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Palladium Catalyzed *meta*-C–H Functionalization of Masked Aromatic Aldehydes

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Abstract

Palladium catalyzed *meta*-C–H functionalization enabled by transient mediators has the potential to extend the utility of directed *ortho*-C–H functionalization to remote positions. However, there have been no reports of palladium catalyzed *meta*-C–H functionalization of aromatic aldehyde derivatives, which are highly versatile intermediates in organic synthesis. Herein we report the development of a directing group that, in the presence of a norbornene derived mediator and an appropriate pyridone ligand, allows palladium catalyzed *meta*-C–H functionalization of masked aromatic aldehydes. Mechanistic insight regarding the impact of the directing group length on this catalysis is also discussed.

Keywords

Aryl-Aldehyde; Benzaldehyde; Meta-C–H Activation; C–H Activation; Palladium; Pyridone Ligand

The aldehyde functional group is among the most versatile functional groups in organic synthesis and can be leveraged to provide access to a wide range of synthetic targets. This versatility causes aromatic aldehydes to serve as popular building blocks in the synthesis of drugs and drug candidates, agrochemicals, and materials. To further expand the versatility of this common building block, it would be ideal to have synthetic methods that selectively functionalize the C–H bonds on the arene portion of either a masked or unmasked aromatic aldehyde. Many groups have recognized this and have developed transition metal catalyzed methodology that functionalizes the *ortho*-C–H bonds of aromatic aldehydes using either pre-installed¹ or transient² directing groups wherein an aryl-alimine serves as the active directing group. However, methods that functionalize the *meta*- or *para*-C–H bonds on aryl-aldehyde derivatives remain scarce. To the best of our knowledge, the sole example of transition metal catalyzed *meta*-C–H functionalization of aromatic aldehyde derivatives is the elegant iridium catalyzed C–H borylation recently developed by the Chattopadhyay group.³ It is important to note that while aromatic aldehydes electronically direct electrophilic aromatic substitution (EAS) reactions to the *meta*-position, this effect is overridden by the directing effects of electron rich substituents and therefore EAS is not a general approach to functionalizing the *meta*-position of these compounds. We recognized

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the lack of a general protocol to functionalize the *meta*-C–H bond of aromatic aldehydes as an opportunity for invention and set out to develop a palladium catalyzed *meta*-C–H functionalization of masked aromatic aldehydes. Herein, we report the development of a new directing group for aromatic aldehydes that serves to temporarily mask the aldehyde functional group and enables palladium catalyzed *meta*-C–H arylation or amination in the presence of an appropriate transient mediator and pyridone ligand.

Though several sterically guided transition metal catalysts have been developed,⁴ the majority of general *meta*-C–H functionalizations, thus far, rely on a directing group to guide the catalyst.^{5–8} Exemplary of this, one approach towards *meta*-C–H functionalization is inspired by the Catellani reaction,⁹ wherein norbornene serves to relay palladium to an adjacent carbon and back. This relay process, when preceded by an *ortho*-cyclopalladation, allows for a net *meta*-C–H functionalization of aromatics.⁸ Since the first successful disclosures of this strategy^{8a,b} our group and others have developed methodology that leverages norbornene derived transient mediators to achieve *meta*-C–H alkylation,^{8a,c} arylation,^{8a-d,g-h} alkynylation,^{8e} amination,^{8e,g} and chlorination^{8f} reactions of a variety of substrates. The apparent generality of this approach prompted us to investigate this catalysis in the context of developing a *meta*-C–H functionalization of masked aromatic aldehydes.

Our initial investigations aimed at utilizing imine based directing groups to initiate our desired catalysis. Sun and coworkers have developed a palladium catalyzed *ortho*-C–H olefination of aryl-aldoximes¹⁰ and the Takemoto group has developed a palladium catalyzed annulation of aryl ketoximes with norbornene,¹¹ albeit in poor yields after long reaction times. Despite the precedent laid forth by these works, we were unable to observe significant *meta*-C–H functionalization with any of the imines we employed in our studies. This led us to hypothesize that the planar 5-membered palladacycles resulting from cyclometalation of aromatic imines with palladium catalysts were too stable to engage in kinetically competent migratory insertion with the transient mediator under conditions that were amenable to the subsequent steps of our desired catalysis. The recalcitrance of such palladacycles to undergo olefin insertion reactions is reflected in the work of Widdowson wherein either strongly acidic or forcing conditions were required to successfully convert imine-derived palladacycles to the desired olefinated products.¹² These failed attempts with imine derived directing groups led us to design a new directing group for aromatic aldehydes.

Our experience in developing *meta*-C–H functionalization reactions with norbornene derived transient mediators has demonstrated to us that pyridine based directing groups that form 7-membered palladacycles synergize well with Catellani inspired *meta*-C–H functionalization.^{8d-g} Such directing groups, in the presence of a palladium pyridonate catalyst and norbornene derived transient mediator, have enabled *meta*-C–H functionalization of aniline,^{8d-f} phenol,^{8d-f}, benzylamine^{8g} derived substrates. This led us to reason that if we could develop an analogous directing group for aryl-aldehydes, we should be able to observe similar generality.

We considered that addition of a 2-(lithiomethyl)pyridine to an aldehyde¹³ and subsequent trapping of the resulting alcohol with TBSCl would provide a masked aldehyde possessing

the requisite functionality to direct palladium to the *ortho*-position, providing a 7-membered palladacycle (see scheme 1). The retro-ene reaction of analogous substrates has been previously studied and found to proceed irreversibly to the aromatic aldehyde with minimal formation of side products, indicating to us that a simple unmasking protocol should be possible.¹⁴ With this in mind, we set out to evaluate the reactivity of these new directing groups.

After a brief optimization (see supporting information), we set out to explore the scope of aryl iodides that could be employed in this transformation. As can be seen in table 1, substitution at the 4-position of the aryl iodide coupling partner is well tolerated (**3b(a-g)**). We were delighted to find that 4-iodobenzaldehyde was a good coupling partner for this transformation as the resulting product **3bb** contains both a masked and an unmasked aldehyde that can be sequentially functionalized. Other notable functional groups that were well tolerated at this position include the free N-H of **2g** and the potentially reactive bromine of **2e**. An evaluation of substituents at the 3-position of the aryl iodide indicates that while electron rich substituents are tolerated, electron poor substitution is favored. 2-Iodomethylbenzoate also served as an efficient coupling partner, though non-coordinating *ortho*-substituents such as a methyl group are not tolerated on the aryl-iodide coupling partner under the current conditions. Both 3,4- and 3,5-disubstituted aryl iodides could be utilized in this reaction and the resulting products were formed in moderate to good yields (**3b(m-o)**). We were delighted to find that several heterocyclic coupling partners could be coupled, as long as they were substituted at the 2-position (**3bp & 3bq**). Finally, under slightly modified reaction conditions^{8g} (see SI for details), *O*-benzoyl hydroxylmorpholine (**4a**) could be used as a coupling partner to effect a *meta*-C–H amination reaction, providing **5ba** in modest yield.

Having established a relatively broad scope of aryl iodide coupling partners that can be used in this transformation we set our sights on evaluating the breadth of the masked aryl-aldehydes that can be employed. Benzaldehyde derived substrate **1a** provided a mixture of mono and di *meta*-arylated products. Electron rich *meta*-substituted substrates **1b-d** provided the desired products in high yields. A gram-scale reaction proceeded well to provide **3bs** in 89% yield, indicating this reaction can be used as a preparative method for preliminary medicinal chemistry investigations. Gratifyingly, substrates bearing halogens (**1e-g**) and electron withdrawing groups (**1h**) at the *meta*-position were suitable substrates when the precatalyst was changed from Pd(OAc)₂ to PdCl₂(MeCN)₂. *Ortho*-substitution was also tolerated, though we noticed a steric effect wherein substituents larger than a methyl group prohibited catalysis. This is likely due to a steric clash between the *ortho*-substituent and the sterically bulky OTBS group of the directing group preceding cyclopalladation, thereby inhibiting the process. *Para*-substitution was also tolerated under these reaction conditions as demonstrated by substrates **1m-n**. The mono-selectivity observed with substrate **1n** is in line with previous work⁸ on this catalysis and we currently attribute it to a sterically induced rotation of the methoxy group after the first arylation that prohibits the second arylation event. Gratifyingly, methoxypyridine derived substrate **1o** that contained a potentially coordinating pyridyl nitrogen successfully participated in this catalysis to provide **3os** in moderate yield.

At this stage we deemed it was important to evaluate the feasibility of an unmasking protocol to reveal the desired aryl-aldehyde. We considered that a retro-aldol like reaction would take place upon heating our substrate in the presence of a slight excess of TBAF. To our delight, heating substrate **3bs** in dilute DMF with 1.1 equivalents of TBAF cleanly provided aryl-aldehyde **5bs**.

Our success in developing a palladium catalyzed *meta*-C–H functionalization of masked aromatic aldehydes prompted us to investigate how the length of the directing group we developed for this transformation influences the catalysis. In order to de-convolute as many steric and electronic effects as possible, we studied the reactivity of substrates **7a–c**. As can be seen from scheme 3, **7a** did not participate in our *meta*-C–H arylation when using **2k** as the coupling partner. This is in line with our studies concerning imine based directing groups that form similar 5-membered palladacycles. As shown in scheme 3a, substrates **7b** and **6c** could successfully couple with **2k** to provide the desired products in moderate to good yields. It is worth noting that changing the silver source to AgOAc was necessary to provide efficient coupling with substrate **7b**; however, a re-evaluation of silver sources did not influence the reactivity of **7a**. To further examine what could be causing the difference in reactivity between these various palladacycles, we attempted *ortho*-C–H olefination reactions of substrates **7a–c** under similar conditions to those employed for our *meta*-C–H functionalization protocol. This was done in an attempt to evaluate the effect of palladacycle ring size on 1,2-migratory insertion, a key event in our desired catalysis. As can be seen from scheme 3b, substrate **7a** did not provide the desired *ortho*-olefinated products in significant yields, while substrates **7b** and **7c** reacted smoothly with ethyl acrylate to provide the desired products in moderate to good yields. This lends support to our hypothesis that the necessity for a larger palladacycle ring size is, at least in part, inherently linked to the migratory insertion step of this catalysis.

A proposed mechanism is depicted in Figure 2. We propose that this reaction proceeds via a Pd(II)/(IV) catalytic cycle. The catalysis is initiated by coordination of the directing group to the palladium catalyst, followed by cyclopalladation to provide palladacycle **II**. This intermediate engages with the transient mediator to relay the palladium to the adjacent site, providing palladacycle **V** after proceeding through intermediates **III** & **IV**. We propose that the directing group we developed for this transformation enables this catalysis by allowing this step to be kinetically facile under our reaction conditions. This newly formed palladacycle undergoes an oxidative addition reaction with an aryl iodide to provide a Pd(IV) intermediate (**VI**) that reductively eliminates to provide a new C–C bond and releases the palladium from the palladacycle to provide intermediate **VII**. β -carbon elimination provides palladacycle **VIII** which undergoes a protodepalladation reaction to release the desired product, regenerating the palladium catalyst **I**.

3. Conclusion

In summary, we have developed a new directing group that allows palladium catalyzed *meta*-C–H functionalization of masked aromatic aldehydes. We have demonstrated that this directing group can serve as a masking group for aromatic aldehydes that is easy to install and remove. Preliminary mechanistic studies indicate that this directing group allows for the

critical migratory insertion step of this catalysis to proceed smoothly. Future efforts are concerned with garnering a better understanding of the role of the pyridone ligand in this catalysis, as well as development of a silver free *meta*-C–H functionalization utilizing norbornene as a transient mediator.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Versatility of aromatic aldehydes

Figure 2.
Proposed Mechanism

Scheme 1.
Synthesis of masked aromatic aldehydes.

Scheme 2.
Unmasking protocol

Scheme 3.
Effect of Palladacycle Ring Size

Table 1.

Scope of electrophilic coupling partners^a

^aReaction Conditions: **1a** (0.1 mmol), **2a-r** (0.25 mmol), Pd(OAc)₂ (10 mol%), **L1** (20 mol%), Ag₂CO₃ (0.25 mmol), PX-NBE (0.15 mmol), CHCl₃ (0.5 mL), 100 °C, 16 h.

^bSee SI for reaction conditions.

Table 2.

Scope of Masked Aryl-Aldehyde Substrates^{a,b}

^aReaction Conditions: **1a-p** (0.1 mmol), **2s** (0.25 mmol), Pd(OAc)₂ (10 mol%), **L1** (20 mol%), Ag₂CO₃ (0.25 mmol), PX-NBE (0.15 mmol), CHCl₃ (0.5 mL), 100 °C, 16 h.

^b **Ar** = 2-NO₂C₆H₄

^c Gram Scale (See SI for details).

^d 10 mol% Pd(MeCN)₂Cl₂ was used instead of Pd(OAc)₂.