

A Strategy for the Controllable Generation of Organic Superbases from Benchtop-Stable Salts

Stephen J. Sujansky[†], Garrett A. Hoteling[†], and Jeffrey S. Bandar^{*[a]}

Organic superbases are a distinct class of strong base that enable numerous modern reaction applications. However, despite their great synthetic potential, widespread use and study of superbases are limited by their air sensitivity and difficult preparation. To address this, we report air-stable carboxylate salts of BTTP and P₂-*t*-Bu phosphazene superbases that, when added to solution with an epoxide, spontaneously generate freebase. These systems function as effective precatalysts and stoichiometric preagents for superbase-promoted addition, substitution and polymerization reactions. In addition to improving the synthesis, shelf stability, handling and recycling of phosphazenes, this approach enables precise regulation of the rate of base generation *in situ*. The activation strategy effectively mimics manual slow addition techniques, allowing for control over a reaction's rate or induction period and improvement of reactions that require strong base but are also sensitive to its presence, such as Pd-catalyzed coupling reactions.

Introduction

Brønsted bases are indispensable tools in synthetic chemistry. For a given application, the exact choice of base can be of critical importance as its properties often dictate reaction outcomes.¹ Organic superbases are a valuable class of base that enable unique applications over more common metal-containing bases (Figure 1, top).² Defined as neutral organic compounds with basicity greater than Proton-sponge[®] ($pK_{a'} = 18.6$ in MeCN), superbases are distinguished by their high solubility in organic media, low nucleophilicity and the formation of conjugate acid ion pairs upon substrate deprotonation.³⁻⁵ These properties are frequently leveraged in the discovery of new base-promoted and -catalyzed reactions.^{2,6} Superbases also enable advances in other areas of methods development, such as cross-coupling and photoredox methodology and in high throughput experimentation technologies.⁷ However, as with all strong bases, organic superbases are high energy compounds that are unstable under ambient conditions, a significant limitation that hinders their wider use and study.⁸ To address this challenge, we herein exploit the unique ion pairing properties of organic superbases to establish a new and improved means for their use. We disclose air-stable superbase salts and additives that, once added to solution, controllably generate the freebase without the use of a separate strong base (Figure 1, bottom). This process functions as a practical superbase precatalyst system and also provides a new way to regulate base introduction to a solution.

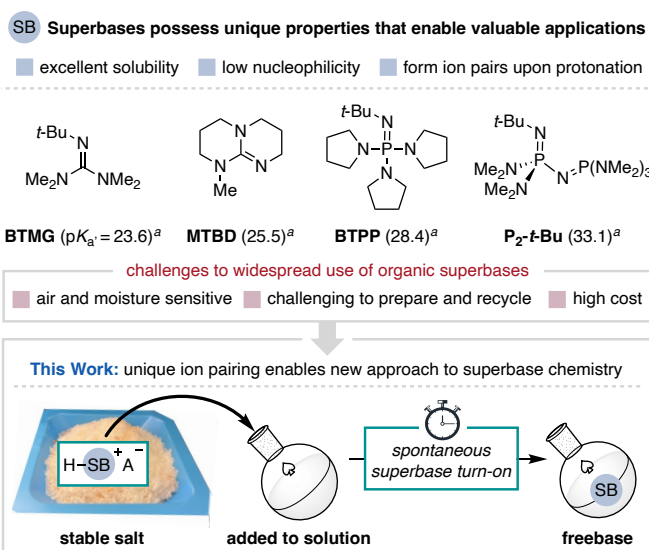


Figure 1. Organic superbases and a new approach to accessing superbases from precatalyst salts. ^a Reported $pK_{a'}$ values in MeCN.¹³

Organic superbases form stable salts when combined with a strong acid, a fundamental contrast to commonly used anionic bases that form neutral conjugate acids (Figure 2, top). Stable superbase salts are most commonly comprised of very weakly basic counteranions (e.g., BF_4^-) and their neutralization requires the use of a separate strong base.⁹ We reasoned, however, that the counteranion of a superbase salt could be a functional component of a design strategy for the controllable generation of freebase in solution. By definition, the counteranion of any stable salt is incapable of directly neutralizing the conjugate acid. Therefore, the key to spontaneous *in situ* activation of such a system is to implement a mechanism by which a weakly basic anion can facilitate superbase generation. This capability has been previously achieved within photocaged base technology wherein light-promoted counteranion decomposition leads to freebase formation.¹⁰ This approach, however, has thus far only been used for photocuring applications and has not been applied towards more traditional synthetic chemistry.¹¹

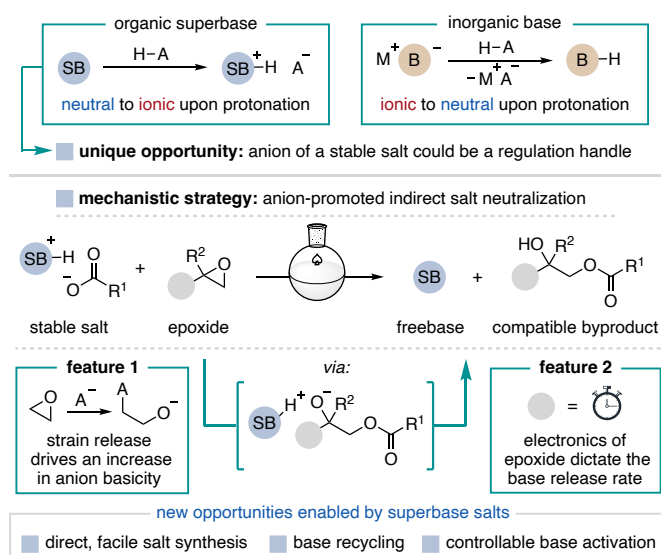


Figure 2. Mechanistic design for superbase precatalyst system.

Herein, we describe a new strategy for the thermal generation of superbases from stable carboxylate salts in the presence of epoxides (Figure 2, bottom). When in solution, the carboxylate ($\text{p}K_{\text{a}} \sim 24$ in MeCN) opens the epoxide, thereby harnessing potential energy (i.e., epoxide ring strain) to create a strongly basic alkoxide intermediate ($\text{p}K_{\text{a}} \sim 43$ in MeCN) that deprotonates the superbase conjugate acid.^[12,13] In principle, the epoxide can be stored independently for easy variation, premixed with the salt for convenience or incorporated into the counteranion structure, so long as activation takes place only in solution. This modular design allows for the carboxylate or epoxide to be adjusted to achieve desired physical properties and reactivity, including the rate of epoxide opening to control the speed of base generation. Importantly, the activation process generates tertiary alcohol byproducts that are compatible with most superbase applications.

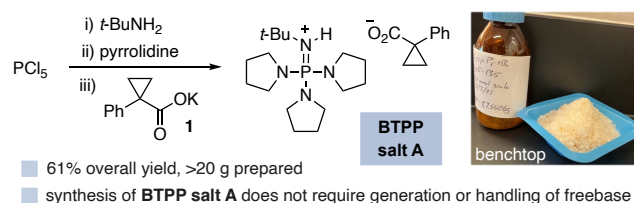
The initial motivation for this work was to address key challenges associated with conducting superbase chemistry. Although superbase hydrochloride salts are readily prepared from commodity chemicals, their neutralization often involves nontrivial procedures such as distillation, air-free purification or the use of hazardous bases.^{14,15} The resulting freebases are air sensitive and typically stored and handled in an inert atmosphere glovebox, resulting in limited convenience and long-term fidelity, as well as high cost.¹⁶ In total, these concerns can stifle the translation of innovative breakthroughs made in discovery settings into more widely used chemistry.¹⁷ In this report, we focus on BTTP and P_2 -*t*-Bu phosphazenes as they are commercially available and among the most commonly used superbases for reaction discovery and methods development. The use of superbase carboxylate salts with this new activation method addresses the aforementioned challenges as the salts can be prepared without the need to access the freebase and can be stored, handled and recycled under ambient conditions (Figure 2, bottom).

Results and Discussion

BTTP Salt Development and Application

BTTP freebase irreversibly reacts with atmospheric CO_2 to form a phosphoramidate, thus necessitating storage and use under inert atmosphere.⁸ This deleterious process also rules out the use of a decarboxylative strategy for superbase salt activation. We therefore sought to identify a stable BTTP salt and effective activation system to overcome these challenges. Superbase carboxylate salts were targeted given that they can be stable salts while still possessing nucleophilic counteranions, as opposed to more commonly isolated salts comprised of nonnucleophilic counteranions (e.g., BF_4^-). After investigating various carboxylates, BTTP salt **A** was identified as a shelf-stable crystalline solid (Figure 3a). BTTP salt **A** is accessible in scalable quantities *via* a one-pot process from PCl_5 , *t*- BuNH_2 and pyrrolidine, followed by anion metathesis with potassium carboxylate salt **1** (Figure 3a, >20 g prepared).

(a) Direct synthesis of a stable BTTP superbase salt on 75 mmol scale



(b) Activation studies of BTTP salt **A** in the presence of epoxides^a

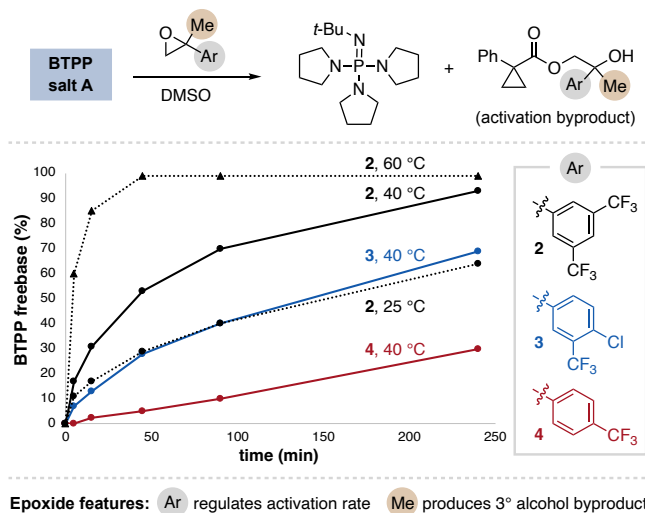


Figure 3. Synthesis and activation of BTTP salt **A**. ^a Activation studies run with 1 equiv BTTP salt **A** and 2 equiv epoxide; all conditions ultimately reach near-complete BTTP generation. See SI for details on data collection and analysis.

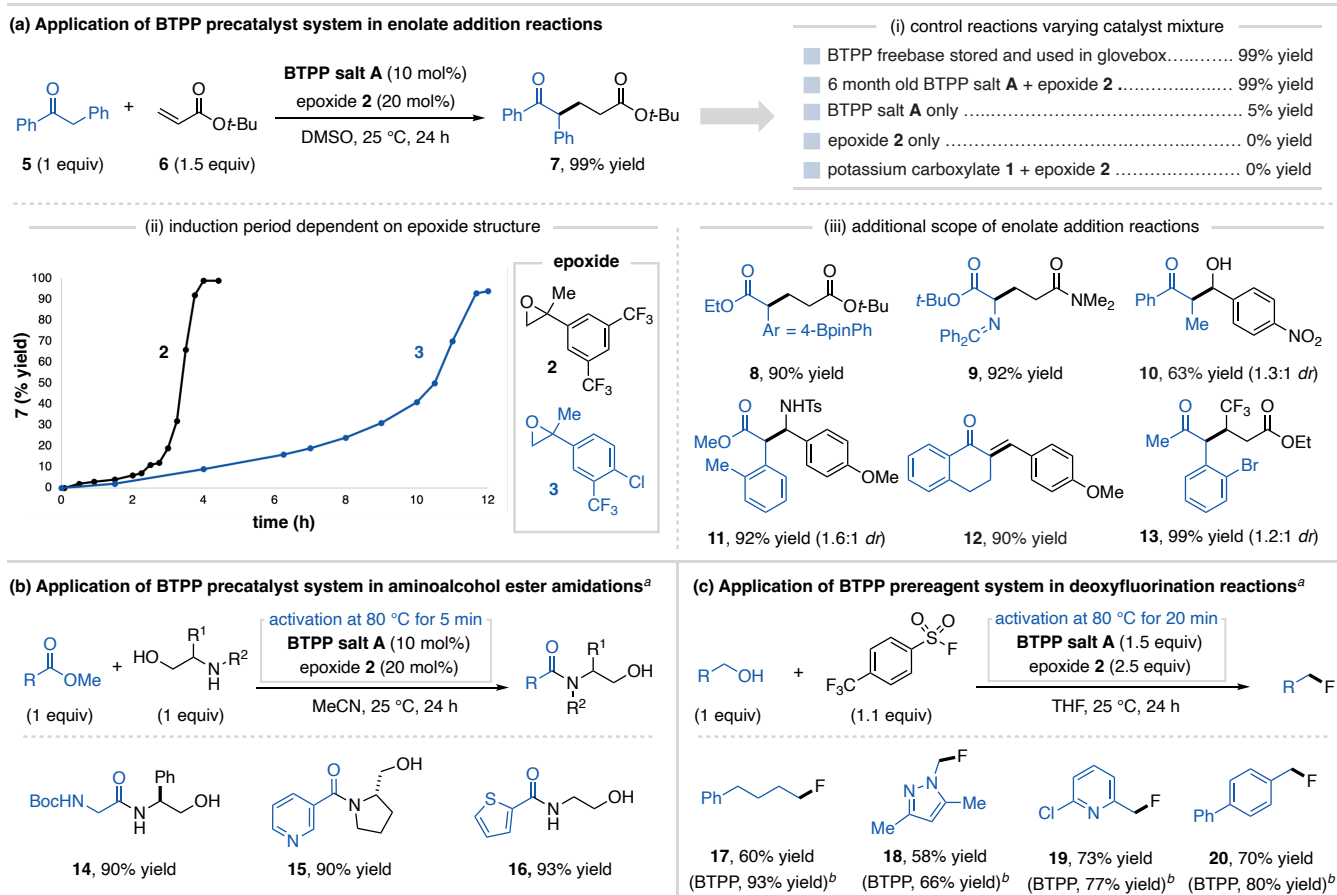


Figure 4. Use of BTTP salt **A** in catalytic and stoichiometric applications. Yields determined by ^1H NMR spectroscopy. ^a Preactivation procedure conducted in DMSO for 4b and THF for 4c. ^b Yields of reactions with commercial BTTP in a N_2 -filled glovebox for comparison.

We next studied the generation of freebase from BTTP salt **A** when mixed with epoxides in solution. We found that aryl-substituted epoxides readily facilitate BTTP generation, as tracked by ^{31}P and ^1H NMR spectroscopy to observe the freebase and activation byproduct, respectively. The activation curves for electronically-differentiated epoxides **2-4** show that the rate of BTTP formation directly correlates with epoxide electrophilicity (Figure 3b). The activation rate is also dependent on the solvent identity, temperature and concentration, with full details in the Supplementary Information. Thus, BTTP salt **A** activation occurs under a variety of conditions, which provides flexibility for its use in synthetic applications.

The successful activation of BTTP salt **A** with epoxides allows this system to function as a precatalyst for superbase-promoted reactions. All reaction applications of the superbase salts in this Article were conducted outside of a glovebox with the use of a Schlenk line. To demonstrate this capability, we selected the Michael addition between deoxybenzoin (**5**) and *tert*-butyl acrylate (**6**) as a model reaction.¹⁸ The combination of BTTP salt **A** and epoxide **2** promotes this reaction in a similar high yield as commercial BTTP that is stored and handled in an inert atmosphere glovebox (Figure 4ai). Consistent with a precatalyst activation process, reaction profiles for the Michael reaction show an induction period that reflects the electrophilicity of the epoxide activator used (Figure 4a(ii)). Further control

experiments show that neither BTTP salt **A** nor epoxides on their own promote this reaction (Figure 4ai). The fact that the combination of potassium carboxylate **1** with epoxide **2** also does not promote this reaction indicates BTTP is a necessary component of the precatalyst system.¹² Additional Michael, aldol and Mannich products are shown in Figure 4a(iii) to demonstrate the precatalyst system's generality (substrates **8-13**). Finally, we note that BTTP salt **A** was regularly handled open-to-air for six months, after which it remained equally effective at promoting these reactions.

We found that direct use of the precatalyst system was not equally as effective as commercial BTTP freebase for certain applications. For example, in the ester amidation reaction in Figure 4b, the aminoalcohol undergoes a competitive side reaction with the epoxide that inhibits BTTP activation.¹⁹ To address this, a five-minute preactivation process (stirring BTTP salt **A** and epoxide **2** at 80 $^\circ\text{C}$ in DMSO) generates a solution of freebase for use in catalytic ester amidation reactions (**14-16**).

BTTP salt **A** and epoxide **2** can also be used in stoichiometric quantities as a prereagent system, a more demanding application that requires full generation of freebase. We studied this utility in the context of a BTTP-promoted deoxyfluorination method developed by the Doyle Group (Figure 4c).²⁰ This reaction was selected as a challenging test for the prereagent system, as the sulfonyl fluoride reagent can potentially react with the carboxylate of BTTP salt **A** or the

activation byproduct. Using a preactivation procedure, the prereagent system provides alkyl fluorides (**17-20**) in good yields, albeit slightly lower than use of commercial BTTP. The tertiary alcohol activation byproduct does not undergo deoxyfluorination, demonstrating its compatibility in superbase-promoted alcohol functionalization reactions.

P₂-t-Bu Salt Development and Application

We next sought to develop salt systems for the stronger P₂-t-Bu base, which is typically sold as a solution in THF under inert atmosphere as its pure, solid form rapidly absorbs ambient moisture.²¹ Slight modification of the carboxylate counteranion provided stable, crystalline P₂-t-Bu salt **A** (Figure 5a). However, activation of this salt with aryl-substituted epoxides (**2** and **21**) is reversible, with only 50% freebase generated at equilibrium (Figure 5b), as confirmed by running the activation process in reverse. We reasoned this equilibrium effect is due to the greater thermodynamic challenge of generating P₂-t-Bu as compared to BTTP. To address this, we found dialkyl-substituted epoxides provide a greater driving force for freebase generation, including spirocyclic epoxide **22** that produces >90% P₂-t-Bu at equilibrium.²² We also identified epoxide **23** that, although only generates 75% freebase at equilibrium, can be stored together with P₂-t-Bu salt **A** to serve as a premixed, all-in-one precatalyst system.²³ Additional activation studies for P₂-t-Bu salt **A** are described in the Supplementary Information.

The P₂-t-Bu precatalyst system was first investigated for the promotion of oxa-Michael addition reactions. This application was selected as such reactions are reversible and require strong, non-coordinating bases that operate in nonpolar media

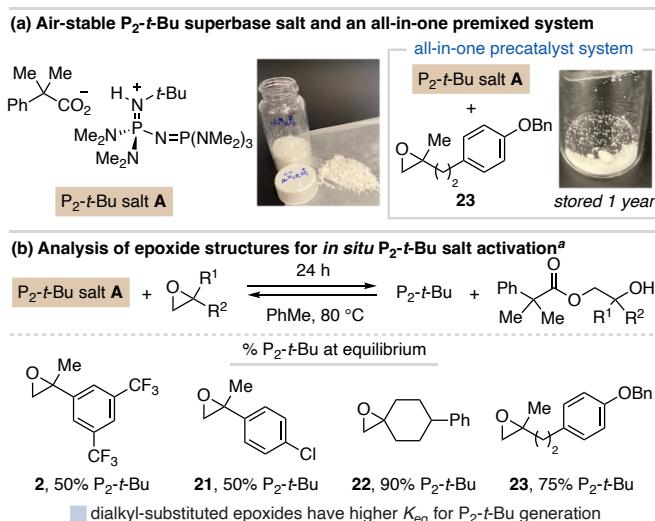
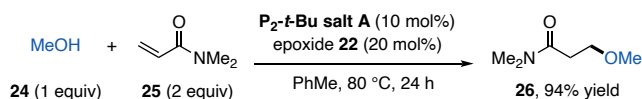


Figure 5. Identification and activation studies of P₂-t-Bu salt **A**. Photos taken on the benchtop. ^a Activation with 1 equiv P₂-t-Bu salt **A** and 2 equiv epoxide, assessed by ³¹P NMR spectroscopy.

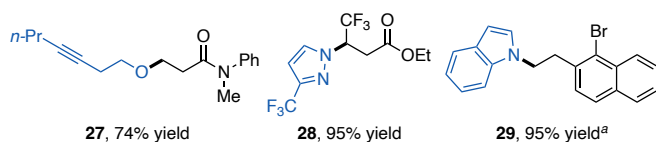
for high yields, making superbases ideal catalysts.²⁴ The simple addition of P₂-t-Bu salt **A** and epoxide **22** to a solution of methanol (**24**) and *N,N*-dimethylacrylamide (**25**) leads to a high-yielding oxa-Michael reaction, similar to the use of commercial P₂-t-Bu in a glovebox (Figure 6a). Notably, use of the all-in-one precatalyst (P₂-t-Bu salt **A** and epoxide **23** stored together) or six-month-old P₂-t-Bu salt **A** also provide high yield. Consistent with P₂-t-Bu serving as the active catalyst, control studies show that neither P₂-t-Bu salt **A** or epoxide **22** catalyze the reaction on their own (Figure 6ai). The P₂-t-Bu precatalyst system is general, as shown by an oxa-Michael reaction with an alkynol

(a) Application of P₂-t-Bu precatalyst system in oxa-/aza-Michael additions

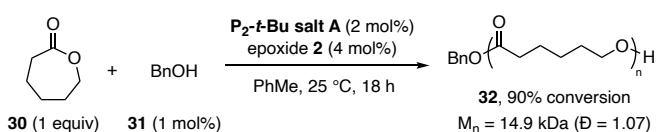


- (i) control reactions varying catalyst mixture
- P₂-t-Bu freebase stored and used in glovebox..... 93% yield
 - 6 month old P₂-t-Bu salt **A** + epoxide **22** 90% yield
 - all-in-one precatalyst (premixed salt **A** + **23**)..... 90% yield
 - P₂-t-Bu salt **A** only 0% yield
 - epoxide **22** only 0% yield
 - potassium carboxylate **1** + epoxide **22** 0% yield

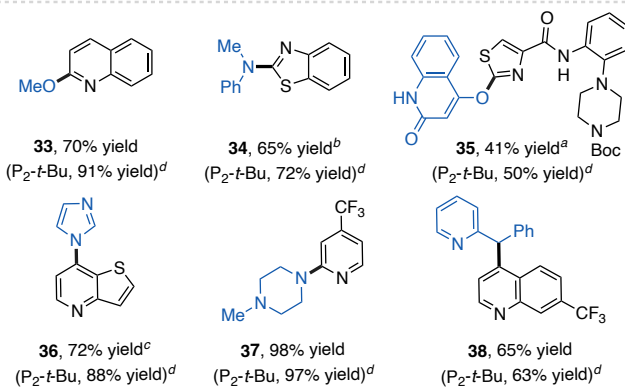
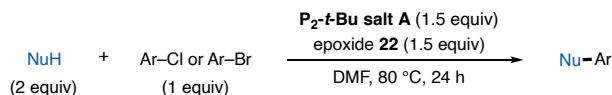
(ii) additional oxa-/aza-Michael addition reactions



(b) Use of P₂-t-Bu precatalyst system in ϵ -caprolactone polymerization



(c) Application of P₂-t-Bu prereagent system in S_NAr reactions



(d) Application of P₂-t-Bu prereagent system in enolate-type alkylation

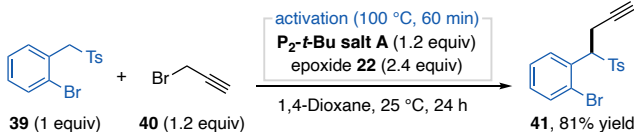


Figure 6. Use of P₂-t-Bu salt **A** in catalytic and stoichiometric reaction applications. Yields determined by ¹H NMR spectroscopy. ^a Reaction run in DMSO. ^b Reaction run in THF. ^c Preactivation at 100 °C for 1 h in PhMe. ^d Yields of reactions setup using commercial P₂-t-Bu in a nitrogen-filled glovebox are provided for comparison.

(27) and related hydroamination reactions between *N*-heterocycles and polarized alkenes (28 and 29, Figure 6aii).²⁵

Beyond small molecule synthetic applications, phosphazene bases are also valued as organocatalysts for controlled anionic polymerization reactions.²⁶ As these reactions are typically conducted at or near room temperature (rt), we used aryl-substituted epoxides that partially activate P₂-*t*-Bu salt **A** at low temperature for polymerization.²⁷ Thus, catalytic P₂-*t*-Bu salt **A** and epoxide **2** promote the polymerization of ϵ -caprolactone (30) with benzyl alcohol (31) initiator to 90% conversion (32, M_n = 14.9 kDa, Đ = 1.07, Figure 6b).²⁸

We next used P₂-*t*-Bu salt **A** and epoxide **22** as a prereagent system for nucleophilic aromatic substitution (S_NAr) reactions. This represents an emerging application of P₂-superbases as they have been shown in high throughput experimentation (HTE) to act as mild bases and uniquely enable challenging S_NAr reactions.²⁹ The prereagent system promotes S_NAr for a broad range of *O*-, *N*-, and *C*-based pronucleophiles (33–38, Figure 6c) with yields typically similar to direct use of commercial P₂-*t*-Bu. We note that a 1 h preactivation procedure is required for substrate **36** as imidazole reacts with epoxide **22**, precluding an effective single addition protocol. A separate stoichiometric application is shown in Figure 6d, where preactivated P₂-*t*-Bu salt **A** promotes the alkylation of benzyl sulfone **39** in 81% yield.³⁰ A preactivation protocol was used as this reaction takes place at 25 °C whereas elevated temperature is required for full P₂-*t*-Bu generation using epoxide **22**.

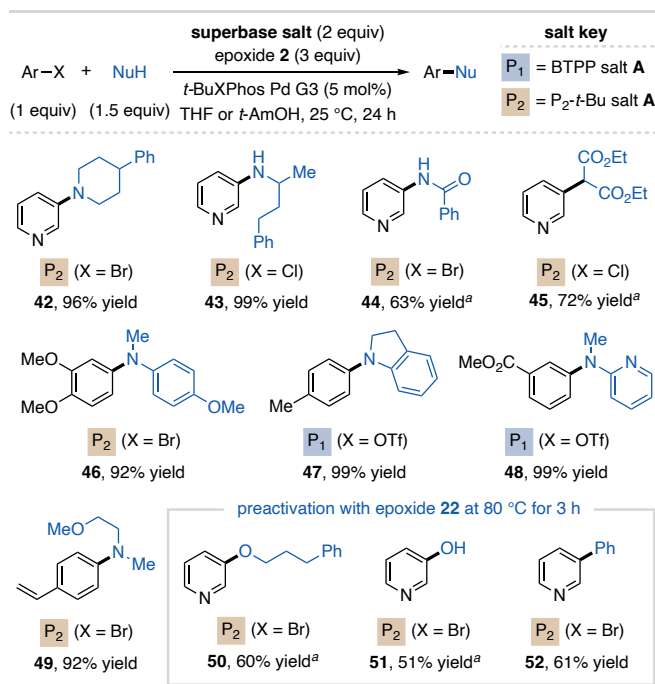


Figure 7. Use of superbase prereagents in Pd-catalyzed cross-coupling reactions. Yields determined by ¹H NMR spectroscopy. ^a *t*-BuBrettPhos Pd G3 (5 mol%) used as catalyst.

Organic superbases also find utility in advanced applications of metal-catalyzed cross-coupling as they provide homogeneous reaction conditions, can enhance functional group tolerance and enable HTE for reaction screening.³¹ In this regard, scientists at

Merck reported the advantages of P₂-Et within Pd-catalyzed coupling reactions, which inspired us to apply the salt systems as prereagents for such methods.³² As shown in Figure 7, superbase carboxylate salts and epoxide **2** added directly to standard Pd catalysis reaction conditions enable high-yielding amination of aryl halides and triflates (42–49). The P₂-*t*-Bu prereagent system is optimal for alkyl amines, while the BTTP system can be used for more acidic aniline partners. Here, epoxide **2** is used for both bases as it activates the salts at 25 °C as compared to epoxide **22**, a process driven to completion by consumption of the base in the coupling reaction. However, C–O (**50** and **51**) and Suzuki couplings (**52**, with water as an additive) require superbase preactivation with epoxide **22** as *O*-pronucleophiles can react with epoxide **2** and prevent superbase activation when all reagents are mixed simultaneously.

Unique Opportunities of Superbase Salt Systems

The phosphazene salt activation systems provide several new opportunities compared to the manner in which strong base-promoted chemistry is typically conducted. First, salt synthesis and employment does not require a discrete neutralization step or handling of freebase. This was illustrated in the 75 mmol scale synthesis of BTTP salt **A** in Figure 3a. This feature also enables recycling of the superbase salts, wherein the recovery of superbase hydrochloride salts from crude reaction mixtures, followed by anion metathesis, effectively regenerates the superbase carboxylate salts. Recovery is especially desirable in stoichiometric applications, as illustrated in Figure 8a by a Pd-catalyzed amination reaction that used 1.1 g of P₂-*t*-salt **A** that was regenerated in 71% yield.

A second feature of the salt system is that, once added to solution, the epoxide identity controls the rate of base generation. This effectively mimics the physical act of freebase addition to a reaction vessel that is traditionally achieved manually or by a syringe pump.³³ Thus, one could view the epoxide component as a modular “timer” that can be adjusted through substituent modification, with more electrophilic epoxides generating base faster. We first observed this effect in the model Michael reaction for BTTP salt **A**, wherein the induction period onset is dictated by epoxide electrophilicity (Figure 4aii). A similar correlation is observed for the rates of Pd-catalyzed coupling reactions of bromobenzene (**56**) and morpholine (**54**) that uses P₂-*t*-Bu salt **A** with various epoxides (Figure 8b).³⁴ We anticipate this strategy could serve as a general way to regulate onset times, rates and potential exotherms of base-promoted reactions.³⁵

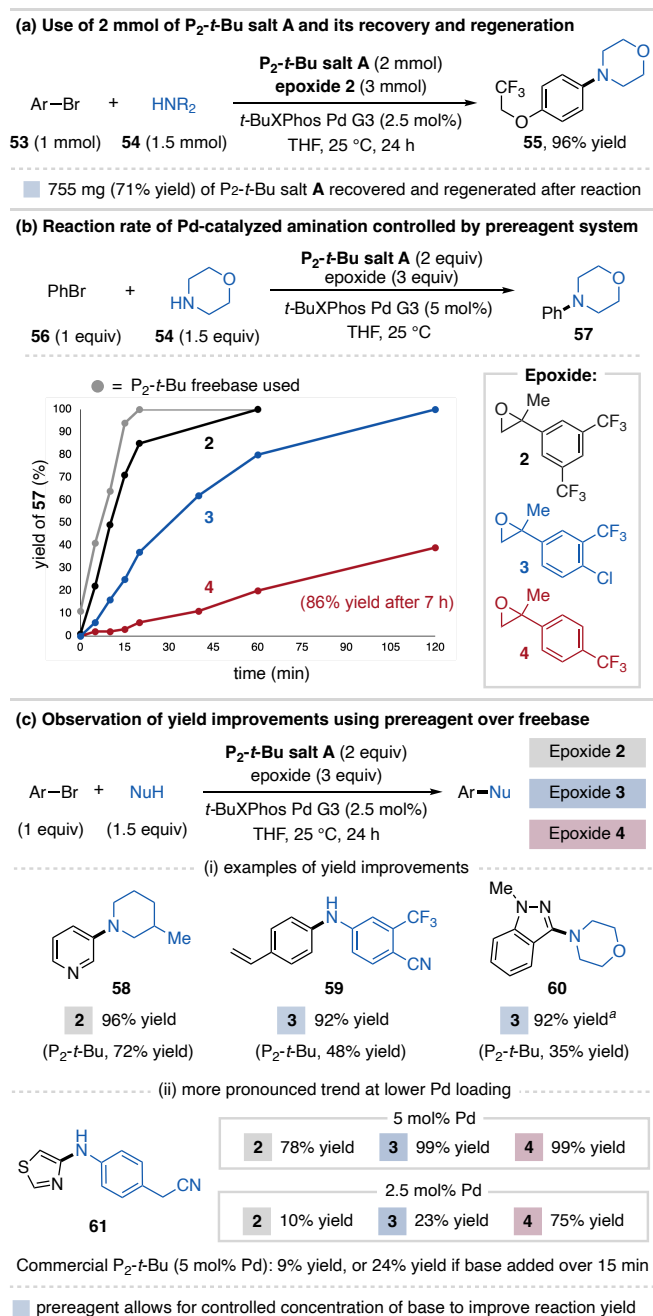


Figure 8. Recovery of superbase salts and use of rate-controlled base generation in Pd-catalyzed amination reactions. Yields determined by ¹H NMR spectroscopy. ^a 5 mol% Pd used.

While investigating Pd-catalyzed amination reactions, we noticed use of the P₂-t-Bu prereagent system often provides higher yields than the commercial freebase, with examples in Figure 8c (**58-60**). Despite their necessity for reaction promotion, strong bases can be detrimental to Pd catalysis due to competitive catalyst binding or undesired side reactions with catalytic intermediates and base-sensitive functional groups.³⁶ Prior work has shown the advantage of slow base addition for Pd-catalyzed amination reactions³³ and, in a similar sense, we speculate the yield improvements of the prereagent system are due to the epoxide opening process that governs base concentration *in situ*. This proposal was examined using

substrate **61**, where use of P₂-t-Bu freebase provides only 9% yield using 5 mol% Pd catalyst. Control studies indicate the amine and aryl halide lose mass balance when mixed solely with stoichiometric P₂-t-Bu, and that the Pd-catalyzed coupling yield increases to 24% when P₂-t-Bu is added manually over 15 minutes. Use of P₂-t-Bu salt **A** with epoxides **2**, **3** and **4** provides increased yields of 78-99%. The yields are inversely correlated with epoxides electrophilicity, a trend that is amplified when the Pd catalyst loading is decreased to 2.5 mol%. Together, these results illustrate how the prereagent system provides a new approach to improving reactions that require strong base but are also sensitive to its presence.³⁷

Improved Superbase Salt Stability

Throughout our studies, BTPP salt **A** and P₂-t-Bu salt **A** remained unchanged over six months during which time they were handled regularly open to air and stored in a benchtop desiccator while not in use.³⁸ However, upon exposure to >60% humidity, the salts begin to absorb moisture and can become difficult to handle. This effect is exacerbated at higher humidity (80-90%) where the salts turn into oil hydrates. If this occurs, a toluene azeotrope restoration process *via* rotary evaporation can regenerate the anhydrous salts, as demonstrated in Figure 9a for BTPP salt **A**. This restoration procedure exploits the fact that the hygroscopic nature of the carboxylate salts differs from freebase decomposition, as neutral phosphazenes react with CO₂ or absorb water and are impossible or challenging to restore, respectively.^{8,14,15b} A second approach we took to address salt hygroscopicity was to alter the carboxylate counteranion. To this end, we found BTPP salt **B** and P₂-t-Bu salt **B** to be substantially less hygroscopic, with no change stored in glass vials open to 84% humidity for 24 h. Additionally, while spread out across weighing paper (a more moisture-sensitive state), the new BTPP and P₂-t-Bu salts maintain crystallinity for 8 and 24 hours on weighing paper in 84% humidity, respectively. These more stable salts perform equally well in reaction applications compared to the original superbase carboxylate salts (details in the Supplementary Information). Storage of the superbase salts in a desiccator or freezer while not in use is recommended.

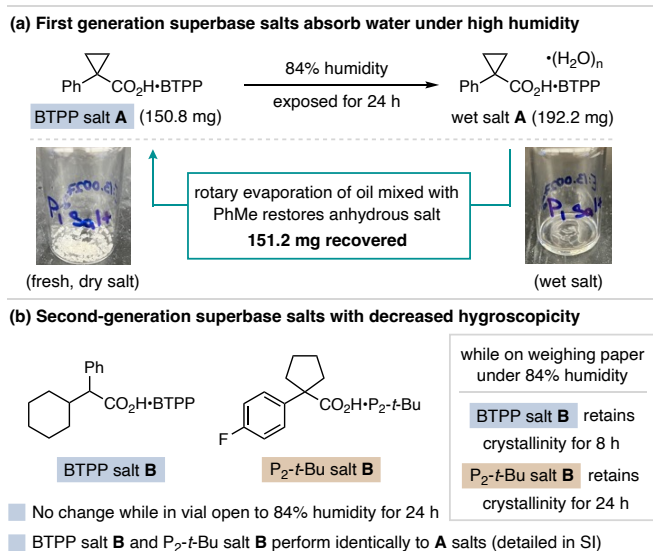


Figure 9. Moisture sensitivity of superbase salts and solutions to address this issue.

Conclusions

In summary, the strategy presented here provides access to organic superbases from benchtop-stable carboxylate salts. These salts, with epoxide additives, are effective precatalysts and preagents for BTPP and P₂-t-Bu using standard Schlenk manifold protocols. The salts are easy to prepare, recyclable and can be regularly handled open to air. We described several scenarios where a preactivation procedure is required to illustrate potential challenges that may be encountered and how they can be addressed when using these salts. Improved activation systems are currently under development, including for the stronger P₄-t-Bu superbase.^[4a,39] The precatalyst systems have the potential to accelerate the discovery of new superbases, superbase-promoted applications and their use by a wider community. More broadly, the mechanistic ability to regulate superbase introduction to solutions presents a myriad of possibilities for improving or manipulating base-promoted reactivity, a prospect that we are currently pursuing in numerous contexts.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Research reported in this publication was supported by the National Science Foundation under Grant No. CHE-1944478. We thank Professor Yiming Wang and Mr. Austin Durham (University of Pittsburgh) for reproducing several reaction applications of the salts described in this report. We thank Mr. Alexander Curtis for assistance with amination substrate **60** and Dr. Ravikumar R. Gowda of the Chen Group at CSU for assistance with analysis of polymer **32**. We also thank Colorado State

University (CSU) for funding and the Analytical Resources Core (RRID: SCR_021758) at CSU for instrument access, training and assistance with sample analysis.

Notes and references

- For selected reviews on the utility of strong bases and their structural effects on reactivity, see: (a) R. K. Henderson, A. P. Hill, A. M. Redman, H.F. Sneddon. *Green Chem.* **2015**, *17*, 945-949. (b) B. Haag, M. Morison, H. Ila, V. Malakhov, P. Knochel. *Angew. Chem. Int. Ed.* **2011**, *50*, 9794-9824. (c) R. E. Mulvey, F. Mongin, M. Uchiyama, Y. Kondo. *Angew. Chem. Int. Ed.* **2007**, *46*, 3802-3824. (d) D. B. Collum, A. J. McNeil, A. Ramirez. *Angew. Chem. Int. Ed.* **2007**, *46*, 3002-3017. (e) C. K. Patel, S. Banerjee, K. Kant, R. Sengupta, N. Aljaar, C. C. Malakar. *Asian J. Org. Chem.* **2023**, *12*, e2023003. (f) T. L. Rathman, W. F. Bailey. *Org. Process Res. Dev.* **2009**, *13*, 144-151.
- For reviews on organic superbases, see: (a) Superbases for Organic Synthesis: Guanidines, Amidines, Phosphazenes and Related Organocatalysts; W. F. Ishikawa, Ed.; Wiley, Chichester, UK, 2009. (b) K. Vazdar, D. Margetić, B. Kovačević, J. Sundermeyer, I. Leito, U. Jahn. *Acc. Chem. Res.* **2021**, *54*, 3108-3123. (c) R. F. Weitkamp, B. Neumann, H.-G. Stammer, B. Hoge. *Chem. Eur. J.* **2021**, *27*, 10807-10825. (d) Y.-H. Wang, Z.-Y. Cao, Q.-H. Li, G.-Q. Lin, J. Zhou, P. Tian. *Angew. Chem. Int. Ed.* **2020**, *59*, 8004-8014.
- Phosphazene superbases are often sold as solutions in THF and hexanes, illustrating their high solubility in non-polar organic media.
- For discussions and measurements of the relative Brønsted basicity versus nucleophilicity of superbases, see: (a) R. Schwesinger, H. Schlemper. *Angew. Chem. Int. Ed.* **1987**, *26*, 1167-1169. (b) E. D. Nacsa, T. H. Lambert. *J. Am. Chem. Soc.* **2015**, *137*, 10246-10253. (c) A. Gholamipour-Shirazi, C. Rolando. *Org. Biomol. Chem.* **2012**, *10*, 8059-8063.
- For example methods that rely on ion pairing of superbase conjugate acids, including in asymmetric catalysis, see: (a) H. Krawczyk, M. Dziegielewska, D. Deredas, A. Albrecht, Ł. Albrecht. *Chem. Eur. J.* **2015**, *21*, 10268-10277. (b) H. J. A. Dale, G. R. Hodges, G. C. Lloyd-Jones. *J. Am. Chem. Soc.* **2019**, *141*, 7181-7193. (c) S. Martinez-Erro, A. Sanz-Marco, A. B. Gomez, A. Vázquez-Romero, M. S. G. Ahlquist, B. Martín-Matute. *J. Am. Chem. Soc.* **2016**, *138*, 13408-13414. (d) H. Kawai, Z. Yuan, E. Tokunaga, N. Shibata. *Org. Biomol. Chem.* **2013**, *11*, 1446-1450. (e) D. L. Orsi, M. R. Yadav, R. A. Altman. *Tetrahedron* **2019**, *75*, 4325-4336.
- T. R. Puleo, S. J. Sujansky, S. E. Wright, J. S. Bandar. *Chem. Eur. J.* **2021**, *27*, 4216-4229.
- For selected examples of phosphazene superbase use in photoredox catalysis, Pd-catalyzed cross-coupling reactions and HTE applications, see: (a) C. D. Matier, J. Schwaben, J. C. Peters, G. C. Fu. *J. Am. Chem. Soc.* **2017**, *139*, 17707-17710. (b) X. Zhang, R. T. Smith, C. Le, S. J. McCarver, B. T. Shireman, N. I. Carruthers, D. W. C. MacMillan. *Nature*, **2020**, *580*, 220-226. (c) L. M. Baumgartner, J. M. Dennis, N. A. White, S. L. Buchwald, K. F. Jensen. *Org. Process. Res. Dev.* **2019**, *23*, 1594-1601. (d) A. B. Santanilla, E. L. Regalado, T. Pereira, M. Shevlin, K. Bateman, L.-C. Campeau, J. Schneeweis, S. Berritt, Z.-C. Shi, P. Nantermet, Y. Liu, R. Helmy, C. J. Welch, P. Vachal, I. W. Davies, T. Cernak, S. D. Dreher. *Science* **2015**, *347*, 49-53. (e) M. R. Uehling, R. P. King, S. W. Kraska, T. Cernak, S. L. Buchwald. *Science* **2019**, *363*, 405-408. (f) D. T. Ahneman, J. G. Estrada, S. Lin, S. D. Dreher, A. G. Doyle. *Science* **2018**, *360*, 186-190.
- For discussions of air sensitivity of strong organic and metal-containing Brønsted bases, see: (a) M.-A. Courtemanche, M.-A. Légaré, E. Rochette, F.-G. Fontaine. *Chem. Commun.* **2015**, *51*,

- 6858-6861. (b) C. Villiers, J.-P. Dognon, R. Pollet, P. Thuéry, M. Ephritikhine. *Angew. Chem. Int. Ed.* **2010**, *49*, 3465-3468. (c) T. L. Rathman, J. A. Schwindeman. *Org. Process Res. Dev.* **2014**, *18*, 1192-1210. (d) L. Chen, J. Zhao, S.-F. Yin, C.-T. Au. *RSC Advances* **2013**, *3*, 3799-3814. (e) R. Wethman, J. Derosa, V. T. Tran, T. Kang, O. Apolar, A. Abraham, R. Kleinmans, S. R. Wisniewski, J. R. Coombs, K. M. Engle. *ACS Catal.* **2021**, *11*, 502-508. (e) See also reviews on strong base chemistry covered in ref 1 and 2, and the procedures for isolation of superbases in ref 14.
- 9 *In situ* generation of superbases from their conjugate acid salts can be enabled through the use of a separate strong base activator. For examples, see: (a) C. Luo, J. V. Alegre-Requena, S. J. Sujansky, S. P. Pajk, L. C. Gallegos, R. S. Paton, J. S., Bandar. *J. Am. Chem. Soc.* **2022**, *144*, 9586-9596. (b) T. Takeda, M. Terada. *J. Am. Chem. Soc.* **2013**, *135*, 15306-15309. (c) D. Uruguchi, S. Sakaki, T. Ooi. *J. Am. Chem. Soc.* **2007**, *129*, 12392-12393. (d) See also 4b.
- 10 For reviews on photobase generators, see: (a) K. Suyama, S. Masamitsu. *Prog. Polym. Sci.* **2009**, *34*, 194-209. (b) N. Zivic, P. K. Kuroishi, F. Dumur, D. Gimes, A. P. Dove, H. Sardon. *Angew. Chem. Int. Ed.* **2019**, *58*, 10410-10422.
- 11 Several reports describe the synthesis of phosphazene photobase generators, although these reagents have not been extensively studied for reaction or polymerization applications; see: (a) X. Sun, J. P. Gao, Z. Y. Wang. *J. Am. Chem. Soc.* **2008**, *130*, 8130-8131. (b) K. Arimitsu, R. Endo. *Chem. Mater.* **2013**, *25*, 4461-4463. (c) D. Aoki, C. Gu, M. Suzuki, Y. Kawamura, K. Arimitsu. *Chem. Lett.* **2023**, *52*, 775-778.
- 12 For the use of epoxides as alkoxide-generating reagents, see: (a) J. Buddrus. *Angew. Chem. Int. Ed.* **1972**, *11*, 1041-1050. (b) J. Buddrus, W. Kimpenhaus. *Chem. Ber.* **1974**, *107*, 2062-2078. (c) S. Tanaka, T. Nakashima, N. Satou, H. Oono, Y. Kon, M. Tamura, K. Sato. *Tetrahedron Lett.* **2019**, *60*, 2009-2013.
- 13 For pK_a values of carboxylic acids, alcohols and superbases shown in Figure 1, see: (a) F. G. Bordwell. *Acc. Chem. Res.* **1988**, *21*, 456-463. (b) E. Rossini, A. D. Bochevarov, E. W. Knapp. *ACS Omega*, **2018**, *3*, 1653-1662. (c) A. Kütt, S. Tshepelevitsch, J. Saame, M. Lökov, I. Kaljurand, S. Selberg, I. Leito. *Eur. J. Org. Chem.* **2021**, *2021*, 1407-1419. (d) S. Tshepelevitsch, A. Kütt, M. Lökov, M. Kaljurand, J. Saame, A. Heering, P. G. Plieger, R. Vianello, I. Leito. *Eur. J. Org. Chem.* **2019**, *40*, 6735-6748.
- 14 For synthetic routes to P_1 -, P_2 - and P_4 -superbases and related strong bases, see: (a) R. Schwesinger. *Chimia* **1985**, *39*, 269. (b) R. Schwesinger, H. Schlemper, C. Hasenfratz, J. Willaredt, T. Dambacher, T. Breuer, C. Ottaway, M. Fletschinger, J. Boele, H. Fritz, D. Putzas, H. W. Rotter, F. G. Bordwell, A. V. Satish, G.-Z. Ji, E.-M. Peters, K. Peters, H. G. von Schnering, L. Walz. *Liebigs Ann. Chem.* **1996**, 1055-1081. (c) R. Schwesinger, T. Dambacher. *Z. Naturforsch. B.* **2006**, *61b*, 1229-1233. (d) D. H. R. Barton, J. D. Elliot, S. D. Géro. *J. Chem. Soc., Chem. Commun.* **1981**, 1136-1137. (e) K. Vazdar, R. Kunetskiy, J. Saame, K. Kaupmees, I. Leito, U. Jahn. *Angew. Chem. Int. Ed.* **2014**, *53*, 1435-1438. (f) J. Tang, J. G. Verkade. *Tetrahedron Lett.* **1993**, *34*, 2903-2904. (g) See also refs 4a and 4b.
- 15 Phosphazene freebases can be accessed by several other alternative routes. For a Staudinger reaction using organic azides and tris(dialkylamino)phosphines en route to P_1 bases, see: (a) A. V. Alexandrova, T. Mašek, S. M. Polyakova, I. Čiřarová, J. Saame, I. Leito, I. M. Lyapkalo. *Eur. J. Org. Chem.* **2013**, 1811-1823. For high vacuum neutralization of hydrates of P_4 phosphazenum hydroxide salts, see: (b) R. F. Weitkamp, B. Neumann, H.-G. Stammer, B. Hoge. *Angew. Chem. Int. Ed.* **2019**, *58*, 14633-14638.
- 16 The commercial cost of phosphazene superbases from Millipore Sigma are: BTPP (25 mL for \$718, or \$8780 per mol); P_1 -*t*-Bu (25 mL for \$1600 or \$15,954 per mol); P_2 -Et (5 mL for \$740, or \$49,247 per mol); P_2 -*t*-Bu (25 mL of 2 M solution for \$1820, or \$36,400 per mol); and P_4 -*t*-Bu 25 mL of 0.8 M solution for \$1460, or \$73,000 per mol).
- 17 For examples and discussions of use of BTPP and cyclic guanidine superbases in production scale-up, see: (a) R. E. H. Jones, P. Aspin, S. H. Davies, I. Mann, C. Priestley, A. D. Roberts, N. Zotova-Eldridge, J. H. Leahy. *Org. Process Res. Dev.* **2022**, *26*, 2646-2655. (b) A. M. Hyde, R. Calabria, R. Arvary, X. Wang, A. Klapars. *Org. Process Res. Dev.* **2019**, *23*, 1860-1871. (c) C. Penverne, B. Hazard, C. Rolando, M. Penhoat. *Org. Process Res. Dev.* **2017**, *21*, 1864-1868.
- 18 D. Truong, B. L. Howard, P. E. Thompson. *Tetrahedron* **2021**, *85*, 132034.
- 19 (a) N. Caldwell, C. Jamieson, I. Simpson, T. Tuttle. (b) N. Caldwell, P. S. Campbell, C. Jamieson, F. Potjewyd, I. Simpson, A. J. B. Watson. *J. Org. Chem.* **2014**, *79*, 9347-9354.
- 20 (a) M. K. Nielsen, C. R. Ugaz, W. Li, A. G. Doyle. *J. Am. Chem. Soc.* **2015**, *137*, 9571-9574. (b) M. K. Nielsen, D. T. Ahneman, O. Riera, A. G. Doyle. *J. Am. Chem. Soc.* **2018**, *140*, 5004-5008. (c) A. M. Żurański, S. S. Gandhi, A. G. Doyle. *J. Am. Chem. Soc.* **2023**, *145*, 7898-7909.
- 21 Pure, solid P_2 -*t*-Bu freebase is very hygroscopic such that exposure to ambient conditions quickly leads to formation of an oily hydrated substance. For example, P_2 -*t*-Bu solid loses its solidity after 15 minutes on weigh paper under 84% humidity.
- 22 Methylenecyclohexane oxides (e.g., **22**) may provide a greater driving force due to increased stereoelectronic stabilization of the alcohol byproduct compared to the epoxide; for discussions, see: (a) R. G. Carlson, N. S. Behn. *Chem. Commun.* **1968**, 339-340. (b) T. Hrenar, I. Primožič, D. Fijan, M. Majerić Elenkov. *Phys. Chem. Chem. Phys.* **2017**, *19*, 31706-31713. (c) I. V. Alabugin, L. Kuhn, N. V. Krivoshchapov, P. Mehaffy, M. G. Medvedev. *Chem. Soc. Rev.* **2021**, *50*, 10212-10252.
- 23 Epoxide **23** is used for an all-in-one system in place of **22**; we found that the epoxide **22** and P_2 -*t*-Bu salt **A** mixture is less stable over time compared to the mixture with **23**.
- 24 For reviews, see: (a) C. F. Nising, S. Bräse. *Chem. Soc. Rev.* **2012**, *41*, 988-999. (b) J. L. Kennemur, R. Maji, M. J. Scharf, B. List. *Chem. Rev.* **2021**, *121*, 14649-14681. For mechanistic investigations of challenging alcohol addition reactions, see ref 9a.
- 25 For reviews on base-catalyzed hydroamination reactions, see: (a) J. Seayad, A. Tillack, C. G. Hartung, M. Beller. *Adv. Synth. Catal.* **2002**, *344*, 795-813. (b) T. E. Müller, K. C. Hultzsich, M. Yus, F. Foubelo, M. Tada. *Chem. Rev.* **2008**, *108*, 3795-3892. (c) B. N. Hemric, T. A. Garcia, A. E. Barni. *Helv. Chim. Acta* **2024**, *107*, e202300160.
- 26 For the use of P_2 -bases for ϵ -caprolactone polymerization, see: H. Alamri, J. Zhao, D. Pahovnik, N. Hadjichristidis. *Polym. Chem.* **2014**, *5*, 5471-5478.
- 27 For examples of bioactive dihydrobenzofurans, see: (a) R. J. Nevagi, S. N. Dighe, S. N. Dighe. *Eur. J. Med. Chem.* **2015**, *97*, 561-581. (b) D. P. Zlotos, R. Jockers, E. Cecon, S. Rivara, P. A. Witt-Enderby. *J. Med. Chem.* **2014**, *57*, 3161-3185. (c) Z. Chen, M. Pitchakuntla, Y. Jia. *Nat. Prod. Rep.* **2019**, *36*, 666-690.
- 28 We note that when the precatalyst system is used, we observe approximately 10% of an oligomer side product that is not present with direct use of P_2 -*t*-Bu; see Supplementary Information.
- 29 For use of P_2 -bases in S_NAr reactions, see ref 7d and: N. J. Gesmundo, B. Sauvagnat, P. J. Curran, M. P. Richards, C. L. Andrews, P. J. Dandliker, T. Cernak. *Nature* **2018**, *557*, 228-232.
- 30 (a) A. Costa, C. Nájera, J. M. Sansano. *Synlett* **2001**, *12*, 1881-1884. (b) A. Costa, C. Nájera, J. M. Sansano. *J. Org. Chem.* **2002**, *67*, 5216-5225.
- 31 For selected examples of organic bases in metal-catalyzed coupling reactions, see ref 7 and: (a) J. M. Dennis, N. A. White, R. Y. Liu, S. L. Buchwald. *J. Am. Chem. Soc.* **2018**, *140*, 4721-4725. (b) S. H. Lau, P. Yu, L. Chen, C. B. Madsen-Duggan, M. J. Williams,

- B. P. Carrow. *J. Am. Chem. Soc.* **2020**, *142*, 20030-20039. (c) G. L. Beutner, J. R. Coombs, R. A. Green, B. Inankur, D. Lin, J. Qiu, F. Roberts, E. M. Simmons, S. R. Wisniewski. *Org. Process Res. Dev.* **2019**, *23*, 1529-1537. (d) S. K. Kashani, J. E. Jessiman, S. G. Newman. *Org. Process Res. Dev.* **2020**, *24*, 1948-1954. (e) J. W. M. MacMillan, R. T. McGuire, M. Stradiotto. *Chem. Eur. J.* **2022**, e202200764.
- 32 For early work using phosphazenes in Pd-catalyzed coupling reactions, see ref 7d and: (a) A. B. Santanilla, M. Christensen, L.-C. Campeau, I. W. Davies, S. D. Dreher. *Org. Lett.* **2015**, *17*, 3370-3373. (b) See also: C. Palomo, M. Oiarbide, R. López, E. Gómez-Bengoia. *Tetrahedron Lett.* **2000**, *41*, 1283-1286.
- 33 For an example of a Pd-catalyzed amination protocol where slow addition of a superbases improves the reaction yield, see: (a) J. M. Dennis, N. A. White, R. Y. Liu, S. L. Buchwald. *ACS Catal.* **2019**, *9*, 3822-3830. For other examples of slow addition improving base-promoted reactions, see: (b) H.-J. Lombart, W. D. Lubel. *J. Org. Chem.* **1996**, *61*, 9437-9446. (c) S. K. Bertilsson, P. G. Andersson. *Tetrahedron*, **2002**, *58*, 4665-4668. (d) D. E. Knutson, M. S. Rashid Roni, M. Y. Mian, J. M. Cook, D. C. Stafford, L. A. Arnold. *Org. Process Res. Dev.* **2020**, *24*, 1467-1476.
- 34 The rates of product formation (**57**) in Figure 8b also correlate with the rate of alcohol activation byproduct appearance, consistent with the epoxide opening process regulating the rate of amination.
- 35 Numerous reports of safety hazards associated with strong base-promoted reactions are available; for examples, see: (a) Q. Yiang, N. R. Babij, S. Good. *Org. Process Res. Dev.* **2019**, *23*, 2608-2626. (b) Q. Yang, B. Canturk, K. Gray, E. McCusker, M. Sheng, F. Li. *Org. Process Res. Dev.* **2018**, *22*, 351-359. (c) Q. Yang, M. Sheng, J. J. Henkelis, S. Tu, E. Wiensch, H. Zhang, Y. Zhang, C. Tucker, D. E. Ejeh. *Org. Process Res. Dev.* **2019**, *23*, 2210-2217. (d) D. B. Brown, A. D. Allian, Y. Chen. *Org. Process Res. Dev.* **2021**, *25*, 1932-1936. (e) M. Power, E. Alcock, G. P. McGlacken. *Org. Process Res. Dev.* **2020**, *24*, 1814-1838. (f) See also refs 1a and 8c.
- 36 For discussions of base coordination to and inhibition of Pd catalytic intermediates in C-N coupling reactions, see refs 31, 33 and: (a) Y. Sunesson, E. Limé, S. O. Nilsson Lill, R. E. Meadows, P.-O. Norrby. *J. Org. Chem.* **2014**, *79*, 11961-11969. (b) S.-T. Kim, B. Pudasaini, M.-H. Baik. *ACS Catal.* **2019**, *9*, 6851-6856.
- 37 For discussions of strong base-promoted decomposition of functional groups seen in Figure 8, such as azoles, indazoles, styrenes and nitriles, see: (a) E. C. Reichert, K. Feng, A. C. Sather, S. L. Buchwald. *J. Am. Chem. Soc.* **2023**, *145*, 3323-3329. (b) A. Sather, T. A. Martinot. *Org. Process Res. Dev.* **2019**, *23*, 1725-1739. (c) M. L. Casey, D. S. Kemp, K. G. Paul, D. D. Cox. *J. Org. Chem.* **1973**, *38*, 2294-2301. (d) K. Inoue, K. Okano. *Asian J. Org. Chem.* **2020**, *9*, 1548-1561. (e) T. R. Puleo, A. J. Strong, J. S. Bandar. *J. Am. Chem. Soc.* **2019**, *141*, 1467-1472.
- 38 The humidity in our laboratory was typically 10-30% during the course of this work, with occasional raises up to approximately 60%.
- 39 R. Schwesinger, Y. Kondo. *Encyclopedia of Reagents for Organic Synthesis*. **2010**. DOI: 10.1002/047084289X.rp150.pub2.