CHEMISTRY
A EUROPEAN JOURNAL

ChemPubSoc Europe

DOI: 10.1002/chem.201303756

Potassium Isopropoxide: For Sulfination It is the Only Base You Need!

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Recently we reported a promising sulfinating system using the Pd-PEPPSI-IPent precatalyst (**6**) to couple challenging substrates under moderate reaction conditions.[1,2] However, unlike cross-coupling with nucleophilic organometallics that readily reduce the Pd^{II} precatalyst, sulfinating with arylthiols using *tert*-butoxide base does not provide an obvious/immediate source of reductant,[3] assuming for now that it is not an electron transfer process. Consequently we showed that reduction could be achieved by pretreatment of **4** or **6** with dibutylmagnesium, morpholine, or LiO*i*Pr, of which the latter is most pragmatic. That said, precatalyst activation with isopropoxide had to be heated to approximately 80 °C, even if the sulfination itself proceeded smoothly at RT, which added inconvenience and an additional step to monitor in the process. This encouraged us to look at the precatalyst reduction step itself in more detail in an attempt to better understand it and devise a simpler, if not *invisible* precatalyst activation process to streamline sulfination using the highly active Pd-NHC catalyst system (Figure 1). This has resulted in much greater understanding of the sulfination mechanism, a vastly easier protocol to follow, and the movement of the process to conditions so mild they would have been considered unattainable even a year ago.[4]

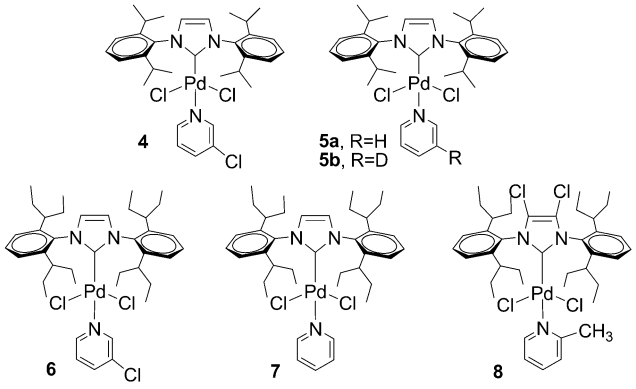

Figure 1. Pd-NHC complexes used in this study.

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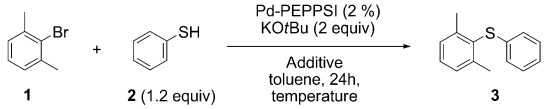
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201303756.

Our initial studies revealed that both isopropoxide (entry 3 vs. 4, and entry 5 vs. 7) and elevated temperatures (entry 1 vs. 2, and entry 5 vs. 6) greatly impact precatalyst activation (Table 1). To track activation in the PEPPSI system, precatalyst **4** (in benzene) was treated with LiO*i*Pr with warming, and progress was followed by ^{1}H NMR spectroscopy (Figure 2). When the base was added (spectrum b), we observed approximately 30 % dissociation of 3-chloropyridine (downfield region, not shown) and the formation of dimer **9**, the structure of which was confirmed by preparing it independently (see the Supporting Information). At this stage there was no evidence of the formation of acetone (1.6 ppm) or isopropanol (1.05 and 3.8 ppm), suggesting that reduction had yet to take place. Upon heating to 50 °C (spectrum c) the first sign of acetone formation took place. When heated to 80 °C (spectrum d), the spectrum had radically changed. The LiO*i*Pr was fully consumed and the acetone peak was now quite prominent with an equimolar amount of *i*PrOH, while the intermediate dimer (**9**) was gone.

At this stage we expected to have the Pd^0-NHC monomer, likely coordinated to 3-chloropyridine, which would then enter the sulfination catalytic cycle directly, or form a new complex with the thiol(s) present (vide infra). Howev-

Table 1. Effect of temperature and isopropoxide base on Pd-PEPPSI precatalyst activation and ensuing sulfination.



Entry	Precatalyst	Additive	*T* [°C]	Yield [%][d]
1	**4**	–	70	0
2	**4**	–	80	90
3	**6**	–	70	0
4	**6**	LiO*i*Pr (20 %)[a]	80, then 23	99
5	**7**	–	23	0
6	**7**	–	70	99
7	**7**	LiO*i*Pr (10 %)	23[b]	99
8	**10**	KO*i*Pr (200 %)[c]	40	99

[a] A mixture containing **1**, the Pd-PEPPSI precatalyst, and LiO*i*Pr was heated to 80 °C for 30 min, cooled to RT, KO*t*Bu and **2** were added, and the reaction was stirred at RT for 24 h. [b] When the reaction was performed using degassed solvent, 90 % conv. to **3** was obtained in just 5 min. [c] No KO*t*Bu was used at all. [d] Percent yield is reported on isolated products following silica gel column chromatography; reactions were performed in duplicate.

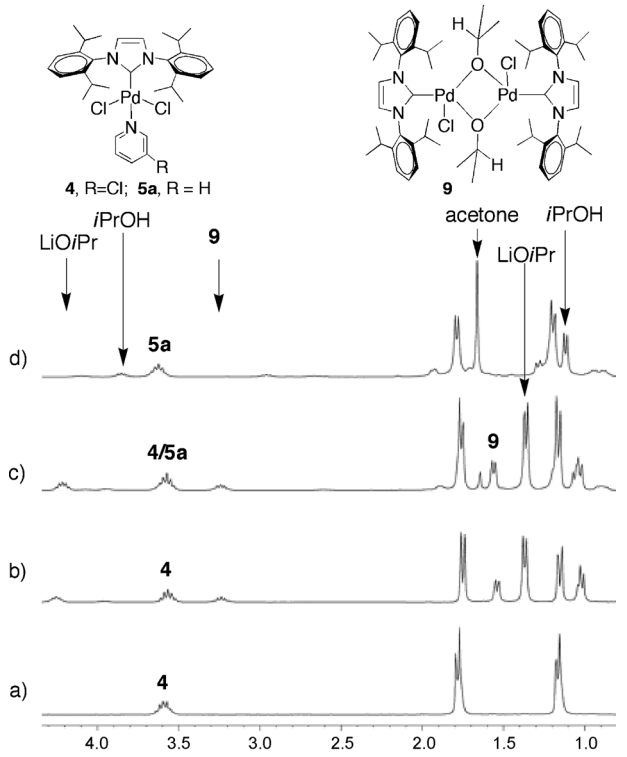


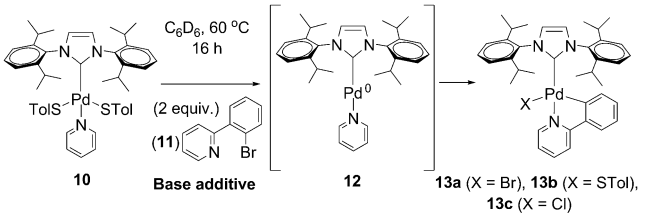
Figure 2. Activation of precatalyst **4** using LiO*i*Pr as a function of temperature. a) Precatalyst **4** in [D_6]benzene at RT; b) sample in a) plus 2.0 equiv of LiO*i*Pr at RT; c) sample in b) warmed to 50 °C; d) sample in c) warmed to 80 °C.

er, we were surprised to isolate the Pd^{II} complex **5a** in approximately 90% yield, which revealed that the 3-chloropyridine ligand had in fact been reduced. To account for this, we propose that Pd^0 is in fact formed concomitant with the oxidation of isopropoxide to acetone and that the activated Pd^0-NHC complex undergoes oxidative addition to the 3-chloropyridine. The equivalent of *i*PrOH that is produced from the above oxidation of LiO*i*Pr then serves as the source of hydride to complete the chloride reduction. To confirm this LiO*i*Pr(D_7) was used with **4** and the 3-deuteriopyridine Pd-NHC complex **5b** was isolated exclusively (see the Supporting Information). Although the source of the hydride is not in question, it is unclear exactly how the reductive steps that are necessary to provide **5a** yield a Pd^{II} complex at the end? We think it is most likely that only a small amount of the Pd^0-NHC complex actually forms, which enters into a catalytic cycle of its own with LiO*i*Pr to reduce all of the 3-chloropyridine. This reduction could happen to intact molecules of **4** directly, or to the 3-chloropyridine that dissociates from it and the pyridine thus produced simply religates to the Pd^{II}-NHC-Cl_2 complex. This would account for the near quantitative yield of **5a**.

On the surface, it would appear that a remarkable amount of chemistry has taken place just to produce a reduced analogue of **4** or **6**. To see if there was any advantage in this "precatalyst pre-activation", we investigated sulfination using **7** in place of **6** (Table 1, entry 7 vs. 4, respectively) and discovered that in fact the simple pyridine derivatives activate much more readily. This result is highly unanticipated as one would have expected the more electron-poor 3-chloropyridine to assist in precatalyst reduction/activation.[5]

When the arylthiol is added to the reaction mixture containing the Pd^{II} precatalyst (i.e., **5**), we believe that thiol/chloride exchange is the first thing to happen that leads to the formation of **10**. One question that arises is whether the reductive elimination of diaryldithiol is the way in which Pd^0 is produced or whether isopropoxide is involved in the direct reduction of **10**? From an enthalpy point of view, reductive elimination of diaryldithiol is not favoured and in fact we have shown that addition of diphenyldithiol to a Pd^0-NHC complex will move the equilibrium fully to the Pd^{II} species even at 0 °C (i.e., Pd^0 oxidatively adds fully to the dithiol).[1a] To examine the potential role of isopropoxide in dithiol precatalyst activation (i.e., **10**) we again turned to ^{1}H NMR spectroscopy to follow the activation process (Table 2). Pd^{II} complex **10** was treated with various basic

Table 2. Base-activation study of dithiol complex **10**.



Entry	Base additive (equiv)	Conversion [%] to **13b**[a]
1	KO*t*Bu (5), LiO*i*Pr (3)	100
2	KO*t*Bu (3)	20
3	LiO*t*Bu (3)	0
4	LiO*i*Pr (3)	0
5	KO*i*Pr (3)	100

[a] Conversion is the percentage of **10** that is transformed into **13b** and was followed and determined by ^{1}H NMR spectroscopy over time.

salts, or salt combinations, and then trapped with **11** to confirm that reduction had taken place. When KO*t*Bu and LiO*i*Pr were used together (entry 1) full conversion to **13b** (via **13a**) was observed, whereas KO*t*Bu (entry 2), LiO*t*Bu (entry 3), or LiO*i*Pr (entry 4) by themselves yielded low or zero conversion. Surprisingly, substitution of KO*i*Pr for LiO*i*Pr (entry 5) led to complete reduction of **10**, which is indicative of both a significant base and counter ion effect. Whereas the reaction mixtures in entries 3 and 4 were homogeneous, those of entries 1 and 5 were heterogeneous. Removal of thiol from solution as the mostly insoluble potassium salt would lower its concentration and help to pull the equilibrium toward **12**, whereas the lithium salts are soluble, which discourages the reduction of **10**. It seems most likely that the small amount of **13b** that is produced (entry 2) does occur via reductive elimination of ditolyldithiol. Although this is not favoured, it would be assisted by cleavage of the dithiol as it forms by KO*t*Bu, a strong reductant, to the potassium thiol salt that precipitates out. To con-

firm this reductant role for KO*t*Bu under the sulfination conditions, we treated **13c** with ditolyldithiol and KO*t*Bu and this led to the quantitative formation of **13b** (see the Supporting Information).

Given that the conversion to **13** with isopropoxide is strongly favoured (vide infra), reduction with this base must be taking place by another pathway. The first clue as to the mechanism at work was the appearance of acetone and isopropanol in the ^{1}H NMR spectrum of entry 5 in Table 2 (see the Supporting Information). If **12** were formed by global reductive elimination of ditolydithiol there would be no free Pd^{II} present to oxidize the isopropoxide. We considered that the isopropoxide-arylthiol adduct (i.e., ArS-O*i*Pr) formed by the cleavage of dithiol in the presence of this base could be susceptible to base-induced elimination of thiolate concomitant with the formation of acetone. However, treatment of ditolyldithiol with KO*i*Pr in the absence of any Pd complex did not yield acetone (see the Supporting Information), thus this method of precatalyst reduction seems unlikely. Taken together, the precatalyst activation mechanism that we propose is shown in Figure 3. Substitution of one thiolate on **16**

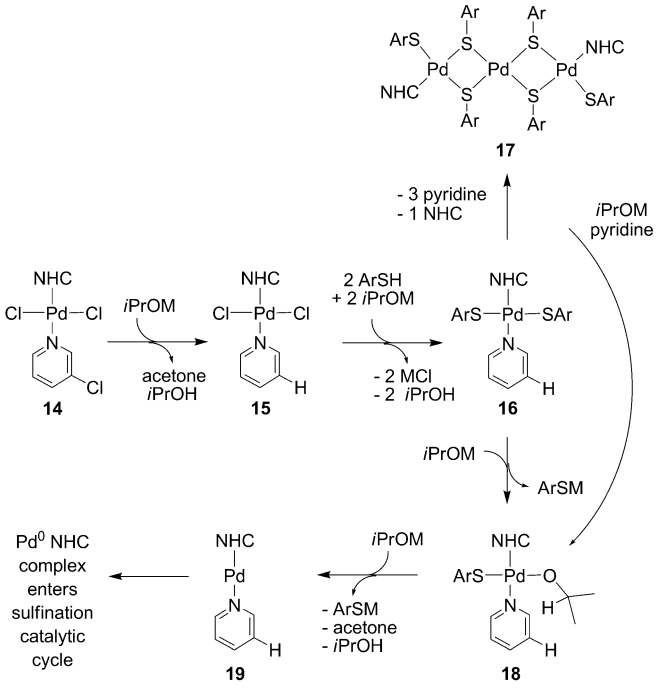


Figure 3. Mechanism of PEPPSI precatalyst activation in sulfination.

with isopropoxide will produce the mixed Pd^{II} salt **18** that can undergo reduction in one of two possible ways. β-Hydride elimination would produce the corresponding ArS−Pd−H species that would yield ArSH upon reductive elimination, which would be driven by formation of insoluble ArSK by isopropoxide (M = K) and pull the equilibrium over. Conversely, deprotonation of the Pd-coordinated isopropoxide by another molecule of KO*i*Pr would produce Pd^0 directly concurrent with the production of acetone and elimination of thiolate, which again as the K salt would precipitate. The Pd^0-NHC complex (**19**) thus produced is able to undergo oxidative addition with the aryl halide present and catalysis ensues. We also discovered that up to 50% of dithiol **16** is drawn further off cycle into resting state **17** that cannot be rescued by KO*t*Bu.[1a] Another vital role of KO*i*Pr that we have uncovered in this study is the cleavage of this tri-Pd complex by isopropoxide, which is just small enough (relative to *tert*-butoxide) to attack Pd, which upon complexation with pyridine would produce **18**, thus **17** is not in equilibrium with **16**.

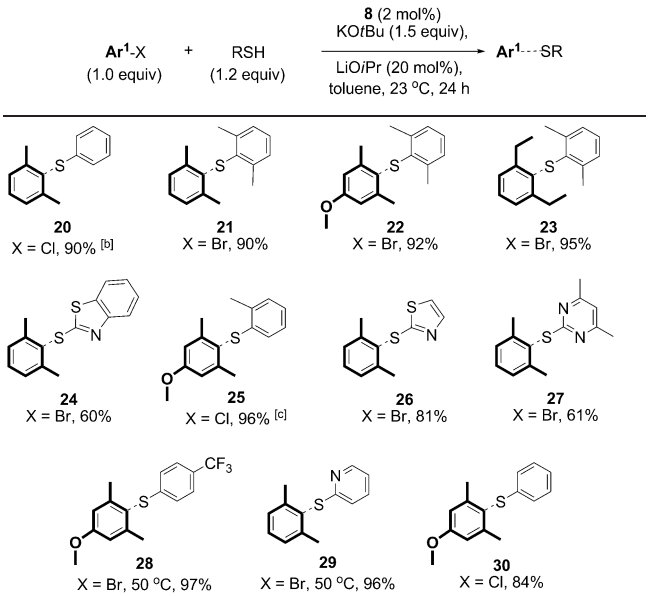
To confirm the necessity of both potassium and isopropoxide for facile sulfination we performed the control reaction with dithiol precatalyst **10** with just KO*i*Pr as base (Table 1, entry 8) and the reaction proceeded smoothly. This result would also suggest that heating to 80 °C with Pd-PEPPSI-IPr (**4**) is only necessary to reduce the 3-chloropyridine ligand as the dithiol Pd^{II} complex activated readily and completed the coupling under mild conditions.

With a thorough understanding of all of the events associated with precatalyst activation in hand, we wanted to press forward to see if a general and highly reactive sulfination system could be created to make sulfination a mild, robust, and widely applicable operation. The most reactive catalysts and associated protocols in the literature require very high temperatures (e.g., 110 °C),[3,4] and even then some moderately deactivated coupling partners (e.g., sterically and/or electronically aryl haldies and thiols) simply do not couple.[3] Precatalyst **8** combines a 2-methylpyridine ligand, which assists in precatalyst activation, and the dichloro NHC carbene core that we have shown to be highly effective in the Negishi coupling of secondary alkyls—another notoriously difficult transformation.[6] Indeed, we were delighted to see that a wide variety of difficult sulfinations could now be carried out routinely at room temperature following one simple protocol in which everything is simply mixed together.[7] Bis di-*ortho*-substituted aryl thiols were readily prepared (e.g., **21**, **23**) indicating that even the most sterically congested coupling partners can be tolerated. Electron-poor heterocyclic thiols posed no obstacles (e.g., **24**, **26**, **27**, **29**). Even the most stercially and electronically deactivated oxidative addition partner could be routinely coupled in excellent yield (e.g., **22**, **25**), even if a highly electron-poor thiol is used (e.g., **28**). Finally, the proficiency of precatalyst **8** was demonstrated as a loading as low as 0.1 mol% still led to complete conversion to product (e.g., **20**).

In conclusion, we have dissected out the details of activation of Pd-PEPPSI precatalysts in sulfination reactions. The signature 3-chloropyridine ligand of the PEPPSI family, which was chosen originally for the general belief of enhanced precatalyst activation capability relative to simple pyridine,[5] actually is fully reduced (i.e., Cl to H) under the reductive conditions of the sulfination protocol using isopropoxide base. So, whether one starts with **4** or **6**, or with the simple corresponding pyridine analogues **5** or **7**, the same Pd^{II} complex then undergoes immediate ligand exchange of thiolate for chloride producing the penultimate

precatalyst (i.e., **16**). A significant portion of this advanced precatalyst is then disproportionated into a tri-Pd complex (i.e., **17**). This resting state cannot be rescued by KO*t*Bu, but KO*i*Pr can, which is presumably a function of the subtle difference in size of the base and the great stability of this resting state species (Table 3). Isopropoxide then reduces di-

Table 3. Sulfination of sterically and electronically deactivated oxidative addition and thiol partners at room temperature.[a]



[a] Reaction components were simply mixed together and allowed to stir for 24 h under argon. [b] The same yield was obtained when the reaction was performed with 0.1 % of **8**. [c] The same reaction with JosiPhos and $Pd(dba)_2$ gave 0 %, whereas BrettPhos-Pd-G3 gave 18 %.

thiol resting state **16** to produce the catalytically active species **19** and sulfination ensues. The presence of potassium, which can come from KO*i*Pr or a mixed base system (i.e., KO*t*Bu, and LiO*i*Pr)[7] is essential for any turnover whatsoever, and this is attributed to the insolubility of KSAr in toluene, which keeps the concentration of the thiolate poison low and thus avoids pushing the active catalyst back into unproductive resting states (i.e., **16** or **17**). Finally, a highly reactive precatalyst (Pd-PEPPSI-IPent^{Cl} *o*-picoline, **8**) has been engineered specifically for sulfination that has a readily dissociatable 2-methylpyridine and the dichloro-NHC core that rapidly drives the catalytic cycle.[6,8] This procedure is operationally simple and works with substrates that will not work with other catalysts currently being used that are considered highly active for sulfination.[9]

Acknowledgements

The authors thank the NSERC Canada for funding this work.

Keywords: catalysis · cross-couple · PEPPSI · sulfination

[1] a) M. Sayah, A. Lough, M. G. Organ, *Chem. Eur. J.* **2013**, *19*, 2749–2756; b) M. Sayah, M. G. Organ, *Chem. Eur. J.* **2011**, *17*, 11719–11722.

[2] For other reports on the high reactivity of the Pd-PEPPSI-IPent precatalyst, see: a) K. H. Hoi, S. Çalimsiz, R. D. J. Froese, A. C. Hopkinson, M. G. Organ, *Chem. Eur. J.* **2012**, *18*, 145–151; b) C. Valente, S. Çalimsiz, K. H. Hoi, D. Mallik, M. Sayah, M. G. Organ, *Angew. Chem.* **2012**, *124*, 3370–3388; *Angew. Chem. Int. Ed.* **2012**, *51*, 3314–3332; c) K. H. Hoi, S. Çalimsiz, R. D. J. Froese, A. C. Hopkinson, M. G. Organ, *Chem. Eur. J.* **2011**, *17*, 3086–3090; d) S. Çalimsiz, M. G. Organ, *Chem. Commun.* **2011**, *47*, 5181–5183; e) S. Çalimsiz, M. Sayah, D. Mallik, M. G. Organ, *Angew. Chem.* **2010**, *122*, 2058–2061; *Angew. Chem. Int. Ed.* **2010**, *49*, 2014–2017; f) M. Dowlut, D. Mallik, M. G. Organ, *Chem. Eur. J.* **2010**, *16*, 4279–4283; g) M. G. Organ, S. Çalimsiz, M. Sayah, K. H. Hoi, A. J. Lough, *Angew. Chem.* **2009**, *121*, 2419–2423; *Angew. Chem. Int. Ed.* **2009**, *48*, 2383–2387.

[3] E. Alvaro, J. F. Hartwig, *J. Am. Chem. Soc.* **2009**, *131*, 7858–7868.

[4] Arylthiol couplings in the literature using different metals and general use, highly active ligand systems all require approximately 100 °C (or higher) in order to achieve any sign of coupling unless the oxidative addition partner is strongly activated (e.g., aryl iodide). For examples, see: a) ref. [3]; b) S. Jammi, P. Barua, L. Rout, P. Saha, T. Punniyamurthy, *Tetrahedron Lett.* **2008**, *49*, 1484–1487; c) M. A. Fernández-Rodríguez, Q. Shen, J. F. Hartwig, *Chem. Eur. J.* **2006**, *12*, 7782–7796; d) L. Cai, J. Cuevas, Y.-Y. Pengb, V. W. Pike, *Tetrahedron Lett.* **2006**, *47*, 4449–4452; e) M. Murata, S. L. Buchwald, *Tetrahedron* **2004**, *60*, 7397–7403; f) G.-Y. Gao, A. J. Colvin, Y. Chen, X. P. Zhang, *J. Org. Chem.* **2004**, *69*, 8886–8892; for a recent review see: g) C. C. Eichman, J. P. Stambuli, *Molecules* **2011**, *16*, 590–608.

[5] J. Nasielski, E. A. B. Kantchev, C. J. O'Brien, M. G. Organ, *Chem. Eur. J.* **2010**, *16*, 10844–10853.

[6] M. Pompeo, N. Hadei, R. D. J. Froese, M. G. Organ, *Angew. Chem.* **2012**, *124*, 11516–11519; *Angew. Chem. Int. Ed.* **2012**, *51*, 11354–11357.

[7] Although the reactions work equally well with KO*i*Pr, the base is not stable for prolonged periods of time, as are KO*t*Bu, and LiO*i*Pr. So, it is easier to allow the transmetallation to take place in situ using these two bases than it is to prepare fresh KO*i*Pr every few weeks to ensure the integrity of the base.

[8] Pd-PEPPSI-IPr and Pd-PEPPSI-IPent are commercially available through Sigma–Aldrich. Pd-PEPPSI-IPent^{Cl} *o*-picoline precatalyst is available through Total Synthesis, Ltd. (www.totalsynthesis.ca).

[9] When the reactions in Table 3 were performed using highly reactive phosphine catalysts, low (or no) conversion was observed (see the Supporting Information).

Received: October 7, 2013
Published online: October 31, 2013

