Diphosphines of dppf-Type Incorporating Electron-Withdrawing Furyl Moieties Substantially Improve the Palladium-Catalysed Amination of Allyl Acetates

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Abstract: Highly active Pd/diphosphine catalytic systems incorporating new, air-stable ferrocenyl-furylphosphines allow nucleophilic allylic amination at room temperature with unprecedented turnover frequencies. For instance, in the presence of 0.01 mol % catalyst the coupling of aniline to allyl acetate occurs at a TOF of more than 10,000 h^{-1}; even the addition of the less nucleophile morpholine to allyl acetate is observed with a TOF of 4250 h^{-1}. The amination of the sterically demanding geranyl acetate, a monoterpene derivative of interest in the flavour industry, at low catalyst loadings demonstrates the scope of this methodology, which provides in addition noticeable advantages in terms of economical (resource- and energy-saving) and sustainable chemistry (high selectivity, no additive, low metal content, and thus easier purification).

Keywords: allylic amination; catalysis; C–N coupling; ferrocene; furylphosphine; palladium

The discovery of the palladium-catalysed allylic alkylation[1] has initiated an intense research effort directed towards the synthesis of useful allylic building blocks.[2] Amination of allyl halides, acetates or malonates has proven to be efficient when conducted in the presence of 1–10 mol % of palladium catalysts and phosphine auxiliaries.[2,3] A critical improvement in this field, connected to both sustainable chemistry and economic concerns, is the necessity to provide catalytic systems minimising the consumption of depletive resources (i.e., palladium combined with sophisticated ligands). We initiated a program aiming to develop air-stable, robust catalytic auxiliaries that could allow accelerated catalytic reactions in the presence of low amounts of metal catalyst to achieve high TONs and high TOFs.[4]

Ferrocenylphosphines were chosen to combine *stability* from the robustness of the ferrocenyl backbone with *enhanced activity* from steric and electronic effects of tunable phosphine's substituents.[5] The synthesis and catalytic properties of dppf-type phosphines (dppf = 1,1′-bis[diphenylphosphino]ferrocene) built with phosphorus bearing heterocyclic substituents have been notably less studied than the chemistry of ferrocenyl heteroannular diphosphines bearing more classical aryl or alkyl substituents.[6] The new ligands 1,1′-bis[di(5-methyl-2-furyl)phosphino]ferrocene (**1**) and 1-[di(5-methyl-2-furyl)phosphino]-1′-(diphenylphosphino)-ferrocene (**2**) are obtained, after work-up procedures, in high to moderate yields (80% and 25%, respectively) from the reaction of lithiated ferrocenes with the bis(5-methyl-2-furyl)bromophosphine $BrP(Fu^{Me})_2$ (Scheme 1).[7] While **1** is isolated as a crystalline orange powder that is easy to handle, **2** is obtained as a sticky orange-brown oil. Both compounds shows stability to air and moisture, even in solution, and no decomposition is observed upon heating them in toluene for several hours. In the solid state **1** is indefinitely stable at room temperature under air.

Following our catalysis objective, the coupling of various amines and allyl acetates (Scheme 2) by palladium complexes stabilised by **1** and **2** was investigated and representative results are summarised in Table 1. It rapidly appeared that highly active catalysts usable in very low concentrations were formed, underlining the tremendous influence of the electron-withdrawing phosphine ligands on the rate of the catalysed reaction. To gain more information on the coordination chemistry of these new catalytic auxiliaries, well-defined palladium complexes were synthesised. The reaction in equimolar quantities of **1** (or **2**) with $PdCl_2(PhCN)_2$ gives

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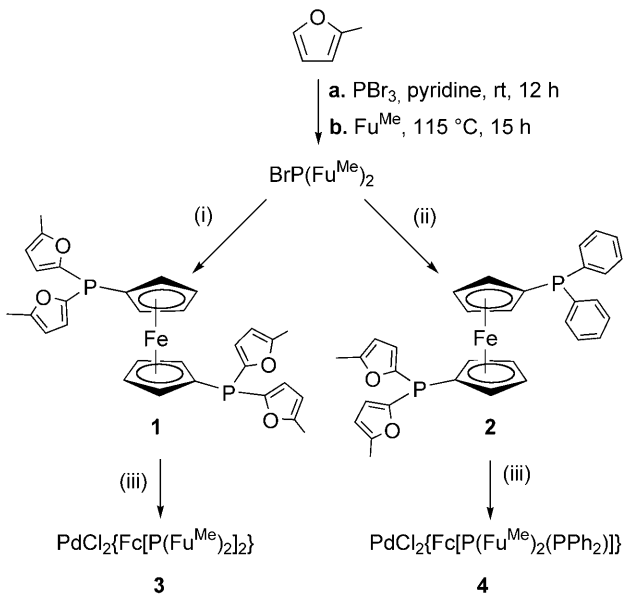
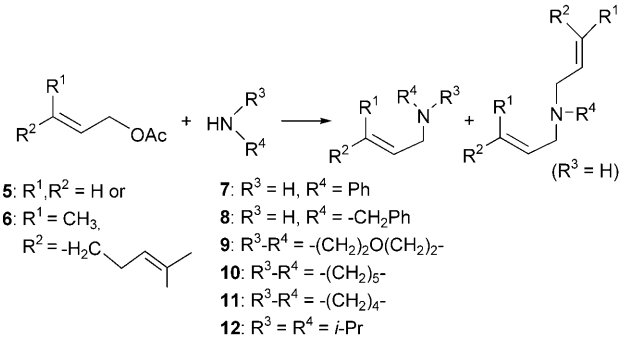


Scheme 1. *Reagents and conditions*: (i) 0.5 equivs. $FeCp_2Li_2$-TMEDA, hexane, room temperature, 2 h; (ii) 1 equiv. $CpFe\{Cp(PPh_2)\}Li$, THF, −50 °C, 12 h; (iii) 1 equiv. $PdCl_2(PhCN)_2$, CH_2Cl_2, room temperature, 20 min.



Scheme 2.

the chelate complex **3**, $PdCl_2\{Fc[P(Fu^{Me})_2]_2\}$ (or **4**, $PdCl_2\{Fc[P(Fu^{Me})_2(PPh_2)]\}$, respectively), see Scheme 1. Compound **3** has been characterised by ^1H, ^{13}C, ^{31}P NMR spectroscopy, and by single crystal X-ray analysis (Fig. 1).[8]

The ^{31}P NMR chemical shifts observed for the ligands and their complexes, and compared to the ones reported for dppf and analogous compounds, confirm the electron-withdrawing influence exerted by the furyl substituents (for **1**, a singlet at $\delta = -63$ ppm is noted, against −17 ppm for dppf). The molecular structure indicates staggered Cp rings with an average dihedral angle of 33.9(4)°. The P–Pd–P angle of 96.98(3)°, more closed than the angle values reported for $PdCl_2$(dppf) structures [99.07(5)[9]], opens for chemical reactions at palladium a larger spatial area "in front" of the P–Pd–P moiety.

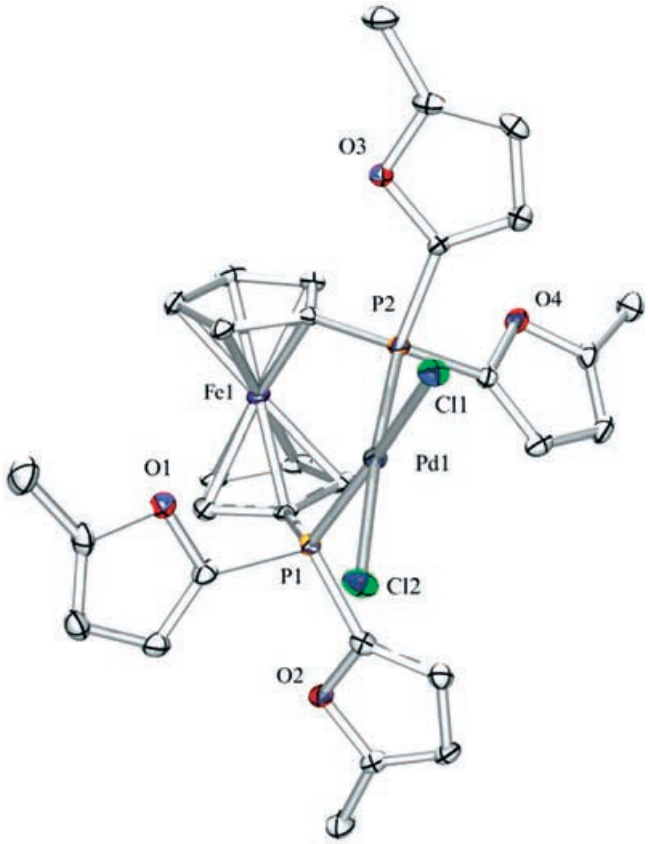


Figure 1. Molecular structure of **3**. Ellipsoids set at 50% probability, H atoms are omitted for clarity. Selected distances (Å) and angles (°): Pd–P1 2.2633(8), Pd–P2 2.2622(8), Pd–Cl1 2.3366(8), Pd–Cl2 2.3333(8); Cl2–Pd–Cl1 89.40 (3), P2–Pd–P1 96.98(3), Ct1–Fe–Ct2 178.05 (13), P1–Ct1–Ct2–P2 37.6 (2).

We tested the reaction of aniline (**7**) with allyl acetate (**5**) at room temperature to compare the efficiency as catalytic auxiliaries of the ferrocenylphosphines **1** and **2** with the related diphosphine dppf (Scheme 2 and Table 1, entries 1–5). After 1 h, in the presence of 1 mol % catalysts a total conversion is obtained from the sterically congested dppf and as well from **1**, with a good selectivity in monoallylamine (96–94%, entries 1 and 3). In the presence of 0.01 mol % low concentration catalysts, using **1** a total conversion is obtained in 1 h at room temperature with a 96% selectivity in monoallylaniline (entry 4), leading us thus, in non-optimised conditions, to estimate a TOF of at least 10,000 h^{-1}. In the same conditions, using **2** the total conversion obtained after 2 h is slightly less selective in monoallylaniline (91%, entry 5). Under identical conditions, dppf as auxiliary shows its limits since a maximum 60% conversion is obtained after 40 h at room temperature (entry 2, TOF 150 h^{-1}). At such low concentrations and temperatures monophosphines are ineffective.

Next we tried to evaluate the scope and limitations of the systems Pd/**1** and Pd/**2** using the same high ratio [sub-

Table 1. Palladium-catalysed allylic amination.

Catalytic system	Allyl acetate	Amine	Conversion Yield [%]	Ratio (mono/di)	Ratio substrate/catalyst	TOF [h^{-1}]	Entry
Pd/dppf	**5**	**7**	100	96/4	100	100	1
			60[a]	97/3	10000	150	2
Pd/**1**	**5**	**7**	100	94/6	100	100	3
			100	96/4	10000	10000	4
Pd/**2**	**5**	**7**	100[b]	91/9	10000	5000	5
Pd/**1**	**5**	**8**	73[c]	75/25	10000	1825	6
Pd/**2**	**5**	**8**	75[d]	76/24	10000	1071	7
Pd/**1**	**5**	**9**	85[b]	–	10000	4250	8
Pd/**2**	**5**	**9**	100[e]	–	10000	3333	9
Pd/**1**	**5**	**10**	100[b]	–	10000	5000	10
Pd/**1**	**5**	**11**	98[b]	–	10000	4900	11
Pd/**1**	**5**	**12**	40[a]	–	10000	100	12
			96[b, g]	–	1000	480	13
Pd/PCy_3	**6**	**7**	7[i]	100/0	100	–	14
Pd/PPh_3	**6**	**7**	29[i]	100/0	100	–	15
Pd/**1**	**6**	**7**	75[f]	100/0	100	5	16
Pd/**1**	**6**	**7**	100[b, h]	55/[j]	100	50	17
Pd/**2**	**6**	**7**	100[b, h]	50/[j]	100	50	18
Pd/**1**	**6**	**9**	60	100/0	100	60	19
			98[f]	100/0	100	5	20
			50[a]	100/0	1000	13	21
			100[e, g]	98/[j]	1000	333	22
			5 >	traces	10000	–	23
Pd/**1**	**6**	**12**	100[e]	traces/[j]	100	–	24

Conditions: catalysts preparation see ref.[8], toluene, room temperature, 1 h.
[a] 40 h.
[b] 2 h.
[c] 4 h.
[d] 7 h.
[e] 3 h.
[f] 20 h.
[g] 80 °C.
[h] 110 °C.
[i] 40 °C.
[j] Unidentified secondary products are formed, presumably allylic isomers.[3c]

strate/catalyst] = 10,000, at room temperature, with various primary and secondary amines of different steric and nucleophilic properties, namely: benzylamine (**8**), morpholine (**9**), piperidine (**10**), pyrrolidine (**11**) and diisopropylamine (**12**). The addition rate is slightly decreased for the reaction of **8** with allyl acetate. Around 75% conversion is observed after 4 h using **1** (TOF 1825 h^{-1}, entry 6) and in 7 h using **2** (TOF 1071 h^{-1}, entry 7). This slower addition rate probably causes the decrease in selectivity mono-/diallylamine. Unexpectedly, excellent results are obtained in the coupling of the less nucleophilic cyclic morpholine:[10] after 2 hours 85% conversion is observed using **1** (TOF 4250 h^{-1}, entry 8) and a total conversion is accessible in 3 h with **2** (TOF 3333 h^{-1}, entry 9). In line with these results the cyclic amines **10** and **11** are converted in high yield after 2 h (TOF 5000 h^{-1} and 4900 h^{-1} entries 10 and 11, respectively). A substantial, presumably steric effect, previously noted,[10] occurs upon coupling of diisopropylamine (**12**) to allyl acetate since, in the presence of 0.01 mol % catalyst, only 40% conversion is observed after 40 h, resulting in a TOF of 100 h^{-1} (entry 12). However, using 0.1 mol % catalyst, 96% conversion of **12** is obtained at 80 °C in 2 hours giving a TOF of 480 h^{-1} (entry 13).

These promising results prompted us to investigate the allylic amination reaction using a much more demanding allyl acetate substrate. A monoterpene derivative [geranyl acetate (**6**)] was chosen, due to both the industrial interest of monoterpenes functionalisation[11] and their steric hindrance. The reaction of **6** on aniline (**7**) at 40 °C in the presence of 1 mol % catalysts using classical monophosphines gives, with Pd/PPh_3, 29% conversion in monoallylamine (entry 5) and only 7% conversion with the bulky electron-rich PCy_3 (entry 4); at room temperature the reactivity being, as expected, even more sluggish. At room temperature using 1 mol % Pd/**1**, 75% conversion in geranylaniline is ob-

tained after 20 h with total selectivity (entry 16). In contrast, complete conversion of **6** is observed in 2 h at elevated temperature (entries 17 and 18), but only 55–50% of the expected geranylaniline is formed, the high temperature being responsible for undesired side reactions.

To identify the limitations of our system, morpholine and diisopropylamine (entries 19–24) were added to geranyl acetate. Surprisingly, the addition of **9** in the presence of 1 mol % catalyst at room temperature give a 60% conversion in 1 h, and an almost total conversion after 20 h. Using 0.1 mol % Pd/**1** at room temperature the addition rate is significantly slower (entry 21). However, an excellent TOF of 333 h^{-1} is obtained at 80 °C with 98% of geranylamine being obtained in 3 h (entry 22). At 0.01 mol % the catalyst becomes inactive. The coupling of the two sterically demanding compounds **6** and **12** did not proceed satisfactorily in presence of 1 mol % Pd/**1** (entry 24). It is noteworthy that the results presented here could probably be optimised, especially concerning solvent and temperature conditions,[3c] since room temperature and toluene were systemically used.

Finally, in order to definitively demonstrate the scope of this methodology, preliminary tests using more diverse examples of functionalised allyl acetate and amines as substrates were carried out. As expected, good to excellent conversions were obtained using diethylamine, aniline, piperidine and morpholine with the substituted allyl acetates cinnamyl acetate and hex-2-en-1-yl acetate. This was not a surprise since these substituted allyl acetates appear *a priori* less demanding than geranyl acetate. From the reaction of cinnamyl acetate with diethylamine, aniline and piperidine a conversion of, respectively, 76%, 65% and 30% was obtained after 20 h at 50 °C with a 0.01 mol % catalyst loading of Pd/**1**. With a higher loading of 0.1 mol % catalyst, a 100% conversion for all the substrates is accessible at room temperature in the same time. In any case, a high regioselectivity of linear/branched product (93/7%) was obtained. Under the latter conditions, hex-2-en-1-yl acetate reacts with piperidine and morpholine to respectively yield the corresponding allylamines in 100 and 98% conversion (ratio linear/branched 94/6%).

The global comparison of catalytic activity for the systems incorporating the related ligands dppf, **1** and **2** (of roughly similar steric features) led us to think that the electronic properties of the furyl group[12] might be at the origin of the impressive TOFs obtained for the coupling of allyl acetate with various primary and secondary aliphatic and cyclic amines. Further work is underway to explain and explore the effectiveness of our ligands in allylic amination and in other attractive palladium-catalysed reactions.

Experimental Section

The syntheses of the palladium complexes and a detailed characterisation of all the compounds are available as Supporting Information.

Synthesis of $Fc[P(Fu^{Me})_2]_2$ (1)

To a stirred suspension of 6.78 g (21.61 mmol) of $FeCp_2Li_2$-TMEDA in 60 mL of hexane was added dropwise a solution of 11.8 g (43.22 mmol) of $BrP(Fu^{Me})_2$ in 25 mL of hexane. After two hours stirring at room temperature, 20 mL of degassed water were added. An orange powder was obtained which was washed three times with hexane and then dried under vacuum. Purification was carried out by dissolution in chloroform and filtration on silica gel; yield of **1**: 9.86 g (17.30 mmol, 80%).

Synthesis of $Fc[P(Fu^{Me})_2(PPh_2)]$ (2)

To a solution of 1.25 g (3.39 mmol) of $BrP(Fu^{Me})_2$ in 20 mL of THF was added at −50 °C a solution of 1.28 g (3.39 mmol) of $CpFe\{Cp(PPh_2)\}Li$ in 40 mL of THF. The mixture was stirred for 12 hours and then evaporated under vacuum to give a brown oil. The crude product was purified by chromatography (toluene/hexane, 1:1) on neutral silica. The first fraction obtained is $CpFeCp(PPh_2)$ (0.520 g, 41% yield) and the 2nd fraction is the dissymmetrical ligand **2** (0.420 g, 25% yield) obtained as a pure orange-brown oil.

Catalytic Reactions; Typical Procedure for a Ratio [substrate/catalyst = 10000]

The palladium/ferrocenyl furylphosphine complexes were prepared by stirring in 10 mL of toluene, under argon for 30 min the diphosphines **1** (0.04 mmol, 22.8 mg) or **2** with $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.01 mmol, 3.65 mg). The same batch of catalyst was used for more than a week without any activity decrease (stable in solution in the refrigerator under argon). 1 mL of the previously prepared catalyst solution (thus 0.001 mmol Pd) was added to the mixture of allyl acetate or geranyl acetate (10 mmol) and amine (20 mmol) in 25 mL toluene. The mixture was stirred at ambient temperature, or 80 °C, or 110 °C during 1 to 40 h. Products were obtained after addition of water, extraction with organic solvents, drying of the organic phase, and chromatography on silica gel.

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References and Notes

[1] M. Morikawa, J. Takahashi, J. Tsuji, *Tetrahedron Lett.* **1965**, *6*, 4387.

[2] M. Johannsen, K. A. Jørgensen, *Chem. Rev.* **1998**, *98*, 1689.

[3] a) O. Kuhn, H. Mayr, *Angew. Chem. Int. Ed.* **1999**, *38*, 343; b) B. M. Trost, L. T. Calkins, C. Oerlet, J. Zambrano, *Tetrahedron Lett.* **1998**, *39*, 1713; c) for rare catalytic systems operating at lower concentration, see: M. Feuerstein, D. Laurenti, H. Doucet, M. Santelli, *J. Mol. Catal. A* **2002**, *182–183*, 471 and references cited therein.

[4] a) J.-C. Hierso, A. Fihri, R. Amardeil, H. Doucet, M. Santelli, V. V. Ivanov, P. Meunier, *Org. Lett.* **2004**, *6*, 3473; b) J.-C. Hierso, A. Fihri, R. Amardeil, P. Meunier, H. Doucet, M. Santelli, B. Donnadieu, *Organometallics* **2003**, *22*, 4490.

[5] For a review on disubstituted ferrocenyl ligands used in catalysis, see: R. C. J. Atkinsson, V. C. Gibson, N. J. Long, *Chem. Soc. Rev.* **2004**, *33*, 313.

[6] a) I. R. Butler, W. R. Cullen, T.-J. Kim, S. J. Rettig, J. Trotter, *Organometallics* **1985**, *4*, 972; b) I. R. Butler, W. R. Cullen, T.-J. Kim, *Synth. React. Inorg. Met.-Org. Chem.* **1985**, *15*, 109; c) B. C. Hamann, J. F. Hartwig, *J. Am. Chem. Soc.* **1998**, *120*, 7369; d) A. L. Boyes, I. R. Butler, S. C. Quayle, *Tetrahedron Lett.* **1998**, *39*, 7763.

[7] This synthetic pathway is alternative to the one described to get the family compound 1,1′-bis[di(2-furyl)phosphino]ferrocene, see: B. C. Hamann, J. F. Hartwig, *J. Am. Chem. Soc.* **1998**, *120*, 3694.

[8] Syntheses, catalytic reactions, characterisation of the ligands, complexes and coupling products are available as electronic supplementary information (ESI).

[9] T. Hayashi, M. Konishi, Y. Kobori, M. Kumada, T. Higuchi, K. Hirotsu, *J. Am. Chem. Soc.* **1984**, *106*, 158.

[10] M. Feuerstein, D. Laurenti, H. Doucet, M. Santelli, *Chem. Commun.* **2001**, 43.

[11] S. Kad, *Topics in Catalysis* **2004**, *27*, 143.

[12] a) N. G. Andersen, B. A. Keay, *Chem. Rev.* **2001**, *101*, 997; b) A. Scrivanti, V. Beghetto, E. Campagna, U. Matteoli, *J. Mol. Catal. A* **2001**, *168*, 75.

