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Communication

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Driving Recursive Dehydration by P^{III}/P^{V} Catalysis: Annulation of Amines and Carboxylic Acids by Sequential C–N and C–C Bond Formation

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Supporting Information Placeholder

ABSTRACT: A method for the annulation of amines and carboxylic acids to form pharmaceutically-relevant azaheterocycles via organophosphorus P^{III}/P^{V} redox catalysis is reported. The method employs a phosphetane catalyst together with a mild bromenium oxidant and terminal hydrosilane reductant to drive successive C–N and C–C bond forming dehydration events via the serial action of a catalytic bromophosphonium intermediate. These results demonstrate the capacity of P^{III}/P^{V} redox catalysis to enable iterative redox-neutral transformations in complement to the common reductive driving force of P^{III}/P^{V} couple.

Progress over the past decade has established the viability of the P^{III}/P^{V}=O redox couple for catalysis.[1-3] In contrast to prior notions about the kinetic inertness of the P=O bond, the incorporation of P into a ring structure can lead to swift deoxygenation by mild reagents such as hydrosilanes.[4,5] By virtue of the reducing potential of the P^{III}/P^{V} couple, many of these transformations are reductive in nature (Figure 1A, left).[6-8] In this vein, we have shown that four-membered ring organophosphorus catalysts effect reductive conversion of nitro[9] and sulfonyl[10] substrates (cf. Figure 1B) in which the ability to recursively renew a reactive P^{III} species under conditions of P^{III}/P^{V} catalysis enables a single catalyst to perform successive deoxygenative operations on a substrate (i.e. auto-tandem catalysis[11]).

In addition to reductive chemistry, the versatile P^{III}/P^{V} driving force can be adapted to achieve net redox-neutral transformations when paired with an appropriate oxidant as evoked in Mukaiyama's conceptualization of an "oxidation-reduction condensation."[12] Within a P^{III}/P^{V}-catalytic context,[13] the introduction of a mild chemoselective halenium oxidant, for instance, can shunt the reductive manifold into a net redox-neutral mode where the key reactive catalytic intermediate is not a phosphine but rather a halophosphonium cation[14,15] (Figure 1A, right). Indeed, halophosphonium intermediates have been invoked by Rutjes and van Delft[5] and Mecinović[16] in the context of P^{III}/P^{V}-catalyzed Appel halogenation and *N*-acylation reactions, respectively.[17] In view of the fact that phosphonium reagents have been described as having "virtually ideal properties as selective oxygen extractors for net dehydration reactions,"[18,19] the potential to achieve recursive dehydrations in an auto-tandem catalytic manner via a net redox-neutral mode of P^{III}/P^{V} catalysis could be expected to present new opportunities for serial bond formation.

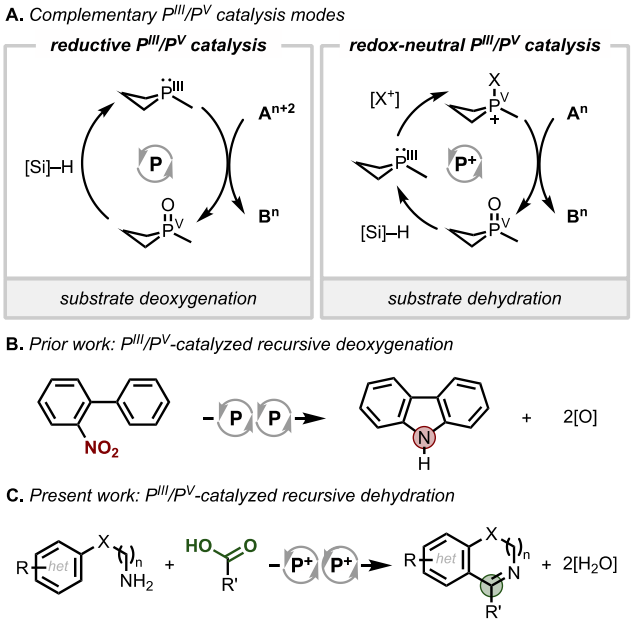
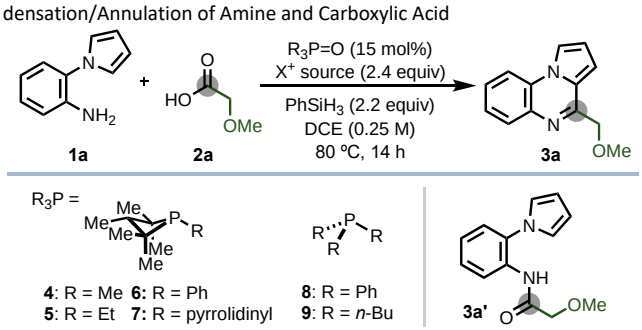


Figure 1. (A) Complementary reductive and redox-neutral modes of P^{III}/P^{V} catalysis. (B) Catalytic heterocyclization of nitrobiaryl by recursive deoxygenation. (C) Catalytic annulation of amines and carboxylic acids by recursive dehydration.

We show here an annulation of amines and carboxylic acids via recursive dehydration driven by a redox-active organophosphorus catalyst cycling in the P^{III}/P^{V} couple (Figure 1C). This auto-tandem catalytic system enables the elaboration of simple, commercially available starting materials into pharmaceutically-relevant azaheterocycles through a condensation/cyclodehydration sequence in a one-pot catalytic protocol. The success of the approach relies on the mutual compatibility and functional interplay of the reducing and oxidizing reagents with the organophosphorus catalyst in order to orchestrate a sequence of distinct C–N and C–C bond-forming events. The ability of P^{III}/P^{V} redox catalysis to encompass such recursive dehydration stands as a complement to existing deoxygenation methods, thus broadening the scope of transformations accessible to this catalytic mode.

Table 1. Discovery and Optimization of Phosphacatalytic Iterative Condensation/Annulation of Amine and Carboxylic Acid



Entry	R_3P=O	X^+ source	Yield (%)[a]
1	**4**•[O]	DEBM	94 (84)[b]
2	**4**•[O]	DEMBM	90
3	**4**•[O]	NBS	10
4	**4**•[O]	DECM	0
5	**4**• [O]	CCl_4	0
6	**5**•[O]	DEBM	26
7	**6**•[O]	DEBM	46
8	**7**•[O]	DEBM	50
9	**8**•[O] or **9**•[O]	DEBM	0
10	none	DEBM	0
11	**4**•[O]	none	0
12	**4**•[O], no $PhSiH_3$	DEBM	0
13	**4**	DEBM	90
14	[**4**•Br]Br	DEBM	87

[a]Yields determined through ^{1}H NMR analysis with the aid of an internal standard. See Supporting Information for full synthetic details and yields of intermediate amide **3a'**. [b]Isolated yield on 0.4 mmol scale. DCE = 1,2-dichloroethane; DEBM = diethyl bromomalonate; DEMBM = diethyl (methyl)bromomalonate; NBS = *N*-bromosuccinimide; DECM = diethyl chloromalonate.

To evaluate the possibility of recursive dehydration driven by P^{III}/P^V redox cycling, the tandem amidation/cyclodehydration of amine **1a** and carboxylic acid **2a** to generate pyrroloquinoxaline **3a** was evaluated (Table 1). Optimal conditions using 1,2,2,3,4,4-hexamethylphosphetane *P*-oxide **4**•[O] [20] as catalyst, diethyl bromomalonate (DEBM) as oxidant, and phenylsilane as terminal reductant yielded the desired product in 94% yield, isolable on 0.4 mmol scale in 84% yield (Table 1, entry 1). A mild, weakly oxidizing bromenium reagent was found to be essential for the redox compatibility of the system, as demonstrated by Rutjes and van Delft;[5] the related diethyl (methyl)bromomalonate (DEMBM) was similarly competent in the transformation (entry 2), but the more strongly-oxidizing *N*-bromosuccinimide resulted in poor conversion to product (entry 3). Chlorenium oxidants such as diethyl chloromalonate (DECM) and carbon tetrachloride gave no dehydrative heterocyclization (entries 4 and 5); instead, amide **3a'** was obtained in 70% yield, indicating chlorophosphonium ion competency in C–N forming amidation but not C–C forming cyclodehydration.[21]

With respect to catalyst, variation of the phosphetane exocyclic moiety to ethyl (**5**•[O], entry 6), phenyl (**6**•[O], entry 7), or pyrrolidino (**7**•[O], entry 8) all resulted in substantial decrease in the efficiency of the reaction, while the use of acylic phosphine oxides (**8**•[O] or **9**•[O], entry 9) fail to promote the cyclocondensation (see SI). Control experiments confirm that no azaheterocycle product is observed in the absence of any of **4**•[O], phenylsilane, or DEBM (entries 10-12).[22] Furthermore, employing P^{III} species **4** or pregenerated bromophosphonium [**4**•Br]Br[23] in place of phosphine oxide **4**•[O] resulted in comparable efficiency, consistent with the notion of P^{III}/P^V=O redox cycling (entries 13-14).

The optimized phosphacatalytic protocol provides direct access to complex azaheterocycles from simple and readily available amine and carboxylic acid starting materials (Figure 2). A variety of carboxylic acids are efficiently incorporated into pyrroloquinoxalines, including those possessing olefinic and aryl functionalities (**3c**-**3i**, 54-89% yields). This protocol was also readily translated to larger scale reactions, as a 5 mmol scale reaction of 1-(2-aminophenyl)pyrrole and butyric acid provided 1.04 g of compound **3b** in 99% yield with 8 mol% loading of organophosphorus catalyst **4**•[O]. As demonstrated by products **3d**–**3i**, the reaction efficiency is relatively independent of substitution on benzoic acid coupling partners, including changing steric profile (54-89% yields). Critically, acids containing polar functionalities, including alkyl ethers, thioethers, sulfonamides, and alkyl halides, undergo efficient iterative dehydration to provide heterocycles in good to excellent yields (**3a, 3j**-**3p**, 41-90% yields). Of particular note are the amino acid-incorporating products **3k** and **3p**, which originate from protected Ts-Gly-OH and Ts-Phe-OH. Further, both primary and secondary haloalkane functionalities are conserved under this P^{III}/P^V-catalytic manifold (**3l** and **3m**, 93% and 98% yields, respectively). Substitution on the aniline ring was well-tolerated; both *ortho*- and *meta*-substituted pyrroloanilines were readily incorporated into heterocyclic scaffolds (**3n** and **3o**, 86% and 95% yields, respectively). Chiral carboxylic acids, such as ibuprofen and naproxen, are incorporated with good yield and high stereochemical fidelity (**3q**, 67 %, 95:5 *e.r.*; **3r**, 68%, 92.5:7.5 *e.r.*) under modified recursive dehydration conditions (precatalyst [**4**•Br]Br, MeCN, 50 ºC; see Supporting Information for full synthetic details).

When *N*-alkyl amine substrates were initially employed under standard conditions, an undesired byproduct arising from *N*-alkylation by DEBM was identified by GCMS. However, replacing DEBM with its methyl-substituted analogue, DEMBM, abated this deleterious pathway, restoring the high degree of redox compatibility necessary for the catalytic system. Consequently, *o*-pyrrolobenzylamine could be efficiently coupled with carboxylic acids via iterative dehydration to provide the corresponding pyrrolo-benzodiazepines, a prevalent bioactive scaffold,[24] in good yields (**3s**-**3u**, 66-86% yields).[25] Heterocycles **3t** and **3u**, compounds investigated by Janssen for their antifungal activity,[26] could be prepared in a single synthetic operation in 86% and 73% yields, respectively. Further, tryptamines and phenethylamines could be transformed into dihydro-β-carboline and dihydroisoquinoline products in good yields (**3v**-**3x**, 70-77% yields).[27] Notably, both of these scaffolds are found in bioactive pharmaceutical agents and natural products,[28] as demonstrated by the assembly in a single step of dihydroisoquinoline natural product 3,4-dihydropapaverine from commercial starting materials with good efficiency (**3x**, 70% yield).

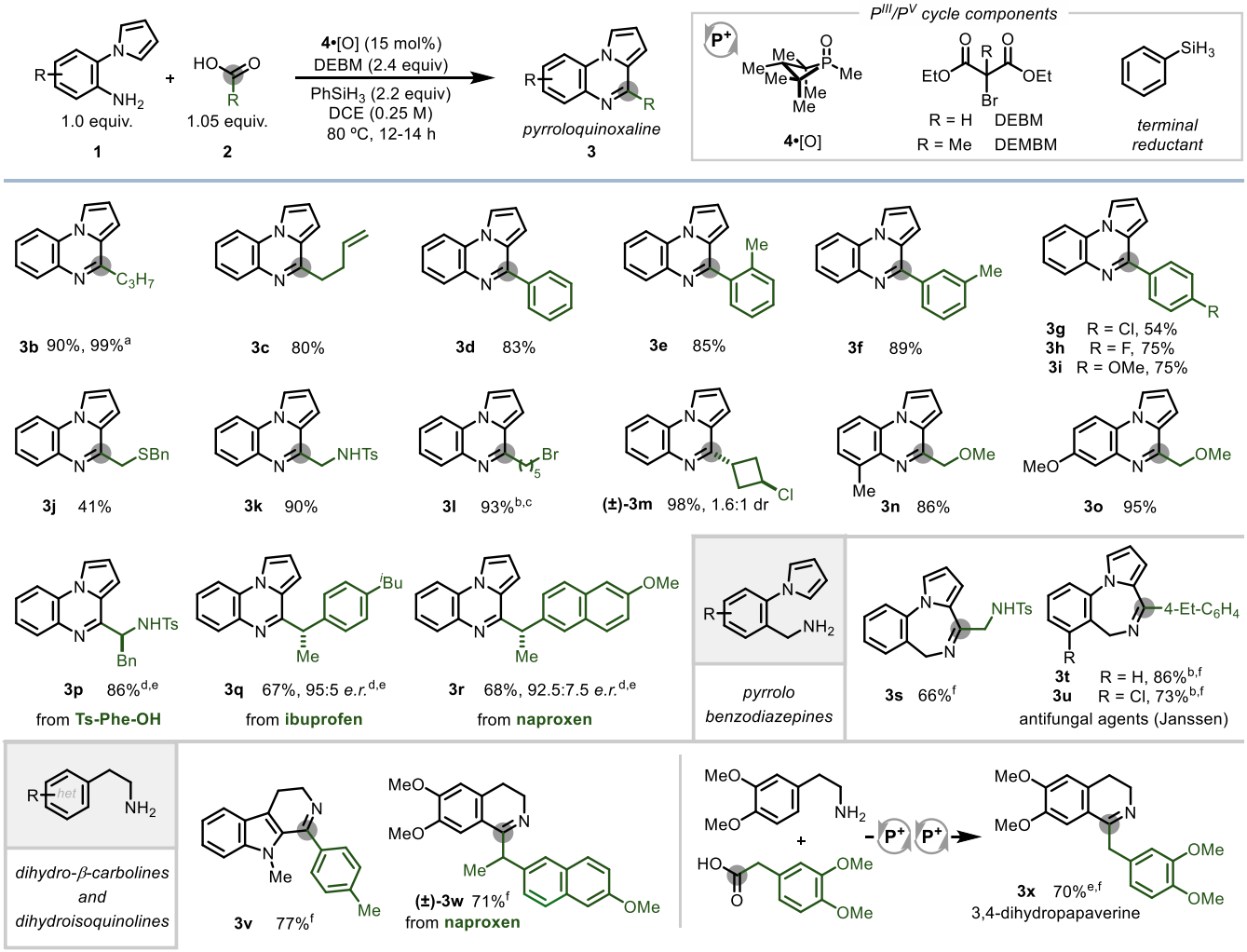


Figure 2. Examples of auto-tandem phosphacatalytic annulation of amines and carboxylic acids. All yields isolated on 0.4 mmol scale unless indicated otherwise. See Supporting Information for full synthetic details. [a]Isolated yield on 5.0 mmol scale, with 8 mol% of **4**•[O]. [b]Reaction conducted with Ph_2SiH_2 (4.4 equiv) in MeCN. [c]Reaction conducted at 60 ºC for 20 h. [d]Reaction conducted on 0.2 mmol scale using 15 mol% of [**4**•Br]Br in MeCN at 50ºC for 20-40 h. [e]Yield determined by ^{1}H NMR with internal standard. [f]Reaction conducted with DEMBM. DEBM = diethyl bromomalonate; DEMBM = diethyl(methyl)bromomalonate; DCE = 1,2-dichloroethane; Bn = benzyl; Ts = tosyl; ^{i}Bu = *iso*-butyl.

Concerning the catalytic mechanism, in situ ^{1}H NMR spectroscopy revealed a rapid initial conversion of reactants **1a** and **2a** into amide intermediate **3a'**, followed by comparatively slow formation of heterocycle **3a** (see SI, Sect. VI), establishing a stepwise reaction sequence for the auto-tandem catalytic process in which C–C bond-forming cyclodehydration is kinetically limiting. Despite the observation that **4**, **4**•[O], or **4**•Br$^+$ are each competent precatalysts (*vide supra*), in situ ^{31}P NMR and DART-MS analyses show that none of these compounds represent the catalytic resting state. Rather, experiments are most consistent with resting state **B1**, an adduct of the phosphacyclic catalyst and amide **A1** (Figure 3A). Indeed, independent reaction of [**4**•Br]Br with **A1** gives rise to spectroscopic signals indistinguishable from those observed under the catalytic steady state, and this species was shown to lead to C–C bond-forming cyclodehydration.[29] Furthermore, spectroscopically indistinguishable species are observed by ^{31}P NMR spectroscopy when either *N*-methylacetamide and *N*,*N*-dimethylacetamide are introduced in lieu of reactive amides to a mixture containing catalytic components (i.e. **4**•[O], $PhSiH_3$, DEBM).

Figure 3B depicts a plausible auto-tandem catalytic reaction mechanism consistent with the foregoing experimental data. From phosphine oxide **4**•[O] as precatalyst, entry to the C–N bond-forming cycle (Figure 3B) is initiated by kinetically-facile phenylsilane-mediated reduction to phosphine **4**, followed by rapid halophilic reaction[30] with DEBM leading to bromophosphonium ion **4**•Br$^+$. Bromophosphonium cation **4**•Br$^+$ effects intermolecular amidation between acid **1** and amine **2**, presumably via intermediate **C** in analogy to established precedent for amine *N*-acylation by activated acyloxyphosphoniums, thereby returning phosphine oxide **4**•[O]. In C–C bond-forming second phase, phosphonium ion **4**•Br$^+$ is again generated by a reduction-oxidation sequence with $PhSiH_3$ and DEBM, respectively. Exchange of bromide for the amide substrate **A** then leads to activated species **B**, which is assigned as the catalytic resting state. Cyclization ensues to provide the product **3**, liberating phosphine oxide **4**•[O] and closing the catalytic cycle.[31] The two noteworthy conclusions emerging from this mechanistic picture are: (1) Turnover of phosphine oxide **4**•[O] to phosphine **4** is not kinetically limiting; and (2) The concentration of reducing phosphine **4** remains negligibly low during catalysis as a function of the efficient reaction with the oxidative halenium shunt.

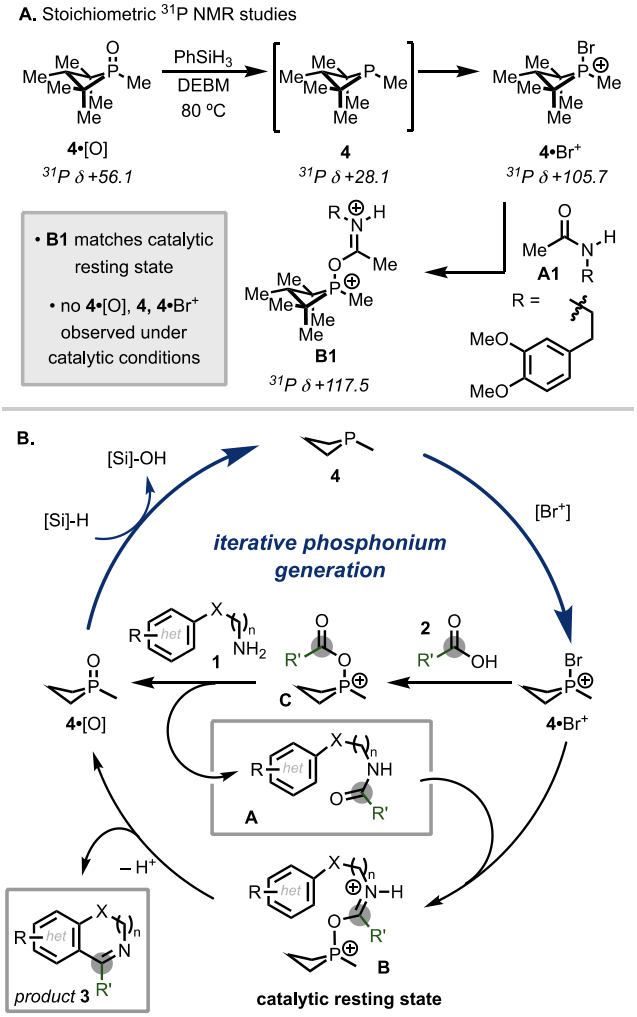


Figure 3. (A) ^{31}P NMR studies. (B) Proposed mechanism of auto-tandem catalytic dehydrative annulation of amines and carboxylic acids. Methyl groups excluded from **4** for clarity. DEBM = diethyl bromomalonate.

The net redox neutral character of the recursive dehydration (and the absence of appreciable concentrations of phosphine **4**) enables chemoselective annulation in preference to established P^{III}/P^{V}-catalyzed reductive transformations. This orthogonality is illustrated in the context of *p*-nitrohydrocinnamic acid (**10**), possessing both carboxylic acid and nitroarene moieties (Figure 4). Under the recursive dehydration conditions described herein, catalyst **4**•[O] drives the selective annulation of carboxylic acid **10** to yield pyrroloquinoxaline **11** in 97% yield. With the same catalyst (**4**•[O]) but omission of the DEBM shunt, the nitro group is then reductively addressed to effect intermolecular C–N cross coupling[9c] and yield fully deoxygenated species **12** in 72% yield. This sequence, in which a single organophosphorus catalyst executes four distinct oxygen excisions, demonstrates the complementarity of the reductive and redox-neutral P^{III}/P^{V}-catalytic manifolds owing to the disparate reactivity of the phosphetane in its different oxidation states as a function of the addition or exclusion of an exogenous oxidant.

In conclusion, we have demonstrated that a small-ring phosphetane catalyst can induce iterative dehydrative C–N and C–C bond-forming reactions, enabling direct azaheterocycle synthesis from carboxylic acids and amines via recursive dehydration. Through the synergistic use of mild hydrosilane reductant and bromenium oxidant, the elements of water can be catalytically removed in the form of an *O*-atom and two protons with complete redox compatibility. We anticipate that this phosphacatalytic dehydration manifold will prove generally enabling for the redox-neutral functionalization of oxygenated organic functionalities to accomplish C–C and C–heteroatom bond forming events via condensation, especially in a recursive fashion.

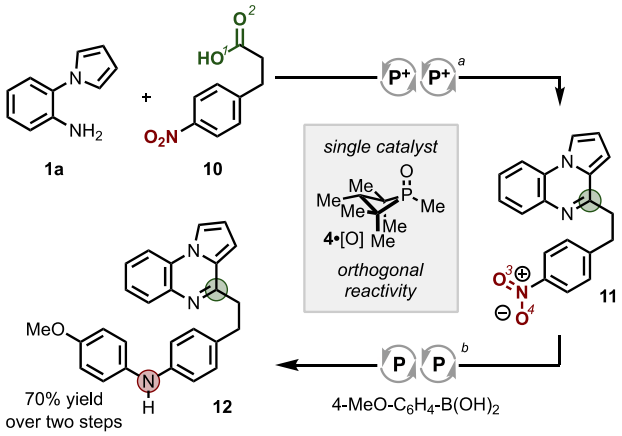


Figure 4. Selective functionalization of carboxylic acid- and nitro-containing substrate via sequential redox-neutral recursive dehydration, then reductive recursive deoxygenation, using a single catalyst **4**•[O]. Reaction conditions: (a) **1a** (1.0 equiv), **10** (1.05 equiv), DEBM (2.4 equiv), $PhSiH_3$ (2.2 equiv), **4**•[O] (15 mol%), DCE, 80 °C; (b) **11** (1.0 equiv), 4-MeO-C_6H_4-$B(OH)_2$ (1.1 equiv), $PhSiH_3$ (2.0 equiv), **4**•[O] (15 mol%), *m*-xylene, 120 °C.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website.

Additional optimization results, mechanistic studies, and synthetic procedures. ^{1}H, ^{13}C, and ^{31}P NMR spectra

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§Authors contributed equally.

Notes

The authors declare no competing financial interest.

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20. Strem item no. 15-8150.

21. Consistent with the notion of sequential C-N then C-C bond forming by serial dehydration events, the optimized protocol using DEBM can be applied to access a wide variety of azaheterocycles via catalytic Bischler-Napieralski-type cyclodehydration of preformed amides (see SI, Sect. V, Table S4, 18 examples).

22. Silanes have been shown to promote amidation, including in phosphine-catalyzed Staudinger amidation. However, low background conversion to amide was observed with $PhSiH_3$ in the absence of either 4•[O] or DEBM (See SI, Sect II, Table S1). See: (a) Ruan, Z.; Lawrence, R. M.; Cooper, C. B. Phenylsilane as an Active Amidation Reagent for the Preparation of Carboxamides and Peptides. *Tetrahedron Lett.* **2006**, *47*, 7649–7651. (b) Sayes, M.; Charette, A. B. Diphenylsilane as a Coupling Reagent for Amide Bond Formation. *Green Chem.* **2017**, *19*, 5060–5064. (c) Andrews, K. G.; Denton, R. M. A More Critical Role for Silicon in the Catalytic Staudinger Amidation: Silanes as Non-Innocent Reductants. *Chem. Commun.* **2017**, *53*, 7982–7985.

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