C–H Activation

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Directed *meta*-Selective Bromination of Arenes with Ruthenium Catalysts

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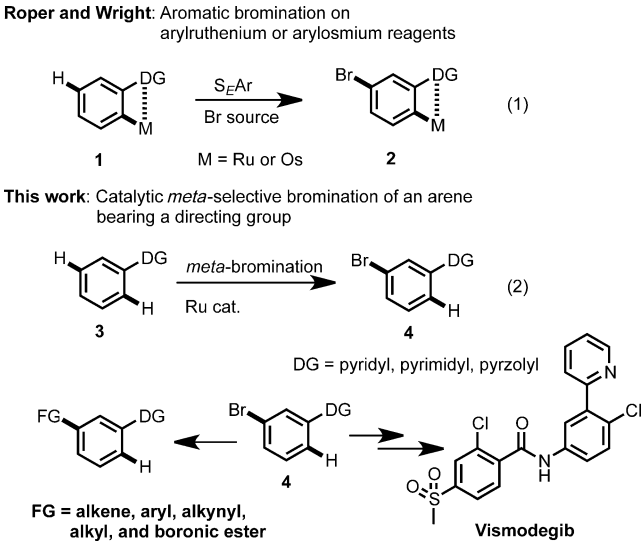
Abstract: *A Ru-catalyzed direct C–H activation/meta-bromination of arenes bearing pyridyl, pyrimidyl, and pyrazolyl directing groups has been developed. A series of bromo aryl pyridines and pyrimidines have been synthesized, and further coupling reactions have also been demonstrated for a number of representative functionalized arenes. Preliminary mechanistic studies have revealed that this reaction may proceed through radical-mediated bromination when NBS is utilized as the bromine source. This type of transformation has opened up a new direction for the radical non-ipso functionalization of metal with regard to future C–H activation development that would allow the remote functionalization of aromatic systems.*

Direct functionalization of non-activated aromatic C–H bond has been considered as one of the most powerful methods in modern molecular design and synthesis. Transition metal catalyzed ligand-assisted *ortho*-C–H activation and direct functionalization has been very well studied in the last decade.[1] However, the methods for *meta*-selective C–H activation are less established.[2] The Smith/Malezcka and Hartwig/Miyaura/Ishihara groups have disclosed *meta*-C–H direct functionalizations under Ir-catalyzed conditions,[3] while Gaunt utilized Cu for the *meta*-arylation.[25] More recently, Ackermann and Frost have reported Ru-catalyzed *meta*-alkylation and sulfonation of aryl pyridines.[4] Later, Yu and Dong discovered Pd-catalyzed remote-directed and norbornene-mediated *meta*-C–H arylation and alkylation.[5] However, these methods so far have only provided approaches for the introduction of a limited set of functional groups. Herein, we report the directed *meta*-bromination for the synthesis of a series of *meta*-substituted aryl pyridines and pyrimidines. During the submission of this manuscript, a similar Ru-catalyzed *meta*-functionalization process for aryl pyridines was also reported.[6] Unlike the Frost and Ackermann procedures, this transformation has also made a variety of representative *meta* functional group introductions possible by further functional group interconversion on the corresponding aryl bromides (Scheme 1).



Scheme 1. *meta*-C–H bromination and the introduction of a range of representative functional groups.

Aryl bromide is one of the most utilized organic intermediates in modern organic chemistry owing to its versatile characteristics. For example, this type of building block is well recognized for the introduction of functional groups by the halogen/main group metal exchange, and transition metal-catalyzed coupling reactions for the functionalization of aromatic systems.[7] The direct bromination of arenes is generally accomplished by: i) The conventional electrophilic aromatic bromination,[8] or more recently developed aromatic bromination under activated conditions;[9] or ii) Directed *ortho*-bromination under Rh-,[10] Pd-,[11] Ru-,[12] or Cu-catalyzed[13] conditions. Inspired by Roper and Wright's early discoveries on electrophilic aromatic substitution reaction (S_EAr) of the aryl organoruthenium or organoosmium reagents (Scheme 1, Eq. 1), the bromination of organometallic reagent **1** is directly occurring selectively at the *para*-position to the metal substituent to give the *meta*-brominated product **2**.[14]

Based on their discoveries, we have proposed an approach to access brominated arenes at the *meta*-position to a directing group in similar regioselective fashion. As demonstrated in Scheme 1, Eq. 2, starting from a directed arene **3**, under plausible directed C–H metallation processes, an *ortho*-metallic intermediate **2** could be formed and analogous to

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Roper and Wright's organometallic bromination, *meta*-brominated arene **4** could be formed after the further reductive elimination of the transition metal or protonation of the organometallic compound to eliminate the transition metal species.

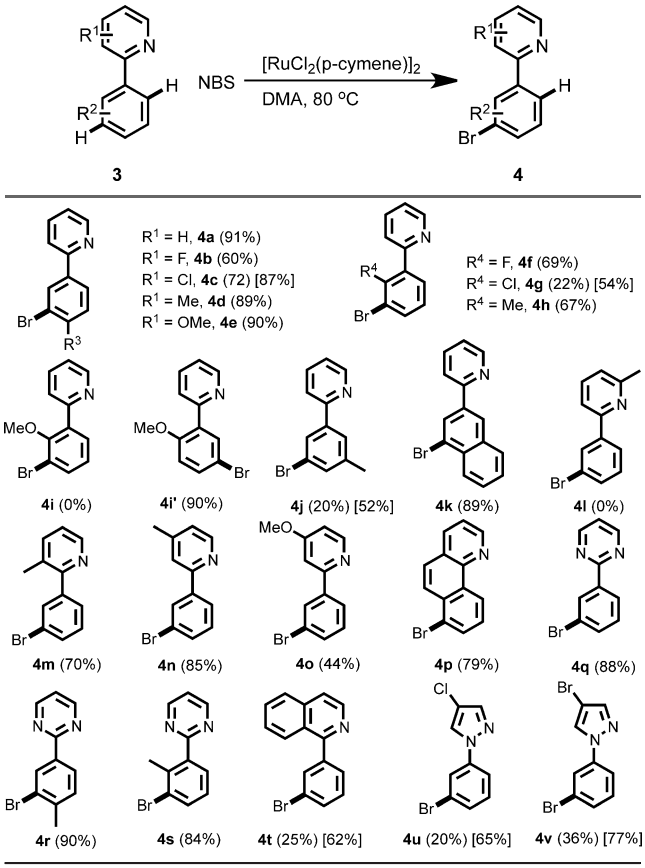
With this hypothesis in hand, we have set up experiments to test its validity. Further inspired by Frost's[4b] sulfonation and Ackermann's[4a,c] alkylation reactions, we chose Ru catalysts for our initial studies. During our preliminary solvent screening, we found that solvents such as toluene, MeCN, dioxane, and DMSO did not give any desired product; in those cases, we have only recovered starting material. Fortunately, when a mixture of 2-phenylpyridine **3a**, 5 mol% of $[RuCl_2(p\text{-cymene})]_2$, and NBS in DMA was heated at 70°C, we found that our desired product **4a** was obtained in good 65% yield with 32% of recovered starting material (Supporting Information, Table S1, entry 1).

The screening of various Ru catalysts was carried out, and we were pleased to find that $[RuCl_2(p\text{-cymene})]_2$ and $RuCl_2(cod)$ both worked very well, as our desired *meta*-brominated product **4a** was isolated in 67% and 63% yields, respectively. However, the commonly used Ru photocatalyst, $Ru(bpy)_3Cl_2$, was less efficient for this type of reaction, while only *ortho*-bromination was observed and the corresponding aryl bromide **4a** was only obtained in 4% yield. Grubbs' catalyst as well as $[RuCp^*Cl_2]_n$ both gave our desired product in good yields. Interestingly, we found that when the Ru^{III} catalyst $RuCl_3$ was utilized,[15] the results were comparable with those with $[RuCl_2(p\text{-cymene})]_2$ (Table S1, entry 6). When the temperature was increased to 80°C, our desired product **4a** was isolated in an excellent 91% yield with an excellent regioselectivity (Table S1, entry 7). Elevated temperature did not provide better selectivity, instead more bisbrominated product **6a** was observed. No product was formed in the absence of Ru catalyst under similar conditions. Other transition metal catalysts, such as Pd and Rh, failed to deliver the desired product **4a**, reactions are instead following the *ortho*-C–H activation/bromination pathways to give the *ortho*-brominated arene **5a** in 73% and 36% yields (Table S1, entries 11 and 12).

With the optimal conditions in hand, we have evaluated the scope and limitations of this reaction. As illustrated in Table 1, a number of substituted 2-pyridyl arenes have been successfully obtained. The *meta*-bromo arenes **4b**–**4e** were successfully obtained in good to excellent yields when the *para*-substituents were electron-rich or electron-deficient groups. Similar reactivity was also observed once the substituents were on the *ortho*-position to the pyridine directing group; the corresponding aryl bromides **4f**–**4h** were isolated in 54%–69% yields respectively.

The synthesis of aryl bromide **4i** was less successful, owing to the strong electron donation of the methoxy group to the arene, and aryl bromide **4i′** was isolated in 90% yield. Once the electron-rich methoxy group was introduced to the *para*-position to the pyridine nitrogen, the reaction yield dropped to 44%. Methyl groups at the *meta*-position gave rise to slightly reduced yield, and methyl substituents at the *ortho*-position leave the reaction intact. We found that bromobenzoquinoline **4p** and bromo-phenylpyrimidine **4q** can also

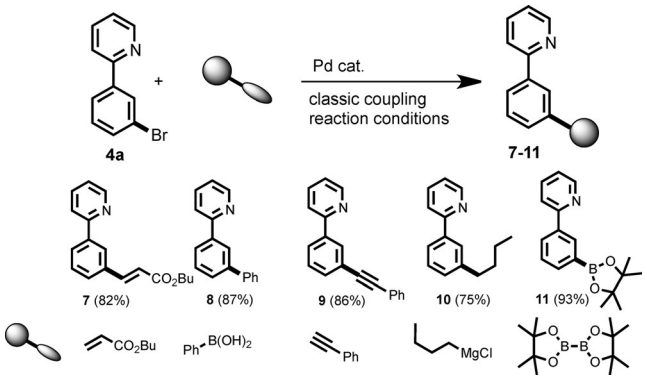
Table 1: Reaction scope on benzamides.[a]



[a] Reaction conditions: Substrate **3** (0.2 mmol), NBS (0.4 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%) in DMA (1.0 mL) at 80°C for 24 h. Isolated yields are in the parentheses, yields based on the recovered starting material are listed in the square brackets.

be achieved in good yields (Table 1). Under the standard reactions conditions, unsubstituted pyrazole underwent background S_EAr reaction to give 4-bromo pyrazole **3v** exclusively in quantitative yield.[16] When halo-pyrazoles were utilized as the directing groups, the syntheses of aryl bromides also became possible to give the corresponding products **4u** and **4v**, albeit with low isolated yields. These experimental observations have opened up a new direction for the future synthesis development. Unfortunately, under similar conditions, the attempts on other arenes bearing commonly used directing groups (the failed examples **4w**–**4ae**, see the Supporting Information, Table S2) and the introduction of other halogens using Selectfluor, NBS, and NIS all failed to give the corresponding aryl halides.

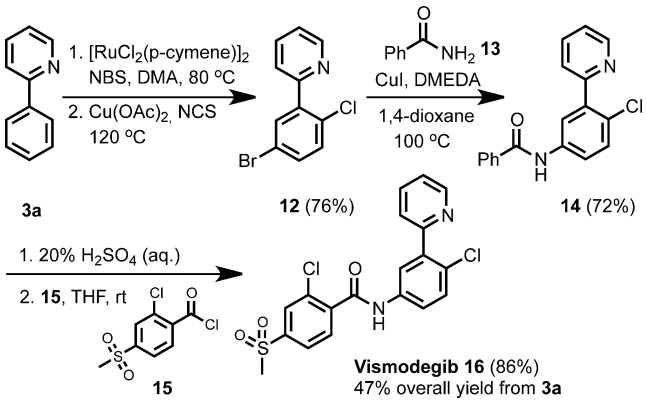
To demonstrate the application of the aryl bromides, Pd-catalyzed coupling reactions of bromobenzene **4a** were carried out.[17,18] As expected, when alkene or aryl boronic acids were used as the coupling partners, the coupled products **7** and **8** were synthesized in over 80% yields (Scheme 2). Coupling reactions of bromobenzene **4a** with acetylene and alkyl Grignard reagent were also fruitful, with the desired alkynyl and alkyl substituted arenes **10** and **11** obtained in 86% and 75% yields, respectively.[19,20] Aryl bromide **4a** could also be converted smoothly into the corresponding boronic ester **11** in excellent yield under standard borylation



Scheme 2. Pd-catalyzed coupling reactions with various coupling partners.

conditions.[21] These reactions allow us to make a variety of *meta*-functionalized arenes in a practical manner (for experimental details see the Supporting Information).

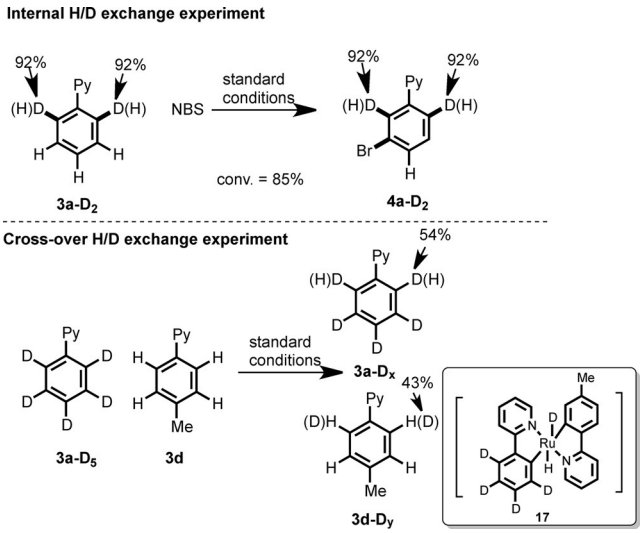
The *meta*-bromination method has also been applied in the concise synthesis of anti-cancer drug Vismodegib **16**. As demonstrated in Scheme 3, the sequential one-pot reaction by



Scheme 3. Synthesis of Vismodegib **16.**

a *meta*-C–H bromination followed by an *ortho*-directed chlorination gave aryl pyridine **12** in 76% yield. After CuI-catalyzed amidation and substituent replacement, our desired product Vismodegib **16** was successfully isolated in an overall 47% yield from cheap and readily available starting material aryl pyridine **3a** (Scheme 3).

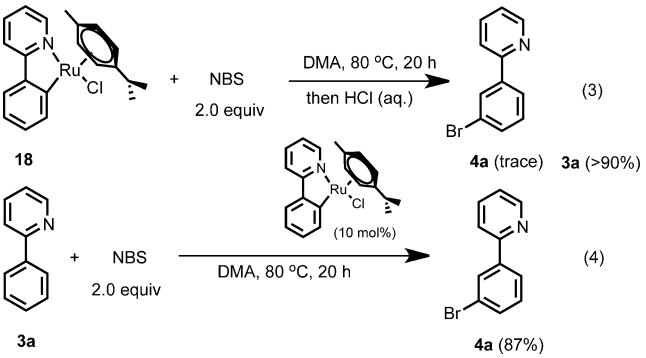
To explore the reaction pathway, we have also carried out H/D exchange experiments. Interestingly, when **3a-D_2** was treated with NBS under our standard conditions, unlike Ackermann and Frost's results,[4] we did not observe any deuterium loss during the reaction, which is similar to the observations we had during our Pd-catalyzed reactions.[22] (Scheme 4) Surprisingly, when the cross-over H/D exchange experiment was carried out, we found that the D has shifted from **3a-D_5** to the structurally similar aryl pyridine **3d**, which showed that deuterium was scrambling within the two molecules. These results indicate that during the C–H activation processes, the H is very likely to be appearing as a possible ligand on the Ru metal center during the process up until the reductive elimination to give the H back to the



Scheme 4. H/D exchange experiments.

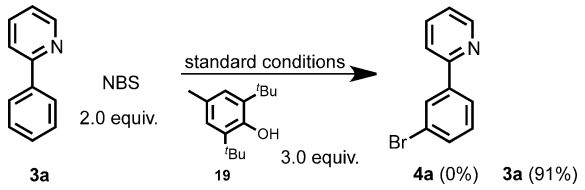
molecule. Furthermore, it is possible that the aryl pyridine was acting as a crucial ligand; a plausible intermediate **17** may form during the transformation, which could explain the H/D cross-over results.

Surprisingly, we found that reaction using prepared aryl ruthenium compound **18** as the starting material under our standard conditions only gave our desired product **4a** in a trace amount, whereas reaction using a catalytic amount of catalyst **18** gave the brominated product in 87% yield. (Scheme 5, Eqs. 3 and 4) These results suggest that catalyst **18** is not an active catalyst with regard to the bromination processes; the aryl pyridine may help this transformation by acting as an external ligand.



Scheme 5. Experiments using stoichiometric amount of Ru catalyst.

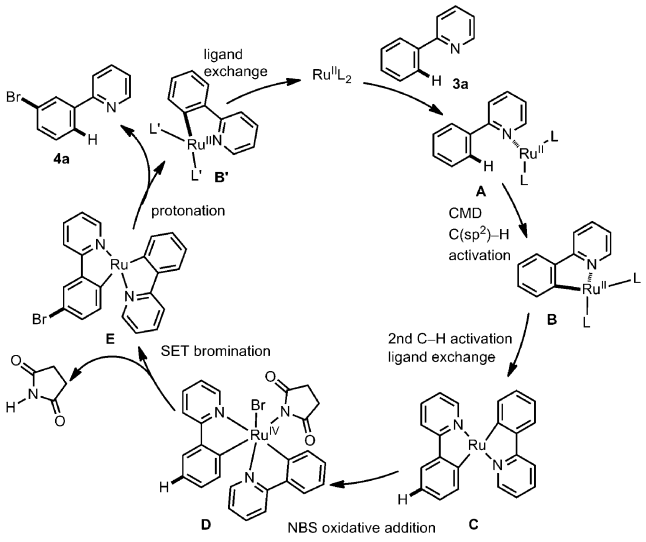
In terms of better understanding of the bromination step, control experiments in the presence of a radical scavenger were carried out (Scheme 6). Interestingly, in the presence of 3.0 equivalents of radical scavenger **19**, the reaction was totally shut down under the standard conditions, similar to Ackermann's observation under their conditions.[4c] No product was observed, and only starting material was recovered. These results indicate that our reaction may undergo radical processes during the bromination step.



Scheme 6. Experiments in the presence of radical scavenger.

With regard to the reaction pathway, kinetic isotope effect experiments were carried out. We found that during the competition experiment between phenyl pyridines **3a** and **3a-D$_3$**, the KIE was calculated as 1.43:1 (Supporting Information, Section 2.15, Scheme S1, Eq. S1). These results showed a possible secondary KIE for the re-aromatization during the S_EAr processes, which may leave the initial directed *ortho*-C–H activation as the primary KIE as the rate-determining step. Comparable KIEs have recently been observed for related ruthenium-catalyzed *meta*-C–H functionalizations.[6b] However, when a mixture of phenylpyridines **3a** and **3a-D$_5$** were introduced in the reaction, a similar KIE value of 1.56:1 was observed after the reaction was heated under the standard conditions for 3 h (Supporting Information, Section 2.15, Scheme S1, Eq. S2). These results revealed that neither the *ortho*-C–H metallation nor deprotonation/re-aromatization is the rate-determining step.

Based on these preliminary experimental results, a plausible reaction mechanism is proposed (Scheme 7). The first C–H activation of aryl pyridine **3a** gives the Ru complex **B**



Scheme 7. A plausible reaction mechanism.

that may undergo a ligand exchange process to form active Ru^{IV} species **C** by a second C–H activation, which has been previously described by Sanford during their studies on aryl pyridine Pd-mediated transformations.[23] In the presence of NBS Ru^{IV}, complex **D** may be generated in the absence of base. The desired *meta*-brominated product **4a** was then formed after the single-electron transfer (SET) bromination adding to the *para*-position of the electron-rich arene[24] to give brominated aryl-Ru **E** with the loss of succinamide, followed by reductive elimination, forming a Ru intermediate **B′**, which after ligand exchange gives the active $Ru^{II}L_2$ species for the next catalytic cycle.

In conclusion, we have developed an approach for the *meta*-selective bromination of arenes by directed C–H metallation. We have demonstrated the usefulness of our methodology by the preparation of a range of *meta*-brominated arenes, as well as the introduction of a number of representative functional groups. Preliminary mechanistic studies have revealed that this reaction may undergo a Ru^{II}/Ru^{IV} catalytic cycle, and the functional group introduction may involve radical processes. Further detailed investigations on the mechanistic studies are still in progress.

Experimental Section

A mixture of phenylpyridine (0.3 mmol), NBS (0.6 mmol), and $[RuCl_2(p\text{-cymene})]_2$ (5 mol%) in DMA (1.5 mL) was heated at 80 °C or 100 °C under air atmosphere for 24–48 h. After the reaction was completed, the reaction mixture was allowed to cool down to room temperature, and H_2O (20 mL) was added. The resulting mixture was extracted with EtOAc (10 mL × 5). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure to provide the crude product. The purification was performed by flash column chromatography on silica gel.

Acknowledgements

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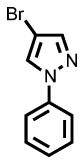
[16] No desired bromobenzene was observed. Bromopyrazole **3v** was isolated in quantitative yield instead under background S_EAr reaction.



3v (36%) [>99%]

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