

# Title: Heterobiaryl synthesis by contractive C–C coupling via P(V) intermediates

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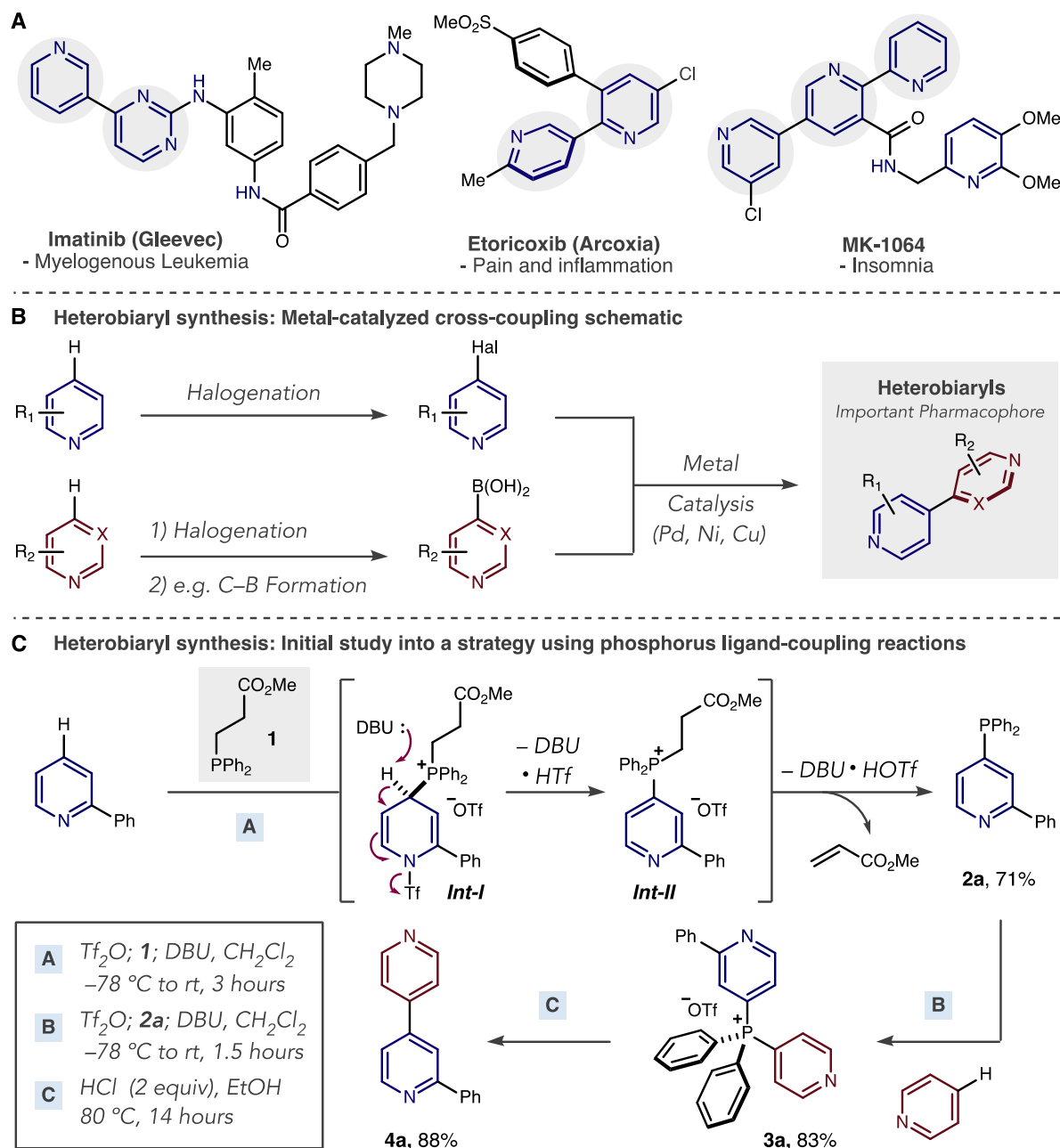
**Abstract:** Heterobiaryls composed of pyridine and diazine rings are key components of pharmaceuticals and often central to pharmacological function. Herein, we present an alternative approach to metal-catalyzed cross-coupling to make heterobiaryls using contractive phosphorus C–C couplings, also termed phosphorus ligand-coupling reactions. The process starts by regioselective phosphorus substitution of the C–H bonds *para* to nitrogen in two successive heterocycles; ligand-coupling is then triggered via acidic alcohol solutions to form the heterobiaryl bond. Mechanistic studies imply that ligand-coupling is an asynchronous process involving migration of one heterocycle to the *ipso* position of the other. The strategy can be applied to complex drug-like molecules containing multiple reactive sites and polar functional groups as well as enabling convergent coupling of drug fragments and late-stage heteroarylation of pharmaceuticals.

**One Sentence Summary:** Phosphorus can be used instead of transition metals to couple complex nitrogen heterocycles.

**Main Text:** Reactions that couple two aromatic rings to make biaryls are amongst the most widely used processes in the pharmaceutical industry (1, 2). Coupling pyridines and diazines results in heterobiaryls, a privileged pharmacophore found in commercial drugs as well as numerous therapeutic candidates, such as the examples shown in Fig. 1A (3-5). These heterocycles often play a key role in drug-receptor binding and impart other important properties such as net polarity, aqueous solubility and resistance to oxidative metabolism. Most conceivable aryl-aryl coupling are possible using metal-catalyzed cross-coupling reactions; these processes feature exceptional chemoselectivity, precise regioselectivity and sufficient robustness to be applied to both drug discovery and manufacture (6-8). However, the same synthetic prowess is not transferable to heteroaryl-heteroaryl coupling, particularly for complex substrates. An alternative strategy that addresses the shortcomings in this fundamental bond-construction would therefore offer new opportunities to incorporate heterobiaryls into therapeutic candidates.

For de novo synthesis of heterobiaryls, a schematic for metal-catalyzed cross-couplings is shown in Fig. 1B (9-15). A minimum of three steps are required, and there are challenges in the coupling step, such as catalyst poisoning and decomposition of starting materials (16). Furthermore, drug-like molecules and intermediates often have multiple reactive sites and a high proportion of polar functional groups, such as basic amines, that interfere with catalytic processes and cause a considerable number of them to fail (15, 17). Another serious problem arises from the lack of methods to prepare the cross-coupling precursors. Although simple heteroaryl halides are commercially available, or can be straightforwardly prepared, direct and

selective halogenation of pyridine and diazine derivatives encountered during drug development remains an unsolved challenge (18, 19). Similarly, synthesizing nucleophilic coupling partners, such as heteroaryl boronic acids, stannanes and organozinc or magnesium compounds is challenging, and they are often prepared from the corresponding heteroaryl halides to begin with (20). Cross-dehydrogenative couplings of heteroarenes have shown some promise, but are currently limited to specific pyridine combinations and are not applicable in complex settings (21).



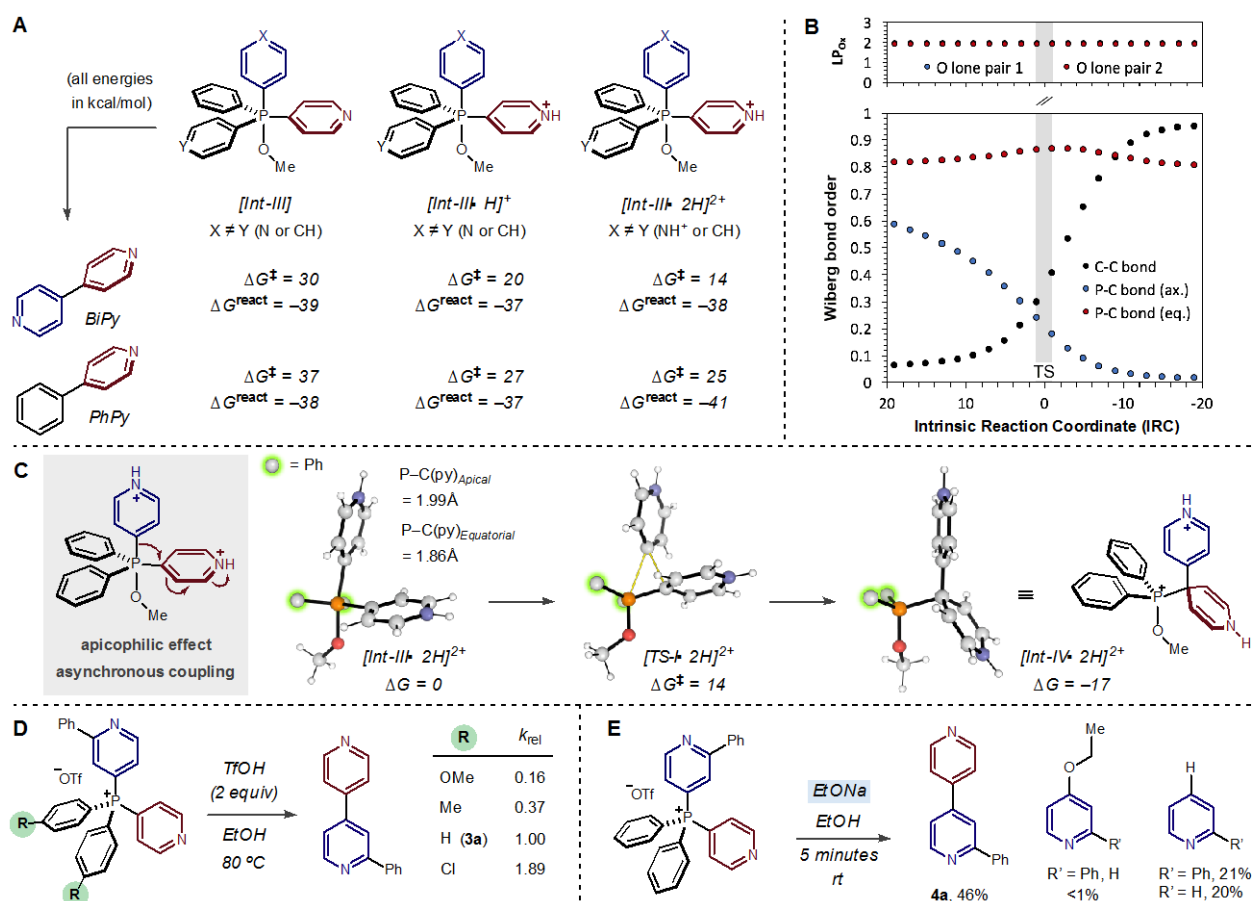
**Fig. 1. Important heterobiaryl-containing drugs and synthetic strategies.** (A) Heterobiaryls in drugs. (B) Heterobiaryls via metal-catalyzed cross-coupling reactions. R denotes a general

organic group; hal, halogen substituent. (C) Test system for heterobiaryl synthesis via phosphorus ligand-coupling reactions. Ph, phenyl group; Me, methyl group; Et, ethyl group; Tf, trifluoromethylsulfonyl; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; equiv, equivalent.

**Reaction development.** The limitations of current heterocycle coupling methods can potentially be overcome by ‘contractive’ phosphorus C–C couplings, often termed phosphorus ligand-coupling reactions, and a test system is shown in Fig. 1C (22-24). The strategy does not rely on heteroaryl halides or partners such as boronic acids and, instead, regioselectively substitutes the C–H bond in each heterocyclic coupling partner by successive C–P bond formations to form a bis-azaarene phosphonium salt; phosphorus ligand-coupling is then triggered to form the heterobiaryl bond via a P(V) intermediate. Heteroaryl-heteroaryl coupling has previously been observed at phosphorus centers, but an inability to transform a generic set of pyridines and diazine precursors into the required bis-azaarene phosphonium salts has restricted these processes to specialized cases (25-29). In our test system, stage A combined the first heterocycle, 2-phenylpyridine, with Tf<sub>2</sub>O at low temperature to form an intermediate pyridinium triflyl salt (not shown), adding fragmentable phosphine **1** (prepared on large scale from diphenyl phosphine and methyl acrylate) (30), results in a *para*-selective reaction to form dearomatized intermediate **Int-I** (31-37). Two equivalents of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) eliminates both the triflyl anion to form phosphonium ion **Int-II**, and then methyl acrylate resulting in heteroaryl phosphine **2a** in good yield. Pyridine was chosen as the second coupling partner in stage B with phosphine **2a** as a nucleophile, resulting in bis-heteroaryl phosphonium salt **3a**, with complete regiocontrol. Several nucleophiles are known to initiate phosphorus ligand-coupling including alkoxides, Grignard reagents and acidic alcohol solutions (22, 25-29); for stage C, we found the latter to be most effective and two equivalents of HCl in EtOH at 80 °C to be optimal, forming heterobiaryl **4a** in excellent yield with diphenylphosphine oxide as a by-product (see Table S1). Notably, we did not observe products from heteroaryl-phenyl or phenyl-phenyl coupling as well as ethoxylation of either heterocyclic in this protocol.

**Mechanistic investigation.** To investigate the reasons for selective heterocycle-heterocycle coupling and the kinetics of the ligand-coupling process, we performed a series of experimental and computational studies. We hypothesized that ethanol attacks the phosphorus center and a P(V) species is formed. Subjecting salt **3a** to a solution of DCl in *d*<sub>4</sub>-methanol results in successive shifts of pyridine proton resonances per equivalent of acid by <sup>1</sup>H NMR and <sup>31</sup>P NMR, and indicates that both pyridines are protonated (see fig. S12). However, no P(V) intermediates were detected in a <sup>31</sup>P NMR study under the reaction conditions. Computational studies do predict that intramolecular ligand-coupling occurs from P(V) intermediate **Int-III** in a stepwise fashion (*vide infra*), and that there is a substantial barrier-lowering effect ( $\Delta G^\ddagger$ ) upon successive protonation of **Int-III** (Fig. 2A) (38). Transition state energies significantly favor pyridine-pyridine coupling over pyridine-phenyl coupling for each protonation state;  $\Delta G^{\text{react}}$  values show that the process is similarly exergonic and irreversible in each case, and reinforces that selective pyridine-pyridine coupling results from kinetic differences in the ligand-coupling transition state rather than thermodynamic factors. The intrinsic reaction coordinate (IRC, Fig. 2B) shows no involvement of alkoxy lone-pairs and negligible changes to the other three equatorial P–C bonds. In the C–C bond-forming transition structure [TS-I·2H]<sup>2+</sup>, a single P–C bond breaks, allowing one ligand to migrate to the *ipso*-carbon of another (Fig. 2C). The intermediate formed in this key step ([Int-IV·2H]<sup>2+</sup>) is a dearomatized adduct characteristic of nucleophilic aromatic substitution, which is predicted to collapse irreversibly ( $\Delta G = -39$  kcal/mol) and with

considerable ease (see figs. S9–S11). This stepwise ligand-coupling is therefore mechanistically distinct from the concerted cleavage of two  $\sigma$ -bonds during reductive elimination at e.g. Pd(II) or in forming dihydrogen from  $\text{PH}_5$ . This latter detail is important because concerted coupling of apical-equatorial substituents from a ( $\text{D}_{3h}$ ) trigonal bipyramidal compound is symmetry-forbidden (fig. S6) (24): in contrast, this stepwise-coupling mechanism permits, and indeed favors, the migration of an apical ligand to an equatorial one ( $[\text{TS-I}\cdot\text{2H}]^{2+}$ ) (fig. S7).



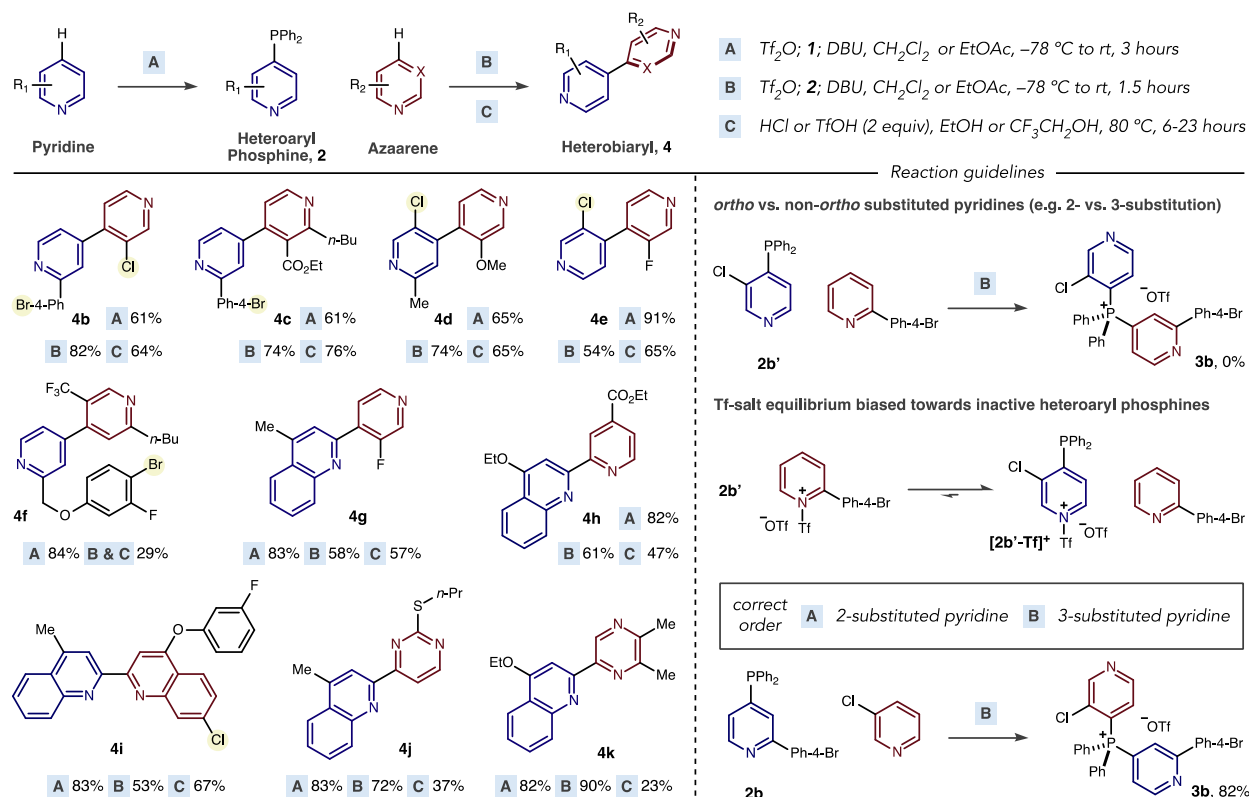
**Fig. 2. Computational and experimental investigation of phosphorus ligand-coupling.** (A) Biaryl-coupling activation barriers (SMD-DLPNO-CCSD(T)/cc-pV(DT)Z// $\omega$ B97XD/6-31+G(d), kcal/mol) decrease upon protonation and consistently favor heterobiaryl formation. Py, pyridine. (B) Computed bond orders show a single (apical) P–C(py) bond breaking along the reaction coordinate, with little involvement of oxygen lone pairs. LP<sub>Ox</sub>, number of electrons in each oxygen lone pair; IRC, intrinsic reaction coordinate. (C) Optimized structures for [Int-III·2H]<sup>2+</sup>, [TS-I·2H]<sup>2+</sup> and [Int-IV·2H]<sup>2+</sup> show stepwise apical-equatorial ligand-coupling. (D) A kinetic study indicates that alcohol addition is rate-limiting. TfOH used in place of HCl due to poor solubility of aryl derivatives. Yields after complete consumption of the phosphonium salts are approximately the same in each case (89%-94%). (E) Room temperature coupling using ethoxide as a nucleophile.

The computed structures of P(V) intermediates, such as **[Int-III·2H]<sup>2+</sup>**, are characterized by stronger, shorter ( $d_{\text{P-C(py)}}$  1.86 Å) bonds to equatorial ligands and weaker, longer ( $d_{\text{P-C(py)}}$  1.99 Å) bonds to those in apical positions. This is a result of the 3-center, 4-electron bond along the L–P–

L axis. Accordingly, the relative stability of P(V) stereoisomeric forms can be readily predicted based on each ligand's capacity to stabilize the build-up of electron density at the apical positions:  $\sigma$ -electron-withdrawing alkoxy and heteroaryl groups preferentially occupy the apical sites (fig. S5). Weaker and more polar apical P–L bonds favor migration in nucleophilic 1,2-rearrangements, in which an equatorial ligand acts as the electrophilic acceptor (fig. S7), leading to ligand-coupling. Phenyl ligands are unfavorable for both donor and acceptor roles in ligand-coupling: apical positions (donors) favor more  $\sigma$ -electron-withdrawing substituents, while pyridyl substituents are superior acceptors. This explains the complete absence of biphenyl and phenyl-heterobiaryl coupled products. N-protonation decreases the activation barrier significantly, from 30 to 20 kcal/mol, increasing the electrophilicity of the equatorial pyridyl group. Successive N-protonation further reduces the activation barrier to 14 kcal/mol, by increasing the  $\sigma$ -electron-withdrawing power of the axial donor ligand and weakening the P–C bond ( $d_{\text{P-C(py)}}$  increases from 1.95 Å in **[Int-III·H]**<sup>+</sup> to 1.99 Å in **[Int-III·2H]**<sup>2+</sup>), whereas equatorial P–C bonds are largely unchanged ( $d_{\text{P-C(py)}}$  in **[Int-III·H]**<sup>+</sup> is 1.87 Å and 1.86 Å in **[Int-III·2H]**<sup>2+</sup>). Computed values of C–O coupling from **Int-[Int-III·2H]**<sup>2+</sup> are also disfavored relative to pyridine-pyridine coupling ( $\Delta G^\ddagger(\text{C-O}) = 18$  kcal/mol vs.  $\Delta G^\ddagger(\text{py-py}) = 14$  kcal/mol, fig. S8) (31).

Figure 2D examines the effect of phosphorus electrophilicity on the rate of heterobiaryl formation. The low energy barrier for ligand-coupling in **[Int-III·2H]**<sup>2+</sup> implies that the rate determining step comes prior to this event and involves attack of the alcoholic solvent at the phosphonium center. We prepared a set of salts with substituted aryl groups that would change the electrophilicity at phosphorus; rate data shows faster heterobiaryl formation as the electrophilicity of the phosphonium increases, and is in line with the above hypothesis. Further experimental verification of the low barriers for ligand-coupling is shown in Figure 2E. Acidic alcohol solutions are inefficient for heterobiaryl formation at lower temperatures (Table S1), however, using ethoxide as a nucleophile, where addition to the phosphonium ion is facile (fig. S15), heterobiaryl synthesis occurs in minutes at room temperature with trace amounts of C–O coupling also observed. Substantial amounts of products resulting from protiodephosphination are formed making this protocol less practical than under acidic conditions.

**Substrate scope exploration.** We next selected a set of pyridines and diazines to examine which substitution patterns and functional groups could be tolerated in the ligand-coupling process (Fig. 3). The reaction is completely selective for the 4-position of pyridines in the vast majority of cases studied, unless a 4-substituent is present, switching selectivity to the 2-position. A variety of 4,4'-bipyridines are accessible using this strategy (**4b-4f**); functional groups such as esters, trifluoromethyl and methoxy groups are accommodated as are halides that would normally be active in metal-catalyzed reactions. Substituents can be present at the 2- or 3-positions of pyridines, and example **4e** shows that a 2-position substituent is not a requirement (*vide infra*). A fluorinated 2,4'-quinoline-pyridine was also synthesized by phosphorus ligand-coupling (**4g**) (39). Examples of 2,2'-systems, **4h** and **4i**, showcase an alternative to Suzuki couplings, where 2-pyridyl and quinolyl boronic acids often decompose during metal-catalyzed reactions (16). Pyrimidine- and pyrazine-containing heterobiaryls **4j** and **4k** were formed via the three-step sequence with lower yields in the coupling step compared with pyridine examples.

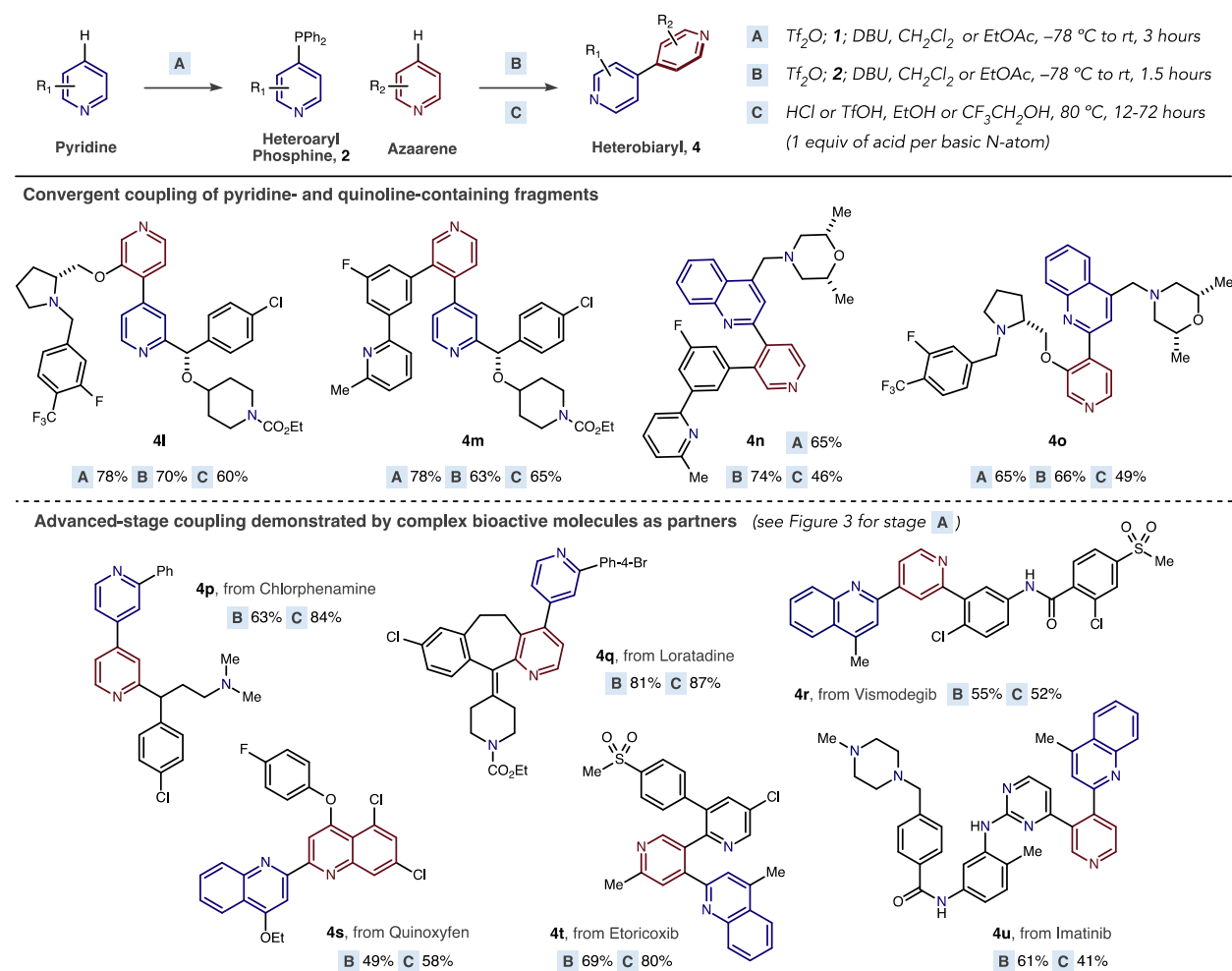


**Fig. 3. Azaarene scope and guidelines for phosphonium salt formation.** Yields of isolated products after each stage are shown. *n*-Bu, normal butyl group; *n*-Pr, normal propyl group; EWG, electron-withdrawing group; EDG, electron-donating group. Reaction guidelines for phosphonium salt formation involving *ortho* and non-*ortho* substituted pyridines as partners. Further details of challenges and limitations are highlighted in fig. S25.

**Reaction guidelines.** During these studies, we have established a general set of reaction guidelines and limitations. First, when coupling 2-substituted pyridines to 3-substituted pyridines, it is important to perform the salt-forming sequence in the correct order (Fig. 3). Taking heterobiaryl **4b** as a representative example, if heteroaryl phosphine **2b'** is used instead in stage B, then salt **3b** is not formed. We believe that a biased Tf-salt equilibrium rapidly develops, and pyridinium-phosphine **[2b'-Tf]<sup>+</sup>** is favored on steric grounds; the 2-substituted pyridine is then not activated for nucleophilic addition, and the desired salt is not formed (fig. S25). Instead, the 2-substituted pyridine should be converted into the corresponding phosphine and used as a nucleophile with the 3-substituted pyridine in stage B. Second, problematic substrates for heteroaryl phosphine and salt formation include pyridines with 2-trifluoromethyl groups, 4-alkyl or aryl substituents, and 2,6-disubstituted pyridines. In general, pyridines and diazines with more than two electron-withdrawing groups or electron-donating groups can result in low yields or no phosphonium salt formation. During ligand-coupling we have observed that: pyridines substituted with bromides and iodides can be dehalogenated; 2-chloro- or fluoro pyridines are not successful; 2-methoxy pyridines proceed with slower rates. For pyridines containing electron-withdrawing groups, using EtOH and HCl can result in ethoxylation. Changing the acid to TfOH avoids this problem and leads us to believe that ethoxylation results from chlorination followed by ethoxylation via an  $\text{S}_{\text{N}}\text{Ar}$  mechanism. Trifluoroethanol is preferred when molecules contain functional groups such as amides and esters that are

susceptible to ethanolysis. In general, one equivalent of acid per basic nitrogen is optimal (*vide infra*).

**Application to complex intermediates.** Our attention then turned to ligand-couplings involving complex azaarenes (Fig. 4). Convergent couplings of pyridine-containing fragments were first examined; these molecules are representative of drug leads, which are promising candidates for a therapeutic target but have sub-optimal pharmacokinetic and pharmacodynamic properties (40). A convergent coupling strategy would enable rapid access to complex heterobiaryls from compounds common in pharmaceutical libraries (41, 42). Four examples in Fig. 4 are shown where the corresponding halide precursors are not commercially available or would be challenging to prepare (**4l-4o**). Heterobiaryl bonds are formed with precise regioselectivity, and the presence of additional saturated and unsaturated nitrogen heterocycles is tolerated in this approach. Three or four equivalents of acid are used in the coupling step in these cases to ensure adequate reaction rates.



**Fig. 4. Heterobiaryl synthesis in complex molecules.** Yields of isolated products after each stage are shown. Further examples of advanced stage couplings are shown in fig. S26.

Next, we investigated whether the ligand-coupling strategy could be applied to advanced intermediates in drug development. Success in this endeavour would offer distinct strategies to

introduce heterobiaryls into complex molecules and alleviate concerns over metal contamination in subsequent biological testing. To demonstrate the feasibility of this approach, we chose a set of existing drug molecules with diverse structures, substitution patterns and functional groups (43).

Using previously synthesized heteroaryl phosphines Fig. 4 shows that heteroarylation is possible in these complex systems with complete control of regio- and site-selectivity. Chlorphenamine, a common antihistamine, and loratadine, an allergy medicine, are competent substrates for this protocol with the resulting heterobiaryls isolated in good overall yields (4p & 4q) that again highlight how halides can be tolerated during the coupling procedure. Vismodegib was converted into a 2,4'-quinoline-pyridine system in moderate yield (4r). A widely-applied fungicide, quinoxifen, was also compatible with the reaction protocol (4s). Etoricoxib and imatinib are challenging examples because they contain multiple reactive sites (34). The structural features in etoricoxib enable selective transformation of the 2,5-disubstituted pyridine (4t), and heteroarylation of the pyridine occurs selectively over the pyrimidine in imatinib to form 4u.

**Outlook.** This phosphorus ligand-coupling method overcomes major limitations of metal-catalyzed approaches by virtue of its compatibility with polar functionalities found in drug like molecules and its circumvention of preformed heteroaryl halides and boronic acids. As well as transforming building block compounds, convergent coupling of drug fragments and heteroarylation of complex pharmaceuticals were demonstrated. The protocol uses readily available reagents under simple conditions and is immediately applicable in medicinal chemistry.

## References and Notes:

1. D. G. Brown, J. Bostrom, Analysis of Past and Present Synthetic Methodologies: Where have All the New Reactions Gone? *J. Med. Chem.* **59**, 4443-4458 (2016). doi:10.1021/acs.jmedchem.5b01409
2. S. D. Roughley, A. M. Jordan, The Medicinal Chemist's Toolbox: An Analysis of Reactions used in the Pursuit of Drug Candidates. *J. Med. Chem.* **54**, 3451-3479 (2011). doi:10.1021/jm200187y
3. R. Capdeville, E. Buchdunger, Glivec (STI571, Imatinib) A Rationally Developed Targeted Anticancer Drug. *Nat. Rev. Drug Discov.* **1**, 493-502 (2002). doi:10.1038/nrd839
4. A. J. Roecker, S. P. Mercer, J. D. Schreier, D. Cox, M. E. Fraley, J. T. Steen, W. Lemaire, J. G. Bruno, H. Harrell, S. L. Garson, A. L. Gotter, S. V. Fox, J. Stevens, P. L. Tannenbaum, T. Prueksaritanont, T. D. Cabalu, D. Cui, J. Stellabott, G. D. Hartman, S. D. Young, C. J. Winrow, J. J. Renger, P. J. Coleman, Discovery of 5"-Chloro-N-[(5,6-dimethoxypyridin-2-yl)methyl]-2,2':5',3"-terpyridine-3'-carboxamide (MK-1064): A Selective Orexin 2 Receptor Antagonist (2-SORA) for the Treatment of Insomnia. *ChemMedChem.* **9**, 311-322 (2014). doi:10.1002/cmdc.201300447
5. S. D. Martina, K. S. Vesta, T. L. Ripley, Etoricoxib: A Highly Selective COX-2 Inhibitor. *Ann. Pharmacother.* **39**, 854-862 (2005). doi:10.1345/aph.1E543
6. M. L. Crawley, B. M. Trost, *Applications of Transition Metal Catalysts in Drug Discovery and Development: An Industrial Perspective*. (Wiley, Hoboken, NJ, 2012), pp. 25-96.
7. A. de Meijere, F. Diederich, *Metal-Catalyzed Cross-Coupling Reactions* (Wiley-VCH, Weinheim, ed. 2, 2004).

8. J. Hassan, M. Sevignon, C. Gozzi, E. Schulz, M. Lemaire, Aryl-Aryl Bond-Formation One Century after the Discovery of the Ullmann Reaction. *Chem. Rev.* **102**, 1359-1469 (2002). doi:10.1021/cr000664r
9. L.-C. Campeau, K. Fagnou, Applications of and Alternatives to  $\pi$ -Electron-Deficient Azine and Organometallics in Metal-Catalyzed Cross-Coupling Reactions. *Chem. Soc. Rev.* **36**, 1058-1068 (2007). doi:10.1039/B616082D
10. D. Zhao, J. You, C. Hu, Recent Progress in Coupling of Two Heterocycles. *Chem. Eur. J.* **17**, 5466-5492 (2011). doi:10.1002/chem.201003039
11. K. L. Billingsley, K. W. Anderson, S. L. Buchwald, A Highly Active Catalyst for Suzuki-Miyaura Cross-Coupling Reactions of Heteroaryl Compounds. *Angew. Chem. Int. Ed.* **45**, 3484-3488 (2006). doi:10.1002/anie.200600493
12. N. Kudo, M. Perseghini, G. C. Fu, A Versatile Method for Suzuki Cross-Coupling Reactions of Nitrogen Heterocycles. *Angew. Chem. Int. Ed.* **45**, 1282-1284 (2006). doi:10.1002/anie.200503479
13. A. S. Guram, X. Wang, E. E. Bunel, M. M. Faul, R. D. Larsen, M. J. Martinelli, New Catalysts for Suzuki-Miyaura Reactions of Heteroatom-Substituted Heteroaryl Chlorides. *J. Org. Chem.* **72**, 5104-5112 (2007). doi:10.1021/jo070341w
14. U. Kiehne, J. Bunzen, A. Lützen, Synthesis of Substituted 2,2'-Bipyridines from 2-Bromo- or 2-Chloropyridines Using Tetrakis(triphenylphosphine)palladium(0) as a Catalyst in a Modified Negishi Cross-Coupling Reaction. *Synthesis*, 1061-1069 (2007). doi:10.1055/s-2007-965952
15. T. Markovic, B. N. Rocke, D. C. Blakemore, V. Mascitti, M. C. Willis, Pyridine Sulfinates as General Nucleophilic Coupling Partners in Palladium-Catalyzed Cross-Coupling Reactions with Aryl Halides. *Chem. Sci.* **8**, 4437-4442 (2017). doi:10.1039/C7SC00675F
16. P. A. Cox, M. Reid, A. G. Leach, A. D. Campbell, E. J. King, G. C. Lloyd-Jones, Base-Catalyzed Aryl-B(OH)<sub>2</sub> Protodeboronation Revisited: From Concerted Proton Transfer to Liberation of a Transient Aryl Anion. *J. Am. Chem. Soc.* **139**, 13156-13165 (2017). doi:10.1021/jacs.7b07444
17. D. C. Blakemore, L. Castro, I. Churcher, D. C. Rees, A. W. Thomas, D. M. Wilson, A. Wood, Organic Synthesis Provides Opportunities to Transform Drug Discover. *Nat. Chem.* **10**, 383-394 (2018). doi:10.1038/s41557-018-0021-z
18. J. A. Joule, K. Mills in *Heterocyclic Chemistry* (Wiley-Blackwell, Oxford, ed. 5, 2013).
19. M. R. Grimmet, Halogenation of Heterocycles: II. Six- and Seven-Membered Rings. *Adv. Heterocycl. Chem.* **58**, 271-329 (1993).
20. M. A. Larsen, J. F. Hartwig, Iridium-Catalyzed C-H Borylation of Heteroarenes: Scope, Regioselectivity, Applications to Late-Stage Functionalization and Mechanism. *J. Am. Chem. Soc.* **136**, 4287-4299 (2014). doi:10.1021/ja412563e
21. H.-Q. Do, O. Daugulis, A General Method for Copper-Catalyzed Arene Cross-Dimerization. *J. Am. Chem. Soc.* **133**, 13577-13586 (2011). doi:10.1021/ja2047717

22. J.-P. Finer in *Ligand Coupling Reactions with Heteroaromatic Compounds* (Tetrahedron Organic Chemistry Series, Pergamon Press, Oxford) vol. 18, chap. 4.
23. K. D. Reichl, A. T. Radosevich, A Phosphine-Mediated Stereocontrolled Synthesis of Z-Enedienes by a Vicinal Dialkynylation of Ethynylphosphonium Salts. *Chem. Commun.* **50**, 9302-9305 (2014). doi:10.1039/c4cc03415e
24. R. Hoffmann, J. M. Howell, E. L. Muetterties, Molecular Orbital Theory of Pentacoordinate Phosphorus. *J. Am. Chem. Soc.* **94**, 3047-3058 (1972). doi:10.1021/ja00764a028
25. F. G. Mann, J. Watson, Conditions of Salt Formation in Polyamines and Kindred Compounds. Salt Formation in the 2-Pyridylamines, Phosphines and Arsines. *J. Org. Chem.* **13**, 502-531 (1948). doi:10.1021/jo01162a007
26. G. R. Newkome, D. C. Hager, New Contractive Coupling Procedure. Convenient Phosphorus Expulsion Reaction. *J. Am. Chem. Soc.* **100**, 5567-5568 (1978). doi:10.1021/ja00485a053
27. Y. Uchida, K. Onoue, N. Tada, F. Nagao, Ligand Coupling Reaction on the Phosphorus Atom, *Tetrahedron Lett.* **30**, 567-570 (1989). doi:10.1016/S0040-4039(00)95256-0
28. Y. Uchida, H. Kozawa, Oae, S, Formation of 2,2'-Bipyridyl by Ligand Coupling on the Phosphorus Atom. *Tetrahedron Lett.* **30**, 6365-6368 (1989). doi:10.1016/S0040-4039(01)93895-X
29. Y. Uchida, N. Echikawa, S. Oae, Reactions of Heteroarylithium Compounds with Phosphorus Trichloride, Phosphorus Oxychloride, and Thionyl Chloride. Formation of Heterocyclic Biaryls. *Heteroat. Chem.* **5**, 409-413 (1994). doi:10.1002/hc.520050414
30. F. Alonso, Y. Moglie, G. Radivoy, M. Yus, Solvent- and Catalyst-Free Regioselective Hydrophosphanation of Alkenes. *Green Chem.* **14**, 2699-2702 (2012). doi:10.1039/C2GC35898K
31. M. C. Hilton, R. D. Dolewski, A. McNally, Selective Functionalization of Pyridines via Heterocyclic Phosphonium Salts. *J. Am. Chem. Soc.* **138**, 13806-13809 (2016). doi:10.1021/jacs.6b08662
32. X. Zhang, A. McNally, Phosphonium Salts as Pseudohalides: Regioselective Nickel-Catalyzed Cross-Coupling of Complex Pyridines and Diazines. *Angew. Chem. Int. Ed.* **56**, 9833-9836 (2017). doi:10.1002/anie.201704948
33. J. L. Koniarczyk, D. Hesk, A. Overgaard, I. W. Davies, A. McNally, A General Strategy for Site-Selective Incorporation of Deuterium and Tritium into Pyridines, Diazines and Pharmaceuticals. *J. Am. Chem. Soc.* **140**, 1990-1993 (2018). doi:10.1021/jacs.7b11710
34. R. D. Dolewski, P. J. Fricke, A. McNally, Site-Selective Switching Strategies to Functionalize Polyazines. *J. Am. Chem. Soc.* **140**, 8020-8026 (2018). doi:10.1021/jacs.8b04530
35. R. G. Anderson, B. M. Jett, A. McNally, A Unified Approach to Couple Aromatic Heteronucleophiles to Azines and Pharmaceuticals. *Angew. Chem. Int. Ed.* **57**, 1-6 (2018). doi:10.1002/anie.201807322

36. E. Anders, F. Markus, Neue Methode Zur Regiospezifischen Substitution Einiger Reaktionsträger *N*-Heteroaromatischer Ringsystem. *Tetrahedron Lett.* **28**, 2675-2676 (1987). doi:10.1016/S0040-4039(00)96178-1
37. P. S. Fier, A Bifunctional Reagent Designed for the Mild, Nucleophilic Functionalization of Pyridines. *J. Am. Chem. Soc.* **139**, 9499-9502 (2017). doi:10.1021/jacs.7b05414
38. Both DLPNO-CCSD(T)/cc-pV(DT)Z and  $\omega$ B97XD/def2-QZVP results are in close-agreement. Full details in the Supplementary Materials.
39. O. Afzal, S. Kumar, M. R. Haider, M. R. Ali, R. Kumar, M. Jaggi, S. Bawa, A Review on Anticancer Potential of Bioactive Heterocycle Quinoline. *Eur. J. Med. Chem.* **97**, 871-890 (2015). doi:10.1016/j.ejmech.2014.07.044
40. R. B. Silverman, M. W. Holladay in *The Organic Chemistry of Drug Design and Drug Action* (Academic Press, San Diego, CA, ed. 3, 2014), chap. 2.
41. D. A. Erlanson, S. W. Fesik, R. E. Hubbard, W. Jahnke, H. Johti, Twenty Years On, The Impact of Fragments on Drug Discovery. *Nat. Rev. Drug. Discov.* **15**, 605-619 (2016). doi:10.1038/nrd.2016.109
42. C. W. Murray, D. C. Rees, The Rise of Fragment-Based Drug Discovery. *Nat. Chem.* **1**, 187-192 (2009). doi:10.1038/nchem.217
43. T. Cernak, K. D. Dysktra, S. Tyagarajan, P. Vachal, S. W. Krska, The Medicinal Chemist's Toolbox for Late Stage Functionalization of Drug-Like Molecules. *Chem. Soc. Rev.* **45**, 546-576 (2016). doi:10.1039/C5CS00628G
44. D. D. Perrin, W. L. F. Amerego, Purification of Laboratory Chemicals (Pergamon Press, Oxford, ed. 3, 1988).
45. A. D. Becke, Density-Functional Thermochemistry. V. Systematic Optimization of Exchange-Correlation Functionals. *J. Chem. Phys.* **107**, 8554-8560 (1997). doi:10.1063/1.475007
46. J.-D. Chai, M. Head-Gordon, Long-Range Corrected Hybrid Density Functionals with Damped Atom-Atom Dispersion Corrections. *Phys. Chem. Chem. Phys.* **10**, 6615-6620 (2008). doi:10.1039/B810189B
47. W. J. Hehre, R. Ditchfield, J. A. Pople, Self-Consistent Molecular Orbital Methods. XII. Further Extensions of Gaussian-Type Basis Sets for use in Molecular Orbital Studies of Organic Molecules. *J. Chem. Phys.* **56**, 2257-2261 (1972). doi:10.1063/1.1677527
48. P. C. Hariharan, J. A. Pople, The Influence of Polarization Functions on Molecular Orbital Hydrogenation Energies. *Theoret. chim. Acta* **28**, 213-222 (1973). doi:10.1007/BF00533485
49. M. M. Francl, W. J. Pietro, W. J. Hehre, J. S. Binkley, M. S. Gordon, D. J. DeFrees, J. A. Pople, Self-Consistent Molecular Orbital Methods. XXIII. A Polarization-Type Basis Set for Second-Row Elements. *J. Chem. Phys.* **77**, 3654-3665 (1982). doi:10.1063/1.444267
50. V. A. Rassolov, M. A. Ratner, J. A. Pople, P. C. Redfern, L. A. Curtiss, 6- 31G\* Basis Set for Third-Row Atoms. *J. Comp. Chem.* **22**, 976-984 (2001). doi:10.1002/jcc.1058

51. T. Clark, J. Chandrasekhar, G. W. Spitznagel, P. von R. Schleyer, Efficient Diffuse Function-Augmented Basis Sets for Anion Calculations. III. The 3- 21+G Basis Set for First-Row Elements, Li–F. *J. Comput. Chem.* **4**, 294-301 (1983). doi:10.1002/jcc.540040303
52. L. Goerigk, S. Grimme, A Thorough Benchmark of Density Functional Methods for General Main group Thermochemistry, Kinetics, and Noncovalent Interactions. *Phys. Chem. Chem. Phys.* **13**, 6670-6688 (2011). doi:10.1039/C0CP02984J
53. A. Bhunia, T. Roy, R. G. Gonnade, A. T. Biju, Rapid Access to Benzoxaphospholes and Their Spiro Analogues by a Three-Component Coupling involving Arynes, Phosphines, and Activated Ketones. *Org. Lett.* **16**, 5132-5135 (2014). doi:10.1021/ol502490t
54. K. Fukui, The Path of Chemical Reactions-The IRC Approach. *Acc. Chem. Res.* **14**, 363-368 (1981). doi:10.1021/ar00072a001
55. S. Grimme, Supramolecular Binding Thermodynamics by Dispersion-Corrected Density Functional Theory. *Chem. Eur. J.* **18**, 9955-9964 (2012). doi:10.1002/chem.201200497
56. GoodVibes, Version 2.0.1, I. Funes-Ardoiz, R. S. Paton, <http://doi.org/10.5281/zenodo.595246> (accessed 13 April 2018).
57. E. Cancès, B. Mennucci, J. Tomasi, A New Integral Equation Formalism for the Polarizable Continuum Model: Theoretical Background and Applications to Isotropic and Anisotropic Dielectrics. *J. Chem. Phys.* **107**, 3032-3041 (1997). doi:10.1063/1.474659
58. B. Mennucci, E. Cancès, J. Tomasi, Evaluation of Solvent Effects in Isotropic and Anisotropic Dielectrics and in Ionic Solutions with a Unified Integral Equation Method: Theoretical Bases, Computational Implementation, and Numerical Applications. *J. Phys. Chem. B* **101**, 10506-10517 (1997). doi:10.1021/jp971959k
59. B. Mennucci, J. Tomasi, Continuum Solvation models: A New Approach to the Problem of Solute's Charge Distribution and Cavity Boundaries. *J. Chem. Phys.* **106**, 5151-5158 (1997). doi:10.1063/1.473558
60. T. B. Mennucci, E. Cancès, The IEF Version of the PCM Solvation Method: An Overview of a New Method Addressed to Study Molecular Solutes at the QM ab initio Level. *J. Mol. Struct. THEOCHEM* **464**, 211-226 (1999). doi:10.1016/S0166-1280(98)00553-3
61. G. Scalmani, M. J. Frisch, Continuous Surface Charge Polarizable Continuum Models of Solvation. I. General Formalism. *J. Chem. Phys.* **132**, 114110 (2010). doi:10.1063/1.3359469
62. A. V. Marenich, C. J. Cramer, D. G. Truhlar, Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric Constant and Atomic Surface Tensions. *J. Phys. Chem. B* **113**, 6378-6396 (2009). doi:10.1021/jp810292n
63. Gaussian 16, Revision A.03, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K.

Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, D. J. Fox, Gaussian, Inc., Wallingford CT, 2016.

64. K. B. Wiberg, Application of the Pople-Santry-Segal CNDO Method to the Cyclopropylcarbinyl and Cyclobutyl Cation and to Bicyclobutane. *Tetrahedron* **1968**, *24*, 1083-1096. doi:10.1016/0040-4020(68)88057-3

65. NBO, version 6.0, E. D. Glendening, J. K. Badenhoop, A. E. Reed, J. E. Carpenter, J. A. Bohmann, C. M. Morales, C. R. Landis, F. Weinhold, Theoretical Chemistry Institute, University of Wisconsin, Madison WI, 2013.

66. The PyMOL Molecular Graphics System, version 2.0.7, Schrödinger, LLC.

67. <https://gist.github.com/bobbypaton> (accessed 13 April 2018)

68. GraphPad Prism, version 5.00 for Windows, GraphPad Software, San Diego California USA, [www.graphpad.com](http://www.graphpad.com).

69. A. Savin, R. Nesper, S. Wengert, T. E. Fassler, ELF: The Electron Localization Function. *Angew. Chem. Int. Ed.* **36**, 1808-1832 (1997). doi:10.1002/anie.199718081

70. Multiwfn, version 3.3.7. T. Lu, F. Chen, Multiwfn: A Multifunctional Wavefunction Analyzer. *J. Comp. Chem.* **33**, 580-592 (2012). doi:10.1002/jcc.22885

71. F. Weigend, R. Ahlrichs, Balanced Basis Sets of Split Valence, Triple Zeta Valence and Quadruple Zeta Valence Quality for H to Rn: Design and Assessment of Accuracy. *Phys. Chem. Chem. Phys.* **7**, 3297-3305 (2005). doi:10.1039/B508541A

72. F. Weigend, Accurate Coulomb-Fitting Basis Sets for H to Rn. *Phys. Chem. Chem. Phys.* **8**, 1057-1065 (2006). doi:10.1039/b515623h

73. G. D. Purvis III, R. J. Bartlett, A Full Coupled-Cluster Singles and Doubles Model: The Inclusion of Disconnected Triples. *J. Chem. Phys.* **76**, 1910-1918 (1982). doi:10.1063/1.443164

74. J. A. Pople, M. Head-Gordon, K. Raghavachari, Quadratic Configuration Interaction. A General Technique for Determining Electron Correlation Energies. *J. Chem. Phys.* **87**, 5968-5975 (1987). doi:10.1063/1.453520

75. C. Riplinger, F. Neese, An Efficient and Near Linear Scaling Pair Natural Orbital Based Local Coupled Cluster Method. *J. Chem. Phys.* **138**, 034106 (2013). doi:10.1063/1.4773581

76. C. Riplinger, B. Sandhoefer, A. Hansen, F. Neese, Natural Triple Excitations in Local Coupled Cluster Calculations with Pair Natural Orbitals. *J. Chem. Phys.* **139**, 134101 (2013). doi:10.1063/1.4821834

77. C. Riplinger, P. Pinski, U. Becker, E. F. Valeev, F. Neese, Sparse Maps—A Systematic Infrastructure for Reduced-Scaling Electronic Structure Methods. II. Linear Scaling Domain Based Pair Natural Orbital Coupled Cluster Theory. *J. Chem. Phys.* **144**, 024109 (2016). doi:10.1063/1.4939030

78. T. H. Dunning Jr, Gaussian Basis Sets for Use in Correlated Molecular Calculations. I. The Atoms Boron Through Neon and Hydrogen. *J. Chem. Phys.* **90**, 1007-1023 (1989). doi:10.1063/1.456153
79. D. E. Woon, T. H. Dunning Jr, Gaussian Basis Sets for Use in Correlated Molecular Calculations. III. The Atoms Aluminum Through Argon. *J. Chem. Phys.* **98**, 1358-1371 (1993). doi:10.1063/1.464303
80. E. R. Davidson, Comment on “Comment on Dunning's Correlation-Consistent Basis Sets”. *Chem. Phys. Lett.* **260**, 514-518 (1996). doi:10.1016/0009-2614(96)00917-7
81. ORCA, version 4.0.1.2, F. Neese, The ORCA program system. *WIREs Comput. Mol. Sci.* **2**, 73-78 (2012).
82. F. Neese, Software update: the ORCA program system, version 4.0. *WIREs Comput. Mol. Sci.* **8**, e1327 (2018).
83. D. G. Liakos, M. Sparta, M. K. Kesharwani, J. M. L. Martin, F. Neese, Exploring the Accuracy Limits of Local Pair Natural Orbital Coupled-Cluster Theory. *J. Chem. Theory Comput.* **11**, 15251539 (2015). doi:10.1021/ct501129s
84. J. Řezáč, P. Hobza, Describing Noncovalent Interactions Beyond the Common Approximations: How Accurate is the “Gold Standard,” CCSD(T) at the Complete Basis Set Limit? *J. Chem. Theory Comput.* **9**, 2151-2155 (2013). doi:10.1021/ct400057w
85. D. G. Truhlar, Basis-Set Extrapolation. *Chem. Phys. Lett.* **294**, 45-48 (1998). doi:10.1016/S0009-2614(98)00866-5
86. E. L. Muetterties, W. Mahler, R. Schmutzler, Stereochemistry of Phosphorus(V) Fluorides. *Inorg. Chem.* **2**, 613-618 (1963). doi:10.1021/ic50007a047
87. A. Klamt, Conductor-like screening model for real solvents: a new approach to the quantitative calculation of solvation phenomena. *J. Phys. Chem.* **99**, 2224–2235 (1995). doi:10.1021/j100007a062
88. A. Klamt, V. Jonas, T. Bürger, J. C. Lohrenz, Refinement and parametrization of COSMO-RS. *J. Phys. Chem. A* **102**, 5074–5085 (1998). doi:10.1021/jp980017s
89. COSMOtherm Version 18.0.0 (Revision 4360), COSMOlogic GmbH & Co KG.
90. F. Eckert, A. Klamt, Fast solvent screening via quantum chemistry: COSMO-RS approach. *AIChE J.* **48**, 369–385 (2002). doi:10.1002/aic.690480220
91. TURBOMOLE, version 7.2.1, University of Karlsruhe and Forschungszentrum Karlsruhe GmbH, 1989-2007, TURBOMOLE GmbH, since 2007.
92. E. J. Corey, and Y. Tian, Selective 4-Arylation of Pyridines by a Nonmetalloorganic Process. *Org. Lett.* **7**, 5535-5537 (2005). doi:10.1021/ol052476z
93. M. A. Abreo, N.-H. Lin, D. S. Garvey, D. E. Gunn, A. M. Hettinger, J. T. Wasicak, P. A. Pavlik, Y. C. Martin, D. L. Donnelly-Roberts, D. J. Anderson, J. P. Sullivan, M. Williams, S. P. Arneric, and M. W. Holladay, Novel 3-Pyridyl Ethers with Subnanomolar Affinity for Central Neuronal Nicotinic Acetylcholine Receptors. *J. Med. Chem.* **39**, 817-825 (1996). doi:10.1021/jm9506884

94. S. Molitor, J. Becker, and V. H. Gessner, Selective Dehydrocoupling of Phosphines by Lithium Chloride Carbenoids. *J. Am. Chem. Soc.* **136**, 5517–1552 (2014). doi:10.1021/ja509381w
95. T. Hirai, and L.-B. Han, Air-Induced *anti*-Markovnikov Addition of Secondary Phosphine Oxides and H-Phosphinates to Alkenes. *Org. Lett.*, **9**, 53–55 (2007). doi:10.1021/ol062505l
96. D. E. Bergbreiter, Y.-C. Yang, and C. E. Hobbs, Polyisobutylene-Supported Phosphines as Recyclable and Regenerable Catalysts and Reagents. *J. Org. Chem.* **76**, 6912–6917 (2011). doi:10.1021/jo201097x
97. R. Sure, S. Grimme, Comprehensive benchmark of association (free) energies of realistic host–guest complexes. *J. Chem. Theory Comput.* **11**, 3785–3801 (2015). doi:10.1021/acs.jctc.5b00296

**Acknowledgments: Funding:** This work was supported by startup funds from Colorado State University. Research in this report was supported by the National Institutes of Health (NIH) under award number R01 GM124094-01 (A.Mc., M.C.H., X. Z., B.T.B.). We acknowledge the RMACC Summit supercomputer, supported by the National Science Foundation (ACI-1532235 and ACI-1532236), the University of Colorado Boulder and Colorado State University, and the Extreme Science and Engineering Discovery Environment (XSEDE) through allocation TG-CHE180006 and TG-CHE180056. XSEDE is supported by the National Science Foundation (ACI-1548562); **Author contributions:** M.C.H., X.Z. and B.T.B. performed the experimental work. The computational studies were performed by J.V.A.R. and R.S.P. All authors contributed to the design of the experimental and computational work and to data analysis, discussed the results, and commented on the manuscript. A.Mc. and R.S.P. wrote the manuscript.; **Competing interests:** The authors declare no competing interests; **Data and materials availability:** All data is available in the main text or the supplementary materials.

## Supplementary Materials

Materials and Methods

Figures S1-S26

Tables S1-S2

Movies S1-S2

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