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Facile Pyridine S_NAr Reactions via *N*-Phosphonium–Pyridinium Intermediates

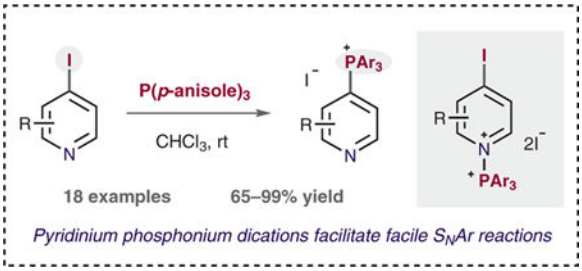
Benjamin T. Boyle, **J. Luke Koniarczyk**, **Andrew McNally**

Department of Chemistry, Colorado State University, Fort Collins, CO 80523, USA

Abstract

Here we report that *N*-phosphonium pyridinium intermediates are unusually reactive for pyridine S_NAr reactions. Specifically, forming phosphonium salts from halopyridines typically requires elevated temperatures and Lewis acid additives. The alternative activation mode described in this paper permits C–P bond formation to occur at ambient temperatures in many cases, and functions across a broad range of substrates.

Graphical Abstract



Keywords

pyridines; S_NAr reaction; phosphonium salts; pyridinium salts

Pyridine-containing molecules are widely used in the chemical sciences as they have applications in pharmaceuticals and agrochemicals in addition to serving as ligands for coordination complexes and components of organic materials.[1–3] Because of this prevalence, methods that derivatize simple pyridines into a diverse set of valuable products are highly sought after. Most pyridine-functionalization strategies involve transforming functional handles such as (pseudo)halides or boronic acids.[4] We have focused on developing phosphonium salts as alternative functional groups for pyridine derivatization and we have shown that they are viable for the formation of a range of carbon–carbon and carbon–heteroatom bonds (Scheme 1A).[5] In particular, phosphorus-ligand-coupling pathways are available through these salts, together with distinct ways of forming structures such as bipyridines.[6] Here we report a new method for forming pyridinylphosphonium salts from

andy.mcnally@colostate.edu.

Supporting Information

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iodopyridines that proceeds via an unusual dicationic *N*-phosphonium–pyridinium intermediate (Scheme 1B).

There are two common ways to form pyridinylphosphonium salts: first, an oxidative reaction of pyridine C–H pre-cursors, where phosphines attack *N*-triflylpyridinium salts (Scheme 2A);[5a,7] and second, S_NAr reactions between 2- and 4-halopyridines and phosphine nucleophiles (Scheme 2B). Although the latter approach requires a preinstalled halide, it sometimes has advantages over the C–H route. For example, the process tolerates such functional groups as alcohols, amines, or carboxylic acids. Also, there is an abundance of commercially available halopyridines. However, the S_NAr process typically requires temperatures of more than 100 °C and Brønsted or Lewis acid additives.[6,8]

We serendipitously found that two equivalents of PPh_3 react with 4-iodopyridine to form salt **1a** (Table 1, entry 1). Notably, the reaction occurred at room temperature and without exogenous acid. We decided to investigate a range of different phosphines to improve the yield of **1a**. Surprisingly, PEt_3 was similarly efficient to PPh_3, but PPh_2Et and $PPhEt_2$ resulted in much higher conversion to **1a** (Table 1, entries 2–4). The more electron-rich triaryl phosphine P(*p*-anisole)$_3$ was similarly effective. Further optimization showed that the most effective protocol used one equivalent of phosphine with $CHCl_3$ as a solvent (Table 1, entries 5–7; see the Supporting Information for further details).

We were intrigued by the mechanism of this substitution process, because the protocol occurs at ambient temperature and iodopyridines are typically the least reactive nucleofuges in S_NAr reactions.[9] There was a noticeable decrease in reaction efficiency when we used sublimed 4-iodopyridine (Table 1, entry 8). We hypothesized that a small amount of contaminant in the commercial material, or a minor amount of decomposition products, might function as a promoter for this reaction. 4-Chloro- and 4-bromopyridine did not react under the same conditions (Scheme 3A), but adding 10 mol% of iodine resulted in similar yields of phosphonium salt **1a**. On the basis of these observations, we proposed the reaction mechanism shown in Scheme 3B. The phosphine first reacts with iodine resulting in an iodophosphonium salt.[10] Next, a ligand-exchange reaction occurs to form the key *N*-phosphonium pyridinium dicationic salt **I**, which facilitates a subsequent S_NAr reaction with the phosphine nucleophile. The $I-^+PAr_3$ cation is regenerated through this reaction in a manner consistent with the requirement for a catalytic amount of iodine. Support for intermediate **I** comes from two reports from the groups of Dutton and Weigland (Scheme 3C), who isolated and characterized DMAP versions of these unusual bis salts.[11,12] To the best of our knowledge, there are no previous examples of the use of these dicationic species for synthetic transformations.

Next, we explored the substrate scope for this C–P bond-forming reaction (Scheme 4). Note that the iodopyridine starting materials were either purchased commercially or were prepared in house, and it was not necessary to add exogenous I_2. Also, we precipitated the phosphonium salt products from the reaction mixtures in high purity. Electron-withdrawing substituents at the 3-position worked well in the reaction, as did electron-donating groups when we raised the temperature to 50 °C (**1b**–**e**). It is notable that hydroxy and amino groups do not interfere with the reaction. We also obtained the 3,5-disubstituted salt **1f** in excellent

yield. The reaction tolerates 2-substituted pyridines, with pyridones, azaindoles and 2-arylpyridines performing well under the reaction conditions (**1g**–**j**). Importantly, S_NAr-active halogens at other positions on the pyridine ring do not erode regioselectivity (**1k** and **1l**). Salt **1m** formed without evidence of cyclization onto the pendent alkene, thereby disfavoring a mechanism involving a radical at the 4-position of the pyridine ring.[13] The reaction was extended to quinolines and 2-iodopyridines (**1n**–**p**), and we also obtained phosphonium salt derivatives of the pharmaceuticals etoricoxib and loratadine (**1q** and **1r**, respectively). The most pertinent limitations of this reaction are the failures to react of 2,6-dihalopyridines or of pyridines with strongly electron-withdrawing groups, such as trifluoromethyl groups, at the 2-position. We found that S_NAr-active iodoarenes did not function in this reaction.

Next, we attempted to detect the proposed *N*-phosphonium–pyridinium dication by using NMR spectroscopy (Figure 1). It was not possible to observe this intermediate from 4-iodopyridine, as the S_NAr reaction occurs too quickly. However, use of pyridine as a substrate did provide some insight. Treating pyridine with 50 mol% I_2 produced an up-field shift of the *ortho* and *para* protons in the ^1H NMR spectra.[14] The corresponding experiment with pyridine and 50 mol% of $I–^+PAr_3$ showed deshielding indicating the presence of a different species, which we assume is the *N*-phosphonium dication. We are currently performing further studies to investigate the mechanism of this reaction.

In summary, we have developed an unusual S_NAr reaction of iodopyridines with phosphine nucleophiles. We postulate an unusual dicationic *N*-phosphonium pyridinium salt as a key intermediate that promotes rapid C–I-to-C–P substitution. We obtained a range of pyridyl phosphonium salts by using this method, including some examples that would be difficult to obtain by conventional S_NAr methods.[15] We are currently investigating other ways of exploiting this pyridine *N*-activating group in our laboratory, and the results will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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(15). **Phosphonium Salts 1a–r: General Procedure** An oven-dried 8 mL vial (<1.0 mmol) or 16 mL vial (1.0–4.0 mmol) equipped with a stirrer bar was charged with the appropriate iodopyridine (1.0 equiv), (*p*-anisole)$_3$P (1.0 equiv), and $CHCl_3$ (0.5 M). The mixture was then stirred at rt, 50 °C, or 80 °C for the appropriate time. The mixture was then diluted with $CHCl_3$, and the product was precipitated with Et_2O (100 mL per 1.0 mmol) at rt. **(3-Chloropyridin-4-yl)[tris(4-methoxyphenyl)]phosphonium Iodide (1b)** Prepared according to general procedure from 3-chloro-4-iodopyridine (72 mg, 0.30 mmol) and (*p*-anisole)$_3$P (106 mg, 0.30 mmol) in $CHCl_3$ (0.6 mL) at rt for 36 h to give a light-brown solid; yield: 174 mg (98%, 0.3 mmol); mp 91–93 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.12–8.59 (m, 2 H), 7.58 (dd, *J* = 12.7, 8.9, 6 H), 7.48–7.10 (m, 7 H), 3.95 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.40 (d, *J* = 3.0), 151.98 (d, *J* = 5.0), 150.11 (d, *J* = 9.8), 136.35 (d, *J* = 12.4), 134.75 (d, *J* = 2.2), 130.32 (d, *J* = 8.4), 129.29 (d, *J* = 88.3), 117.02 (d, *J* = 14.5), 105.78 (d, *J* = 100.0), 56.51. ^{31}P NMR (162 MHz, $CDCl_3$) δ = 21.08. LRMS (ESI + APCI): *m/z* $[M - I]^+$ calcd for $C_{26}H_{24}ClNO_3P$: 464.1; found: 464.2.

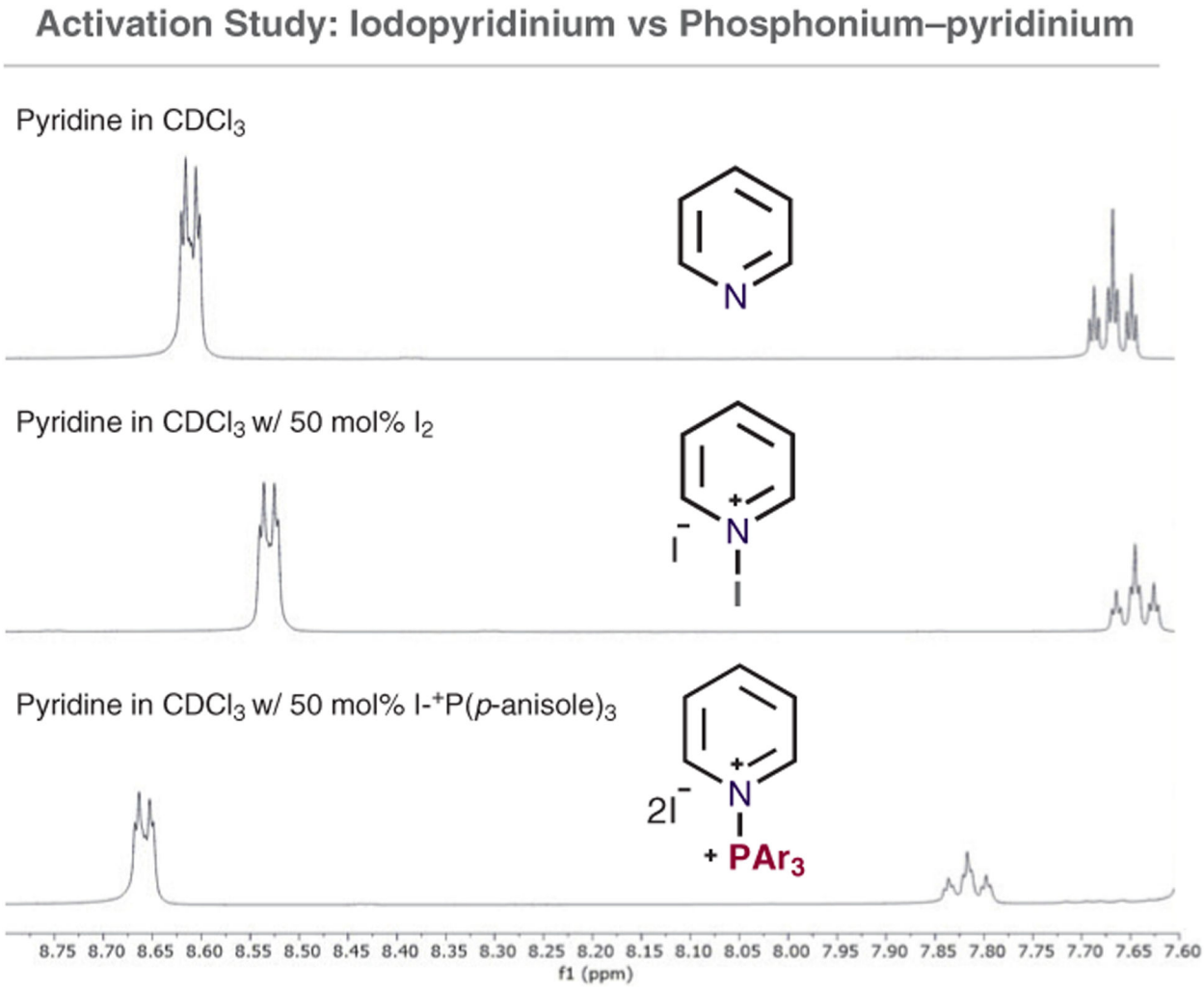
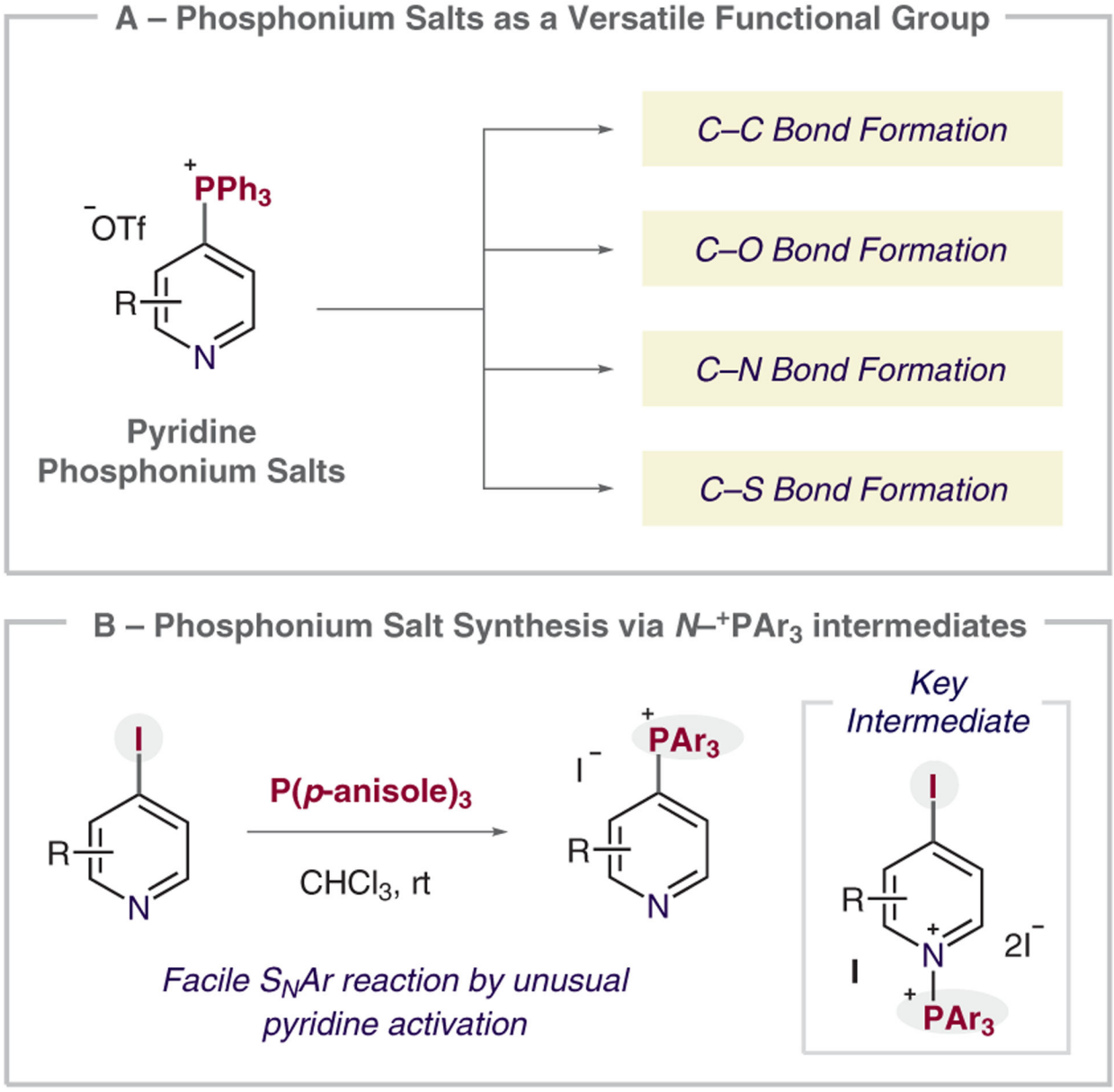
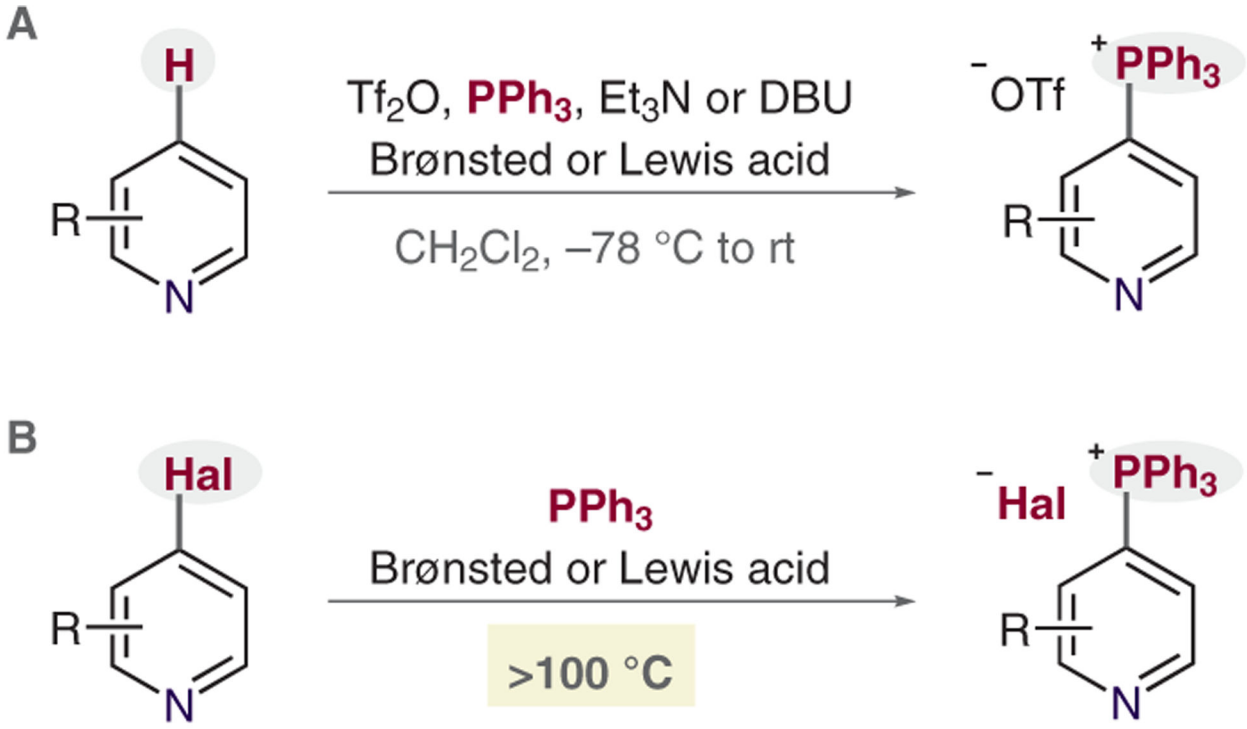


Figure 1.
I_2 and I–$^{+}$P(*p*-anisole)$_3$ spiking study for N-activation of pyridine

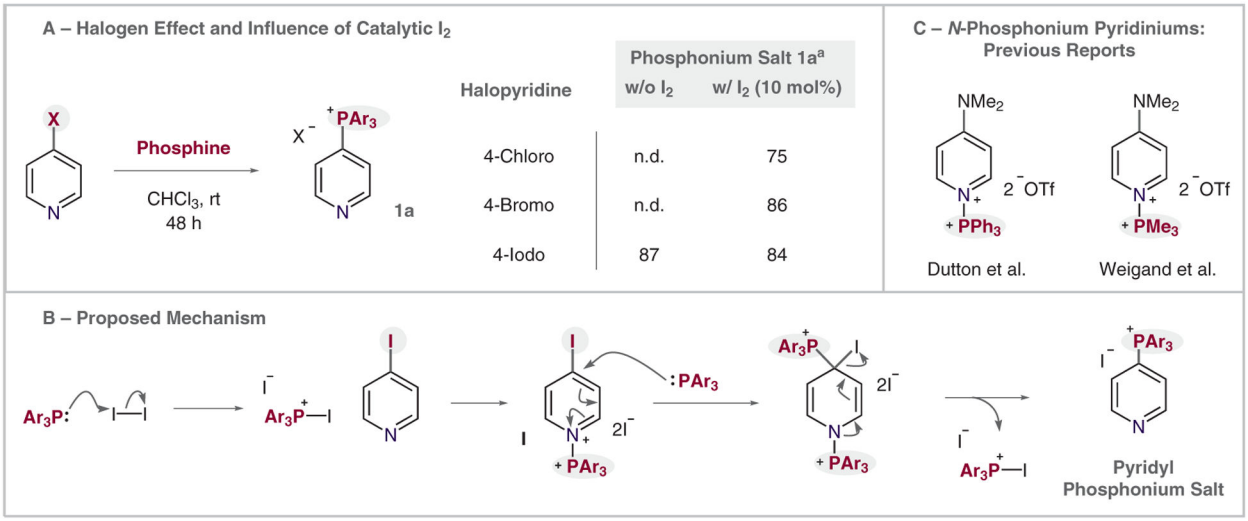


Scheme 1.

(A) Synthetic utility of heterocyclic phosphonium salts. (B) N + PAr_3 activation strategy for facile phosphonium salt synthesis.

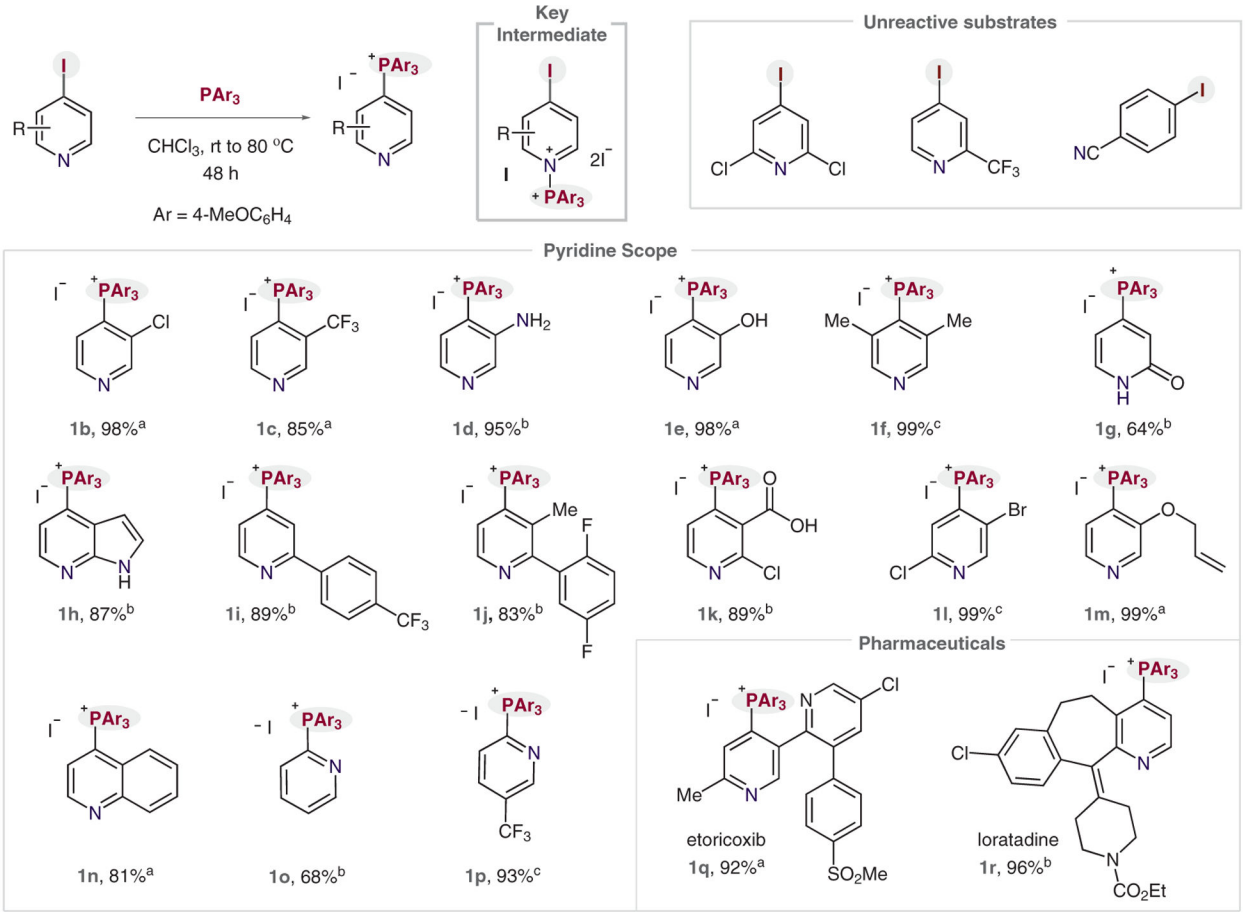


Scheme 2.
Common routes to pyridine phosphonium salts



Scheme 3.

Experimental mechanistic insights and proposed mechanism. (A) Halogen effect and influence of catalytic I_2. Yields were determined by ^1H NMR with $CHPh_3$ as internal standard. (B) Proposed reaction mechanism. (C) Previous reports of *N*-phosphonium pyridiniums.

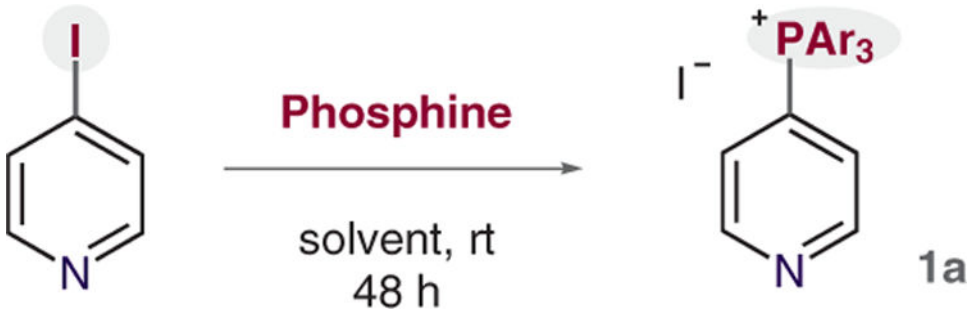


Scheme 4.

Reaction scope. *Reagents and conditions*: Iodopyridine (1.0 equiv), P(*p*-anisole)$_3$ (1.0 equiv), $CHCl_3$ (0.1 M), 0–80 °C, ≤48 h. Isolated yields shown. [a] rt. [b] 50 °C. [c] 80 °C.

Table 1

Optimization of Pyridyl Phosphonium Salt Formation



Entry	Phosphine (equiv)	Solvent	Residual 4-iodopyridine[a] (%)	Yield[3] (%)
1	PPh_3 (2.0)	CH_2Cl_2	71	5
2	PEt_3 (2.0)	CH_2Cl_2	64	8
3	$EtPPh_2$ (2.0)	CH_2Cl_2	10	79
4	$PhPEt_2$ (2.0)	CH_2Cl_2	4	86
5	P(*p*-anisole)$_3$ (2.0)	CH_2Cl_2	3	89
6	P(*p*-anisole)$_3$ (2.0)	$CHCl_3$	1	85
7	**P(*p*-anisole)$_3$ (1.0)**	**$CHCl_3$**	**3**	**97**
8[b]	P(*p*-anisole)$_3$ (1.0)	$CHCl_3$	34	66

[a]Determined by ^{1}H NMR with $CHPh_3$ as internal standard.

[b]Reaction performed with sublimed 4-iodopyridine.