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Potassium 2,2,5,7,8-Pentamethylchroman-6-oxide: A Rationally Designed Base for Pd-Catalysed Amination

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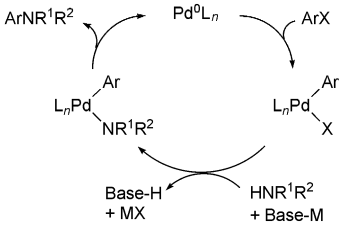
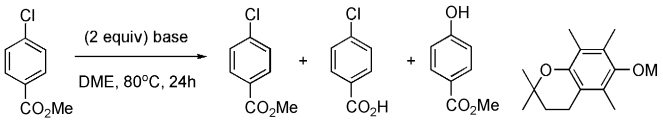
Metal-catalysed amination of aryl halides has become perhaps the method of choice to prepare substituted aniline derivatives.[1] Since the first amination of a non-metal amide complex in 1983 using catalytic amounts of metal,[2] considerable strides have been made in catalyst design, reaction optimization, and mechanistic understanding of this valuable transformation involving simple amines.[3] That said, the nature of, and role/effect of the ancillary base that is necessary to complete the catalytic cycle (Scheme 1)[4] has been



Scheme 1. Putative Pd-catalysed amination mechanism.

far less studied experimentally.[5] Perhaps this is not surprising as bases that are available to the synthetic chemist are pretty much assumed to be all known, and it is generally perceived to be a matter of screening them to see which one performs the best for a particular application. Certainly cation effects can be quite pronounced, but the anionic 'business end' of the salt pair for amination has been limited primarily to carbonates and alkoxides.[6,7]

When considering the general, putative amination mechanism (Scheme 1), the base's role, on the surface, would be deprotonation of the aryl palladium ammonium complex. Assuming a pK_a value of approximately 8–10 for this proton, carbonate is barely suitable for deprotonation (pK_a HCO_3^- ca. 10.3),[8] which is further exacerbated by its negligible solubility in organic solvents. Particle size, hence surface area, has been shown to be critical to the success of amination protocols employing carbonate suggesting that deprotonation most likely takes place on the surface of the heterogeneous base.[9] The gentle nature of carbonates makes them compatible with a broad spectrum of functional groups (e.g., alcohols, amines, ketones, nitriles, esters, amides), thus appealing for use in amination. However, many amination protocols show a first-order dependence on base with the consequence that couplings using carbonate generally require very high reaction temperatures and prolonged reaction times.[10] Conversely, strong alkoxide bases, such as *tert*-butoxide (pK_a *tert*-butyl alcohol ca. 18), are also widely employed in amination. They are quite soluble in organic media and highly effective deprotonating agents leading to greatly improved reaction rates when compared with carbonate. For example, we recently demonstrated that Pd-PEPPSI-IPent precatalyst (see structure **8**; PEPPSI = pyridine, enhanced, precatalyst, preparation, stabilisation, and initiation; IPent = *N*,*N*-bis(2,6-diisopentylphenylimidazolium)) quantitatively couples 4-chlorocyanobenzene with morpholine at 80 °C over approximately 3 h with Cs_2CO_3 as base; the same reaction using KO*t*Bu at room temperature was complete within 10 s![10] However, KO*t*Bu is poorly functional group tolerant, which means that aminations employing it are limited to substrates that are relatively simple, for example lacking the functionality listed above. To illustrate this point, consider the simple reaction in Scheme 2. Compound **1**, a typical substrate for amination, was exposed to amination conditions using KO*t*Bu in DME at 80 °C[10] and this led to the complete degradation of **1**.



	1	2	3	
KO*t*Bu	0	40	60	**4a**, M = H **4b**, M = K, **4c**, M = Na
4b	100	0	0	**4d**, M = Li

Scheme 2. Base compatibility test with methyl 4-chlorobenzoate.

With the goal of increasing substrate scope, while keeping reaction times as short as possible, we took a step back and re-evaluated the structure of the base as it pertains to reactivity in metal-catalysed amination. While soluble alkoxides clearly are well capable of deprotonation leading to desirable kinetics, their relatively strong nucleophilicity diminishes their selectivity, which curtails their wide-spread use. If the

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base could be softened, while simultaneously diminishing nucleophilicity, a more balanced base for amination could be realised. To this end, bases with conjugate acid pK_a values between 11 and 15 were targeted. We investigated 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (pK_a guanidinium ca. 13.5) and potassium trimethylsilanoxide whose pK_a is in the same vicinity as carbonate (pK_a silanol ca. 11) but it is fully soluble. Neither base showed any hint of reactivity in preliminary amination studies. Both bases should be suitable for deprotonation; it is possible that catalyst poisoning, in particular with DBU, could be the source of the problem. In any case, we continued our search and next considered phenoxide-derived bases. While this choice might appear esoteric, there is precedence for the use of phenoxide itself, or substituted derivatives thereof, in amination[5] and amino carbonylation[11] reactions. Phenol has a pK_a of 9.95, which we deemed to be lower than desired (i.e., simple phenoxide would be too weak a base), and further phenoxide is a known nucleophile in Pd-catalysed substitution reactions that could lead to selectivity and product contamination problems.[11] Interestingly, while the methoxy group in anisole is viewed as a strong electron donor in electrophilic aromatic substitution, *p*-OCH_3 only increases the pK_a of phenol to 10.2. Perhaps even more enlightening is that the pK_a of *p*-cresol is essentially the same (10.19) as that of *p*-methoxyphenol. This would suggest that the lone pairs of the methoxy substituent are not drawn strongly into conjugation with the ring. The presence of the phenolic oxygen atom would disfavour delocalisation of electron density into the ring, thus minimising the destabilisation brought about by the OCH_3 group that would increase the pK_a, thus improving basicity. Further, $A^{1,3}$-type strain builds between the ring and the methyl group when one of the lone pairs on oxygen is brought into conjugation with it. We reasoned if the alkoxy oxygen atom could be fixed conformationally such that one lone pair was locked into full conjugation with the aromatic ring that we could 'force' the pK_a value up, thus increasing the rate of amination where deprotonation was rate limiting.[10] To this end we turned to nature and examined the structure of α-tocopherol (vitamin E), whose pK_a has been highly studied as a function of its biological activity. In water, the pK_a of α-tocopherol has been shown to vary between 11 and 13 with different surfactant-like additives.[12] Inspired by this, we examined a truncated version of α-tocopherol, specifically 2,2,5,7,8-pentamethyl-6-chromanol (**4a**). Using proprietary in-house software, we calculated the pK_a of **4a** to be 11.4; as a control, phenol was determined to be 9.9, which compares well with the experimental data.[13] When the potassium chromanoxide salt **4b** was allowed to react under the same conditions as KO*t*Bu with **1** (Scheme 2), there was no degradation whatsoever of the sensitive starting material. As part of our design, the methyl groups that flank the phenoxide site offset the stonger basicity of α-tocopherol by sterically reducing its nucleophilicity, which seems to be validated by this result.

With the compatibility study results in hand, we attempted a test coupling to see how **4b** compared with other commonly used amination bases using precatalyst **8**[14,15] (Figure 1). In the absence of sensitive functionality, the impressively high reactivity of KO*t*Bu in combination with **8** is clear. Also clear is the vastly slower reactivity of Cs_2CO_3. We were delighted that **4b** was not only suitable for the reaction, but that it showed vastly improved kinetics relative to Cs_2CO_3 completing the transformation in approximately 2 h. The sodium salt **4c** had similar reactivity relative to **4b**, while the lithium salt (**4d**) showed essentially no reactivity. This could be due to poor solubility of **4d**, however addition of a strong lithium chelater ([12]crown-4) did not significantly improve the situation.

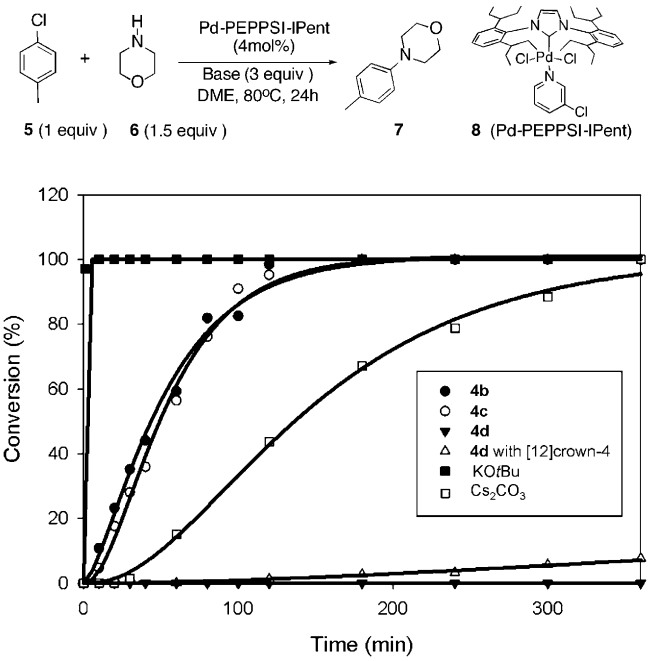


Figure 1. Comparison of the rates of amination of *p*-chlorotoluene with morpholine by Pd-PEPPSI-IPent using KO*t*Bu, Cs_2CO_3, and the K (**4b**), Na (**4c**), and Li (**4d**) salts of 2,2,5,7,8-pentamethyl-6-chromanol.

To further evaluate our base design, we stripped off the second ring providing **9b** and this was accompanied by a significant drop in reactivity (Figure 2). While the alkoxide end of **9b** would be similarly hindered, **9b** is, overall, less cumbersome than **4b** and this should improve the base's performance from a steric point of view. Thus, the diminished performance would be consistent with the basis for the reactivity of **4b** being primarily electronic (i.e., pK_a) and that in the absence of the conformational lock the alkoxy group does little to enhance the phenol's basicity. Removal of the flanking methyl groups (i.e. **9a**) renders the base totally ineffective for this transformation and the starting materials were untouched after 24 h.

Having established the mildness of **4b** with base-sensitive compounds, and its very good reactivity as a base in the control amination reaction, it remained to demonstrate its utility in the amination of base-sensitive aryl chlorides and amines (see Tables 1 and 2). For demonstration purposes, the reaction was performed with substrates possessing a

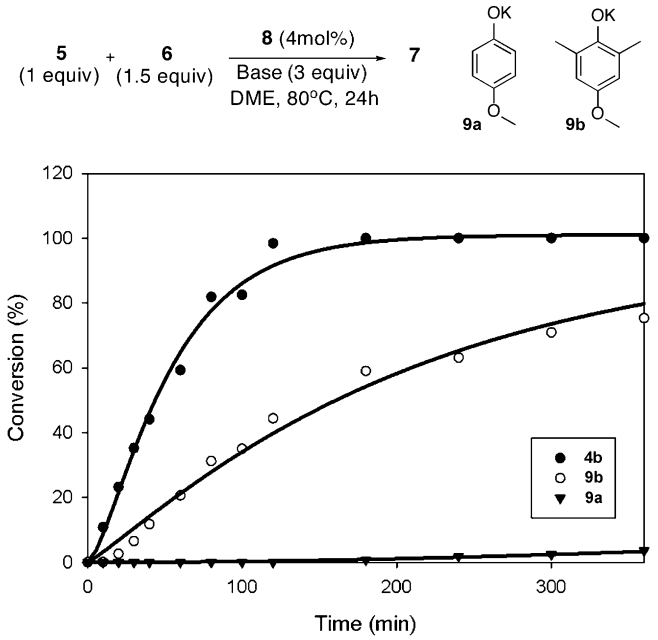


Figure 2. Comparison of the rates of amination of *p*-chlorotoluene with morpholine by Pd-PEPPSI-IPent using various phenoxide bases.

ketone (**10**, **14**), ester (**12**), carbamate (**15**), or nitrile (**11**) using two structurally diverse, highly reactive catalyst systems for amination, the NHC complex **8** (Table 1) and the phosphine-based Pd-RuPhos catalyst (Table 2).[17] In most cases, when KO*t*Bu was used there was minimal (or no) amination product observed and the starting material con-

Table 1. Amination reactions involving base-sensitive substrates by Pd-PEPPSI-IPent using KO*t*Bu and **4b**. Reported yields [%] were determined on isolated material following silica gel chromatography; reactions were performed in duplicate. [a] 3 equiv of base used. [b] Aryl bromide was used.

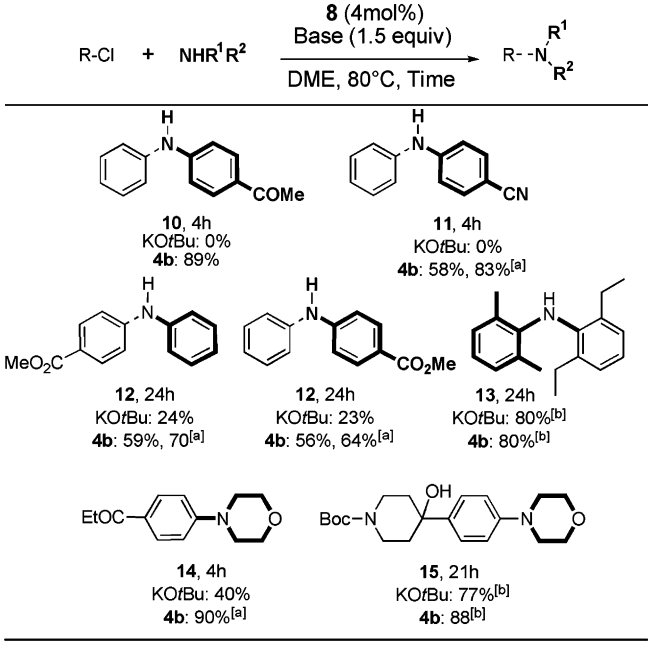
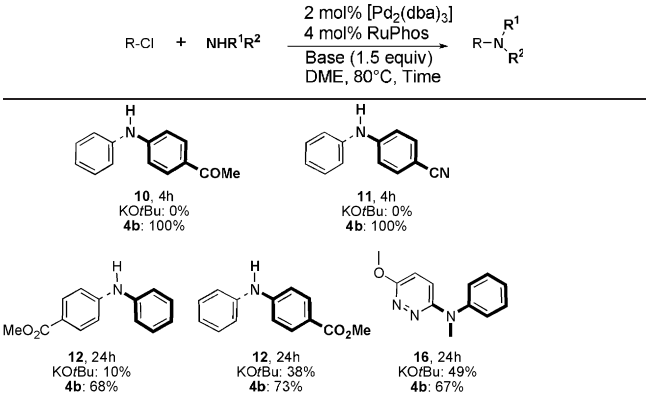


Table 2. Amination reactions involving base-sensitive substrates by the Pd-RuPhos catalyst using KO*t*Bu and **4b**. Reported yields [%] were determined on isolated material following silica gel chromatography; reactions were performed in duplicate.



taining the base-sensitive group was not detected in the crude product mixtures, indicating that it had been fully decomposed under these standard amination conditions. Notably, **4b** efficiently produced the highly hindered product **13** (Table 1), which typically requires forcing conditions, such as butoxide base. Additionally, starting materials that contain alcohols (e.g., leading to **15**, Table 1), which will be deprotonated before coupling begins with either KO*t*Bu or **4b**, also produce high product yields.

In conclusion, we have rationally designed a base from first principles for Pd-catalysed amination. The base, potassium 2,2,5,7,8-pentamethyl-6-chromanoxide (**4b**),[17] has the necessary basicity (pK_a ca. 11.4) to facilitate the efficient deprotonation of the corresponding aryl palladium ammonium complexes to give desirable kinetics, while having diminished nucleophilicity to mitigate undesired side reactions with base-sensitive functional groups. The base has shown excellent reactivity and selectivity with both highly reactive phosphine- and NHC-based Pd catalysts indicating that **4b** will have high compatibility, thus good generality and broad uptake in metal-catalysed amination reactions.

Experimental Section

General procedure for Pd-PEPPSI-IPent-catalysed amination: In air, a vial (3 mL screw-cap threaded) equipped with a stir bar was charged with **8** (15.8 mg, 4 mol %). Caesium carbonate (489 mg, 1.5 mmol) or KO*t*Bu (84.2 mg, 0.75 mmol) were weighed out in the glovebox and transferred into the reaction vial under argon. The vial was sealed with a Teflon-lined screw cap and purged with argon (3×). When potassium phenoxide bases were used, the corresponding phenol (0.75 mmol) was added to a vial containing an equimolar amount of KH in DME (0.25 mL), and the mixture was stirred until the effervescence subsided (ca. 10 min). The aryl halide (0.5 mmol), amine (0.75 mmol) and DME (0.25 mL) were added subsequently by using a syringe. Alternatively, if the aryl halide was a solid at room temperature, it was introduced into the reaction vial prior to purging with argon. The solution was stirred at 80 °C for the indicated time, after which it was diluted with diethyl ether (2 mL) and filtered through a plug of silica covered with celite. The reaction vial and

silica pad were rinsed with additional diethyl ether (10 mL) and the organic layers combined. The solvent was removed in vacuo and the residue purified by using a Biotage Isolera UV-VIS Flash Purification System with prepacked silica cartridges.

General procedure for Pd-RuPhos-catalysed amination: The above procedure for **8** was used with the following exceptions: $[Pd_2(dba)_3]$ (9.2 mg, 2 mol%; dba = dibenzylideneacetone) and the RuPhos ligand (9.3 mg, 4 mol%) were loaded into a reaction vial in a glove box and the vial was sealed with a Teflon-lined screw cap and purged with argon (3×). DME (0.25 mL) was added and the solution was stirred for 10 min to allow the Pd-RuPhos complex to form. From this point forward, all other reaction components were introduced as detailed above for **8** and the reactions were conducted and analysed also as outlined above.

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Keywords: amination · bases · N-heterocyclic carbenes · palladium · synthetic methods

[1] a) *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: E. I. Negishi), Wiley-Interscience, New York, **2002**; b) A. de Meijere and F. Diederich in *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed., Wiley-VCH, Weinheim, **2004**; c) J. F. Hartwig in *Organotransition Metal Chemistry*, University Science Books, California, **2010**.

[2] N. V. Kondratenko, A. A. Kolomeitsev, V. O. Mogilevskaya, N. M. Varlamova, L. M. Yagupol'skii, *J. Org. Chem. USSR.* **1986**, *22*, 1547–1554. Translated from: *Zh. Org. Khim.* **1986**, *22*, 1721–1729.

[3] a) A. S. Guram, R. A. Rennels, S. L. Buchwald, *Angew. Chem.* **1995**, *107*, 1456–1459; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1348–1350; b) J. Louie, J. F. Hartwig, *Tetrahedron Lett.* **1995**, *36*, 3609–3612.

[4] S. Shekhar, P. Ryberg, J. F. Hartwig, J. S. Mathev, D. G. Blackmond, E. R. Strieter, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 3584–3591.

[5] a) L. M. Alcazar-Roman, J. F. Hartwig, *J. Am. Chem. Soc.* **2001**, *123*, 12905–12906; b) S. Shekhar, J. F. Hartwig, *Organometallics* **2007**, *26*, 340–351.

[6] M. G. Organ, G. A. Chass, D.-C. Fang, A. C. Hopkinson, C. Valente, *Synthesis* **2008**, 2776–2797.

[7] For examples of amination using LHMDS, see: a) I. C. Lerma, M. J. Cawley, K. Arentsen, J. S. Scott, S. E. Pearlson, J. Hayler, S. Caddick, *J. Organomet. Chem.* **2005**, *690*, 5841–5848; b) K. W. Anderson, R. E. Tundel, T. Ikawa, R. A. Altman, S. L. Buchwald, *Angew. Chem.* **2006**, *118*, 6673–6677; *Angew. Chem. Int. Ed.* **2006**, *45*, 6523–6527; c) D. Maiti, B. P. Fors, J. L. Henderson, Y Nakamura, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 57–68.

[8] All pK_a values cited in this manuscript were recorded in water and compared directly on that basis.

[9] C. Meyers, B. U. W. Maes, K. T. J. Loones, G. Bal, G. L. F. Lemière, R. A. Dommisse, *J. Org. Chem.* **2004**, *69*, 6010–6017.

[10] K. H. Hoi, S. Çalimsiz, R. D. J. Froese, A. C. Hopkinson, M. G. Organ, *Chem. Eur. J.* **2011**, *17*, 3086–3090, and references therein.

[11] J. R. Martinelli, T. P. Clark, D. A. Watson, R. H. Munday, S. L. Buchwald, *Angew. Chem.* **2007**, *119*, 8612–8615; *Angew. Chem. Int. Ed.* **2007**, *46*, 8460–8463.

[12] C. J. Drummond, F. Grieser, *Biochimica et Biophysics Acta* **1985**, *836*, 275–278.

[13] The calculations were performed by Dr. Jeff Zablocki at Gilead Pharmaceuticals, Inc., Foster City, California.

[14] For other cross-coupling reactions demonstrating the high catalytic performance of Pd-PEPPSI-IPent, see: a) M. G. Organ, S. Calimsiz, M. Sayah, K. H. Hoi, A. J. Lough, *Angew. Chem.* **2009**, *121*, 2419–2423; *Angew. Chem. Int. Ed.* **2009**, *48*, 2383–2387; b) S. Çalimsiz, M. Sayah, D. Mallik, M. G. Organ, *Angew. Chem.* **2010**, *122*, 2058–2061; *Angew. Chem. Int. Ed.* **2010**, *49*, 2014–2017; c) M. Dowlut, D. Mallik, M. G. Organ, *Chem. Eur. J.* **2010**, *16*, 4279–4283; d) C. Valente, M. E. Belowich, N. Hadei, M. G. Organ, *Eur. J. Org. Chem.* **2010**, *23*, 4343–4354.

[15] Pd-PEPPSI-IPent is now commercially available through Sigma–Aldrich (Catalogue Number 732117).

[16] All compounds prepared in this study were evaluated by ^1H and ^{13}C NMR spectroscopy and mass spectrometry. The spectra thus obtained were consistent with spectral data reported in the literature.

[17] 2,2,5,7,8-Pentamethyl-6-chromanoxide is now commercially available through Sigma–Aldrich (Catalogue Number 430676).

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