Organic LETTERS

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Palladium(II)-Catalyzed, Heteroatom-Directed, Regioselective C−H Nitration of Anilines Using Pyrimidine as a Removable Directing Group

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Supporting Information

ABSTRACT: A new palladium-catalyzed, heteroatom-directed strategy for C−H nitration of anilines is described. This C−H functionalization reaction is highly *ortho*-selective and results in very good yields. The highlight of the work is the use of pyrimidine as the removable directing group. This approach constitutes one of the rare methods of *ortho*-nitration of anilines, a reaction that is normally very difficult to achieve via traditional approaches.

Nitroarenes are important building blocks in organic synthesis and very often are important constituents of pharmaceutically relevant molecules.[1] The nitration of aromatics is a very well-developed reaction, with a variety of strategies being developed to direct the selectivity, usually with the help of electronic factors.[2] Some drawbacks exist, nonetheless, for these methods that employ electronic effects, and compatibility of functional groups with such methods has always been a problem. Issues of site selectivity as well as overnitration of highly activated arenes such as anilines, phenols, or alkylbenzenes have also been associated with such methods.[3] To circumvent such problems, several methods have been developed, including *ipso*-substitution[4] and metal-catalyzed nitration of aryl halides, pseudohalides, and organometallic compounds.[5] Transition-metal-catalyzed C−H bond functionalization reactions have recently been developed to achieve a direct nitration of aromatic C−H bonds.[6] In general, directing group strategies are usually adopted, often proceeding via cyclometalation, to direct the selectivity at the desired position.[7] Of these, the synthetic utility of the method is greatly enhanced when removable directing groups are employed. Nitrogen-containing heterocycles such as pyridine, pyrimidine, etc. have proven to be the most efficient directing groups (DGs) in organic synthesis, but the synthetic utility was low because of the difficulty in removing or modifying the directing groups after the transformation.[8] Therefore, in the past few years, new methods have been developed to remove these DGs, thereby making these thermodynamically stable DGs more useful in organic synthesis.[9] Recently, Liu and co-workers used pyridine as a removable directing group to achieve the selective *ortho*-nitration of phenols.[6h]

We have been interested in the synthesis of pyrimidine-based nitro compounds, especially since they are pharmacologically quite relevant (Figure 1).[10] In this regard, we envisioned that starting from simple anilines using the pyrimidine as the directing group in the C−H nitration of the corresponding *N*-arylaminopyrimidine could easily lead us to molecular frameworks of the type shown in Figure 1. Not only would this lead us to the desired target molecules, but upon removal of the pyrimidine group it would also constitute a method for the selective *ortho*-nitration of anilines. In this process, the pyrimidine could be regarded as a removable directing group. For this purpose, it would be necessary to develop a catalytic system that would be compatible to the *N*-(arylamino)-pyrimidine system.

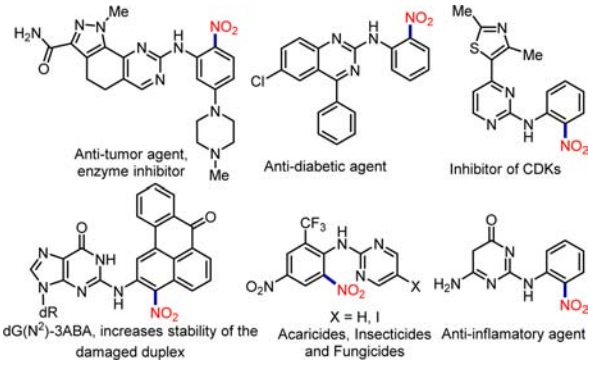


Figure 1. 2-Nitro-*N*-(arylamino)pyrimidine core in biologically active molecules.

We report herein the *N*-pyrimidine-directed palladium-catalyzed regioselective *ortho*-nitration of anilines by which a general and regiospecific synthesis of substituted *o*-nitroanilines from the related anilines has been successfully achieved. To the best of our knowledge, this represents the first example of

Received: December 8, 2015
Published: January 22, 2016

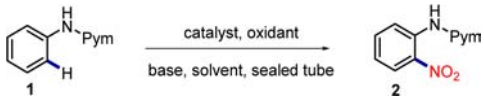
DOI: 10.1021/acs.orglett.5b03493
Org. Lett. 2016, 18, 448−451

pyrimidine as a removable directing group for the direct *ortho*-C−H nitration of anilines.

To begin, the nitration of *N*-phenylpyrimidin-2-amine (**1**) with $Pd(OAc)_2$ was chosen as a model reaction to screen the reaction conditions. The reaction of *N*-phenylpyrimidin-2-amine was the first investigated in the presence of $AgNO_3$ as the nitro source and $K_2S_2O_8$ as an oxidant in DCE at 80 °C. The corresponding product was isolated in 55% yield. Encouraged by this result, we then investigated different nitro sources and observed that $AgNO_2$ was the most competent, providing complete conversion. Next, the addition of a protic source in the form of acetic acid resulted in significant improvement in the yield. We scanned a number of other additives as well as oxidants and found that AcOH and $K_2S_2O_8$ were the most efficient for a good conversion (see the Supporting Information for more details). Among several scanned solvents, only DCE was found to be more suitable for cleaner reaction.

Through extensive optimization, we determined that the reaction proceeded to completion within 6−8 h at 80 °C in the presence of $Pd(OAc)_2$ (10 mol %), $AgNO_2$ (2.0 equiv), $K_2S_2O_8$ (2.0 equiv), and AcOH (3.0 equiv) in DCE with high yields (Table 1). We then proceeded to investigate the effect of the

Table 1. Optimization Studies[a]



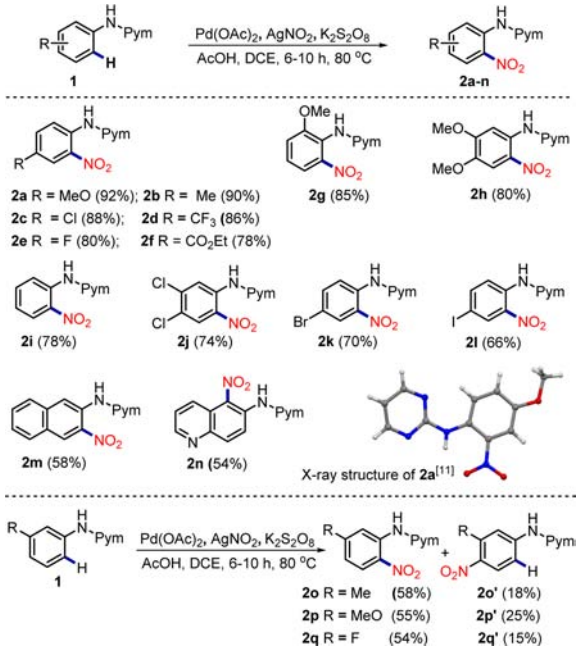
entry	catalyst/(10 mol %)	nitro source /(2.0 equiv)	oxidant /(2.0 equiv)	additive /(3.0 equiv)	solv/(0.1 M)	yield/%
1	$Pd(OAc)_2$	$AgNO_3$	$K_2S_2O_8$	-	DCE	55
2	$Pd(OAc)_2$	HNO_3	$K_2S_2O_8$	-	DCE	10
3	$Cu(OAc)_2$	$AgNO_3$	$K_2S_2O_8$	O_2	TCP	16
4	**$Pd(OAc)_2$**	**$AgNO_2$**	**$K_2S_2O_8$**	**AcOH**	**DCE**	**78**
5	$Pd(OAc)_2$	$^tBuNO_2$	$K_2S_2O_8$	AcOH	DCE	10
6	$Pd(OAc)_2$	$AgNO_2$	$PhI(OAc)_2$	AcOH	DCE	35
7	$Pd(OAc)_2$	$AgNO_2$	Oxone	AcOH	DCE	45
8	$Pd(OAc)_2$	$AgNO_2$	$K_2S_2O_8$	TFA	DCE	30
9	$Pd(OAc)_2$	$AgNO_2$	$K_2S_2O_8$	AcOH	$CHCl_3$	35
10	$[Ru(p\text{-}cym)Cl_2]_2$	$AgNO_2$	$K_2S_2O_8$	AcOH	DCE	10

[a]Pym = 2-pyrimidine, DCE = 1,2-dichloroethane, TCP = 1,2,3-trichloropropane. All yields are isolated yields.

directing group on the efficiency of the nitration reaction. Unfortunately, under the optimized conditions, when *N*-phenylacetamide was used as the substrate, we observed a low conversion and concomitant decomposition of the starting material. This clearly indicates that the weakly coordinating oxygen directing group may not be practical for this type of transformation. Since the presence of a strong coordinating group was crucial for the reaction, we then moved to the *N*-pyridyl group, which has been widely applied in transition-metal-catalyzed C−H functionalization reactions.[6h,8] However, this also failed to make a difference in the yield.

With these optimal conditions in hand, we studied the scope and generality of the protocol with various substituted anilines. As described in Scheme 1, the reactions of different substituted anilines bearing either electron-donating (−Me, −OMe) or electron-withdrawing substituents (−CF_3 and halogens) gave the corresponding C−H nitration product in excellent to moderate yields (**2a−q**). In all cases, the reaction showed excellent regio- and chemoselectivity as the majority of substrates

Scheme 1. Substrate Scope[a]

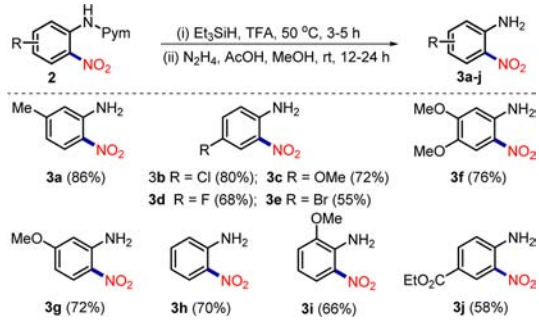


[a]All yields are isolated yields.

gave predominantly (>90%) mononitration products, and the substituent pattern on the phenyl ring had no effect on regioselectivity. In some cases, when *meta*-substituted anilines were subjected to the C−H nitration reaction, a separable mixture of regioisomers was obtained with nitration of the less hindered C−H bond occurring predominantly (**2o,p**).[5p] Most interestingly, readily functionalizable bromo-, iodo-, and chloro-substituted anilines were also well tolerated under the present conditions to afford the corresponding products **2c**, **2j**, **2k**, and **2l** in good yields.

The removal of the pyrimidine directing group was necessary to emphasize the efficiency of the method. Unfortunately, most of the conditions reported in the literature[9] did not work for our substrates, and even after 48 h there was almost no conversion; only the starting material was recovered. After several trials, we successfully removed the directing group in high yields, in a two-step sequence: first, the pyrimidine ring was reduced by triethylsilane in TFA at 50 °C for 2 h, which was then followed by treatment with N_2H_4/AcOH in MeOH at rt for 12−24 h, to yield the *o*-nitroanilines from the corresponding anilines (Scheme 2).[12] A series of *o*-nitroanilines with different

Scheme 2. Removal of the Pyrimidine Directing Group[a]



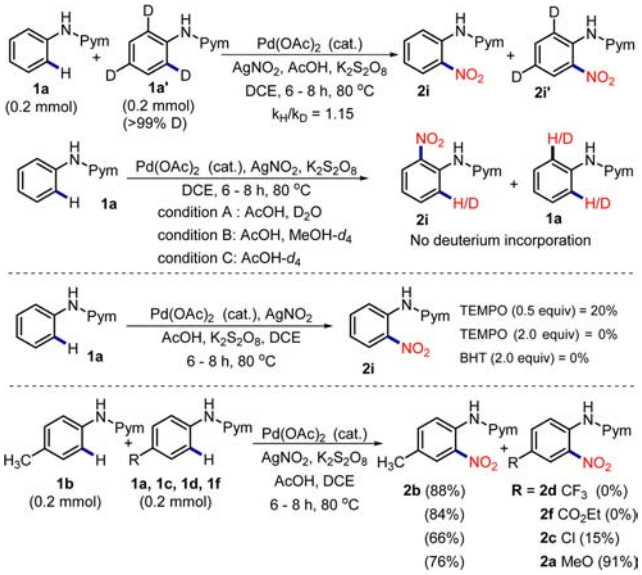
[a]All yields are isolated yields.

DOI: 10.1021/acs.orglett.5b03493
Org. Lett. 2016, 18, 448−451

substituent patterns could be regiospecifically synthesized in good to moderate yields. Interestingly, the removal of the pyrimidine group from halo-substituted nitroanilines was also achieved with good yields to result in functionalized starting materials for further transition-metal-catalyzed cross-coupling reactions. While optimizing the reaction conditions, we observed that heating at 60−80 °C in the second step resulted in the *o*-diamine compounds, but yields of these were low due to problems associated with the isolation of the diamine product.

To gain insight into the mechanism of the C−H nitration reaction, a series of experiments were conducted. In the competitive C−H nitration of *N*-phenylpyrimidin-2-amine (**1a**) and *N*-phenyl [D_3] pyrimidin-2-amine (**1a′**), we measured the kinetic isotope effect (KIE).[13] ^{1}H NMR analysis of the product mixture revealed a moderately low value of 1.15 for k_H/k_D (Scheme 3).

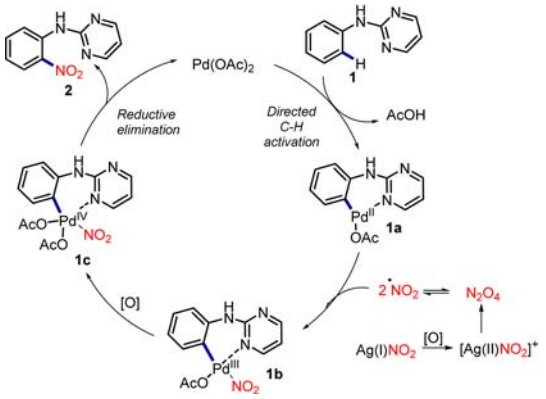
Scheme 3. Mechanistic Studies



To check whether the C−H activation step was reversible, we carried out the reaction in the presence of D_2O as well as MeOH-d_4 or AcOH-d_4. In all three cases, no deuterium incorporation was observed, either in the recovered starting material or the product. This indicated that in this transformation, the formation of the palladacycle may not be a reversible step. To probe the possibility of radical species in the catalysis, the reaction was performed under the optimized conditions in the presence of TEMPO (2.0 equiv), a radical-trapping agent (Scheme 3). The reaction failed to give any nitration product. This indicates that the reaction may involve a radical process.

To explore further the electronic effect on the rate of the reaction, we performed intermolecular competition experiments between an electron-rich substrate and electron-deficient substrates under the optimized conditions. Interestingly, electron-rich substrates were preferentially functionalized, and electron-neutral substrates such as chlorine produced a mixture of products (Scheme 3). A competition reaction with electron-rich and electron-poor substrates in the presence of AcOH-d_4 did not lead to any deuteration. On the basis of our observations and earlier precedents, a plausible reaction pathway is proposed in Scheme 4. Although details about the mechanism are still unclear, a pathway for this reaction can be proposed as follows.

Scheme 4. Plausible Mechanism



The first step is most probably the coordination of Pd(II) to the nitrogen atom from the pyrimidine substrate followed by a chelate-directed C−H activation to form the six-membered cyclopalladated intermediate. In the next step, the in situ generated NO_2 radical undergoes coordination with this palladacycle to form Pd(III) intermediate **1b**[6f,14] followed by one-electron oxidation by another NO_2 radical to form the Pd(IV) intermediate **1c**. The final step involves carbon−nitrogen bond-forming reductive elimination to lead to the nitration product, and Pd(IV) is returned back as Pd(II). It is also quite likely that the reaction involves a binuclear palladium species, which proceeds through a Pd(II)/ Pd(III) and/or Pd(II)/ Pd(IV) catalytic cycle. A slight excess of AcOH is necessary for the polar protic environment and the fast conversion to Pd(IV).

In summary, we have developed an efficient, palladium-catalyzed, direct C−H nitration of anilines with high levels of chemo- and regioselectivity by utilizing pyrimidine as a removable directing group. The present method tolerates a variety of functional groups and allows the synthesis of diverse 2-nitroaniline derivatives in good to excellent yields. Additionally, this protocol is also compatible with halogen functional groups, which offers a potential for further structural modification.This method is therefore likely to find broad utility in synthesis since it is one of the very rare methods of *ortho*-nitration of anilines, a reaction that is normally very difficult to achieve via traditional approaches.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03493.

Experimental procedures and full spectroscopic data for all new compounds (PDF)
X-ray data for **2a** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Funding from DST-India (SB/S1/OC-10/2014) and CSIR-India (02(205)/14/EMR-II) is gratefully acknowledged. G.G.P. thanks CSIR for a Research Fellowship. A.B. thanks IISERB for a

DOI: 10.1021/acs.orglett.5b03493
Org. Lett. 2016, 18, 448−451

BS−MS Fellowship. We thank Mr. Lalit Mohan Jha, IISERB, for the X-ray data. We also thank the Director, IISERB, for funding and infrastructural facilities.

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DOI: 10.1021/acs.orglett.5b03493
Org. Lett. 2016, 18, 448−451