Asymmetric Catalysis Hot Paper

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Interrupted Pyridine Hydrogenation: Asymmetric Synthesis of δ-Lactams

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Dedicated to Professor David A. Evans on the occasion of his 80th birthday

Abstract: *Metal-catalyzed hydrogenation is an effective method to transform readily available arenes into saturated motifs, however, current hydrogenation strategies are limited to the formation of C–H and N–H bonds. The stepwise addition of hydrogen yields reactive unsaturated intermediates that are rapidly reduced. In contrast, the interruption of complete hydrogenation by further functionalization of unsaturated intermediates offers great potential for increasing chemical complexity in a single reaction step. Overcoming the tenet of full reduction in arene hydrogenation has been seldom demonstrated. In this work we report the synthesis of sought-after, enantioenriched δ-lactams from oxazolidinone-substituted pyridines and water by an interrupted hydrogenation mechanism.*

Metal-catalyzed hydrogenation is known to be a simple and powerful method to increase molecular complexity.[1] In particular, the hydrogenation of easily accessible N-heteroarenes such as pyridines offers access to important saturated azacycles.[2] This established reaction is limited solely to the formation of new C–H and N–H bonds; additional synthetic manipulations are required to introduce further chemical functionality.[3] The stepwise transfer of molecular hydrogen in arene hydrogenation yields intermediates with double bonds remaining, which in principle offer the possibility of further functionalization (Figure 1).[4] Nevertheless, harnessing unsaturated intermediates in arene hydrogenation for other C–X bond forming events is unknown in the literature, although the partial hydrogenation of certain substrates like benzene or phenol has been achieved.[5] Recently, Donohoe and co-workers reported a pioneering combination of C–H and C–C bond formation in a transfer hydrogenation of pyridinium salts.[6] Protected tetrahydropyridines were thus synthesized using iridium-catalyzed hydride transfer followed by hydroxymethylation. This precedent underlines the huge potential of an interrupted hydrogenation strategy to rapidly build up chemical complexity, yet, further method development is necessary to elevate this approach to a general synthetic strategy. We now report a pyridine hydrogenation interrupted by nucleophilic substitution of an unsaturated intermediate. Our procedure enables the synthesis of valuable δ-lactams by Pd-catalyzed hydrogenation of oxazolidinone-substituted pyridines in the presence of water.[7]

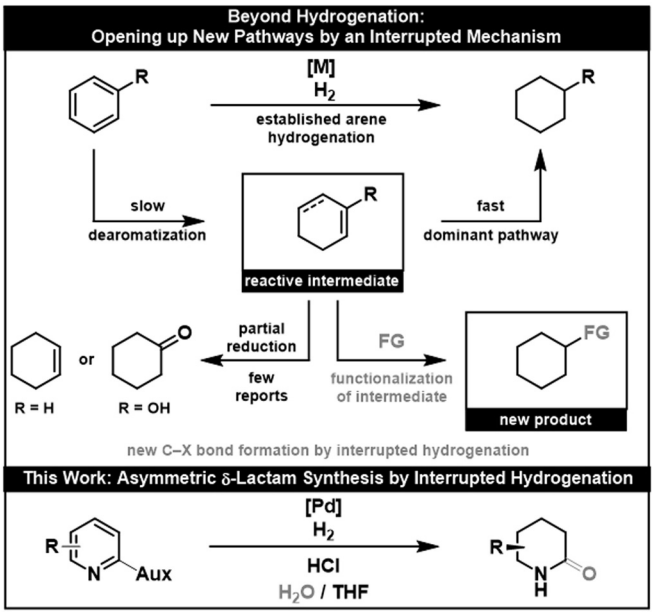

Figure 1. Mechanistic pathways of unsaturated intermediates in arene hydrogenation and this work. Aux = chiral auxiliary.

Lactams, such as 2-piperidones, are important building blocks and represent core motifs in many pharmaceuticals and natural products.[8] Despite interest in this moiety, synthetic access to enantioenriched δ-lactams remains challenging.[9] In this regard, we envision metal-catalyzed hydrogenation as a powerful strategy to address this problem. However, the synthesis of 2-piperidones via direct asymmetric hydrogenation[10] of pyridone precursors is hampered by amide resonance and, to the best of our knowledge, has never been achieved.[11] In contrast, our procedure starts with oxazolidinone-substituted pyridines, which are readily available from cheap and abundant 2-halogenated pyridines in a single step.[12] The oxazolidinone is cleaved within the reaction, thus acting as a traceless chiral auxiliary which can be fully recycled.

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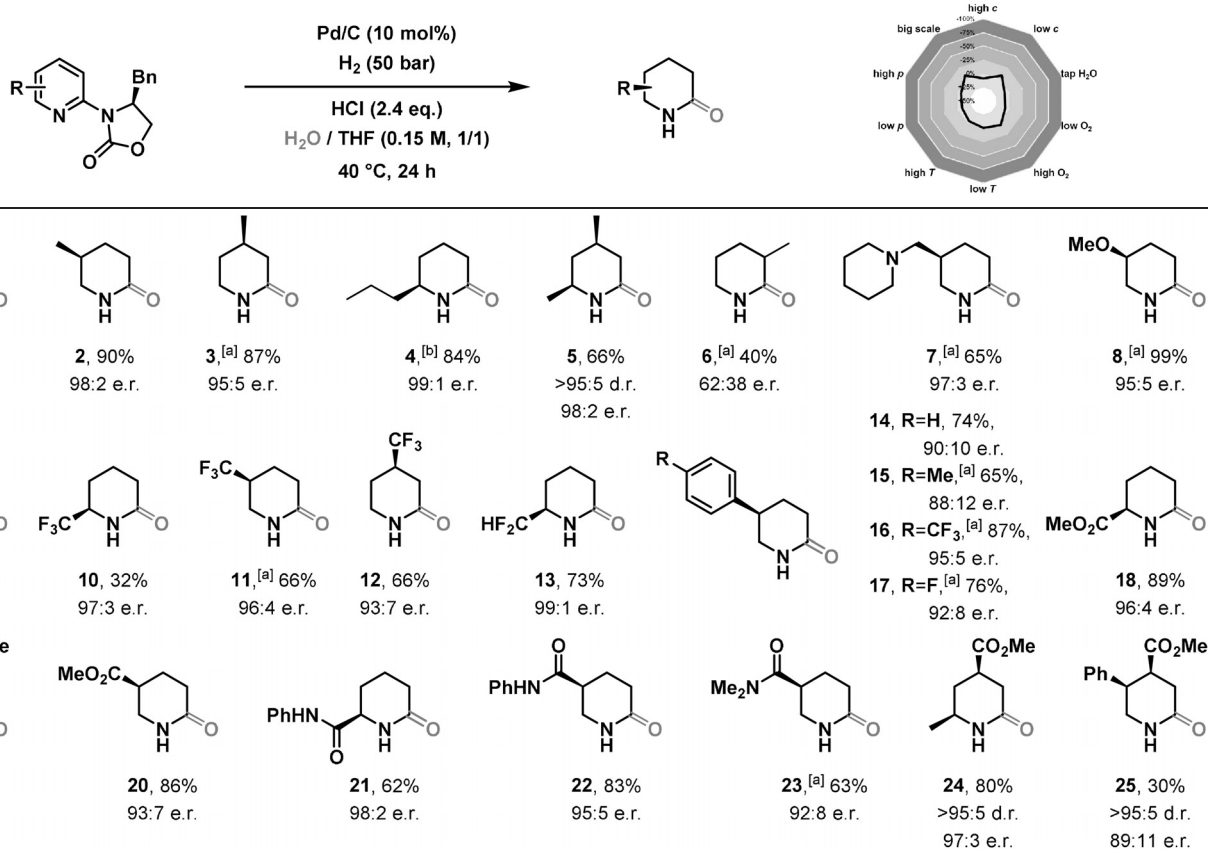
After our initial discovery, we studied the influence of the reaction parameters in more detail (see Supporting Information for details). The presence of strong Brønsted acids like hydrochloric acid is essential.[13] Using weak Brønsted acids like formic acid resulted in the exclusive formation of piperidine product (Table S1, Entry 7). Furthermore, different solvents were tested, with a combination of THF and H_2O giving the best result (Table S1, Entries 1–6). The nature of the catalyst is also decisive for the reaction outcome.While various Pd catalysts generally gave the desired δ-lactam in high yields and enantioselectivities, other catalysts such as PtO_2, Ru/C or Rh/C resulted in little or no yield (Table S2, Entries 2–9). Various oxazolidinones from the chiral pool provided the product in a high enantiomeric ratio while a benzyl substituent gave the best result (Table S2, Entries 10–12).[14] Lowering the hydrogen pressure to 25 bar results in a decrease of the enantiomeric ratio (Table S2, Entry 13). To investigate the reproducibility of our new method, we performed a reaction-condition-based sensitivity screen (Table 1; see Supporting Information for details).[15]

With optimized conditions in hand, we investigated the reaction scope of this new transformation. A series of alkylated δ-lactams (**1**–**4**) was synthesized in high yields and excellent enantiomeric ratios. Furthermore, our method was capable of forming multiple stereocenters in a highly selective fashion. Dimethylated lactam **5** was isolated in 66% yield with a 98:2 enantiomeric ratio and only one diastereomer observed. Additional functional groups such as basic azacycles (**7**) or alkyl ethers (**8**) were tolerated without significant decrease in yield or enantiomeric ratio. Although hydrogenation of fluorinated arenes is challenging,[16] several fluorinated δ-lactams (**9**–**13**) were prepared containing CF, CF_3, and CF_2H groups in moderate to good yields. Interestingly, a chemoselective hydrogenation of the pyridine core over a phenyl substituent was observed for our catalytic system to give various substituted phenyl-piperidones (**14**–**17**). Moreover, δ-lactams carrying important carbonyl functionalities such as esters and amides (**18**–**23**) were prepared in moderate to high yields and high enantiomeric ratios. Disubstituted δ-lactams **24** and **25** were synthesized highly selectively with only one diastereomer observed in 97:3 and 89:11 enantiomeric ratios, respectively. Substitution in the pyridine 3-position however decreased product formation and resulted in an almost racemic mixture (**6**, see Supporting Information for details).

The absolute configurations of δ-lactams **1** and **10** were unambiguously determined by X-ray analysis and are in accordance with our previous observations (Figure 2, see Supporting Information for details).[17,7a,b]Based on the Horiuti–Polanyi mechanism[18] for heterogeneous hydrogenation, the absolute configuration of the products with substituents in 4- and 5- position are assigned analogously (see Scheme S1).

Table 1: Reaction scope for the palladium-catalyzed synthesis of 2-piperidones. See Supporting Information for full experimental details.



[a] 4-Isopropyloxazolidinone as chiral auxiliary. [b] 4-*tert*-Butyloxazolidinone as chiral auxiliary. [c] Epimeric (*R*)-isopropyloxazolidinone as chiral auxiliary.

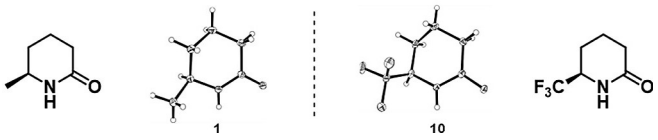
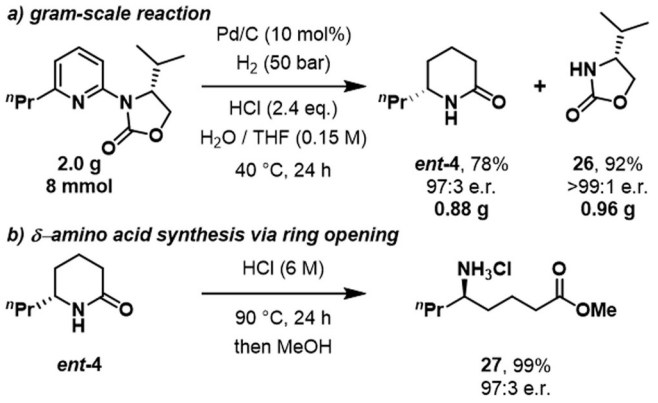


Figure 2. Absolute configuration of δ-lactams **1** and **10**.

In agreement with this model, a deuteration experiment confirms the addition of deuterium to one diastereotopic face of the pyridine exclusively (see Supporting Information for details).

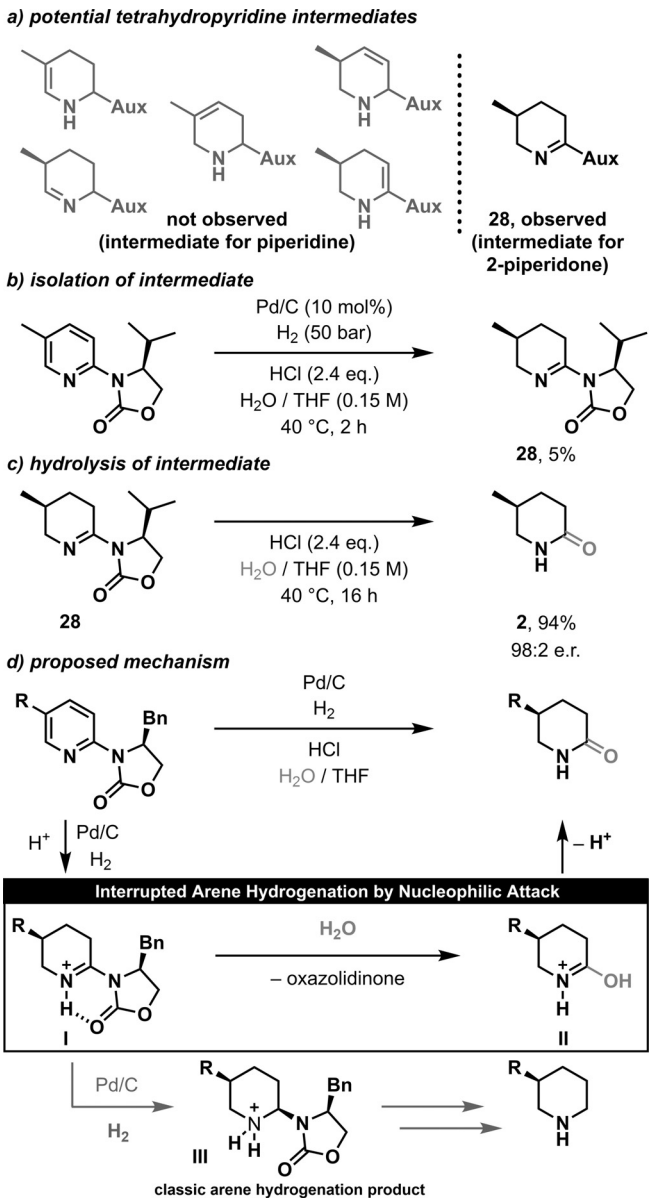
Subsequently, we investigated the scalability of our procedure and the possibility of recycling the auxiliary. The hydrogenation was performed on a 2 g scale without significant loss in yield or enantiomeric ratio (Scheme 1, a). Lactam ***ent*-4** was obtained in 78% yield and 97:3 enantiomeric ratio and oxazolidinone **26** was recovered in 92% yield and > 99:1 e.r. thus outlining its good recyclability.



Scheme 1. Gram-scale reaction and ring opening.

As further product application, δ-lactam ***ent*-4** was hydrolyzed to give the δ-amino acid methyl ester **27** in 99% yield and 97:3 e.r. after heating in hydrochloric acid for 24 h and treatment with methanol (Scheme 1, b).

Intrigued by these observations, we investigated the reaction mechanism. To identify potential intermediates, the reaction was stopped after 2 h and the mass of an intermediate with one remaining double bond was detected by GC-MS (Scheme 2, a). Although unsaturated intermediates are very short-lived in arene hydrogenation and are rapidly further hydrogenated, imine **28** was isolated in 5% yield (Scheme 2, b). Conversion of imine **28** in water/ THF with hydrochloric acid in the absence of Pd catalyst and H_2 provided the δ-lactam product in almost quantitative yield (Scheme 2, c). Thus, imine **28** is an intermediate species in our procedure and can undergo nucleophilic substitution with water. It is worth mentioning that only imine **28** as one of six potential intermediates in this reaction is suitable to hydrolyze to yield the desired 2-piperidone (Scheme 2, a). Based on these experiments we postulate the following reaction mechanism (Scheme 2, d): By addition of a Brønsted acid, the basic nitrogen of the oxazilidinone-substituted pyridine is protonated and forms a stable conformer through hydrogen bonding to the oxazolidinone. Owing to the steric repulsion of the oxazolidinone substituent of this rigid conformation, a diastereoselective hydrogenation of the unhindered face of the pyridine proceeds to set the new stereocenter. After the addition of two equivalents of H_2, oxazolidinone-substituted imine **I** is formed (see Scheme S1). In contrast to a classic arene hydrogenation, this intermediate, following our new protocol, does not undergo another catalytic reduction (see product **III)** but reacts with water in a nucleophilic substitution. In this substitution, the oxazolidinone is released and therefore serves as a recyclable, traceless auxiliary. The resulting iminium **II** tautomerizes rapidly to yield the final δ-lactam product.



Scheme 2. Mechanistic investigation and proposal.

In summary, we have disclosed a heteroarene hydrogenation interrupted by nucleophilic substitution. Hydrogenation of oxazolidinone-substituted pyridines gives access

to enantioenriched δ-lactams by applying oxazolidinones as traceless chiral auxiliaries. Our procedure was used to access a plethora of sought-after δ-lactams in high yields and excellent enantiomeric ratios. Harnessing unsaturated intermediates in arene hydrogenation is an underexplored research area and overcomes the inherent limitation of forming solely C–H and N–H bonds. We see huge potential in this research direction since it tremendously increases molecular complexity in a single step.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis · heterogeneous catalysis · hydrogenation · lactams · nitrogen heterocycles

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