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P_2Et Phosphazene: A Mild, Functional Group Tolerant Base for Soluble, Room Temperature Pd-Catalyzed C–N, C–O, and C–C Cross-Coupling Reactions

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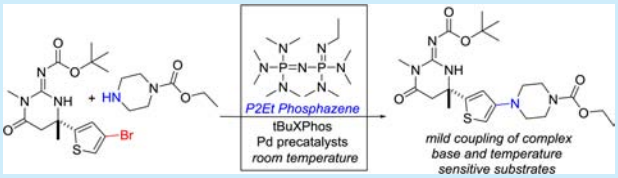
Supporting Information

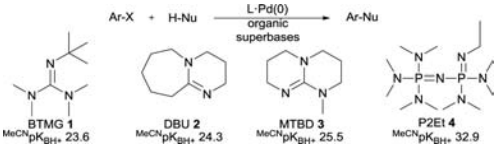
ABSTRACT: The non-nucleophilic organic superbase P_2Et phosphazene can enable a broad range of palladium-catalyzed cross-coupling reactions, including C–C, C–N, and C–O couplings of aryl chlorides, bromides, and iodides at room temperature. The mildness and substrate compatibility of this chemistry can deliver immediate synthetic utility for the preparation of complex molecules.



Over the past two decades, rational mechanism-based evolution of ligand structure has enabled the development of tremendous new reactivity in palladium-catalyzed cross-coupling reactions.[1] This ligand evolution, along with the advancement of palladium precatalyst complexes,[2] has enabled ambient temperature catalysis, greatly improving the reaction tolerance of sensitive functionality on substrates. The alkali metal bases that can promote ambient temperature Pd-couplings, such as NaOtBu and LiHMDS, however, can be incompatible with base-sensitive functionality and can act as nucleophiles themselves in cross-couplings,[3] while weaker inorganic bases such as K_3PO_4, K_2CO_3, and Cs_2CO_3 are insoluble and typically require the use of higher temperatures (>60 °C), which can also lead to substrate decomposition. In principle soluble organic bases could be used in Pd catalysis; however, common amine bases are either not basic enough, can bind and inhibit palladium catalysts,[4] or can decompose under reaction conditions,[5] limiting their use in catalysis.

We reasoned that organic superbases,[6] which can be both strongly basic (reported pK_{BH+} values up to ~47 in MeCN) and highly hindered around their Lewis basic cores, should minimize catalyst inhibition (Scheme 1) resulting in high reactivity and are non-nucleophilic so they may be very substrate tolerant as well. Organic superbases, which are largely unexplored in transition-metal catalysis,[7] are also attractive because they do not form Lewis or Brønsted acidic counterion byproducts, which may lead to undesired side reactions associated with metallic bases. In addition, superbases are soluble in a wide variety of organic solvents and tend to lead to fully solubilized reactions that can have advantages in reproducibility relative to heterogeneous cross-coupling reactions. Finally, organic superbases offer the opportunity to tune steric and electronic properties, an advantage that is absent in current state-of-the-art technologies.

Scheme 1. Organic Superbases in Pd-Catalyzed Cross-Coupling Reactions



We desired to develop homogeneous room temperature Pd-catalyzed reactions in the context of miniaturized nanomole-scale high-throughput experimentation screening.[7d] We therefore elected to evaluate superbases in these reactions over a broad range of Pd-catalyzed reactions. To this end, we studied the Pd-catalyzed cross-coupling of 3-bromopyridine **5**, with seven representative nucleophiles **6**–**12** (1° amine, 2° amine, 1° alcohol, water, 1° amide, malonate, and aryl boronate ester) under 96 different conditions, screening four commercially available organic superbases[8] spanning a range of pK_{BH+} and different steric environments, four Buchwald second or third generation precatalysts,[2] and six solvents. The electrophile 3-bromopyridine **5** was chosen as a model substrate for this work because it is important for new catalytic systems to be able to overcome the problematic reaction inhibition of N-heterocyclic substrates,[9] which are critical in pharmaceutical drug discovery. The results shown in Scheme 2 reveal a matrix of optimal conditions for each nucleophile involving different base–catalyst–solvent combinations.

In general, P_2Et phosphazene[10] **4** showed significantly higher reactivity than the other bases and, in combination with tBuXPhos or tBuBrettPhos G3 precatalysts, showed strong reactivity across all of the diverse nucleophiles examined. In addition to the nucleophiles reported here, these conditions

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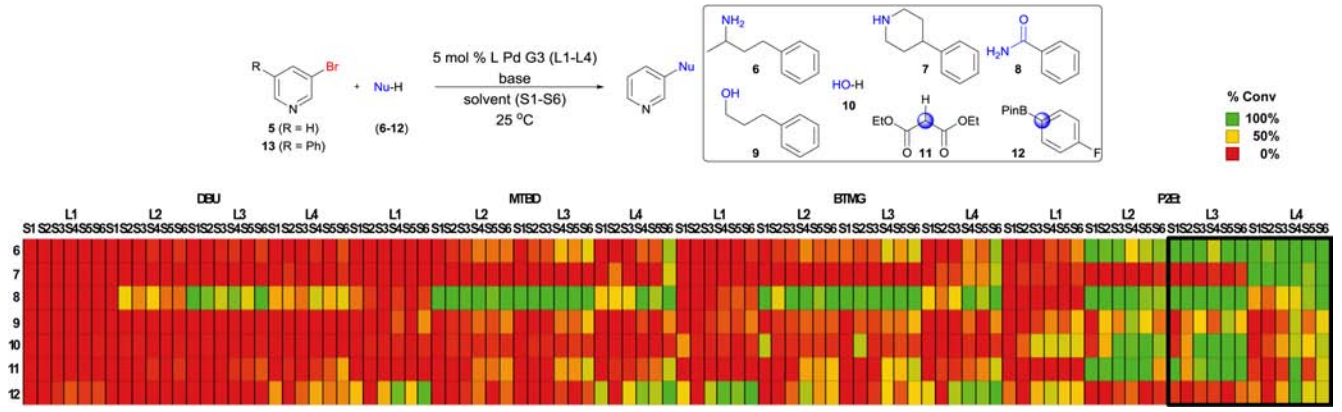
Scheme 2. Nucleophile and Solvent Scope[a]

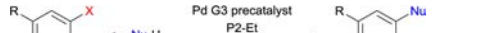


[a]Reaction conditions: L Pd G2 or G3 (Buchwald second/third Generation precatalyst, 0.5 μmol), **5** (10 μmol), **6**−**12** (15 μmol), solvent (0.1 M in **5**), rt, 22 h. L1 was different per nucleophile (**6**, **8**, BrettPhos; 7, RuPhos; **9**, **10** RockPhos; **11**, Ad_2nBuP; **12**, XPhos), L2 = AdBrettPhos, L3 = *t*-BuBrettPhos, L4 = *t*-BuXPhos. S1 = Tol., S2 = CPME, S3 = THF, S4 = *tert*-amyl alcohol, S5 = NMP, S6 = DMSO. Heat map color guide: red, 0−50%; yellow, 50−90%; green, >90−100% conversion.

were also found to couple carbamates, amidines, sulfonamides, and N-heterocycles.[7d] While Pd cross-coupling catalysts are typically optimized to very specific conditions for each new class of nucleophile coupling (catalyst, base, and solvent choices), the observed general reactivity with P_2Et offers an advantage to practitioners. Of additional note was the excellent reactivity of P_2Et across diverse solvents such as the nonpolar solvent toluene, ethereal solvents THF and CPME, polar aprotic solvents DMSO and NMP, and the protic solvent *tert*-amyl alcohol. We next sought to evaluate the relative reactivity of various aryl electrophiles with the P_2Et base (Table 1), investigating the performance of 3-pyridyl bromide, chloride, and iodide with the same seven representative nucleophiles.[11] All of the electrophilic coupling partners gave complete conversion and excellent yields with each nucleophile in either DMSO or *tert*-amyl alcohol, using between 1 and 5 mol % catalyst. The P_2Et system represents the first non-nucleophilic, ambient temperature, soluble coupling conditions for most of the nucleophile couplings reported in this work which should have important implications in complex synthetic settings such as natural products synthesis and drug discovery.[12]

In order to evaluate the functional group tolerability of the P_2Et system, we employed a robustness test approach[13] in which we added equimolar amounts of aryl ester **16** or alkyl ester **17** to a secondary C−N coupling reaction of piperidine **7**, to 3-bromopyridine **5** (Table 2).[14] Successful C−N coupling in the presence of aryl and alkyl esters can be challenging due to competitive side-product formation resulting from Claisen condensations and/or ester amidation, especially in the presence of an inhibiting heterocyclic substrate. Reactions using the strong organometallic bases NaOtBu, LiHMDS, and $Zn(HMDS)_2$ at ambient temperature (and also at 85 °C) gave low conversion to product and pronounced decomposition of the esters to the aforementioned Claisen and amidation side products. As expected, the use of Cs_2CO_3 protected the esters

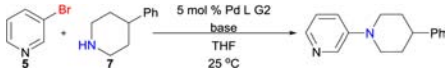
Table 1. Electrophile Scope Scale-up Experiments[a]



entry	Nu-H	yield (% Pd) 5, R = H; 13, R = Ph	14	15
1	6	99% (1%) R = H	95% (1%)[c] R = H	96% (1%)[c] R = H
2	7	87% (5%) R = H	94% (2%)[c] R = H	94% (2%)[c] R = H
3	8	89% (1%)[b] R = H	91% (5%)[b,c] R = H	80% (2%)[c] R = H
4	9	94% (5%)[b,c] R = H	95% (5%)[b,c] R = H	82% (5%)[b,c] R = H
5	10	82% (5%)[b,c] R = Ph	---	---
6	11	92% (1%)[b,c] R = H	90% (5%)[c] R = H	87% (5%)[b,c] R = H
7	12	92% (5%) R = H	93% (5%)[c,d] R = H	100% (5%)[c] R = H

[a]Reaction conditions: tBuXPhos (2, 4, or 10 μmol), **5**, **13**, **14**, **15** (200 μmol), **6**−**12** (300 μmol), P_2-Et (400 μmol), DMSO (0.2 M in **5**), rt, 22 h.. [b]tBuBrettPhos Pd G3 used instead of tBuXPhos. [c]*tert*-Amyl alcohol. [d]MTBD. Reported yields were determined by ^1H NMR analysis. See Supporting Information for details.

Table 2. Amine Coupling Ester Robustness Test[a]



entry	ester	base	% ay	% ester
1	16	NaOtBu	9%	22%
2		LiHMDS	11%	13%
3		$Zn(HMDS)_2$	17%	36%
4		Cs_2CO_3*	41%	> 99%
5		**P2Et**	**97%**	**> 99%**
6	17	NaOtBu	9%	13%
7		LiHMDS	12%	0%
8		$Zn(HMDS)_2$	13%	24%
9		Cs_2CO_3*	42%	> 99%
10		**P2Et**	**89%**	**> 99%**

[a]Reaction conditions: RuPhos Pd G2 for all reactions except entries 5 and 10, where used tBuXPhos Pd G3, and entries 3 and 8, which used tBu_3P Pd G2 (1 μmol), **5** (20 μmol), **6**−**12** (30 μmol), **16**−**17** (20 μmol), P_2Et (40 μmol), THF (0.2 M in **5**), rt, 22 h. *Reaction run at 85 °C.

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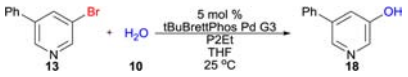
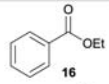
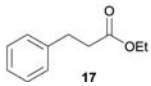
from side reactions, but at the expense of lower conversion even at 85 °C. By contrast, P_2Et afforded complete conversion and excellent yields in the C−N coupling at room temperature, and the esters were largely untouched.[15] We next evaluated the prospect that the P_2Et system would be mild enough to hydroxylate the heteroaryl bromide **13** in the presence of alkyl and aryl esters.[16] Indeed we were able to cleanly form the desired hydroxypyridine **18** without touching the esters (Table 3).

Table 3. Water Coupling Ester Robustness Test[a]



entry	ester	base	yield	% ester
1	 16	P2Et	87%	> 99%
2	 17	P2Et	92%	96%

[a]Reaction conditions: tBuBrettPhos Pd G3 (5 μmol), **13** (100 μmol), **10** (150 μmol), **16**−**17** (100 μmol), P_2Et (200 μmol), THF (0.2 M in **5**), rt, 22 h.

Encouraged by these results, we evaluated the application of our system toward a complex pharmaceutically relevant target, which we had previously observed to be base sensitive.[17] A comparative study with the conditions that were used in Table 3 was undertaken for the coupling of densely functionalized heteroaryl bromide **19** with the base-sensitive piperazine **20** and is presented in Figure 1.

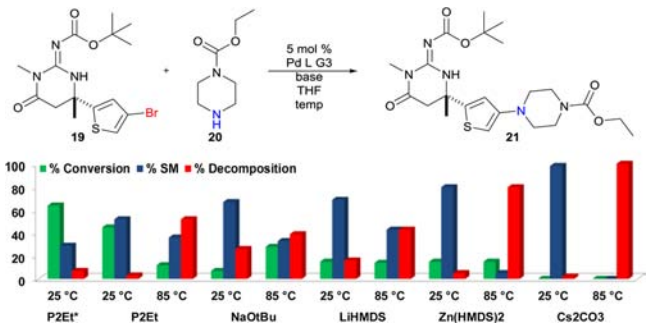


Figure 1. Complex aryl halide Pd C−N arylation. Reaction conditions: Reactions used RuPhos Pd G2 (for LiHMDS/NaOtBu), tBu_3P Pd G2 (for $Zn(HMDS)_2$) and tBuXPhos Pd G3 (for P_2Et). Aryl bromide **19** (5 μmol), amine **20** (7.5 μmol), base (10 μmol), 16 h. Percentages are based on liquid chromatography analysis of crude reactions. *10 mol % tBuXPhos Pd G3, P_2Et (15 μmol) gave a 67% isolated yield of **21** on 200 μmol scale.

The use of P_2Et as a base in this reaction at ambient temperature resulted in superior reactivity and functional group tolerance when compared to other methods. This study also highlights the negative impact that heating can have on complex substrates. For instance, the use of Cs_2CO_3 at 85 °C led to complete substrate decomposition and no product formation.

In order to better understand the remarkable reactivity conferred by P_2Et phosphazene, we compared the initial kinetic profiles of reactions moderated by P_2Et relative to other organic superbases in a Pd C−N arylation reaction (Figure 2).

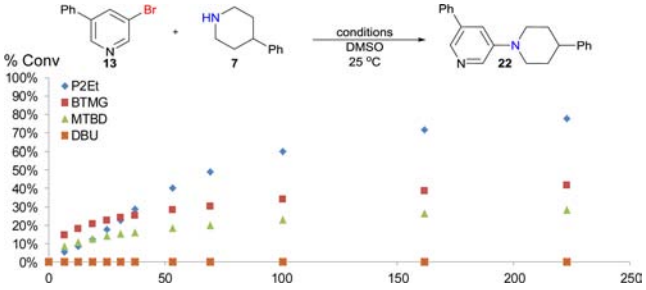


Figure 2. Reaction rates of Pd C−N arylations. Reaction conditions: *t*-BuXPhos Pd G3 (5 mol %), 3-bromo-5-phenylpyridine (**13**, 400 μmol), 4-phenylpiperidine (**7**, 600 μmol), base (**1**−**4**, 800 μmol), DMSO (0.2 M in **13**), rt.

Our initial reaction screening (Scheme 2) showed that BTMG, MTBD, and P_2Et were competent bases to promote effective C−N coupling while DBU was unreactive. In this kinetic profiling, however, MTBD and BTMG both show a significantly slower reaction course relative to P_2Et. This observed behavior of DBU, BTMG, and MTBD is consistent with Lewis basic catalyst inhibition, recently attributed through DFT calculations to the formation of highly stable prereductive elimination complexes in which both the phosphine ligand and Lewis base are coordinated to Pd.[4] It is possible that P_2Et, when presented with a suitably hindered Pd-phosphine complex, may not inhibit catalysis because of a high level of steric congestion which would result from its binding to the catalyst. The fact that BrettPhos and RuPhos, which have been demonstrated for room temperature C−N couplings with strong metal bases,[18] do not work at all with P_2Et as the base provides further evidence for this hypothesis. These ligands bear dicyclohexylphosphines, while the catalysts that are effective with P_2Et feature di-*tert*-butyl or diadamantyl phosphines. These results strongly suggest that there is a certain threshold of steric congestion on the phosphine which can prevent catalyst inhibition by P_2Et. However, effects related to phosphine electron density cannot be dismissed at this point in our study.

In conclusion, organic superbases can enable a broad reaction scope of electro- and nucleophiles in Pd-catalyzed cross-coupling reactions. The P_2Et system was found to have distinct reactivity across a diverse set of reactions at room temperature in a variety of solvents. Importantly, in contrast to previously reported methods, this system is highly tolerant of base sensitive functional groups as demonstrated via a robustness test with esters and by C−N arylation of a densely functionalized substrate. Organic superbases offer an alternative variable for design in this important class of reactions to combine with ligand design and development. The relationship between the base's pK_{BH+} and steric parameters opens a new avenue for potential tunability of the base structure, enabling substrate-specific reactivity and expanded use in other transition-metal catalyzed reactions. Studies aimed at increasing understanding of the high reactivity of organic superbases and optimizing their structures are ongoing.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01648.

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Notes

The authors declare no competing financial interest.

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(11) 5-Phenyl-3-bromopyridine **13** was used in place of **5** for the water couplings because the product was easier to quantify by UPLC analysis. Also, the aryl chloride and aryl iodide variants of **13** are not commercially available and were not interrogated.

(12) P_2Et Phosphazene has been minimally used in transition metal catalysis, likely due to the current expense of this base. For many complex, sensitive synthetic targets in drug discovery or natural products synthesis, the cost of the reaction substrate prepared through multistep synthesis is much higher than this base cost.

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(18) The couplings of amines **6** (with Brettphos Pd G3) and **7** (with RuPhos Pd G2) with bromide **13** have not been reported in the literature at room temperature, so we independently verified that LiHMDS is indeed capable of coupling these nucleophiles at rt (5% catalyst, THF, 1.5 equiv of nucleophile, 2 equiv of base, 18 h).

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