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Ligand Promoted *meta*-C–H Chlorination of Anilines and Phenols

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Abstract: Pd-catalyzed *meta*-C–H chlorination of anilines and phenols is developed using norbornene as the mediator. The presence of heterocycles, including indole, thiophene and indazole, are tolerated. The identification of a new pyridone-based ligand is crucial for the success of this *meta*-C–H chlorination reaction. Subsequent diverse transformations of the chlorinated products demonstrate the versatility of *meta*-C–H chlorination.

The efficiency and scope of directed *ortho*-C–H functionalization reactions of arenes has been substantially improved in the past decade.[1] In contrast, directed *meta*-C–H activation remains a significant challenge due to the difficulty of assembling a macrocyclic, cyclophane-like transition state. The use of U-shaped directing templates to direct *meta*-C–H activation reactions demonstrated the feasibility of overcoming the constraint of distance and geometry. However, the scope of both substrates and transformations remains significantly inferior to *ortho*-C–H functionalizations.[2] The Ru(II) catalyzed *meta*-C–H functionalization *via ortho*-cyclometallation and subsequent functionalization at the *meta*-position is also a promising and elegant approach, though it has only been demonstrated with a small set of substrates thus far.[3] Several other approaches towards the *meta*-C–H functionalization of aromatics have also been reported, though the generality of these approaches remains to be established.[4] Recently, directed *meta*-C–H arylation[5] and alkylation[5a,5c] has been achieved by using norbornene as a transient mediator. In general, a diverse range of *meta*-C–H functionalizations *via* this approach remains to be demonstrated. Herein we report the first example of *meta*-C–H chlorination using this approach. The development of a new pyridone-based ligand is crucial for the success of this reaction. The versatile reactivity of aryl chlorides allows installation of a wide range of functional groups to suit a broad range of synthetic applications. In addition, *meta*-chlorinated aryls are also found in many FDA approved pharmaceuticals (Fig. 1).[6]

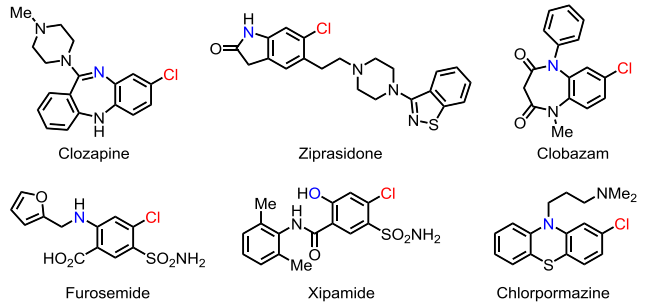
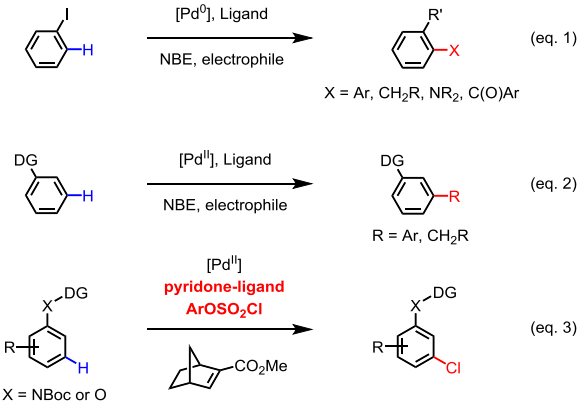


Figure 1. Selected pharmaceuticals containing the *meta*-chloro aniline or phenol structure.

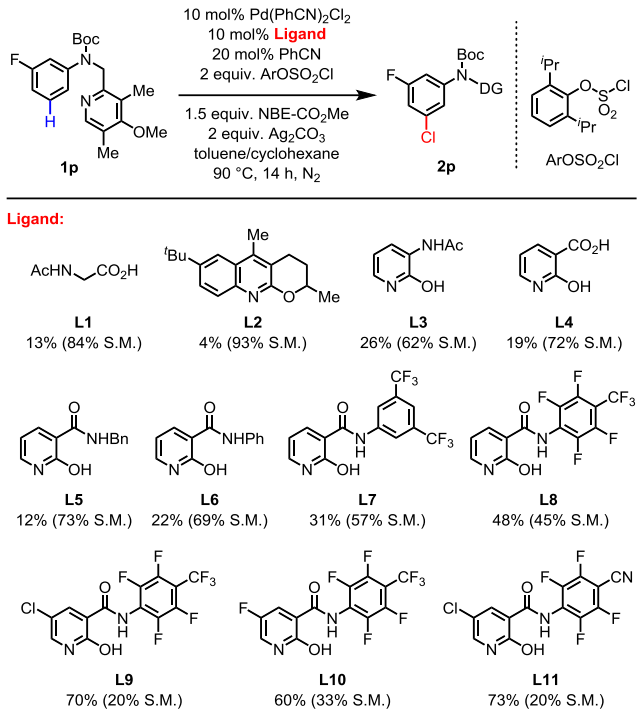
In the Catellani reaction, norbornene is used to relay palladium from the *ipso*-position to *ortho*-position of aryl iodides *via* carbopalladation of the norbornene double bond and subsequent cyclopalladation.[7] This reactivity has been exploited to develop a variety of transformations analogous to the Catellani reaction (Eq 1).[8] The ability of norbornene to relay palladium from one carbon to the adjacent carbon of an arylpalladium species has recently been exploited to achieve *meta*-C–H activation reactions initiated by directed *ortho*-C–H palladation (Eq 2).[5] Although the scope of arenes has been substantially expanded by the development of new ligands, many transformations demonstrated in *ortho*-C–H functionalizations remain to be realized for *meta*-C–H bonds.[5] Given that halides can be converted to various motifs through subsequent transformations, development of *meta*-C–H halogenation would facilitate the installation of a wide range of functional groups at the *meta*-position of aromatics. However, the compatibility of the Catellani relay step with halogenation has not been demonstrated to date. In addition, the *ortho*-C–H palladation in the catalytic cycle of the *meta*-C–H functionalization could lead to *ortho*-C–H halogenation with all the well-known C–H halogenating reagents



Our initial experimentation used *N*-chlorosuccinimide (NCS) as the chlorination reagent. Only *ortho*-chlorinated product was detected under various conditions when using this electrophile.[9] These results indicated that NCS reacts with the *ortho*-aryl palladium(II) intermediates faster than the norbornene. Following this reasoning, we began to search for chlorinating reagents that are less electrophilic, but could still serve as an oxidant in Pd(II)/(IV) catalysis. Among various chlorinating reagents, we found aryl chlorosulfate, initially utilized by the Buchwald group for Pd-catalyzed chlorosulfonylation,[10] is potentially suitable for *meta*-C–H chlorination.[11] In the presence of $Pd(PhCN)_2Cl_2$, benzonitrile, NBE-CO_2Me, and silver carbonate, the use of mono-*N*-protected amino acid ligand Ac-Gly-OH[12] gave the desired

product in 13% NMR yield (Table 1). While pyridine **L2** is a poor ligand, pyridone derived ligands[5e] gave promising results (**L3**–**6**: 10-30% yields). Since tuning the *N*-protecting group on **L3** did not afford a noticeable improvement (see Supporting Information), we focused on modification of the amide group of **L6**. Increasing the acidity of the amide was found to improve the yield of the reaction (**L7**, **L8**). Chloride substitution at the 5-position of the pyridone further improved the yield to 70% (**L9**). Fluoride substitution at the same position, however, is less effective (**L10**). Replacing the CF_3 in **L9** by a CN group gave a similar result (**L11**). Other norbornene derivatives gave significantly lower yield (see supporting information).[13] Although the necessity of silver carbonate for the formation of the products led us to propose that Ag^+ promotes the activation of S–Cl bond of chlorosulfate during the oxidation of palladium(II) intermediate. It is possible that Ag^+ also oxidizes Pd(0) or Pd(II) species in the catalytic cycle by a one-electron transfer pathway.

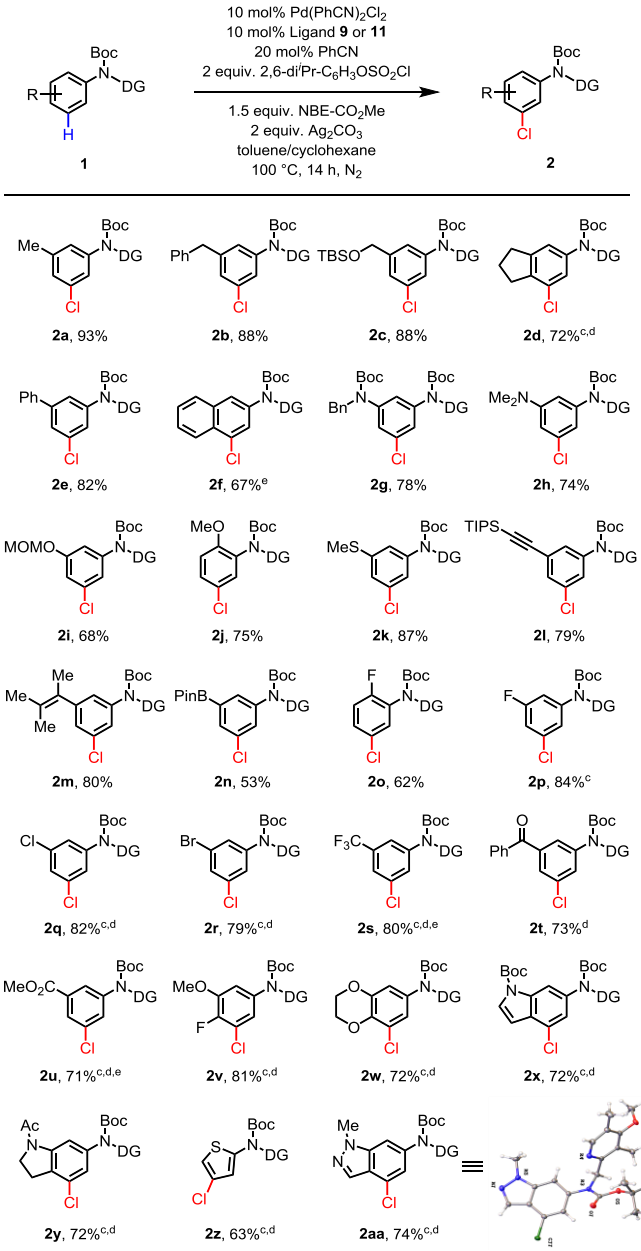
Table 1. Ligand Screening of the *meta*-C–H Chlorination.[a,b]



[a]Reaction conditions: $Pd(PhCN)_2Cl_2$ (10 mol%), Ligand (10 mol%), PhCN (20 mol%), arene **1p** (0.1 mmol), 2,6-di^{i}Pr-$C_6H_3OSO_2Cl$ (2.0 equiv.), NBE-CO_2Me (1.5 equiv.), Ag_2CO_3 (2.0 equiv.), toluene (1 mL), cyclohexane (1 mL), 90 °C, 14 h, N_2. [b]The yield was determined by ^{1}H NMR analysis of the crude product using 1,1,2,2-tetrachloroethane as an internal standard.

With the optimized ligands (**L9** and **L11**) and reaction conditions in hand, a wide range of aniline substrates were subjected to the standard *meta*-chlorination conditions (Table 2). *Meta*-alkylated and arylated anilines gave the *meta*-chlorinated products in excellent yields (**2a**–**2f**). *Meta*-chlorination of **1a** using 5 mol% catalyst also proceeded to give **2a** in 72% yield (see supporting information). *Meta*-chlorination of highly electron-rich arenes containing Me_2N, OMe and MeS groups also proceeded smoothly without the formation of side products derived from the electrophilic chlorination (**2g**–**2k**). The tolerance of alkynyl and alkenyl groups (**2l**, **2m**) is noteworthy as these functional groups are known to react with electrophilic sources of chlorine, thus demonstrating the mildness and selectivity of this transformation. Intriguingly, aryl borate remained largely intact in the presence of silver salts during the *meta*-chlorination (**2n**). Various electron-withdrawing groups including fluoro (**2o**, **2p**), chloro (**2q**), bromo (**2r**), trifluoromethyl (**2s**), carbonyl (**2t**), and carboxyl (**2u**) are also compatible with the reaction. A number of medicinally important heterocyclic substrates were also smoothly converted to the *meta*-chlorinated products **2w**–**2aa** in good yields. Hydroxyl group and pyridines are not compatible with current reaction conditions. Unsubstituted aniline substrate, **1ab**, was converted to the di-substituted product in 77% yield (Eq 4). The feasibility of extending this protocol to phenol substrates was also demonstrated with modified conditions (Eq 5). A gram-scale reaction was conducted and the product **2a** was obtained in 87% yield (Eq 6).

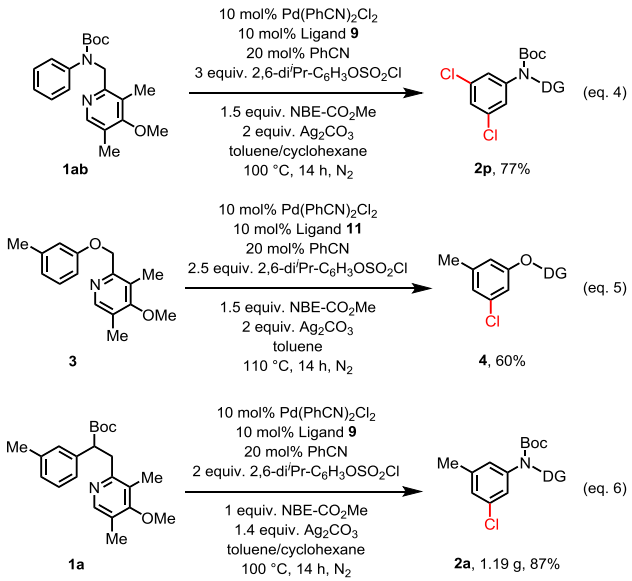
Table 2. Substrate Scope of the C(sp^2)–H Chlorination of Anilines.[a,b]



[a]Reaction conditions: $Pd(PhCN)_2Cl_2$ (10 mol%), Ligand **9** (10 mol%), PhCN (20 mol%), arene **1** (0.1 mmol), 2,6-di^{i}Pr-$C_6H_3OSO_2Cl$ (2.0 equiv.), NBE-CO_2Me (1.5 equiv.), Ag_2CO_3 (2.0 equiv.), toluene (1 mL), cyclohexane (1 mL), 100 °C, 14 h, N_2. [b]Isolated yield. [c]110 °C. [d]Ligand **L11**. [e]$Pd(PhCN)_2Cl_2$ (15 mol%), Ligand (15 mol%).

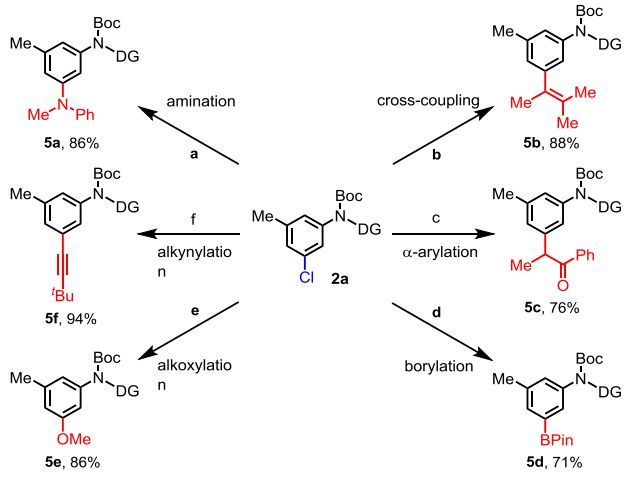
To demonstrate the utility of this *meta*-chlorination reaction, we performed diversification of **2a** using the *meta*-chloro group as a synthetic handle (Scheme 1). Aniline **2a** was converted into a wide range of desirable synthons in good yields by known

methods including amination[14], cross-coupling[15], α-arylation[16], borylation[17], methoxylation[18], and alkynylation[19]. Notably, none of the functional groups, shown in scheme 1, can currently be installed through previously reported norbornene-mediated *meta*-C–H activation methods. Furthermore, the pyridine directing group was readily removed by treatment with hydrobromic acid in excellent yield (see supporting information for details).



To gain insights into the two C–H activation steps of the catalytic cycle, we measured the parallel kinetic isotope effects (KIE) (Scheme 2). The results indicate that neither *ortho*- nor *meta*-C–H cleavage is the rate-limiting step. The competition experiments reveal that electron neutral substrate (**1a**) is more reactive than both electron rich and deficient substrates (**1ac**, **1t**).

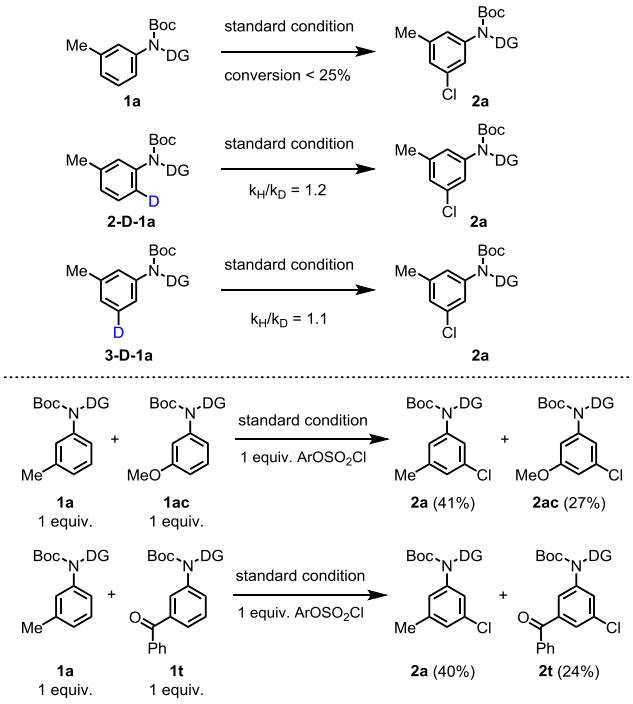
Scheme 1. Diversification of *meta*-Chloro Aniline.



Reaction conditions: [a]$Pd_2(dba)_3$ (3 mol%), DavePhos (9 mol%), PhMeNH (1.5 equiv.), arene **2a** (0.1 mmol), NaO^{t}Bu (1.4 equiv.), toluene (0.4 mL), 80 °C. [b]$Pd(OAc)_2$ (4 mol%), XPhos (8 mol%), 3-Methyl-2-buten-2-ylboronic acid pinacol ester (2.0 equiv.), arene **2a** (0.1 mmol), K_3PO_4 (3.0 equiv.), THF (1 mL), 60 °C. [c]$Pd(OAc)_2$ (5 mol%), MePhos (10 mol%), propiophenone (1.2 equiv.), arene **2a** (0.1 mmol), NaO^{t}Bu (1.3 equiv.), toluene (0.2 mL), 80 °C. [d]$Pd(OAc)_2$ (5 mol%), XPhos (10 mol%), B_2Pin_2 (2.0 equiv.), arene **2a** (0.1 mmol), KOAc (3.0 equiv.), dioxane (0.4 mL), 110 °C. [e]$Pd_2(dba)_3$ (3 mol%), ^{t}BuXPhos (12 mol%), MeOH (10 equiv.), arene **2a** (0.1 mmol), NaO^{t}Bu (1.4 equiv.), dioxane (0.4 mL), 100 °C. [f]$Pd(MeCN)_2Cl_2$ (6 mol%), XPhos (18 mol%), *tert*-butylacetylene (1.4 equiv.), arene **2a** (0.1 mmol), Cs_2CO_3 (2.5 equiv.), MeCN (0.4 mL), 90 °C.

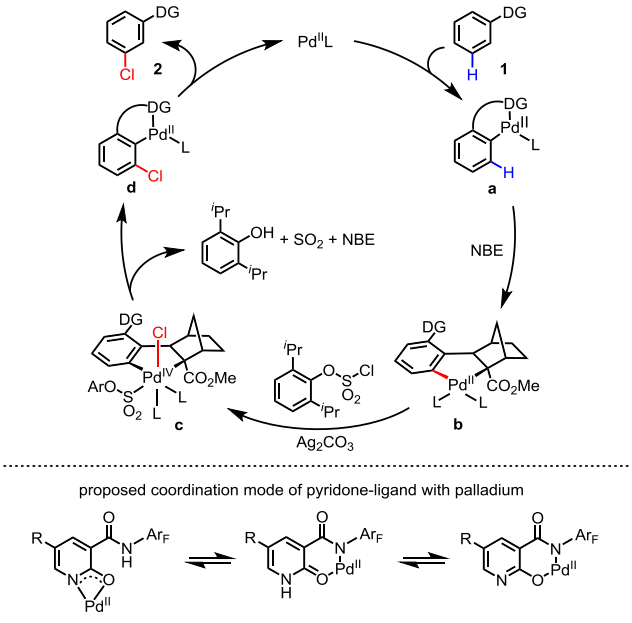
Based on the previous work by our group and others, a proposed catalytic cycle for the norbornene mediated *meta*-chlorination is depicted in scheme 3. Key to the success of this catalytic cycle is selective oxidation of palladacycle **b** by the chlorosulfate. Intermediate **b** arises from intermediate **a** through norbornene insertion and metalation. We hypothesize that the oxidation of **b** produces Pd(IV) intermediate **c** through palladium insertion into the S–Cl bond of the aryl chlorosulfate. Reductive elimination from this proposed intermediate would form the C–Cl bond at the *meta*-position. Meanwhile, sulfate on palladium (intermediate **c**) could be degraded into sulfur dioxide and phenol.[11,20] Norbornene is then released *via* β-carbon elimination, which generates intermediate **d**. Protodemetalation of the aryl–palladium bond yields the final product **2** and regenerates the palladium catalyst.

Scheme 2. KIE Studies and Competition Experiments.



In summary, we have developed the first example of directed *meta*-selective C(sp^2)–H chlorination of arenes. The reaction, promoted by a new pyridone ligand, displays outstanding functional group tolerance. *Meta*-C(sp^2)–H chlorination of other classes of substrates will be reported in due course.

Scheme 3. Proposed Mechanism.



Acknowledgements. We gratefully acknowledge The Scripps Research Institute and NIH (NIGMS, 2R01 GM102265).

Supporting Information Available: Experimental procedures and spectral data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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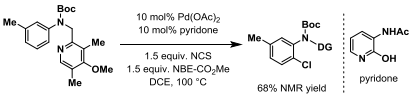

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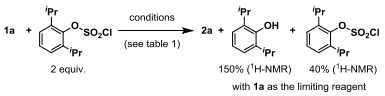

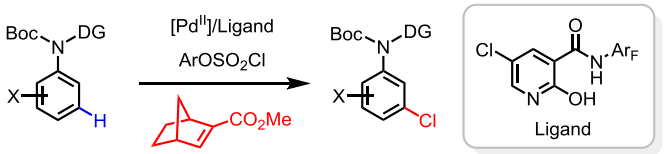

Excellent Functional Group Tolerance

X = alkyl, (hetero)aryl, alkenyl, alkynyl, Me_2N, MeO

MeS, BPin, F, Cl, Br, CF_3, carbonyl, carboxyl