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Sulfination by Using Pd-PEPPSI Complexes: Studies into Precatalyst Activation, Cationic and Solvent Effects and the Role of Butoxide Base**

Mahmoud Sayah,[a] Alan J. Lough,[b] and Michael G. Organ*[a]

Abstract: The activation of PEPPSI precatalysts has been systematically studied in Pd-catalysed sulfination. Under the reactions conditions of the sulfide and KO*t*Bu in toluene, the first thing that happens is exchange of the two chlorides on the PEPPSI precatalyst with the corresponding sulfides, creating the first resting state; it is via this complex that all Pd enters the catalytic cycle. However, it is also from this same complex that a tri-Pd complex forms, which is a more persistent resting state. Under standard reaction conditions, this complex is catalytically inactive. However, if additional pyridine or a smaller base (i.e., KOEt) is added, this complex is broken down, presumably initially back to the first resting state and it is again capable of entering the catalytic cycle and completing the sulfination. Of note, once the tri-Pd complex forms, one equivalent of Pd is lost to the transformation. Related to this, the nature of the cation of the sulfide salt and solvent dielectric is very important to the success of this transformation. That is, the less soluble the salt the better the performance, which can be attributed to lowering sulfide concentration to avoid the movement of the Pd-NHC complex into the above described off-cycle sulfinated resting states.

Keywords: homogeneous catalysis · palladium · PEPPSI · sulfination

Introduction

The presence of aryl– and alkyl–sulfur motifs in the structure of natural products, therapeutics and drug candidates makes the formation of C–S linkages an important pursuit in synthetic chemistry.[1] Unfortunately, many of the methods that have been developed to introduce sulfur into target molecules involve rather harsh conditions, which is especially true for aryl sulfides.[2] Catalysis offers the promise of much gentler reaction conditions although late transition metals, such as Pd, can be poisoned by the relatively soft sulfur centre. That said, there have been significant developments in sulfination by using Pd catalysts with phosphane ligands.[3]

The sulfination catalytic cycle (Figure 1) has been thoroughly investigated by Hartwig and co-workers, who have postulated a number of off-cycle resting states (e.g., **3**, **6**).[4] To add to these challenges, if reduction [H] of the precatalyst (**1**) is slow, additional deleterious side reactions with Pd can occur, further compromising catalysis. Unlike the situation with nucleophilic organometallics in cross coupling, or alkyl amines in amination chemistry, the mechanism by which Pd^{II} is reduced to Pd^0 is less clear with aryl sulfides. With phosphane ligands, Hartwig proposed that, although energetically disfavoured, reductive elimination (RE) of diaryl disulfide from **3** was the most plausible pathway for Pd^0 (**2**) to be introduced to the catalytic cycle, given rate studies in their investigation.[4] The authors were not able to confirm the existence of the disulfide in their reactions and attributed this to its consumption given the reductive conditions of the coupling.

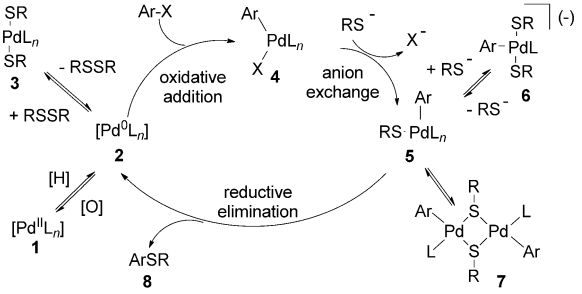

Figure 1. Putative catalytic cycle for Pd-catalysed sulfination.

Results and Discussion

Recently we reported that N-heterocyclic carbene (NHC)-based Pd-PEPPSI-IPent (PEPPSI = pyridine-enhanced pre-

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[**] PEPPSI = Pyridine-enhanced precatalyst preparation stabilisation and initiation.

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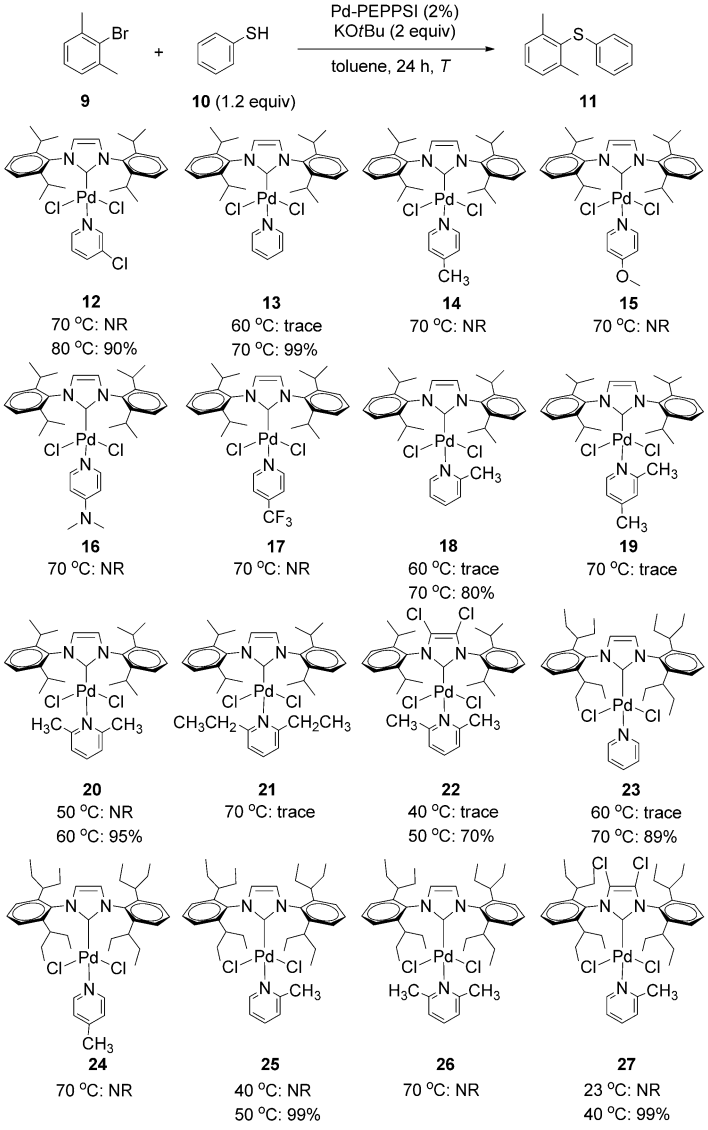
catalyst preparation stabilisation and initiation; IPent = 1,3-bis(2,6-diisopentylphenyl)imidazol-2-ylidene) was highly effective for sulfinating strongly deactivated substrates at room temperature, although precatalyst activation with Bu_2Mg, morpholine or isopropoxide was necessary.[5] Precatalyst activation appeared not to be necessary with phosphane ligands and encouraged us to look deeper at the electronic and steric parameters of the ligands on Pd. We investigated the challenging coupling of thiophenol (**10**) to the hindered oxidative addition partner **9** (Scheme 1). Beginning our study with the IPr NHC core (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene), we found that heating to 80 °C with KO*t*Bu was sufficient to activate Pd-PEPPSI-IPr (**12**) and drive catalysis without additional additives. When the 3-chloropyridine-based PEPPSI precatalyst system was designed, we expected that the electronegative chlorine



Scheme 1. Sulfination of 2-bromo-1,3-dimethylbenzene (**9**) with thiophenol (**10**) using a variety of Pd-PEPPSI complexes without activators at different temperatures.

would assist in dissociating the pyridine moiety.[6] When we performed the coupling with the simple pyridine derivative **13**, we were surprised to find it was consistently activated at a temperature 10 °C lower than catalyst **12**.[7] Interestingly, introducing a substituent at the 4-position of the pyridyl moiety (**14**–**17**), even an electron-withdrawing one (e.g., **17**) completely suppressed precatalyst activation. In another interesting twist, introduction of substituents at the 2-position, even an electron-donating one (**18**),showed good reactivity, although, adding an additional substituent to the 4-position (**19**) proved detrimental. When both *ortho* positions were occupied by methyl groups, the activation temperature dropped by an additional 10 °C (**20**). Presuming that precatalyst activation is preceded by exchange of the two chlorides to sulfides (vide infra), the increased bulk can be viewed to have two divergent effects.[8] Bulk at the *ortho* position could slow ligand exchange to the larger sulfide that could impact activation overall, but this was not observed. Conversely, the increased bulk could drive disulfide RE and promote precatalyst activation. Electronically, the placement of substituents, even electron-donating ones, appear to reduce bond order between the palladium and nitrogen atoms because the bulk of the substituent elongates this coordinate bond, rendering the metal more electrophilic, and thus possibly more likely to undergo reduction (see Table 1 and Figure 2 for crystal structures of key disulfide resting states).[8] Similarly, the Pd–S bond length is longer with *ortho*-substituted pyridine complexes, also facilitating RE of disulfide. With these thoughts in mind we made two additional modifications to the IPr scaffold. Further increasing the bulk at the *ortho*-positions from methyl to ethyl (**21**) shut down catalyst activation entirely. Conversely, placement of chlorine atoms on the NHC backbone (**22**) lowered the activation temperature by an additional ten degrees to 50 °C. It is tempting to suggest that this additional boost in reactivity is solely due to electronic factors, but the chlorine atoms also push the N-aryl groups inward toward Pd, meaning that they could have a steric role, despite the distance from the Pd centre.[9]

Table 1. Effect of ligated pyridine motif on Pd–S, Pd–N and Pd–C bond lengths of resting states **28** and **29** derived from precatalysts **13** and **20**, respectively. For ORTEP representation of crystal structures **28** and **29** see Figure 2.

	Pd–S bond [Å]	Pd–N bond [Å]	Pd–C bond [Å]
28	2.333	2.077	1.978
29	2.347	2.096	1.985

Given that Pd-PEPPSI-IPent was found to be much more reactive than the IPr derivatives in previously reported coupling reactions,[5,10] we shifted attention to modifications of the IPent platform. While the simple pyridine derivative (**23**) did not show greatly improved activation relative to **13**, the mono-*ortho*-methyl derivative (**25**) reduced the activation temperature to 50 °C. In addition to the increased size of the *N*-phenyl substituent itself, further increasing the

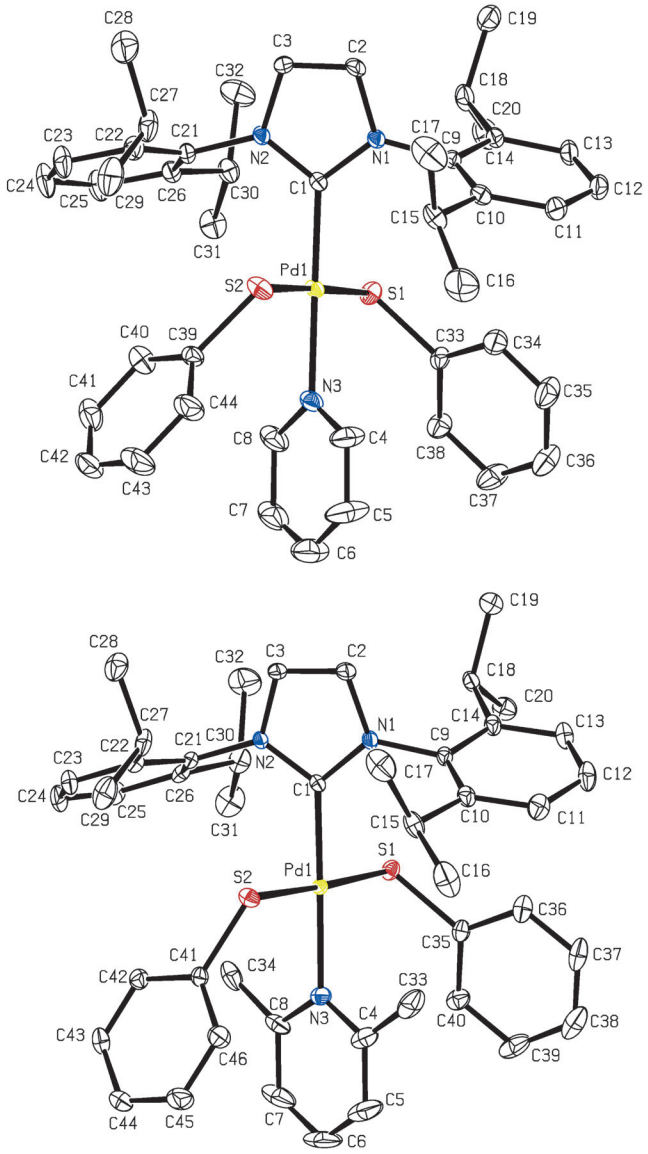
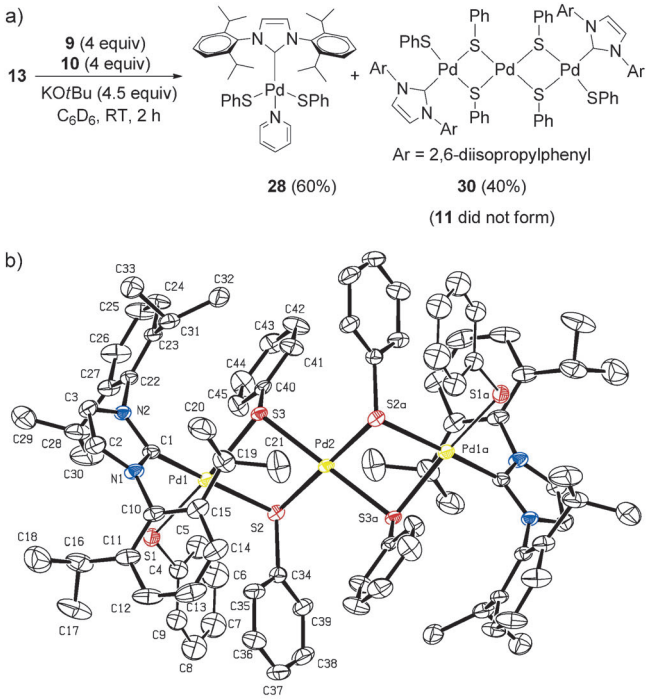


Figure 2. ORTEP representation of crystal structures **28** (top) and **29** (bottom) with ellipsoids drawn at the 30% level; hydrogen atoms omitted for clarity.



	Cat.	T [°C]	Conv. [%]
i)	**28**	70	90
ii)	**30**	80	0
iii)	**30** + 6% pyridine	80	92
iv)	**30** + 2 equiv KOEt instead of KO*t*Bu	70	89

Scheme 2. Pd complexes formed from interactions with phenylsulfide. ORTEP representation of the crystal structure of **30** (ellipsoids drawn at the 30% level).[8]

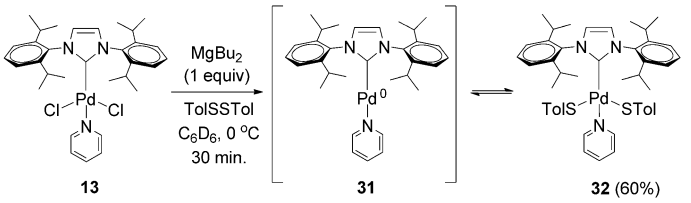
bulk on the pyridine (**26**) rendered the complex less active. Finally, as was observed with the IPr platform, chlorinating the NHC backbone led to optimal precatalyst **27**[11] that could be smoothly activated at 40°C without the aid of any additive to promote Pd^{II} reduction.

In order to gain additional insight into the mechanism of activation, we followed the reaction with stoichimetric precatalyst **13** by ^{1}H NMR spectroscopy (Scheme 2a).[12] By keeping the temperature below that which is necessary for reduction (i.e., RT), we could follow the rapid conversion of **13** to disulfide **28**. We then took **28**, which is stable and can be purified by column chromatography, and subjected it to the reaction conditions from Scheme 1 and near quantitative sulfination was observed. These experiments confirm that the dichloro precatalysts first undergo rapid ligand exchange to the disulfide (e.g., **28**) and it is this species that undergoes reduction and enters the main catalytic cycle.

When the reaction mixture containing stoichiometric precatalyst **13** from the NMR experiment was left to stand, two visibly different crystals formed. Careful separation of these crystals, followed by X-ray analysis confirmed the structures of revealed complex **28** (Figure 2) and tripalladium complex **30**, which we could then identify and track by ^{1}H NMR spectroscopy.[13] This interesting tripalladium species, which has lost one NHC, has no catalytic activity as these crystals failed to produce any sulfinated product under the reaction conditions (Scheme 2b, ii). However, when additional pyridine or KOEt (Scheme 2b, iii and iv) was added to the reaction, **30** was broken down liberating NHC–$Pd(SPh)_2$, presumably, which then completes the reaction.

While diphenyldisulfide is suggested to be susceptible to reduction under sulfination conditions,[4] its presence, however brief, could shift the equilibrium back to the more stable Pd^{II} complex (e.g., Figure 1). To examine this, precatalyst **13** was reduced with one equivalent of dibutylmagnesium, immediately followed by addition of ditolyldisulfide [TolSSTol; all at 0°C, Eq. (1)]. The sequence was monitored

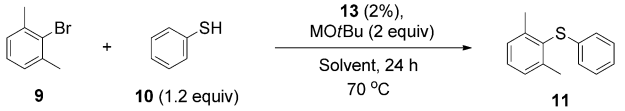
by ^{1}H NMR spectroscopy and in the end **32** was isolated (60%).[12] Conversely, when **32** by itself was heated to 100°C no disulfide was observed, although approximately half of it underwent RE of the carbene to produce **34**. To confirm that Pd^0 is formed from **32** under our sulfination conditions, **33** was added to the reaction to trap the active catalyst (**31**) as complex **35**. In the absence of base, the starting materials were recovered. However, when KO*t*Bu was used, intermediate **35** was observed with **34** accounting for the mass balance. When lithium isopropoxide was added in addition to KO*t*Bu to ensure complete reduction of **32**, quantitative conversion to **35** was observed. So, in the sulfination process precatalyst **13** gives rise to **32** in situ that reductively eliminates disulfide to produce the active NHC–Pd^0 complex **31**, which then enters the catalytic cycle.



(1)

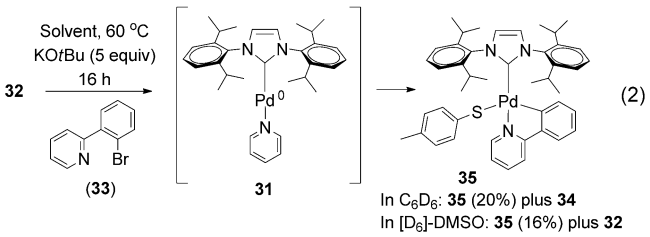
When the sulfination reactions carried out in this study proceeded well, the physical appearance of the mixture throughout the course of the reaction followed a pattern. Potassium thiolate is insoluble in toluene, leading to a highly heterogeneous mixture that was a challenge to stir at the beginning, but gradually became fully homogeneous as the reaction progressed. The choice of cation is known to be important in amination reactions, so we evaluated different thiolate salts. The sodium salt, which was similarly insoluble, failed to provide any sulfinated product at 70°C, but when heated to 90°C led to 40% conversion (Table 2, entry 2). Conversely, the lithium salt failed to form any product (entry 3), but unlike the potassium or sodium thiolates, was fully soluble. As solubility may play a key role, we examined other solvents. In every case in which the potassium thiolate was soluble (Table 2, entries 5–8), sulfination failed to proceed at all. To ensure that this was not a consequence of the precatalyst failing to activate, the reaction in DMSO was pre-activated with Bu_2Mg and only trace product was observed (entry 6). Furthermore, we know that our standard sulfination conditions in DMSO reduce **32** as we were able to isolate **35** as shown in Equation (2).

Table 2. Effect of cation and solvent on sulfination using precatalyst **13**.



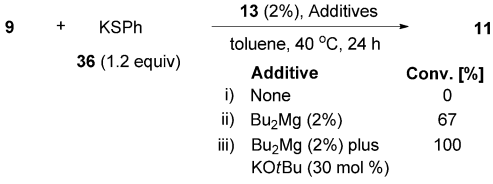
	Solvent	Cation [M]	Appearance	Result
1	toluene	K	heterogeneous	100% conv.
2	toluene	Na	heterogeneous	NR[a]
3	toluene	Li	fully soluble	NR
4	THF	K	heterogeneous	35% conv.[b]
5	DMSO	K	fully soluble	NR
6	DMSO	K	fully soluble	NR[c]
7	NMP[d]	K	fully soluble	NR
8	isopropanol	K	fully soluble	trace

[a] Reaction did not proceed at 70°C, but did proceed to 40% conversion when heated to 90°C. [b] When the reaction was run for 48 h, 60% conversion was observed. [c] When catalyst **13** was pre-activated with Bu_2Mg the reaction proceeded to 15% conversion. Again, the mixture was fully homogeneous.



(2)

Key to the success of sulfination is the presence of butoxide base. Reduction of the dithiane by butoxide introduces more active catalyst into the catalytic cycle and helps to prevent movement of the equilibrium back toward **32**. Activation of resting state **30** does not occur thermally (Scheme 2b, ii), only when either pyridine or KOEt (Scheme 2b, iii and iv) was added, suggesting that butoxide is too hindered to break down **30**, which liberates NHC–$Pd(SPh)_2$. Nonetheless, when Bu_2Mg-activated **13** was reacted with pre-formed potassium thiolate, the reaction was sluggish [Eq. (3) path ii]. However, when a catalytic amount of butoxide was added, the reaction proceeded quantitatively [Eq. (3) path iii]. With KSPh already in the flask, this clearly points to an additional role for butoxide, which we attribute to catalyst activation and the continuous reduction of any dithiane that forms.



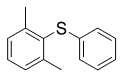
(3)

Conclusion

In this report we have systematically designed a series of highly active NHC-based precatalysts specific for sulfination. In amination studies, **12** activates spontaneously at room temperature and couples aniline nucleophiles with high efficiency under identical reaction conditions (toluene, KO*t*Bu)[10a] verifying the unique off-cycle poisoning that faces sulfination. Soluble thiolate salts in toluene, such as LiSAr, or the use of high dielectric solvents such as *N*-methyl-2-pyrrolidone (NMP) or DMSO, suppresses the transformation. We believe that the low solubility and therefore, the low concentration of the thiolate ion in solvents such as toluene, is essential for good reactivity.

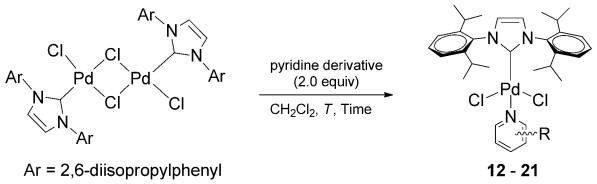
Experimental Section

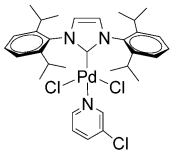
General coupling procedure: In a glovebox, an oven-dried vial (4 mL screw-cap threaded) equipped with magnetic stir bar was charged with Pd-PEPPSI catalyst (2 mol%) and KO*t*Bu (60 mg, 2 equiv, 0.5 mmol). The vial was sealed with a Teflon®-lined screw cap, removed from the glovebox and **9** (1 equiv, 0.25 mmol) was added by microliter syringe followed by toluene (2 mL). Compound **10** (1.2 equiv, 0.3 mmol) was added dropwise and the reaction was stirred at the indicated temperature for 24 h. At this point the reaction was cooled to room temperature and undecane (25 μL) was added. Thereafter a 20 μL aliquot were filtered through a plug of silica gel and eluted with EtOAc into a GC vial for GC-MS analysis.



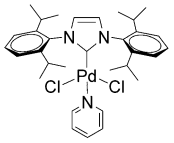
(2,6-Dimethylphenyl)(phenyl)sulfane (11): Following the general procedure, the reaction was conducted using Pd-PEPPSI precatalyst **27** (4.8 mg, 2 mol%) at 40°C for 24 h. After chromatography (pentane, R_f=0.3)(2,6-dimethylphenyl)(phenyl)sulfane (53 mg, 99%) was obtained as a pale-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.30–7.19 (m, 5H), 7.10 (t, J=7.2 Hz, 1H), 6.97 (d, J=7.2 Hz, 2H), 2.47 ppm (s, 6H). Spectral data were in accordance with those reported in the literature.[14]

General procedure for the synthesis of complexes 12–21 starting from the chloro-bridged NHC-IPr Dimer: An oven-dried vial (4 mL screw-cap threaded) equipped with magnetic stir bar was charged with the dimer (50 mg, 0.044 mmol). The vial was sealed with a Teflon®-lined screw cap and the indicated pyridine derivative (2 equiv) was added by syringe under argon followed by CH_2Cl_2 (1 mL). The solution was stirred at the indicated temperature and time, whereupon it was filtered through a small plug of silica and eluted with CH_2Cl_2 (4 mL). Solvent was removed under reduced pressure to afford pure product in all cases.

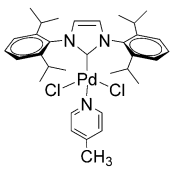




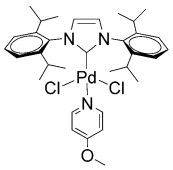
Synthesis of complex 12: Following the general procedure with *meta*-chloropyridine (10 mg, 0.088 mmol), the reaction was stirred at room temperature for 1 h providing **12** (57 mg, 95%) as a yellow powder. Spectral data were in accordance with those reported in the literature.[7]



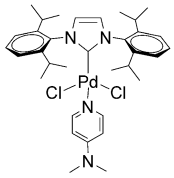
Synthesis of complex 13: Following the general procedure with pyridine (7 mg, 0.088 mmol), the reaction was stirred at room temperature for 1 h providing **13** (57 mg, 98%) as a yellow powder. Spectral data were in accordance with those reported in the literature.[7]



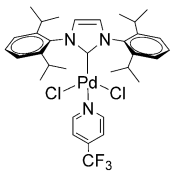
Synthesis of complex 14: Following the general procedure with *para*-methylpyridine (8.2 mg, 0.088 mmol), the reaction was stirred at room temperature for 1 h providing **14** (57 mg, 98%) as a yellow powder. M.p. >300°C (decomp); ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.39 (d, J=4.8 Hz, 2H), 7.51 (t, J=7.8 Hz, 2H), 7.37 (d, J=7.8 Hz, 4H), 7.14 (s, 2H), 6.91 (d, J=4.8 Hz, 2H), 3.19 (sept, J=6.9 Hz, 4H), 2.23 (s, 3H), 1.50 (d, J=6.9 Hz, 12H), 1.14 ppm (d, J=6.9 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=155.2, 150.6, 149.1, 146.5, 135.0, 130.1, 127.9, 127.7, 127.5, 124.8, 124.7, 123.9, 28.6, 26.2, 23.1, 20.8 ppm; HRMS (ES): *m*/*z* calcd for $C_{66}H_{86}Cl_4N_6NaPd_2$ [2M<M+>Na]$^+$: 1332.4081; found: 1332.4056.



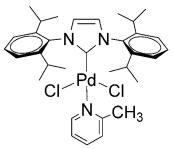
Synthesis of complex 15: Following the general procedure with *para*-methoxypyridine (9.6 mg, 0.088 mmol), the reaction was stirred at room temperature for 1 h providing **15** (57.5 mg, 97%) as a pale-yellow powder. M.p. 215°C (decomp); ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.38 (d, J=6.4 Hz, 2H), 7.51 (t, J=7.6 Hz, 2H), 7.36 (d, J=7.6 Hz, 4H), 7.13 (s, 2H), 6.60 (d, J=6.4 Hz, 2H), 3.75 (s, 3H), 3.20 (sept, J=6.8 Hz, 4H), 1.50 (d, J=6.8 Hz, 12H), 1.13 ppm (d, J=6.8 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.3, 155.3, 152.3, 146.6, 135.1, 130.2, 124.9, 124.0, 109.9, 55.5, 28.7, 26.3, 23.2 ppm; HRMS (EI): *m*/*z* calcd for $C_{33}H_{43}ClN_3OPd$ [*M*−Cl]$^+$: 638.2129; found: 638.2131.



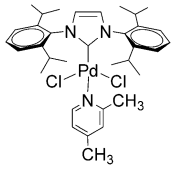
Synthesis of complex 16: Following the general procedure with *para*-*N*,*N*-dimethylypyridine (10.8 mg, 0.088 mmol), the reaction was stirred at room temperature for 1 h providing **16** (58 mg, 97%) as a yellow powder. M.p. 285°C (decomp); ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.07 (d, J=6.6 Hz, 2H), 7.49 (t, J=7.5 Hz, 2H), 7.35 (d, J=7.5 Hz, 4H), 7.11 (s, 2H), 6.22 (d, J=6.6 Hz, 2H), 3.22 (sept, J=6.8 Hz, 4H), 2.89 (s, 3H), 1.50 (d, J=6.8 Hz, 12H), 1.13 ppm (d, J=6.8 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=156.8, 154.2, 150.1, 146.6, 135.2, 129.9, 124.7, 123.9, 106.2, 38.9, 28.6, 26.2, 23.2 ppm; HRMS (EI): *m*/*z* calcd for $C_{34}H_{46}ClN_4Pd$ [*M*−Cl]$^+$: 651.2446; found: 651.2437.



Synthesis of complex 17: Following the general procedure with *para*-trifluoromethylpyridine (13 mg, 0.088 mmol), the reaction was stirred at room temperature for 16 h providing **17** (62 mg, 99%) as a yellow powder. M.p. >300°C (decomp); ^{1}H NMR (400 MHz, CD_2Cl_2): δ=8.90 (d, J=5.6 Hz, 2H), 7.56 (t, J=7.6 Hz, 2H), 7.46–7.40 (m, 6H), 7.22 (s, 2H), 3.18 (sept, J=6.4 Hz, 4H), 1.48 (d, J=6.4 Hz, 12H), 1.15 ppm (d, J=6.4 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=153.2, 152.6, 146.6, 139.3 (q, J=34.5 Hz), 134.9, 130.3, 125.1, 124.0, 119.9, 119.8, 28.7, 26.3, 23.2 ppm; HRMS (EI): *m*/*z* calcd for $C_{33}H_{40}ClF_3N_3Pd$ [*M*−Cl]$^+$: 676.1897; found: 676.1917.

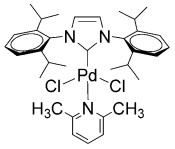


Synthesis of complex 18: Following the general procedure with *ortho*-methylpyridine (8.2 mg, 0.088 mmol), the reaction was stirred at room temperature for 1 h providing **18** (56 mg, 97%) as a yellow powder. M.p. 195°C (decomp); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.24 (brs, 1H), 7.55 (brs, 2H), 7.41 (brs, 5H), 7.17 (brs, 2H), 6.96 (brs, 2H), 3.19 (brs, 4H), 2.57 (s, 3H), 1.48 (brs, 12H), 1.13 ppm (brs, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=159.2, 157.1, 150.2, 146.9, 136.8, 135.2, 135.1, 135.0, 130.1, 125.2, 124.8, 123.7, 121.4, 28.7, 26.3, 24,9, 23.1, 22.6 ppm; HRMS (ES): *m*/*z* calcd for $C_{33}H_{44}Cl_2N_3Pd$ [*M*+H]$^+$: 660.1943; found: 660.1923.

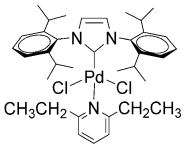


Synthesis of complex 19: Following the general procedure with 2,4-dimethylpyridine (9.5 mg, 0.088 mmol), the reaction was stirred at room temperature for 1 h providing **19** (57 mg, 96%) as a yellow powder. M.p. 224°C (decomp); ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.06 (brs, 1H), 7.54 (brs,

2H), 7.41 (brs, 4H), 7.16 (brs, 2H), 6.81 (brs, 2H), 3.19 (brs, 4H), 2.51 (brs, 3H), 2.16 (brs, 3H), 1.48 (brs, 12H), 1.13 ppm (brs, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.6, 157.6, 157.4, 156.2, 150.2, 149.7, 148.5, 147.8, 146.9, 137.8, 135.3, 135.2, 135.1, 135.0, 131.1, 130.1, 126.1, 124.8, 123.8, 122.6, 121.7, 28.7, 26.4, 24.7, 24.4, 23.2, 22.9, 22.7, 22.6, 20.7, 17.9 ppm; HRMS (ES): *m*/*z* calcd for $C_{34}H_{46}Cl_2N_3Pd$ $[M+H]^+$: 672.2104; found: 672.2111.

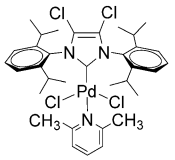


Synthesis of complex 20: Following the general procedure with 2,6-dimethylpyridine (9.5 mg, 0.088 mmol), the reaction was stirred at room temperature for 4 h providing **20** (59 mg, 99%) as a yellow powder. Spectral data were in accordance with those reported in the literature.[7]

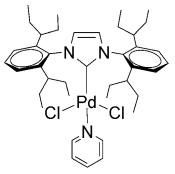


Synthesis of complex 21: Following the general procedure with 2,6-diethypyridine (12 mg, 0.088 mmol), the reaction was stirred at 40 °C for 16 h providing **21** (59 mg, 95%) as a yellow powder. M.p. >300 °C (decomp); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58 (t, *J* = 8.1 Hz, 2H), 7.45–7.37 (m, 5H), 7.20 (s, 2H), 6.82 (d, *J* = 7.8 Hz, 2H), 3.31–3.17 (m, 8H), 1.43 (d, *J* = 7.2 Hz, 12H), 1.11 (d, *J* = 7.2 Hz, 12H), 1.02 ppm (t, *J* = 7.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.5, 158.2, 147.4, 137.5, 135.1, 130.0, 124.8, 123.6, 120.1, 31.3, 28.8, 26.6, 22.5, 12.5 ppm; HRMS (ES): *m*/*z* calcd for $C_{36}H_{50}Cl_2N_3Pd$ $[M+H]^+$: 700.2417; found: 700.2434.

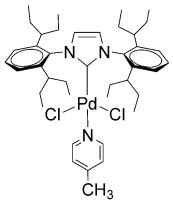
General procedure for the synthesis of complexes 22–27: An oven-dried vial (4 mL screw-cap threaded) equipped with magnetic stir bar was charged with the indicated imidazolium chloride salt (1 equiv, 0.1 mmol), Cs_2CO_3 (5 equiv, 164 mg, 0.5 mmol) and pyridine derivative (1 mL) that served as the solvent. The vial was sealed with a Teflon®-lined screw cap, and the reaction was stirred at 90 °C for 24 h. At that time the mixture was filtered through a small plug of silica (eluted with CH_2Cl_2 (5 mL)). The filtrate was concentrated to 0.5 mL under reduced pressure and loaded onto a silica column and flashed using the indicated eluent system.



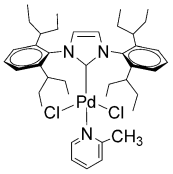
Synthesis of complex 22: Following the general procedure, the reaction was conducted using IPr^{Cl}·HCl (49.5 mg, 0.1 mmol) and 2,6-dimethylpyridine providing **22** (31 mg, 41%) as a yellow powder following column chromatography (pentane/CH_2Cl_2 1:1, R_f = 0.2). M.p. 215 °C (decomp); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 7.6 Hz, 2H), 7.45 (t, *J* = 7.6 Hz, 4H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.78 (d, *J* = 7.6 Hz, 2H), 3.07 (sept, *J* = 6.4 Hz, 4H), 2.57 (s, 6H), 1.46 (d, *J* = 6.4 Hz, 12H), 1.20 ppm (d, *J* = 6.4 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.6, 158.8, 148.1, 137.5, 132.2, 130.9, 124.4, 122.3, 120.2, 28.9, 25.5, 24.9, 24.3 ppm; HRMS (EI): *m*/*z* calcd for $C_{34}H_{43}Cl_3N_3Pd$ $[M-Cl]^+$: 704.1557; found: 704.1543.



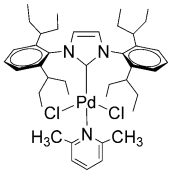
Synthesis of complex 23: Following the general procedure, the reaction was conducted using IPent·HCl (54 mg, 0.1 mmol) and pyridine providing **23** (60.6 mg, 80%) as a yellow powder following column chromatography (pentane/CH_2Cl_2 5:1, R_f = 0.31). M.p. 161 °C (decomp); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.59 (d, *J* = 5.4 Hz, 2H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.24 (brs, 4H), 7.12–7.07 (m, 4H), 2.84 (m, 4H), 2.17 (m, 4H), 1.88 (m, 4H), 1.58 (sept, *J* = 7.2 Hz, 8H), 1.15 (t, *J* = 7.2 Hz, 12H), 0.84 ppm (t, *J* = 7.2 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.6, 151.4, 144.6, 137.2, 136.7, 129.0, 125.2, 123.9, 41.1, 28.7, 27.1, 12.9, 11.1 ppm; HRMS (ES): *m*/*z* calcd for $C_{40}H_{58}Cl_2N_3Pd$ $[M+H]^+$: 756.3043; found: 756.3057.



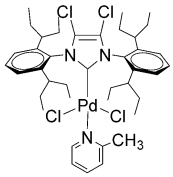
Synthesis of complex 24: Following the general procedure, the reaction was conducted using IPent·HCl (54 mg, 0.1 mmol) and *para*-methylpyridine providing **24** (64 mg, 83%) as a yellow powder following column chromatography (pentane/CH_2Cl_2 5:1, R_f = 0.31). M.p. 191 °C (decomp); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.42 (d, *J* = 5.7 Hz, 2H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.25 (d, *J* = 7.5 Hz, 4H), 7.07 (s, 2H), 6.90 (d, *J* = 5.7 Hz, 2H), 2.83 (m, 4H), 2.23 (s, 3H), 2.14 (m, 4H), 1.87 (m, 4H), 1.55 (m, 8H), 1.12 (t, *J* = 7.2 Hz, 12H), 0.79 ppm (t, *J* = 7.2 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.1, 150.7, 148.9, 144.6, 136.7, 129.0, 125.2, 124.7, 41.1, 28.7, 27.1, 20.8, 12.9, 11.1 ppm; HRMS (ES): *m*/*z* calcd. for $C_{41}H_{60}Cl_2N_3Pd$ $[M+H]^+$: 770.3199; found: 770.3246.



Synthesis of complex 25: Following the general procedure, the reaction was conducted using IPent·HCl (54 mg, 0.1 mmol) *ortho*-methylpyridine providing **25** (61 mg, 79%) as a yellow powder following column chromatography (pentane/CH_2Cl_2 4:1, R_f = 0.30). M.p. 250 °C (decomp); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.25 (d, *J* = 5.1 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 2H), 7.39 (t, *J* = 8.1 Hz, 1H), 7.29 (d, *J* = 7.8, 4H), 7.12 (s, 2H), 6.98–6.90 (m, 2H), 2.85 (m, 4H), 2.57 (s, 3H), 2.10 (m, 4H), 1.85 (m, 4H), 1.52 (m, 8H), 1.07 (t, *J* = 7.2 Hz, 12H), 0.78 ppm (t, *J* = 7.2 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4, 156.4, 150.4, 145.0, 136.9, 136.7, 136.2, 128.7, 125.2, 124.9, 121.2, 40.5, 27.9, 27.8, 26.2, 25.1, 12.5, 10.4 ppm; HRMS (ES): *m*/*z* calcd for $C_{41}H_{60}Cl_2N_3Pd$ $[M+H]^+$: 770.3199; found: 770.3228.



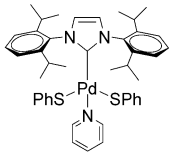
Synthesis of complex 26: Following the general procedure, the reaction was conducted using IPent·HCl (54 mg, 0.1 mmol) and 2,6-dimethylmethylpyridine providing **26** (68 mg, 87%) as a yellow powder following column chromatography (pentane/CH_2Cl_2 6:1, R_f = 0.35). M.p. 298 °C (decomp); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47 (t, *J* = 7.8 Hz, 2H), 7.33–7.23 (m, 5H), 7.18 (s, 2H), 6.75 (d, *J* = 7.5 Hz, 2H), 2.82 (m, 4H), 2.58 (s, 6H), 2.05 (m, 4H), 1.84 (m, 4H), 1.53 (m, 8H), 1.06 (t, *J* = 7.2 Hz, 12H), 0.78 ppm (t, *J* = 7.2 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.9, 158.3, 145.5, 137.2, 135.7, 128.6, 125.3, 124.8, 122.1, 40.2, 27.2, 25.6, 25.0, 12.3, 9.9 ppm; HRMS (ES) *m*/*z* calcd for $C_{42}H_{62}Cl_2N_3Pd$ $[M+H]^+$: 784.3356; found: 784.3388.



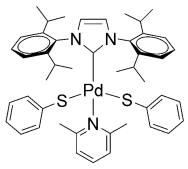
Synthesis of complex 27: Following the general procedure, the reaction was conducted using $IPent^{Cl}$·HCl (60.6 mg, 0.1 mmol) and *ortho*-methylpyridine providing **27** (50 mg, 59%) as a yellow powder following column chromatography (pentane/CH_2Cl_2 2:1, R_f = 0.25). M.p. 185 °C (decomp); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 6.0 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 2H), 7.41 (t, *J* = 7.2 Hz, 1H), 7.35 (d, *J* = 7.6, 4H), 6.99–6.93 (m, 2H), 2.97 (brs, 4H), 2.52 (s, 3H), 2.01–1.85 (m, 8H), 1.73–1.64 (m, 4H), 1.54–1.45 (m, 4H), 1.08 (t, *J* = 7.2 Hz, 12H), 0.82 ppm (t, *J* = 7.2 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.8, 159.3, 150.3, 145.6, 136.9, 133.1, 129.4, 126.3, 125.4, 121.4, 120.7, 40.3, 26.9, 25.8, 24.9, 12.3, 10.3 ppm; HRMS (ES): *m*/*z* calcd for $C_{41}H_{58}Cl_4N_3Pd$ $[M+H]^+$: 838.242; found: 838.2454.

General procedure for the synthesis of complexes 28, 29, 30 and 32: In the glovebox, an oven-dried vial (4 mL screw-cap threaded) equipped with magnetic stir bar was charged with the corresponding Pd-PEPPSI complex (1 equiv, 0.15 mmol) and KO*t*Bu (55 mg, 3.1 equiv, 0.465 mmol). The vial was sealed with a Teflon®-lined screw cap and removed from the

glovebox whereupon the corresponding thiol (3 equiv, 0.45 mmol) was added followed by toluene (2 mL). The reaction mixture was stirred at the indicated temperature and time after which the reaction vial was centrifuged and the supernatant transferred to a round bottom flask. The remaining solid was washed with toluene (3×1 mL), centrifuging each time, and the combined supernatant was evaporated under reduced pressure and the residue purified as indicated.

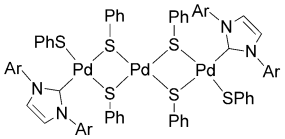


Synthesis of complex 28: Following the general procedure **13** (97 mg, 0.15 mmol) and **10** (3 equiv, 0.45 mmol) were reacted at room temperature for 2 h. The supernatant obtained from the centrifugation process was evaporated and the product was purified by crystallising **29** out of solution using pentane/CH_2Cl_2 at −20 °C, which left **28** in the mother liquor as a clean product. Solvent removal provided **28** (82 mg, 60 %) as a red powder. M.p. 82–84 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.35 (d, J = 4.8 Hz, 2H), 7.43 (t, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 4H), 7.23 (s, 2H), 7.0 (t, J = 8.0 Hz, 1H), 6.50–6.39 (m, 12H), 3.19 (sept, J = 8.0 Hz, 4H), 1.50 (d, J = 8.0 Hz, 12H), 1.16 ppm (d, J = 8.0, 12H); ^{13}C NMR (75 MHz, C_6D_6): δ = 169.2, 151.7, 147.5, 146.8, 136.7, 135.0, 132.5, 130.0, 126.3, 124.6, 124.1, 122.2, 121.0, 29.3, 26.5, 23.2 ppm; HRMS (EI): m/z calcd. for $C_{44}H_{53}N_3S_2Pd$ $[M+H]^+$: 792.2637; found: 792.2648.



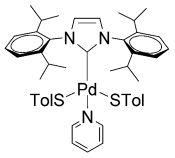
Synthesis of complex 29: Following the general procedure, **20** (101 mg, 0.15 mmol) and **10** (3 equiv, 0.45 mmol) were reacted at 50 °C for 18 h. The supernatant obtained from the centrifugation process was evaporated and the product was purified by crystallising **29** out of solution using pentane/CH_2Cl_2 at −20 °C, which left **36** in the mother liquor as a clean product. Solvent removal provided **36** (41 mg, 30 %) as a dark-orange powder. M.p. 140–143 °C; ^{1}H NMR (400 MHz, C_6D_6): δ = 7.50–7.39 (m, 6H), 6.74–6.72 (m, 6H), 6.61 (t, J = 9.0 Hz, 2H), 6.51 (t, J = 9.0 Hz, 4H), 6.26 (t, J = 6.0 Hz, 1H), 5.81 (d, J = 6.0, 2H), 3.62 (sept, J = 6.0 Hz, 4H), 2.59 (s, 6H), 1.71 (d, J = 6.0 Hz, 12H), 1.12 ppm (d, J = 6.0 Hz, 12H); ^{13}C NMR (75 MHz, C_6D_6): δ = 170.4, 158.2, 147.1, 144.9, 137.2, 135.8, 135.5, 129.8, 128.1, 126.5, 124.9, 123.9, 122.7, 121.2, 29.3, 27.4, 26.5, 22.9 ppm; HRMS (EI): m/z calcd for $C_{40}H_{50}N_3SPd$ $[M-SC_6H_5]^+$: 710.2760; found: 710.2770; X-ray crystallographic analysis is included below.

Synthesis of complex 30: Following the general procedure, 13 (97 mg, 0.15 mmol) and 10 (3 equiv, 0.45 mmol) were reacted at room temperature for 2 h. The supernatant obtained from the centrifugation process was evaporated and the product was crystallised from pentane/CH_2Cl_2, chilled at − 20 °C for 1 h to give **29** as a clean product leaving **28** in the mother liquor. Compound **29** (35 mg, 40 %) were isolated as a yellow powder. M.p. 283 °C (decomp); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.26 (m, 4H), 7.16–7.11 (m, 12H), 6.07 (d, J = 8.0 Hz, 4H), 6.89–6.79 (m, 14H), 6.37 (brs, 12H), 3.19 (s, J = 6.8 Hz, 8H), 1.27 (d, J = 6.8, 24H), 1.05 ppm (d, J = 6.8, 24H); ^{13}C NMR (75 MHz, C_6D_6): δ = 175.9, 151.9, 148.2, 146.4, 136.2, 132.1, 130.9, 129.3, 127.1, 125.9, 124.2, 123.3, 120.5, 119.3, 28.8, 26.5, 22.4 ppm.

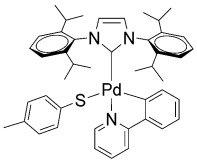


Ar = 2,6-diisopropylphenyl

Synthesis of complex 32: Following the general procedure, **13** (97 mg, 0.15 mmol) and tolylthiol (3 equiv, 0.45 mmol) were reacted at room temperature for 1 h. The supernatant obtained from the centrifugation process was evaporated and the product was purified by crystallising impurities from pentane and leaving **31** in the mother liquor as a clean product. Solvent removal provided **32** (113 mg, 80 %) as a yellow powder. M.p. 88–90 °C; ^{1}H NMR (400 MHz, C_6D_6): δ = 8.83 (d, J = 4.0 Hz, 2H), 7.45 (t, J = 8.0 Hz, 2H), 7.39 d, J = 8.0 Hz, 4H), 6.86–6.83 (m, 6H), 6.50 (d, J = 8.0 Hz, 4H), 6.25 (t, J = 4.0 Hz, 1H), 6.02 (t, J = 4.0 Hz, 2H), 3.6 (sept, J = 8.0 Hz, 4H), 2.0 (s, 6H), 1.85 (d, J = 8.0 Hz, 12H), 1.26 ppm (d, J = 8.0 Hz, 12H); ^{13}C NMR (75 MHz, C_6D_6): δ = 169.7, 151.6, 146.8, 143.6, 136.7, 134.8, 132.4, 129.8, 129.6, 124.7, 124.0, 122.1, 29.2, 26.4, 23.2, 20.5 ppm; HRMS (EI): m/z calcd for $C_{46}H_{56}N_3S_2Pd$ $[M+H]^+$: 820.2950; found: 820.2957.



Preparation of compound 34 from 32: An oven-dried vial (4 mL screw-cap threaded) equipped with a magnetic stir bar was charged with complex **31** (30 mg, 0.031 mmol) followed by [D_6]benzene. The vial was sealed with a Teflon®-lined screw cap and the heated to 100 °C for 16 h. The ^{1}H NMR spectrum of this transformation indicated 62 % conversion of **31** to **33**. At this time, the solvent was removed under reduced pressure and the product was purified using column chromatography (pentane/EtOAc 30:1, R_f = 0.35) providing (12 mg, 59 %) as a dark-orange solid. M.p. 198–200 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.28 (m, 6H), 6.88 (brs, 3H), 6.70 (d, J = 9.0 Hz, 3H), 7.37 (d, J = 9.0 Hz, 2H), 5.66 (d, J = 9.0 Hz, 2H), 2.16 (s, 3H), 1.91 (s, 3H), 1.61 (brs, 4H), 1.44 (d, J = 6.0 Hz, 6H), 1.14 (d, J = 6.0 Hz, 6H), 0.81 ppm (d, J = 6.0 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.7, 146.4, 145.7, 140.8, 136.7, 135.5, 134.0, 133.4, 131.8, 130.7, 129.6, 127.7, 126.7, 125.0, 124.1, 29.7, 28.7, 28.4, 26.2, 23.5, 22.6, 21.0, 20.8 ppm; HRMS (EI): m/z calcd for $C_{34}H_{43}N_2S$ $[M-SC_7H_7]^+$: 511.3146; found: 511.3142.



Reaction between 32 and 33 in the presence of KO*t*Bu to produce 35 [Eq. (2)]: In the glovebox an NMR tube was loaded with **31** (100 mg, 0.122 mmol) and KO*t*Bu (72.5 mg, 5 equiv, 0.61 mmol). A septum was placed on top of the tube and once outside the glovebox **32** (57 mg, 2 equiv, 0.244 mmol) was added under argon atmosphere followed by C_6D_6 (1 mL). The tube was left to stand in an oil bath at 60 °C for 16 h at which time a ^{1}H NMR spectrum was recorded that revealed 22 % conversion to **34** had taken place The solvent was removed under reduced pressure and the product was purified by column chromatography (pentane/diethyl ether 7:1, R_f = 0.24) providing **34** (19 mg, 20 %) as a dark-yellow solid. M.p. 171–173 °C; ^{1}H NMR (400 MHz, C_6D_6): δ = 9.66 (d, J = 5.2 Hz, 1H), 7.43 (d, J = 7.6 Hz, 2H), 7.29–7.24 (m, 2H), 7.25–7.07 (m, 8H), 6.89 (s, 2H), 6.79 (d, J = 8.0 Hz, 1H), 6.68 (d, J = 7.6 Hz, 2H), 6.54 (t, J = 8.0 Hz, 1H), 6.09 (t, J = 8.0 Hz, 1H), 3.84 (sept, J = 6.8 Hz, 2H), 3.42 (sept, J = 6.4 Hz, 2H), 2.19 (s, 3H), 1.89 (d, J = 6.8 Hz, 6H), 1.24 (d, J = 6.8 Hz, 6H), 1.16 (d, J = 6.4 Hz, 6H), 1.09 ppm (d, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, C_6D_6): δ = 181.2, 165.5, 164.0, 151.3, 147.5, 147.4, 147.0, 144.8, 138.3, 136.8, 136.3, 132.3, 129.8, 128.4, 127.6, 124.8, 124.1, 123.9, 123.2, 122.8, 121.2, 117.1, 29.2, 28.4, 26.7, 26.0, 23.1, 22.9, 20.6 ppm; HRMS (EI): m/z calcd for $C_{38}H_{44}N_3Pd$ $[M-C_6H_5S]^+$: 648.2567; found: 648.2589.

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[11] Pd-PEPPSI-IPent^{Cl}, which has a 3-chloropyrdine moiety, (see ref. [9]) and the 2-methylpyridine derivative **27**, which is especially easy to activate, are both available through Total Synthesis Ltd. In Toronto, see: totalsynthesis.ca.
[12] For reaction conditions used in the NMR studies, see the Supporting Information.
[13] When the reaction was performed under the same conditions but for 30 min instead of 2 h, only **28** was formed as determined by ^{1}H NMR spectroscopy. Therefore, the formation of **28** and **30** show time dependency, that is, **28** forms first and then **30** starts to form, apparently from **28**.
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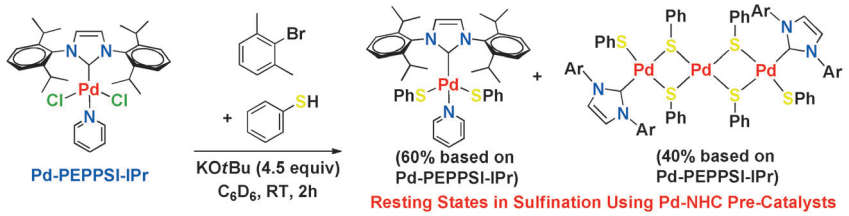

Resting States in Sulfination Using Pd-NHC Pre-Catalysts

On activation duty: The activation of PEPPSI precatalysts has been evaluated in the sulfination of aryl halides (see figure). Substitution of the two chlorides on Pd with two sulfides occurs immediately, even at low temperature, and it is this species that is reduced and enters the catalytic cycle. Butoxide base is involved in precatalyst activation and maintaining a healthy level of active catalyst to ensure high catalytic performance. Examination of the cation of the sulfide salt and solvent dielectric revealed that solubility is very important to the success of this transformation.

Pd-Catalysed Sulfination

M. Sayah, A. J. Lough,
*M. G. Organ**..... ■■■–■■■

Sulfination by Using Pd-PEPPSI Complexes: Studies into Precatalyst Activation, Cationic and Solvent Effects and the Role of Butoxide Base