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

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 the 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. 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. By virtue of the reducing potential of the P^{III}/P^{V} couple, many of these transformations are reductive in nature. In this vein, we have shown that four-membered ring organophosphorus catalysts effect reductive conversion of nitro and sulfonyl 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., autotandem catalysis).

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.” Within a P^{III}/P^{V}-catalytic context, 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 (Figure 1A, right). Indeed, halophosphonium intermediates have been invoked by Rutjes and van Delft and Mecinovic in the context of P^{III}/P^{V}-catalyzed Appel halogenation and N-acylation reactions, respectively. In view of the fact that phosphonium reagents have been described as having “virtually ideal properties as selective oxygen extractors for net dehydrogenation reactions,” the potential to achieve recursive dehydrogenations in an autotandem 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.

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 autotandem catalytic system enables the elaboration of simple 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 to orchestrate a sequence of dehydration reactions, the potential to achieve recursive dehydrogenations in an autotandem 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.

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distinct C–N and C–C bond-forming events. The ability of $^{\text{III}}/^{\text{V}}$ 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.

To evaluate the possibility of recursive dehydration driven by $^{\text{III}}/^{\text{V}}$ 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 $4\cdot[\text{O}]$ 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 bromonium reagent was found to be essential for the redox compatibility of the system, as demonstrated by Rutjes and van Delft; 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). Chloreon 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.

With respect to catalyst, variation of the phosphetane exocyclic moiety to ethyl $5\cdot[\text{O}]$, entry 6), phenyl $6\cdot[\text{O}]$, entry 7), or pyrrolidino $7\cdot[\text{O}]$, entry 8) all resulted in substantial decrease in the efficiency of the reaction, while acrylic phosphate oxides $8\cdot[\text{O}]$ or $9\cdot[\text{O}]$, entry 9) fail to promote the cyclocondensation (see Supporting Information). Control experiments confirm that no azaheterocycle product is observed in the absence of any of $4\cdot[\text{O}]$, phenylsilane, or DEBM (entries 10–12). Furthermore, employing $^{\text{III}}$ species 4 or pregenerated bromophosphonium $[4\cdot\text{Br}]$Br in place of phosphine oxide $4\cdot[\text{O}]$ resulted in comparable efficiency, consistent with the notion of $^{\text{III}}/^{\text{V}}$ redox cycling (entries 13 and 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 $4\cdot[\text{O}]$. 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 $^{\text{III}}/^{\text{V}}$-catalytic manifold (3i, 3m, 93% and 98% yields, respectively). Substitution on the aniline ring was well-tolerated; both ortho- and meta-substituted pyrroloamines 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 stereochirality fidelity (3q, 67%, 95:5 enantiomeric ratio (e.r.); 3r, 68%, 92:5:7 e.r.) under modified recursive dehydration conditions (precatalyst $[4\cdot\text{Br}]$Br, MeCN, 50 °C; 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 gas chromatography–mass spectrometry (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-pyrrlobenzylamine could be efficiently coupled with carboxylic acids via iterative dehydration to provide the corresponding pyrrolobenzodiazepines, a prevalent bioactive scaffold, in good yields (3s–3u, 66–86% yields). Heterocycles 3t and 3u, compounds investigated by Janssen for their antifungal activity, could be prepared in a single synthetic operation in 86% and 73% yields, respectively. Further, trypamine and phenethyamines could be transformed into dihydro-$\beta$-carboline and dihydroisoquinoline products in good yields (3v–3x, 70–77% yields). Notably, both of these scaffolds are found in bioactive pharmaceutical agents and natural products, as demonstrated by the assembly in a single
Concerning the catalytic mechanism, in situ 1H 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 Supporting Information, Section VI), establishing a stepwise reaction sequence for the autotandem catalytic process in which C−C bond-forming cyclodehydration is kinetically limiting. Despite the observation that 4, 4·[O], and 4·Br⁺ are each competent precatalysts (vide supra), in situ 31P NMR and direct analysis in real time (DART) mass spectrometry (MS) analyses show that none of these compounds represent the catalytic resting state. Rather, experiments are most consistent with resting state B1, which is an adduct of the phosphacyclic catalyst and amide A1 (Figure 3A). Indeed, independent reaction of 4·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. Furthermore, spectroscopically indistinguishable species are observed by 31P NMR spectroscopy when either N-methylacetamide or N,N-dimethylacetamide are introduced in lieu of reactive amides to a mixture containing catalytic components (i.e., 4·[O], PhSiH₃, DEBM).

Figure 3B depicts a plausible autotandem 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 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 PhSiH₃ 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. 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.

The net redox neutral character of the recursive dehydration (and the absence of appreciable concentrations of phosphine 4) enables chemoselective annulation of amines and carboxylic acids. Methyl groups excluded from 4 for clarity.

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.

**ASSOCIATED CONTENT**

* Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b06277.

Additional optimization results, mechanistic studies, and synthetic procedures. 1H, 13C, and 31P NMR spectra (PDF)

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**Notes**

The authors declare no competing financial interest.

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![Figure 3.](image_url)  
Figure 3. (A) 31P NMR studies, resonance of major diastereomer. (B) Proposed mechanism of autotandem catalytic dehydrative annulation of amines and carboxylic acids. Methyl groups excluded from 4 for clarity.

![Figure 4.](image_url)  
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), PhSiH3 (2.2 equiv), 4·[O] (15 mol %), DCE, 80 °C; (b) 11 (1.0 equiv), 4-MeO-C6H4-B(OH)2 (1.1 equiv), PhSiH3 (2.0 equiv), 4·[O] (15 mol %), m-xylene, 120 °C.

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REFERENCES

(1) (a) O’Brien, C. J.; Tellez, J. L.; Nixon, Z. S.; Kang, L. J.; Carter, A. L.; Kunkel, S. R.; Przeworski, K. C.; Chass, G. A. Recycling the Waste: The Development of a Catalytic Wittig Reaction. Angew. Chem., Int. Ed. 2009, 48, 6838−6839. (b) O’Brien, C. J. Catalytic Wittig and Mitsunobu Reactions. U.S. Patent 8,901,365, Dec 2, 2014.

(2) (a) van Kalkeren, H. A.; van Delft, F. L.; Rutjes, F. P. J. T. Organophosphorus Catalysis to Bypass Phosphine Oxide Waste. ChemSusChem 2013, 6, 1615−1624. (b) Guo, H.; Fan, Y. C.; Sun, Z.; Wu, Y.; Kwon, O. Phosphate Organocatalysis. Chem. Rev. 2018, 118, 10049−10093.

(3) For reviews discussing P=O catalysis, see: (a) Marsden, S. P. Catalytic Variants of Phosphate Oxide-Mediated Organic Transformations. In Sustainable Catalysis; Dunn, P. J.; Hii, K. K.; Krische, M.; Williams, T. Eds.; John Wiley & Sons, Inc.: New York, 2013; pp 339−361. (b) Denmark, S. E.; Stavenger, R. A. Asymmetric Catalysis of Aldol Reactions with Chiral Lewis Bases. Acc. Chem. Res. 2000, 33, 432−440. (c) Denmark, S. E.; Beutner, G. L. Lewis Base Catalysis in Organic Synthesis. Angew. Chem., Int. Ed. 2008, 47, 1560−1638. (d) Benaglia, M.; Rossi, S. Chiral Phosphine Oxides in Present-Day Organocatalysis. Org. Biomol. Chem. 2010, 8, 3824−3830.

(4) Marsi, K. L. Phenylenesilane Reduction of Phosphate Oxides with Complete Stereoselectivity. J. Org. Chem. 1974, 39, 265−267.

(5) (a) van Kalkeren, H. A.; Leender, G. H. M.; Hommersom, C. R. A.; Rutjes, F. P. J. T.; van Delft, F. L. In Situ Phosphate Oxide Reduction: A Catalytic Appel Reaction. Chem. − Eur. J. 2011, 17, 11290−11295. (b) van Kalkeren, H. A.; van Delft, F. L.; Rutjes, F. P. J. T. Catalytic Appel Reactions. Pure Appl. Chem. 2012, 85, 817−828.

(6) Zhao, W.; Yan, P. K.; Radoshevich, A. T. A. Phosphetane Catalysts Deoxygenative Condensation of α-Keto Esters and Carboxylic Acids via P=O/P=O Redox Cycling. J. Am. Chem. Soc. 2015, 137, 616−619.

(7) For phosphocatalytic Staudinger and related reactions: (a) van Kalkeren, H. A.; Bruins, J. J.; Rutjes, F. P. J. T.; van Delft, L. Organophosphorus Catalysed Staudinger Reduction. Adv. Synth. Catal. 2012, 354, 1417−1421. (b) van Kalkeren, H. A.; te Grotenhuis, C.; Haasjes, F. S.; Hommersom, C. R. A.; Rutjes, F. P. J. T.; van Delft, F. L. F. Organo Phosphorus-Catalyzed Intramolecular Csp2−N Amination: Evidence for a Nitrenoid in Catalytic Cadogan Cyclizations. J. Am. Chem. Soc. 2018, 140, 3103−3113. (c) Nykaza, T. V.; Cooper, J. C.; Li, G.; Mahieu, N.; Ramirez, A.; Xiaov, M. R.; Radoshevich, A. T. Intermolecular Reductive C−C Cross Coupling of Nitroarenes and Boronic Acids by P=O/P=O Catalysis. J. Am. Chem. Soc. 2018, 140, 15200−15205.

(8) (a) Ghosh, A.; Lecomte, M.; Kim-Lee, S.-H.; Radoshevich, A. T. Phosphorus Catalyzed Deoxygenation of Sulfonyl Chlorides: Electrophilic (Fluororalkyl)sulfenylation by P=O/P=O Redox Cycling. Angew. Chem., Int. Ed. 2019, 58, 2864−2869.

(9) Fogg, D. E.; dos Santos, E. N. Tandem Catalysis: A Taxonomy and Illustrative Review. Coord. Chem. Rev. 2004, 248, 2365−2379.

(10) (a) Muijaya, T. Oxidation-Reduction Condensation. Angew. Chem., Int. Ed. Engl. 1976, 15, 94−103. (b) Muijaya, T. Explorations into New Reaction Chemistry. Angew. Chem., Int. Ed. 2004, 43, 5590−5614.

(11) (a) Buonomo, J. A.; Aldrich, C. C. Mitsunobu Reactions Catalytic in Phosphate and a Fully Catalytic System. Angew. Chem., Int. Ed. 2015, 54, 13041−13044. (b) Hirose, D.; Gazvoda, M.; Kosmrlj, J.; Taniguchi, T. The “Fully Catalytic System” in Mitsunobu Reaction Has Not Been Realized Yet. Org. Lett. 2016, 18, 4036−4039.

(12) (a) Muijaya, T. Applications in Catalysis. Coord. Chem. Rev. 2004, 248, 2864−2869. (c) Nykaza, T. V.; Cooper, J. C.; Li, G.; Mahieu, N.; Ramirez, A.; Xiaov, M. R.; Radoshevich, A. T. Intermolecular Reductive C−C Cross Coupling of Nitroarenes and Boronic Acids by P=O/P=O Catalysis. J. Am. Chem. Soc. 2018, 140, 15200−15205.

(13) (a) Buonomo, J. A.; Aldrich, C. C. Mitsunobu Reactions Catalytic in Phosphate and a Fully Catalytic System. Angew. Chem., Int. Ed. 2015, 54, 13041−13044. (b) Hirose, D.; Gazvoda, M.; Kosmrlj, J.; Taniguchi, T. The “Fully Catalytic System” in Mitsunobu Reaction Has Not Been Realized Yet. Org. Lett. 2016, 18, 4036−4039.

(14) (a) Muijaya, T. Applications in Catalysis. Coord. Chem. Rev. 2004, 248, 2365−2379. (c) Nykaza, T. V.; Cooper, J. C.; Li, G.; Mahieu, N.; Ramirez, A.; Xiaov, M. R.; Radoshevich, A. T. Intermolecular Reductive C−C Cross Coupling of Nitroarenes and Boronic Acids by P=O/P=O Catalysis. J. Am. Chem. Soc. 2018, 140, 15200−15205.

(15) For halophosphonium cations as Lewis acids, see: (a) Caputo, C. B.; Hounjet, L. J.; Dobrovetsky, R.; Stephan, D. W. Lewis Acidity of Organofluorophosphonium Salts: Hydrodefluorination by a Saturated Acceptor. Science 2013, 341, 1374−1377. (b) Bayne, J. M.; Stephan, D. W. Phosphorus Lewis Acids: Emerging Reactivity and Applications in Catalysis. Chem. Soc. Rev. 2016, 45, 765−774.

(16) Lenstra, D. C.; Rutjes, F. P. J. T.; Mecinović, J. Triphenylphosphine-Catalysed Amide Bond Formation Between Carboxylic Acids and Amines. Chem. Commun. 2014, 50, 5763−5766.

(17) P=O-catalyzed deoxygenation and amidation reactions using phosphine oxide and oxalyl chloride have been developed: (a) Denton, R. M.; An, J.; Adeniran, B. Phosphate Oxide-Catalysed Chlorination Reactions of Alcohols Under Appel Conditions. Chem. Commun. 2010, 46, 3025−3027. (b) Denton, R. M.; Tang, X.; Przeslak, A. Catalysis of Phosphorus(V)-Mediated Transformations: Dichlorination Reactions of Epoxides Under Appel Conditions. Org. Lett. 2010, 12, 4678−4681. (c) Denton, R. M.; An, J.; Adeniran, B.; Blake, A. J.; Lewis, W.; Poulton, A. M. Catalytic Phosphorus(V)-Mediated Nucleophilic Substitution Reactions: Development of a Catalytic Appel Reaction. J. Org. Chem. 2011, 76, 6749−6767. (d) An, J.; Tang,
X.; Moore, J.; Lewis, W.; Denton, R. M. Phosphorus(V)-Catalyzed Deoxydichlorination Reactions of Aldehydes. Tetrahedron 2013, 69, 8769–8776. (e) Yu, T.-Y.; Wang, Y.; Xu, P.-F. An Unusual Triphenylphosphine Oxide Catalyzed Stereoselective 1,3-Dichlorination of Unsaturated Ketoesters. Chem. - Eur. J. 2014, 20, 98–101. (f) Tang, X.; An, J.; Denton, R. M. A Procedure for Appel Halogenations and Dehydrations Using a Polystyrene Supported Phosphine Oxide. Tetrahedron Lett. 2014, 55, 799–802. (g) Jiang, L.; Yu, J.; Niu, F.; Zhang, D.; Sun, X. A High-Efficient Method for the Amidation of Carboxylic Acid Derivatives Promoted by Triphenylphosphine Oxide and Oxaeryl Chloride. Heteroat. Chem. 2017, 28, No. e21364.

(18) Hendrickson, J. B.; Hussejn, M. S. Seeking the Ideal Dehydrating Reagent. J. Org. Chem. 1987, 52, 4137–4139.

(19) Phosphonium salts are widely used as peptide-coupling reagents: (a) El-Faham, A.; Albericio, F. Peptide Coupling Reagents, More than a Letter Soup. Chem. Rev. 2011, 111, 5657–6602. (b) Berchel, M.; Jaffrès, P.-A. Recent Developments in Phosphonium Chemistry. In Organophosphorus Chemistry: From Molecules to Applications; Jaroshenko, V., Ed.; Wiley-VCH: Weinheim, Germany, 2019; pp 78–84.

(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 Supporting Information, Section V, Table S4, 18 examples).

(22) Silanes have been shown to promote amidation, including in phosphine-catalyzed Staudinger amidation. However, low background racemization even at room temperature; see: Movassaghi, M.; Hill, M. D. A Versatile Cyclodehydration Reaction for the Synthesis of Isoquinoline and β-Carbolines Derivatives. Org. Lett. 2008, 10, 3485–3488.

(23) For comparison, s was formed in 31% yield using DEBM (yield by ’H NMR analysis with the aid of an internal standard).

(24) For the synthesis of halophosphonium from phosphine oxides, see: (a) Ruan, Z.; Lawrence, R. M.; Cooper, C. B. Phenylsilane Catalytic Bischler-Napieralski-type cyclodehydration of preformed amides (see Supporting Information, Section II, Table S1). See: (a) Ruam, 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.

(25) For the synthesis of halophosphonium from phosphine oxides, see: (a) Nikitin, K.; Müller-Bunz, H.; Gilheany, D. Direct Evidence of a Multicentre Halogen Bond: Unexpected Contraction of the P–XXX–P Fragment in Triphenylphosphine Dihalides. Chem. Commun. 2013, 49, 1434–1436. (b) Jennings, E. V.; Nikitin, K.; Orttin, Y.; Gilheany, D. G. Degenerate Nucleophilic Substitution in Phosphonium Salts. J. Am. Chem. Soc. 2014, 136, 16217–16226. (c) Nikitin, K.; Jennings, E. V.; Al Sulaimi, S.; Orttin, Y.; Gilheany, D. G. Dynamic Cross-Exchange in Halophosphonium Species: Direct Observation of Stereoinversion in the Course of an S² Process. Angew. Chem., Int. Ed. 2018, 57, 1480–1484.

(26) For comparison, s was formed in 31% yield using DEBM (yield by ‘H NMR analysis with the aid of an internal standard).

(27) Compound 3w is formed racemically under both standard and modified conditions (as used for 3p-3s). 3,4-Dihydroisoquinolines bearing α-stereogenic centers are known to undergo facile thermal racematization even at room temperature; see: Movassaghi, M.; Hill, M. D. A Versatile Cyclodehydration Reaction for the Synthesis of Isoquinoline and β-Carbolines Derivatives. Org. Lett. 2008, 10, 3485–3488.

(28) (a) McKenzie, E.; Nettleship, L.; Slaytor, M. New Natural Products from Peganum harmala. Phytochemistry 1975, 14, 273–275. (b) Cao, R.; Peng, W.; Wang, Z.; Xu, A. β-Carbolines Alkaloids: Biochemical and Pharmacological Functions. Curr. Med. Chem. 2007, 14, 479–500. (c) Rommelspacher, H.; Susilo, R. Tetrahydroisoquinolines and β-Carbolines: Putative Natural Substances in Plants and Mammals. In Progress in Drug Research; Jucker, E., Ed.; Birkhäuser Verlag: Basel, Switzerland, 1985; Vol. 29, pp 415–459.

(29) Whaley, W. M.; Govindachari, T. R. The Preparation of 3,4-Dihydroisoquinolines and Related Compounds by the Bischler-Napieralski Reaction. Org. React. 1951, 6, 74–144.

(30) (a) Hoffmann, H.; Diehr, H. J. Phosphonium Salt Formation of the Second Kind. Angew. Chem., Int. Ed. Engl. 1964, 3, 737–746. (b) Zefirov, N. S.; Makhon’kov, D. I. X-philic Reactions. Chem. Rev. 1982, 82, 615–624.

(31) The classical Bischler-Napieralski reaction is understood to proceed via elimination of oxaphosphonium to generate a nitroinum ion, as evidenced by the formation of side-product alkene deriving from retro-Ritter reaction. For no substrates described in this manuscript was alkene formation observed, but the intermediacy of a nitroinum ion cannot be ruled out in this chemistry. See: (a) Fodor, G.; Nagubandi, S. Correlation of the von Braun, Ritter, Bischler-Napieralski, Beckmann and Schmidt Reactions via Nitritium Salt Intermediates. Tetrahedron 1980, 36, 1279–1300. (b) Nagubandi, S.; Fodor, G. The Mechanism of the Bischler-Napieralski Reaction. J. Heterocycl. Chem. 1980, 17, 1457–1463.