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Uniting Amide Synthesis and Activation by P^{III}/P^{V}-Catalyzed Serial Condensation: Three-Component Assembly of 2-Amidopyridines

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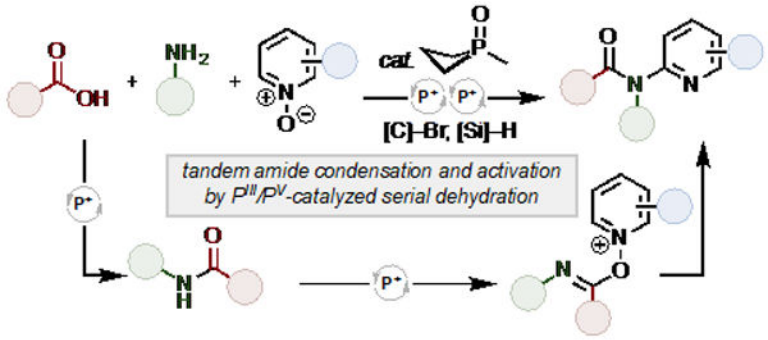
Abstract

An organophosphorus (P^{III}/P^{V} redox) catalyzed method for the three-component condensation of amines, carboxylic acids, and pyridine *N*-oxides to generate 2-amidopyridines via serial dehydration is reported. Whereas amide synthesis and functionalization usually occur under divergent reaction conditions, here a phosphetane catalyst—together with a mild bromenium oxidant and terminal hydrosilane reductant—is shown to drive both steps chemoselectively in an auto-tandem catalytic cascade. The ability to both prepare and functionalize amides under the action of a single organocatalytic reactive intermediate enables new possibilities for the efficient and modular preparation of medicinal targets.

Graphical Abstract



Amides are common targets in biological and medicinal chemistry,[1,2] but challenging substrates for chemical derivatization.[3] Resultantly, a diverse synthetic toolbox of mild reagents supports amide coupling,[4] but amide activation[5] generally employs strongly electrophilic reagents—chiefly Tf_2O[6] as exemplified in the work of Charette,[7] Movassaghi,[8]

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ASSOCIATED CONTENT

Supporting Information.

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

General methods and synthetic procedures; mechanistic studies; ^{1}H, ^{13}C, and ^{19}F NMR spectra.

The authors declare no competing financial interest.

Huang,[9] and Maulide[10,11]—to accomplish functionalization of the typically inert amide moiety.[12–13,14] Notwithstanding the power of Tf_2O-mediated amide activation, the highly electrophilic nature of this reagent necessitates sequencing of the amide preparation and functionalization operations, and generally precludes the use of substrates containing Lewis basic functionalities, including amines.[15] This lack of cross-compatibility between amide coupling and activation enforces a practice whereby these two related reactions are taken as disparate synthetic tasks—performed in sequence (Figure 1A, top).

Recognizing that amide synthesis and electrophilic amide activation are both condensation processes, we considered whether a mild dehydrating electrophile—generated iteratively under catalytic conditions—would permit tandem dehydrative amidation/activation events in which the amide serves as a reactive intermediate. In line with Mukaiyama's "oxidation-reduction condensation" concept for irreversible dehydration,[16] recent results from our lab have established that iterative generation of a mild halophosphonium species within the P^{III}/P^{V} redox cycle[17] permits recursive dehydration (Figure 1A, bottom).[18] Under such a manifold, amides can be generated through condensation[19] and utilized *in situ* as valuable synthetic intermediates for further activation[20] and functionalization.[21]

Here, we report a P^{III}/P^{V}=O catalyzed[22] multicomponent cascade amide condensation and activation for intermolecular coupling, enabled by serial dehydration (Figure 1B). This approach provides rapid access to the valuable 2-amidopyridine pharmacophore,[23] typified by the analgesic propiram, WHO essential medicine dabigatran, and anti-Alzheimer's candidate lecozotan (Figure 1C). By expressing a net redox neutral reactivity in the P^{III}/P^{V}=O redox couple to drive serial condensation, a chemoselective assemblage of simple starting materials is achieved in a single reaction,[24] establishing a perspective on amides as veritable synthetic intermediates in catalytic tandem cascades.

Inspired by amide functionalization methods[25] from Abramovitch[26] and Movassaghi,[27] we envisioned a chemoselective tandem dehydrative three-component coupling[28] of amines, carboxylic acids, and pyridine *N*-oxides,[29] assembling 2-amidopyridines in a modular fashion. To probe this hypothesis, 1,2,2,3,4,4-hexamethyl phosphetane *P*-oxide **1**·[O][30] was evaluated in the coupling of acetic acid (**2**), propylamine (**3**), and 4-phenylpyridine *N*-oxide (**4**) to 2-amidopyridine **5**. In practice, 93% yield of **5** (86% isolated yield on 0.5 mmol scale) was obtained with 15 mol% **1**·[O], along with 2.2 equiv. diethyl(methyl)bromomalonate (DEMBM)[31] as oxidant, 3.0 equiv. diphenylsilane as reductant, and 1.0 equiv. of Hünig's base at 40 °C in 1.0 M acetonitrile (Table 1, entry 1). The stoichiometry of oxidant and reductant required are in line with iterative P^{III}/P^{V} redox cycling to formally strip two equivalents of H_2O from the substrate molecules, whereas omitting any of **1**·[O], DEMBM, or Ph_2SiH_2 resulted in no product formation, indicating that P^{III}/P^{V} redox cycling is essential (see SI for expanded table).[32] Critically, this reaction allows for evaluation of the chemoselectivity of the organophosphorus redox catalyst for the intended amide condensation/activation manifold, as phosphonium electrophiles, such as peptide-coupling reagent PyBroP,[33] are known to activate pyridine *N*-oxides for reaction with nucleophiles.[34] Notably, 2-aminopyridine **8** is not observed, even at lower conversion to product **5** (vide infra). While precise tuning of Hünig's base loading to effectively quench the acid generated under this redox condensation manifold was necessary for maximal efficiency (entries 2

and 3), lutidine could be used in place of Hünig's base with minimal effect (entry 4). With respect to catalyst, the *P*- phenyl phosphetane **6**·[O] could be used at the expense of some efficiency, while **7**·[O][35] proved to be ineffective, presumably due to lability at the α-unsubstituted cyclic methylene centers (entries 5 and 6).

In order to probe more specifically the sequence of bond-forming events, the coupling of **2** and **4** with 4-fluoroaniline (**9**) to **10** was monitored by ^{19}F NMR spectroscopy (Figure 2A).[36] Over the course of the first six hours, depletion of **9** and formation of the corresponding amide intermediate **11** was observed, with no formation of 2-aminopyridine **12**. Subsequently, once **9** was completely consumed, formation of product **10** was observed as the acetanilide **11** was dehydrated. This reaction profile is consistent with sequential dehydrative activation via an amide intermediate as proposed.[37] Independently, **11** and **4** could be dehydratively coupled to **10** under identical conditions with adjustment of reagent stoichiometry (see SI). In contrast, in the isolated reaction of **4** with **9**, no coupling to 2-aminopyridine **12** was observed by ^{19}F NMR or LC-MS (see SI). Thus, catalytically-generated bromophosphonium **1**·Br$^+$ is not effective for activation of the *N*-oxide, in contrast to *N*-oxide activation observed with PyBroP. This observed reactivity profile is in good agreement with stoichiometric reaction of [**1**·Br]Br with the reaction components.[38] In concert, these data support a reaction pathway of amide condensation followed by amide activation to generate imidoyloxypyridinium **13** and rearrangement to yield 2-amidopyridine[39] product **10** (Figure 2B), enabled by the catalytic generation of bromophosphonium ion **1**·Br$^+$ as a general, mild, and selective dehydrating species (see SI for full catalytic cycle).[40]

With an understanding of the reaction parameters and mechanism, scope of the reaction upon variation of the carboxylic acid coupling partner was evaluated (Figure 3). Straight-chain alkyl carboxylic acids (**14**–**18**, 61–78% yield) bearing various functional groups, including aryl fluoride (**15**), alkyl bromide (**16**), ether (**17**), and sulfonamide (**18**)could be transformed under the standard reaction conditions. Carboxylic acids bearing branching α-carbon centers (**19** and **20**, 77 and 83% yield, respectively) demonstrated equivalent efficiency. Further, benzoic acids bearing a wide variety of substitutions were successfully utilized in this reaction (**21**–**24**, 60–71% yield). A benzoic acid bearing a pendant alkyl ethyl ester provided the desired coupled product **24** in 63% yield with no evidence of ester reactivity, highlighting the mild nature of this catalytic dehydrative platform. A variety of heterocycle-containing carboxylic acids could be incorporated into this reaction, as benzotriazole[41] (**25**, 60% yield), unprotected *N*-H indole[42] (**26**, 71% yield), thiophene (**27**, 72% yield), *N*-Me benzimidazole[43] (**28**, 63% yield), and benzothiazole (**29**, 62% yield) moieties evidenced no deleterious side effects from the inherent reactivity of the heterocycle. A variety of undesired side-reaction pathways are available to these heterocyclic substrates through reaction with strong electrophiles, highlighting the advantageous nature of catalytic generation of a mild, selectively-activating phosphonium ion for tandem dehydration sequences on functionality-rich substrates.

Variation of the amine coupling partner to demonstrate scope and generality is also shown in Figure 3. Various primary alkyl amines containing reactive functionalities were

incorporated into 2-amidopyridines with good to excellent efficiency (**30**–**40**, 55–98% yield). β-Phenethylamines are readily functionalized (**30**–**32**, 66–84% yield); notably, 3,4-dimethoxyphenethylamine yielded the desired product **31** in 70% yield, with minimal (<5%) cyclodehydration onto the pendant electron-rich arene ring observed. Similarly, owing to the mild reaction temperature and inclusion of the bromenium oxidant, 4-nitrophenethylamine could be incorporated into this tandem dehydrative platform with no reaction at the nitroarene moiety (**32**, 66% yield).[44] Benzylamine could also be functionalized as desired (**33**, 85% yield), despite potential degradation pathways available to a putative *N*-benzyl nitrilium cation.[45] Further, amino acid esters of various chain lengths could be incorporated into the transformation directly from their commercial hydrochloride salts (**34**–**36**, 55–77% yield). Indazole-containing product **37** was delivered in 90% yield, demonstrating the ability of this system to incorporate pharmaceutically relevant heterocyclic motifs.[46] Similarly, primary amines with tethered basic tertiary amines[47] provided the desired products (**38**–**40**, 84–98% yield) without the need for exogenous amine base, evidencing the mild, chemoselective conditions are highly tolerant of Brønsted and Lewis basic functionality.[48] α-Secondary amine 4-amino-1-methylpiperidine could deliver **40** in 92% yield, despite the possibility of retro-Ritter reaction occurring from a putative nitrilium cation.[49]

A wide variety of anilines of varying electronic natures were competent in the tandem dehydrative catalytic transformation, with lutidine serving as the ideal base (**41**–**48**, 66–86% yield). Tolerated functionality include ether (**41**, 85% yield), chloro (**42**, 70% yield), fluoro (**12**, 78% yield), ester (**43**, 66% yield), and trifluoromethyl (**44**, 67% yield) groups, as well as sterically-encumbering *ortho*-substitution (**45** and **46**, 81 and 70% yield, respectively). This lack of apparent deleterious steric effects highlights the utility of complementary C–N bond-forming platforms. Bis-heteroaryl amide products containing benzodioxane[50] (**47**, 77% yield) and indazole[46] (**48**, 86% yield) cores demonstrate the efficacy of this catalytic protocol for incorporating heterocyclic motifs common in pharmaceutical chemistry into complex molecular scaffolds. Further, when varying both amine and carboxylic acid components, it was observed that less electron-rich *N*-aryl benzamide intermediates do not undergo appreciable activation under the standard conditions. However, this can be mitigated upon heating the reaction slightly to 80 °C delivering the amide-activated, three-component coupled product (**49** and **50**, 43 and 50% yield, respectively).

Variation of the pyridine *N*-oxide coupling partner was also evaluated (Figure 4A).[51] Replacement of the 4-Ph substituent with 4-Me and 4-H had minimal effect on efficiency, as products **51** and **52** were both formed in excellent yield (82 and 84%, respectively). From a 10 mmol scale reaction, **52** was able to be isolated in equal yield, affording 1.50 g of product, demonstrating the scalability of this transformation. 3-Methylpyridine *N*-oxide was functionalized to **53** in 71% yield, with 1.2:1 rr, indicating minimal steric or electronic influence on the C–N regioselectivity.[52] Given the broad generality of the transformation with respect to the amine and acid coupling partners, the functionalization[53] of bioactive pyridine scaffolds[54] via their *N*-oxides was undertaken to assess the utility of this new catalytic transformation in complex molecule derivatization (Figure 4B). Commonly-used pesticide pyriproxyfen, containing multiple ether linkages, was derivatized to yield **54** in 66% yield. Further, basal cell carcinoma drug vismodegib was functionalized

to product **55** in 63% yield. Notably, the *N*-aryl benzamide moiety, a competent substrate for activation under the catalytic system, was untouched in the reaction carried out at 40 °C. In addition, the oxidized sulfone was not observed to undergo any reductive reaction. In combination with earlier results, these examples demonstrate the utility of this organophosphorus-catalyzed transformation in the derivatization of complex molecules bearing sensitive functionality frequently present in biologically active compounds.

In conclusion, we have demonstrated that organophosphorus-catalyzed serial dehydration serves as an effective platform for both amide coupling and activation, enabling a convergent synthesis of 2-amidopyridines by three-component coupling of amines, carboxylic acids, and pyridine *N*-oxides. The ability to both access and functionalize an amide in situ establishes organophosphorus redox catalysis as a distinct, valuable modality within the expanding amide activation toolbox. The evident chemoselectivity and functional interplay of the catalyst, reagents and substrates in the title transformation portends further development of cascade condensation reactions driven by this catalytic manifold.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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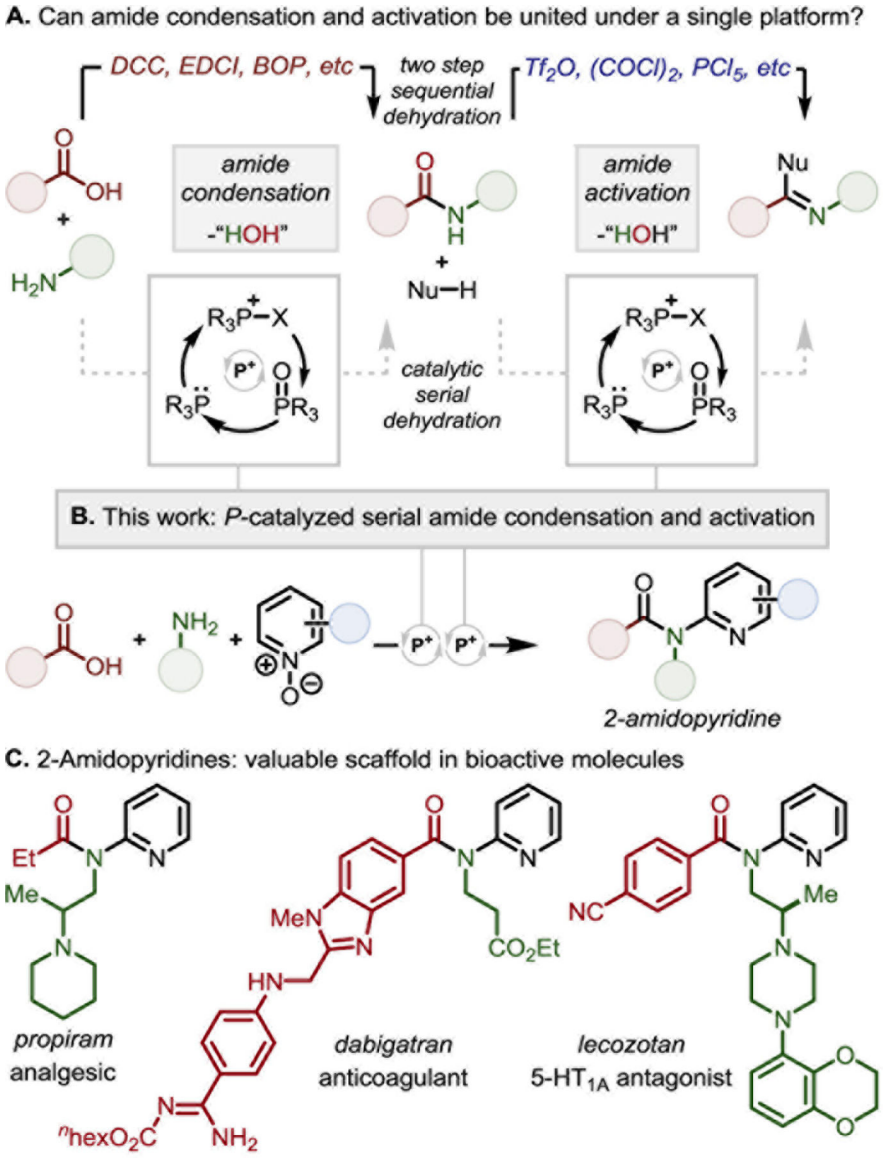


Figure 1.

(**A**) Amide condensation and activation utilize different reagents due to reactivity differences – can they be chemoselectively carried out in tandem via a unified phosphacatalytic platform? (**B**) Organophosphorus-catalyzed condensation of amines, carboxylic acids, and pyridine *N*-oxides to 2-amidopyridines via serial dehydration. (**C**) Pharmaceutical agents containing 2-amidopyridine core.

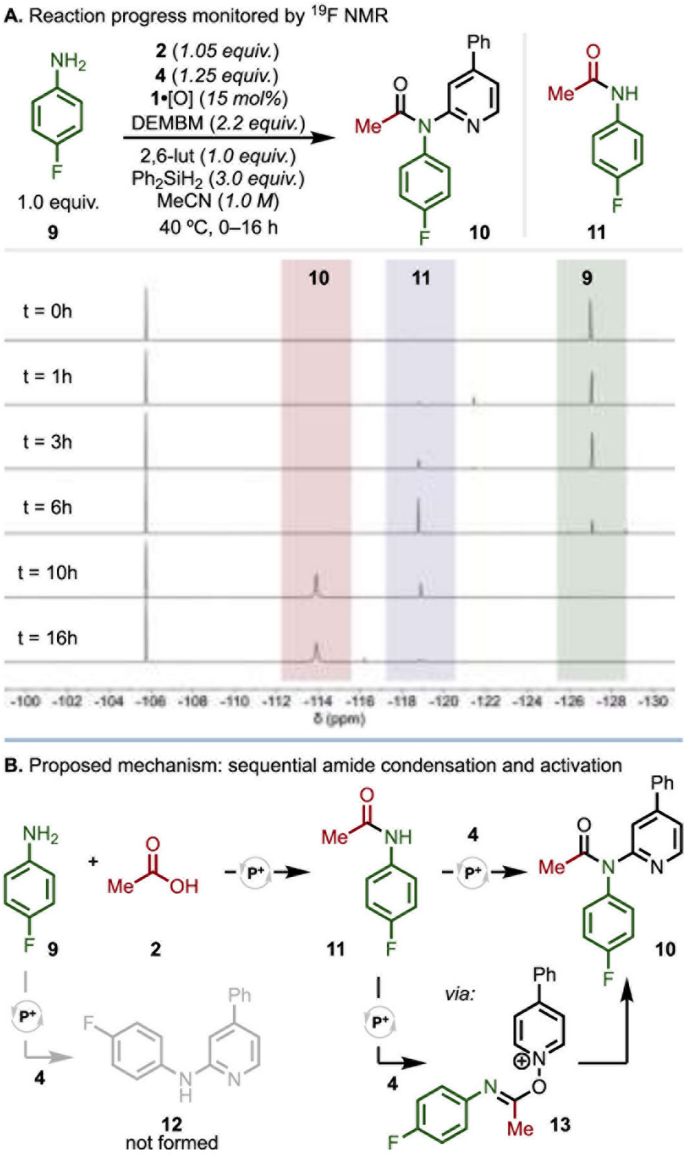


Figure 2.

(**A**) Time-stacked ^{19}F NMR spectra (in $CDCl_3$) of the coupling of **9** with **2** and **4** at the indicated time points, showing aniline **9** (δ −127.3 ppm), acetanilide **11** (δ −118.8 ppm), and 2-amidopyridine **10** (δ −113.9 ppm), with 4,4'-difluorobenzophenone internal standard (δ −105.8 ppm). (**B**) Proposed reaction mechanism proceeding through amide condensation and activation, not pyridine *N*-oxide activation.

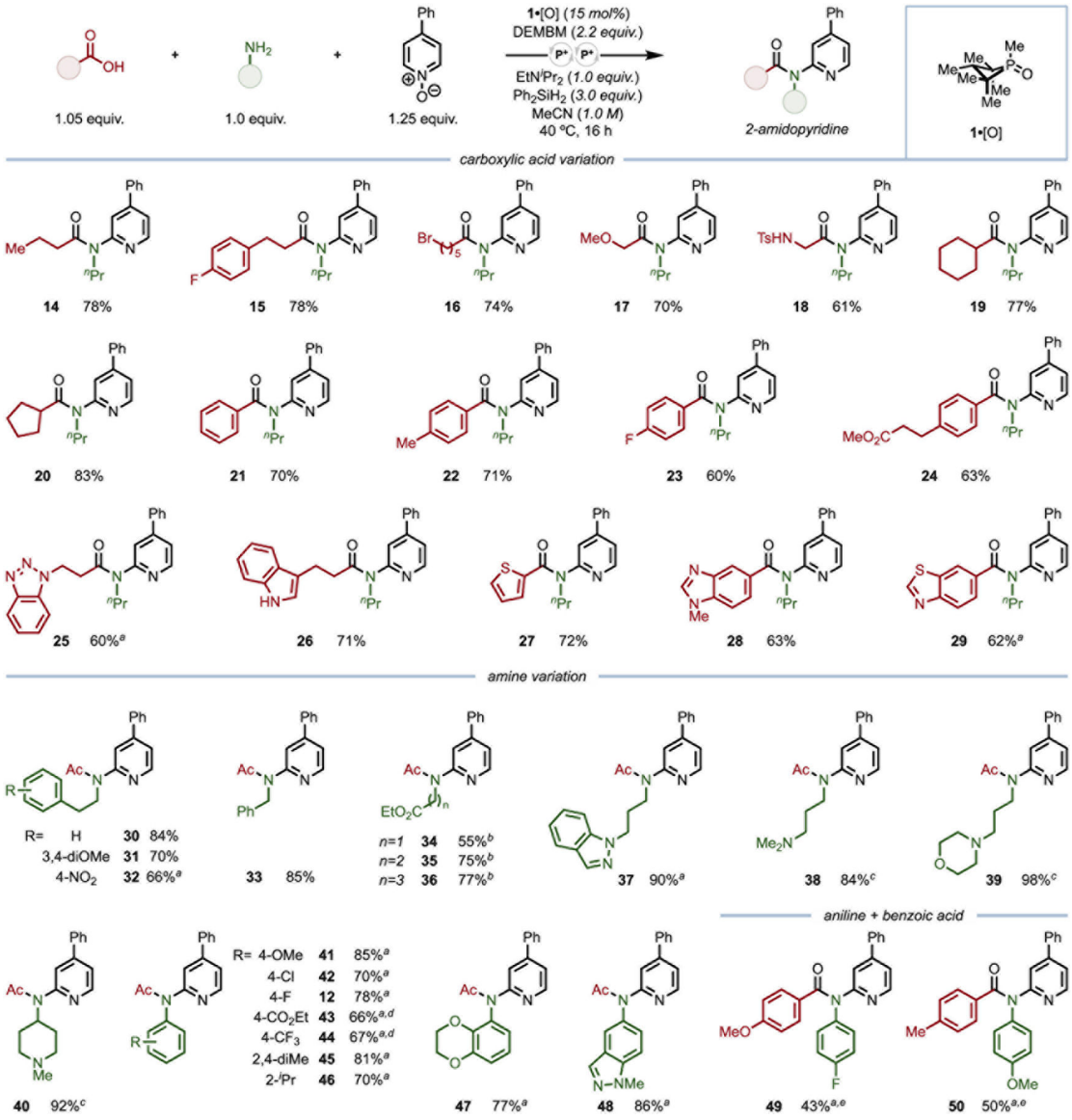


Figure 3.

Synthetic scope of three-component serial dehydrative coupling of amines, carboxylic acids, and pyridine *N*-oxides. All yields isolated on 0.5 mmol scale. [a] 2,6-Lutidine in place of EtN^{i}Pr$_2$. [b] Amine hydrochloride salt, 2,6-lutidine (2.0 equiv.) in place of EtN^{i}Pr$_2$. [c] No EtN^{i}Pr$_2$. [d] 60 °C. [e] 80 °C.

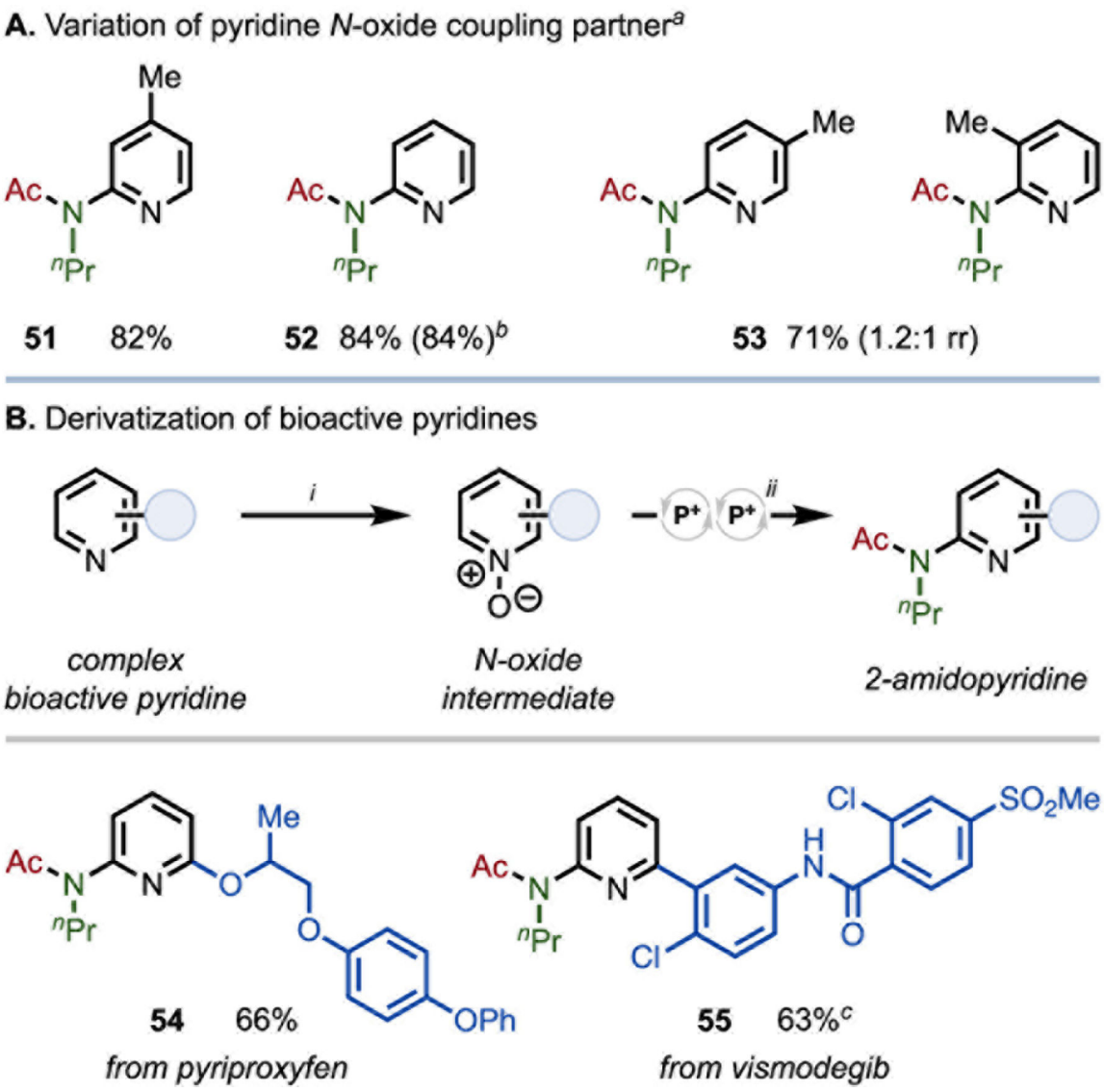
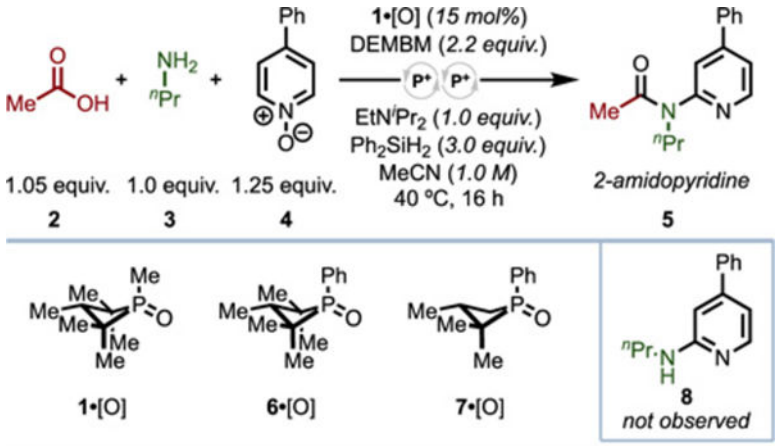


Figure 4.

(**A**) Variation of pyridine *N*-oxide in tandem dehydration coupling. (**B**) Derivatization of pharmaceuticals by phosphacatalytic serial dehydrative amide condensation and amide activation. See SI for full synthetic details. All yields isolated. [i] *m*CPBA (1.05 equiv., 77%), CH_2Cl_2, 18 h. [ii] **2** (1.05 equiv.), **3** (1.0 equiv.), pyridine *N*-oxide (1.25 equiv.), **1**·[O] (15 mol%), DEMBM (2.2 equiv.), EtN^iPr_2 (1.0 equiv.), Ph_2SiH_2 (3.0 equiv.) MeCN (1.0 M), 40 °C, 16 h. [a]Conditions as in Figure 3. [b]Yield in parentheses on 10.0 mmol scale; 1.50 g **52** isolated. [c]20 h. *m*CPBA = *meta*-chloroperoxybenzoic acid.

Table 1.

Optimized conditions and variations.



Entry	deviation from standard	Yield of 5 (%)[a]
1	none	93 (86)[b]
2	2.0 equiv. EtN^{i}Pr$_2$	71
3	0 equiv. EtN^{i}Pr$_2$	78
4	2,6-lutidine in place of EtN^{i}Pr$_2$	88
5	**6**·[O] in place of **1**·[O]	85
6	**7**·[O] in place of **1**·[O]	0

[a]Yield determined by ^{1}H NMR against internal standard on 0.125 mmol scale reaction.

[b]Isolated yield on 0.5 mmol scale reaction. DEMBM = diethyl(methyl)bromomalonate, 1,2-DCE = 1,2-dichloroethane.