

Pd-Catalyzed Semmler–Wolff Reactions for the Conversion of Substituted Cyclohexenone Oximes to Primary Anilines

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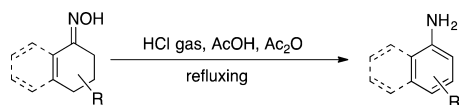
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Supporting Information

ABSTRACT: Homogeneous Pd catalysts have been identified for the conversion of cyclohexenone and tetralone *O*-pivaloyl oximes to the corresponding primary anilines and 1-aminonaphthalenes. This method is inspired by the Semmler–Wolff reaction, a classic method that exhibits limited synthetic utility owing to its forcing conditions, narrow scope, and low product yields. The oxime N–O bond undergoes oxidative addition to Pd⁰(PCy₃)₂, and the product of this step has been characterized by X-ray crystallography and shown to undergo dehydrogenation to afford the aniline product.

Aromatic amines are prevalent in pharmaceuticals, agrochemicals, and functional organic materials.¹ Of such structures, primary anilines (ArNH₂) are among the most difficult to access via metal-catalyzed C–N coupling with aryl halides or arylboronic acid derivatives (e.g., Ullmann–Goldberg, Buchwald–Hartwig, Chan–Lam). Strategies to address this challenge include the use of ammonia surrogates, such as benzyl amine and *tert*-butyl carbamate,² which can undergo C–N coupling and yield the parent aniline upon deprotection. Recent efforts have identified catalytic methods compatible with ammonia as the nitrogen nucleophile,³ as well as uncatalyzed reactions of aryl boron reagents with methoxy- or aryloxyamines.⁴ The Semmler–Wolff reaction is a classic but rarely used method for the synthesis of aromatic primary amines involving dehydration of cyclohexenone- and tetralone-derived oximes. This reaction is typically carried out under harsh conditions with anhydrous HCl gas in refluxing AcOH/Ac₂O (Scheme 1).^{5–8} It

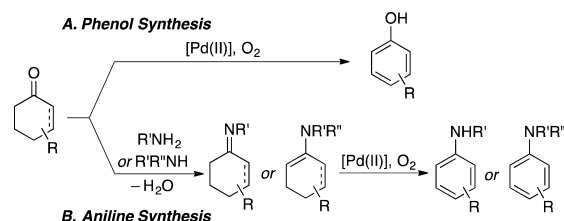
Scheme 1. Semmler–Wolff Reaction



exhibits limited functional group compatibility, and it typically affords products in moderate to low ($\leq 60\%$) yields, with the Beckmann rearrangement as a common side reaction. Here, we show that homogeneous Pd catalysts overcome many of these limitations in the conversion of cyclohexenone and tetralone *O*-acyl oximes to the corresponding primary aromatic amines.

We recently reported Pd-catalyzed methods for aerobic dehydrogenation of diverse substituted cyclohexanones and cyclohexenones to phenols (Scheme 2A).^{9,10} These reactions complement metal-catalyzed cross-coupling routes to such

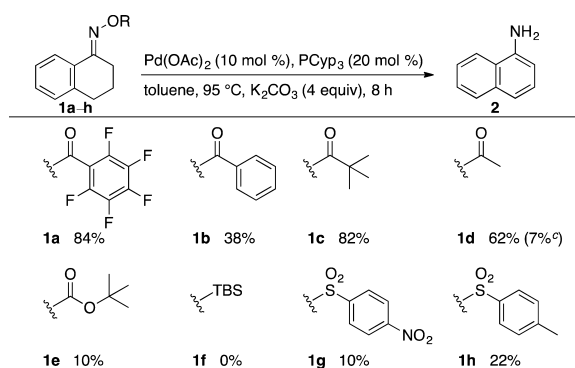
Scheme 2. Known Pd-Catalyzed Aerobic Dehydrogenation Routes to Substituted Phenols and Anilines



molecules, and we envisioned that analogous methods could be used to prepare anilines. Dehydrogenation of preformed cyclohexanone-derived enamines has been used to prepare tertiary anilines, but these reactions exhibit relatively narrow scope and often use undesirable stoichiometric oxidants.^{11,12} Our preliminary efforts focused on in situ condensation of an amine with the ketone, followed by dehydrogenation of the imine or enamine intermediate (Scheme 2B). These reactions were complicated by parallel dehydrogenation of the ketone and imine/enamine and led to mixtures of phenol and aniline products. Independently, however, the groups of Yoshikai and Li identified suitable Pd catalysts and substrate partners for this transformation, enabling good yields of various secondary and tertiary aryl amines via this strategy.¹³ The condensation of ammonia with ketones is not strongly favored, and it is unlikely that primary anilines could be prepared by a similar approach. Oximes are quite stable, however, and the Semmler–Wolff precedent raised the prospect of identifying Pd catalysts to enhance the synthetic utility of this transformation. Oxidative addition of N–O bonds has been exploited in various Pd^{0/II}-catalyzed reactions,¹⁴ and the oxime could therefore serve as an internal oxidant to promote Pd-mediated dehydrogenation of the substrate.

A number of different 1-tetralone oxime derivatives (**1a–h**) were synthesized and tested under a variety of catalytic conditions (Chart 1, Table 1). The *O*-pentafluorobenzoyl and *O*-pivaloyl derivatives **1a** and **1c** led to the highest yield of 1-aminonaphthalene **2**. Lower yields were obtained with the benzoyl and acetyl derivatives, and very low yields were obtained with the carbonate, siloxy, and sulfonate derivatives **1e–h**. The reaction with the *O*-acetyl derivative (**1d**) led to a 7% yield of *N*-acetyl-1-aminonaphthalene as a side product. On the basis of these observations, we opted to proceed with pivaloyl oxime

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Chart 1. Comparison of *O*-Substituents in the Conversion of Tetralone Oximes to 1-Aminonaphthalene (**2**)^{a,b}

^aReaction conditions: **1a–h** (0.2 mmol), Pd(OAc)₂ (0.02 mmol), tricyclopentylphosphine (0.04 mmol), K₂CO₃ (0.8 mmol), toluene (2.2 mL). ^b¹H NMR yield; internal standard = tetrachloroethane. ^cYield of *N*-acetyl-1-aminonaphthalene.

Table 1. Reaction Optimization for Conversion of Tetralone Pivaloyl Oxime to 1-Aminonaphthalene (**2**)

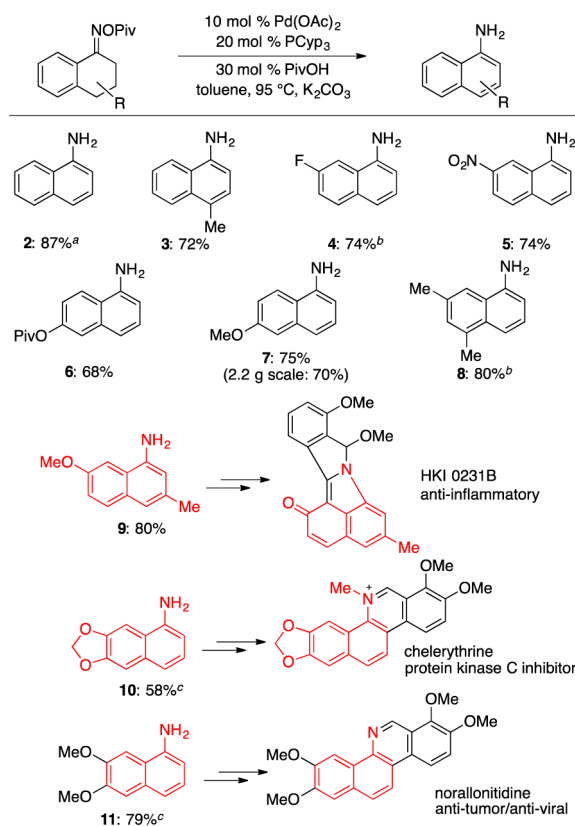
entry	palladium	ligand	additive	% conv/ % yield ^b
1	10% Pd(P(<i>o</i> -tol) ₃) ₂			50/24
2	5% Pd ₂ (dba) ₃			56/23
3	10% Pd(PPh ₃) ₄			96/70
4	5% Pd ₂ (dba) ₃	20% PPh ₃		99/63
5	5% Pd ₂ (dba) ₃	20% PCy ₃		99/68
6	10% Pd(OAc) ₂	20% PCyp ₃		97/82
7	10% Pd(OAc) ₂	20% PCy ₃		97/80
8	10% Pd(OAc) ₂	20% PPh ₃		74/37
9	10% Pd(OAc) ₂	20% dppe		73/62
10	10% Pd(OAc) ₂	20% dppf		78/44
11 ^a	10% Pd(OAc) ₂	20% PCyp ₃	30% PivOH	99/87

^aReaction conditions of entry 11: **1c** (0.2 mmol), Pd(OAc)₂ (0.02 mmol), tricyclopentylphosphine (0.04 mmol), PivOH (0.06 mmol), K₂CO₃ (0.8 mmol), toluene (2.2 mL). ^b¹H NMR yield; internal standard, tetrachloroethane.

derivatives rather than the more expensive pentafluorobenzoyl derivatives.

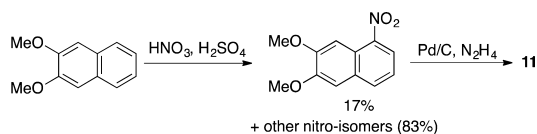
Representative catalyst screening data for the conversion of 1-tetralone pivaloyl oxime to 1-aminonaphthalene are summarized in Table 1 (see Supporting Information for additional data).¹⁵ Pd(PPh₃)₄ gave full conversion and 70% yield (entry 3), while other Pd⁰ sources, including Pd(P(*o*-tol)₃)₂ or Pd₂(dba)₃, were less effective (entries 1 and 2). Good yields could be obtained by combining Pd₂(dba)₃ with an appropriate phosphine ligand (entries 4 and 5), and even better results were obtained by using Pd(OAc)₂ with 2 equiv of a phosphine ligand (entries 6–11). Further screening studies revealed that the optimal result could be obtained with a Pd(OAc)₂/tricyclopentylphosphine (PCyp₃) catalyst system, containing pivalic acid (30 mol %; entry 11, 87% yield of **2**). The idea of testing pivalic acid as an additive was inspired by precedents in which pivalate/pivalic acid serves as a proton shuttle in C–H activation.¹⁶

Upon the identification of suitable reaction conditions, a variety of substituted tetralone-derived oximes were tested and

Table 2. Aromatization of Substituted Tetralone Pivaloyl Oximes^a

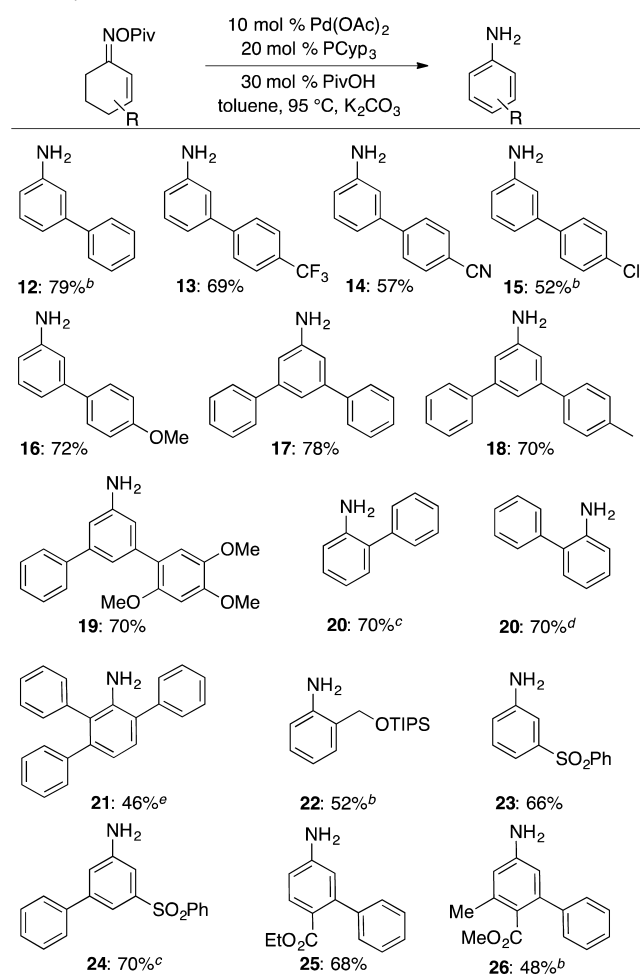
^aReaction conditions: pivaloyl oxime (0.2 mmol), Pd(OAc)₂ (0.02 mmol), tricyclopentylphosphine (0.04 mmol), PivOH (0.06 mmol), toluene (2.2 mL). ^bStructural data were analyzed after acetylation. ^cReaction temperature, 120 °C.

shown to react with good yields (Table 2). The formation of **5** is noteworthy because of the presence of a sensitive nitro group, which is not tolerated under Semmler–Wolff aromatization conditions. Formation of **7** was successfully reproduced on 2.2 g scale. Several aminonaphthalene products (**9**, **10**, and **11**) represent key intermediates in the synthesis of pharmaceutically active compounds. A previously reported synthesis of the 3 α -hydroxysteroid dehydrogenase inhibitor HKI0231B prepared aminonaphthalene **9** in 50% yield via aromatization of the tetralone tosyl oxime in the presence of strong base (KOH, refluxing MeOH).^{6d} The Pd-catalyzed method described here generates **9** in 80% isolated yield. Aminonaphthalene **10** is the central intermediate in the preparation of benzo[*c*]-phenanthridine alkaloids such as chelerythrine, fagardine, and decarine. The yield of **10** is only 58% under the present conditions, but this result is significantly better than the 28% yield obtained under classical Semmler–Wolff conditions.¹⁷ Compound **11** is an intermediate in the synthesis of the anti-tumor/anti-viral alkaloid, norallonitidine.¹⁸ Efficient access to **11** via this Pd-catalyzed method (79% yield) may be compared to a previously reported route (Scheme 3), in which classical electrophilic nitration affords a mixture of difficult-to-separate nitronaphthalene products,^{19,20} and only 17% of this mixture consists of the nitronaphthalene precursor to **11**. These results highlight the regioselectivity advantage of (catalytic) Semmler–Wolff methods relative to nitration/reduction routes to substituted anilines. Complications were encountered in the

Scheme 3. Previously Reported Route to **11**¹⁹

reaction of 6-bromo-1-tetralone; unsuccessful reaction of this substrate (not shown) suggests that competing oxidative addition of Ar-Br to Pd^0 can initiate unwanted side reactions. Efforts to engage 2-tetralone pivaloyl oxime in this reaction resulted in only low yield (32%).

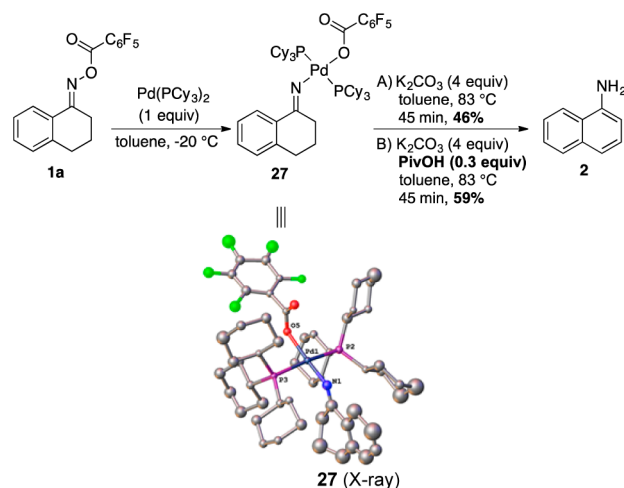
The catalytic conditions also proved to be successful for the aromatization of cyclohexenone-derived pivaloyl oximes (Table 3). An array of primary anilines was obtained, including products with cyano, trifluoromethyl, and chloro substituents. The more sterically hindered 2-phenyl- and 6-phenylcyclohexenone oximes proceed effectively to 2-aminobiphenyl (**20**) in 70% yield, and even the 2,5,6-triphenyl derivative affords the corresponding aniline **21** in 46% yield. A silyl ether group (in **22**) was retained under the catalytic reaction conditions, unlike traditional

Table 3. Aromatization of Substituted Cyclohexenone Pivaloyl Oximes^a

^aReaction conditions: pivaloyl oxime (0.2 mmol), $\text{Pd}(\text{OAc})_2$ (0.02 mmol), tricyclopentylphosphine (0.04 mmol), PivOH (0.06 mmol), K_2CO_3 (0.8 mmol), toluene (2.2 mL). ^bStructural data were analyzed after acetylation. ^cDerived from 2-phenylcyclohexenone. ^dDerived from 6-phenylcyclohexenone. ^eReaction temperature, 120 °C.

Semmler–Wolff conditions, which result in a product with both *N*- and *O*-acetyl groups.^{6a} Cyclohexenone oximes bearing sulfone substituents were compatible with the reaction conditions, and the corresponding sulfone-substituted anilines **23** and **24** were obtained in good yield. Reactions of 4-alkoxycarbonyl-cyclohexenone derivatives afforded the corresponding anilines **25** and **26**.²¹

Oxidative addition of oxime *N*–*O* bonds to Pd^0 has been utilized in a number of catalytic transformations, including aza–Heck coupling and directed *C*–*H* activation/*C*–*N* reductive elimination reactions.¹⁴ Several different oxime and L_nPd^0 derivatives were evaluated in an effort to probe the viability of this fundamental step as a prelude to aniline formation in the present catalytic reactions.²² The reaction of tetralone pivaloyl oxime with a stoichiometric amount of $\text{Pd}(\text{PPh}_3)_4$ led to a complex product mixture, but the combination of tetralone pentafluorobenzoyl oxime **1a** and $\text{Pd}(\text{PCy}_3)_2$ afforded the *N*–*O* oxidative addition product **27**, which was characterized by NMR spectroscopy and X-ray crystallography (Scheme 4). Upon

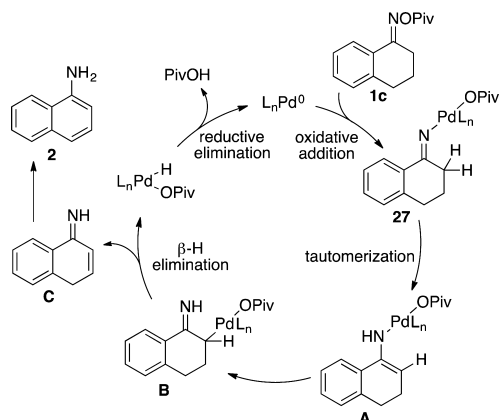
Scheme 4. Stoichiometric Oxidative Addition/Aromatization Sequence and X-ray Crystal Structure of **27**

heating in toluene, **27** reacts to afford 1-aminonaphthalene in 46% yield. The reaction proceeds with somewhat faster rate and in higher yield (59%) if it is carried out in the presence of pivalic acid and K_2CO_3 , which are valuable additives in the catalytic reaction.

On the basis of these observations, we propose the mechanism shown in Scheme 5. Oxidative addition of the tetralone oxime **1c** affords intermediate **27**, which can undergo tautomerization to afford the enamine-derived amido- Pd^{II} species **A**. Further isomerization of this species results in conversion of this *N*-bound enamido- Pd^{II} species to its *C*-bound isomer **B**. β -Hydride elimination from **C** generates the primary imine, which can tautomerize to its more stable isomer, 1-aminonaphthalene (**2**). We speculate that the beneficial effect of the pivalic acid under catalytic and stoichiometric conditions (Table 1 and Scheme 5, respectively) reflects its ability to facilitate proton-transfer reactions involved in the tautomerization step. The base (K_2CO_3) is heterogeneous under the reaction conditions, but it could play a similar role, in addition to promoting the reductive elimination step, which forms carboxylic acid as a stoichiometric byproduct.

In summary, these results show that homogeneous Pd catalysts promote efficient Semmler–Wolff-type reactions for conversion

Scheme 5. Proposed Catalytic Cycle



of readily accessible tetralone and cyclohexenone pivaloyl oxime derivatives to the corresponding primary anilines. These reactions provide an important demonstration of the complementarity of dehydrogenation and cross-coupling methods to access valuable substituted aromatic molecules.

■ ASSOCIATED CONTENT

Supporting Information

Additional catalyst screening data, experimental procedures, and full compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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