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

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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.

Graphical Abstract:

Keywords

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,

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Supporting Information

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Experimental procedures and spectral data (PDF)

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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 Csp²–Csp³ 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 pseudohalides 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 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–⁺PPh₃ 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 PPh₃-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 °C (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 and 9).¹³ We hypothesized that the additive 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.

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 °C is optimal in the latter two cases. Silyl ethers and carbazole fragments are also tolerated (**2f** and **2g**). Benzylzinc is a reasonable coupling partner (**2h**), and cyclopropyl- and cyclobutylzincs result in high yields of alkylated products (**2i** and **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–hydrometalation 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-CF₃-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 lead to trace amounts of products and attempted alkylation of a 3,5-dimethylphosphonium 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 because of 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** given the preference of forming phosphonium salts on 3-substituted pyridines over 2-substituted isomers. Pyridine-containing structures possessing a benzhydryl center, a protected pyrrolidine (**2aa** and **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** and **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 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 pyridylphosphonium salts.^{8e} 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 with methods employing halogenated heterocycles as partners will provide new opportunities in drug-development programs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1. Chemoselective Co-Catalyzed Alkylations^a

^aIsolated yields shown are of a mixture of **2aq** and **2ar**. Standard C–P bond formation: **1as** (1.0 equiv), TiF_2O (1.0 equiv), PPh_3 (1.1 equiv), DBU (1.0 equiv) CH_2Cl_2 , -78°C to rt. Switch C–P bond formation: **1as** (1.0 equiv), TiF_2O (2.0 equiv), PPh_3 (2.0 equiv), NEt_3 (2.0 equiv) CH_2Cl_2 , -78°C to rt. Co-catalysis: 10 mol % $\text{Co}(\text{acac})_3$, 10 mol % **L3**, *N*-Methylimidazole (1.5 equiv), THF, 50°C .

Table 1.

Development of a Phosphonium Salt Alkylation Reaction

entry	catalyst system	additive	temp °C	yield 2 ^a	yield 3 ^a
1	Ni(COD) ₂ , SIPr·HCl NaOtBu	-	50	37%	20%
2	Ni(COD) ₂ , PCy ₃	-	50	45%	20%
3	Ni(COD) ₂ , di- <i>t</i> Buipy	-	50	37%	22%
4	Pd(OAc) ₂ , SiMesr·HCl NaOtBu	-	50	3%	2%
5	Pd(OAc) ₂ , PCy ₃	-	50	8%	3%
6	Co(acac) ₃ , L1	-	50	10%	<1%
7	Co(acac) ₃ , L1	-	23	12%	<1%
8	Co(acac) ₃ , L2	-	23	47%	<1%
9	Co(acac) ₃ , L2	<i>N</i> -Me imidazole	23	67%	<1%
10	Co(acac) ₃ , L2	ZnCl ₂	23	26%	<1%
11 ^b	Co(acac) ₃ , L2	<i>N</i> -Me imidazole	23	79%	<1%
12 ^b	Co(acac) ₃ , L3	<i>N</i> -Me imidazole	23	86% (78%) ^c	<1%

^aYields calculated by GC using 1,3,5-trimethoxybenzene as a standard. THF concentration 0.1 M.^bTHF concentration 0.033 M.^cIsolated yield.

Table 2.

Scope of Alkyl Zinc Reagents^a ^a Isolated yields of products are shown.^b The reaction was run at 50 °C.^c 10 mol % Co(acac)₃ and 10 mol % L3 used.

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Table 3.

^aTypical salt-forming conditions: azine (1.0 equiv), Tf₂O (1.0 equiv), PPh₃ (1.1 equiv), DBU (1.1 equiv) CH₂Cl₂ or EtOAc, -78 °C to rt.

^bIsolated yields of products as single regioisomers (unless stated) are shown with yields of phosphonium salts in parentheses.

^cThe reaction was conducted at 50 °C.

^dA 3.5:1 mixture of **2u** and 2,4-dicyclobutylpyridine was observed in the crude ¹H NMR spectrum.