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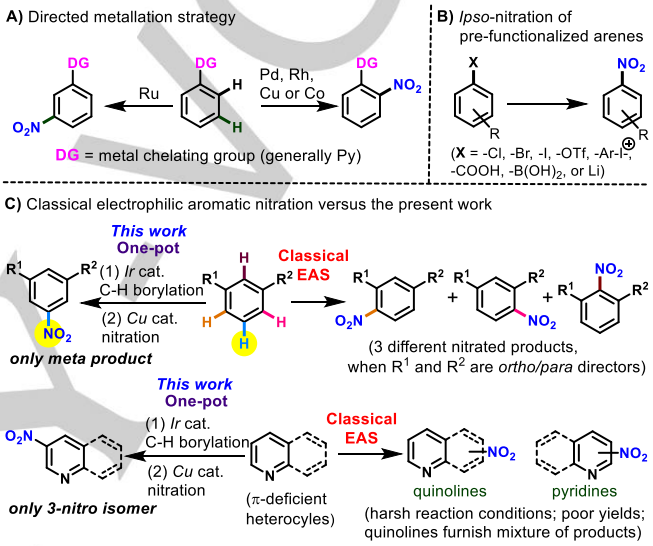
COMMUNICATION

Meta-Nitration of Arenes Bearing *Ortho*/*Para* Directing Group(s) via C-H Borylation

Xuejing Li,[a] Xingwang Deng,[a] Anthony G. Coyne,[b] and Rajavel Srinivasan*[a]

Abstract: Herein we report the *meta*-nitration of arenes bearing *ortho*/*para* directing group(s) using the iridium-catalyzed C-H borylation reaction followed by a newly developed copper(II)-catalyzed transformation of the crude aryl pinacol boronate esters into the corresponding nitroarenes in a one-pot fashion. This protocol allows the synthesis of *meta* nitrated arenes that are tedious to prepare or require multistep synthesis using the existing methods. The reaction tolerates a wide array of *ortho*/*para*-directing groups such as -F, -Cl, -Br, -CH_3, -Et, -*i*Pr -OCH_3 and -OCF_3. It also provides regioselective access to the nitro derivatives of π-electron deficient heterocycles such as pyridine and quinoline derivatives. The application of this method is demonstrated in the late-stage modification of complex molecules and also in the gram-scale preparation of an intermediate *en route* to the FDA-approved drug Nilotinib. Finally, we have shown that the nitro product obtained by this strategy can also be directly converted to the aniline or hindered amine via Baran's amination protocol.

Aromatic nitration is among the important reactions that are widely carried out in industry and academic settings. This is due to the versatility of the nitroarenes as they are found in dyes, polymers, energetic materials, agrochemicals and pharmaceutics[1]. Apart from this, they are the key intermediates for the synthesis of anilines, another fundamental building block found in a vast number of medicines and materials[1a,d]. Nitroarenes are generally prepared using the classical Electrophilic Aromatic Substitution (EAS) reaction[1,2]. However, there are a few inherent limitations associated with this reaction. Firstly, this reaction requires the use of strong mineral acids that limits the substrate scope.[1c, 1d] Secondly, the regioselectivity of this reaction is always dictated by the electronics of the substituents[2]. Electron rich groups and halogen substituents on the arenes tend to generate a mixture of *ortho* and *para* substituted products as major isomers. For example, classical electrophilic nitration of *m*-chlorotoluene furnished a mixture of 3 different nitrated products that are *ortho* or *para* to the -Cl and –CH_3 groups and without the formation of any *meta* nitrated product (Table 2 B).[3] On the other hand, arenes containing electron withdrawing substituents are sluggish towards electrophilic aromatic nitration, harsher reaction conditions are needed when more than one electron withdrawing groups are present on the arene[4]. Lastly, privileged heterocycles such as pyridines and quinolines often don't undergo electrophilic aromatic nitration and require extremely vigorous conditions for the reaction to occur with inefficient yields[5]. Moreover, quinolines tend to produce multiple nitrated products when subjected to electrophilic aromatic nitration, (e.g.,) quinoline produced a mixture of 5- and 8-nitroquinoline in 38% and 34% yields respectively in a classical nitration reaction.[6]



Scheme 1. [A] Regioselective aromatic nitration using metalation strategies. [B] *ipso*-nitration of suitably pre-functionalized arenes. [C] Comparison of the present work with the classical electrophilic aromatic nitration method.

Recently, directed metalation-based C-H functionalization reactions are attracting the attention of chemists[7]. Ruthenium-catalyzed directing group (DG)-assisted *meta*-selective nitration of arenes are reported[8] (Scheme 1A). Although attractive, this approach requires the installation of a DG (such as pyridyl, pyrimidyl, oxime, etc.). In most of the examples, the DGs are not removable from the substrates. In other cases, an additional step is required to remove the DG. Moreover, no heteroarenes such as pyridines or quinolines were demonstrated as substrates for the nitration, rather they act as DGs. Further, there are numerous directed *ortho*-metalation-based protocols available to access *ortho*-nitrated products[9], but this is not of interest in context to our current aim, which is to access the *meta* isomer. Finally, *ipso*-nitration can solve the selectivity problem (scheme 1B)[10]. But this approach requires the presence of a pre-functionalized group (such as –$B(OH)_2$, -halide, -COOH, etc.) at the *meta* position of the starting material. Again, the selectivity problem arises to access these pre-functionalized starting materials. Hence, the substrate availability severely limits the application of this approach, especially when it comes to multi-substituted (hetero)arene starting materials. Considering the above discussed limitations, there is a necessity for the development of strategies to prepare *meta*-substituted nitroarenes from simple and readily available substrates bearing *ortho*/*para* directing

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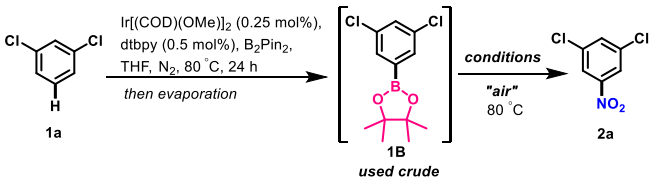
group(s). There is also a clear void to access the nitrated products of certain π-deficient heteroarenes in a regioselective fashion.

In order to overcome the *meta*-selective C-H nitration problem of arenes bearing *ortho*/*para* directing group(s), we envisioned a strategy that could integrate the sterically controlled iridium-catalyzed arene C-H borylation reaction with a method to transform the crude aryl boronate formed to nitroarene. Herein, we present such a strategy where an aryl *meta* C-H is converted to *meta* C-NO_2 via C-H borylation. The key to this transformation was finding the right set of conditions for converting the *in situ* generated ArBpin to $ArNO_2$.

Table 1. Screen of reaction conditions for the nitration of the crude boronate ester obtained via C-H borylation[a]



Entry	Catalyst[b]	Nitrating agent[c]	Solvent	Base[d]	Yield (%)[e]
1[f]	$CuSO_4.5H_2O$	$NaNO_2$	MeOH	-	trace
2[f]	$Cu(OAc)_2$	$NaNO_2$	MeOH	-	trace
3[f]	$CuSO_4.5H_2O$	$NaNO_2$	CH_3CN	-	trace
4	$CuSO_4.5H_2O$	$NaNO_2$	CH_3CN	-	10%
5	$Cu(OAc)_2$	$NaNO_2$	CH_3CN	-	32%
6	$Cu(OTf)_2$	$NaNO_2$	CH_3CN	-	15%
7	$Cu(NO_3)_2.3H_2O$	$NaNO_2$	CH_3CN	-	25%
8	Cu-TMEDA	$NaNO_2$	CH_3CN	-	trace
9	Cu_2O	$NaNO_2$	CH_3CN	-	trace
10	$Cu(OAc)_2$	$AgNO_2$	CH_3CN	-	23%
11	$Cu(OAc)_2$	KNO_2	CH_3CN	-	26%
12	$Cu(OAc)_2$	TBAN	CH_3CN	-	trace
13	$Cu(OAc)_2$	$NaNO_2$	DMF	-	13%
14	$Cu(OAc)_2$	$NaNO_2$	THF	-	trace
15	$Cu(OAc)_2$	$NaNO_2$	EtOH: H_2O (6:1)	-	trace
16[g]	$Cu(OAc)_2$	$NaNO_2$	H_2O or CH_2Cl_2		0%
17	**$Cu(OAc)_2$**	**$NaNO_2$**	**CH_3CN**	**TEA**	**70%**
18	$Cu(OAc)_2$	$NaNO_2$	CH_3CN	Pyridine	40%
19	$Cu(OAc)_2$	$NaNO_2$	CH_3CN	NH_4OH	25%
20	-	$NaNO_2$	CH_3CN	TEA	0%

[a] Reaction was performed on a 0.25 mmol scale. [b] 15 mol% of the catalyst was used. [c] 3.0 equiv. used [d] 2.5 equiv. used. [e] Yield recorded after purification by silica-chromatography. [f] Reactions performed at room temperature. [g] Reaction performed at 40 °C

Iridium-catalyzed C-H borylation of arenes is an established strategy to install –Bpin at the less hindered site on the arenes.[11] The regiochemistry of the products is controlled more by steric factors than electronic or the directing effects of the substituents. Generally, a 1,3-disubstituted arene delivers *meta* borylated product in a regioselective fashion. Moreover, the reaction has been demonstrated to be amenable for process chemistry.[12] The selectivity of the borylation step coupled with functional group tolerance has been utilized for the one-pot transformation of an aryl C-H to phenol[13a], N,N'-disubstituted aniline and ether[13b], halides[13c-e], nitrile[13f], -CF_3[13g,h], alkyl[13j-l], aryl[13m-p] and 1,2,3-triazole[13q]. However, this method has not been utilized for the one-pot transformation of arene C-H to nitroarene, a fundamental transformation of organic chemistry, which we describe herein.

Ipso-nitration of aryl boronic acids is a well-documented protocol. There are two key reports of copper (II)-catalyzed *ipso*-nitration of aryl boronic acid, but with certain limitations: (1) Fu's Cu_2O catalyzed method requires longer reaction time (36 h to 48 h) with moderate yields and requires 7.0 equivalents of $NaNO_2$, (toxic and harmful to environment) to effect the nitration[10j] (2) Yan's Cu_2O catalyzed requires two equivalents of the aryl boronic acid starting material as the formation of biaryl byproduct was inevitable under their conditions[10k]. Both of these methods didn't work with our strategy as we use the boronate ester instead of the free boronic acid. A number of other *ipso*-nitration methods were reported with boronic acids as substrate, however, notably, none of these methods demonstrated the nitration with aryl boronate esters. This could due to the lack of reactivity of the boronate esters (Bpin) when compared to the free boronic acid derivatives or due to mechanistic reasons in some cases[10d]. We found an isolated single example wherein N,N-dimethylaniline functionalized with –Bpin at the *para* position, when subjected to C-H nitration using $AgNO_3$ and NBS, predominantly produced the *ipso*-nitration product instead of the desired isomer[14]. However, when we subjected this conditions to the crude boronate obtained from the iridium-catalyzed reaction, the reaction failed with no traces of the desired product. Later, we started a thorough investigations of conditions for converting the crude boronates obtained via the C-H borylation of arenes to the nitroarenes using copper catalysis.

We commenced the reaction optimization using 1,3-dichlorobenzene as a substrate. Initially the iridium-catalyzed C-H borylation was performed on the substrate using $Ir[(cod)OMe]_2$/dtbpy and B_2Pin_2 system heated at 80 °C in THF for 24 h. The solvent was removed and the crude ArBpin was used directly without any further purification for the optimization of the subsequent nitration reaction (Table 1). Initially, traces of the nitroarene product was observed when the reaction was carried out at room temperature in MeOH and using $CuSO_4.5H_2O$ or $Cu(OAc)_2$ as catalyst (15 mol%) and $NaNO_2$ as nitrating agent in an atmosphere of air (Table 1, entries 1 and 2). However, ArOMe was observed as a major side product in these reactions. When the solvent was changed to CH_3CN, and heated at 80 °C in the presence of 15 mol% of $Cu(OAc)_2$, the desired product was isolated in 32% yield (Table 1, entry 5). Following these results, an array of copper (II) catalysts, solvents, nitrating reagents were screened. Out of the copper sources screened, $Cu(OAc)_2$ turned out to be the best followed by $Cu(NO_3)_2.3H_2O$ (25% yield, Table 1, entry 7). $NaNO_2$ outperformed other nitrating agents such as KNO_2, $AgNO_2$, and $N(nBu)_4NO_2$ (TBAN) (Table 1, entries 10 to 12). CH_3CN was most effective when compared to other solvents (Table 1, entries 13 to 16). The use of anhydrous CH_3CN was essential as it helped to reduce the formation of the protodeboronated by-product and generally excess solvent was used to effect the nitration. The reaction in H_2O or CH_2Cl_2 did not furnish any desired product (Table 1, entry 16). Finally, the use of trimethylamine (TEA) (2.5 equiv) as an additive boosted the reaction yield to 70% (Table 1, entry 17). This may be due to the stabilizing effect of the amine on the copper catalyst[15]. Other bases such as pyridine and ammonium hydroxide performed poorer when compared to TEA. In the absence of any copper source, no desired product was observed using the optimized conditions (Table 1, entry 20).

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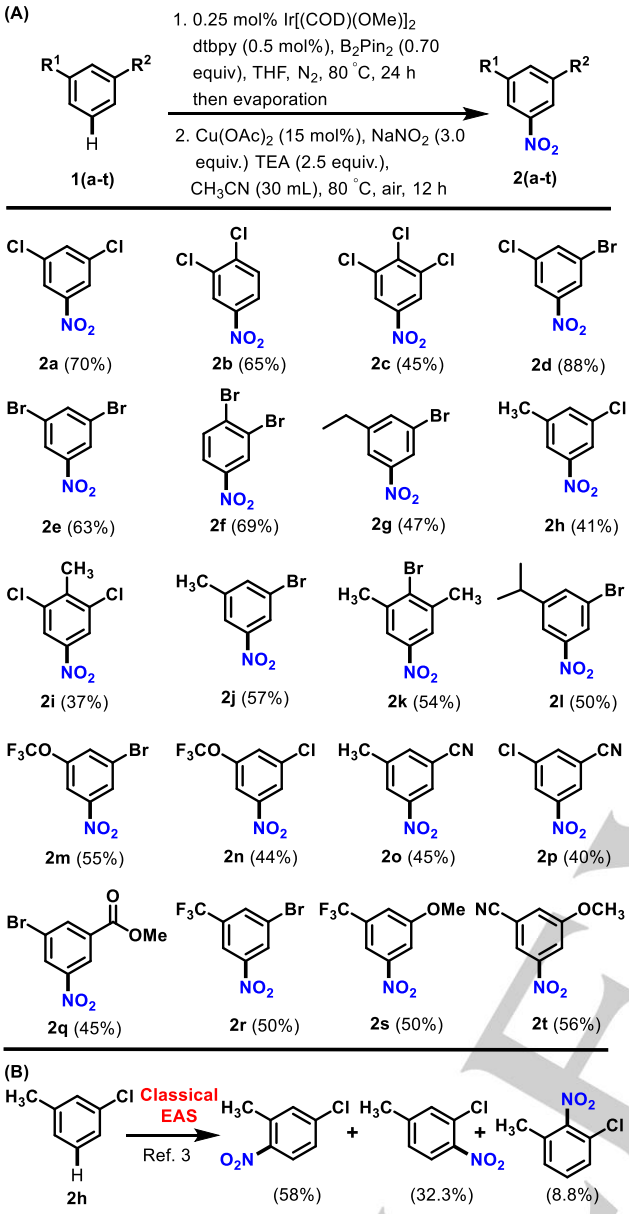


Table 2. [A] Scope of arenes in the C-H borylation/nitration sequence. Reactions were performed on 1.0 mmol scale. [B] Classical nitration on **2h**

Having obtained the optimized conditions (Table 1, entry 17), the substrate scope for the one-pot reaction sequence was evaluated to obtain the *meta* nitrated products (Table 2A). A variety of arenes were subjected to C-H borylation reaction. After the reaction, volatile materials were removed *in vacuo* and the crude ArBpin residue was dissolved in anhydrous CH_3CN (30 mL) and subjected to nitration using $Cu(OAc)_2$, $NaNO_2$, and trimethylamine as a base and heating at 80 °C for 12 h open to air. Substrates containing two or more *ortho*/*para* directing groups (such as -F, -Cl, -Br, -CH_3, Et, *i*Pr, and –OCF_3) underwent the reaction sequence well to afford the *meta* nitrated products (entries **2a** to **2n**) in modest to good yields. Substrates containing at least one *ortho*/*para* directing group (such as –Cl, Br, and –OCH_3) also afforded the *meta* nitrated products (entries **2o** to **2t**) in modest yields. Other functional groups such as –CN, -$COOCH_3$, -CF_3, etc. tolerated the reaction sequence well. 1-bromo-3-chlorobenzene (entry **2d**) furnished the highest yield of 88%. A few substrates such as benzofuran failed in the reaction sequence and produced mainly the biaryl side product. In general, arenes bearing halogen substituents performed well in the reaction sequence. It should be noted that under classical nitration methods, all these products are not possible to obtain or obtained as mixture of isomers in inefficient yields and are difficult to separate.

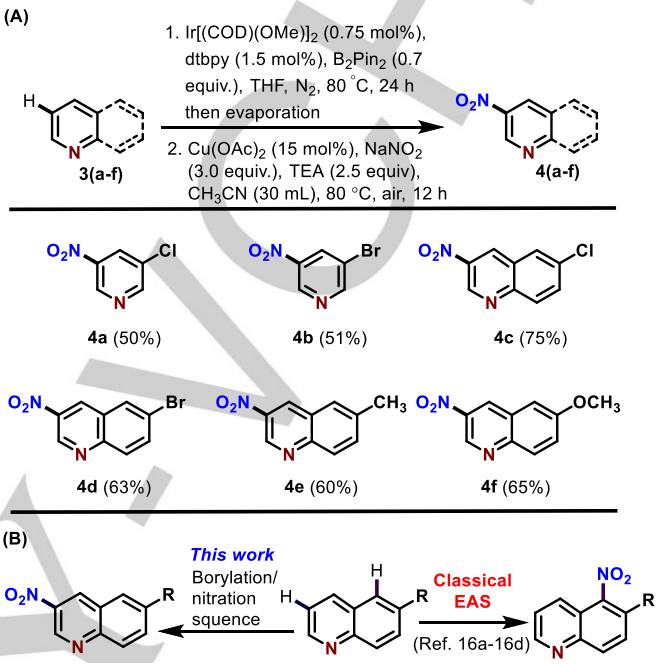
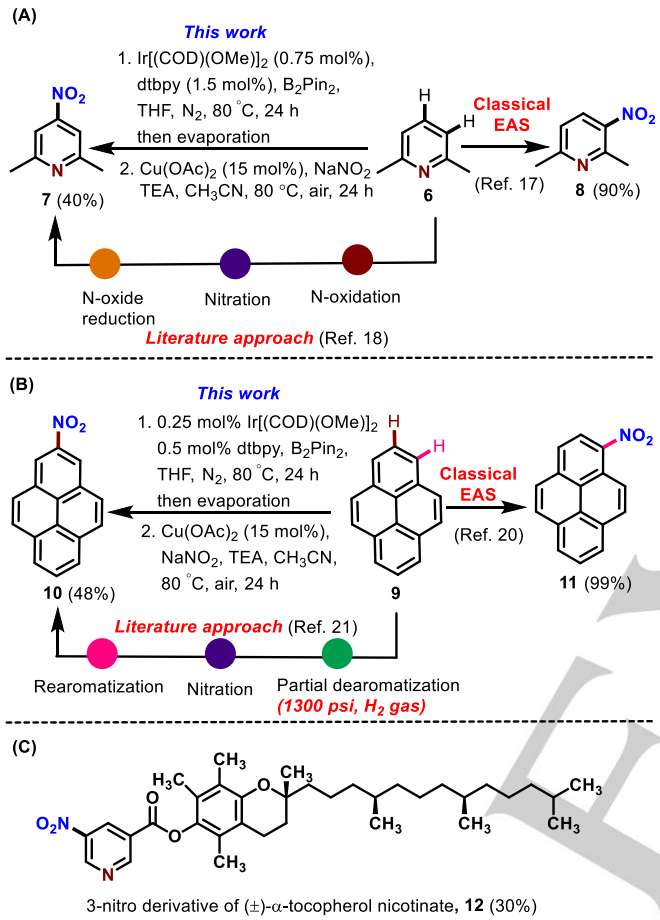


Table 3. [A] Scope of π-electron deficient heteroarenes in the C-H borylation/nitration sequence. Reactions were performed on 1.0 mmol scale. [B] Comparison of our approach with the classical nitration of quinoline derivatives

Having successfully synthesized the *meta* nitroarenes, this protocol was applied to heteroarenes such as pyridines and quinolines (Table 3 A). Both these scaffolds were chosen because they are π-electron deficient ring systems and require extremely vigorous conditions in order to undergo the classical aromatic nitration reaction. Using this protocol, 3-chloropyridine and 3-bromopyridine were converted into *meta nitrated* products **4a** and **4b** in 50 and 51% yields respectively. Various 6-substituted quinolines were converted into their respective 3-nitroquinoline derivatives (**4c** to **4f**) in 60 to 75% yields. *Ortho*/*para* directing groups such as -Cl, -Br, -CH_3 and -OCH_3 were tolerated in the reaction sequence. Under classical nitration conditions quinolines (**3c** to **3f**) all offered the respective 5-nitroquinolines (Table 3B).[16] This again demonstrates the usefulness of our approach in getting unique products that are impossible to obtain via the classical nitration methods.

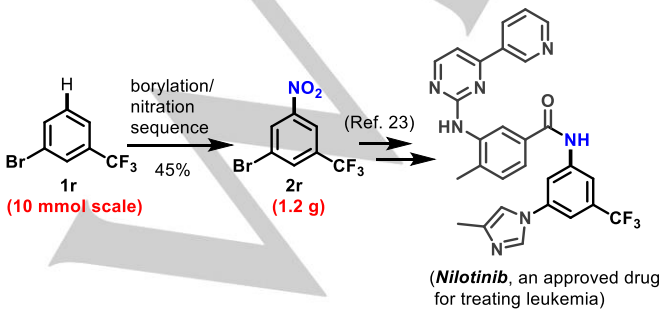
Classical nitration of 2,6-dimethylpyridine, **6** furnishes 2,6-dimethyl-3-nitropyridine, **8** in excellent yield of 90%[17], However, the synthesis of other regioisomers, 2,6-dimethyl-4-nitropyridine, **7** from 2,6-dimethylpyridine requires 3 separate synthetic steps[18]. Using our approach, the same compound **7** can be prepared from 2,6-dimethylpyridine in one-pot in 40% yield (Scheme 2A). Next, this methodology was applied to more complex molecules. Pyrene finds important applications in materials science due to its optoelectronic properties[19]. It is considered as a fragment of graphene and hence selective chemical modification of pyrene is a topic of interest. Classical nitration of Pyrene, **9** is very facile,

furnishing 1-nitropyrene, **11** in 99% yield[20]. However, the synthesis of 2-nitropyrene, **10** requires a 3-step synthesis starting from pyrene via a high pressure (1300 psi of H_2 gas) partial dearomatization strategy[21]. But, by using our approach, the 2-nitropyrene, **10** was exclusively obtained in 48% yield (Scheme 2B). This approach also worked well with medicinally important (±)-α-tocopherol nicotinate to yield the 3-nitro isomer, **12** in 30% yield (Scheme 2C).



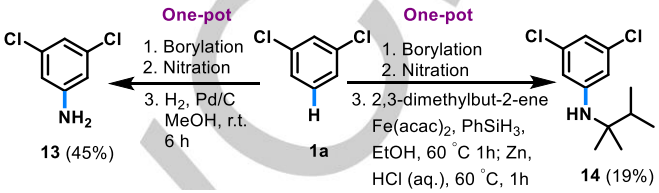
Scheme 2. [A] Nitration at the *meta* position with respect to the two –CH_3 groups. [B] 2-nitropyrene synthesis via our approach. [C] Late-stage nitration of (±)-α-tocopherol nicotinate

The applicability of this approach was further demonstrated in the synthesis of an important intermediate, *en route* to Nilotinib. Nilotinib is a second-generation protein tyrosine kinase inhibitor used to treat chronic myeloid leukemia (CML)[22]. This methodology was successfully demonstrated for the gram-scale synthesis of 1-bromo-3-nitro-5-(trifluoromethyl) benzene, **2r**, an intermediate *en route* to Nilotinib[23], starting from the arene precursor **1r** (10 mmol) with an isolated yield of 45% (Scheme 3).



Scheme 3. Scale-up of an intermediate *en route* to Nilotinib

Nitroarenes are versatile intermediates in organic synthesis. The nitroarenes obtained by this approach can be used directly for further derivatization, without the need for any purification (Scheme 4). Arene **1a**, was subjected to C-H borylation/nitration/hydrogenation to afford the aniline **13** in 45% yield in a one-pot fashion. Similarly, the crude nitro compound obtained from arene **1a** was subject to Baran's amination protocol[24] to afford the hindered aniline derivative **14** in 19% yield in a one-pot fashion.



Scheme 4. Other one-pot borylation/nitration/reduction sequences

To conclude, a one-pot C-H borylation/copper-catalyzed nitration sequence to access *meta* nitroarenes from the respective arene (C-H) precursors bearing *ortho*/*para* directing group(s) was developed. The copper-catalyzed conversion of the crude aryl boronate ester (ArBpin) to $ArNO_2$ was the key to the success of this method. This approach allows the preparation of *meta* nitrated products that are difficult to prepare by the existing routes. The method was extended to π-electron deficient heterocylces to obtain the 3-nitro derivatives that are impossible to obtain via the classical electrophilic nitration protocols. Complex molecules such as pyrene can be nitrated at the 2-position that is complimentary to the classical EAS product. Late-stage modification of medicinally important (±)-α-tocopherol nicotinate was also demonstrated. Further, an important intermediate *en route* to Nilotinib was prepared on a gram-scale using our approach. Lastly, this approach was extended to further functionalize the crude nitroarene into aniline or Baran's aminated product in a one-pot fashion starting from the arene C-H. We believe this methodology will simplify the ways to make *meta* nitroarenes and deliver useful products that cannot be obtained by the classical EAS reaction or requires multistep using the existing approaches.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest

Keywords: *meta* nitration • C-H borylation • one-pot reaction • copper catalysis • nitro(hetero)arenes

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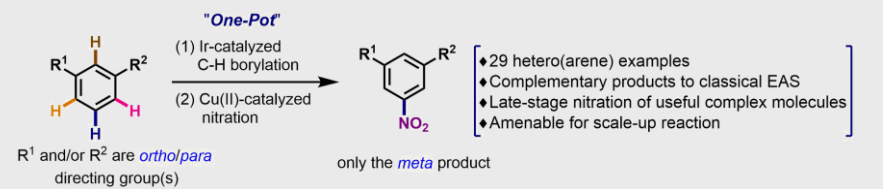

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Meta-Nitration of Arenes Bearing *Ortho*/*Para* Directing Group(s) Via C-H Borylation

Meta-Nitration: A one-pot method for the *meta*-nitration of arenes bearing *ortho*/*para* directing group(s) is reported. The method relies on the C-H borylation of the arenes, followed by copper(II)-catalyzed nitration of the crude ArBpin. This methodology is further extended to π-electron deficient heteroarenes and complex molecules to obtain synthetically useful nitrated products that require multistep synthesis to obtain by the classical nitration methods.