Letter

Cobalt-Catalyzed Alkylation of Drug-Like Molecules and Pharmaceuticals Using Heterocyclic Phosphonium Salts

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Cobalt-Catalyzed Alkylation of Drug-Like Molecules and Pharmaceuticals Using Heterocyclic Phosphonium Salts

Xuan Zhang and Andrew McNally*

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523, United States.

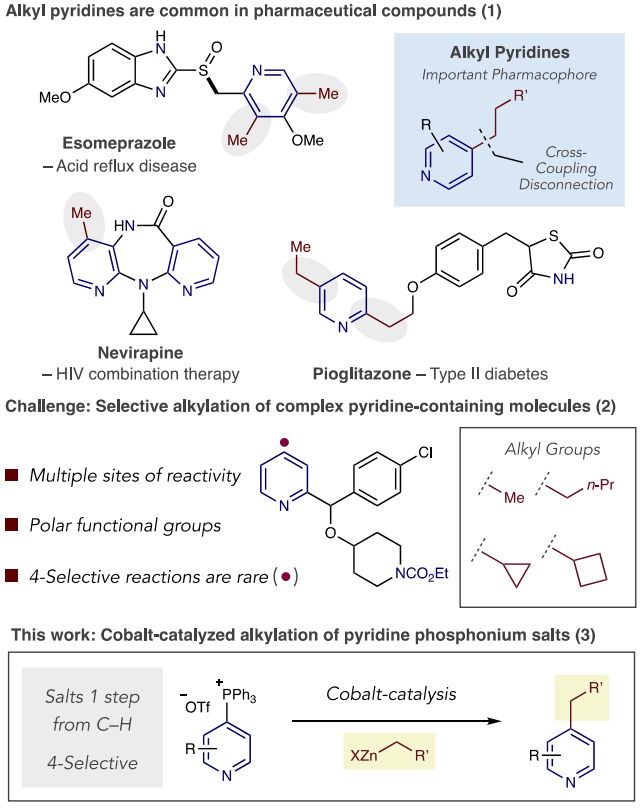
Supporting Information Placeholder

ABSTRACT: Alkylated pyridines are common in pharmaceuticals, and metal catalysis is frequently used to prepare this motif via Csp^2-Csp^3 coupling processes. We present a cobalt-catalyzed coupling reaction between pyridine phosphonium salts and alkylzinc reagents that can be applied to complex drug-like fragments and for late-stage functionalization of pharmaceuticals. The reaction generally proceeds at room temperature, and 4-position pyridine C–H bonds are the precursors in this strategy. Given the challenges in selectively installing (pseudo)halides in complex pyridines, this two-step process enables sets of molecules to be alkylated that would be challenging using traditional cross-coupling methods.

Pyridines, alkylation, late-stage, phosphonium salts, cross-coupling, cobalt-catalysis, alkyl Negishi.

Pyridines are important pharmacophores in therapeutic compounds, but their precise function is a combined effect of the heterocycle and its adorning substituents.[1] Alkylated pyridines are particularly common, and examples of their occurrence in marketed drugs are shown in eq 1. The alkyl groups serve various roles in drug development, such as occupying hydrophobic pockets, changing binding properties of the Lewis basic nitrogen atom, protecting against oxidative metabolism as well as serving as linkers to other portions of the molecule.[2] The effect of alkyl groups on pyridines is also relevant for other applications such as ligands, materials and redox active molecules in batteries.[3,4] As such, methods to add alkyl groups to pyridines are broadly useful in several disciplines of applied chemistry.

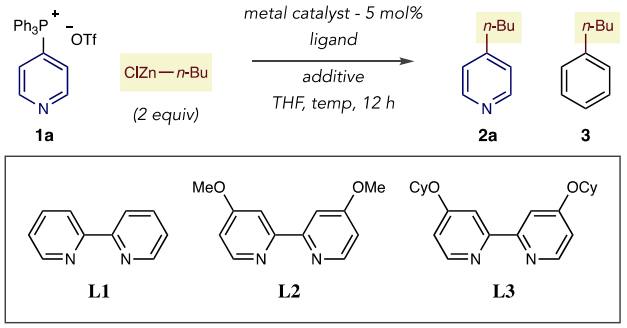
Coupling reactions are modular and efficient ways of forming Csp^2-Csp^3 bonds between pyridines and functionalized carbon-bearing groups. Several methods exist to install alkyl groups via C–H functionalization reactions including Minisci-type reactions and metal-catalyzed coupling reactions with alkenes.[5,6] Despite significant progress, controlling regioselectivity and tolerating a broad range of pyridines can be problematic in these respective reaction types. Adding organometallics to pyridinium salts is another approach and Fier recently showed an example where an alkyl group was added via this



reaction pathway.[7] The most common methods to make alkylated pyridines are transition metal-catalyzed cross-coupling reactions between pyridyl(pseudo)halides and alkyl organometallic reagents.[8] These reactions are broadly effective to alkylate pyridine building blocks where halide or psuedohalides are commercially available, or can be

prepared. In drug development however, pyridine-containing molecules are often complex and devoid of cross-coupling handles. Furthermore, these molecules have multiple reactive sites, substitutional variability and an excess of polar function groups making selective (pseudo)halogenation of C–H bonds challenging, or impossible, using existing methods (eq 2). Our goal was therefore to address this challenge using an alternative cross-coupling precursor, and herein we present a cobalt-catalyzed coupling reaction between alkylzinc reagents and pyridine phosphonium salts (eq 3). The reaction

Table 1. Development of a Phosphonium Salt Alkylation Reaction



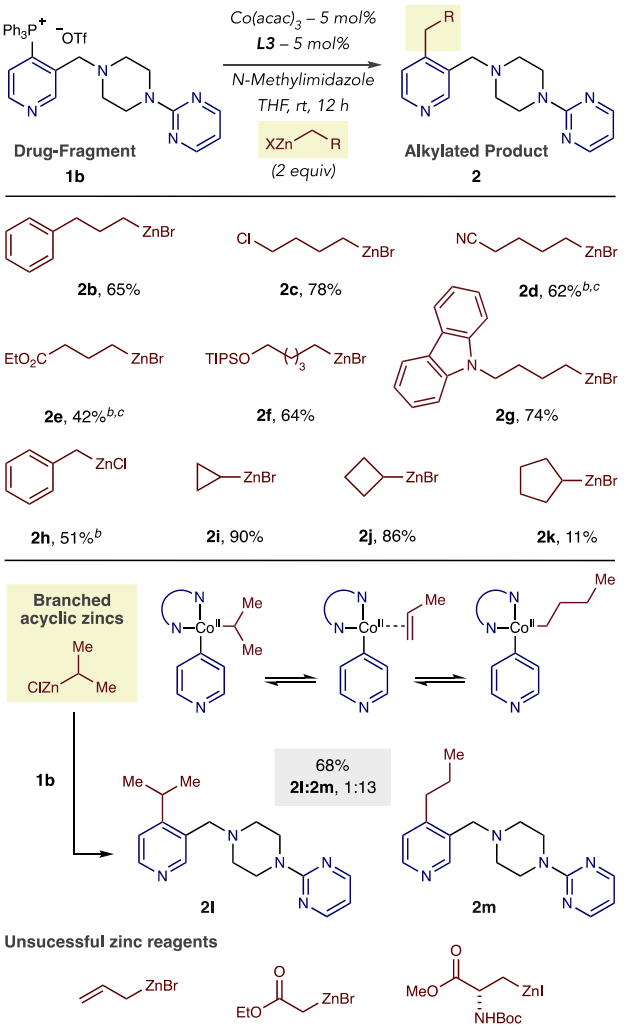
entry	catalyst system	additive	temp °C	yield **2a**[a]	yield **3**[a]
1	$Ni(COD)_2$, SIPr•HCl NaO*t*Bu	–	50	37%	20%
2	$Ni(COD)_2$, PCy_3	–	50	45%	20%
3	$Ni(COD)_2$, di-*t*Bubpy	–	50	37%	22%
4	$Pd(OAc)_2$, SIMesr•HCl NaO*t*Bu	–	50	3%	2%
5	$Pd(OAc)_2$, PCy_3	–	50	8%	3%
6	$Co(acac)_3$, **LI**	–	50	10%	<1%
7	$Co(acac)_3$, **LI**	–	23	12%	<1%
8	$Co(acac)_3$, **L2**	–	23	47%	<1%
9	$Co(acac)_3$, **L2**	*N*-Me imidazole	23	67%	<1%
10	$Co(acac)_3$, **L2**	$ZnCl_2$	23	26%	<1%
11[b]	$Co(acac)_3$, **L2**	*N*-Me imidazole	23	79%	<1%
12[b]	$Co(acac)_3$, **L3**	*N*-Me imidazole	23	86% (78%)[c]	<1%

[a]Yields calculated by GC using 1,3,5-trimethoxybenzene as a standard. THF concentration 0.1 M. [b]THF concentration 0.033 M.[c]Isolated yield.

operates at room temperature and forms a diverse set of alkylated pyridines from C–H precursors.

Our laboratory is developing a program where phosphonium groups can serve as generic functional handles to functionalize pyridines and diazines.[9] This strategy overcomes significant deficiencies of using heteroaryl (pseudo)halides as the C–$^+PPh_3$ group can be directly and selectively installed on a broad range of substrates, and subsequent transformations are compatible with polar functional groups that are often found in drug like-molecules.[10] Furthermore, the reaction is 4-selective for pyridines, a position that is difficult to access using most methods. We have previously shown that phosphonium ions can serve as pseudohalides in a nickel-catalyzed coupling process with (hetero)aryl boronic acids. Combining a Ni(0) catalyst with an NHC ligand was crucial for selective heterocycle vs. phenyl coupling using PPh_3-derived azine salts.[9d] Our attempts at developing an alkylation reaction began with pyridine phosphonium salt **1a** and butylzinc as a coupling partner in THF at 50 ºC (Table 1). Entry 1 shows that our previous nickel-system results in an unselective mixture of butylpyridine **2a** and phenyl-coupling product **3**. Using phosphine or bipyridine ligands were similarly unselective, as were ligated palladium catalysts (entries 2–5). We instead turned our attention to cobalt-catalysis and tested a Co(III) salt with bipyridine (**L1**) as a ligand.[11,12] Gratifyingly, the reaction was selective for pyridine **2a** with only traces of butylbenzene **3** observed in the reaction mixture (entry 6), although the reaction efficiency was low. Conducting the reaction at room temperature resulted in a similar yield of **2a** (entry 7). Methoxy substituted bipyridine **L2** was significantly more effective as a ligand indicating that increased electron density at the metal center improves reactivity. A screen of Lewis basic additives revealed that *N*-Me imidazole further increase the efficiency of the reaction (entries 8 & 9).[13] We hypothesized that the additive

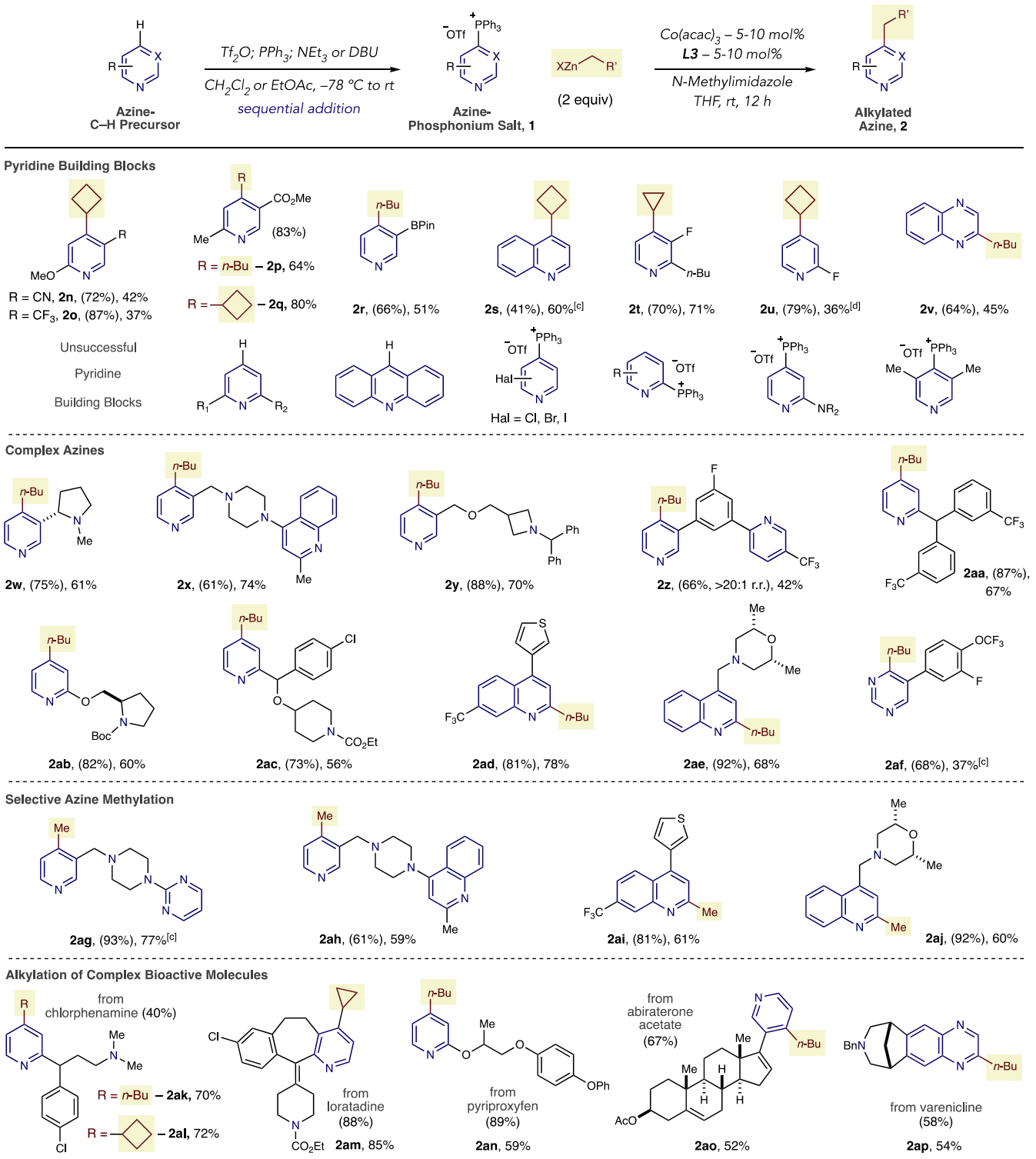
Table 2. Scope of Alkyl Zinc Reagents[a]



[a]Isolated yields of products are shown. [b]The reaction was run at 50 ºC. [c]10 mol% $Co(acac)_3$ and 10 mol% **L3** used.

sequesters the ZnClOTf byproduct; entry 10 shows that adding a Zn(II) salt at the outset of the reaction is deleterious to the yield of the process and supports our hypothesis. The reaction was further improved by decreasing the concentration to 0.033 M (entry 11) and employing cyclohexyloxy-substituted bipyridine **L3** is the most effective protocol (entry 12). We assume a low valent ligated cobalt species (Co(0) or Co(I)) is the active catalyst and a typical oxidative addition-transmetalation-reductive elimination sequence constitutes the catalytic cycle.

Table 3. Scope of Pyridine Building Blocks, Drug-Like Fragments and Complex Bioactive Molecules[a,b]



[a]Typical salt-forming conditions: azine (1.0 equiv), Tf_2O (1.0 equiv), PPh_3 (1.1 equiv), DBU (1.1 equiv) CH_2Cl_2 or EtOAc, –78 ºC to rt. [b]Isolated yields of products as single regioisomers (unless stated) are shown with yields of phosphonium salts in parentheses. [c]The reaction was conducted at 50 ºC. [d]A 3.5:1 mixture of **2u** and 2,4-dicyclobutylpyridine was observed in the crude ^1H NMR spectrum.

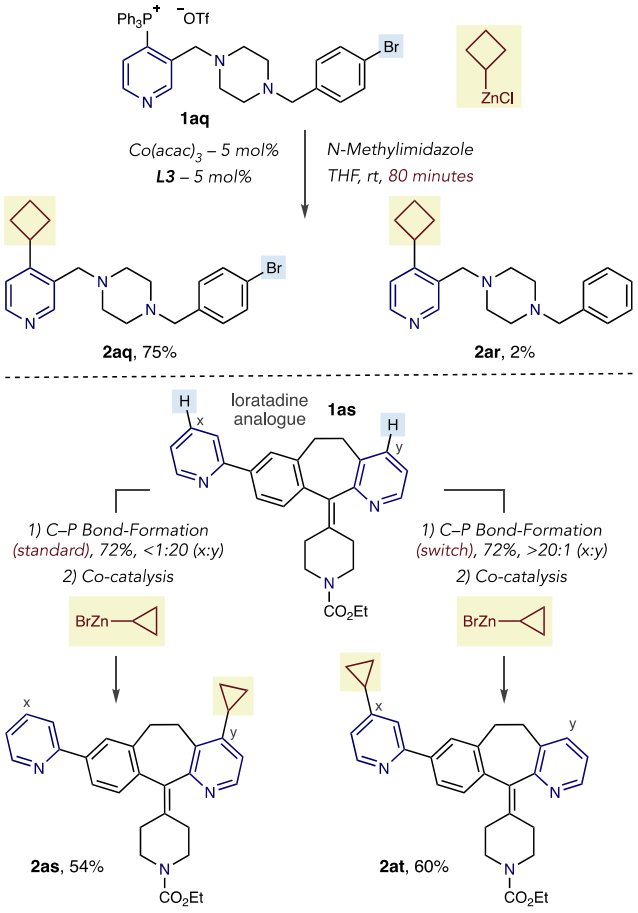
The scope of alkylzinc reagents was examined using phosphonium salt **1b** as a representative substrate (Table 2).[9f] Linear zinc reagents, containing phenyl, chloro, cyano and ester groups, provide products **2b**-**2e** in moderate to good yields (**2b**-**2e**); conducting the reaction at 50 ºC is optimal in the latter two cases. Silyl ethers and carbazole fragments are also tolerated (**2f** & **2g**). Benzylzinc is a reasonable coupling partner (**2h**), and cyclopropyl- and cyclobutylzincs result in high yields of alkylated products (**2i** & **2j**).

Cyclopentylzincs are less effective in this process but usable quantities of **2k** were obtained; we are uncertain of the exact reasons for the decreased yields, but we presume that an unfavorable steric interaction is operative. This point was exemplified when *iso*-propylzinc was examined; an isomeric mixture of products **2l** and **2m** were obtained with the linear product significantly favored. Our hypothesis is that branched to linear isomerism occurs at a Co(II)-species via a reversible β-hydride elimination-hydrometallation sequence, and that the less hindered linear alkylcobalt isomer undergoes reductive elimination more rapidly.[14] Examples of unsuccessful coupling reactions include allyl zinc reagents, where a complex mixture of products was observed, α-zinc carbonyls and a iodozinc amino acid derivative.

In Table 3, we applied the phosphonium-mediated coupling process to a range azine-containing structures. Pyridine building blocks containing functional groups such as cyano, trifluoromethyl, esters, methoxy, and boronic esters are tolerated (**2n-2r**). Quinoline salts are amenable to the strategy and **2s** was obtained as a single regioisomer. A 3-fluoropyridine salt performed well in the Co-coupling reaction (**2t**), however, a 2-substituted isomer was formed along with the corresponding bis-alkylated product in a 3.5:1 ratio (**2u**). Substrates that result in low salt yields or give no C–P bond-formation include 2,6-disubstituted pyridines, acridines, 2-CF_3-pyridines and pyridines with more than two electron-withdrawing groups or electron-donating groups. Limitation of pyridyl phosphonium salts in the zinc coupling process include chloro-, bromo-, and iodopyridines that result in mixtures of alkylated products via the C–Hal and C–P bonds as well as bis-alkylation (*vide infra*). At this point, 2-pyridylphosphonium salts are unsuccessful as coupling partners as well as salts derived from 2,2-bipyridines. Amino substituents at the 2-position of lead to trace amounts of products and attempted alkylation of a 3,5-dimethylphonium salt resulted in return of the C–H precursor.

Next, a set of complex azines that approximate structures encountered in medicinal chemistry programs was tested.[10] Starting with 3-substituted pyridines, nicotine could be taken through the two-step process and alkylated in moderate yield (**2w**). Alkylated pyridines **2x** and **2y** are notable due to the presence of other heterocycles and basic amines. Site-selective alkylation reactions are desirable, and a butyl group could be selectively installed on the 3-substituted pyridine in **2z** due to the preference of forming phosphonium salts on 3-substituted pyridines over 2-substituted isomers. Pyridine-containing structures possessing a benzhydril center, a protected pyrrolidine (**2aa** & **2ab**) as well as a precursor to the antihistamine bepotastine (**2ac**) can also be alkylated. Quinolines are alkylated at the 2-position when the 4-position is substituted (**2ad** & **2ae**). A pyrimidine was also alkylated in this protocol, and although the yield of **2af** was low, a single regioisomer was formed; C–P bond cleavage and return of the C–H precursors was the main side product in this reaction. Methylation of azines is a common strategy in drug development and we tested MeZnCl in this coupling process.[15,16] While less efficient than *n*-BuZnCl as a coupling reagent, four examples of pyridines and quinolines were alkylated in reasonable yields (**2ag-2aj**).[17]

Late-stage functionalization of therapeutic compounds is an area of current importance in medicinal chemistry and we examined five drug compounds in the phosphonium-mediated strategy.[18] The antihistamine, chlorphenamine is effective in this protocol with butylated and cyclobutylated



derivatives **2ak** and **2al** obtained in good yields. Loratadine was cyclopropanated at the 4-position

Scheme 1. Chemoselective Co-Catalyzed Alkylations[a]

[a]Isolated yields shown are of a mixture of **2aq** and **2ar**. Standard C–P bond formation: **1as** (1.0 equiv), Tf_2O (1.0 equiv), PPh_3 (1.1 equiv), DBU (1.0 equiv) CH_2Cl_2, –78 ºC to rt. Switch C–P bond formation: **1as** (1.0 equiv), Tf_2O (2.0 equiv), PPh_3 (2.0 equiv), NEt_3 (2.0 equiv) CH_2Cl_2, –78 ºC to rt. Co-catalysis: 10 mol% $Co(acac)_3$, 10 mol% **L3**, *N*-Methylimidazole (1.5 equiv), THF, 50 ºC.

of the pyridine moiety in excellent yield (**2am**). Pyriproxyfen, a pesticide, is also alkylated efficiently (**2an**). A steroidal treatment for prostate cancer, abiraterone acetate, can be conveniently converted into alkylated derivative **2ao**, and a protected version of varenicline, possessing a quinoxaline core, is alkylated adjacent to the heterocyclic nitrogen atom (**2ap**).

We next explored chemoselective Co-catalyzed couplings and site-selective switching reactions in polyazine substrates (Scheme 1). In our Ni-catalyzed Suzuki-reaction, aryl bromides preferentially react over pyri dylphosphonium salts.[8d] In this Co-catalyzed process, we found the opposite order of chemoselectivity. Salt **1aq**,

containing an aryl bromide, was subjected to the standard coupling conditions at a short reaction time. The major outcome is cyclobutylation of the pyridine ring (**2aq**) with minor amounts of debrominated product **2ar**. No evidence of coupling via the C–Br bond was detected in the reaction mixture, unlike our observations of halopyridines. Using our previously developed method to control site-selective C–P bond-formation, we made two phosphonium ion isomers of loratadine analogue **1as** in >20:1 selectivity.[9h] Each isomer was subsequently alkylated to make cyclopropane analogues **2as** and **2at** in reasonable yields and demonstrates the compatibility of the Co-coupling process with the site-selective switching strategy.

In summary, we have shown that pyridine phosphonium salts, selectively installed in one step from C–H precursors, can serve as coupling partners in a cobalt-catalyzed cross-coupling reaction with alkylzinc reagents. This simple, room temperature process can generate alkylated analogues in a range of complex pyridine-containing molecules and serve as a strategy for late-stage alkylation of pharmaceuticals. The distinct scope compared to methods employing halogenated heterocycles as partners will provide new opportunities in drug-development programs.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org

AUTHOR INFORMATION

Corresponding Author

*andy.mcnally@colostate.edu

ORCID

Andrew McNally: 0000-0002-8651-1631

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(12) Cobalt halides can be used as catalysts but are marginally less efficient than $Co(acac)_3$. See Supporting Informtion for more details.

(13) See the Supporting Information for an additive screen and evaluation of other solvents (toluene, 1,4-dioxane, CH_2Cl_2 and MeCN).

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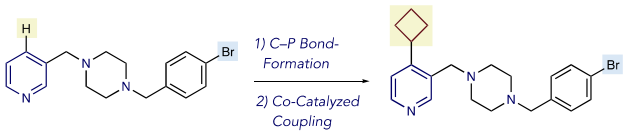
Cobalt-Catalyzed Coupling of Pyridine Phosphonium Salts with Alkyl Zinc Reagents



Room temperature coupling • Drug-like molecules • Chemoselective