.02 (2x3H, s, CH₂OSi(CH₃)₂C(CH₃)₃). ¹³C{¹H} NMR (acetone-*d*₆, 100.62 MHz, 298K): δ 135.4 (NCHN), 134.4 (d, *J*_{PC} = 86.1 Hz, C_q PPh₂), 132.1 (d, *J*_{PC} = 96.6 Hz, C_q PPh₂), 132.0-131.8 (CH PPh₂), 131.9 (d, *J*_{PC} = 11.0 Hz, CH PPh₂), 131.8 (d, *J*_{PC} = 3.0 Hz, CH PPh₂), 131.2 (d, *J*_{PC} = 10.3 Hz, CH PPh₂), 128.5 (d, *J*_{PC} = 12.4 Hz, CH PPh₂), 128.4 (d, *J*_{PC} = 12.7 Hz, CH PPh₂), 122.6 (NCH=CH), 121.6 (NCH=CH), 83.8 (d, *J*_{PC} = 12.1 Hz, C_q Cp^A), 76.3-76.2 (m, 2xCH Cp^A), 74.5 (d, *J*_{PC} = 94.1 Hz, C_q Cp^A), 71.1 (CH Cp^B), 70.9 (d, *J*_{PC} = 10.0 Hz, CH Cp^A), 61.3 (CH₂OSi(CH₃)₂C(CH₃)₃), 51.8 (CH₂Im⁺), 47.5 (CH₂Fc), 25.3 (CH₂OSi(CH₃)₂C(CH₃)₃), 17.8 (CH₂OSi(CH₃)₂ C(CH₃)₃), -6.3 (2xCH₂OSi(CH₃)₂C(CH₃)₃). ³¹P{¹H} NMR (acetone-*d*₆, 161.99 MHz, 298K): δ 40.08. MS (ESI) *m/z* 641 [M⁺] (100), 415 [M⁺-ImCH₂CH₂OTBDMS] (5). HRMS (ES⁺) calcd for C₃₄H₄₂⁵⁴FeN₂OSSiP 639.1921; found 639.1922.

2.2.2 Ferrocenyl thiophosphine-imidazolium salt (*rac*-4-I**).** Ferrocenyl thiophosphine-ammonium salt **2** (0.58 g, 1.2 mmol) and imidazole **3** (1.3 g, 6.2 mmol) were dissolved in degassed MeCN (60 mL) and the mixture was heated at reflux for 72 h. The solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography on silicagel (eluent: CH₂Cl₂/MeOH 95:5). The product was obtained as an orange solid (0.19 g, 20% yield). ¹H{³¹P} NMR (acetone-*d*₆, 400 MHz, 298K): δ 8.94 (1H, app. s, NCHN), 7.87-7.85 (2H, m, CH PPh₂), 7.70-7.56 (4H, m, CH PPh₂), 7.45 (1H, m, NCH=CH), 7.44-7.43 (4H, m, CH PPh₂), 7.38 (1H, app. s, NCH=CH), 6.48 (1H, d, *J*_{HH} = 14.2 Hz, AB system, CH₂Fc), 5.49 (1H, d, AB system, *J*_{HH} = 14.2 Hz, CH₂Fc), 5.32 (1H, m, CH Cp^A), 4.67 (1H, t, *J*_{HH} = 2.6 Hz, CH Cp^A), 4.47 (5H, s, CH Cp^B), 4.22 (1H, dt, AB system, *J*_{HH} = 14.0 Hz, 4.6 Hz, CH₂Im⁺), 4.05 (1H, dt, AB system, *J*_{HH} = 13.9 Hz, 5.1 Hz, CH₂Im⁺), 3.96 (1H, m, CH Cp^A), 3.92 (2H, t, *J*_{HH} = 4.9 Hz, CH₂OSi(CH₃)₂C(CH₃)₃), 0.87 (9H, s, CH₂OSi(CH₃)₂C(CH₃)₃), 0.04+0.03 (2x3H, s, CH₂OSi(CH₃)₂C(CH₃)₃). ¹³C{¹H}{³¹P} NMR (acetone-*d*₆, 100.62 MHz, 298K): δ 135.5 (NCHN), 134.5 (C_q PPh₂), 132.2 (C_q PPh₂), 131.9 (CH PPh₂), 131.8 (CH PPh₂), 131.7 (CH PPh₂), 131.3 (CH PPh₂), 128.5 (CH PPh₂), 128.4 (CH PPh₂), 122.6 (NCH=CH), 121.6 (NCH=CH), 83.8 (C_q Cp^A), 76.4 (CH Cp^A), 76.2 (CH Cp^A), 74.5 (C_q Cp^A), 71.1 (CH Cp^B), 70.8 (CH Cp^A), 61.4 (CH₂OSi(CH₃)₂C(CH₃)₃), 51.8 (CH₂Im⁺), 47.5 (CH₂Fc), 25.3 (CH₂OSi(CH₃)₂C(CH₃)₃), 17.8 (CH₂OSi(CH₃)₂ C(CH₃)₃), -6.2, -6.3 (CH₂OSi(CH₃)₂C(CH₃)₃). ³¹P{¹H} NMR (acetone-*d*₆, 161.99 MHz, 298K): δ 40.06. MS (ESI) *m/z* 641 [M⁺] (100), 415

[M⁺–ImCH₂CH₂OTBDMS] (6). HRMS (ES⁺) calcd for C₃₄H₄₂⁵⁴FeN₂OSSiP 639.1921; found 639.1928.

2.2.3 Ferrocenyl phosphine-imidazolium salt (*rac*-5-BF₄). Raney® nickel (ca. 100 eq.) was placed in a degassed Schlenk flask, rinsed with degassed MeOH (3*20 mL) then with degassed MeCN (3*20 mL) and finally degassed MeCN (20 mL) was added. The ferrocenyl thiophosphine-imidazolium salt **4-BF₄** (280 mg, 0.4 mmol) was added as a solid to the mixture, which was stirred for 24 h at room temperature. After completion of the reaction (³¹P NMR control), the orange solution was filtered on Celite® and the stationary phase was rinsed with degassed MeCN until the eluted solution was colorless. The orange solution was concentrated under reduced pressure to give an orange solid. This solid was purified by filtration under argon on a path of silicagel (eluent: CH₂Cl₂/MeOH 95/5) in order to eliminate traces of phosphine oxide (detected by ³¹P NMR spectroscopy). Yield of **5-BF₄** (140 mg): 52%. ¹H NMR (CDCl₃, 400 MHz, 298K): δ 8.62 (1H, app. s, NCHN), 7.55-7.50 (2H, m, CH PPh₂), 7.45-7.41 (3H, m, CH PPh₂), 7.27-7.17 (3H, m, CH PPh₂), 7.05-7.00 (2H, m, CH PPh₂), 6.91 (1H, t, J_{HH} = 1.8 Hz, NCH=CH), 6.74 (1H, t, J_{HH} = 1.8 Hz, NCH=CH), 5.47 (1H, d, AB system, J_{HH} = 14.4 Hz, 3.1 Hz, CH₂Fc), 5.34 (1H, d, AB system, J_{HH} = 14.4 Hz, CH₂Fc), 4.94-4.92 (1H, m, CH Cp^A), 4.49 (1H, t, J_{HH} = 2.6 Hz, CH Cp^A), 4.15 (5H, s, CH Cp^B), 4.04-3.98 (2H, m, CH₂Im⁺), 3.94-3.93 (1H, m, CH Cp^A), 3.83-3.80 (2H, m, CH₂OSi(CH₃)₂C(CH₃)₃), 0.85 (9H, s, CH₂OSi(CH₃)₂C(CH₃)₃), 0.01 (2x3H, s, CH₂OSi(CH₃)₂C(CH₃)₃). ¹³C{¹H} NMR (CDCl₃, 100.62 MHz, 298K): δ 139.3 (d, J_{PC} = 101.4 Hz, C_q PPh₂), 135.8 (NCHN), 134.7 (d, J_{PC} = 20.8 Hz, CH PPh₂), 132.4 (d, J_{PC} = 19.0 Hz, CH PPh₂), 128.5-128.3 (CH PPh₂), 122.1 (NCH=CH), 120.7 (NCH=CH), 84.2 (d, J_{PC} = 27.2 Hz, C_q Cp^A), 73.6 (d, J_{PC} = 3.4 Hz, CH Cp^A), 72.9 (d, J_{PC} = 3.8 Hz, CH Cp^A), 71.5 (CH Cp^A), 70.3 (CH Cp^B), 61.5 (CH₂OSi(CH₃)₂C(CH₃)₃), 52.1 (CH₂Im⁺), 48.9 (d, J_{PC} = 10.8 Hz, CH₂Fc), 25.8 (CH₂OSi(CH₃)₂C(CH₃)₃), 18.0 (CH₂OSi(CH₃)₂C(CH₃)₃), -5.6 (2xCH₂OSi(CH₃)₂C(CH₃)₃); second C_q Cp^A under solvent signal. ³¹P{¹H} NMR (CDCl₃, 161.99 MHz, 298K): δ -27.0. MS (ESI) m/z 609 [M⁺] (100), 383 [M⁺–ImCH₂CH₂OTBDMS] (33), 641 [M⁺+S] (13). HRMS (ES⁺) calcd for C₃₄H₄₂⁵⁶FeN₂OSSiP 609.2153; found 609.2155.

2.2.4 Ferrocenyl phosphine-imidazolium salt (*rac*-5-I). Raney® nickel (ca. 100 eq.) was placed in a degassed Schlenk flask, rinsed with degassed MeOH (3*20 mL) then with degassed MeCN (3*20 mL) and finally degassed MeCN (20 mL) was added. The ferrocenyl

thiophosphine-imidazolium salt **4-I** (190 mg, 0.26 mmol) was added as a solid to the mixture, which was stirred for 24 h at room temperature. After completion of the reaction (^{31}P NMR control), the orange solution was filtered on Celite® and the stationary phase was rinsed with degassed MeCN until the eluted solution was colorless. The orange solution was concentrated under reduced pressure to give an orange solid. This solid was purified by filtration under argon on a path of silicagel (eluent: $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 95/5) in order to eliminate traces of phosphine oxide (detected by ^{31}P NMR spectroscopy). Yield of **5-I**: 61% (110 mg). ^1H NMR (CDCl_3 , 400 MHz, 298K): δ 9.69 (1H, app. s, NCHN), 7.55-7.50 (2H, m, CH PPh₂), 7.44-7.41 (3H, m, CH PPh₂), 7.26-7.18 (3H, m, CH PPh₂), 7.06-7.01 (2H, m, CH PPh₂), 6.99-6.98 (1H, m, NCH=CH), 6.77-6.76 (1H, m, NCH=CH), 5.56 (1H, d, AB system, $J_{\text{HH}} = 14.4$ Hz, CH_2Fc), 5.46 (1H, dd, AB system, $J_{\text{HH}} = 14.3$ Hz, 3.1 Hz, CH_2Fc), 5.11 (1H, s, CH Cp^A), 4.50 (1H, t, $J_{\text{HH}} = 2.6$ Hz, CH Cp^A), 4.23-4.15 (2H, m, CH_2Im^+), 4.16 (5H, s, CH Cp^B), 3.93 (1H, m, CH Cp^A), 3.88-3.85 (2H, m, $\text{CH}_2\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 0.85 (9H, s, $\text{CH}_2\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 0.02+0.01 (2x3H, s, $\text{CH}_2\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$). $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 161.99 MHz, 298K): δ -27.1.

2.2.5 Palladium complex (6). The ferrocenylphosphine-imidazolium salt **5-BF₄** (200 mg, 0.25 mmol) was placed in dry, degassed MeCN (10 mL) and $\text{PdCl}_2(\text{MeCN})_2$ (74.5 mg, 0.29 mmol) and *t*BuONa (30 mg, 0.32 mmol) were successively added. The mixture was heated at 50°C for 24 h, then the solvent was concentrated under reduced pressure. The residue was purified by flash column chromatography on silicagel (eluent: $\text{CH}_2\text{Cl}_2/\text{Acetone}$ 95:5) to give a pale orange solid (243 mg, 77% yield). ^1H NMR (CDCl_3 , 400 MHz, 298K): δ 8.04 (2H, dd, $J_{\text{HH}} = 7.7$ Hz, $J_{\text{HP}} = 12.1$ Hz, CH PPh₂), 7.55-7.51 (1H, m, CH PPh₂), 7.45 (2H, td, $J_{\text{HH}} = 7.6$ Hz, $J_{\text{HP}} = 2.6$ Hz, CH PPh₂), 7.38-7.34 (1H, m, CH PPh₂), 7.25 (2H, td, $J_{\text{HH}} = 7.8$ Hz, $J_{\text{HP}} = 2.5$ Hz, CH PPh₂), 6.91-6.87 (2H, m, CH PPh₂), 6.87 (1H, app. s, NCH=CH), 6.84 (1H, app. s, NCH=CH), 6.50 (1H, d, AB system, $J_{\text{HH}} = 14.9$ Hz, CH_2Fc), 4.79-4.75 (2H, m, Cp^A + CH_2Fc), 4.44-4.39 (1H, m, CH_2Im^+), 4.39 (1H, t, $J_{\text{HH}} = 2.7$ Hz, CH Cp^A), 4.36 (5H, s, CH Cp^B), 3.96 (1H, t, $J_{\text{HH}} = 10.2$ Hz, $\text{CH}_2\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 3.57 (1H, app. s, CH Cp^A), 3.51 (1H, dt, $J_{\text{HH}} = 11.1$ Hz, 3.2 Hz, $\text{CH}_2\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 2.86 (1H, ddd, $J_{\text{HH}} = 13.0$ Hz, 9.1 Hz, 2.9 Hz, CH_2Im^+), 0.83 (9H, s, $\text{CH}_2\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), -0.01, -0.04 (2x3H, s, $\text{CH}_2\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100.62 MHz, 298K): δ 156.2 (d, $J_{\text{CP}} = 9.9$ Hz, NCN), 136.0 (d, $J_{\text{CP}} = 10.3$ Hz, CH PPh₂), 134.9 (d, $J_{\text{CP}} = 55.0$ Hz, C_q PPh₂), 131.4 (d, $J_{\text{CP}} = 2.9$ Hz, *p*-CH PPh₂), 130.6 (d, $J_{\text{CP}} = 11.3$ Hz, CH PPh₂), 130.0 (d, $J_{\text{CP}} = 2.0$ Hz, *p*-CH PPh₂), 128.4 (d, $J_{\text{CP}} = 10.5$ Hz, CH PPh₂), 127.7 (d, $J_{\text{CP}} = 55.1$ Hz, C_q PPh₂), 127.6 (d, $J_{\text{CP}} = 11.2$ Hz, CH PPh₂), 123.6

(NCH=CH), 120.1 (NCH=CH), 87.1 (d, $J_{\text{CP}} = 13.4$ Hz, $\text{C}_q \text{Cp}^{\text{A}}$), 74.3 (d, $J_{\text{CP}} = 2.7$ Hz, CH Cp^{A}), 73.2 (d, $J_{\text{CP}} = 6.6$ Hz, CH Cp^{A}), 71.4 (Cp^{B}), 70.9 (d, $J_{\text{CP}} = 57.4$ Hz, $\text{C}_q \text{Cp}^{\text{A}}$), 70.1 (d, $J_{\text{CP}} = 6.4$ Hz, CH Cp^{A}), 62.3 ($\text{CH}_2\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 52.5 (CH_2Im), 49.6 (CH_2Fc), 25.8 ($\text{CH}_2\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 18.0 ($\text{CH}_2\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), -5.4, -5.5 ($2 \times \text{CH}_2\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$). $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3 , 161.99 MHz, 298K): δ 4.4. MS (ESI) m/z 789 [M-Cl+Ca] (95), 767 [$\text{M-Cl+H}_2\text{O}$] (100), 740 (68).

2.3 General procedure for Suzuki-Miyaura catalytic experiments

A Schlenk tube was charged with the bromoaryl reagent (1.4 mmol), arylboronic acid (1.2 eq.), K_2CO_3 (2.4 eq.), Pd complex 6 (0.1 mol% or 0.5 mol%) and dry, degassed toluene (10 mL). The mixture was heated at 70°C (4-bromoanisole) or 40°C (2-methyl-1-bromonaphthalene). 0.5 mL aliquots were collected during the run for kinetic monitoring. The solution was allowed to cool to room temperature, neutralized with aqueous HCl (0.5 M), extracted with diethylether and either filtered on a short path of silicagel before GC analysis (4-bromoanisole) or analyzed by ^1H NMR (2-methyl-1-bromonaphthalene). For the catalytic runs in the presence of mercury, the same procedure was used adding 0.2 mL of Hg before starting the reaction.

3. Results and discussion

3.1 Synthesis of palladium complex 6

The palladium complex that gave the best results in terms of combined activity/enantioselectivity is the one bearing a methyl substituent on the NHC. In order to keep the stereoelectronic environment as close as possible to this complex, a derivative possessing a short alkyl chain on the NHC was chosen for installing the grafting function (Figure 2). The presence of a terminal hydroxyl group should allow us to envisage a wide range of coupling partners: the hydroxyl group could either be used directly under basic conditions with electrophiles, or converted into a leaving group to enable reactions with nucleophiles.

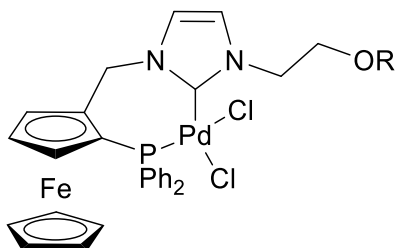
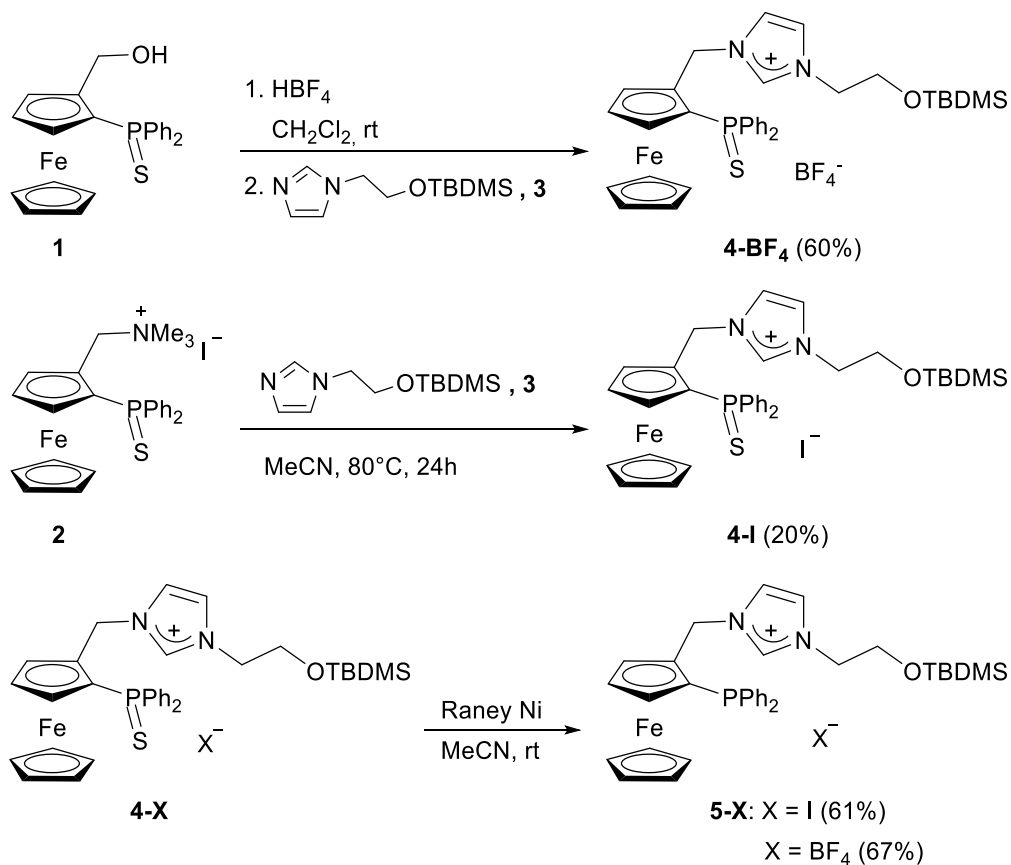


Figure 2. Structure of phosphine/NHC palladium complexes envisaged for immobilization with R = H, *Si*-*t*-Bu(Me)₂ or Ts.

Racemic 1,2-disubstituted ferrocenyl substrates were used to develop and optimize the synthesis of the palladium complexes. The synthesis of the thiophosphine/imidazolium salt **4** was carried out via a reaction between ferrocenyl alcohol *rac*-**1** and functionalized imidazole **3** in the presence of HBF₄ (**4-BF₄**), or alternatively via a reaction between ferrocenyl ammonium salt *rac*-**2** and functionalized imidazole **3** (**4-I**, Scheme 1). The latter was prepared in two steps from imidazole, according to already reported procedures.[28,29,34]



Scheme 1. Synthesis of functionalized phosphine/ imidazolium salts *rac*-**5**.

Although the synthesis via ferrocenyl alcohol **1** requires more synthetic steps from commercial *N,N*-dimethylaminomethyl ferrocene, the yield of imidazolium salt *rac*-**4-BF₄** was higher than that of *rac*-**4-I**. The *tert*-butyldimethylsilyl (TBDMS) protecting group was not affected by the strongly acidic conditions and no deprotected alcohol was observed after the reaction.

¹H NMR (acetone-*d*₆) spectra of imidazolium salts *rac*-**4** show the expected signal at $\delta = 8.63$ ppm (*rac*-**4-BF₄**) and $\delta = 8.94$ ppm (*rac*-**4-I**), respectively, characteristic of the acidic C22 proton (NCHN). AB systems were observed for the diastereotopic protons of the methylene bridge situated between the ferrocenyl and imidazolyl moieties for the two salts, as well as for protons of the ethyl chain linking the imidazolyl and OTBDMS groups, which is consistent with the presence of planar chirality at ferrocene. The ³¹P NMR signal appeared at $\delta = 40.08$ ppm (*rac*-**4-BF₄**) and $\delta = 40.06$ ppm (*rac*-**4-I**), respectively, which is typical of an S-protected phosphino group. The structure of functionalized imidazolium salt *rac*-**4-BF₄** was confirmed by X-ray diffraction methods (Figure 3). The main bond lengths and angles are all within the expected range, for both imidazolium salt [34] and complex [28,29], with a square-planar or slightly distorted square-planar geometry for the latter. Both structures present a disorder in the TBDMS protecting group, which is very frequently observed in the literature.[35]

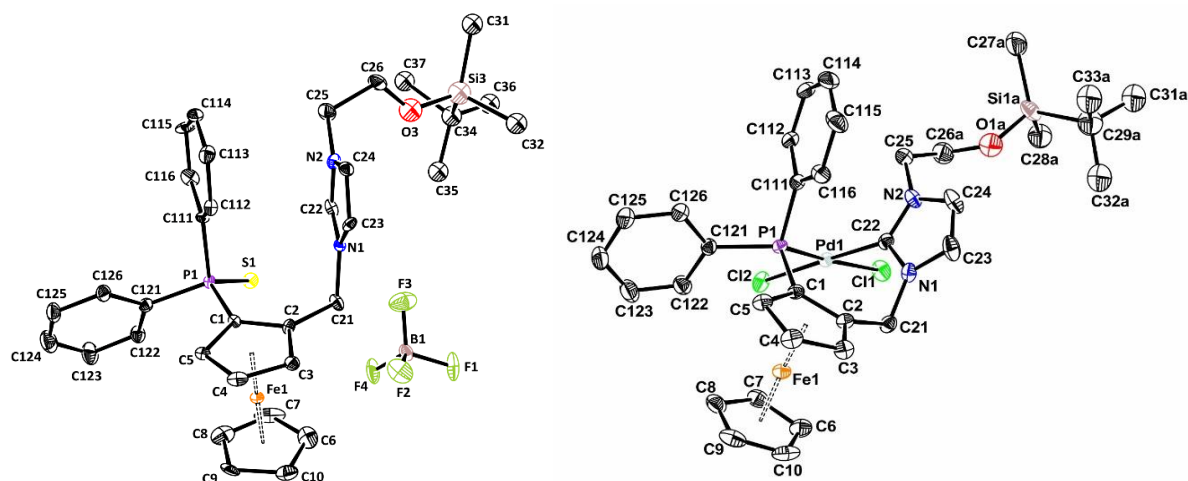
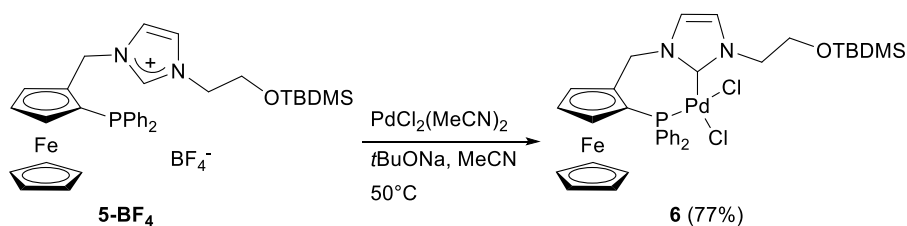


Figure 3. ORTEP representations of imidazolium salt **4-BF₄** (left) and *rac*-**6** (right) with the atom labeling scheme. Ellipsoids are shown at the 30% level. All H atoms are omitted for clarity. **4-BF₄**: for the sake of clarity, only one of the disordered part is represented and the BF₄ anion is omitted. Selected bond distances (Å) and angles (deg) are as follows. **4-BF₄**: C(22)-

N(1) = 1.349(8), C(22)-N(2) = 1.323(8), C(23)-C(24) = 1.352(9), C(1)-P(1) = 1.795(6); N(1)-C(22)-N(2) = 107.8(6). *rac*-**6**: C(22)-Pd(1) = 1.987(4), P(1)-Pd(1) = 2.2588(10), Cl(1)-Pd(1) = 2.3450(10), Cl(2)-Pd(1) = 2.3471(10); C(22)-Pd(1)-P(1) = 84.73(11), C(22)-Pd(1)-Cl(1) = 86.37(11), P(1)-Pd(1)-Cl(2) = 97.64(4).

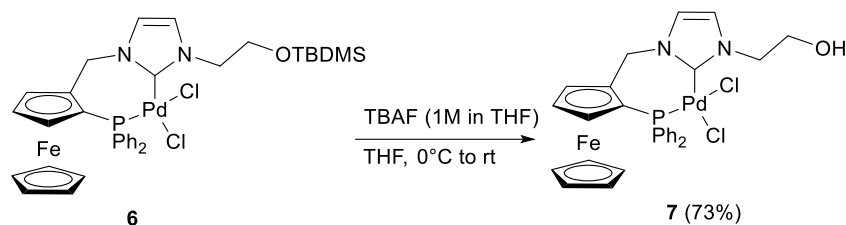
The phosphorus atom was then deprotected by reaction with an excess of Raney nickel in acetonitrile.[28,29] Both phosphine/imidazolium salts *rac*-**5-I** and *rac*-**5-BF₄** were obtained in moderate yields and characterized by NMR. The total deprotection of the phosphine group was confirmed by the strong shift of the ³¹P NMR signal from δ 40.0 ppm to δ -27.0 ppm. The palladium complex was then prepared from imidazolium salt *rac*-**5-BF₄** by deprotonation with *t*-BuONa in MeCN, in the presence of PdCl₂(MeCN)₂ (Scheme 2). Complex *rac*-**6** was obtained in 77% yield in a racemic form, as a light orange, air-stable solid, after purification by column chromatography. Its formation was first evidenced by ¹H NMR by the disappearance of the acidic proton at 8.63 ppm. The TBDMS group was also observed with two signals at 0.83 and -0.01/-0.04 ppm. The ¹³C NMR spectrum showed a signal at 156.2 ppm for the carbenic carbon, which is characteristic for such a palladium(II) complex.[35] The structure of complex *rac*-**6** was also confirmed by X-ray crystallography (Figure 3).



Scheme 2. Synthesis of functionalized *rac*-palladium(II) complex **6**.

Preliminary tests have also been carried out to check the integrity of the palladium complex upon deprotection of the hydroxyl group, in view of further functionalization and grafting. To our delight, the removal of the TBDMS protecting group occurred cleanly in the presence of TBAF (Scheme 3), as the ¹H NMR spectrum (DMSO-*d*₆) of complex **7** revealed the absence of typical TBDMS signals at 0.83 and -0.01/-0.04 ppm. The ³¹P NMR spectrum displayed a signal at 4.9 ppm, showing a virtually unchanged environment around palladium compared to complex

6. Unfortunately, the low solubility of **7** in most solvents, maybe due to O-H...Cl-Pd bonding, prevented its full NMR characterization for now. ~~Further work is in progress to carry out the synthesis of tosylated palladium complex.~~

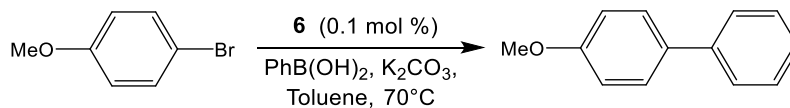


Scheme 3. Deprotection of hydroxyl group on *rac*-palladium(II) complex **6**.

3.2 Catalytic results

Grafting of the palladium complex on a surface or its incorporation in a polymeric structure may change its catalytic properties. It was therefore necessary to evaluate the catalytic activity of the molecular species, bearing the pendant CH₂CH₂OTBDMS arm, in order to establish a point of comparison with the heterogeneized complexes.

Complex *rac*-**6** was therefore tested in the Suzuki-Miyaura cross-coupling of 4-bromoanisole with phenylboronic acid as model reaction (Scheme 4). The conditions that gave the best results with the non-functionalized palladium complex were applied, i.e. 0.1 mol% of palladium complex **6**, potassium carbonate as a base, at 70°C in toluene. The mild temperature used should help to preserve the catalyst from decomposition when grafted on surfaces.



Scheme 4. Suzuki-Miyaura coupling of 4-bromoanisole with phenylboronic acid.

A kinetic follow-up of the reaction using commercial reagents without any purification showed a very good activity in the first minutes, with 67% conversion after only 7 min, then a slowdown with 86% conversion after 4 h (Figure 4 - Top). This reactivity is consistent with that of the non-functionalized palladium complex, where 83% yield was reached after 1

h.[28,29,36] This is a first indication that the presence of a functionalized alkyl chain in place of a methyl group is not detrimental to activity, even at a lower catalyst loading (0.01 mol %). We also observed that the addition of 50% more reagents after 80 min relaunched biaryl production, highlighting the fact that the catalyst is still active (Figure 4). Finally, an experiment with yield monitoring performed at room temperature with 0.1% catalyst showed that the system remained active for at least 10 days, reaching a 45% yield (Figure 4). Those results underline the robustness of the palladium complex.

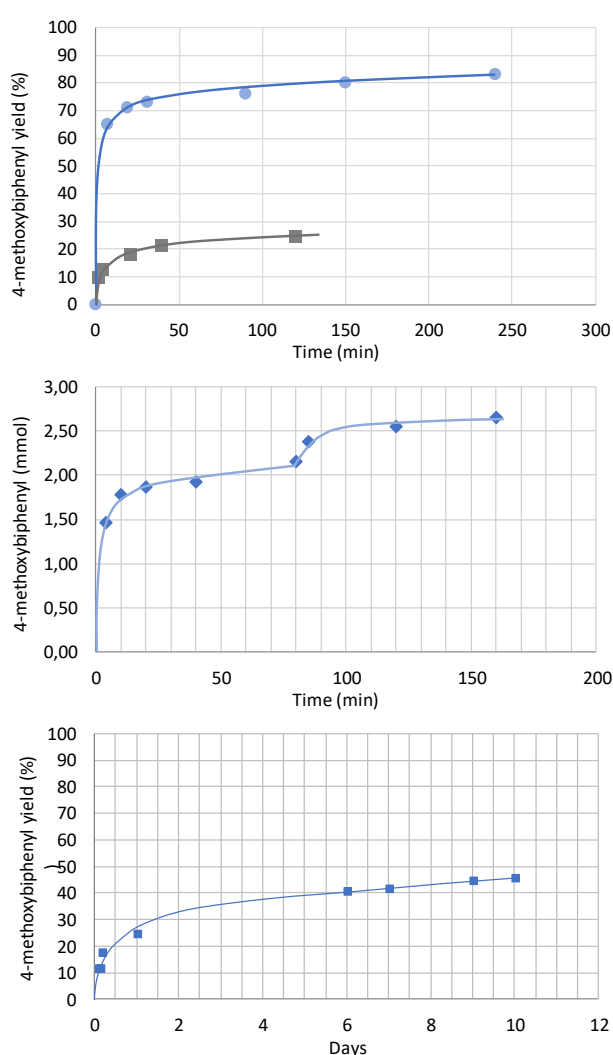


Figure 4. GC kinetic follow-up of the yield of 4-methoxybiphenyl with 0.1% (circles) and 0.01% (squares) catalyst loading (Top). Formation of 4-methoxybiphenyl (mmol) vs time with addition of 50% more reagents after 80 min (Middle). Yield of 4-methoxybiphenyl with 0.1% catalyst loading at room temperature (Bottom).

The use of a fixed quantity of water, either as a co-solvent or as an additive, is mentioned in many studies and was often shown to have a positive effect on activity.[37-40] This will be a main concern when working with a catalyst grafted on hygroscopic supports such as silica, as the drying conditions of the system may not comply with the stability of the grafted catalyst. We thus investigated the addition of small amounts of water, therefore used here as an additive. We first controlled the water contents in the reagents using thermo-gravimetric analysis (TGA), finding 9.7% and 4.2% of water in the base and the boronic acid, respectively. The removal of water occurring around 150°C, both were dry under vacuum at 160 °C for 4 hours before use. Dehydration was confirmed by TGA and the remaining water content was less than 0.4 %. Taking the 4-bromoanisole amount as a reference, we performed reactions with 0, 0.5, 1, 10 and 50 molar equivalents of water (respectively 0, 0.13, 0.26, 2.6 and 13.0 volume % of water in the reaction mixture). The kinetics appeared to be strongly dependent on the water content. The yield of 4-methoxybiphenyl increased from 35% (dry conditions, 240 min) to 77% after addition of only 1 equivalent of water and reached 91% with 10 equivalents. However, with higher concentrations (50 equivalents of water), the rate decreased.

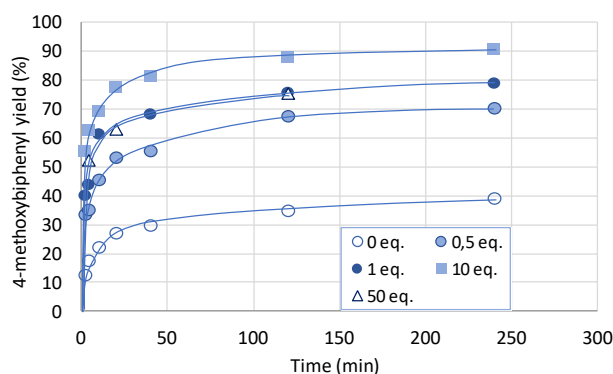


Figure 5. Water influence on the reaction kinetics.

These results may be partly explained by a better solubility of the inorganic base (K_2CO_3) and of the boronic acid in the organic medium (toluene). Indeed, with 10 and 50 equivalents of water (respectively 2.6 and 13.0 volume %), the cloudy solution turned clear. However, the increased activity observed with the lowest water contents, i.e. 0.5 or 1 equivalents, which only represent 0.13 and 0.26 vol. % of water, may involve another effect. Working on the effect of

anionic bases such as CO_3^{2-} or HO^- (which is produced from carbonates in the presence of water), previous studies [38-40] have demonstrated that these bases can coordinate to the metal center, accelerating to some extent both the transmetalation and the reductive elimination steps. However, higher concentrations have a deleterious impact on the kinetics, giving rise to unreactive $\text{ArB}(\text{OH})_3^-$ intermediates.[38-40] Our results are in agreement with these previously established trends. Slightly grey precipitates were observed when 10 and 50 eq. of water were used, therefore we also suspect the formation of Pd nanoparticles (Pd NPs). We have thus replicated the reactions with 0 eq. and 1 eq. of H_2O , with and without addition of mercury which is known to trap nanoparticles (0 eq/Hg and 1 eq/Hg, respectively, Figure 6). Anhydrous conditions gave the same kinetics, confirming that in this case, the reaction is carried out by the molecular complex only. With 1 eq. of water, the addition of mercury decreased the yield (13% drop at 110 min) due to Pd NPs trapping. With 10 eq. of water the drop in yield is even sharper (-25% at 110 min), confirming that water addition favors the formation of Pd NPs. Other NHC-palladium complexes, bearing a pendant functionalized arm on the ligand, have shown very interesting activities in Suzuki-Miyaura reactions carried out in/on water, but no mention was made of NPs formation.[41,42]

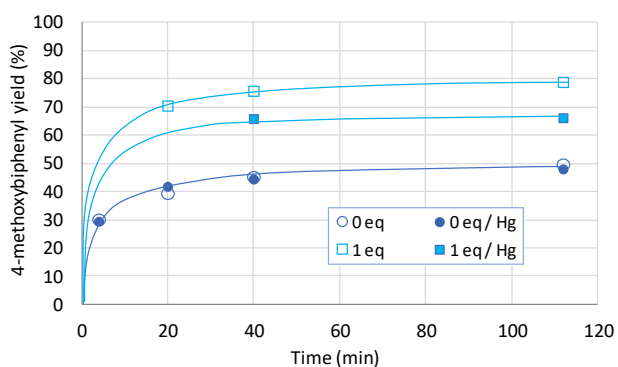
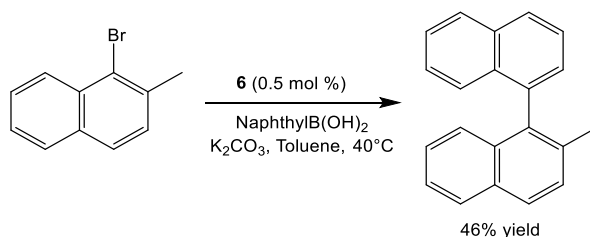


Figure 6. Influence of the addition of Hg on the reaction kinetics, in the presence of 0 eq. or 1 eq. of H_2O .

The formation of Pd NPs during Suzuki-Miyaura reactions is a commonly observed phenomenon that could become a problem when working with heterogeneized catalysts,[1, 31-33] as the Pd NPs formed cannot be recovered after reaction. Therefore if we want to get an efficient grafted catalyst, we will likely have to work under quasi-anhydrous conditions that preclude the formation of NPs, even though it is to the detriment of activity. Finally, the S.-M.

coupling of more challenging, bulky substrates was investigated, as our final objective is the asymmetric version of the Suzuki-Miyaura reaction.



Scheme 5. S.-M. coupling of 1-bromo-2-methylnaphthalene with naphthylboronic acid.

The coupling of 1-bromo-2-methylnaphthalene with naphthylboronic acid was thus carried out with 0.5 mol% of palladium complex *rac*-**6**, at 40°C for 24 h (Scheme 5). In this case, the presence of the pendant CH₂CH₂OTBDMS chain had a non-negligible influence on yield since 46% of 2-methylbinaphthyl were obtained, against 88% with the Pd complex bearing a methyl substituent [28]. This is consistent with the results obtained with phosphine/NHC palladium complexes bearing a different environment around the NHC: the combination of bulky substrates and bulky substituents on the ligand can be detrimental to catalytic activity.[29]

4. Conclusions

We have fully characterized a new functionalized catalyst. Kinetic experiments have shown that the functionalized arm does not alter the catalyst efficiency with small substrates. The addition of water increases the rate of the reaction but also favors catalyst decomposition via the formation of Pd NPs, which are also active in the Suzuki-Miyaura coupling. This better understanding of the catalyst behavior is essential to develop efficient flux chemistry applications and notably in the asymmetric version of this reaction.

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