Non-Symmetrical Bis-Azine Biaryls from Chloroazines: A Strategy Using Phosphorus Ligand-Coupling

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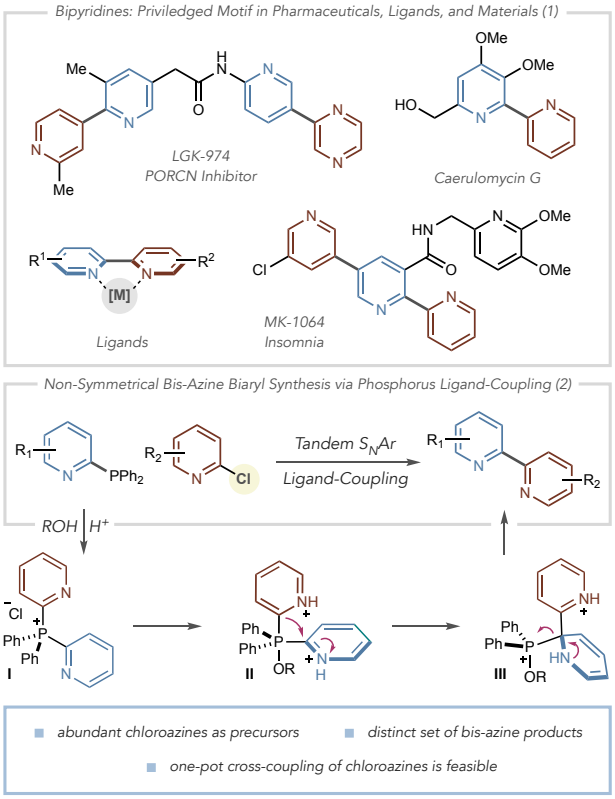
Supporting Information Placeholder

ABSTRACT: Distinct approaches to synthesize bis-azine biaryls are in demand as these compounds have multiple applications in the chemical sciences and are challenging targets for metal-catalyzed cross-coupling reactions. Most approaches focus on developing new reagents as the formal nucleophilic coupling partner that can function in metal-catalyzed processes. We present an alternative approach using pyridine and diazine phosphines as nucleophilic partners and chloroazines where the heterobiaryl bond is formed via a tandem S_NAr-phosphorus ligand-coupling sequence. The heteroaryl phosphines are prepared from chloroazines and are bench stable solids. Using this strategy, a range of bis-azine biaryls can be formed from abundant chloroazines that would be challenging using traditional approaches and a one-pot cross-electrophile coupling of two chloroazines is feasible.

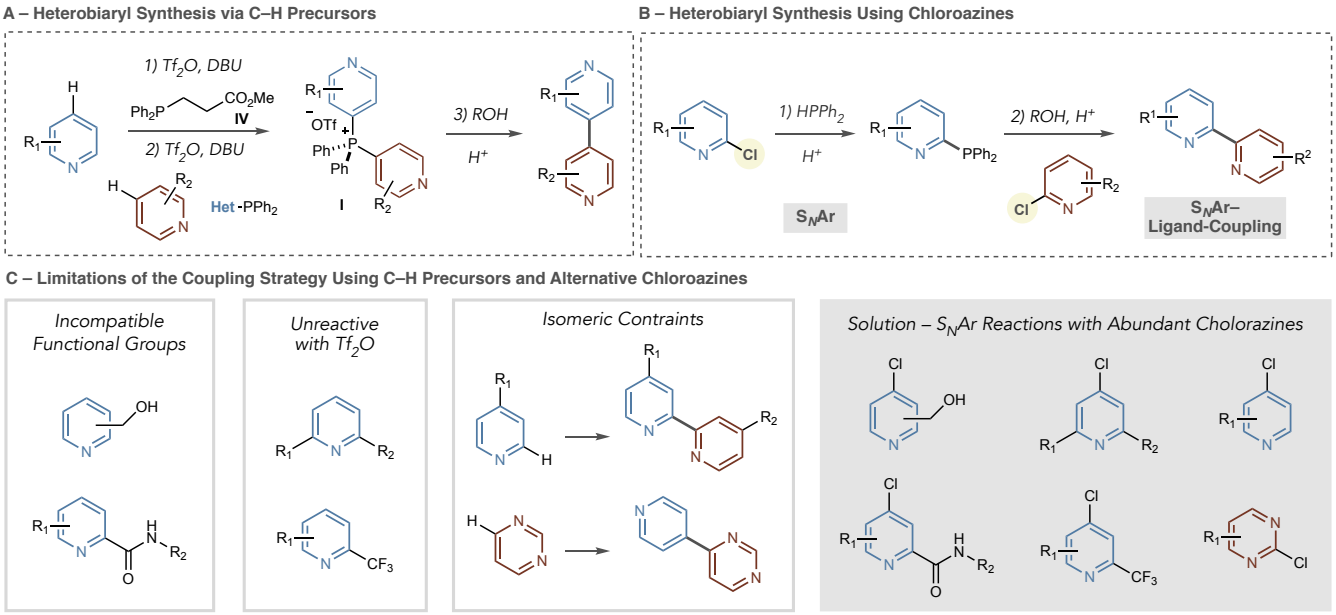
Bis-azine biaryls are widely applied in the chemical sciences with applications in drug development, as ligands for metal complexes and as components of materials (eq 1).[1] Transition metal catalyzed cross-coupling reactions are most commonly used to synthesize non-symmetrical variants, however, pyridine and diazine couplings represent some of the most challenging cases for this class of reactions.[2] Readily available and stable cross-coupling precursors are often limiting factors; haloazines are relatively abundant from commercial sources compared to nucleophilic partners such as pyridyl zincs, stannanes, silanes and Grignards that often have to be prepared and carefully handled.[3] Suzuki-Miyaura reactions are the most widely applied in medicinal chemistry as azine boronic acids are typically bench-stable powders.[4] Despite this advantage, halopyridines remain dramatically more commercially available than pyridine boronic acids, and 2-substituted pyridine boronic acids have a proclivity to decompose during cross-coupling reactions.[5,6] Herein we show that azinylphosphines can serve as nucleophilic partners and couple with haloazines where the biaryl bond is formed via a phosphorus ligand-coupling reaction.[7] These phosphines are straightforward to prepare from haloazines and are bench-stable. Preliminary examples of a net cross-electrophile coupling are shown via a one-pot coupling of two heteroaryl halides.

Several groups have developed alternatives to azine boronic acids for metal-catalyzed cross-coupling reactions. Potassium trifluoroborate salts and MIDA boronates display enhanced stability compared to boronic acids, but a general platform for azine-azine coupling has yet to be established using these reagents.[8] Willis advanced this area by demonstrating that pyridyl sulfinate salts and allyl sulfones are viable alternatives for Suzuki couplings.[9] Recently, we reported an alternative strategy to form bis-azine biaryls by constructing bis-azine phosphonium salts from C–H precursors and then exploiting phosphorus ligand-coupling reactions to form



the biaryl bond.[10] However, the inherent selectivity of the two C–P bond-forming steps restrict access to bis-azine biaryls within some isomeric patterns such as 2,2'-bipyridines (*vide infra*). Furthermore, certain functional groups and azine substitution patterns are not tolerated. We envisioned a strategy analogous to metal-catalyzed cross-coupling using chloroazines and heteroaryl phosphines as precursors (eq 2). This approach could overcome limitations of current metal-catalyzed processes as well as result in a suite of bis-azine biaryls that are beyond the scope of our original report. Pyridyl and diazinyl phosphines, prepared in one step from chloroazines, can function as nucleophiles and couple with a second chloroazine via a tandem S_NAr-ligand-coupling sequence; the mechanism involves forming a bis-heteroarylphosphonium salt (**I**) that is intercepted in acidic alcohol or aqueous solutions to form a P(V) alkoxyphosphorane intermediate (**II**). In line with our previous studies, we anticipated that subsequent ligand-coupling would proceed via an asynchronous process, involving a dearomatized species **III** as a discrete intermediate.

Scheme 1. Limitations of Heterobiaryl Synthesis Using C–H Precursors and an Alternative Strategy via Chloroazines

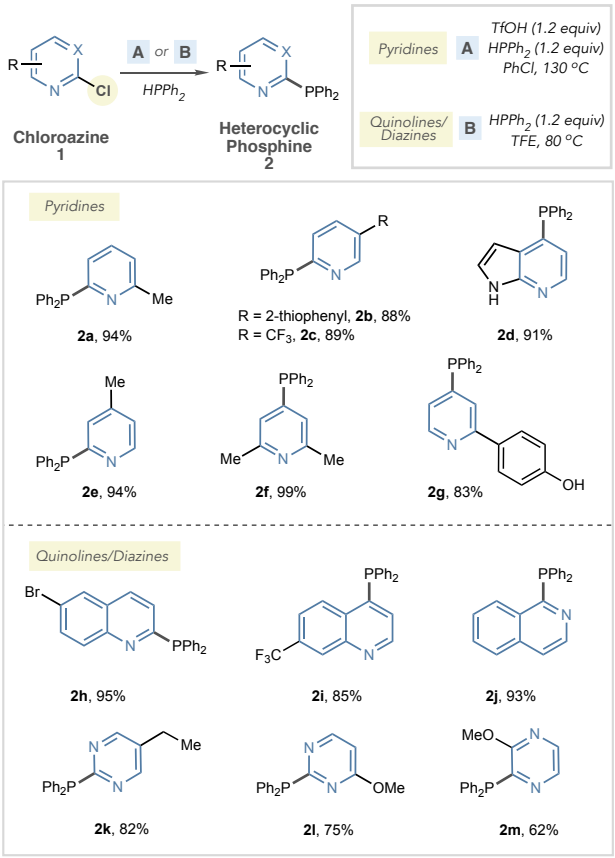


Scheme 1 shows specific limitations of our previous approach using azine C–H bonds as precursors and potential solutions using chloroazines. In the former case, two C–P bond-forming reactions are required to form bis-heterocyclic phosphonium salt **I** (Scheme 1A). Fragmentable phosphine **IV** is used with Tf_2O and DBU as a base to form an azinylphosphine (not shown); the process is then repeated with the second azine coupling partner to form salt **I**. Under these conditions, common functional groups such as alcohols, phenols and alkyl-substituted amides,[11,12] are not tolerated due to their propensity to react with Tf_2O (Scheme 1C). Pyridines with certain substitution patterns are also not amenable; 2,6-disubstituted pyridines and 2-CF_3 pyridines are unsuccessful as the sp^2 nitrogen atom is either too sterically crowded or reduced in nucleophilicity such that reaction with Tf_2O is ineffective. For pyridines and quinolines, both C–P bond-forming reactions are inherently 4-selective, whereas 2-position selectivity can only be achieved when the 4-position is blocked. Using this sequence to prepare 2,2'-bipyridines for example, 4-position substituents must be present to ensure the correct positional selectivity. Similarly, C–P bond-formation in diazines is also inherently selective; pyrimidines react at the 4-position in this manifold, and this selectivity restricts the possible isomeric patterns in the resulting bis-azine biaryl. The strategy in Scheme 1B can potentially overcome these issues by using S_NAr reactions with chloroazines for each C–P bond-forming event. Scheme 1C shows classes of readily available chloroazines where the previous functional group incompatibilities and regiomeric constraints can be addressed.

We first developed conditions for S_NAr couplings between chloroazines and $HPPh_2$ and intentionally prepared heteroarylphosphines that were precluded from our previous study by steric, electronic or isomeric constraints.[10] For 2- and 4-chloropyridines, heating in chlorobenzene at 130 °C with one equivalent of TfOH was effective, and pyridylphosphines **2a-2g** were formed in high yields (condition set A) and addresses the aforementioned restrictions in C–P bond formation (*vide supra*). For more S_NAr active substrates, such as chloroquinolines, chloroisoquinolines and chlorodiazines,[13] trifluoroethanol (TFE) at 80 °C was sufficient and acid activation is not required (condition set B). Notably, these conditions allow access to phosphines at the 2-position of quinolines and pyrimidines. We found that these heteroarylphosphines are bench-stable but, as a precaution, they were kept in a –20 °C refrigerator for long-term storage.

With a set of heterocyclic phosphines in hand, we next developed one-pot procedures to form bis-azine biaryls via the tandem S_NAr-ligand-coupling sequence (Table 2). We found that coupling reactions could be separated into three categories depending on the ease

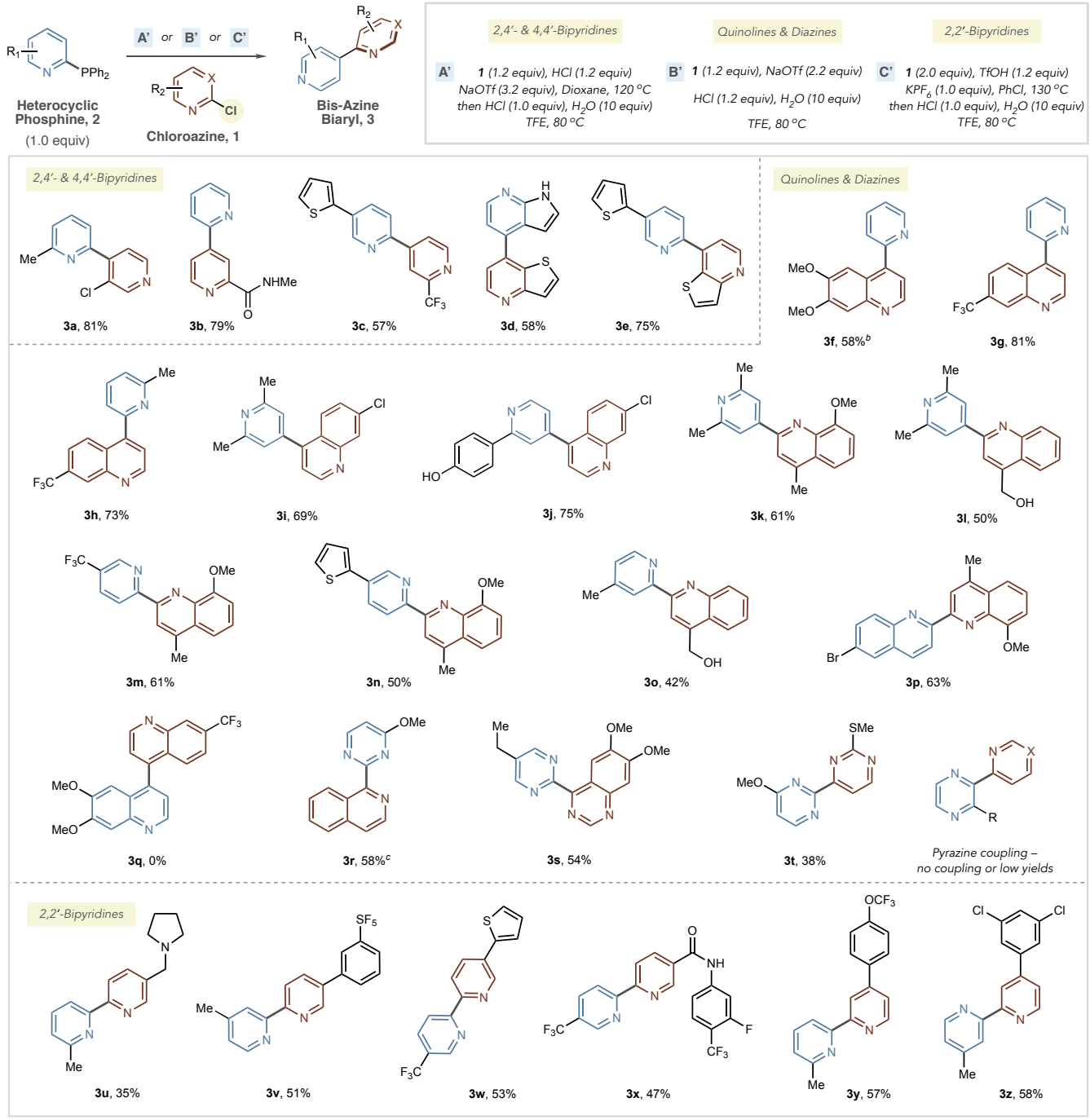
Table 1. S_NAr Reactions to Form Heteroarylphosphines[a]



[a]Isolated yields are reported.

of the S_NAr process. First, 2,4-and 4,4'-bipyridines were synthesized in a two-stage process; heating the phosphine and chloropyridine in dioxane at 120 ºC with one equivalent each of HCl and NaOTf drives the S_NAr reaction to completion and forms the bis-heterocyclic phosphonium salt.[14] Then, a further equivalent of HCl, ten equivalents of H_2O, and TFE are added, and heating at 80 ºC is optimal for the ligand-coupling process (condition set A'). Without NaOTf, the S_NAr reaction does not reach full conversion, and we presume that bis-azine phosphonium salt formation is promoted by anion exchange and precipitation of NaCl. By employing these conditions, a set of 2,4- and 4,4'- bipyridines are formed in reasonable yields (**3a-3e**). Bipyridine **3b** is notable as the alkyl amide group was incompatible with our previous protocol. Second, chloroquinolines and chlorodiazines couple heteroarylphosphines using single-stage protocol. In line with observations in Table 1, these heterocycles undergo more facile S_NAr with processes and the tandem S_NAr-ligand-coupling sequence is performed in TFE at 80 ºC with H_2O, HCl and NaOTf as additives (condition set B'). By employing these conditions, a set of 2,4- and 4,4- pyridine-quinolines are formed (**3f-3l**) and include examples of pyridines with 2,6-disubstitution, 4-position C–H bonds, as well as products containing phenols and alcohols. Furthermore, 2,2-pyridine-quinoline systems **3m-3o** can also be synthesized that are challenging to prepare via Suzuki-Miyaura couplings (*vide infra*). Similarly, **3p** is a

Table 2. Tandem S_NAr-Ligand-Coupling Reactions to Form Non-Symmetrical Bis-Azine Biaryls[a]

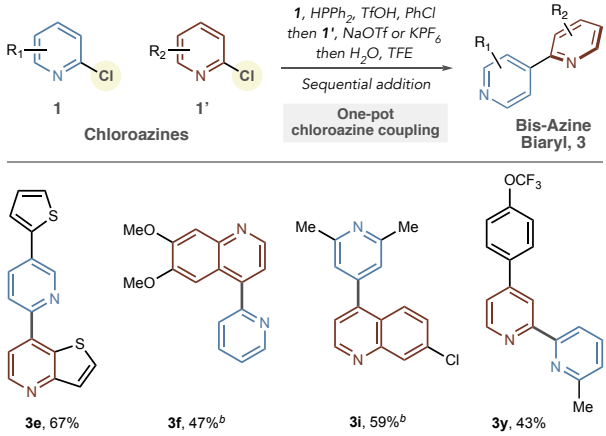


[a]Isolated yields are reported. [b]**3f** was formed using a two-stage protocol: 1.2 equiv chloroazine, 2.2 equiv NaOTf, TFE, 80 ºC then 1.2 equiv HCl and 10 equiv water were added. [c]TfOH used instead of HCl.

2,2'-biquinoline that includes a C–Br bond that would typically be active in transition metal-catalyzed processes. However, an attempt to form 4,4'-biquinoline **3q** failed; we presume unfavorable steric interactions occur in the ligand-coupling transition state in this case. Diazines can be used as both formal donor phosphines and acceptor chlorides; a 2-pyrimidylphosphine was coupled with a chloroisoquinoline in moderate yield (**3r**), and diazine-diazine coupling is possible using this approach (**3s-3t**). At this point pyrazines perform poorly as coupling partners; a short survey of pyridine, quinoline and diazine partners resulted in no coupled products or poor yields (see the Supporting Information). Third, we targeted 2,2'-bipyridines using this strategy due to the challenges in synthesizing these systems using Suzuki-Miyaura cross-coupling reactions (*vide supra*). Condition set A' was modified to C', where changes in solvent, acid and additive resulted in higher yields of bipyridine products (see Supporting Information). Examples **3u-3z** display a variety of isomeric patterns, as well as substituents such as aliphatic amines, SF_5 groups, thiophenes, amides and chlorides. As with all other examples in Table 2, these bipyridine products could not be formed using our previous approach from C–H precursors.[10] The moderate yields obtained approximate those in our previous report involving 2,2'-bipyridine couplings, and further investigations into the mechanism of this process are ongoing.[15]

Finally, we developed a one-pot, net cross-electrophile coupling of two chloroazines in a stage-wise protocol involving sequential addition of reagents (Table 3).[16] We hypothesized that the heteroarylphosphine could be formed *in situ* and reacted with the second chloroazine via a tandem S_NAr-ligand-coupling sequence from Table 2. The four examples, **3e**, **3f**, **3i** and **3y**, in Table 3 show that pyridine-pyridine and pyridine-quinoline couplings are viable using this process forming products in reasonable yields, with 2,2'-, 2,4'- and 4,4'-conectivity between the two heterocycles. Current efforts are focused on increasing the efficiency of these process, as well as expanding the scope to other azine-azine couplings.

Table 3. One-Pot Cross-Coupling of Chloroazines[a]



[a]Isolated yields are reported. [b]TFE/Toluene 1:1 used in the final stage.

In summary, we have developed an alternative strategy to form bis-azine biaryls by coupling azinylphosphines with chloroazines. The reaction proceeds via a tandem S_NAr-ligand-coupling sequence, and the heteroaryl phosphines are bench-stable solids that are prepared themselves from chloroazines in a separate step. A diverse set of bis-azine biaryl products can be formed, including substitution patterns such as 2,2'-bipyridines, that are challenging for traditional metal-catalyzed approaches. Abundant chloroazines, simple protocols and valuable bis-azine biaryl products make this approach useful for medicinal chemists.

ASSOCIATED CONTENT

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

Experimental procedures and spectral data (PDF)

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