

New Developments in Aromatic Halogenation, Borylation, and Cyanation

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Abstract: Several green procedures have been developed for synthesizing functionalized aromatics: i) AuCl_3 -catalyzed halogenation of aromatic compounds, including aryl boronates; ii) Fe_2O_3 -catalyzed direct aromatic C–H bond borylation; iii) Pd-catalyzed direct cyanation of indoles; iv) direct conversion of arylamines to pinacol boronates.

Keywords: Au-catalyzed · Borylation · Cyanation · Fe-catalyzed · Green chemistry · Halogenation · Metal-free reactions



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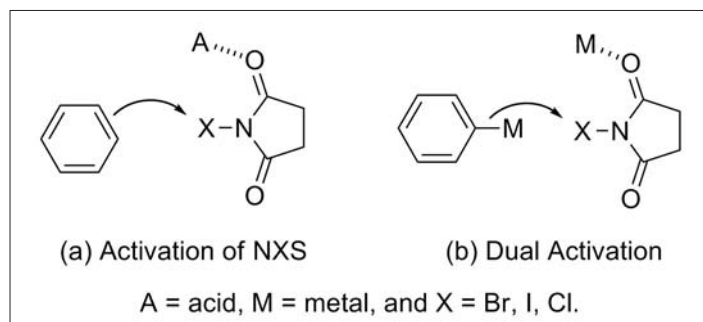
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1. Introduction

The development of new methods to functionalize inert chemical bonds, such as aromatic carbon–hydrogen (C–H) and carbon–nitrogen (C–N) bonds, is highly important because these methods can serve as the bridge that links cheap and readily available materials to valuable and useful products. Mild, efficient and sustainable transformations of this type will undoubtedly find widespread applications across nearly every branch of chemical fields, including the synthesis of pharmaceuticals, natural products, agrochemicals, polymers, and feedstock commodity chemicals. As part of our ongoing research program on the development of practical transformations towards functionalized aromatic compounds, we have focused our efforts on maximally meeting the request of green chemistry. In this context, we have been interested in using metal catalysts (Au, Fe and Pd) to facilitate the conversion of aromatic C–H bonds into carbon–halogen (C–X, X = Cl, Br, I), carbon–boron (C–B) and carbon–carbon (C–C) bonds, respectively.^[1–4] We have also developed a metal-free borylation process that converts arylamines to arylboronates.^[5] This review briefly summarizes our recent studies.

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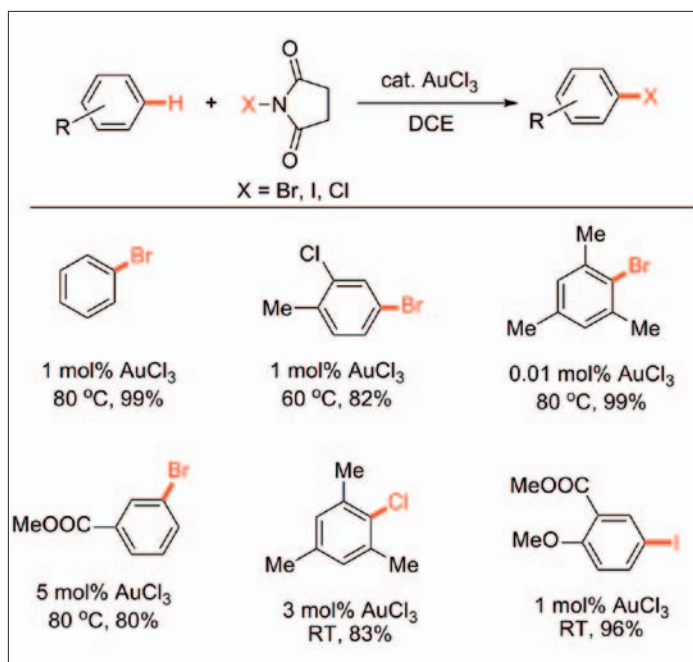
Scheme 1.
Halogenation through
dual activation.

2. Gold(III)-catalyzed Halogenation of Arenes

Halogenation of aromatic compounds is one of the essential and frequently used reactions in both industrial and academic settings. The commonly used halogenating reagents in laboratories are *N*-bromo-, *N*-iodo-, and *N*-chlorosuccinimide (NBS, NIS, and NCS, respectively) owing to their ease of handling, as well as the generation of relatively inert succinimide as the by-product. Previous studies have focused primarily on enhancing the halogenating ability of NXS (X = Br, I, Cl) by using Lewis acid catalyst, which activates the carboxyl group (Scheme 1a).^[6–8] However, the catalysts used are in most cases not sufficiently efficient, and high catalyst loading (10% to one equivalent) is required in many cases. Lewis acid is used as solvent in particular cases. Consequently, there is still great need to develop a practical procedure for the efficient halogenation of aromatic compounds under milder reaction conditions.

Since previous studies have already focused on the activation of the halogenating source, we therefore conceive that the activation of arene substrates may provide an alternative mode of activation with the potential of increased catalytic efficiency. A dual activation process as shown in Scheme 1b is thus proposed, which involves the activation of the *N*-halosuccinimide by gold catalyst on one hand, and direct auration of the arene substrate on the other hand. We have observed that gold(III) catalyst demonstrates unique catalytic properties in halogenations, while the use of other acids in this system, such as FeCl₃, FeBr₃, BF₃·OEt₂ (commonly used to activate *N*-halosuccinimide), NH₄NO₃ and ZrCl₄, give substantially lower yields.^[1]

AuCl₃-catalyzed halogenation has wide substrate scope, including aromatic substrates bearing moderately electron-withdrawing substituents (Scheme 2). In the cases of electron-rich arenes, not only bromination, but also chlorination can be achieved. The regioselectivity of the reaction is dominated by the electronic properties of the substituents. Halogenation with electron-rich arenes provides high yields



Scheme 2.
AuCl₃-catalyzed
halogenation.

under mild conditions with very low catalyst loading (down to 0.01 mol %). Arenes bearing moderately electron-withdrawing groups require higher catalyst loading and longer reaction times. Unfortunately, aromatic substrates bearing strongly electron-withdrawing groups, such as nitro group, are not reactive. The nearly quantitative yields and the clean reaction system with only succinimide as by-product make this reaction very attractive as a preparative method.

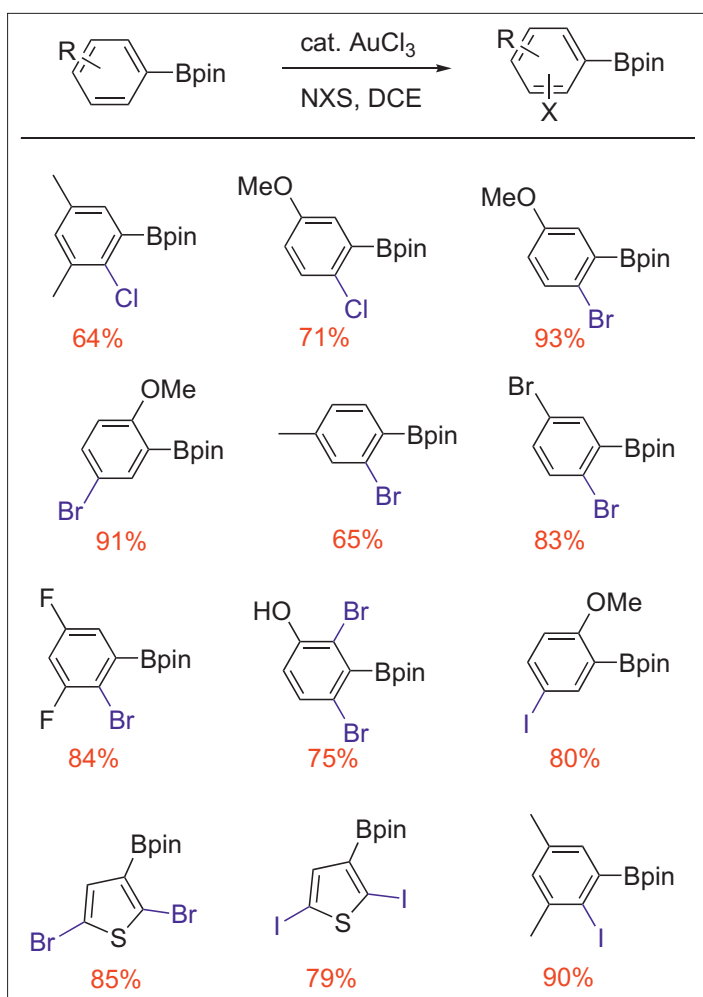
In recent years, considerable attention has been paid to functionalized arylboronic compounds due to their usefulness in organic synthesis and other fields.^[9–14] Arylboronic acids and esters bearing halogen atom are extraordinary valuable because they afford the possibility to construct complex molecules by conducting multiple-step cross-coupling reactions.^[15,16] In general, the halogenation conditions are too harsh for aromatic boronates, because deborylation occurs very easily under the conventional halogenation conditions.^[17–19] Therefore, it is necessary to develop methodology to achieve halogenation of aromatic boron compounds under mild conditions so that the boron group can remain intact during the halo-

genation process.^[20] For this purpose, we have further extended the AuCl₃-catalyzed halogenation reaction by employing arylboronates as substrates (Scheme 3).^[2]

A variety of arylboronates substances have been subjected to AuCl₃-catalyzed halogenations. The results show that AuCl₃ catalyzes a wide range of arylboronates, including those bearing heterocyclic rings. The substituent group can be halogen, methyl, methoxy, trifluoromethoxy, and

hydroxyl group. The reaction provides the corresponding halogenation products in good to excellent yields with the retention of the boron group. Interestingly, most of these halogenated boronates are unknown compounds, which may reflect the difficulties associated with the traditional method in preparing such functionalized aromatic boronates.

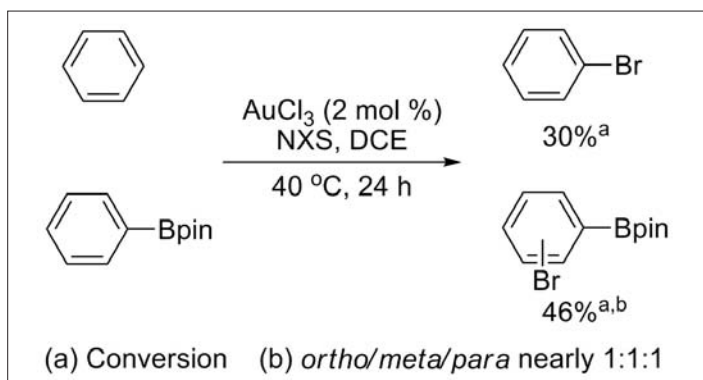
While exploring the AuCl₃-catalyzed halogenation of arylboronates, we were puzzled by an intriguing question: how does the boronate group affect the halogenation activity and regioselectivity. We have investigated this issue by comparing the halogenation of benzene and pinacol phenylboronate under identical conditions. The experiments suggest that the pinacol boronate group is a weakly activating and *ortho/para*-directing group (Scheme 4). This may be due to a smaller value of electronegativity than that of carbon (2.04 versus 2.55), resulting in the inductive effect of boron being electron-donating. On the other hand, since boron has an empty *p*-orbital, the resonance effect is electron-withdrawing, which is opposite to its inductive effect. However, the boron may be complexed with a Lewis base (such as carbonyl oxygen of succinimide) in the



reaction system, which may counteract the electron-withdrawing effect.^[21]

In addition, to demonstrate the utility of the halogenated boronates, we have carried out experiments of consecutive Suzuki-Miyaura coupling reactions to demonstrate the rapid construction of aromatic compounds with complex structure (Scheme 5).

As shown in Scheme 5, we have demonstrated that AuCl_3 is an extraordinarily efficient catalyst for aromatic halogenation. In particular, arylboronates can be halogenated with



Scheme 4. Comparison of the reactivity in AuCl_3 -catalyzed bromination.

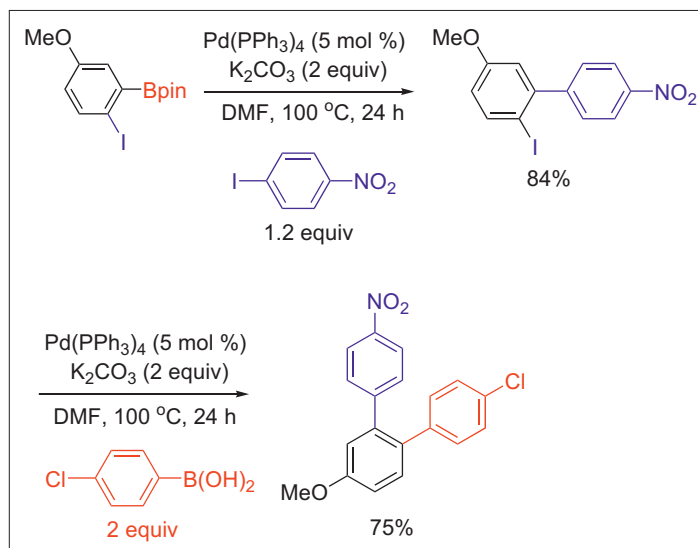
Scheme 3. Au(III) -catalyzed halogenation of arylboronates.

3. Iron-catalyzed Direct Borylation of Arenes

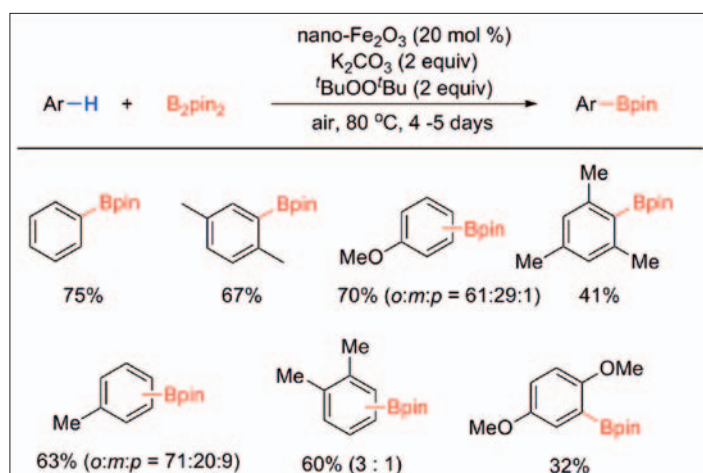
Borylation *via* C–H bond activation attracts great attention because of high efficiency as well as atom economy.^[22] Direct borylation of arenes *via* C–H bond activation have been reported by several groups in recent years,^[23] however, all of them utilize noble metal, such as iridium or rhodium. The application of inexpensive and nontoxic catalyst in such transformations is obviously more attractive and reflects the trend of green chemistry. In 2010, we published the primary results of an iron-catalyzed direct borylation of arenes (Scheme 6).^[3]

Among various iron catalysts, Fe_2O_3 shows the highest catalytic activity. Nano- Fe_2O_3 slightly increases the yields, presumably due to the fact that nanoscale heterogeneous catalysts have more surface area and consequently have enhanced catalytic activity. The substrate scope has been investigated under the optimized conditions (Scheme 6). The borylation of anisole gives a mixture of products of *ortho*, *meta* and *para* substitution, in which *ortho*-borylated product predominates. This selectivity is consistent with traditional electrophilic aromatic substitution reactions. In contrast, the regioselectivity of Rh- and Ir-catalyzed borylation of arenes is controlled by steric effect of the substituents. For methyl-substituted arenes, only aromatic C–H bonds are functionalized under these conditions.

Although the efficiency of this nano- Fe_2O_3 -catalyzed system still needs to be improved, it opens up new possibilities to develop direct aromatic borylation with inexpensive iron catalysts.



Scheme 5. Applications of halogenated boronates in consecutive coupling reactions.

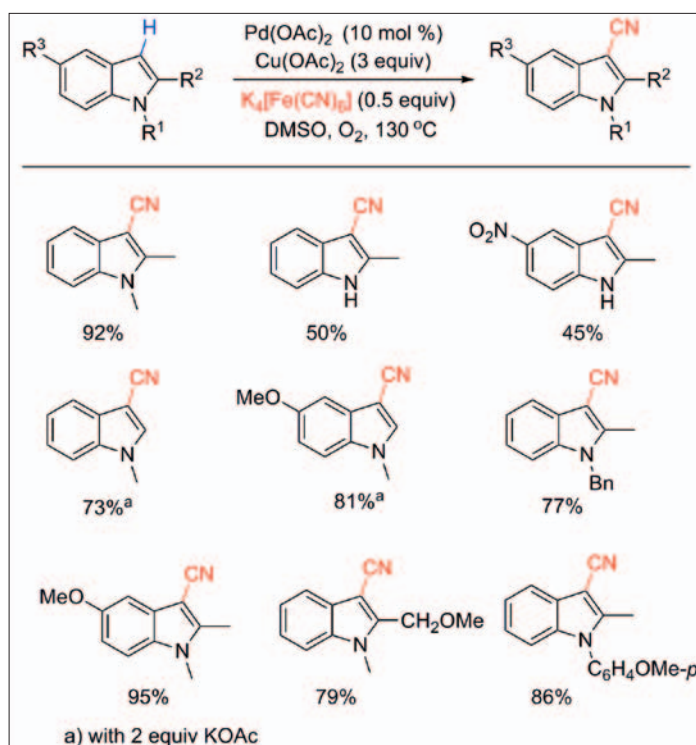


Scheme 6. Iron-catalyzed direct borylation of arenes.

4. Palladium-catalyzed Direct Cyanation of Indoles

Aryl nitriles have found wide application, especially in the fields of pharmacy and agriculture. They are also important intermediates in organic synthesis. Traditional approaches for the preparation of aromatic cyanides rely on functional group transformation, such as the Sandmeyer reaction^[24] and the Rosenmund-von Braun reaction.^[25] Recently, transition-metal-catalyzed cyanation of aryl halides has emerged as a useful method for preparing aromatic cyanides.^[26–29] Compared with the traditional transformations, the direct cyanation of C–H bond is much more attractive in terms of step, atom and redox economy. While some achievements have been made in this arena by employing a directing group,^[30–32] more general aromatic cyanation through direct C–H bond activation remains a challenging task. In 2010, we reported the first Pd-catalyzed direct cyanation of indoles (Scheme 7).^[14]

In this reaction, $K_4[Fe(CN)_6]$ is used as the cyano source and offers the advantage of nontoxicity. Equivalent copper and oxygen are used as the terminal oxidants. The only by-product in this Pd-catalyzed cyanation is derived from homocoupling of indole at the C(2) and C(3) positions. We found that addition of potassium acetate (KOAc) in the system could dramatically suppress the homocoupling. Besides, the substituents on pyrrole ring of the indoles significantly affect the reaction. Electron-withdrawing groups either on C(2) or on nitrogen completely deactivate the indole substrate toward cyanation, while electro-donating groups seem to promote the cyanation reaction. On the contrary, the electronic nature of substituents on the benzene ring of the indoles has relatively less effect on the cyanation.



Scheme 7. Palladium-catalyzed direct cyanation of indoles.

5. Direct Conversion of Arylamines to Arylboronates

Arylboronic compounds have found wide application in organic synthesis, particularly for the Suzuki-Miyaura cross-coupling reaction.^[9,10] This has created an increasing demand for various boronic acids and esters from both academia and industry. The traditional method for preparing arylboronic acid is by the nucleophilic reaction of Grignard reagents or lithium reagents with $B(OMe)_3$.^[33,34] Although this method is widely practiced, the drawback is also apparent: anhydrous conditions, and poor functional group tolerance. The development of alternative borylation methods has continued over the years. In 1995, Miyaura and co-workers reported the palladium-catalyzed borylation from aryl halides.^[35] More recently, great efforts have been directed toward the transition metal-catalyzed direct borylation of aromatic C–H bonds.^[22]

All of these approaches require metal in the transformations, either as catalysts or as stoichiometric reagents. The metal may contaminate the final boron products and cause environmental problems in large-scale production. In 2010, we developed a metal-free direct conversion of aryl amines to arylboronic pinacol esters at room temperature (Scheme 8).^[5] This novel transformation follows a Sandmeyer-type reaction sequence: the arylamine is first converted into the corresponding diazonium ion by reaction with *tert*-butyl nitrite, and then the diazonium ion reacts

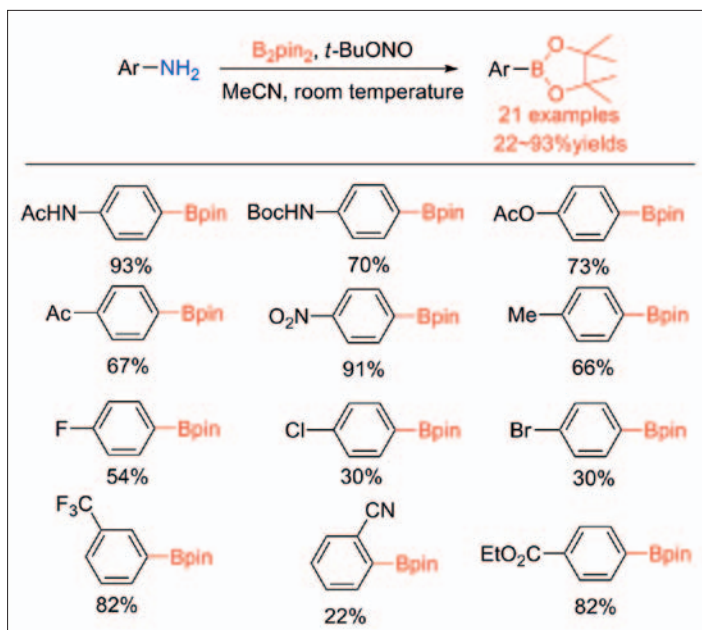
with the diboron reagent B_2pin_2 to deliver the final product.

A variety of arylamines are subjected to the optimized reaction conditions. All the borylation reactions complete at room temperature within two hours, and afford the corresponding products with good to excellent yields. Reaction with substrates bearing either an electron-donating group or an electron-withdrawing group affords the corresponding boronates in good yields. However, for some *ortho*-substituted arylamines the reaction only results in trace product. These results demonstrate that the reaction is significantly subject to steric and electronic effects.

The advantages of this novel transformation could be summarized as follows: First, compared with aryl halides, arylamines are generally cheap and largely available. Secondly, the metal-free process avoids unnecessary metal contamination in products. Thirdly, the reaction condition is tolerant of ambient air and moisture. All of these allow this method to be an alternative important method for arylboronates synthesis.

6. Conclusion

In summary, we have developed several highly efficient and environmentally benign transformations that convert cheap and easily available starting materials for functionalizing aromatics. These transformations have the potential to be used both in academic laboratories and



Scheme 8. Direct borylation of arylamines.

in industry. Further exploration of green procedures is currently undergoing in our laboratory.

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