Ni-catalyzed deaminative cross-electrophile coupling of Katritzky salts with halides via C—N bond activation

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The reductive cross-coupling of sp³-hybridized carbon centers represents great synthetic values and insurmountable challenges. In this work, we report a nickel-catalyzed deaminative cross-electrophile coupling reaction to construct C(sp)—C(sp³), C(sp)—C(sp³), and C(sp³)—C(sp³) bonds. A wide range of coupling partners including aryl iodides, bromoalkynes, or alkyl bromides are stitched with alkylpyridinium salts that derived from the corresponding primary amines. The advantages of this methodology are showcased in the two-step synthesis of the key lactonic moiety of (+)-compactin and (+)-mevinolin. The one-pot procedure without isolation of alkylpyridinium tetrafluoroborate salt is also proven to be successful. This cross-coupling strategy of two electrophiles provides a highly valuable vista for the convenient installation of alkyl substituents and late functionalizations of sp³ carbons.

INTRODUCTION

Transition metal–catalyzed radical cross-coupling has become one of the most fundamental transformations in materials science, biology, and organic chemistry. Remarkable progress has been made in this research area during the past several decades, providing a complementary technique to the venerable Heck, Suzuki, and Negishi reactions (1–3). However, forging sp³-hybridized carbon centers remains a great challenge mainly due to the weak nucleophilic reactivity of sp³ carbon centers and their innate difficulties in coordination with metals (4–7). In recent years, various alkyl radical precursors including halides (4, 8–11), silicones (12), dihydropyridine (13), carboxylic acids (14–16), sulfones (17), and others (18–20) have been used for radical cross-coupling reactions (Fig. 1A).

Primary amines are prevalent in biologically active natural products and drug molecules. As inexpensive and abundant building blocks, amines are broadly used in synthetic chemistry (21, 22). However, the use of amines as alkyl electrophile precursors for radical cross-electrophile coupling transformations is yet to be described. Notably, Watson and co-workers (23, 24) recently reported elegant Suzuki-Miyaura and Negishi cross-coupling reactions using primary amines as alkyl sources through C—N activation. Their strategy consisted of conversion of primary amines to redox-active alklypyridinium salts (Katritzky pyridium salts), which were reacted with arylboronic acids or organozinc reagents via a single-electron transfer process (Fig. 1B). The redox-active alklypyridinium salts were subsequently used as alkyl halide surrogates in a photo-induced Minisci reaction by Glorious and co-workers (25). Recently, Aggarwal, Shi, and Glorious (26–28) reported deaminative borylation of Katritzky pyridium salts using bis-(catecholato)diboron. Gryko (29) have developed a Giese-type deaminative alkylamination and alkenylation using the corresponding sulfones. Xiao and co-workers (30) developed a visible light–initiated deaminative alkyl–Heck–type reaction between Katritzky salts derived from aliphatic primary amines and alkenes, which afforded the products in good yields. In these examples, bond formation is achieved by the reaction between nucleophilic reagents with the Katritzky salts derived from primary amines. However, the use of amines as alkyl electrophile precursors for radical cross-electrophile coupling transformations is yet to be described, especially direct construction of C(sp³)—C(sp³) and C(sp³)—C(sp) bonds. On the other hand, the Doyle group developed a Ni-catalyzed enantioselective cross-electrophile coupling reaction of styrenyl aziridines with aryl iodides (31). Following our keen interest in cross-electrophile coupling reactions (32), we envisaged whether the coupling of primary amines with electrophilic halides could be achieved by the mediation of the corresponding Katritzky salts. Such approach occupies a clear edge over conventional cross-coupling procedures in avoiding air- and moisture-sensitive organometallic reagents. Here, we report the first Ni-catalyzed cross-electrophile coupling between alklypyridinium salts and halides through C—N bond activation (Fig. 1B).

RESULTS

We began our study with evaluation of the conditions for this envisioned cross-coupling reaction between 4-iodotoluene 1-a and pyridinium salts 1 derived from 2-(benzo[d][1,3]dioxol-5-yl)ethan-1-amine and 2,4,6-triphenylpyrylium tetrafluoroborate. The desired product was obtained in 77% yield with 10 mole percent (mol %) NiBr₂•diglyme catalyst and 10 mol % tridentate ligand L3 in the presence of 2.5 equivalents (equiv) of zinc at 60°C under argon atmosphere (entry 1; Fig. 1C). When NiI₂ instead of NiBr₂•diglyme was used as a catalyst, the yield decreased markedly to 45% (entry 2).

Reducive metal species were found to be important for this transformation, as evidenced by the low yield (56%) obtained when using Mn as reducing reagent (entry 3). Bidentate ligands L1 and L2 led to only trace amount of product 3a, indicating that the additional coordinating site of L3 was crucial for achieving reactivity (entries 4 and 5). Further evaluation of the reaction conditions by lowering the reaction temperature, performing the reaction under air or changing the solvent to dioxane did not result in any improvement on the yield (entries 6 to 8).

Under the optimized reaction conditions, we explored the substrate generality of this cross-electrophile coupling with various aryl iodides and tetrafluoroborate pyridinium salts (Fig. 2). Aryl iodides with electron-withdrawing and electron-donating substituents were tolerated in the reaction. The methyl (2 and 3)—, phenyl (8)—, and p-Cl-phenyl (15)—substituted coupling products were obtained in

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good yields. Different alkyl substituents on the pyridinium salts performed equally well, and the desired products were obtained in 44 to 70% yields (9 to 12). Thiophene-substituted pyridinium salts also proceeded smoothly (13 to 15). Extending the alkyl chains did not influence the reaction performance (5, 16, 17 and 6, 18). Secondary amines such as cyclohexyl amine and cyclobutyl amine could serve as electrophiles (19 and 20) to afford the secondary alkyl-substituted amines in 67 and 71% yields, respectively. Benzylamine did not react under the optimized conditions, presumably due to the stability of benzyl radical. During the preparation of pyridinium tetrafluoroborate salts, we could not obtain several substrates by simple filtration and an additional purification step was required. This limitation prompted us to investigate the reaction in a one-pot manner without isolation of Katritzky salts. When the primary amine was activated in situ and treated to the standard conditions, the cross-coupled product 3 was achieved in 75% yield by in situ reaction and 76% yield by the standard conditions.

Next, we examined whether alkynyl halides could also participate in this Ni-catalyzed cross-electrophile coupling reaction to construct C(sp³)–C(sp³) bonds. Such transformations have never been explored with primary amines (23–30). After careful screening of the nickel catalysts and ligands, we found that the reaction of (bromoethynyl) triisopropylsilane and 1-phenethyl-2,4,6-triphenylpyridinium tetrafluoroborate with the combination of Ni(acac)₂/dtbpy L1 as catalyst afforded alkyne 23 in 67% yield (68% from the in situ reaction). Unlike the reaction of iodobenzene electrophiles, bidentate bipyrindyl ligand exhibited good catalytic activity for this reaction. We also attempted introducing additives in the reaction mixture, and no improvement was observed (see the Supplementary Materials for the details of the optimization of the reaction conditions). As shown in Fig. 2B, triisopropylsilyl (TIPS)–substituted bromoethyne reacted smoothly with a series of tetrafluoroborate pyridinium salts under standard conditions to afford the corresponding alkyl-substituted amines in 52 to 71% yields. Note that 2-arylethylamine–, 3-phenylpropylamine–, 4-phenylbutylamine–, and 2-thienylmethylamine–derived pyridinium salts were suitable substrates for this reaction.

Despite the coupling of aryl iodides, alkyl bromides were tested with alkylpyridinium salts to form the C(sp³)–C(sp³) bond (Fig. 2C). Phenylethyl bromide reacted smoothly to furnish the corresponding product 29 in 53% yield. The reaction between phenylethyl bromide and the salt of piperazine proceeded to give the product 33 in 50% yield. The substrates bearing long alkyl chain and cyclohexyl also afforded the desired products 30 and 31 in 48 and 55% yield, respectively. Notably, a linear alkyl bromide bearing an ester was tolerated in this reaction to afford the product 32 in moderate yield (40%). To further demonstrate the utility of the Ni-catalyzed cross-electrophile coupling reaction, we attempted Katritzky pyridinium salts derived from several natural bioactive amines. The amine derivative of atorvastatin precursor was coupled with 4-iodotoluene under the standard conditions to afford 21 in 53% yield. Moreover, we demonstrated that the estrone surrogate aryl iodide was converted to 22 in 46% yield.

In addition, this strategy has been applied to the synthesis of the lactonic moiety of (+)-compactin and (+)-mevinolin, which previously required 10 steps to synthesize (Fig. 3) (33). Starting from commercially available 34, a two-step sequence was developed to install the phenyl group to furnish the key intermediate 35 in 55% yield.

We carried out further mechanistic studies to gain insight into this transformation. A mixture of iodobenzene and zinc flake (325 mesh) in N,N′-dimethylformamide (DMF) was heated to 60°C for 8 hours, and no reaction occurred (see the Supplementary Materials). The full recovery of iodobenzene suggested that the reaction may proceed through a single-electron transfer process rather than generating organozinc species. The reaction of 2-phenylethylamine trifluoroacetate with iodobenzene did not occur under the standard conditions, indicating that tetrafluoroborate pyridinium salt is irreplaceable in the reaction. The addition of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) suppressed this reaction, and only 27% yield of product 2 was obtained (71% under the standard conditions). In addition, the trapped alkyl radical TEMPO adduct was detected by electrospray ionization mass spectrometry (ESI-MS), which indicates that a radical process is involved (see the Supplementary Materials).

**DISCUSSION**

On the basis of the above control experiments and previous reports (23–30, 34), a radical cross-coupling pathway via C–N bond cleavage and reductive elimination was proposed for this reaction (Fig. 4).
Initially, reduction of the Ni(II) salt by Zn affords the active Ni(0) catalyst, which underdoes oxidative addition into the C–X bond of halide 2 to give the intermediate R-Ni(II)X A (35). A is subsequently reduced by zinc to R-Ni(I) intermediate B, which undergoes a second oxidative addition step to pyridinium 1. This step may proceed via stepwise single-electron transfer with the possibility of radical trapping within a solvent cage to afford intermediate C before generation of R-Ni(III)(alkyl)X intermediate D (36). Reductive elimination

Fig. 2. Substrate scope of the reaction. *Isolated yields. †Condition A: Pyridinium salts (0.2 mmol), NiBr2•diglyme (0.02 mmol), L3 (0.02 mmol), zinc flake (−325 mesh, 99.9%) (0.5 mmol), aryl iodide 2 (0.3 mmol), and DMF (2.0 ml), 60°C. ‡Condition B: Pyridinium salts (0.2 mmol), Ni(acac)2 (0.02 mmol), L1 (0.02 mmol), zinc flake (−325 mesh, 99.9%) (0.5 mmol), bromoalkynes (0.3 mmol), and DMF (1.0 ml), 60°C. §Condition C: Pyridinium salts (0.2 mmol), Ni(COD)2 (0.04 mmol), tetrabutylammonium iodide (0.1 mmol), zinc flake (−325 mesh, 99.9%) (0.5 mmol), bromoalkanes (0.8 mmol), and dimethylamine (1.0 ml), 60°C.

Fig. 3. Synthesis of the precursor to the key lactonic moiety in (+)-compactin and (+)-mevinolin.
from D forms the desired product 3 and nickel(I) species E, which is reduced by zinc to facilitate the next catalytic cycle (35).

In summary, we have described a new cross-electrophile coupling reaction using alkyl amine–derived alkylpyridinium tetrafluoroborate salts as a coupling partner. The reaction was conducted under mild conditions and tolerated a wide range of substrates including highly reactive alkynyl bromides. Furthermore, an in situ reaction without isolation of alkylpyridinium tetrafluoroborate salt proved to be successful, underscoring the great value of this reaction.

MATERIALS AND METHODS

General information

All manipulations were carried out under argon atmosphere. Commercially available reagents were used as received without purification. Column chromatography was carried out on silica gel (300 to 400 mesh). Analytical thin-layer chromatography (TLC) was performed on glass plates of Silica Gel GF254 with detection by ultraviolet. 1H and 13C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AVANCE 400 MHz/500 MHz spectrometer with tetramethylsilane (TMS) as reference. Infrared spectra were obtained on a KBr pellet using an Agilent Cary 630 instrument on a diamond plate using attenuated total reflection. High-resolution MS was conducted on an Agilent 6540 Q-TOF LC-MS equipped with an ESI probe operating in positive ion mode.

General procedure for the Ni-catalyzed cross-electrophile coupling of pyridinium salts with bromoalkynes

An oven-dried 25-ml Schlenk tube equipped with a stir bar was charged with redox-active pyridinium salts 1 (0.2 mmol, 1.0 equiv), Ni(acac)_2 (0.02 mmol), 2,2′:6′,2″-terpyridine (0.02 mmol), and zinc flake (−325 mesh, 99.9%) (0.5 mmol). The tube was then evacuated and back-filled with argon (three times). Anhydrous DMF (1 ml) and bromoalkynes (0.3 mmol) were added under argon. The resulting mixture was allowed to stir for 8 hours under argon atmosphere at 60°C (oil bath). The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with water and brine and dried over Na$_2$SO$_4$. The organic layer was concentrated under vacuum by rotary evaporator in a water bath at 45°C. Flash column chromatography or preparative TLC provided the product.

General procedure for the Ni-catalyzed cross-electrophile coupling of pyridinium salts with bromoalkanes

An oven-dried 25-ml Schlenk tube equipped with a stir bar was charged with redox-active pyridinium salts 1 (0.2 mmol, 1.0 equiv), Ni(cod)$_2$ (0.04 mmol), 2,2′:6′,2″-terpyridine (0.04 mmol), tetra-n-butylammonium iodide (0.1 mmol), and zinc flake (−325 mesh, 99.9%) (0.5 mmol). The tube was then evacuated and back-filled with argon (three times). Anhydrous dimethylamine (1 ml) and bromoalkanes (0.8 mmol) were added under argon. The resulting mixture was allowed to stir for 8 hours under argon atmosphere at 60°C (oil bath). The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with water and brine and dried over Na$_2$SO$_4$. The organic layer was concentrated under vacuum by rotary evaporator in a water bath at 45°C. Flash column chromatography provided the product.

General procedure for the in situ activation of primary amines

Cross-coupling with iodobenzene

A culture tube was charged with primary amines (0.1 mmol) and 2,4,6-triphenylpyrylium tetrafluoroborate (1.2 equiv). EtOH (1.0 ml) was added, and the culture tube was sealed. The mixture was stirred at 100°C overnight. After that, EtOH was removed under vacuum. NiBr$_2$·diglyme (0.02 mmol), 2,2′:6′,2″-terpyridine (0.02 mmol), zinc flake (−325 mesh, 99.9%) (0.5 mmol), iodobenzene (0.3 mmol), and anhydrous DMF (2 ml) were added under argon. The resulting mixture was allowed to stir for 8 hours under argon atmosphere at 60°C (oil bath). The reaction mixture was quenched with 1 M HCl and extracted with EtOAc. The organic layer was washed with water and brine and dried over Na$_2$SO$_4$. The organic layer was concentrated under vacuum by rotary evaporator in a water bath at 45°C. Flash column chromatography or preparative TLC provided the product.

Cross-coupling with bromoalkynes

A culture tube was charged with 0.1 mmol primary amines (1.0 equiv) and 2,4,6-triphenylpyrylium tetrafluoroborate (1.2 equiv). EtOH (1.0 ml) was added, and the mixture was refluxed overnight. After that, EtOH was removed under vacuum. Ni(acac)$_2$ (0.02 mmol), 4′-di-tert-butyl-2,2′-bipyridine (0.02 mmol), and zinc flake (−325 mesh, 99.9%) (0.5 mmol) were added. The tube was then evacuated and back-filled with argon (three times). Anhydrous DMF (1 ml) and bromoalkynes (0.3 mmol) were added under argon. The resulting reaction mixture was quenched with 1 M HCl and extracted with EtOAc. The organic layer was washed with water and brine and dried over Na$_2$SO$_4$. The organic layer was concentrated under vacuum by rotary evaporator in a water bath at 45°C. Flash column chromatography or preparative TLC provided the product.
mixture was allowed to stir for 8 hours under argon atmosphere at 60°C (oil bath). The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with water and brine and dried over Na₂SO₄. The organic layer was concentrated under vacuum by rotary evaporator in a water bath at 45°C. Flash column chromatography provided the product.

SUPPLEMENTARY MATERIALS

Table S1. Optimization of cross-coupling with bromoalkynes.

Table S2. Optimization of cross-coupling with alkyl bromides.

REFERENCES AND NOTES